Chemistry of Heterocyclic Compounds, Vol. 50, No. 6, September, 2014 (Russian Original Vol. 50, No. 6, June, 2014)

DIASTEREOSELECTIVE ACYLATION OF RACEMIC HETEROCYCLIC AMINES WITH *N*-TOSYL-(*S*)-PROLYL CHLORIDE AND ITS STRUCTURAL ANALOGS

S. A. Vakarov[1], D. A. Gruzdev[1]*, E. N. Chulakov[1], L. Sh. Sadretdinova[1], M. A. Ezhikova[1], M. I. Kodess[1], G. L. Levit[1], and V. P. Krasnov[1]

A comparative study on the kinetic resolution of racemic amines (2,3-dihydro-4H-1,4-benzoxazine and 1,2,3,4-tetrahydroquinoline derivatives) via diastereoselective acylation with N-tosyl-(S)-prolyl chloride and its structural analogs was performed. The effect of resolving agent structure on the stereoselectivity of heterocyclic amine acylation was examined. The highest stereoselectivity was achieved in the case of acylation with acyl chlorides bearing a conformationally restricted pyrrolidine ring and an aromatic substituent in the protecting group at the nitrogen atom.

Keywords: acyl chlorides, proline, racemic amines, acylation, diastereoselectivity, kinetic resolution.

Kinetic resolution (KR) of racemic mixtures [1] is currently one of the most important methods for the preparation of enantiomerically pure amines and their derivatives. Acylation reactions are frequently used for KR of racemic amines [2-4]. In this case, one of the amide isomers is formed faster, while the unreacted amine becomes enriched with another enantiomer.

Recently, enantiomerically pure heterocyclic amines have been frequently prepared by enantioselective acylation in the presence of enzymes [5-7] or synthetic catalysts [8-12], as well as by diastereoselective acylation with chiral acylating agents [13-15].

We have performed systematic studies of KR of racemic heterocyclic amines *via* diastereoselective acylation with *N*-protected amino acyl chlorides [16-20] and 2-arylpropionyl chlorides [20-24]. This approach allows to study the factors affecting stereoselectivity and also to obtain amine enantiomers with optical purity more than 99%. The use of natural amino acids as readily available enantiopure resolving agents provides a significant structural diversity of these agents.

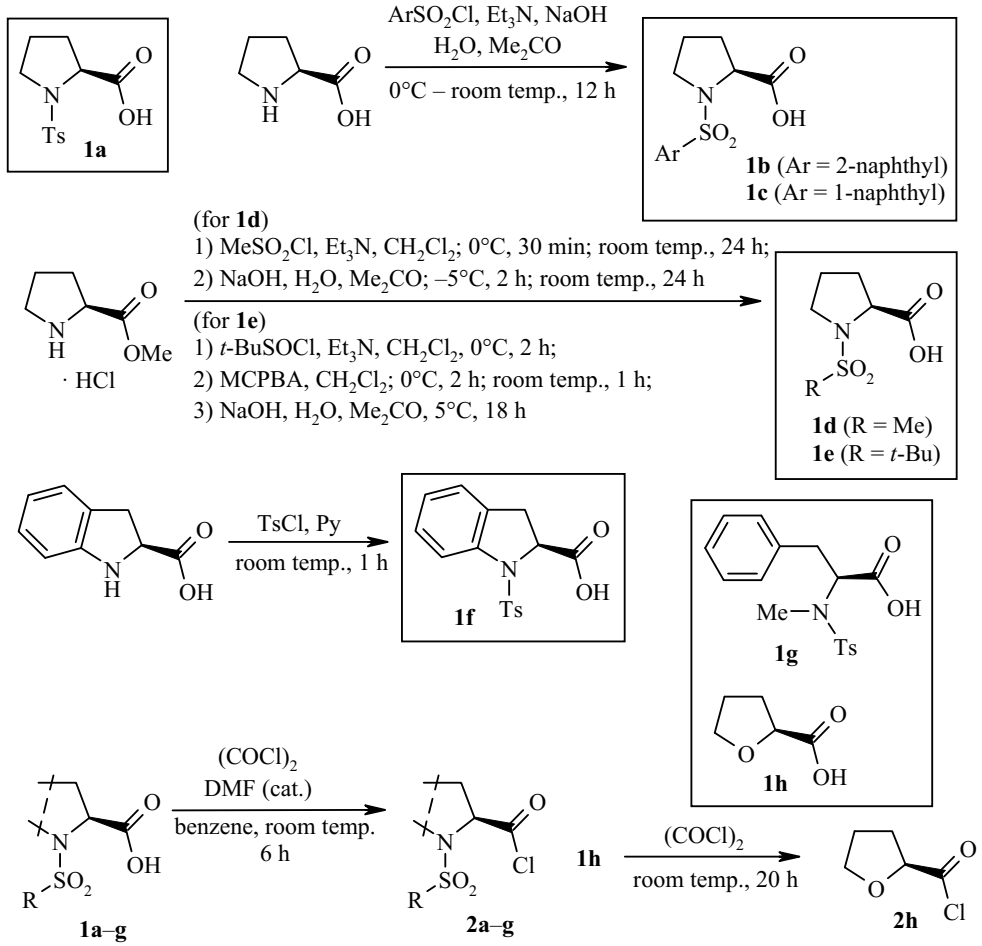
We have previously studied KR of a series of heterocyclic amines *via* acylation with *N*-tosyl-(*S*)-prolyl chloride and established that the reactions of this compound with racemic aromatic heterocyclic amines occur with remarkable diastereoselectivity [25, 26].

*To whom correspondence should be addressed, e-mail: gruzdev-da@ios.uran.ru.

[1]I. Ya. Postovskii Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences, 22 S. Kovalevskoi St. / 20 Akademicheskaya St., Yekaterinburg 620137, Russia.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 908-927, June, 2014. Original article submitted March 12, 2014.

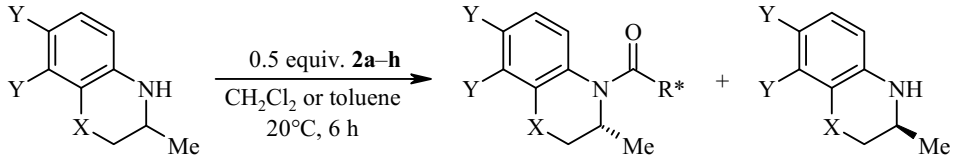
In the current work, we continued the study of reagent structure effect on the stereochemical outcome of acylation. For this purpose, we performed acylation of racemic heterocyclic amines with *N*-tosyl-(*S*)-prolyl chloride (**2a**) and its structural analogs **2b**-**h** obtained from the corresponding acids **1a**-**h**. (*S*)-Proline derivatives **2a**-**c** have different aryl fragments in the protecting group. Reagents **2d**,**e** contain aliphatic sulfamide groups of different volume. *N*-Tosyl-(*S*)-indoline-2-carbonyl chloride (**2f**) has an additional annelated fragment, while compound **2g** is an acyclic analog of acyl chloride **2f**. Acyl chloride **2h** may be considered as an oxygen-containing analog of proline derivatives.



We have previously prepared acyl chloride **2a** using the reaction of acid **1a** with oxalyl chloride in the presence of DMF [25, 26]. New acylating agents **2b**-**h** were obtained from acids **1b**-**h** by analogous procedure and were used without further purification. *N*-Protected amino acids **1b**,**c**,**e**,**f** were obtained from (*S*)-proline or (*S*)-indoline-2-carboxylic acid and the respective sulfonyl chlorides by analogy with published methods [27-29]. *N*-Mesyl-(*S*)-proline (**1d**) was synthesized from (*S*)-proline methyl ester by mesylation and subsequent hydrolysis of the ester group.

Acyl chlorides **2a**-**d**,**f**,**g** were air-stable crystalline compounds, the derivatives of *tert*-butylsulfonyl-(*S*)-proline **2e** and (*S*)-tetrahydrofuran-2-carboxylic acid **2h** were unstable upon storage and were used freshly prepared (purity not less than 96% according to ^{1}H NMR spectroscopy data).

Acylation of the racemic amines **3a**-**c** was performed for 6 h at amine–acyl chloride 2:1 molar ratio and 0.1 M initial concentration of amine. Previously, we have established that the solvent of choice for KR of amine **3a** with acyl chloride **2a** is dichloromethane, and that for KR of amines **3b,c** is toluene [26]; therefore the stereoselectivity of acylation with reagents **2b**-**h** was investigated in the solvents most suitable for each amine (Table 1).



(*RS*)-**3a–c** (*R*,*S*)-**4–11 a**, (*R*,*S*)-**4–10 b** (*R*,*S*)-**4–7**,**9–10 c** (major) (*S*)-**3a–c** (major)

3a, **4-11 a** X = O, Y = F; **3b**, **4-10 b** X = O, Y = H; **3c**, **4-10 c** X = CH_2, Y = H

The diastereomeric excess (*de*, %) of formed amides **5-11** was determined by HPLC on silica gel and by ^{1}H NMR spectroscopy. The enantiomeric excess (*ee*, %) of unreacted amines **3a-c** was determined by HPLC on chiral stationary phase (Chiralcel OD-H). Based on the values of *de* and *ee* the racemate conversion (*C*, %) and selectivity factor (*s*) were calculated [1]:

$$C = [ee_{amine} / (ee_{amine} + de_{amide})]\times 100,$$
$$s = \ln[(1 - C)\times(1 - ee_{amine})]/\ln[(1 - C)\times(1 + ee_{amine})].$$

The results of diastereoselective acylation of racemic amines **3a-c** with acyl chlorides **2a-h** are presented in Table 1.

TABLE 1. Results of Diastereoselective Acylation of Amines **3a-c** with Acyl Chlorides **2a-h***

Amine	Resolving agent	Solvent	(*R,S*)-amide (*de*, %)*[2]	*ee* of (*S*)-amine, %*[3]	Conversion, *C*, %	Selectivity factor, *s*
3a	**2a**	CH_2Cl_2	**4a** (83)	67	45	21*[4]
	2b		**5a** (78)	69	47	16
	2c		**6a** (79)	52	40	14
	2d		**7a** (70)	54	43	9.7
	2e		**8a** (81)	39	33	14
	2f		**9a** (80)	68	46	18
	2g		**10a** (41)	30	42	3.1
	2h		**11a** (21)	16	43	1.8
	2g	toluene	**10a** (73)	34	32	9.0
3b	**2a**	toluene	**4b** (85)	75	47	28*[4]
	2b		**5b** (80)	79	50	22
	2c		**6b** (72)	61	46	12
	2d		**7b** (54)	45	45	5.2
	2e		**8b** (74)	50	40	11
	2f		**9b** (86)	76	47	28
	2g		**10b** (59)	48	45	6.2
3c	**2a**	toluene	**4c** (70)	59	46	10*[4]
	2b		**5c** (54)	51	48	5.5
	2c		**6c** (45)	37	46	3.7
	2d		**7c** (26)	19	42	2.0
	2f		**9c** (67)	57	46	8.9
	2g		**10c** (36)	26	42	2.7

*The average values for 2-4 parallel experiments.

*[2]HPLC data (ReproSil 100 Si).

*[3]HPLC data (Chiralcel OD-H).

*[4]Previously reported data [26].

As in the case of using acyl chloride **2a** as a resolving agent [26], the products of acylation of amines **3a**-**c** with its structural analogs **2b**-**h** contained predominantly (*R*,*S*)-amides **5**-**11**, while the unreacted amines were enriched in (*S*)-enantiomers. Individual (*R*,*S*)-diastereoisomers of amides **5**-**9**, **11** were isolated from the KR products by recrystallization or flash chromatography. The absolute configuration of (*R*,*S*)-amides **5a**,**c**, **7b** was established by X-ray structural analysis, based on the known configuration of the acyl fragment (Figs. 1, 2). Major (*R*,*S*)-diastereoisomers of amides **10b**,**c** could not be isolated as individual compounds from the KR products. In the case of amides **5a**,**c**, **6a**, **7b**,**c**, **11a**, chromatographic separation also provided minor (*S*,*S*)-diastereoisomers. In order to unambiguously assign the HPLC peaks and NMR signals, (*S*,*S*)-amides **5b**, **9a**,**c**, **10b**,**c** were synthesized starting from enantiomerically pure amines (*S*)-**1a-c**.

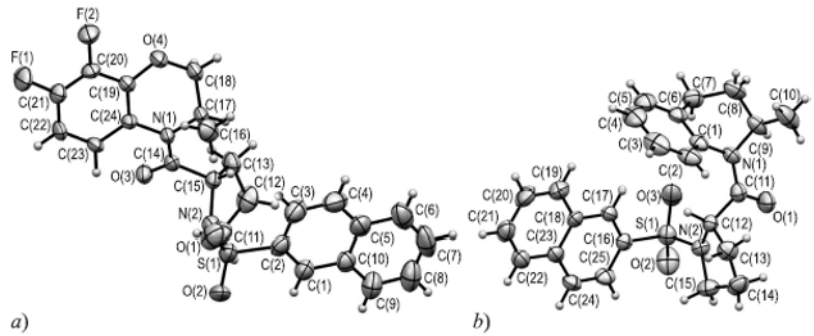


Fig. 1. The structures of (*R*,*S*)-amides **5a** (*a*) and **5c** (*b*) with atoms represented by thermal vibration ellipsoids of 50% probability.

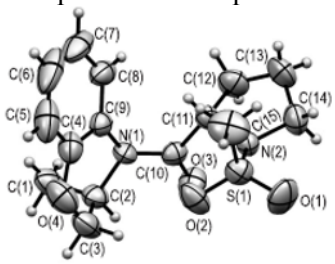


Fig. 2. The structure of amide (*R*,*S*)-**7b** with atoms represented by thermal vibration ellipsoids of 50% probability.

The KR of amines **3a**-**c** with *N*-arylsulfonyl-(*S*)-prolyl chlorides **2a**-**c** demonstrated that increased volume of aromatic substituent in the protecting group of resolving agent did not improve the stereoselectivity. Thus, the stereoselectivity of acylation with naphthylsulfonyl-(*S*)-prolyl chlorides **2b**,**c** in all cases was lower than in the case of acylation with the tosyl derivative **2a**. Acylation of 2-methyl-1,2,3,4-tetrahydroquinoline (**3c**) with acyl chlorides **2b**,**c** occurred with lower stereoselectivity than acylation of 2,3-dihydrobenzoxazine derivatives **3a**,**b**. At the same time, the KR of racemic amine **3b** with acyl chloride **2b** occurred with higher efficiency than the KR with isomeric acyl chloride **2c** (in toluene at 20°C, selectivity factor *s* was 22 and 12, respectively).

The KR of racemic amines **3a**-**c** with *N*-mesyl-(*S*)-prolyl chloride (**2d**), which did not contain aromatic groups in its structure, occurred less selectively compared to the KR with acyl chlorides **2a**-**c**. Thus, the KR of racemate **3a** in dichloromethane at 20°C led to amide (*R*,*S*)-**7a** with *de* 70% (*s* 9.7); while in the case of amines **3b**,**c** in toluene the selectivity factor *s* was 5.2 and 2.0, respectively.

By the example of KR of racemic dihydrobenzoxazines **3a**,**b** with acyl chlorides **2d**,**e**, it was shown that an increased volume of alkyl substituent in the protecting group of resolving agent led to a substantial increase of acylation stereoselectivity, accompanied by decreased conversion of racemate. Nevertheless, the selectivity factor *s* did not exceed 14 in the case of acylation with the acyl chloride **2e** and was lower than in the case of using arylsulfonyl-(*S*)-prolyl chlorides.

Acylation of amine **3a** with (*S*)-tetrahydrofuran-2-ylcarbonyl chloride (**2h**) was significantly less selective than acylation with *N*-sulfonylprolyl chlorides: the amide (*R*,*S*)-**11a** was isolated with *de* 21% (*s* 1.8).

