Kinetic resolution of racemic 6-substituted 1,2,3,4-tetrahydroquinaldines with chiral acyl chlorides. Experiment and quantum chemical simulation*

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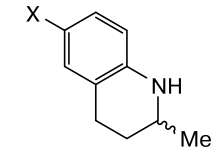
A comparative study of the kinetic resolution (KR) of racemic 6-substituted 2-methyl-1,2,3,4-tetrahydroquinolines with acyl chlorides of (*S*)-naproxen, *N*-phthaloyl-(*S*)-leucine, and (*R*)-*O*-phenyllactic acid was carried out. The selectivity factors in the KR of racemic amines with acyl chlorides of (*S*)-naproxen and (*R*)-*O*-phenyllactic acid were shown to be approximately the same and higher than those for the KR of *N*-phthaloyl-(*S*)-leucyl chloride. The reasons for the stereodifferentiation in the KR of racemic tetrahydroquinaldines containing groups of different electronic properties by acyl chlorides of three different chiral acids were explained using the DFT method. The conditions for stabilizing π—π interactions of aromatic fragments of the reagents, which do not occur in the same form in the transition state and lead to the minor diastereoisomeric product, are created in the transition state of the faster acylation reaction with (*S*)-naproxen and (*R*)-*O*-phenyllactic acyl chlorides. In the case of the KR of 2-methyl-1,2,3,4-tetrahydroquinoline and 2-methyl-6-methoxy-1,2,3,4-tetrahydroquinoline with *N*-phthaloyl-(*S*)-leucyl chloride, the acylation diastereoselectivity is determined, most likely, by conformational factors. The individual (*S*)-enantiomer of 2-methyl-6-methoxy-1,2,3,4-tetrahydroquinoline of high optical purity was synthesized using the KR of the racemate with (*S*)-naproxen acyl chloride.

Key words: kinetic resolution, racemic amines, acyl chlorides, acylation, selectivity, transition state, density functional theory.

Kinetic resolution (KR) of racemates is a chemical process in which one of the enantiomers forms the product more rapidly than another enantiomer under the action of the chiral non-racemic agent.[1] The KR method is among the efficient modern methods for the synthesis of enantiomerically pure amines and their derivatives. Stereoselective acylation under the action of chiral resolving agents (CRAs) or in the presence of chiral catalysts is often used for the KR of racemic amines.[2—5] If the chiral center is in the acyl fragment of the CRA, then the KR products are diastereomerically enriched amides and enantiomerically enriched unreacted substrate.

We studied the KR of racemic heterocyclic amines, including 2-methyl-1,2,3,4-tetrahydroquinoline (**1**), as a result of diastereoselective acylation with chiral acyl chlorides.[6—18] The major advantage of this approach is caused by a broad accessibility of chiral acids and simplicity of the process. We have previously found that the efficient KR of racemic amines is achieved by using 2-arylpropionyl chlorides,[6,8,11,13] *N*-protected amino acyl chlorides,[6,7,9,10,12—15,17] and 2-aryloxy acyl chlorides[16,18] as CRAs.

In this work, we performed for the first time the comparative study of the KR of racemic 6-methoxy- and 6-nitro-2-methyl-1,2,3,4-tetrahydroquinolines (compounds **2** and **3**) by representatives of three different groups of resolving agents: acyl chlorides of (*S*)-naproxen (**4**), *N*-phthaloyl-(*S*)-leucine (**5**), and (*R*)-*O*-phenyllactic acid (**6**) under the conditions identical to the earlier studied KR of racemic amine **1**.[10,13,16]



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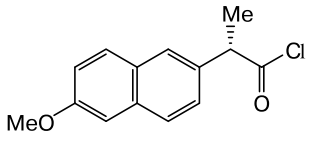

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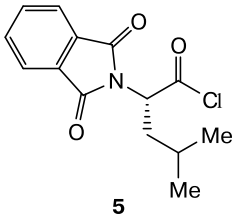

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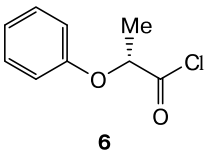

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X = H (**1**), MeO (**2**), NO_2 (**3**)

* Dedicated to Academician of the Russian Academy of Sciences V. N. Charushin on the occasion of his 70th birthday.

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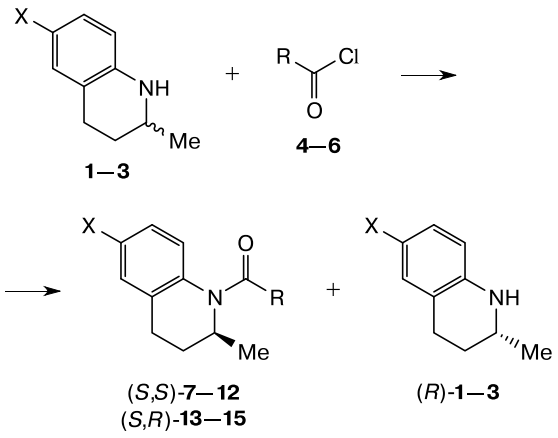
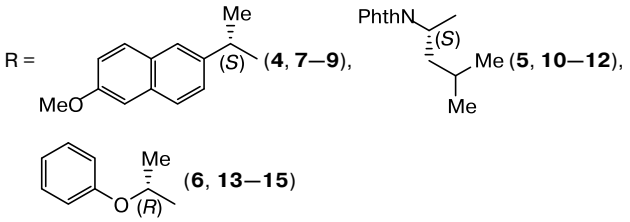
Results and Discussion

The kinetic resolution of racemic amines **2** and **3** was carried out in dichloromethane at an amine—acyl chloride molar ratio of 2 : 1 at 20 and –20 °C for 6 h, and the initial concentration of racemic amine was 0.1 mol L^{-1} (Scheme 1).

Scheme 1



X = H (**1**, **7**, **10**, **13**), OMe (**2**, **8**, **11**, **14**), NO_2 (**3**, **9**, **12**, **15**)



Reagents and conditions: 4—6 (0.5 equiv.), CH_2Cl_2, 6 h, 20 °C (–20 °C).

The diastereomeric excess (*de*, %) of the amides formed in the reaction mixture was determined by reversed-phase HPLC (RP-HPLC), and the enantiomeric excess (*ee*, %) of unreacted amines **2** and **3** was determined by HPLC on a Chiralcel OD-H chiral stationary phase. When comparing the retention times of unreacted amines on the HPLC chromatograms with the published data,[12,19] it has been found that the (*R*)-enantiomer prevails in unreacted amines in all cases and, hence, the (*S*)-enantiomers more rapidly enter into acylation with all studied acyl chlorides (see Scheme 1). In each case, based on the experimentally determined *de* values of amides and *ee* values of unreacted amines (*R*)-**2** and (*R*)-**3**, we calculated the conversion (*C*) and selectivity factor (*s*), being the ratio of the rate constants of the fast and slow reacting enantiomers: $s = k_{fast}/k_{slow}$.[1] The stereochemical results of the KR of amines **2**, **3**, and **1** (for comparison) are given in Table 1. Individual (*S,S*)- and (*S,R*)-diastereomers of amides **8**, **9**, **11**, **14**, and **15** were isolated by preparative HPLC after the treatment of the reaction mixture.

As can be seen from the data presented in Table 1, the stereoselectivity of acylation with (*S*)-naproxen acyl chloride (**4**) in dichloromethane at 20 °C increased in the series **3** (X = NO_2) > **1** (X = H) > **2** (X = OMe), and the selectivity factor *s* is 23, 15, and 8, respectively. In all cases, the acylation selectivity increased with decreasing temperature at a similar regularity. It should be mentioned that the electron-withdrawing nitro group in position 6 of amine strongly decreases its nucleophilicity leading to a low conversion (see Table 1). Similar regularities were observed for acylation with (*R*)-phenoxypropionyl chloride (**6**): the selectivity factor *s* in the acylation of amines **3**, **1**, and **2** at 20 °C was 27, 13, and 8, respectively.

The stereoselectivity of acylation of amines **1** and **2** with *N*-phthaloyl-(*S*)-leucyl chloride (**5**) was approximately the same (*s* = 13 and 11 at 20 °C; *s* = 19 at –20 °C) (see Table 1) and lower than that in the case of acyl chlorides **4** and **6**. It should specially be mentioned that the acylation of amine **3** containing the electron-withdrawing nitro group with acyl chloride **5** did not occur: no formation of amides **12** was observed in the reaction mixture, and unreacted racemic amide **3** (*ee* 0) was isolated quantitatively.

Thus, the stereoselectivity in KR of amines **1—3** with acyl chlorides **4—6** depends on the nature of the substituent in position 6 of amine. Therefore, it is of interest to study the structures of the diastereomeric transition states by quantum chemical methods.

There were earlier attempts to explain reasons for the stereoselectivity in the acylative KR of racemic amines.[20] However, it has only recently been found on the basis of the calculations in terms of the density functional theory (DFT) that the acylation of heterocyclic amines with chiral acyl chlorides proceeds *via* the S_N2-like concerted mechanism; *i.e.*, the nucleophile is added simultaneously with the elimination of the HCl molecule *via* the four-center transition state.[21] It was shown for the KR of racemic benzoxazines with acyl chlorides of 2-aryloxy acids that aromatic interactions between the reactants played a significant role in stereodifferentiation and determined a high selectivity of the process. In this work, the geometries of the diastereomeric transition states (TSs) and the corresponding free Gibbs energies for the reactions of amines **1—3** with acyl chlorides **4—6** were determined using the DFT method at the CPCMC-CH_2Cl_2-B3LYP-D3-gCP/def2-TZVP//B3LYP-D3-gCP/def2-SVP level of theory, which (as shown previously) described well the quantitative dependence of the acylation selectivity on the reactant structure.[21,22]

The structures of the diastereomeric TSs in the reaction of amine **1** with acyl chloride **4** are shown in Fig. 1. The four-center TS is schematically shown in Fig. 1, *a*. For the reactions of acyl chlorides with amines, the formed C—N bond and cleaved C—Cl bond are orthogonal

Table 1. Results of the KR of amines **1—3** with acyl chlorides **4—6** in dichloromethane[a]

Amine	X	Acyl chloride	*T*/°C	Amide	*de*[b]	(*R*)-amine *ee*[c]	*C*[d]	*s*[e]
					%			
1	H	**4**	20	(*S,S*)-**7**	77.0	66.0	46	15[13]
2	OMe	**4**	20	(*S,S*)-**8**	62.9	62.3	50	8
3	NO_2	**4**	20	(*S,S*)-**9**	89.1	28.0	24	23
1	H	**4**	−20	(*S,S*)-**7**	72.8	61.6	46	12[13]
2	OMe	**4**	−20	(*S,S*)-**8**	68.7	63.7	49	11
3	NO_2	**4**	−20	(*S,S*)-**9**	94.0	2.9	3	33
1	H	**5**	20	(*S,S*)-**10**	76.0	60.4	44	13[10]
2	OMe	**5**	20	(*S,S*)-**11**	74.0	54.3	42	11
3	NO_2	**5**	20	(*S,S*)-**12**	—	0	—	—
1	H	**5**	−20	(*S,S*)-**10**	80.2	64.7	44	19[10]
2	OMe	**5**	−20	(*S,S*)-**11**	83.2	55.0	40	19
1	H	**6**	20	(*S,R*)-**13**	74.0	66.7	47	13[16]
2	OMe	**6**	20	(*S,R*)-**14**	62.9	62.3	50	8
3	NO_2	**6**	20	(*S,R*)-**15**	88.1	52.3	37	27
2	OMe	**6**	−20	(*S,R*)-**14**	71.2	65.2	48	12
3	NO_2	**6**	−20	(*S,R*)-**15**	93.3	19.4	17	35

[a] The average values of two to four parallel experiments are presented.
[b] According to RP-HPLC (see Experimental).
[c] According to HPCL on Chiralcel OD-H (see Experimental).
[d] Conversion, $C = [ee_{amine}/(ee_{amine} + de_{amide})] \cdot 100\%$.[1]
[e] Selectivity factor, $s = \ln[(1 - C)(1 - ee_{amine})]/\ln[(1 - C)(1 + ee_{amine})]$.[1]

(the N—C—Cl angle is 85.4—91.9°). The O=C—Cl and N—C=O angles lie in a range of 105.5—114.5°, which corresponds to the Bürgi—Dunitz trajectory typical of the nucleophilic addition to the carbonyl group.[23] The distance between the Cl atom and H atom of amine ranges from 2.2 to 2.5 Å, which is consistent with the assumption about the Coulomb interactions between them.

In the acylation of amines **1—3** with acyl chloride **4**, aromatic interactions of the corresponding fragments of the reactants by the π—π-stacking type with a non-strictly parallel arrangement of the aromatic rings (see Fig. 1, *a*) occur in all cases of the TSs of the reactions leading to the predominant (*S,S*)-diastereomer ((*S,S*)-TS). In the energetically unfavorable (*R,S*)-TS, the 6-methoxynaphthyl group of acyl chloride **4** passes from a *gauche*-conformation to *trans*-conformation with respect to the nitrogen atom due to the van der Waals and Coulomb repulsion interactions with the benzene ring of amine. As a result, dispersion interactions of the aromatic fragments of the reactants in the (*R,S*)-TS become impossible (see Fig. 1, *b*).

A lower energy of the (*S,R*)-TSs compared to that of (*R,R*)-TSs in the reactions of amines **1—3** with acyl chloride **6** is also determined by stacking stabilizing interactions, which do not occur for steric reasons in the energetically

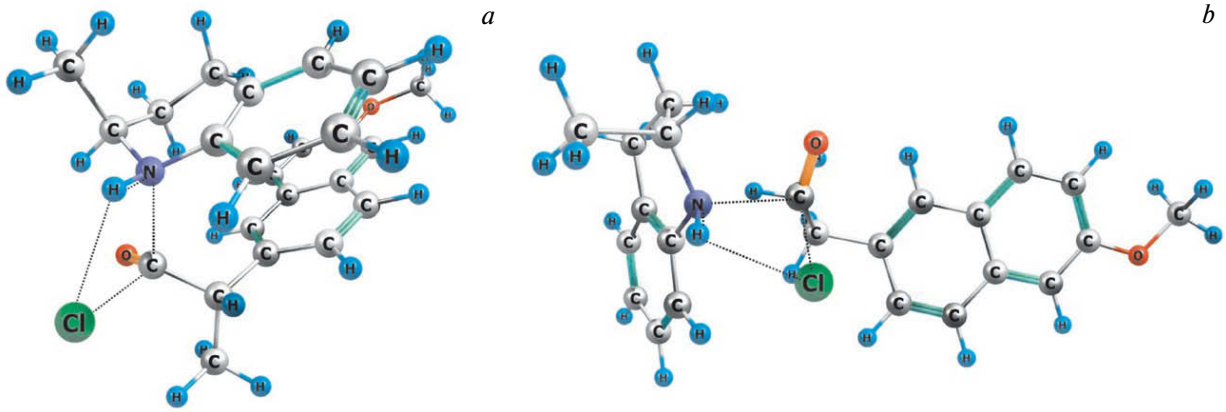


Fig. 1. Geometry of the diastereomeric TSs in the reaction of amine **1** with acyl chloride **4** in dichloromethane: TS leading to predominant amide (*S,S*)-**7** (*a*) and TS leading to minor amide (*R,S*)-**7** (*b*). The four-centered TS is designated by dash lines.