The presence of an annelated aromatic fragment in the structure of *N*-tosyl-(*S*)-indoline-2-ylcarbonyl chloride (**2f**) did not result in improved acylation stereoselectivity of amines **3a**-**c**. For example, the KR with acyl chlorides **2a**,**f** occurred with a similar selectivity (Table 1).

The KR of racemic amines **3a**-**c** *via* acylation with acyl chloride **2g** having an acyclic structure occurred much less selectively than the KR using reagents **2a**,**f**. However, the diastereoselectivity of acylation of racemic 7,8-difluoro-3-methylbenzoxazine **3a** with acyl chloride **2g** in toluene was higher than that in dichloromethane (*s* 9.0 and 3.1, respectively). It may be explained by the peculiarities of solvation of the reagents. Stereoselectivity of acylation of heterocyclic amines with *N*-sulfonyl-(*S*)-prolyl chlorides is likely due to the presence of a rigid five-membered ring in the resolving agent molecule, which determines the arrangement of chlorocarbonyl and sulfamide groups during the interaction with the chiral amine molecule.

The higher efficiency of the KR of heterocyclic amines with acyl chlorides **2a**-**c**,**f** having aromatic substituents at the sulfonyl group, compared to alkylsulfonylprolyl chlorides **2d**,**e**, provides an evidence for the significant role of aromatic interactions in the process of stereodiscrimination [16, 17].

The differences in the stereoselectivity of acylation of non-fluorinated amines **3b**,**c** with *N*-tosyl- (**2a**) and *N*-naphthylsulfonyl-(*S*)-prolyl chlorides **2b**,**c** was in agreement with our previously proposed model [26], according to which the relative orientation of the reagent molecules is dictated by π-stacking between the aromatic rings of amine (δ^-) and the arylsulfonyl group of the resolving agent (δ^+). Due to the higher electron density in naphthyl system (reagents **2b**,**c**) compared to phenyl ring (reagent **2a**) the parallel arrangement with the electron-rich aromatic ring of the amine in the transition state produced energetically less favored π-stacking interactions.

Apparently, the aromatic interactions between the amine molecule and the indoline ring of reagent **2f** are also less favored than the stacking interaction with the electron-deficient phenyl fragment of tosyl group.

The significant stereoselectivity of acylation of benzoxazine derivatives **3a**,**b** with acyl chloride **2e** containing a *tert*-butyl group could likely be explained by the steric hindrances created by the *N*-protecting group (Fig. 3*a*,*b*). Besides that, the reaction of acyl chloride **2e** with (*R*)-amines may be facilitated by the nonpolar CH–π interactions between the amine molecule and the pyrrolidine fragment of acylating agent (Fig. 3*c*). The methyl group of *N*-mesyl-(*S*)-prolyl chloride (**2d**) probably causes no significant steric hindrances, resulting in low stereoselectivity.

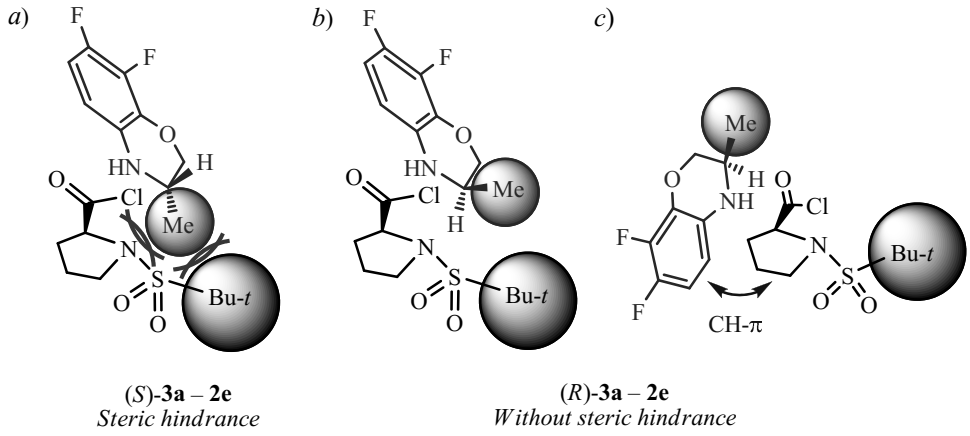


Fig. 3. The proposed stereodifferentiation mechanism during the acylation of amine **1a** with acyl chloride **2e**.

Thus, we have studied the diastereoselective acylation of racemic heterocyclic amines (2,3-dihydro-4*H*-1,4-benzoxazine and 1,2,3,4-tetrahydroquinoline derivatives) with *N*-tosyl-(*S*)-prolyl chloride and its structural analogs and demonstrated that the reaction proceeds highly stereoselectively in the cases of acylating agents containing a conformationally rigid pyrrolidine fragment and aromatic substituents in the *N*-sulfonyl group.

EXPERIMENTAL

The ^{1}H NMR spectra of compounds **1d**, **2h** and amides **5-11** were recorded on a Bruker Avance 500 instrument (500 MHz), those of the other compounds were recorded on a Bruker DRX-400 instrument (400 MHz) in DMSO-d_6 (amides **5-11**) or $CDCl_3$ (the rest of compounds). ^{19}F NMR spectra were recorded on a Bruker Avance 500 instrument (470 MHz) in DMSO-d_6. The internal references were TMS (for ^{1}H nuclei) and hexafluorobenzene (for ^{19}F nuclei). The NMR spectra of amides **5-11** were recorded at 100°C, the spectra of the rest of compounds – at room temperature. High-resolution mass spectra were obtained on an 1200 Infinity instrument (Agilent Technologies) with a 6540 Accurate-Mass Q-TOF (Agilent Technologies) detector, using electrospray ionization in positive ion mode; drying with N_2 (350°C, 10 l/min, 2.7 atm); capillary voltage 3.5 kV. Elemental analysis was performed on a Perkin Elmer 2400 II analyzer. Melting points were determined on SMP3 apparatus (Barloworld Scientific). Specific rotation was determined on a Perkin Elmer 341 polarimeter. HPLC analysis was performed on a Knauer Smartline-1100 chromatograph using a ReproSil 100 Si column (250 × 4.6 mm, 5 μm, for amides **5-11**), a Chiralcel OD-H column (Daicel Corp., Japan, 250 × 4.6 mm, for amines **3a-c**); with detection at 220 nm, eluent flow rate 1 ml/min. Flash chromatography was performed on 230-400 mesh silica gel from Alfa Aesar, UK. TLC analysis was performed on Sorbfil plates (Imid, Russia).

(*S*)-Proline methyl ester hydrochloride [30], *N*-tosyl-(*S*)-prolyl chloride (**2a**) [26], *N*-methyl-*N*-tosyl-(*S*)-phenylalanyl chloride (**2g**) [31], (*RS*)-7,8-difluoro-3-methyl-2,3-dihydro-4*H*-1,4-benzoxazine (**3a**) [32], (*S*)-7,8-difluoro-3-methyl-2,3-dihydro-4*H*-1,4-benzoxazine ((*S*)-**3a**) [21], (*RS*)-3-methyl-2,3-dihydro-4*H*-1,4-benzoxazine (**3b**) [32], (*S*)-3-methyl-2,3-dihydro-4*H*-1,4-benzoxazine ((*S*)-**3b**) [19], (*RS*)-2-methyl-1,2,3,4-tetrahydroquinoline (**3c**) [33], and (*S*)-2-methyl-1,2,3,4-tetrahydroquinoline ((*S*)-**3c**) [19] were obtained according to published methods. The other reagents were commercially available. Amides **4a-c** were described previously [25, 26].

***N*-Naphthylsulfonyl-(*S*)-prolines 1b,c (General Method)**. A solution of (*S*)-proline (0.58 g, 5.00 mmol) in 0.5 N NaOH solution (10 ml) at 0°C was stirred and treated with Et_3N (0.77 ml, 5.50 mmol) and then with the corresponding naphthylsulfonyl chloride (1.19 g, 5.25 mmol) in acetone (5 ml). The reaction mixture was stirred for 12 h at room temperature, then acidified with 1 N HCl to pH 1-2 and left for 24 h at 10°C. The precipitate was filtered off and recrystallized from EtOH–H_2O mixture (compound **1b**) or hexane–$CHCl_3$ (compound **1c**).

***N*-(2-Naphthylsulfonyl)-(*S*)-proline (1b)**. Yield 1.37 g (90%). White powder. Mp 136-137°C (mp 133-135°C [34], mp 138°C [35]). $[\alpha]_D^{20}$ -88.3° (*c* 1.0, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.72-1.81 (1H, m, 4-CH_B); 1.91-2.02 (2H, m, 3-CH_B, 4-CH_A); 2.10-2.18 (1H, m, 3-CH_A); 3.35 (1H, dt, *J* = 9.7, *J* = 7.4) and 3.58 (1H, ddd, *J* = 9.9, *J* = 6.5, *J* = 3.7, 5-CH_2); 4.38 (1H, dd, *J* = 8.2, *J* = 3.5, 2-CH); 4.50-6.00 (1H, br. s, COOH); 7.62-7.69 (2H, m, H-6,7 naphthyl); 7.87 (1H, dd, *J* = 8.7, *J* = 1.6, H-5 naphthyl); 7.92-7.95 (1H, m, H-8 naphthyl); 7.99-8.01 (2H, m, H-3,4 naphthyl); 8.46 (1H, d, *J* = 1.6, H-1 naphthyl). Found, %: C 58.71; H 4.87; N 4.46; S 10.62. $C_{15}H_{15}NO_4S$. Calculated, %: C 59.00; H 4.95; N 4.59; S 10.50.

***N*-(1-Naphthylsulfonyl)-(*S*)-proline (1c)**. Yield 1.36 g (89%). White powder. Mp 125-126°C (mp 126°C [36], mp 80°C [37]). $[\alpha]_D^{20}$ -51.7° (*c* 1.1, MeOH) ($[\alpha]_D^{20}$ -53.2° (*c* 1.0, MeOH) [36]). ^{1}H NMR spectrum was identical to that described previously [37]. Found, %: C 58.83; H 4.79; N 4.58; S 10.19. $C_{15}H_{15}NO_4S$. Calculated, %: C 59.00; H 4.95; N 4.59; S 10.50.

***N*-Methylsulfonyl-(*S*)-proline (1d)**. A solution of (*S*)-proline methyl ester hydrochloride (16.56 g, 0.1 mol) and Et_3N (56 ml, 0.4 mol) in CH_2Cl_2 (100 ml) was cooled to 0°C, and mesyl chloride (7.74 ml,

0.1 mol) was added dropwise. The reaction mixture was stirred for 30 min at 0°C and for 24 h at room temperature, then washed with 1 N HCl (2×15 ml), saturated NaCl solution (4×20 ml), 5% $NaHCO_3$ solution (2×20 ml), and H_2O (2×20 ml). The organic layer was dried over $MgSO_4$, evaporated under vacuum, the residue was recrystallized from hexane–EtOAc mixture, and ***N*-methylsulfonyl-(*S*)-proline methyl ester** was obtained. Yield 9.12 g (44%). Colorless powder. Mp 60-63°C. $[\alpha]_D^{20}$ -83.6° (*c* 1.1, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.96-2.11 (3H, m, 3-CH_B, 4-CH_2); 2.29 (1H, dtd, *J* = 12.4, *J* = 8.6, *J* = 7.3, 3-CH_A); 3.02 (3H, s, C$\underline{H}_3SO_2$); 3.45 (1H, ddd, *J* = 9.1, *J* = 6.8, *J* = 5.6) and 3.56 (1H, dt, *J* = 9.1, *J* = 7.2, 5-CH_2); 3.76 (3H, s, COOC$\underline{H}_3$); 4.51 (1H, dd, *J* = 8.6, *J* = 3.7, 2-CH). Found, %: C 40.81; H 6.59; N 6.87; S 15.70. $C_7H_{13}NO_4S$. Calculated, %: C 40.57; H 6.32; N 6.76; S 15.47.

A solution of *N*-methylsulfonyl-(*S*)-proline methyl ester (2.07 g, 10 mmol) in acetone (100 ml) was treated at -5°C with 2 N NaOH (12 ml, 24 mmol). The reaction mixture was stirred for 2 h at -5°C and for 24 h at room temperature, then acidified with 1 N HCl to pH 4-5 and evaporated under vacuum. The residue was treated with CH_2Cl_2 (20 ml) and H_2O (20 ml), stirred, the organic layer was separated, washed with H_2O (4×20 ml), and dried over $MgSO_4$. The solution was evaporated, the residue was recrystallized from hexane–EtOAc mixture. Yield 1.04 g (54%). Colorless powder. Mp 76-78°C. $[\alpha]_D^{20}$ -73.3° (*c* 1.0, MeOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.01-2.08 (2H, m, 4-CH_2); 2.20 (1H, dtd, *J* = 12.8, *J* = 5.8, *J* = 3.9) and 2.33 (1H, dq, *J* = 12.8, *J* = 8.6, 3-CH_2); 3.01 (3H, s, CH_3); 3.47 (1H, dt, *J* = 9.2, *J* = 6.2) and 3.54 (1H, dt, *J* = 9.2, *J* = 7.4, 5-CH_2); 4.53 (1H, dd, *J* = 8.7, *J* = 3.9, 2-CH); 5.0-7.0 (1H, br. s, COOH). Found, %: C 37.54; H 6.00; N 7.28; S 16.82. $C_6H_{11}NO_4S$. Calculated, %: C 37.30; H 5.74; N 7.25; S 16.59.

***N*-(*tert*-Butylsulfonyl)-(*S*)-proline (1e)**. A. A solution of (*S*)-proline methyl ester hydrochloride (3.15 g, 19 mmol) in CH_2Cl_2 (200 ml) was treated with Et_3N (26.5 ml, 190 mmol) at 0°C, followed by dropwise addition of *tert*-butylsulfinyl chloride (5.34 g, 38 mmol) solution in CH_2Cl_2 (70 ml). The reaction mixture was stirred for 2 h at 0°C, washed with 1 N HCl (2×100 ml), saturated NaCl solution (2×100 ml), and 5% $NaHCO_3$ solution (2×100 ml). The organic layer was dried over $MgSO_4$, evaporated, the residue was purified by flash chromatography (eluent benzene–EtOAc), giving *N*-*tert*-butylsulfinyl-(*S*)-proline methyl ester as a mixture of diastereomers. Yield 3.28 g (74%), colorless oil.

B. A solution of *N*-*tert*-butylsulfinyl-(*S*)-proline methyl ester (3.27 g, 14 mmol) in CH_2Cl_2 (500 ml) was cooled to 0°C, and MCPBA (4.83 g, 28 mmol) was added. The reaction mixture was stirred for 2 h at 0°C and for 1 h at room temperature, then washed with 5% $NaHCO_3$ solution (2×100 ml) and with saturated Na_2SO_3 solution (2×100 ml). The organic layer was dried over $MgSO_4$ and evaporated. The obtained oil (2.96 g) was dissolved in acetone (125 ml), the solution was cooled to -5°C and treated with 1 N NaOH (30 ml). The reaction mixture was stirred for 2 h and left overnight at 5°C, then washed with Et_2O (2×50 ml), acidified with 1 N HCl to pH 1, and extracted with CH_2Cl_2 (3×50 ml). The organic layer was dried over $MgSO_4$ and evaporated, hexane (40 ml) was added to the residue, the precipitate was filtered off. Yield 2.01 g (45%, calculated from (*S*)-proline methyl ester). White powder. Mp 133-135°C (hexane). $[\alpha]_D^{20}$ -66.6° (*c* 1.0, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.41 (9H, s, $C(CH_3)_3$); 1.92-2.16 (3H, m, 3-CH_B, 4-CH_2); 2.28 (1H, dq, *J* = 12.5, *J* = 8.3, 3-CH_A); 3.43-3.55 (1H, m) and 3.73 (1H, dt, *J* = 9.5, 7.0, 5-CH_2); 4.53 (1H, dd, *J* = 8.4, *J* = 3.8, 2-CH); 5.0-8.0 (1H, br. s, COOH). Found, %: C 46.02; H 7.25; N 5.78; S 13.61. $C_9H_{17}NO_4S$. Calculated, %: C 45.94; H 7.28; N 5.95; S 13.63.