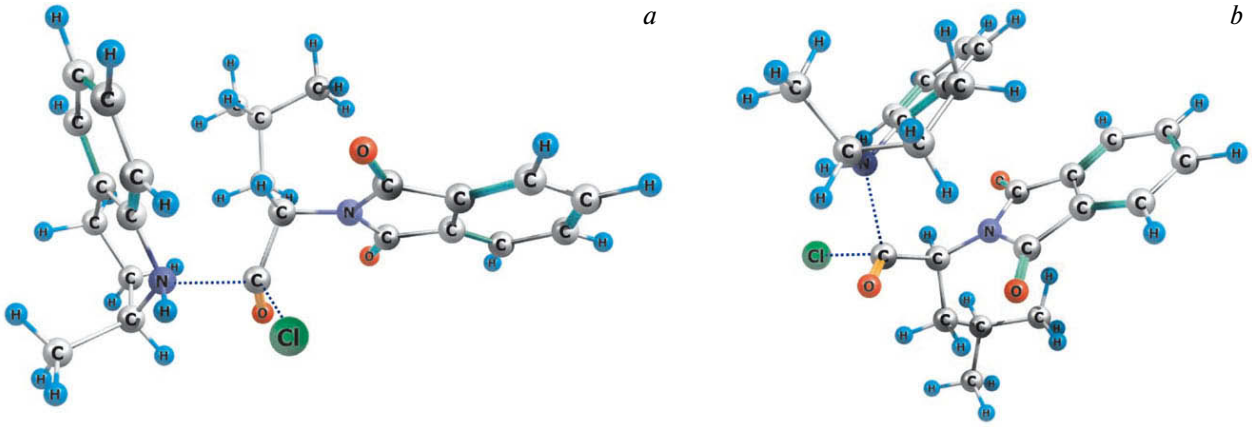


Fig. 2. Geometries of energetically more favorable (*S*,*S*)-TS (*a*) and less favorable (*R*,*S*)-TS (*b*) in the reaction of amine **1** with acyl chloride **5**.

unfavorable (*R*,*R*)-TS because of strongly approached benzene rings, which results in the Coulomb and van der Waals repulsion interactions, and synclinal position of the Cl atom and phenoxy group.

For the acylation of amines **1** and **2** with acyl chloride **5**, the conformation relative to the bond between the carbonyl carbon atom and chiral carbon atom of the acylating agent in the TSs required an additional analysis. It was found by the conformational search for the TS that in the energetically favorable (*S*,*S*)-TS the *N*-phthaloyl group existed in the *trans*-conformation to the nitrogen atom of amine (Fig. 2, *a*), whereas the isobutyl group occupies this position in the energetically less favorable (*R*,*S*)-TS (Fig. 2, *b*).

The values of the free activation energies of the TSs, which were calculated as the difference between the Gibbs energy of the TS and reagent complex (RC), are presented in Table 2. The RC structure was determined from the geometry of the TS by the optimization with the fixation of the Cl–C(O) bond length equal to that in the molecule of the corresponding initial acyl chloride. The geometries of the reactant complexes according to the presence or absence of aromatic interactions predominantly corresponded to the TS structure.

The free Gibbs activation energies (see Table 2) corresponds, on the whole, to the experimental values determined from the selectivity factor *s* and, in the case of acylation with acyl chlorides **4** and **6**, depend on the substituent in position 6 of tetrahydroquinaldine. It has been shown that the (*S*,*S*)-TSs are preferable compared to the (*R*,*S*)-TSs, and (*S*,*S*)-amides are predominantly

Table 2. Calculated difference in the activation Gibbs energies ($\Delta\Delta G^{\#}$) of the competitive TSs and the factor *s* at the CPCMC-CH_2Cl_2-B3LYP-D3-gCP/def2-TZVP//B3LYP-D3-gCP/def2-SVP level of theory compared to the experimental factor *s* values and the $\Delta\Delta G^{\#}$ values calculated on the basis of factor *s*

Amine	Acyl chloride	Predominant amide diastereomer	*T*/K	Calculation		Experiment	
				$\Delta\Delta G^{\#}$/ kJ mol^{-1}	s_{calc} [a]	$\Delta\Delta G^{\#}$ [b]/kJ mol^{-1}	s_{exp}
1	**4**	(*S*,*S*)-**7**	293	6.63	15	6.59	15[13]
	4	(*S*,*S*)-**7**	253	6.65	23.6	5.23	12[13]
2	**4**	(*S*,*S*)-**8**	293	5.49	9.5	5.07	8
	4	(*S*,*S*)-**8**	253	5.99	17.3	5.04	11
3	**4**	(*S*,*S*)-**9**	293	8.07	24.5	7.64	23
	4	(*S*,*S*)-**9**	253	7.14	29.8	7.35	33
1	**5**	(*S*,*S*)-**10**	293	6.09	12.2	6.25	13[10]
	5	(*S*,*S*)-**10**	253	5.40	13.1	6.19	19[10]
2	**5**	(*S*,*S*)-**11**	293	5.92	11.4	5.84	11
	5	(*S*,*S*)-**11**	253	6.60	23	6.19	19
1	**6**	(*S*,*R*)-**13**	293	6.09	12.2	6.25	13[16]
2	**6**	(*S*,*R*)-**14**	293	5.57	9.8	5.07	8
	6	(*S*,*R*)-**14**	253	5.83	16	5.23	12
3	**6**	(*S*,*R*)-**15**	293	7.94	26	8.03	27
	6	(*S*,*R*)-**15**	253	8.32	52	7.48	35

[a] $s_{calc} = e^{-\Delta\Delta G^{\#}/(RT)}$.
[b] $\Delta\Delta G^{\#} = -RT\ln s$.

formed, as in experiment, in the reactions of amines **1—3** with acyl chlorides **4** and **5**. In the reactions of amines **1—3** with acyl chloride **6**, the (*S,R*)-TSs are energetically preferable compared to the (*R,R*)-TSs.

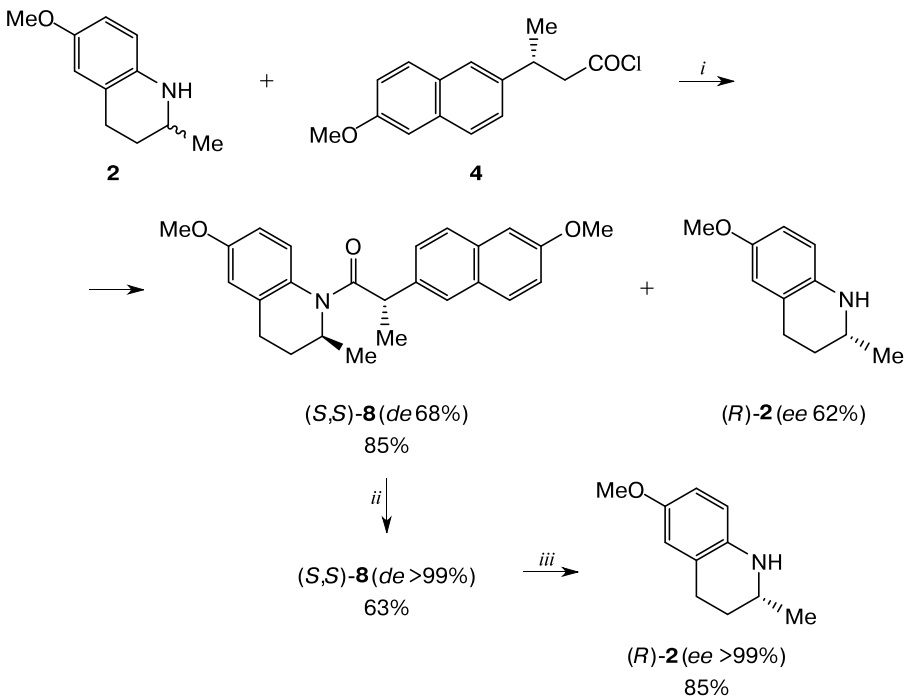
According to the calculated Gibbs activation energies $\Delta G^{\#}$, 6-methoxytetrahydroquinaldine (**2**) is the most nucleophilic amine in the studied series. The acylation stereoselectivity of amines **1—3** with acyl chlorides **4** and **6** increased in the series **2** ⩽ **1** < **3** in both experiment and calculation, which is consistent with the concept about an increase in steric hindrances with decreasing N—CO bond length as the nucleophilicity of amine decreases.[20] The lower the nucleophilicity of amine, the closer its approach to the reaction center needed for TS formation and the stronger repulsive interactions of amine with the atoms lying near the reaction center.