***N*-Tosyl-(*S*)-indoline-2-carboxylic acid (1f)**. A solution of (*S*)-indoline-2-carboxylic acid (0.49 g, 3.0 mmol) in pyridine (12 ml) was cooled to 0°C, TsCl (0.69 g, 3.6 mmol) was added. The reaction mixture was stirred for 1 h at room temperature. The obtained solution was poured into H_2O (120 ml), washed with $CHCl_3$ (2×20 ml), then acidified with 4 N HCl to pH 2-3, and extracted with EtOAc (3×40 ml). The organic layer was washed with saturated aqueous NaCl solution (3×40 ml), dried over $MgSO_4$, treated with activated carbon, and evaporated. The precipitate was recrystallized from H_2O–MeOH mixture (7.0 : 5.5 ml). Yield 0.68 g (71%). Colorless powder. Mp 159-162°C (H_2O–MeOH). $[\alpha]_D^{20}$ +120° (*c* 1.0, MeOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.38 (3H, s, CH_3); 3.11 (1H, dd, *J* = 16.5, *J* = 10.7) and 3.24 (1H, dd, *J* = 16.5, *J* = 4.2, 3-CH_2); 4.77 (1H, dd, *J* = 10.7, *J* = 4.2, 2-CH); 7.03-7.08 (2H, m, H indoline); 7.22-7.26 (3H, m, H indoline, H Ts); 7.62-7.64 (3H,

m, H indoline, H Ts); 3.0-9.0 (1H, br. s, COOH). Found, %: C 60.57; H 4.89; N 4.72; S 10.03. $C_{16}H_{15}NO_4S$. Calculated, %: C 60.55; H 4.76; N 4.41; S 10.10.

Acyl chlorides 2b-f (General Method). A suspension of *N*-sulfonylproline **1b-e** (5.0 mmol) or the acid **1f** in benzene (20 ml) was treated with oxalyl chloride (0.92 ml, 10.5 mmol) and DMF (5 μl). The reaction mixture was stirred at room temperature for 6 h and evaporated. Hexane (20 ml) was added to the residue, and the mixture was left overnight at low temperature. The precipitate was filtered off and dried under vacuum over P_2O_5.

***N*-(2-Naphthylsulfonyl)-(*S*)-prolyl Chloride (2b)**. Yield 1.55 g (96%). Colorless powder. Mp 109-110°C (mp 107-109°C [34]). $[\alpha]_D^{20}$ -80.4° (*c* 1.0, $CHCl_3$) ($[\alpha]_D^{20}$ -81.6° (*c* 1.0, $CHCl_3$) [34]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.79-1.88 (1H, m) and 1.93-2.04 (1H, m, 4-CH_2); 2.17-2.26 (2H, m, 3-CH_2); 3.43 (1H, dt, *J* = 9.6, *J* = 7.4) and 3.55 (1H, ddd, *J* = 9.6, *J* = 7.4, *J* = 4.8, 5-CH_2); 4.72 (1H, dd, *J* = 7.6, *J* = 5.3, 2-CH); 7.62-7.70 (2H, m, H-6,7 naphthyl); 7.85 (1H, dd, *J* = 8.7, *J* = 1.8, H-8 naphthyl); 7.92-7.94 (1H, m, H-5 naphthyl); 7.99-8.01 (2H, m, H-3,4 naphthyl); 8.45 (1H, d, *J* = 1.8, H-1 naphthyl). Found, %: C 55.24; H 4.26; N 4.46. $C_{15}H_{14}ClNO_3S$. Calculated, %: C 55.64; H 4.36; N 4.33.

***N*-(1-Naphthylsulfonyl)-(*S*)-prolyl Chloride (2c)**. Yield 1.42 g (88%). Colorless powder. Mp 59-62°C (hexane–CH_2Cl_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.87-2.05 (2H, m, 4-CH_2); 2.20-2.33 (2H, m, 3-CH_2); 3.48-3.54 (2H, m, 5-CH_2); 4.84 (1H, dd, *J* = 8.5, *J* = 4.2, 2-CH); 7.54-7.71 (3H, m, H-3,6,7 naphthyl); 7.94 (1H, d, *J* = 8.2, H-4 naphthyl); 8.10 (1H, d, *J* = 8.2, H-2 naphthyl); 8.27 (1H, dd, *J* = 7.3, *J* = 1.0, H-5 naphthyl); 8.79 (1H, d, *J* = 8.7, H-8 naphthyl). Found, %: C 55.94; H 4.24; N 4.37; S 10.04. $C_{15}H_{14}ClNO_3S$. Calculated, %: C 55.64; H 4.36; N 4.33; S 9.90.

***N*-Methylsulfonyl-(*S*)-prolyl Chloride (2d)**. Yield 0.97 g (92%). Colorless powder. Mp 59-62°C (hexane–CH_2Cl_2). $[\alpha]_D^{20}$ -67.4° (*c* 1.0, benzene). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.00-2.12 (2H, m, 4-CH_2); 2.27-2.34 (1H, m) and 2.44 (1H, dtd, *J* = 13.3, *J* = 9.1, *J* = 7.2, 3-CH_2); 3.02 (3H, s, CH_3); 3.48 (1H, ddd, *J* = 9.3, *J* = 7.4, *J* = 5.1) and 3.61 (1H, dt, *J* = 9.3, *J* = 7.4, 5-CH_2); 4.83 (1H, dd, *J* = 9.0, *J* = 4.0, 2-CH). Found, %: C 34.20; H 4.79; N 6.68. $C_6H_{10}ClNO_3S$. Calculated, %: C 34.05; H 4.76; N 6.62.

***N-tert*-Butylsulfonyl-(*S*)-prolyl Chloride (2e)**. Yield 1.21 g (95%). Colorless amorphous powder. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.41 (9H, s, $C(CH_3)_3$); 1.97-2.07 (2H, m, 4-CH_2); 2.23 (1H, ddt, *J* = 13.2, *J* = 6.4, *J* = 3.8) and 2.39 (1H, dq, *J* = 13.2, *J* = 8.4, 3-CH_2); 3.44-3.49 (1H, m) and 3.79 (1H, dt, *J* = 9.7, *J* = 7.0, 5-CH_2); 4.98 (1H, dd, *J* = 8.4, *J* = 3.8, 2-CH).

***N*-Tosyl-(*S*)-indoline-2-carbonyl Chloride (2f)**. Yield 1.61 g (96%). Colorless powder. Mp 123-125°C. $[\alpha]_D^{20}$ +71.1° (*c* 0.94, benzene). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.39 (3H, s, CH_3); 3.24 (1H, dd, *J* = 16.7, *J* = 4.9) and 3.34 (1H, dd, *J* = 16.7, *J* = 10.8, 3-CH_2); 5.05 (1H, dd, *J* = 10.8, *J* = 4.9, 2-CH); 7.02-7.11 (2H, m, H indoline); 7.23-7.26 (3H, m, H indoline, H Ts); 7.57-7.59 (1H, m, H indoline); 7.69 (2H, d, *J* = 8.2, H Ts). Found, %: C 57.15; H 4.37; N 4.48. $C_{16}H_{14}ClNO_3S$. Calculated: C 57.23; H 4.20; N 4.17.

(*S*)-Tetrahydrofuran-2-carbonyl Chloride (2h). A solution of (*S*)-tetrahydrofuran-2-carboxylic acid (**1h**) (0.20 g, 1.72 mmol) in oxalyl chloride (1.5 ml, 17.20 mmol) was stirred for 20 h under argon atmosphere, evaporated, dried under vacuum. Yield 0.16 g (70%). Colorless oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.94-2.03 (2H, m, 4-CH_2); 2.24 (1H, dddd, *J* = 13.1, *J* = 7.5, *J* = 6.7, *J* = 5.1) and 2.39 (1H, dtd, *J* = 13.1, *J* = 8.6, *J* = 7.0, 3-CH_2); 4.00-4.07 (2H, m, 5-CH_2); 4.73 (1H, dd, *J* = 8.6, *J* = 5.1, 2-CH).

KR of Racemic Amines 3a-c. **Preparation of Amides 5-11 (General Method)**. A solution of amine **3a** (1.0 mmol) in a chosen solvent (5 ml) (CH_2Cl_2 in the case of amides **5-9a**, **11a**, toluene in the case of the amide **10a**), or amine **3b**,**c** in toluene (5 mL) at 20°C was treated with a solution of acyl chloride **2a-h** (0.5 mmol) in the same solvent (5 ml). (The study of KR was performed with 0.3 mmol of amine **3a-c** in 1.5 ml of solvent and 0.15 mmol of the acyl chloride **2a-h** in 1.5 ml of the same solvent). The reaction mixture was stirred for 6 h at 20°C, washed with HCl (4 N in the case of amine **3a**, 1 N in the case of amines **3b**,**c**; 2×4 ml), thus separating unreacted amines enriched in the (*S*)-isomers. The organic layer containing amides **5-11** was washed with saturated NaCl solution (4×5 ml), 5% $NaHCO_3$ solution (2×5 ml), H_2O (2×5 ml), dried over $MgSO_4$, and

evaporated. The amide diastereomers were separated by recrystallization or flash chromatography (eluent benzene–EtOAc).

The acidic aqueous solutions of unreacted amines **3a-c** were neutralized with Na_2CO_3 and extracted with $CHCl_3$ (2×5 ml). The organic layer was washed with H_2O (2×5 ml), dried over $MgSO_4$, and evaporated.

(3*R*,2'*S*)-7,8-Difluoro-3-methyl-*N*-[*N*'-(2-naphthylsulfonyl)prolyl]-2,3-dihydro-4*H*-1,4-benzoxazine ((*R*,*S*)-5a). Yield 116 mg (49%) after flash chromatography (slow-eluting diastereomer). Colorless powder. Mp 203-204°C. $[\alpha]_D^{20}$ -242° (*c* 1.0, $CHCl_3$). HPLC (hexane–2-PrOH, 10:1): *de* > 99%, τ_R 9.9 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.18 (3H, d, *J* = 6.9, CH_3); 1.64-1.73 (1H, m, 4-CH_B proline); 1.98-2.05 (2H, m, 3-CH_B proline, 4-CH_A proline); 2.11-2.20 (1H, m, 3-CH_A proline); 3.42-3.55 (2H, m, 5-CH_2 proline); 4.25 (1H, dd, *J* = 10.8, *J* = 2.9) and 4.36 (1H, dd, *J* = 10.8, *J* = 1.4, 2-CH_2); 4.68 (1H, dd, *J* = 8.3, *J* = 4.0, 2-CH proline); 4.80-4.87 (1H, m, 3-CH); 6.79 (1H, td, *J* = 9.7, *J* = 8.2, H-6); 7.15-7.22 (1H, m, H-5); 7.59-7.71 (3H, m, H naphthyl); 7.96-8.04 (3H, m, H naphthyl); 8.15 (1H, s, H-1 naphthyl). ^{19}F NMR spectrum, δ, ppm: 2.5-2.6 (1F, m, F-8); 21.3-21.8 (1F, m, F-7). Found, *m*/*z*: 473.1348 $[M+H]^+$. $C_{24}H_{23}F_2N_2O_4S$. Calculated, *m*/*z*: 473.1341.

(3*S*,2'*S*)-7,8-Difluoro-3-methyl-*N*-[*N*'-(2-naphthylsulfonyl)prolyl]-2,3-dihydro-4*H*-1,4-benzoxazine ((*S*,*S*)-5a). Yield 12 mg (5%) after flash chromatography (fast-eluting diastereomer). Colorless powder. Mp 161-162°C. $[\alpha]_D^{20}$ +90.0° (*c* 0.6, $CHCl_3$). HPLC (hexane–2-PrOH, 10:1): *de* 98.6%, τ_R 5.7 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.17 (3H, d, *J* = 6.9, CH_3); 1.64-1.73 (1H, m) and 1.79-1.86 (1H, m, 4-CH_2 proline); 1.93-2.04 (2H, m, 3-CH_2 proline); 3.42 (1H, ddd, *J* = 13.1, *J* = 9.7, *J* = 6.2) and 3.44 (1H, ddd, *J* = 13.1, *J* = 9.8, *J* = 6.5, 5-CH_2 proline); 4.18 (1H, dd, *J* = 11.0, *J* = 2.9) and 4.41 (1H, dd, *J* = 11.0, *J* = 1.5, 2-CH_2); 4.89 (1H, qdd, *J* = 6.9, *J* = 3.0, *J* = 1.6, 3-CH); 5.07 (1H, dd, *J* = 8.1, *J* = 4.3, 2-CH proline); 6.93 (1H, td, *J* = 9.8, *J* = 8.2, H-6); 7.56 (1H, ddd, *J* = 9.5, *J* = 5.3, *J* = 2.5, H-5); 7.63-7.71 (2H, m, H-6,7 naphthyl); 7.85 (1H, dd, *J* = 8.7, *J* = 1.8, H-3 naphthyl); 8.01 (1H, d, *J* = 8.1, H naphthyl); 8.09 (1H, d, *J* = 8.7, H-4 naphthyl); 8.12 (1H, d, *J* = 8.0, H naphthyl); 8.45 (1H, d, *J* = 1.8, H-1 naphthyl). ^{19}F NMR spectrum, δ, ppm: 2.3-2.4 (1F, m, F-8); 21.1-21.3 (1F, m, F-7). Found, %: C 60.85; H 4.40; F 7.80; N 5.96; S 7.01. $C_{24}H_{22}F_2N_2O_4S$. Calculated, %: C 61.01; H 4.69; F 8.04; N 5.93; S 6.79.

(3*R*,2'*S*)-3-Methyl-*N*-[*N*'-(2-naphthylsulfonyl)prolyl]-2,3-dihydro-4*H*-1,4-benzoxazine ((*R*,*S*)-5b). Yield 70 mg (32%) after recrystallization from a mixture of hexane–EtOAc. Colorless powder. Mp 178-179°C. $[\alpha]_D^{20}$ -324° (*c* 1.1, $CHCl_3$). HPLC (hexane–2-PrOH, 20:1): *de* > 99%, τ_R 11.1 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.15 (3H, d, *J* = 6.9, CH_3); 1.59-1.68 (1H, m, 4-CH_B proline); 1.96-2.18 (3H, m, 3-CH_2 and 4-CH_A proline); 3.42 (1H, ddd, *J* = 9.7, *J* = 7.1, *J* = 6.0) and 3.52 (1H, dt, *J* = 9.7, *J* = 6.6, 5-CH_2 proline); 4.19 (1H, dd, *J* = 10.9, *J* = 1.8) and 4.23 (1H, dd, *J* = 10.9, *J* = 2.8, 2-CH_2); 4.71 (1H, dd, *J* = 8.1, *J* = 4.3, 2-CH proline); 4.79-4.87 (1H, m, 3-CH); 6.82 (1H, ddd, *J* = 8.2, *J* = 7.1, *J* = 1.3, H-7); 6.98 (1H, dd, *J* = 8.2, *J* = 1.3, H-8); 7.16 (1H, ddd, *J* = 8.2, *J* = 7.1, *J* = 1.2, H-6); 7.21-7.26 (1H, m, H-5); 7.48-7.53 (1H, m, H naphthyl); 7.61-7.70 (2H, m, H naphthyl); 7.93-8.01 (3H, m, H naphthyl); 8.06 (1H, s, H naphthyl). Found, %: C 66.32; H 5.48; N 6.39; S 7.56. $C_{24}H_{24}N_2O_4S$. Calculated, %: C 66.04; H 5.54; N 6.42; S 7.35.