The calculations show that the N—CO bond in the TS in the case of amine **3** is shorter than those for amines **1** and **2** and the van der Waals repulsions of the fragments and aromatic systems close to the reaction center in the TSs leading to the minor diastereomer are maximal. In addition, it has previously been found that the stabilizing energy of stacking interactions of the nitrosubstituted aromatic compounds is higher than that of the unsubstituted ones[24] due to a lower Coulomb repulsion of the π-systems when the electron density is shifted toward the nitro group, which can be observed in our case as well in the energetically favorable TS with 6-nitrosubstituted amine **3** as compared to tetrahydroquinaldines **1** and **2**.

The DFT calculations also showed that the reactions of acyl chloride **5** with amines **1** and **2** involved no explicit interactions between the aromatic fragments of the reactants according to the π—π-stacking type. The *N*-phthaloyl group is located in the *trans*-conformation to the nitrogen atom of amine in the (*S,S*)-TS leading to the predominant diastereomer, whereas it is the isobutyl group in the (*R,S*)-TS (see Fig. 2). Stereoselectivity is caused by the difference in steric hindrances that are created by this group. It is most likely that the conformational factors (rather than those associated with nonvalent interactions of aromatic fragments) cause the situation that the selectivity factor values *s* are nearly the same for amines **1** and **2** in experiment and calculation (see Table 2) and are independent of the electronic effect of substituent X (see Scheme 1).

It has been found that the KR of amine **2** with acyl chlorides **4** and **6** is characterized by close values of selectivity factor, but acyl chloride **4** is somewhat more accessible in large amounts. In addition, the possibility of separating a mixture of the formed (*S,S*)- and (*R,S*)-diasteremeric amides by recrystallization is an important advantage of (*S*)-naproxen acyl chloride (**4**) compared to other acyl chlorides studied. Therefore, acyl chloride **4** was chosen as the resolving agent for the preparative isolation of (*S*)-2-methyl-6-methoxy-1,2,3,4-tetrahydroquinoline ((*S*)-**2**). Acylation was carried out in dichloromethane at −20 °C (Scheme 2). Amide (*S,S*)-**8** (*de* 68%) was isolated in a yield of 85% (relative to acyl chloride **4**). The single recrystallization from a hexane—Pr^{i}OH mixture made

Scheme 2



Reagents and conditions: *i*. **4** (0.5 equiv.), CH_2Cl_2, −20 °C, 6 h; *ii*. hexane—Pr^{i}OH, recrystallization; *iii*. HCl—AcOH, 92—95 °C.

it possible to obtain diastereomerically pure (*S*,*S*)-**8** (*de* >99%) in an overall yield of 53% (see Scheme 2). The unreacted (*R*)-enantiomer of amine **2** (*ee* 62%) was isolated in a yield of 48%.

The standard procedure of acidic hydrolysis (under reflux in a mixture of concentrated HCl and AcOH) of diastereomerically pure amide (*S*,*S*)-**8** resulted in the (*S*)-enantiomer of amine **2** (*ee* > 99%) in a yield of 85% (see Scheme 2). The total yield of amine (*S*)-**2** (based on the starting racemate) was 23%. The acidic hydrolysis of amide (*S*,*S*)-**8** was not accompanied by the racemization of the chiral center in the amine residue and led to enantiomerically pure amine.

It should be mentioned that the methods for synthesis of (*S*)-enantiomer of amine **2** described in the literature and based on catalytic hydrogenation in the presence of the chiral catalysts make it possible to obtain the target product with *ee* 78—81%.[18,25]

Thus, we comparatively studied the kinetic resolution of racemic amines **1**—**3** with acyl chlorides of (*S*)-naproxen, *N*-phthaloyl-(*S*)-leucine, and (*R*)-*O*-phenyllactic acid. The selectivity factors in the KR of racemic amines **1**—**3** with acyl chlorides **4** and **6** were shown to be approximately the same and higher than those for acyl chloride **5**. The reasons for stereodifferentiation in the KR of racemic amines **1**—**3** containing the groups different in electronic properties with acyl chlorides of three different chiral acids were explained using the DFT method at the CPCMC-CH_2Cl_2-B3LYP-D3-gCP/def2-TZVP//B3LYP-D3-gCP/def2-SVP level of theory. The competitive acylation reactions proceed *via* the concerted mechanism. The conditions for the stabilizing π—π-interactions of the reactants are created in the transition state of the faster acylation reactions involving acyl chlorides **4** and **6**, while they are not created in the same form for steric reasons in the transition state leading to the minor diastereoisomer of the product. In the case of the KR of amines **1** and **2** with acyl chloride **5**, the acylation diastereoselectivity is determined, most likely, by conformational factors. The individual (*S*)-enantiomer of amine **2** of high optical purity was obtained using the KR of the racemate with (*S*)-naproxen acyl chloride.

Experimental

Racemic 2-methyl-6-methoxy-1,2,3,4-tetrahydroquinoline (**2**)[26] and 2-methyl-6-nitro-1,2,3,4-tetrahydroquinoline (**3**)[27] were synthesized by the earlier described methods. (*S*)-2-(6-Methoxynaphth-2-yl)propionyl (**4**),[13] *N*-phthaloyl-(*S*)-leucyl (**5**),[10] and (*R*)-2-phenoxypropionyl (**6**)[16] chlorides were synthesized using known procedures. Other reagents were commercially available. The solvents were purified by standard methods.

^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE-500 spectrometer (500 and 126 MHz, respectively) in a solution of DMSO-d_6. Chemical shifts were measured relative to $SiMe_4$ as the internal standard for ^1H and relative to the solvent signal (δ_C 39.5) for ^{13}C. The full assignment of ^1H and ^{13}C signals was performed using 2D ^1H—^{13}C HSQC and HMBC experiments. The 1D and 2D NMR experiments for amides (*S*,*S*)-**8** and (*R*,*S*)-**8** were carried out at 120 °C, and those for other compounds were conducted at room temperature.

Melting points were determined on a Stuart SMP3 instrument (Barloworld Scientific, Great Britain). Elemental analysis was carried out on a CHNS/O Perkin—Elmer 2400 II automated analyzer. Optical rotations were measured on a Perkin—Elmer M341 polarimeter (Perkin—Elmer Instruments, USA). Specific rotation is expressed in (deg mL) (g dm)$^{-1}$, and the solution concentration is given in g (100 mL)$^{-1}$.

Diastereomeric excess of amides **8**, **9**, **11**, **14**, and **15** was determined on an Agilent 1100 chromatograph (Phenomenex Luna C18(2) column, 250×4.6 mm, elution rate 0.8 mL min^{-1}, detection at 230 nm, eluent MeCN—H_2O).

Enantiomeric excess of amines **2** and **3** was determined on a Knauer Smartline-1100 chromatograph (Chiralcel OD-H column, 250×4.6 mm, elution rate 1 mL min^{-1}, detection at 220 nm, hexane—Pr^iOH (40 : 1) eluent for **2** ($\tau_{(R)}$ 10.1 min, $\tau_{(S)}$ 12.2 min); hexane—Pr^iOH—MeOH (95 : 4 : 1) for **3** ($\tau_{(R)}$ 20.5 min, $\tau_{(S)}$ 22.8 min)).

Preparative resolution of diastereomeric amides **8**, **9**, **11**, **14**, and **15** was conducted on a Shimadzu LC-20 Prominence chromatograph (Phenomenex Luna C18(2) column, 250×21.6 mm, detection at 254 nm, eluent flow rate 10 mL min^{-1}; MeCN—H_2O (70 : 30) eluent for **8**, **9**, and **11** and MeCN—H_2O (65 : 35) eluent for **14** and **15**). The volume of the injected sample was 1 mL.