(2*R*,2'*S*)-2-Methyl-*N*-[*N*'-(2-naphthylsulfonyl)prolyl]-1,2,3,4-tetrahydroquinoline ((*R*,*S*)-5c). Yield 87 mg (40%) after recrystallization from a mixture of hexane–EtOAc. Colorless powder. Mp 215-216°C. $[\alpha]_D^{20}$ -358° (*c* 1.0, $CHCl_3$). HPLC (hexane–2-PrOH, 20:1): *de* > 99%, τ_R 10.1 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.04 (3H, d, *J* = 6.5, CH_3); 1.28-1.35 (1H, m, 3-CH_B); 1.50-1.58 (1H, m, 4-CH_B proline); 1.95-2.08 (3H, m, 4-CH_B, 3-CH_B proline, 4-CH_A proline); 2.38 (1H, ddt, *J* = 13.0, *J* = 7.7, *J* = 5.3, 3-CH_A); 2.66-2.70 (2H, m, 4-CH_A, 3-CH_A proline); 3.33-3.39 (1H, m) and 3.46-3.53 (1H, m, 5-CH_2 proline); 4.38 (1H, dd, *J* = 8.0, *J* = 4.4, 2-CH proline); 4.73 (1H, sextet, *J* = 6.8, 2-CH); 6.98 (1H, d, *J* = 7.8, H-5); 7.17 (1H, td, *J* = 7.7, *J* = 1.6, H-6); 7.28 (1H, td, *J* = 7.5, *J* = 1.2, H-7); 7.32 (1H, dd, *J* = 8.5, *J* = 1.8, H naphthyl); 7.35-7.37 (1H, m, H-8); 7.60-7.68 (2H, m, H naphthyl); 7.87-7.93 (3H, m, H naphthyl); 7.95-7.98 (1H, m, H naphthyl). Found, %: C 69.26; H 6.13; N 6.62; S 7.38. $C_{25}H_{26}N_2O_3S$. Calculated, %: C 69.10; H 6.03; N 6.45; S 7.38.

(2*S*,2'*S*)-2-Methyl-*N*-[*N*'-(2-naphthylsulfonyl)prolyl]-1,2,3,4-tetrahydroquinoline ((*S*,*S*)-5c). Yield 24 mg (11%) after flash chromatography (fast-eluting diastereomer). Colorless powder. Mp 144-146°C. $[\alpha]_D^{20}$ +192° (*c* 0.4, $CHCl_3$). HPLC (hexane–2-PrOH, 10:1): *de* > 99%, τ_R 7.1 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.02 (3H, d, *J* = 6.6, CH_3); 1.23-1.30 (1H, m, 3-CH_B); 1.48-1.57 (3H, m, 3-CH_B proline, 4-CH_2 proline);

1.81-1.90 (1H, m, 3-CH_A proline); 2.31 (1H, ddt, *J* = 13.0, *J* = 7.7, *J* = 5.2, 3-CH_A); 2.42 (1H, ddd, *J* = 15.0, *J* = 10.0, *J* = 5.2) and 2.62 (1H, dt, *J* = 15.0, *J* = 5.2, 4-CH_2); 3.38-3.47 (2H, m, 5-CH_2 proline); 4.64 (1H, sextet, *J* = 6.8, 2-CH); 4.97 (1H, dd, *J* = 7.7, *J* = 4.5, 2-CH proline); 7.18 (1H, td, *J* = 7.5, *J* = 1.0, H-6); 7.23 (1H, d, *J* = 7.7, H-5); 7.33 (1H, t, *J* = 7.5, H-7); 7.52 (1H, d, *J* = 7.8, H-8); 7.64-7.71 (2H, m, H-6,7 naphthyl); 7.82 (1H, dd, *J* = 8.7, *J* = 1.8, H-3 naphthyl); 8.01 (1H, d, *J* = 8.0, H naphthyl); 8.08 (1H, d, *J* = 8.7, H-4 naphthyl); 8.13 (1H, d, *J* = 7.8, H naphthyl); 8.46 (1H, d, *J* = 1.8, H-1 naphthyl). Found, %: C 69.25; H 6.01; N 6.44; S 7.64. $C_{25}H_{26}N_2O_3S$. Calculated, %: C 69.10; H 6.03; N 6.45; S 7.38.

(3*R*,2'*S*)-7,8-Difluoro-3-methyl-*N*-[*N*'-(1-naphthylsulfonyl)prolyl]-2,3-dihydro-4*H*-1,4-benzoxazine ((*R*,*S*)-6a). Yield 102 mg (43%) after flash chromatography (slow-eluting diastereomer). Colorless powder. Mp 146-149°C. $[\alpha]_D^{20}$ -203° (*c* 1.0, $CHCl_3$). HPLC (hexane–2-PrOH, 20:1): *de* > 99%, τ_R 12.8 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.13 (3H, d, *J* = 6.9, CH_3); 1.74-1.84 (1H, m, 4-CH_B proline); 1.99-2.09 (2H, m, 3 CH_B proline, 4-CH_A proline); 2.17-2.25 (1H, m, 3-CH_A proline); 3.48-3.57 (2H, m, 5-CH_2 proline); 4.08 (1H, dd, *J* = 10.9, *J* = 2.8) and 4.36 (1H, dd, *J* = 10.9, *J* = 1.4, 2-CH_2); 4.72-4.77 (1H, m, 3-CH); 4.80 (1H, dd, *J* = 8.4, *J* = 3.5, 2-CH proline); 6.82 (1H, ddd, *J* = 9.8, *J* = 9.6, *J* = 8.2, H-6); 7.05-7.11 (1H, m, H-5); 7.52 (1H, t, *J* = 7.8, H naphthyl); 7.57-7.64 (2H, m, H naphthyl); 7.96 (1H, d, *J* = 7.7, H naphthyl); 8.03-8.05 (1H, m, H naphthyl); 8.18 (1H, dm, *J* = 8.2, H naphthyl); 8.59 (1H, d, *J* = 8.4, H naphthyl). ^{19}F NMR spectrum, δ, ppm: 2.4-2.6 (1F, m, F-8); 21.2-21.5 (1F, m, F-7). Found, %: C 61.09; H 4.79; F 7.74; N 5.81; S 6.95. $C_{24}H_{22}F_2N_2O_4S$. Calculated, %: C 61.01; H 4.69; F 8.04; N 5.93; S 6.79.

(3*S*,2'*S*)-7,8-Difluoro-3-methyl-*N*-[*N*'-(1-naphthylsulfonyl)prolyl]-2,3-dihydro-4*H*-1,4-benzoxazine ((*S*,*S*)-6a). Yield 14 mg (6%) after flash chromatography (fast-eluting diastereomer). Yellowish powder. Mp 66-69°C. $[\alpha]_D^{20}$ +39.1° (*c* 0.6, $CHCl_3$). HPLC (hexane–2-PrOH, 20:1): *de* 98.4%, τ_R 7.4 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.14 (3H, d, *J* = 6.9, CH_3); 1.75-1.83 (1H, m) and 1.84-1.89 (1H, m, 4-CH_2 proline); 1.97-2.04 (1H, m) and 2.07-2.14 (1H, m, 3-CH_2 proline); 3.44-3.49 (2H, m, 5-CH_2 proline); 4.11 (1H, dd, *J* = 11.0, *J* = 2.9) and 4.38 (1H, dd, *J* = 11.0, *J* = 1.5, 2-CH_2); 4.83 (1H, qdd, *J* = 6.9, *J* = 2.9, *J* = 1.5, 3-CH); 5.18 (1H, dd, *J* = 8.3, *J* = 4.0, 2-CH proline); 6.89 (1H, td, *J* = 9.8, *J* = 8.3, H-6); 7.50 (1H, ddd, *J* = 9.5, *J* = 5.4, *J* = 2.4, H-5); 7.61-7.68 (3H, m, H naphthyl); 8.03-8.05 (1H, m, H naphthyl); 8.18-8.21 (2H, m, H naphthyl); 8.71 (1H, dm, *J* = 8.6, H naphthyl). ^{19}F NMR spectrum, δ, ppm: 2.36-2.48 (1F, m, F-8); 21.15-21.25 (1F, m, F-7). Found,%: C 60.82; H 4.95; N 5.59. $C_{24}H_{22}F_2N_2O_4S$. Calculated, %: C 61.01; H 4.69; N 5.93.

(3*R*,2'*S*)-3-Methyl-*N*-[*N*'-(1-naphthylsulfonyl)prolyl]-2,3-dihydro-4*H*-1,4-benzoxazine ((*R*,*S*)-6b). Yield 68 mg (31%) after flash chromatography (slow-eluting diastereomer). Colorless powder. Mp 114-117°C. $[\alpha]_D^{20}$ -278° (*c* 1.0, $CHCl_3$). HPLC (hexane–2-PrOH, 20:1): *de* 99%, τ_R 7.7 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.10 (3H, d, *J* = 6.9, CH_3); 1.70-1.79 (1H, m, 4-CH_B proline); 2.01-2.12 (2H, m, 3-CH_B proline, 4-CH_A proline); 2.15-2.22 (1H, m, 3-CH_A proline); 3.44-3.58 (2H, m, 5-CH_2 proline); 4.07 (1H, dd, *J* = 10.9, *J* = 2.8) and 4.15 (1H, dd, *J* = 10.9, *J* = 1.5, 2-CH_2); 4.71-4.78 (1H, m, 3-CH); 4.83 (1H, dd, *J* = 8.3, *J* = 3.6, 2-CH proline); 6.83 (1H, ddd, *J* = 8.0, *J* = 7.4, *J* = 1.4, H-6); 6.92 (1H, dd, *J* = 8.2, *J* = 1.4, H-8); 7.11 (1H, ddd, *J* = 8.2, *J* = 7.4, *J* = 1.4, H-7); 7.14-7.18 (1H, m, H-5); 7.47 (1H, t, *J* = 7.8, H naphthyl); 7.53-7.62 (2H, m, H naphthyl); 7.86-7.88 (1H, m, H naphthyl); 8.00-8.03 (1H, m, H naphthyl); 8.15 (1H, dm, *J* = 8.2, H naphthyl); 8.57 (1H, dm, *J* = 8.5, H naphthyl). Found, %: C 66.36; H 5.54; N 6.18; S 7.55. $C_{24}H_{24}N_2O_4S$. Calculated, %: C 66.04; H 5.54; N 6.42; S 7.35.

3-Methyl-*N*-[*N*'-(1-naphthylsulfonyl)prolyl]-2,3-dihydro-4*H*-1,4-benzoxazine (6b) (mixture of diastereoisomers). Yield 70 mg (32%) after flash chromatography. Colorless amorphous powder. HPLC (hexane–2-PrOH, 20:1): (*R*,*S*)/(*S*,*S*) = 64:36; τ_R (*S*,*S*)-**6b** 5.7 min, τ_R (*R*,*S*)-**6b** 7.7 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.10 (1.92H, d, *J* = 6.9, CH_3 (*R*,*S*)); 1.11 (1.08H, d, *J* = 6.9, CH_3 (*S*,*S*)); 1.70-1.85 (1.36H, m, 4-CH_B proline (*R*,*S*), 4-CH_2 proline (*S*,*S*)); 1.96-2.12 (2H, m, 3-CH_B proline (*R*,*S*), 3-CH_2 proline (*S*,*S*), 4-CH_A proline (*R*,*S*)); 2.15-2.22 (0.64H, m, 3-CH_A proline (*R*,*S*)); 3.45-3.58 (2H, m, 5-CH_2 proline); 4.03-4.08 (1H, m, 2-CH_B); 4.15 (0.64H, dd, *J* = 10.9, *J* = 1.5, 2-CH_A (*R*,*S*)); 4.19 (0.36H, dd, *J* = 11.0, *J* = 1.5, 2-CH_A (*S*,*S*)); 4.71-4.80 (1H, m, 3-CH); 4.83 (0.64H, dd, *J* = 8.4, *J* = 3.5, 2-CH proline (*R*,*S*)); 5.23 (0.36H, dd, *J* = 7.8, *J* = 4.0, 2-CH proline (*S*,*S*)); 6.83 (0.64H, ddd, *J* = 8.0, *J* = 7.5, *J* = 1.4, H-6 (*R*,*S*)); 6.85-6.94 (1.36H, m, H-6

(*S*,*S*), H-8 (*S*,*S*), H-8 (*R*,*S*)); 7.04-7.18 (1.64H, m, H-5 (*R*,*S*), H-7 (*R*,*S*), H-7 (*S*,*S*)); 7.45-7.69 (3.36H, m, H-5 (*S*,*S*), H naphthyl); 7.87 (0.64H, d, *J* = 7.5, H naphthyl (*R*,*S*)); 8.00-8.06 (1H, m, H naphthyl); 8.14-8.23 (1.36H, m, H naphthyl); 8.57 (0.64H, d, *J* = 8.4, H naphthyl (*R*,*S*)); 8.73 (0.36H, d, *J* = 8.5, H naphthyl (*S*,*S*)). Found, %: C 68.32; H 5.54; N 5.77. $C_{24}H_{24}N_2O_4S \cdot 0.5C_6H_6$. Calculated, %: C 68.19; H 5.72; N 5.89.

(2*R*,2'*S*)-2-Methyl-*N*-[*N*'-(1-naphthylsulfonyl)prolyl]-1,2,3,4-tetrahydroquinoline ((*R*,*S*)-6c). Yield 80 mg (37%) after flash chromatography (slow-eluting diastereomer). Colorless powder. Mp 146-150°C. $[\alpha]_D^{20}$ -271° (*c* 0.6, $CHCl_3$). HPLC (hexane–2-PrOH, 20:1): *de* 98.2%, τ_R 7.7 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.02 (3H, d, *J* = 6.5, CH_3); 1.25-1.32 (1H, m, 3-CH_B); 1.58-1.65 (1H, m, 4-CH_B proline); 2.00-2.11 (3H, m, 3-CH_2 proline, 4-CH_A proline); 2.30 (1H, ddt, *J* = 13.0, *J* = 7.6, *J* = 5.4, 3-CH_A); 2.56 (1H, ddd, *J* = 15.0, *J* = 9.8, *J* = 5.3) and 2.62 (1H, dt, *J* = 15.0, *J* = 5.4, 4-CH_2); 3.36-3.42 (1H, m) and 3.49-3.54 (1H, m, 5-CH_2 proline); 4.54 (1H, dd, *J* = 8.0, *J* = 3.6, 2-CH proline); 4.67 (1H, sextet, *J* = 6.9, 2-CH); 6.96 (1H, d, *J* = 7.7, H naphthyl); 7.18 (1H, td, *J* = 7.5, *J* = 1.5, H-6); 7.23 (1H, td, *J* = 7.5, *J* = 1.3, H-7); 7.29 (1H, d, *J* = 7.5, H-5); 7.42 (1H, t, *J* = 7.8, H naphthyl); 7.51 (1H, ddd, *J* = 8.5, *J* = 7.0, *J* = 1.4, H naphthyl); 7.58 (1H, ddd, *J* = 8.1, *J* = 7.0, *J* = 1.4, H naphthyl); 7.71 (1H, d, *J* = 7.5, H-8); 7.99 (1H, dm, *J* = 8.2, H-4 naphthyl); 8.12 (1H, dm, *J* = 8.2, H naphthyl); 8.46 (1H, d, *J* = 8.6, H naphthyl). Found, %: C 68.93; H 5.94; N 6.36; S 7.54. $C_{25}H_{26}N_2O_3S$. Calculated, %: C 69.10; H 6.03; N 6.45; S 7.38.

2-Methyl-*N*-[*N*'-(1-naphthylsulfonyl)prolyl]-1,2,3,4-tetrahydroquinoline (6c) (mixture of diastereoisomers). Yield 96 mg (44%) after flash chromatography. Colorless amorphous powder. HPLC (hexane–2-PrOH, 20:1): (*R*,*S*)/(*S*,*S*) = 52:48; τ_R (*S*,*S*)-**6c** 6.6 min, τ_R (*R*,*S*)-**6c** 7.7 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.98 (1.44H, d, *J* = 6.5, CH_3 (*S*,*S*)); 1.02 (1.56H, d, *J* = 6.5, CH_3 (*R*,*S*)); 1.24-1.32 (1H, m, 3-CH_B); 1.52-1.66 (1.96H, m, 3-CH_B proline (*S*,*S*), 4-CH_B proline (*R*,*S*), 4-CH_2 proline (*S*,*S*)); 1.85-1.92 (0.48H, m, 3-CH_A proline (*S*,*S*)); 2.00-2.11 (1.56H, m, 3-CH_2 proline (*R*,*S*), 4-CH_A proline (*R*,*S*)); 2.25-2.34 (1H, m, 3-CH_A); 2.38-2.46 (0.48H, m, 4-CH_B (*S*,*S*)); 2.53-2.65 (1.52H, m, 4-CH_2 (*R*,*S*), 4-CH_A (*S*,*S*)); 3.37-3.54 (2H, m, 5-CH_2 proline); 4.54 (0.52H, dd, *J* = 7.8, *J* = 3.6, 2-CH proline (*R*,*S*)); 4.58-4.71 (1H, m, 2-CH); 5.13 (0.48H, dd, *J* = 8.2, *J* = 3.9, 2-CH proline (*S*,*S*)); 6.96 (0.52H, d, *J* = 8.0, H naphthyl (*R*,*S*)); 7.15-7.71 (7H, m, H Ar); 7.98-8.24 (2.48H, m, H naphthyl); 8.46 (0.52H, d, *J* = 8.6, H naphthyl (*R*,*S*)); 8.76 (0.48H, d, *J* = 8.4, H naphthyl (*S*,*S*)). Found, %: C 69.13; H 6.02; N 6.41; S 7.36. $C_{25}H_{26}N_2O_3S$. Calculated, %: C 69.10; H 6.03; N 6.45; S 7.38.

(3*R*,2'*S*)-7,8-Difluoro-3-methyl-*N*-(*N*'-methylsulfonylprolyl)-2,3-dihydro-4*H*-1,4-benzoxazine ((*R*,*S*)-7a). Yield 69 mg (38%) after flash chromatography (slow-eluting diastereomer). Yellowish powder. Mp 73-77°C. $[\alpha]_D^{20}$ -178° (*c* 1.2, $CHCl_3$). HPLC (hexane–2-PrOH, 5:1): *de* > 99%, τ_R 16.8 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.16 (3H, d, *J* = 6.8, 3-CH_3); 1.92-2.09 (3H, m, 3-CH_B proline, 4-CH_2 proline); 2.31-2.40 (1H, m, 3-CH_A proline); 2.87 (3H, s, CH_3SO_2); 3.39-3.47 (2H, m, 5-CH_2 proline); 4.21 (1H, dd, *J* = 11.0, *J* = 2.9) and 4.35 (1H, dd, *J* = 11.0, *J* = 1.4, 2-CH_2); 4.71-4.76 (2H, m, 2-CH proline, 3-CH); 6.88 (1H, ddd, *J* = 10.1, *J* = 9.6, *J* = 8.1, H-6); 7.45-7.53 (1H, m, H-5). ^{19}F NMR spectrum, δ, ppm: 2.2-2.3 (1F, m, F-8); 21.0-21.1 (1F, m, F-7). Found, *m*/*z*: 361.1032 $[M+H]^+$. $C_{15}H_{19}F_2N_2O_4S$. Calculated, *m*/*z*: 361.1028.

7,8-Difluoro-3-methyl-*N*-[*N*'-methylsulfonyl-(*S*)-prolyl]-2,3-dihydro-4*H*-1,4-benzoxazine (7a) (mixture of diastereoisomers). Yield 54 mg (30%) after flash chromatography. Yellow amorphous powder. HPLC (hexane–2-PrOH, 5:1): (*R*,*S*)/(*S*,*S*) = 68:32; τ_R (*S*,*S*)-**7a** 10.3 min, τ_R (*R*,*S*)-**7a** 16.8 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.14-1.18 (3H, m, 3-CH_3); 1.85-2.09 (3H, m, 3-CH_B proline, 4-CH_2 proline); 2.15-2.24 (0.32H, m, 3-CH_A proline (*S*,*S*)); 2.31-2.40 (0.68H, m, 3-CH_A proline (*R*,*S*)); 2.87 (2.04H, s, CH_3SO_2 (*R*,*S*)); 2.94 (0.96H, s, CH_3SO_2 (*S*,*S*)); 3.39-3.47 (2H, m, 5-CH_2 proline); 4.12 (0.32H, dd, *J* = 11.0, *J* = 2.9, 2-CH_B (*S*,*S*)); 4.21 (0.68H, dd, *J* = 11.0, *J* = 2.9, 2-CH_B (*R*,*S*)); 4.34-4.39 (1H, m, 2-CH_A); 4.71-4.76 (1.36H, m, 2-CH proline (*R*,*S*), 3-CH (*R*,*S*)); 4.85 (0.32H, qdd, *J* = 6.8, *J* = 2.9, *J* = 1.4, 3-CH (*S*,*S*)); 4.99 (0.32H, dd, *J* = 8.3, *J* = 4.4, 2-CH proline (*S*,*S*)); 6.85-6.92 (1H, m, H-6); 7.47-7.53 (1H, m, H-5). ^{19}F NMR spectrum, δ, ppm: 2.2-2.3 (1F, m, F-8); 20.9-21.1 (1F, m, F-7). Found, %: C 50.00; H 5.17; F 10.37; N 7.73. $C_{15}H_{18}F_2N_2O_4S$. Calculated, %: C 49.99; H 5.03; F 10.54; N 7.77.

(3*R*,2'*S*)-3-Methyl-*N*-[*N*'-methylsulfonylprolyl]-2,3-dihydro-4*H*-1,4-benzoxazine ((*R*,*S*)-7b). Yield 71 mg (44%) after flash chromatography (slow-eluting diastereomer). Yellowish powder. Mp 105-108°C.

$[\alpha]_D^{20}$ -240° (*c* 1.0, $CHCl_3$). HPLC (hexane–2-PrOH–MeOH, 100:8:2): *de* > 99%, τ_R 14.4 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.13 (3H, d, *J* = 6.8, 3-CH_3); 1.92-2.10 (3H, m, 3-CH_B proline, 4-CH_2 proline); 2.34-2.41 (1H, m, 3-CH_A proline); 2.93 (3H, s, CH_3SO_2); 3.39-3.47 (2H, m, 5-CH_2 proline); 4.14 (1H, dd, *J* = 10.9, *J* = 2.8) and 4.19 (1H, dd, *J* = 10.9, *J* = 1.7, 2-CH_2); 4.68-4.72 (1H, m, 3-CH); 4.75 (1H, dd, *J* = 8.4, *J* = 4.0, 2-CH proline); 6.85-6.90 (2H, m, H-7,8); 7.05 (1H, ddd, *J* = 8.2, *J* = 7.3, *J* = 1.5, H-6); 7.55-7.60 (1H, m, H-5). Found, %: C 55.54; H 6.28; N 8.45; S 9.92. $C_{15}H_{20}N_2O_4S$. Calculated, %: C 55.54; H 6.21; N 8.64; S 9.88.

(3*S*,2'*S*)-3-Methyl-*N*-[*N*'-methylsulfonylprolyl]-2,3-dihydro-4*H*-1,4-benzoxazine ((*S*,*S*)-7b). Yield 21 mg (13%) after flash chromatography (fast-eluting diastereomer). Yellowish powder. Mp 48-54°C. $[\alpha]_D^{20}$ +95.9° (*c* 1.0, $CHCl_3$). HPLC (hexane–2-PrOH–MeOH, 100:8:2): *de* > 99%, τ_R 9.0 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.12 (3H, d, *J* = 6.8, 3-CH_3); 1.81-1.94 (2H, m, 4-CH_2 proline); 1.98-2.06 (1H, m) and 2.11-2.18 (1H, m, 3-CH_A proline); 2.95 (3H, s, CH_3SO_2); 3.43 (2H, t, *J* = 6.8, 5-CH_2 proline); 4.07 (1H, dd, *J* = 10.9, *J* = 3.0) and 4.20 (1H, dd, *J* = 10.9, *J* = 1.7, 2-CH_2); 4.78 (1H, qdd, *J* = 6.8, *J* = 3.0, *J* = 1.7, 3-CH); 5.03 (1H, dd, *J* = 8.4, *J* = 4.4, 2-CH proline); 6.85-6.91 (2H, m, H-7,8); 7.05 (1H, ddd, *J* = 8.2, *J* = 7.3, *J* = 1.5, H-6); 7.63-7.67 (1H, m, H-5). Found, %: C 55.97; H 6.30; N 8.38; S 10.03. $C_{15}H_{20}N_2O_4S$. Calculated, %: C 55.54; H 6.21; N 8.64; S 9.88.

(2*R*,2'*S*)-2-Methyl-*N*-[*N*'-methylsulfonylprolyl]-1,2,3,4-tetrahydroquinoline ((*R*,*S*)-7c). Yield 27 mg (17%) after flash chromatography (fast-eluting diastereomer). Colorless powder. Mp 130-132°C. $[\alpha]_D^{20}$ -334° (*c* 0.5, $CHCl_3$). HPLC (hexane–2-PrOH, 10:1): *de* > 99%, τ_R 11.2 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.02 (3H, d, *J* = 6.5, 2-CH_3); 1.26-1.34 (1H, m, 3-CH_B); 1.86-1.93 (1H, m, 4-CH_B proline); 2.07-2.15 (2H, m, 3-CH_B proline, 4-CH_A proline); 2.27-2.35 (2H, m, 3-CH_A, 3-CH_A proline); 2.51-2.63 (2H, m, 4-CH_2); 2.73 (3H, s, CH_3SO_2); 3.36 (1H, ddd, *J* = 9.2, *J* = 7.3, *J* = 5.7) and 3.42 (1H, dt, *J* = 9.2, *J* = 6.7, 5-CH_2 proline); 4.42 (1H, dd, *J* = 8.3, *J* = 3.8, 2-CH proline); 4.69 (1H, sextet, *J* = 6.8, 2-CH); 7.12-7.23 (4H, m, H-5,6,7,8). Found, %: C 59.49; H 7.00; N 8.74; S 9.98. $C_{16}H_{22}N_2O_3S$. Calculated, %: C 59.60; H 6.88; N 8.69; S 9.94.

(2*S*,2'*S*)-2-Methyl-*N*-[*N*'-methylsulfonylprolyl]-1,2,3,4-tetrahydroquinoline ((*S*,*S*)-7c). Yield 13 mg (8%) after flash chromatography (fast-eluting diastereomer). Pale-yellow oil. $[\alpha]_D^{20}$ +198° (*c* 0.5, $CHCl_3$). HPLC (hexane–2-PrOH, 10:1): *de* 96.2 %, τ_R 8.3 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.02 (3H, d, *J* = 6.6, 2-CH_3); 1.26-1.34 (1H, m, 3-CH_B); 1.57-1.63 (1H, m, 4-CH_B proline); 1.76-1.96 (3H, m, 3-CH_2 proline, 4-CH_A proline); 2.30 (1H, ddt, *J* = 13.1, *J* = 7.5, *J* = 5.5, 3-CH_A); 2.42-2.50 (1H, m) and 2.64 (1H, dt, *J* = 15.0, *J* = 5.4, 4-CH_2); 2.94 (3H, s, CH_3SO_2); 3.35-3.43 (2H, m, 5-CH_2 proline); 4.68 (1H, dquin, *J* = 7.5, *J* = 6.6, 2-CH); 4.93 (1H, dd, *J* = 8.2, *J* = 4.2, 2-CH proline); 7.15 (1H, td, *J* = 7.4, *J* = 1.2, H-6); 7.20-7.24 (2H, m, H-5,7); 7.37-7.39 (1H, m, H-8). Found, %: C 59.84; H 7.07; N 8.42; S 9.83. $C_{16}H_{22}N_2O_3S$. Calculated, %: C 59.60; H 6.88; N 8.69; S 9.95.

(3*R*,2'*S*)-*N*-[*N*'-*tert*-Butylsulfonylprolyl]-7,8-difluoro-3-methyl-2,3-dihydro-4*H*-1,4-benzoxazine ((*R*,*S*)-8a). Yield 48 mg (24%) after recrystallization from EtOH. Colorless crystals. Mp 162-164°C. $[\alpha]_D^{20}$ -172° (*c* 1.0, $CHCl_3$). HPLC (hexane–2-PrOH, 20:1): *de* 99.4%, τ_R 13.6 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.15 (3H, d, *J* = 6.8, 3-CH_3); 1.26 (9H, s, $C(CH_3)_3$); 1.85-2.12 (3H, m, 3-CH_B proline, 4-CH_2 proline); 2.31-2.41 (1H, m, 3-CH_A proline); 3.48-3.62 (2H, m, 5-CH_2 proline); 4.20 (1H, dd, *J* = 10.9, *J* = 2.8) and 4.34 (1H, dd, *J* = 10.9, *J* = 1.4, 2-CH_2); 4.72-4.78 (1H, m, 3-CH); 4.87 (1H, dd, *J* = 8.2, *J* = 3.6, 2-CH proline); 6.87 (1H, ddd, *J* = 10.1, *J* = 9.6, *J* = 8.2, H-6); 7.38-7.50 (1H, m, H-5). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): 2.3-2.4 (1F, m, F-8); 20.9-21.2 (1F, m, F-7). Found, %: C 53.66; H 6.10; F 9.54; N 6.69; S 7.83. $C_{18}H_{24}F_2N_2O_4S$. Calculated, %: C 53.72; H 6.01; F 9.44; N 6.96; S 7.97.

***N*-[*N*'-*tert*-Butylsulfonyl-(*S*)-prolyl]-7,8-difluoro-3-methyl-2,3-dihydro-4*H*-1,4-benzoxazine (8a)** (mixture of diastereoisomers). Yield 38 mg (19%) after flash chromatography. Colorless oil. HPLC (hexane–2-PrOH, 20:1): (*R*,*S*)/(*S*,*S*) = 65:35; τ_R (*S*,*S*)-**8a** 7.0 min, τ_R (*R*,*S*)-**8a** 13.6 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.13-1.16 (3H, m, 3-CH_3); 1.26 (5.85H, s, $C(CH_3)_3$ (*R*,*S*)); 1.32 (3.15H, s, $C(CH_3)_3$ (*S*,*S*)); 1.78-2.25 (3.35H, m, 3-CH_2 proline (*S*,*S*), 3-CH_B proline (*R,S*), 4-CH_2 proline); 2.32-2.40 (0.65H, m, 3-CH_A proline (*R*,*S*)); 3.45-3.63 (2H, m, 5-CH_2 proline); 4.11 (0.35H, dd, *J* = 11.1, *J* = 2.9, 2-CH_B (*S*,*S*)); 4.20 (0.65H, dd, *J* = 11.0, *J* = 2.8, 2-CH_B (*R,S*)); 4.34 (0.65H, dd, *J* = 11.0, *J* = 1.4, 2-CH_A (*R*,*S*)); 4.38 (0.35H, dd, *J* = 11.1,

J = 1.5, 2-CH_A (*S*,*S*)); 4.72-4.78 (0.65H, m, 3-CH (*R*,*S*)); 4.80-4.89 (1H, m, 3-CH (*S*,*S*), 2-CH proline (*R*,*S*)); 5.10 (0.35H, dd, J = 8.3, J = 3.7, 2-CH proline (*S*,*S*)); 6.84-6.93 (1H, m, H-6); 7.40-7.53 (1H, m, H-5). ^{19}F NMR spectrum, δ, ppm: 2.3-2.5 (1F, m, F-8); 20.9-21.3 (1F, m, F-7). Found, %: C 53.90; H 6.19; F 9.63; N 6.73; S 8.21. $C_{18}H_{24}F_2N_2O_4S$. Calculated, %: C 53.72; H 6.01; F 9.44; N 6.96; S 7.97.