Kinetic resolution of amine 2 with acyl chlorides 4—6 (general procedure). A solution of acyl chloride **4** (**5** or **6**) (0.28 mmol) in CH_2Cl_2 (2.8 mL) was added as one portion at a specified temperature to a solution of amine **2** (100.0 mg, 0.56 mmol) in CH_2Cl_2 (2.8 mL). The reaction mixture was kept at a specified temperature for 6 h and subsequently washed with 1 *M* HCl (2×5 mL) (acidic washing solutions were collected separately), a saturated solution of NaCl (3×5 mL), a 5% solution of $NaHCO_3$ (10 mL), and water (2×5 mL). The organic layer was dried over $MgSO_4$ and evaporated to dryness. The obtained mixture of diastereomers of the corresponding amide was analyzed by HPLC (Phenomenex Luna C18(2)). The acidic water layer was neutralized by Na_2CO_3 and extracted with $CHCl_3$ (2×3 mL), and the organic layer was washed with water (2×3 mL), dried with $MgSO_4$, and evaporated to dryness. The obtained unreacted amine was analyzed by chiral HPLC (Chiralcel OD-H).

Kinetic resolution of amine 3 with acyl chlorides 4—6 (general procedure). A solution of acyl chloride **4** (**5** or **6**) (0.26 mmol) in CH_2Cl_2 (2.6 mL) was added as one portion at a specified temperature to a solution of amine **3** (100.0 mg, 0.52 mmol) in CH_2Cl_2 (2.6 mL). The reaction mixture was kept at a specified temperature for 6 h and consequently washed with a 3% solution of NH_4OH (2×5 mL) (to neutralize unreacted acyl chloride), a saturated solution of NaCl (3×5 mL), and water (2×5 mL). The organic layer was dried over $MgSO_4$ and evaporated to dryness. The diastereomeric composition of amides was determined in a mixture with unreacted amine by HPLC (Phenomenex Luna C18(2)). Unreacted amine was isolated from the mixture by flash chromatography on silica gel (benzene—ethyl acetate (9 : 1) eluent), and the enantiomeric composition was determined by chiral HPLC (Chiralcel OD-H).

Preparative resolution of diastereomers of amides 8, 9, 11, 14, and 15 (general procedure). After KR, a weighed sample (300 mg) of each mixture of diastereomers **8**, **9**, **11**, **14**, and **15** (*de* 63—89%)

was dissolved in MeCN (10 mL). The obtained solutions were injected by portions into a preparative chromatograph (the volume of the injected sample was 1 mL). The fractions with individual diastereomers were combined, evaporated, and dried to obtain individual diastereomers in 90—95% yield (based on their content in the mixture).

(2*S*,2′*S*)-2-Methyl-6-methoxy-*N*-[2′-(6″-methoxynaphth-2″-yl)propionyl]-1,2,3,4-tetrahydroquinoline [(*S*,*S*)-8]. The yield was 219.9 mg (90%), colorless crystals, m.p. 143—144 °C. $[\alpha]_D^{20}$ −16.7 (*c* 1.0, $CHCl_3$). HPLC (MeCN—H_2O, 70 : 30): τ 14.0 min; *de* 99.2%. ^{1}H NMR, δ: 0.92 (d, 3 H, C(2)Me, *J* = 6.5 Hz); 1.10—1.15 (m, 1 H, C(3)H_B); 1.46 (d, 3 H, C(2′)Me, *J* = 6.8 Hz); 1.70—1.78 (m, 1 H, C(4)H_B); 2.07—2.13 (m, 1 H, C(3)H_A); 2.24 (dt, 1 H, C(4)H_A, *J* = 14.8 Hz, *J* = 4.9 Hz); 3.74 (s, 3 H, C(6)OMe); 3.84 (s, 3 H, C(6″)OMe); 4.37 (q, 1 H, C(2′)H, *J* = 6.8 Hz); 4.66 (sextet, 1 H, C(2)H, *J* = 6.7 Hz); 6.56 (d, 1 H, C(5)H, *J* = 2.6 Hz); 6.84 (dd, 1 H, C(7)H, *J* = 8.6 Hz, *J* = 2.7 Hz); 6.99 (br.d, 1 H, C(3″)H, *J* = 8.2 Hz); 7.07 (dd, 1 H, C(7″)H, *J* = 8.9 Hz, *J* = 1.5 Hz); 7.13–7.19 (m, 2 H, C(1″)H, C(5″)H); 7.25 (d, 1 H, C(8)H, *J* = 8.6 Hz); 7.54–7.56 (m, 2 H, C(8″)H, C(4″)H). ^{13}C NMR, δ: 18.24 (C(3′)); 19.29 (C(2)Me); 24.50 (C(4)); 31.23 (C(3)); 41.43 (C(2′)); 47.24 (C(2)); 54.67 (C(6)OMe); 54.86 (C(6′)OMe); 105.90 (C(5″)); 111.40 (C(7)); 112.14 (C(5)); 117.52 (C(7″)); 124.54 (C(1″)); 125.10 (C(3″)); 125.76 (C(4″)); 126.48 (C(8)); 127.88 (C(8″a)); 128.14 (C(8″)); 129.77 (C(8a)); 132.44 (C(4″a)); 136.26 (C(2″)); 136.46 (br.s, C(4a)); 156.63 (C(6″)); 156.82 (C(6)); 172.15 (C(1′)). Found (%): C, 77.02; H, 6.87; N, 3.49. $C_{25}H_{27}NO_3$. Calculated (%): C, 77.09; H, 6.99; N, 3.60.

(2*R*,2′*S*)-2-Methyl-6-methoxy-*N*-[2′-(6″-methoxynaphth-2″-yl)propionyl]-1,2,3,4-tetrahydroquinoline [(*R*,*S*)-8]. The yield was 52.9 mg (95%), light yellow oil. $[\alpha]_D^{20}$ −322 (*c* 1.0, $CHCl_3$). HPLC (MeCN—H_2O, 70 : 30): τ 17.4 min; *de* > 99.9%. ^{1}H NMR, δ: 1.04 (d, 3 H, C(2)Me, *J* = 6.6 Hz); 1.25—1.30 (m, 1 H, C(3)H_B); 1.38 (d, 3 H, C(2′)Me, *J* = 6.8 Hz); 2.11—2.18 (m, 1 H, C(3)H_A); 2.45 (ddd, 1 H, C(4)H_B, *J* = 15.2 Hz, *J* = 9.4 Hz, *J* = 5.9 Hz); 2.62 (dt, 1 H, C(4)H_A, *J* = 15.2 Hz, *J* = 5.5 Hz); 3.79 (s, 3 H, C(6)OMe); 3.91 (s, 3 H, C(6″)OMe); 4.15 (q, 1 H, C(2′)H, *J* = 6.8 Hz); 4.81 (sextet, 1 H, C(2)H, *J* = 6.6 Hz); 6.73 (dd, 1 H, C(7)H, *J* = 8.7 Hz, *J* = 2.4 Hz); 6.82 (d, 1 H, C(5)H, *J* = 2.4 Hz); 7.02 (d, 1 H, C(8)H, *J* = 8.7 Hz); 7.18 (dd, 1 H, C(7″)H, *J* = 8.9 Hz, *J* = 2.1 Hz); 7.30 (br.d, 1 H, C(5″)H, *J* = 2.0 Hz); 7.49 (dd, 1 H, C(3″)H, *J* = 8.3 Hz, *J* = 1.4 Hz); 7.76—7.80 (m, 3 H, C(4″)H, C(8″)H, C(1″)H). ^{13}C NMR, δ: 19.14 (C(2)Me); 20.41 (C(3′)); 24.66 (C(4)); 30.88 (C(3)); 41.80 (C(2′)); 47.03 (C(2)); 54.74 (C(6′)OMe); 54.79 (C(6)OMe); 106.03 (C(5″)); 111.04 (C(7)); 112.44 (C(5)); 117.69 (C(7″)); 124.68 (C(1″)); 125.73 (C(3″)); 126.15 (C(8)); 126.23 (C(4″)); 128.17 (C(8″a)); 128.40 (C(8″)); 129.61 (C(8a)); 132.60 (C(4″a)); 135.30 (br.s, C(4a)); 137.14 (C(2″)); 156.61 (C(6)); 156.80 (C(6″)); 171.85 (C(1′)). Found (%): C, 76.98; H, 6.85; N, 3.85. $C_{25}H_{27}NO_3$. Calculated (%): C, 77.09; H, 6.99; N, 3.60.