(3*R*,2'*S*)-*N*-[*N*'-*tert*-Butylsulfonylprolyl]-3-methyl-2,3-dihydro-4*H*-1,4-benzoxazine ((*R*,*S*)-8b). Yield 59 mg (32%) after recrystallization from EtOH. Colorless crystals. Mp 109-110°C. $[\alpha]_D^{20}$ -190° (*c* 1.0, $CHCl_3$). HPLC (hexane–2-PrOH, 20:1): *de* 98.2%, τ_R 8.3 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.12 (3H, d, J = 6.8, 3-CH_3); 1.24 (9H, s, $C(CH_3)_3$); 1.85-2.14 (3H, m, 3-CH_B proline, 4-CH_2 proline); 2.32-2.41 (1H, m, 3-CH_A proline); 3.50-3.63 (2H, m, 5-CH_2 proline); 4.13 (1H, dd, J = 11.0, J = 2.8) and 4.18 (1H, dd, J = 11.0, J = 1.8, 2-CH_2); 4.67-4.75 (1H, m, 3-CH); 4.92 (1H, dd, J = 8.4, J = 3.6, 2-CH proline); 6.83-6.90 (2H, m, H-7,8); 7.02-7.07 (1H, m, H-6); 7.48-7.57 (1H, m, H-5). Found, %: C 58.87; H 7.06; N 7.39; S 8.47. $C_{18}H_{26}N_2O_4S$. Calculated, %: C 58.99; H 7.15; N 7.64; S 8.75.

***N*-[*N*'-*tert*-Butylsulfonyl-(*S*)-prolyl]-3-methyl-2,3-dihydro-4*H*-1,4-benzoxazine (8b)** (mixture of diastereoisomers). Yield 35 mg (19%) after flash chromatography. Colorless oil. HPLC (hexane–2-PrOH, 20:1): (*R*,*S*)/(*S*,*S*) = 70:30; τ_R (*S*,*S*)-**8b** 5.3 min, τ_R (*R*,*S*)-**8b** 8.3 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.10-1.16 (3H, m, 3-CH_3); 1.24 (6.3H, s, $C(C\underline{H}_3)_3$ (*R*,*S*)); 1.33 (2.7H, s, $C(C\underline{H}_3)_3$ (*S*,*S*)); 1.73-2.15 (3.3H, m, 3-CH_2 proline (*S*,*S*), 3-CH_B proline (*R*,*S*), 4-CH_2 proline); 2.32-2.41 (0.7H, m, 3-CH_A proline (*R*,*S*)); 3.45-3.64 (2H, m, 5-CH_2 proline); 4.06 (0.3H, dd, J = 11.0, J = 3.2, 2-CH_B (*S*,*S*)); 4.12-4.23 (1.7H, m, 2-CH_2 (*R*,*S*), 2-CH_A (*S*,*S*)); 4.67-4.75 (0.7H, m, 3-CH (*R*,*S*)); 4.75-4.82 (0.3H, m, 3-CH (*S*,*S*)); 4.92 (0.7H, dd, J = 8.6, J = 3.6, 2-CH proline (*R*,*S*)); 5.17 (0.3H, dd, J = 8.4, J = 3.6, 2-CH proline (*S*,*S*)); 6.83-6.90 (2H, m, H-7,8); 7.03-7.07 (1H, m, H-6); 7.48-7.57 (0.7H, m, H-5 (*R*,*S*)); 7.61-7.64 (0.3H, m, H-5 (*S*,*S*)). Found, %: C 59.18; H 7.37; N 7.39; S 9.01. $C_{18}H_{26}N_2O_4S$. Calculated, %: C 58.99; H 7.15; N 7.64; S 8.75.

(3*R*,2'*S*)-7,8-Difluoro-3-methyl-*N*-(*N*'-tosylindolin-2-ylcarbonyl)-2,3-dihydro-4*H*-1,4-benzoxazine ((*R*,*S*)-9a). Yield 61 mg (25%) after flash chromatography (slow-eluting diastereomer). Colorless powder. Mp 169-170°C. $[\alpha]_D^{20}$ -141° (*c* 0.82, $CHCl_3$). HPLC (hexane–2-PrOH, 40:1): *de* > 99%, τ_R 7.8 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.22 (3H, d, J = 6.9, 3-CH_3); 2.33 (3H, s, Ar$C\underline{H}_3$); 3.14 (1H, dd, J = 16.3, J = 5.8) and 3.51 (1H, dd, J = 16.3, J = 10.5, 3-CH_2 indoline); 4.33 (1H, dd, J = 10.9, J = 3.0) and 4.41 (1H, dd, J = 10.9, J = 1.4, 2-CH_2); 4.88-4.93 (1H, m, 3-CH); 5.25 (1H, dd, J = 10.5, J = 5.8, 2-CH indoline); 6.91 (1H, ddd, J = 10.0, J = 9.5, J = 8.1, H-6); 6.98 (1H, td, J = 7.5, J = 1.0, H indoline); 7.13-7.19 (2H, m, H indoline); 7.26 (2H, d, J = 8.1, H Ts); 7.34-7.38 (2H, m, H-5, H indoline); 7.44 (2H, br. d, J = 8.1, H Ts). ^{19}F NMR spectrum, δ, ppm: 2.6-2.7 (1F, m, F-8); 21.7-22.0 (1F, m, F-7). Found, %: C 61.95; H 4.54; F 7.44; N 5.95; S 6.72. $C_{25}H_{22}F_2N_2O_4S$. Calculated, %: C 61.97; H 4.58; F 7.84; N 5.78; S 6.62.

(3*R*,2'*S*)-3-Methyl-*N*-(*N*'-tosylindolin-2-ylcarbonyl)-2,3-dihydro-4*H*-1,4-benzoxazine ((*R*,*S*)-9b). Yield 90 mg (40%) after flash chromatography (slow-eluting diastereomer). Colorless powder. Mp 184-187°C. $[\alpha]_D^{20}$ -162° (*c* 1.1, $CHCl_3$). HPLC (hexane–2-PrOH, 40:1): *de* 98.4%, τ_R 6.9 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.18 (3H, d, J = 6.7, 3-CH_3); 2.30 (3H, s, Ar$C\underline{H}_3$); 3.16 (1H, dd, J = 16.3, J = 6.3) and 3.52 (1H, dd, J = 16.3, J = 10.4, 3-CH_2 indoline); 4.24 (1H, dd, J = 10.8, J = 1.5) and 4.32 (1H, dd, J = 10.8, J = 3.0, 2-CH_2); 4.88-4.95 (1H, m, 3-CH); 5.23 (1H, dd, J = 10.4, J = 6.3, 2-CH indoline); 6.91 (1H, ddd, J = 8.1, J = 7.4, J = 1.3, H indoline); 6.96-7.00 (2H, m, H indoline); 7.12-7.38 (9H, m, H Ar). Found, %: C 66.83; H 5.30; N 6.33; S 7.10. $C_{25}H_{24}N_2O_4S$. Calculated, %: C 66.95; H 5.39; N 6.25; S 7.15.

3-Methyl-*N*-(*N*'-tosyl-(*S*)-indolin-2-ylcarbonyl)-2,3-dihydro-4*H*-1,4-benzoxazine (9b) (mixture of diastereoisomers). Yield 168 mg (12%) after flash chromatography. Colorless amorphous powder. HPLC (hexane–2-PrOH, 40:1): (*R*,*S*)/(*S*,*S*) = 70:30; τ_R (*S*,*S*)-**9b** 5.9 min, τ_R (*R*,*S*)-**9b** 6.9 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.17-1.20 (3H, m, 3-CH_3); 2.30 (2.1H, s, Ar$C\underline{H}_3$ (*R*,*S*)); 2.34 (0.9H, s, Ar$C\underline{H}_3$ (*S*,*S*)); 2.93-2.97 (0.3H, m, 3-CH_B indoline (*S*,*S*)); 3.16 (0.7H, dd, J = 16.3, J = 6.3, 3-CH_B indoline (*R*,*S*)); 3.28 (0.3H, dd, J = 16.0, J = 10.8, 3-CH_A indoline (*S*,*S*)); 3.52 (0.7H, dd, J = 16.3, J = 10.5, 3-CH_A indoline (*R*,*S*)); 4.18 (0.3H, dd, J = 10.9, J = 2.9, 2-CH_B (*S*,*S*)); 4.22-4.27 (1H, m, 2-CH_B (*R*,*S*), 2-CH_A (*S*,*S*)); 4.32 (0.7H, dd, J = 10.8, J = 3.0, 2-CH_A (*R*,*S*)); 4.80-4.85 (0.3H, m, 3-CH (*S*,*S*)); 4.88-4.95 (0.7H, m, 3-CH (*R*,*S*)); 5.23 (0.7H, dd,

J = 10.5, *J* = 6.3, 2-CH indoline (*R*,*S*)); 5.66 (0.3H, dd, *J* = 10.8, *J* = 4.8, 2-CH indoline (*S*,*S*)); 6.89-7.39 (11.1H, m, H Ar); 7.70-7.76 (0.9H, m, H Ar). Found, %: C 66.86; H 5.19; N 6.26; S 7.15. $C_{25}H_{24}N_2O_4S$. Calculated, %: C 66.95; H 5.39; N 6.25; S 7.15.

(2*R*,2'*S*)-2-Methyl-*N*-(*N*'-tosylindolin-2-ylcarbonyl)-1,2,3,4-tetrahydroquinoline ((*R*,*S*)-9c). Yield 56 mg (25%) after flash chromatography (slow-eluting diastereomer). Colorless amorphous powder. $[\alpha]_D^{20}$ -184° (*c* 0.7, $CHCl_3$). HPLC (hexane–2-PrOH, 40:1): *de* 95.6%, τ_R 10.6 min. 1H NMR spectrum, δ, ppm (*J*, Hz): 1.09 (3H, d, *J* = 6.5, 2-CH_3); 1.35 (1H, dddd, *J* = 13.0, *J* = 9.8, *J* = 7.3, *J* = 5.8) and 2.44 (1H, ddt, *J* = 13.0, *J* = 7.6, *J* = 5.3, 3-CH_2); 2.27 (3H, s, ArC$\underline{H}_3$); 2.63-2.78 (2H, m, 4-CH_2); 3.19 (1H, dd, *J* = 16.2, *J* = 6.6) and 3.38 (1H, dd, *J* = 16.2, *J* = 10.3, 3-CH_2 indoline); 4.81 (1H, sextet, *J* = 6.9, 2-CH); 4.87 (1H, dd, *J* = 10.3, *J* = 6.6, 2-CH indoline); 6.94-7.39 (12H, m, H Ar). Found, %: C 70.18; H 5.99; N 6.17; S 7.03. $C_{26}H_{26}N_2O_3S$. Calculated, %: C 69.93; H 5.87; N 6.27; S 7.18.

(3*R*,2'*S*)-7,8-Difluoro-3-methyl-4-(*N*'-methyl-*N*'-tosylphenylalanyl)-2,3-dihydro-4*H*-1,4-benzoxazine ((*R*,*S*)-10a). Yield 135 mg (54%) after recrystallization from mixture hexane–EtOAc. Colorless powder. Mp 150-151°C. $[\alpha]_D^{20}$ -134° (*c* 1.0, $CHCl_3$). HPLC (hexane–2-PrOH, 160:1): *de* > 99.5%, τ_R 10.7 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.12 (3H, d, *J* = 6.8, 3-CH_3); 2.37 (3H, s, ArC$\underline{H}_3$); 2.74 (1H, dd, *J* = 13.8, *J* = 7.0) and 3.24 (1H, dd, *J* = 13.8, *J* = 8.0, C$\underline{H}_2$Ph); 2.95 (3H, s, NCH_3); 3.71 (1H, dd, *J* = 10.9, *J* = 2.7) and 4.22 (1H, dd, *J* = 10.9, *J* = 1.3, 2-CH_2); 4.62-4.67 (1H, m, 3-CH); 5.20 (1H, dd, *J* = 8.0, *J* = 7.0, NCHCO); 6.80 (1H, td, *J* = 9.8, *J* = 8.0, H-6); 6.87-6.95 (1H, m, H Ph); 7.12-7.14 (2H, m, H Ph); 7.20-7.29 (5H, m, H-5, H Ts, H Ph); 7.38 (2H, d, *J* = 8.2, H Ts). ^{19}F NMR spectrum, δ, ppm: 2.3-2.4 (1F, m, F-8); 21.5-21.7 (1F, m, F-7). Found, %: C 62.21; H 4.96; N 5.60; F 7.19; S 6.56. $C_{26}H_{26}F_2N_2O_4S$. Calculated, %: C 62.39; H 5.24; N 5.60; F 7.59; S 6.41.

7,8-Difluoro-3-methyl-4-(*N*'-methyl-*N*'-tosyl-(*S*)-phenylalanyl)-2,3-dihydro-4*H*-1,4-benzoxazine (10a) (mixture of diastereoisomers). Yield 153 mg (61%) after flash chromatography. Colorless powder. Mp 139-142°C. HPLC (hexane–2-PrOH, 160:1): (*R*,*S*)/(*S*,*S*) = 87:13; τ_R (*S*,*S*)-**10a** 8.1 min, τ_R (*R*,*S*)-**10a** 10.7 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.88 (0.39H, d, *J* = 6.8, 3-CH_3 (*S*,*S*)); 1.12 (2.61H, d, *J* = 6.8, 3-CH_3 (*R*,*S*)); 2.37 (2.61H, s, ArC$\underline{H}_3$ (*R*,*S*)); 2.39 (0.39H, s, ArC$\underline{H}_3$ (*S*,*S*)); 2.60 (0.13H, dd, *J* = 13.4, *J* = 5.8, 3-CH_B phenylalanine (*S*,*S*)); 2.74 (0.87H, dd, *J* = 13.7, *J* = 7.0, 3-CH_B phenylalanine (*R*,*S*)); 2.95 (2.61H, s, NCH_3 (*R*,*S*)); 3.00 (0.39H, s, NCH_3 (*S*,*S*)); 3.08 (0.13H, dd, *J* = 13.4 *J* = 9.0, 3-CH_A phenylalanine (*S*,*S*)); 3.24 (0.87H, dd, *J* = 13.7, *J* = 8.0, 3-CH_A phenylalanine (*R*,*S*)); 3.72 (0.87H, dd, *J* = 11.0, *J* = 2.8, 2-CH_B (*R*,*S*)); 3.87 (0.13H, br. d, *J* = 11.0, 2-CH_B (*S*,*S*)); 4.22 (0.87H, dd, *J* = 11.0, *J* = 1.5, 2-CH_A (*R*,*S*)); 4.25 (0.13H, dd, *J* = 11.0, *J* = 1.5, 2-CH_A (*S*,*S*)); 4.62-4.67 (0.87H, m, 3-CH (*R*,*S*)); 4.74-4.80 (0.13H, m, 3-CH (*S*,*S*)); 5.20 (0.87H, dd, *J* = 8.0, *J* = 7.0, NCHCO (*R*,*S*)); 5.24 (0.13H, dd, *J* = 9.0, *J* = 5.8, NCHCO (*S*,*S*)); 6.80 (0.87H, td, *J* = 9.8, *J* = 8.0, H-6 (*R*,*S*)); 6.86-6.99 (1.13H, m, H-6 (*S*,*S*), H Ph); 7.12-7.40 (8.61H, m, H-5 (*R*,*S*), H Ph, H Ts); 7.49-7.54 (0.13H, m, H-5 (*S*,*S*)); 7.63 (0.26H, d, *J* = 8.2, H Ts (*S*,*S*)). ^{19}F NMR spectrum, δ, ppm: 2.3-2.4 (0.87F, m, F-8 (*R*,*S*)); 2.6-2.7 (0.13F, m, F-8 (*S*,*S*)); 21.5-21.8 (1F, m, F-7). Found, %: C 62.20; H 5.15; N 5.56; S 6.53. $C_{26}H_{26}F_2N_2O_4S$. Calculated, %: C 62.39; H 5.24; N 5.60; S 6.41.