(2*S*,2′*S*)-2-Methyl-*N*-[2′-(6″-methoxynaphth-2″-yl)propionyl]-6-nitro-1,2,3,4-tetrahydroquinoline [(*S*,*S*)-9]. The yield was 260.9 mg (92%), light yellow powder, m.p. 118—121 °C. $[\alpha]_D^{20}$ +149.8 (*c* 1.0, $CHCl_3$). HPLC (MeCN–H_2O, 70 : 30): τ 14.2 min; *de* > 99.9%. ^{1}H NMR, δ: 0.82 (br.s, 3 H, C(2)Me); 1.30 (br.s, 1 H, C(3)H_B); 1.44 (d, 3 H, C(2′)Me, *J* = 6.7 Hz); 1.98 (br.s, 1 H, C(4)H_B); 2.13 (qd, 1 H, C(3)H_A, *J* = 13.0 Hz, *J* = 6.5 Hz); 2.51—2.57 (m, 1 H, C(4)H_A, overlapped with signal from DMSO); 3.84 (s, 3 H, C(6″)OMe); 4.48 (q, 1 H, C(2′)H, *J* = 6.7 Hz); 4.63 (sextet, 1 H, C(2)H, *J* = 6.6 Hz); 7.06 (br.s, 1 H, C(3″)H); 7.09 (dd, 1 H, C(7″)H, *J* = 8.9 Hz, *J* = 2.4 Hz); 7.22 (d, 1 H, C(5″)H, *J* = 2.4 Hz); 7.30 (br.s, 1 H, C(1″)H); 7.62—7.65 (m, 2 H, C(4″)H, C(8″)H); 7.82 (d, 1 H, C(8)H, *J* = 8.8 Hz); 7.87 (d, 1 H, C(5)H, *J* = 2.5 Hz); 8.11 (dd, 1 H, C(7)H, *J* = 8.8 Hz, *J* = 2.5 Hz). ^{13}C NMR, δ: 19.34 (br.s, C(2)Me); 19.56 (C(3′)); 24.03 (C(4)); 30.44 (br.s, C(3)); 42.80 (C(2′)); 48.95 (C(2)); 55.07 (OMe); 105.62 (C(5″)); 118.65 (C(7″)); 121.50 (C(7)); 122.66 (C(5)); 125.39 (C(1″)); 125.65 (C(3″)); 126.89 (C(4″)); 126.97 (C(8)); 128.26 (C(8″a)); 128.86 (C(8″)); 132.92 (C(4″a)); 135.22 (br.s, C(4a)); 136.25 (C(2″)); 143.50 (C(8a)); 143.78 (C(6)); 157.03 (C(6″)); 173.30 (C(1′)). Found (%): C, 71.17; H, 5.81; N, 6.96. $C_{24}H_{24}N_2O_4$. Calculated (%): C, 71.27; H, 5.98; N, 6.93.

(2*R*,2′*S*)-2-Methyl-*N*-[2′-(6″-methoxynaphth-2″-yl)propionyl]-6-nitro-1,2,3,4-tetrahydroquinoline [(*R*,*S*)-9]. The yield was 15.5 mg (95%), light yellow oil. $[\alpha]_D^{20}$ −389.4 (*c* 1.0, $CHCl_3$). HPLC (MeCN—H_2O, 70 : 30): τ 18.1 min; *de* > 99.9%. ^{1}H NMR, δ: 1.09 (d, 3 H, C(2)Me, *J* = 6.6 Hz); 1.33—1.41 (m, 1 H, C(3)H_B); 1.44 (d, 3 H, C(2′)Me, *J* = 6.6 Hz); 1.64 (br.s, 1 H, C(3)H_A); 2.61 (dt, 1 H, C(4)H_B, *J* = 16.5 Hz, *J* = 6.1 Hz); 2.80 (ddd, 1 H, C(4)H_A, *J* = 16.5 Hz, *J* = 9.1 Hz, *J* = 6.8 Hz); 3.88 (s, 3 H, C(6″)OMe); 4.29 (q, 1 H, C(2′)H, *J* = 6.6 Hz); 4.67 (sextet, 1 H, C(2)H, *J* = 6.2 Hz); 7.16 (dd, 1 H, C(7″)H, *J* = 8.9 Hz, *J* = 2.6 Hz); 7.31 (d, 1 H, C(5″)H, *J* = 2.6 Hz); 7.48 (dd, 1 H, C(3″)H, *J* = 8.4 Hz, *J* = 1.8 Hz); 7.68 (br.s, 1 H, C(8)H); 7.77 (br.d, 1 H, C(1″)H, *J* = 1.5 Hz); 7.82 (d, 1 H, C(8″)H, *J* = 8.4 Hz); 7.83 (d, 1 H, C(4″)H, *J* = 8.4 Hz); 8.05 (dd, 1 H, C(7)H, *J* = 9.0 Hz, *J* = 2.7 Hz); 8.10 (d, 1 H, C(5)H, *J* = 2.7 Hz). ^{13}C NMR, δ: 18.70 (C(2)Me); 21.74 (C(3′)); 23.47 (C(4)); 28.69 (br.s, C(3)); 43.21 (C(2′)); 48.26 (C(2)); 55.14 (OMe); 105.74 (C(5″)); 118.77 (C(7″)); 121.02 (C(7)); 123.59 (C(5)); 125.11 (C(1″)); 126.04 (C(3″)); 126.29 (C(8)); 127.42 (C(4″)); 128.52 (C(8″a)); 129.19 (C(8″)); 132.98 (br.s, C(4a)); 133.18 (C(4″a)); 136.51 (C(2″)); 142.83 (C(8a)); 143.35 (C(6)); 157.20 (C(6″)); 172.74 (C(1′)). Found (%): C, 71.16; H, 6.08; N, 7.04. $C_{24}H_{24}N_2O_4$. Calculated (%): C, 71.27; H, 5.98; N, 6.93.

(2*S*,2′*S*)-2-Methyl-6-methoxy-*N*-[*N*-phthaloyl-(*S*)-leucyl]-1,2,3,4-tetrahydroquinoline [(*S*,*S*)-11]. The yield was 245.3 mg (94%), white powder, m.p. 111—115 °C. $[\alpha]_D^{20}$ +375 (*c* 1.0, $CHCl_3$). HPLC (MeCN—H_2O, 70 : 30): τ 16.8 min; *de* > 99.9%. ^{1}H NMR, δ: 0.32 (br.s, 3 H, C(6′)H); 0.63 (d, 3 H, C(5′)H, *J* = 6.3 Hz); 0.70 (br.s, 1 H, C(3′)H_B); 0.99 (d, 3 H, C(2)Me, *J* = 6.4 Hz); 1.11 (br.s, 1 H, C(3)H_B); 1.27 (br.s, 1 H, H(4′)); 2.30—2.41 (br.m, 2 H, C(4)H_B, C(3)H_A); 2.56 (td, 1 H, C(3′)H_A, *J* = 13.0 Hz, *J* = 3.0 Hz); 2.65 (dт, 1 H, C(4)H_A, *J* = 14.6 Hz, *J* = 4.0 Hz); 3.79 (s, 3 H, C(6)OMe); 4.52 (sextet, 1 H, C(2)H, *J* = 7.0 Hz); 5.52 (dd, 1 H, C(2′)H, *J* = 12.5 Hz, *J* = 3.1 Hz); 6.94–7.00 (m, 2 H, C(5)H, C(7)H); 7.38 (d, 1 H, C(8)H, *J* = 8.4 Hz); 7.88—7.93 (m, 4 H, Phth). ^{13}C NMR, δ: 19.96 (C(6′)); 20.53 (br.s, C(2)Me); 22.81 (C(5′)); 24.51 (C(4′)); 26.34 (br.s, C(4)); 32.75 (br.s, C(3)); 33.84 (br.s, C(3′)); 49.39 (C(2)); 51.83 (C(2′)); 55.39 (OMe); 112.08 (C(7)); 112.96 (C(5)); 123.18 (C(4″), C(7″)); 126.03 (C(8)); 128.88 (C(4a)); 131.20 (C(3″a), C(7″a)); 134.75 (C(5″), C(6″)); 138.60 (br.s, C(8a)); 157.77 (C(1″), C(3″)); 168.45 (C(1′)). Found (%): C, 71.51; H, 6.76; N, 6.40. $C_{25}H_{28}N_2O_4$. Calculated (%): C, 71.41; H, 6.71; N, 6.66.