3-Methyl-4-(*N*'-methyl-*N*'-tosyl-(*S*)-phenylanalyl)-2,3-dihydro-4*H*-1,4-benzoxazine (10b) (mixture diastereoisomers). Yield 233 mg (80%) after flash chromatography. Colorless amorphous powder. HPLC (hexane–2-PrOH, 80:1): (*R*,*S*)/(*S*,*S*) = 45:55; τ_R (*S*,*S*)-**10b** 5.6 min, τ_R (*R*,*S*)-**10b** 6.3 min. 1H NMR spectrum, δ, ppm (*J*, Hz): 0.89 (1.65H, d, *J* = 6.8, 3-CH_3 (*S*,*S*)); 1.10 (1.35H, d, *J* = 6.8, 3-CH_3 (*R*,*S*)); 2.37 (1.35H, s, ArC$\underline{H}_3$ (*R*,*S*)); 2.38 (1.65H, s, ArC$\underline{H}_3$ (*S*,*S*)); 2.61 (0.55H, dd, *J* = 13.5, *J* = 6.6, 3-CH_B phenylalanine (*S*,*S*)); 2.76 (0.45H, dd, *J* = 13.9, *J* = 7.1, 3-CH_B phenylalanine (*R*,*S*)); 2.97 (1.35H, s, NCH_3 (*R*,*S*)); 3.00 (1.65H, s, NCH_3 (*S*,*S*)); 3.03 (0.55H, dd, *J* = 13.5, *J* = 8.5, 3-CH_A phenylalanine (*S*,*S*)); 3.25 (0.45H, dd, *J* = 13.9, *J* = 7.8, 3-CH_A phenylalanine (*R*,*S*)); 3.65 (0.45H, dd, *J* = 10.9, *J* = 2.4, 2-CH_B (*R*,*S*)); 3.82 (0.55H, dd, *J* = 11.0, *J* = 3.0, 2-CH_B (*S*,*S*)); 4.04 (0.45H, dd, *J* = 10.9, *J* = 1.6, 2-CH_A (*R*,*S*)); 4.10 (0.55H, dd, *J* = 11.0, *J* = 1.7, 2-CH_A (*S*,*S*)); 4.54-4.60 (0.45H, m, 3-CH (*R*,*S*)); 4.71 (0.55H, qdd, *J* = 6.8, *J* = 3.0, *J* = 1.7, 3-CH (*S*,*S*)); 5.25 (0.45H, t, *J* = 7.6, NCHCO (*R,S*)); 5.30 (0.55H, br. t, *J* = 7.8, NCHCO (*S,S*)); 6.77-7.68 (13H, m, H Ar). Found, %: C 67.18; H 6.25; N 5.81; S 6.98. $C_{26}H_{28}N_2O_4S$. Calculated, %: C 67.22; H 6.07; N 6.03; S 6.90.

2-Methyl-*N*-(*N*'-methyl-*N*'-tosyl-(*S*)-phenylalanyl)-1,2,3,4-tetrahydroquinoline (10c) (mixture of diastereoisomers). Yield 104 mg (45%) after flash chromatography. Colorless amorphous powder. HPLC (hexane–2-PrOH–MeOH, 1000:8:4): (*R*,*S*)/(*S*,*S*) = 50:50; τ_R (*R*,*S*)-**10c** 6.5 min, τ_R (*S*,*S*)-**10c** 7.0 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.93 (1.5H, d, *J* = 6.5, 2-CH_3 (*S*,*S*)); 0.97 (1.5H, d, *J* = 6.5, 2-CH_3 (*R*,*S*)); 1.17-1.27 (1H, m, 3-CH_B); 2.08-2.21 (1.5H, m, 3-CH_A, 3-CH_B phenylalanine (*S*,*S*)); 2.34-2.40 (3.5H, m, 4-CH_B (*R*,*S*), Ar$C\underline{H}_3$); 2.48-2.56 (1H, m, 4-CH_A (*R*,*S*), 4-CH_B (*S*,*S*)); 2.59-2.65 (1H, m, 4-CH_A (*S*,*S*), 3-CH_A phenylalanine (*S*,*S*)); 2.71 (0.5H, dd, *J* = 13.7, *J* = 7.0, 3-CH_B phenylalanine (*R*,*S*)); 2.90 (1.5H, s, NCH_3 (*R*,*S*)); 3.03 (1.5H, s, NCH_3 (*S*,*S*)); 3.29 (0.5H, dd, *J* = 13.7, *J* = 7.9, 3-CH_A phenylalanine (*R*,*S*)); 4.55-4.58 (1H, m, 2-CH); 5.05 (0.5H, t, *J* = 7.5, NCHCO (*R*,*S*)); 5.32 (0.5H, t, *J* = 7.5, NCHCO (*S*,*S*)); 6.47-7.49 (13H, m, H Ar). Found, %: C 70.03; H 6.54; N 6.06; S 6.86. $C_{27}H_{30}N_2O_3S$. Calculated, %: C 70.10; H 6.54; N 6.06; S 6.93.

(3*R*,2'*S*)-7,8-Difluoro-3-methyl-*N*-[tetrahydrofuran-2-ylcarbonyl]-2,3-dihydro-4*H*-1,4-benzoxazine ((*R*,*S*)-11a). Yield 46.1 mg (31%) after flash chromatography (slow-eluting diastereomer). Yellowish powder. Mp 69-72°C. $[\alpha]_D^{20}$ -38.5° (*c* 1.3, $CHCl_3$). HPLC (hexane–2-PrOH, 20:1): *de* > 99%, τ_R 11.7 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.18 (3H, d, *J* = 6.8, CH_3); 1.82-1.96 (2H, m, 4-CH_2 tetrahydrofuran); 2.04-2.11 (1H, m) and 2.19-2.25 (1H, m, 3-CH_2 tetrahydrofuran); 3.80 (1H, td, *J* = 7.7, *J* = 6.1) and 3.85 (1H, td, *J* = 7.7, *J* = 6.7, 5-CH_2 tetrahydrofuran); 4.20 (1H, dd, *J* = 11.0, *J* = 2.8) and 4.35 (1H, dd, *J* = 11.0, *J* = 1.6, 2-CH_2); 4.74 (1H, qdd, *J* = 6.8, *J* = 2.8, *J* = 1.6, 3-CH); 4.83 (1H, dd, *J* = 7.7, *J* = 5.1, 2-CH tetrahydrofuran); 6.84 (1H, ddd, *J* = 10.2, *J* = 9.6, *J* = 8.2, H-6); 7.59 (1H, ddd, *J* = 9.6, *J* = 5.5, *J* = 2.6, H-5). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): 1.8 (1F, ddd, *J* = 21.0, *J* = 8.2, *J* = 2.6, F-8); 20.3 (1F, ddd, *J* = 21.0, *J* = 10.2, *J* = 5.5, F-7). Found, %: C 59.38; H 5.48; F 13.27; N 4.99. $C_{14}H_{15}F_2N_2O_3$. Calculated, %: C 59.36; H 5.34; F 13.41; N 4.94.

(3*S*,2'*S*)-7,8-Difluoro-3-methyl-*N*-[tetrahydrofuran-2-ylcarbonyl]-2,3-dihydro-4*H*-1,4-benzoxazine ((*S*,*S*)-11a). Yield 25.3 mg (17%) after flash chromatography (fast-eluting diastereomer). Yellowish powder. Mp 82-85°C. $[\alpha]_D^{20}$ +137° (*c* 0.5, $CHCl_3$). HPLC (hexane–2-PrOH, 20:1): *de* 99.0%, τ_R 6.2 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.14 (3H, d, *J* = 6.9, CH_3); 1.82-1.90 (1H, m, 4-CH_B tetrahydrofuran); 1.94-2.01 (2H, m, 3-CH_B tetrahydrofuran, 4-CH_A tetrahydrofuran); 2.13-2.21 (1H, m, 3-CH_A tetrahydrofuran); 3.80 (1H, td, *J* = 7.8, *J* = 5.6) and 3.84 (dt, *J* = 7.8, *J* = 6.7, 5-CH_2 tetrahydrofuran); 4.17 (1H, dd, *J* = 10.9, *J* = 2.9) and 4.37 (1H, dd, *J* = 10.9, *J* = 1.5, 2-CH_2); 4.76 (1H, dd, *J* = 7.1, *J* = 5.7, 2-CH tetrahydrofuran); 4.87 (1H, qdd, *J* = 6.9, *J* = 2.9, *J* = 1.5, 3-CH); 6.87 (1H, ddd, *J* = 10.1, *J* = 9.6, *J* = 8.2, H-6); 7.63 (1H, ddd, *J* = 9.6, *J* = 5.3, *J* = 2.5, H-5). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): 2.1 (1F, ddd, *J* = 21.0, *J* = 8.2, *J* = 2.5, F-8); 20.7 (1F, ddd, *J* = 21.0, *J* = 10.1, *J* = 5.3, F-7). Found, %: C 59.64; H 5.47; F 13.30; N 4.96. $C_{14}H_{15}F_2NO_3$. Calculated, %: C 59.36; H 5.34; F 13.41; N 4.94.

(3*S*,2'*S*)-3-Methyl-*N*-[*N*'-(2-naphthylsulfonyl)prolyl]-2,3-dihydro-4*H*-1,4-benzoxazine ((*S*,*S*)-5b). A solution of acyl chloride **2b** (324 mg, 1 mmol) in MeCN (10 ml) was added to a solution of amine (*S*)-**3b** (149 mg, 1 mmol) and *N*,*N*-diethylaniline (149 mg, 1 mmol) in MeCN (10 ml) at 20°C. Benzene (10 ml) was added to the reaction mixture after 24 h, the solution was washed with 1 N HCl (2×10 ml), saturated NaCl solution (3×15 ml), 5% $NaHCO_3$ solution (2×15 ml), H_2O (2×15 ml), dried over $MgSO_4$, and evaporated. The residue was recrystallized from a hexane–EtOAc mixture. Yield 275 mg (63%). Colorless powder. Mp 141-142°C. $[\alpha]_D^{20}$ +121° (*c* 1.2, $CHCl_3$). HPLC (hexane–2-PrOH, 20:1): *de* 98.6%, τ_R 6.8 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.13 (3H, d, *J* = 6.8, CH_3); 1.63-1.70 (1H, m) and 1.73-1.81 (1H, m, 4-CH_2 proline); 1.87-2.00 (2H, m, 3-CH_2 proline); 3.42-3.47 (2H, m, 5-CH_2 proline); 4.11 (1H, dd, *J* = 11.1, *J* = 3.1) and 4.23 (1H, dd, *J* = 11.1, *J* = 1.7, 2-CH_2); 4.82 (1H, qdd, *J* = 6.8, *J* = 3.1, *J* = 1.7, 3-CH); 5.12 (1H, dd, *J* = 8.1, *J* = 4.2, 2-CH proline); 6.88-6.95 (2H, m, H-7,8); 7.07 (1H, ddd, *J* = 8.1, *J* = 7.3, *J* = 1.2, H-6); 7.63-7.71 (3H, m, H-5, H naphthyl); 7.85 (1H, dd, *J* = 8.6, *J* = 1.9, H naphthyl); 8.00-8.02 (1H, m, H naphthyl); 8.08-8.13 (2H, m, H naphthyl); 8.45-8.47 (1H, m, H naphthyl). Found, %: C 65.99; H 5.58; N 6.31. $C_{24}H_{24}N_2O_4S$. Calculated, %: C 66.04; H 5.54; N 6.42.

(*S*,*S*)-Amides 9a,c, 10b,c (General Method). A solution of acyl chloride **2f** or **2g** (0.5 mmol) in toluene (5 ml) was added to a solution of the amine (*S*)-**3a**, (*S*)-**3b** or (*S*)-**3c** (1.0 mmol) in toluene (5 ml) at 20°C. The reaction mixture after 24 h was washed with HCl solution (4 N for amine (*S*)-**3a**; 1 N for amines (*S*)-**3b** and

(*S*)-**3c**) (2×5 ml); with saturated NaCl solution (3×15 ml); 5% $NaHCO_3$ solution (10 ml), and H_2O (2×15 ml). The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by recrystallization or flash chromatography.

(3*S*,2'*S*)-7,8-Difluoro-3-methyl-*N*-(*N*'-tosylindolin-2-ylcarbonyl)-2,3-dihydro-4*H*-1,4-benzoxazine ((*S*,*S*)-9a). Yield 180 mg (72%) after flash chromatography. Colorless amorphous powder. $[\alpha]_D^{20}$ +112° (*c* 0.96, $CHCl_3$). HPLC (hexane–2-PrOH, 40:1): *de* > 99%, τ_R 6.4 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.22 (3H, d, *J* = 6.8, 3-CH_3); 2.35 (3H, s, ArC<u>H</u>$_3$); 3.00 (1H, dd, *J* = 16.4, *J* = 5.0) and 3.36 (1H, dd, *J* = 16.4, *J* = 11.0, 3-CH_2 indoline); 4.24 (1H, dd, *J* = 11.1, *J* = 2.8) and 4.43 (1H, dd, *J* = 11.1, *J* = 1.5, 2-CH_2); 4.88 (1H, qdd, *J* = 6.8, *J* = 2.8, *J* = 1.5, 3-CH); 5.62 (1H, dd, *J* = 11.0, *J* = 5.0, 2-CH indoline); 6.89-6.98 (2H, m, H-6, H Ar indoline); 7.11-7.17 (2H, m, H indoline); 7.25-7.27 (1H, m, H indoline); 7.33-7.35 (2H, m, H Ts); 7.74-7.76 (2H, m, H Ts); 7.56 (1H, ddd, *J* = 9.5, *J* = 5.4, *J* = 2.5, H-5). ^{19}F NMR spectrum, δ, ppm: 2.3-2.4 (1F, m, F-8); 21.3-21.4 (1F, m, F-7). Found, %: C 61.99; H 4.39; N 5.45; S 6.60. $C_{25}H_{22}F_2N_2O_4S$. Calculated, %: C 61.97; H 4.58; N 5.78; S 6.62.

(2*S*,2'*S*)-2-Methyl-*N*-(*N*'-tosylindolin-2-ylcarbonyl)-1,2,3,4-tetrahydroquinoline ((*S*,*S*)-9c). Yield 134 mg (60%) after flash chromatography. Colorless amorphous powder. $[\alpha]_D^{20}$ +176° (*c* 0.63, $CHCl_3$). HPLC (hexane–2-PrOH, 40:1): *de* 97.8%, τ_R 9.5 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.08 (3H, d, *J* = 6.6, 2-CH_3); 1.29-1.38 (1H, m, 3-CH_B); 2.30-2.38 (4H, m, ArC<u>H</u>$_3$, 3-CH_A); 2.54 (1H, ddd, *J* = 15.4, *J* = 10.0, *J* = 5.3, 4-CH_B); 2.65-2.71 (2H, m, 4-CH_A, 3-CH_B indoline); 2.85-2.93 (1H, m, 3-CH_A indoline); 4.68 (1H, sextet, *J* = 6.8, 2-CH); 5.51 (1H, dd, *J* = 11.0, *J* = 4.7, 2-CH indoline); 6.92 (1H, td, *J* = 7.5, *J* = 1.2, H Ar); 7.03 (1H, d, *J* = 7.6, H Ar); 7.13 (1H, t, *J* = 7.6, H Ar); 7.20 (1H, td, *J* = 7.5, *J* = 1.2, H Ar); 7.25-7.33 (5H, m, H Ar); 7.48 (1H, d, *J* = 7.8, H Ar); 7.68 (2H, d, *J* = 8.3, H Ts). Found, %: C 69.64; H 5.86; N 6.13; S 7.04. $C_{26}H_{26}N_2O_3S$. Calculated, %: C 69.93; H 5.87; N 6.27; S 7.18.

(3*S*,2'*S*)-3-Methyl-4-(*N*'-methyl-*N*'-tosylphenylalanyl)-2,3-dihydro-4*H*-1,4-benzoxazine ((*S*,*S*)-10b). Yield 167 mg (72%) after recrystallization from hexane–EtOAc mixture. Colorless powder. Mp 118-119°C. $[\alpha]_D^{20}$ -6.4° (*c* 1.1, $CHCl_3$). HPLC (hexane–2-PrOH, 80:1): *de* > 99%, τ_R 5.6 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.89 (3H, d, *J* = 6.8, 3-CH_3); 2.38 (3H, s, ArC<u>H</u>$_3$); 2.61 (1H, dd, *J* = 13.5, *J* = 6.6) and 3.03 (1H, dd, *J* = 13.5, *J* = 9.1, CH_2Ph); 3.00 (3H, s, NCH_3); 3.82 (1H, dd, *J* =11.0, *J* =2.9) and 4.10 (1H, dd, *J* = 11.0, *J* = 1.7, 2-CH_2); 4.71 (1H, qdd, *J* = 6.8, *J* = 2.9, *J* = 1.7, 3-CH); 5.30 (1H, br. t, *J* = 7.3, NCHCO); 6.83 (1H, dd, *J* = 8.2, *J* = 1.4, H-8); 6.90 (1H, ddd, *J* = 8.2, *J* = 7.2, *J* = 1.3, H-7); 6.92-6.97 (2H, m, H Ph); 7.07 (1H, ddd, *J* = 8.2, *J* = 7.2, *J* = 1.4, H-6); 7.11-7.18 (3H, m, H Ph); 7.35 (2H, d, *J* = 8.1, H Ts); 7.60 (2H, d, *J* = 8.1, H Ts); 7.66-7.69 (1H, dd, *J* = 8.2, *J* = 1.3, H-5). Found, %: C 67.03; H 6.40; N 5.70; S 6.89. $C_{26}H_{28}N_2O_4S$. Calculated, %: C 67.22; H 6.07; N 6.03; S 6.90.

(2*S*,2'*S*)-2-Methyl-*N*-(*N*'-methyl-*N*'-tosylphenylalanyl)-1,2,3,4-tetrahydroquinoline ((*S*,*S*)-10c). Yield 134 mg (58%) after flash chromatography. Colorless powder. Mp 105-107°C. $[\alpha]_D^{20}$ +119° (*c* 1.0, $CHCl_3$). HPLC (hexane–2-PrOH–MeOH, 1000:8:4): *de* > 99.6%, τ_R 7.0 min. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.93 (3H, d, *J* = 6.5, 2-CH_3); 1.17-1.25 (1H, m, 3-CH_B); 2.09-2.20 (2H, m, 3-CH_A, 3-CH_B phenylalanine); 2.35 (3H, s, ArC<u>H</u>$_3$); 2.48-2.54 (1H, m, 4-CH_B); 2.59-2.65 (2H, m, 4-CH_A, 3-CH_A phenylalanine); 3.03 (3H, s, NCH_3); 4.59 (1H, sextet, *J* = 6.8, 2-CH); 5.32 (1H, t, *J* = 7.5, NCHCO); 6.66 (2H, d, *J* = 7.3, H Ph); 7.03-7.31 (8H, m, H-5,6,7, H Ph, H Ts); 7.43 (1H, d, *J* = 7.9, H-8); 7.49 (2H, d, *J* = 8.2, H Ts). Found, *m*/*z*: 463.2054 $[M+H]^+$. $C_{27}H_{31}N_2O_3S$. Calculated, *m*/*z*: 463.2050.

X-ray diffraction study of amides (*R*,*S*)-5a, (*R*,*S*)-5c, and (*R*,*S*)-7b was performed on an Xcalibur-3 X-ray diffractometer with a CCD detector according to the standard procedure (λMoKα radiation, graphite monochromator, ω-scanning). The crystals for analysis were obtained by room temperature evaporation of MeOH or 2-PrOH solutions. The data were acquired and processed with the CrysAlis software package [38]. The structures of compounds were solved by direct method, using the SHELXS-97 software and refined with SHELXL-97 [39] in anisotropic approximation (isotropically for hydrogen atoms). The hydrogen atom positions were partially solved and refined independently, and partially included in the refinement according to the "rider" model with dependent thermal parameters. The X-ray structural analysis data were deposited at the

Cambridge Crystallographic Data Center (deposits CCDC 987552, CCDC 987553, CCDC 987554, respectively).

Compound (*R*,*S*)-5a ($C_{24}H_{22}F_2N_2O_4S$, *M* 472.50). Crystal dimensions 0.25×0.20×0.15 mm, a colorless prism. Triclinic syngony, *a* 6.8959(14), *b* 7.831(2), *c* 11.565(3) Å; α 103.74(4), β 96.90(3), γ 115.09(2)°; *V* 531.8(2) Å^3; space group *P*1; *Z* 1; d_{calc} 1.475 g/cm^3; μ 0.206 mm^{-1}; 3.01 < θ < 28.28. The completeness for θ ≤ 25.50° 96.8%. A total of 4075 reflections were collected (2487 independent, R_{int} 0.0229), 1512 reflections with $I > 2\sigma(I)$. *S* by F^2 1.002. The final refinement parameters: $R_1(I > 2\sigma(I))$ 0.0336, $wR_2(I > 2\sigma(I))$ 0.0609. R_1 0.0698 (all data), wR_2 0.0647 (all data).

Compound (*R*,*S*)-5c ($C_{25}H_{26}N_2O_3S$, *M* 434.54). Crystal dimensions 0.25×0.20×0.15 mm, a colorless prism. Trigonal syngony, *a* 10.2248(4), *b* 10.2248(4), *c* 18.2595(15) Å; α 90.00, β 90.00, γ 120.00°; *V* 1653.21(16) Å^3; space group $P3_1$; *Z* 3; d_{calc} 1.309 g/cm^3; μ 0.176 mm^{-1}; 3.20 < θ < 28.29. The completeness for θ ≤ 28.29° 99.9%. A total of 10798 reflections were collected (5109 independent, R_{int} 0.0230), 3647 reflections with $I > 2\sigma(I)$. *S* by F^2 1.000. The final refinement parameters: $R_1(I > 2\sigma(I))$ 0.0313, $wR_2(I > 2\sigma(I))$ 0.0524. R_1 0.0524 (all data), wR_2 0.053 (all data).

Compound (*R*,*S*)-7b ($C_{15}H_{20}N_2O_4S$, *M* 324.39). Crystal dimensions 0.24×0.19×0.12 mm, a colorless prism. Orthorhombic syngony, *a* 8.1623(4), *b* 9.5289(8), *c* 20.660(2) Å; α 90.00, β 90.90, γ 90.00°; *V* 1606.9(2) Å^3; space group $P2_12_12_1$; *Z* 4; d_{calc} 1.341 g/cm^3; μ 0.221 mm^{-1}; 2.68 < θ < 27.10. The completeness for θ ≤ 26.00° 98.1%. A total of 5837 reflections were collected (3320 independent, R_{int} 0.0290), 1800 reflections with $I > 2\sigma(I)$. *S* by F^2 1.000. The final refinement parameters: $R_1(I > 2\sigma(I))$ 0.0341, $wR_2(I > 2\sigma(I))$ 0.0564. R_1 0.0753 (all data), wR_2 0.0591 (all data).

The work was performed with financial support from the Russian Foundation for Basic Research (grants 13-03-00674, 13-03-12188), Ural Branch of the Russian Academy of Sciences (project 12-P-3-1030), and the Grants Council of the President of the Russian Federation (grant NSh-3656.2014.3).

The authors would like to express their gratitude to Candidate of Chemical Sciences P. A. Slepukhin for performing the X-ray diffraction.

REFERENCES

1. H. B. Kagan and J. C. Fiaud, *Top. Stereochem.*, **18**, 249 (1988).
2. M. Breuer, K. Ditrich, T. Habicher, B. Hauer, M. Keβeler, R. Stürmer, and T. Zelinski, *Angew. Chem., Int. Ed.*, **43**, 788 (2004).
3. C. E. Müller and P. R. Schreiner, *Angew. Chem., Int. Ed.*, **50**, 6012 (2011).
4. V. P. Krasnov, D. A. Gruzdev, and G. L. Levit, *Eur. J. Org. Chem.*, 1471 (2012).
5. E. Busto, V. Gotor-Fernández, and V. Gotor, *Chem. Rev.*, **111**, 3998 (2011).
6. W. Ding, M. Li, R. Dai, and Y. Deng, *Tetrahedron: Asymmetry*, **23**, 1376 (2012).
7. A. Hietanen, K. Lundell, L. T. Kanerva, and A. Liljeblad, *ARKIVOC*, v, 60 (2012).
8. F. O. Arp and G. C. Fu, *J. Am. Chem. Soc.*, **128**, 14264 (2006).
9. M. Anstiss and A. Nelson, *Org. Biomol. Chem.*, **4**, 4135 (2006).
10. M. Binanzer, S.-Y. Hsieh, and J. W. Bode, *J. Am. Chem. Soc.*, **133**, 19698 (2011).
11. I. Kreituss, Y. Murakami, M. Binanzer, and J. W. Bode, *Angew. Chem., Int. Ed.*, **51**, 10660 (2012).
12. S.-Y. Hsieh, M. Binanzer, I. Kreituss, and J. W. Bode, *Chem. Commun.*, 8892 (2012).
13. A. G. Al-Sehemi, R. S. Atkinson, J. Fawcett, and D. R. Russell, *Chem. Commun.*, 43 (2000).
14. A. G. Al-Sehemi, R. S. Atkinson, and C. K. Meades, *Chem. Commun.*, 2684 (2001).
15. A. G. Al-Sehemi, R. S. Atkinson, and J. Fawcett, *J. Chem. Soc., Perkin Trans. 1*, 257 (2002).
16. D. A. Gruzdev, G. L. Levit, V. P. Krasnov, E. N. Chulakov, L. Sh. Sadretdinova, A. N. Grishakov, M. A. Ezhikova, M. I. Kodess, and V. N. Charushin, *Tetrahedron: Asymmetry*, **21**, 936 (2010).

17. G. L. Levit, D. A. Gruzdev, V. P. Krasnov, E. N. Chulakov, L. Sh. Sadretdinova, M. A. Ezhikova, M. I. Kodess, and V. N. Charushin, *Tetrahedron: Asymmetry*, **22**, 185 (2011).
18. D. A. Gruzdev, G. L. Levit, M. I. Kodess, and V. P. Krasnov, *Khim. Geterotsikl. Soedin*, 805 (2012). [*Chem. Heterocycl. Compd.*, **48**, 748 (2012).]
19. D. A. Gruzdev, G. L. Levit, and V. P. Krasnov, *Tetrahedron: Asymmetry*, **23**, 1640 (2012).
20. D. A. Gruzdev, E. N. Chulakov, G. L. Levit, M. A. Ezhikova, M. I. Kodess, and V. P. Krasnov, *Tetrahedron: Asymmetry*, **24**, 1240 (2013).
21. V. N. Charushin, V. P. Krasnov, G. L. Levit, M. A. Korolyova, M. I. Kodess, O. N. Chupakhin, M. H. Kim, H. S. Lee, Y. J. Park, and K.-C. Kim, *Tetrahedron: Asymmetry*, **10**, 2691 (1999).
22. V. P. Krasnov, G. L. Levit, I. N. Andreyeva, A. N. Grishakov, V. N. Charushin, and O. N. Chupakhin, *Mendeleev Commun.*, **12**, 27 (2002).
23. E. N. Chulakov, D. A. Gruzdev, G. L. Levit, L. Sh. Sadretdinova V. P. Krasnov, and V. N. Charushin, *Izv. Acad. Nauk*, *Ser. Khim.*, 926 (2011). [*Russ. Chem. Bull.*, **60**, 948 (2011).]
24. E. N. Chulakov, G. L. Levit, A. A. Tumashov, L. Sh. Sadretdinova, and V. P. Krasnov, *Khim. Geterotsikl. Soedin*, 779 (2012). [*Chem. Heterocycl. Compd.*, **48**, 724 (2012).]
25. V. P. Krasnov, G. L. Levit, I. M. Bukrina, I. N. Andreeva, L. Sh. Sadretdinova, M. A. Korolyova, M. I. Kodess, V. N. Charushin, and O. N. Chupakhin, *Tetrahedron: Asymmetry*, **14**, 1985 (2003).
26. D. A. Gruzdev, S. A. Vakarov, G. L. Levit, and V. P. Krasnov, *Khim. Geterotsikl. Soedin*, 1936 (2013). [*Chem. Heterocycl. Compd.*, **49**, 1795 (2014).]
27. Y. Kacem, A. Bouraoui, V. Ratovelomanana-Vidal, J.-P. Genet, and B. Ben Hassine, *C. R. Chim.*, **5**, 611 (2002).
28. C. B. Hudson and A. V. Robertson, *Aust. J. Chem.*, **20**, 1935 (1967).
29. S. Hanessian and X. Wang, *Synlett*, 2803 (2009).
30. S. Guttmann, *Helv. Chim. Acta*, **44**, 721 (1961).
31. E. N. Chulakov, D. A. Gruzdev, G. L. Levit, K. V. Kudryavtsev, and V. P. Krasnov, *Tetrahedron: Asymmetry*, **23**, 1683 (2012).
32. I. Hayakawa, Y. Tanaka, and T. Hiramitsu, Eur. Pat. Appl. 0047005.
33. W. Oldham and I. B. Johns, *J. Am. Chem. Soc.*, **61**, 3289 (1939).
34. R. Shimizu, T. Kakimoto, K. Ishii, Y. Fujimoto, H. Nishi, and N. Tsumagari, *J. Chromatogr.*, **357**, 119 (1986).
35. E. Fischer and P. Bergell, *Ber. Dtsch. Chem. Ges.*, **35**, 3779 (1902).
36. T. Fujita, Y. Okuda, M. Yoshihara, and T. Maeshima, *J. Macromol. Sci.*, *Chem.*, **A25**, 327 (1988).
37. Y. Abe, S. Fukui, Y. Koshiji, M. Kobayashi, T. Shoji, S. Sugata, H. Nishizawa, H. Suzuki, and K. Iwata, *Biochim. Biophys. Acta*, *Protein Struct. Mol. Enzymol.*, **1433**, 188 (1999).
38. R. C. Clark and J. S. Reid, *Acta Crystallogr.*, *Sect. A: Found. Crystallogr.*, **A51**, 887 (1995).
39. G. M. Sheldrick, *Acta Crystallogr.*, *Sect. A: Found. Crystallogr.*, **A64**, 112 (2008).