(2*R*,2′*S*)-2-Methyl-6-methoxy-*N*-[*N*-phthaloyl-(*S*)-leucyl]-1,2,3,4-tetrahydroquinoline [(*R*,*S*)-11]. The yield was 36.7 mg (94%), light yellow oil. $[\alpha]_D^{20}$ −172 (*c* 1.0, $CHCl_3$). HPLC

(MeCN—H_2O, 70 : 30): τ 11.7 min; *de* > 99.9%. ^{1}H NMR, δ: 0.84 (d, 3 H, C(6′)H, *J* = 6.5 Hz); 0.91 (br.s, 1 H, C(3)H_B); 0.94 (d, 3 H, C(5′)H, *J* = 6.5 Hz); 0.99 (br.s, 3 H, C(2)Me); 1.36 (br.s, 1 H, C(4′)H); 1.78 (br.s, 1 H, C(3′)H_B); 1.95—2.09 (br.m, 2 H, C(4)H_B, C(3′)H_A); 2.15—2.26 (br.m, 2 H, C(3)H_A, C(4)H_A); 3.50 (s, 3 H, C(6)OMe); 4.48 (br.s, 1 H, C(2)H); 5.20 (dd, 1 H, C(2′)H, *J* = 10.0 Hz, *J* = 4.3 Hz); 6.18 (br.s, 1 H, C(5)H); 6.57 (br.d, 1 H, C(7)H, *J* = 8.4 Hz); 7.20 (d, 1 H, C(8)H, *J* = 8.4 Hz); 7.60—7.78 (m, 4 H, Phth). ^{13}C NMR, δ: 20.61 (br.s, C(2)Me); 21.66 (C(5′)); 23.42 (C(6′)); 24.02 (C(4′)); 25.62 (br.s, C(4)); 32.32 (br.s, C(3)); 38.91 (br.s, C(3′) (overlapped with DMSO); 49.40 (C(2′)); 49.61 (br.s, C(2)); 55.04 (OMe); 11.78 (C(5)); 112.80 (C(7)); 122.54 (C(4″), C(7″)); 125.41 (br.s, C(8)); 129.16 (C(4a)); 130.63 (C(3″a), C(7″a)); 134.33 (C(5″), C(6″)); 136.69 (br.s, C(8a)); 156.68 (br.s, C(6)); 166.32 (C(1″), C(3″)); 164.43 (C(1′)). Found (%): C, 71.48; H, 6.73; N, 6.44. $C_{25}H_{28}N_2O_4$. Calculated (%): C, 71.41; H, 6.71; N, 6.66.

(2*S*,2′*R*)-2-Methyl-6-methoxy-*N*-(2′-phenoxypropionyl)-1,2,3,4-tetrahydroquinoline [(*S*,*R*)-14]. The yield was 224.8 mg (92%), white crystals, m.p. 71—75 °C. $[\alpha]_D^{20}$ +184 (*c* 1.0, $CHCl_3$). HPLC (MeCN—H_2O, 70 : 30): τ 10.6 min; *de* > 99.9%. ^{1}H NMR, δ: 1.00 (br.s, 3 H, C(2)Me); 1.06—1.22 (br.m, 1 H, C(3)H_B); 1.59 (br.s, 3 H, C(2′)Me); 2.02—2.38 (br.m, 2 H, C(4)H_B, C(3)H_A); 2.54—2.76 (br.m, 1 H, C(4)H_A); 3.75 (s, 3 H, C(6)OMe); 4.61 (br.s, 1 H, C(2)H); 4.92—5.54 (br.m, 1 H, C(2′)H); 7.30–7.50 (br.m, 8 H, Ar). ^{13}C NMR, δ: 18.63 (C(3′)); 20.06 (C(2)Me); 25.91 (C(4)); 31.92 (C(3)); 47.94 (C(2)); 55.19 (OMe); 69.21 (C(2′)); 111.66 (C(5)); 113.07 (C(7)); 114.59 (2×C(2″)); 120.96 (C(4″)); 126.32 (C(8)); 128.68 (C(4a)); 129.23 (2×C(3″)); 137.69 (C(8a)); 156.88 (C(6)); 157.48 (C(1″)); 169.18 (C(1′)). Found (%): C, 73.68; H, 7.25; N, 4.36. $C_{20}H_{23}NO_3$. Calculated (%): C, 73.82; H, 7.12; N, 4.30.

(2*R*,2′*R*)-2-Methyl-6-methoxy-*N*-(2′-phenoxypropionyl)-1,2,3,4-tetrahydroquinoline [(*R*,*R*)-14]. The yield was 52.3 mg (94%), light yellow oil. $[\alpha]_D^{20}$ −308 (*c* 1.0, $CHCl_3$). HPLC (MeCN—H_2O, 65 : 35): τ 12.0 min; *de* > 99.9%. ^{1}H NMR, δ: 1.00 (d, 3 H, C(2)Me, *J* = 6.4 Hz); 1.11 (br.s, 3 H, C(2′)Me); 1.36—1.86 (br.m, 1 H, C(3)H_B); 1.99—2.38 (br.m, 2 H, C(4)H_B, C(3)H_A); 2.52—2.85 (br.m, 1 H, C(4)H_A); 3.74 (s, 3 H, C(6)OMe); 4.67 (sextet, 1 H, C(2)H, *J* = 6.7 Hz); 5.04—5.48 (br.m, 1 H, C(2′)H); 6.73 (dd, 1 H, C(7)H, *J* = 8.6 Hz, *J* = 2.3 Hz); 6.78—6.92 (br.m, 3 H, C(2″)H, C(5)H); 6.95 (t, 1 H, C(4″)H, *J* = 7.5 Hz); 7.12—7.25 (br.s, 1 H, C(8)H); 7.30 (dd, 2 H, C(3″)H, *J* = 8.5 Hz, *J* = 7.5 Hz). ^{13}C NMR, δ: 16.84 (C(3′)); 20.44 (C(2)Me); 26.13 (C(4)); 32.40 (C(3)); 48.37 (C(2)); 55.17 (OMe); 70.53 (C(2′)); 111.86 (C(7)); 112.75 (C(5)); 115.18 (br.s, 2×C(2″)); 120.90 (C(4″)); 126.20 (C(8)); 128.85 (C(4a)); 129.52 (2×C(3″)); 138.08 (br.s, C(8a)); 156.96 (C(6)); 157.44 (br.s, C(1″)); 169.09 (C(1′)). Found (%): C, 73.73; H, 7.17; N, 4.36. $C_{20}H_{23}NO_3$. Calculated (%): C, 73.82; H, 7.12; N, 4.30.

(2*S*,2′*R*)-2-Methyl-6-nitro-*N*-(2′-phenoxypropionyl)-1,2,3,4-tetrahydroquinoline [(*S*,*R*)-15]. The yield was 251.2 mg (90%), light yellow powder, m.p. 109—113 °C. $[\alpha]_D^{20}$ +310 (*c* 1.0, $CHCl_3$). HPLC (MeCN—H_2O, 65 : 35): τ 11.8 min; *de* > 99.9%. ^{1}H NMR, δ: 1.00 (br.d, 3 H, C(2)Me, *J* = 6.1 Hz); 1.45—1.60 (br.m, 4 H, C(3)H_B, C(2′)Me); 2.14—2.21 (br.m, 1 H, C(3)H_A); 2.56—2.62 (br.m, 1 H, C(4)H_B); 2.84—2.90 (br.m, 1 H, C(4)H_A); 4.58 (br.sextet, 1 H, C(2)H, *J* = 6.0 Hz); 5.42 (br.q, 1 H, C(2′)H, *J* = 6.3 Hz); 6.66 (br.d, 2 H, C(2″)H, *J* = 7.2 Hz); 6.89 (br.t, 1 H, C(4″)H, *J* = 7.0 Hz); 7.19 (br.t, 2 H, C(3″)H, *J* = 7.2 Hz); 7.64 (br.d, 1 H, C(8)H, *J* = 8.6 Hz); 7.94 (br.d, 1 H, C(7)H, *J* = 8.6 Hz); 8.10 (br.s, 1 H, C(5)H). ^{13}C NMR, δ: 17.25 (C(3′)); 19.05 (C(2)Me); 23.87 (C(4)); 29.54 (C(3)); 48.70 (C(2)); 70.65 (C(2′)); 114.59 (2×C(2″)); 121.12 (C(4″)); 121.48 (C(7)); 123.32 (C(5)); 125.78 (C(8)); 129.34 (2×C(3″)); 134.19 (br.s, C(4a)); 142.42 (C(8a)); 143.76 (C(6)); 156.61 (C(1″)); 169.97 (C(1′)). Found (%): C, 67.15; H, 5.99; N, 8.40. $C_{19}H_{20}N_2O_4$. Calculated (%): C, 67.05; H, 5.92; N, 8.23.

(2*R*,2′*R*)-2-Methyl-6-nitro-*N*-(2′-phenoxypropionyl)-1,2,3,4-tetrahydroquinoline [(*R*,*R*)-15]. The yield was 19.6 mg (94%), light yellow oil. $[\alpha]_D^{20}$ −421 (*c* 1.0, $CHCl_3$). HPLC (MeCN—H_2O, 65 : 35): τ 13.0 min; *de* > 99.9%. ^{1}H NMR, δ: 1.05 (d, 3 H, C(2)Me, *J* = 6.6 Hz); 1.45 (d, 3 H, C(2′)Me, *J* = 6.5 Hz); 1.54—1.66 (m, 1 H, C(3)H_B); 2.13—2.23 (m, 1 H, C(3)H_A); 2.66 (dt, 1 H, C(4)H_B, J_1 = 16.4 Hz, J_2 = 6.3 Hz); 2.87 (ddd, 1 H, C(4)H_A, *J* = 16.4 Hz, *J* = 8.4 Hz, *J* = 6.8 Hz); 4.73 (sextet, 1 H, C(2)H, *J* = 6.2 Hz); 5.38 (q, 1 H, C(2′)H, *J* = 6.5 Hz); 6.88 (dd, 2 H, C(2″)H, *J* = 8.7 Hz, *J* = 1.1 Hz); 6.96 (t, 1 H, C(4″)H, *J* = 7.4 Hz); 7.30 (dd, 2 H, C(3″)H, *J* = 8.7 Hz, *J* = 7.4 Hz); 7.66 (d, 1 H, C(8)H, *J* = 8.9 Hz); 8.01 (dd, 1 H, C(7)H, *J* = 8.9 Hz, *J* = 2.8 Hz); 8.12 (d, 1 H, C(5)H, *J* = 2.8 Hz). ^{13}C NMR, δ: 17.68 (C(3′)); 18.59 (C(2)Me); 23.47 (C(4)); 29.29 (C(3)); 48.57 (C(2)); 71.69 (C(2′)); 114.96 (2×C(2″)); 121.19 (C(4″)); 121.20 (C(7)); 123.60 (C(5)); 126.26 (C(8)); 129.60 (2×C(3″)); 133.69 (br.s, C(4a)); 142.19 (C(8a)); 143.82 (C(6)); 156.69 (C(1″)); 170.07 (C(1′)). Found (%): C, 67.21; H, 6.03; N, 8.24. $C_{19}H_{20}N_2O_4$. Calculated (%): C, 67.05; H, 5.92; N, 8.23.

(*S*)-2-Methyl-6-methoxy-1,2,3,4-tetrahydroquinoline [(*S*)-2]. A solution of acyl chloride **4** (0.35 g, 1.41 mmol) in CH_2Cl_2 (14 mL) was added to a solution of amine **2** (0.5 g, 2.82 mmol) in CH_2Cl_2 (14 mL) under stirring at −20 °C. The reaction mixture was stirred at −20 °C for 6 h and then consecutively washed with 1 *M* HCl (2×15 mL) (acidic washing solutions were collected separately), a saturated solution of NaCl (3×15 mL), a 5% solution of $NaHCO_3$ (2×15 mL), and water (2×15 mL). The organic layer was dried over $MgSO_4$ and evaporated to dryness. The obtained amide (*S*,*S*)-**8** (0.47 g, *de* 68%) was recrystallized from a hexane—Pr^iOH (20 : 1) mixture (20 mL). Amide (*S*,*S*)-**8** was obtained as colorless crystals in a yield of 0.294 g (*de* 99.5%, overall yield based on acyl chloride was 53%). A weighed sample of amide (*S*,*S*)-**8** (0.294 g, 0.75 mmol) was dissolved in glacial AcOH (5 mL), concentrated HCl (5 mL) was added to the obtained solution, and the resulting mixture was heated at 92—95 °C for 6 h. The reaction mixture was poured to water (100 mL). The formed precipitate was filtered off. The filtrate was neutralized by Na_2CO_3 to pH 8—9. The formed oil was extracted with benzene (3×10 mL). The organic layer was washed with a saturated solution of NaCl (2×15 mL), dried over $MgSO_4$, and evaporated to dryness. The product was purified by flash chromatography on silica gel (benzene—ethyl acetate (95 : 5) as eluent). The yield was 113 mg (85%), light yellow oil. $[\alpha]_D^{20}$ −84.6 (*c* 2.2, $CHCl_3$) (*cf.* Ref. 19: $[\alpha]_D^{20}$ −65.3 (*c* 3.1, $CHCl_3$); *ee* 78%). HPLC (hexane—Pr^iOH (40 : 1)): τ 12.2 min; *ee* 99.2%. The ^{1}H and ^{13}C NMR spectra were identical to those described in the literature.[25] Found (%): C, 74.79; H, 8.64; N, 8.15. $C_{11}H_{15}NO$. Calculated (%): C, 74.54; H, 8.53; N, 7.90.

Quantum chemical calculations. Graphical simulation and primary optimization of the transition state geometry were performed by molecular mechanics and molecular dynamics methods (Ammp software package) and in the framework of the VEGA ZZ program.[28,29] As a result, the model structures of all diastereomers of the transition states were obtained. The DFT

calculations based on the model structures were performed using the ORCA 4.2.1 program.[30,31] The solvent (CH_2Cl_2) effect was taken into account using the CPCMC implicit solvatation model implemented in ORCA 4.2.1. Dispersion effects were corrected using the Grimme semiempirical pairwise dispersion correction scheme (D3).[32–36] The entropy contributions to the free Gibbs energies were calculated using the Quasi-RRHO approach for the calculation of corrections for vibrational motions.[37] The geometric parameters and total electronic energies of single-point calculations (E_{FSP}) of the reactants, reagent complexes, and TSs were calculated using the hybrid meta-GGA Becke—Lee—Yang—Parr (B3LYP) functional[38,39] and def2-SVP and def2-TZVP Ahlrich´s basis sets.[40] The search for transition states at the first stage and primary calculation of the Hessian in the gas phase were performed at the B3LYP-D3/def2-SVP level of theory with a change in the length of the N—CO key bond. Every iteration during geometry optimization was accompanied by the determination of the energy of single-point calculations as a sum of the total energy and dispersion correction D3 along with the correction of the basis superposition error by the type of "geometric counterbalance" gCP.[41] The subsequent geometry optimization of the ground and transition states (using the OptTS function for TS), numerical calculations of the vibration frequencies, and calculations of the energy parameters of the solvated structures were performed using the def2-TZVP basis set in CH_2Cl_2. The value of the entropy component corresponding to the symmetry number $n = 1$ (since all reagents are chiral compounds) were chosen for the calculation of the free Gibbs energy.[42]

This study was performed with the use of the equipment of the Center for Joint Use "Spectroscopy and Analysis of Organic Compounds" of the I. Ya. Postovsky Institute of Organic Synthesis (Ural Branch of the Russian Academy of Sciences, UB RAS).

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This paper does not contain description of studies on animals or humans.

The authors declare no competing of interests.

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