Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 153–167

TETRAHEDRON: *ASYMMETRY*

Stereoselective synthesis of (*R*)- and (*S*)-2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylic acids, -carboxylates and -carboxamides

Matej Breznik, Valentina Hrast, Alenka Mrcina and Danijel Kikelj *

University of Ljubljana, Faculty of Pharmacy, Aškerčeva 7, 1000 Ljubljana, Slovenia

Received 6 November 1998; accepted 26 November 1998

Abstract

(*R*)-Monomethyl 2-methyl-2-(2-nitrophenoxy)malonates obtained by PLE catalyzed hydrolysis of the corresponding dimethyl malonates undergo solvent-dependent enantioselective cyclization to afford (*R*)-methyl 2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates and (*S*)-2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylic acids, respectively. These compounds are easily converted to enantiomerically and diastereomerically pure carboxamides, which are used as peptidomimetic building blocks.

1. Introduction

In the course of our ongoing research programme directed towards the design and synthesis of mimetics of biologically active peptides,[1,2] 2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylic acids **5** and derivatives thereof were envisaged as interesting peptidomimetic[3,4] building blocks. In order to investigate the influence of chirality on biological activity within the peptidomimetic class of compounds under study, pure enantiomers of these key synthons were required. Enantiomers of the parent compound, 2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylic acid (**5a**) became readily available by resolution of the racemic acid with (*R*)- and (*S*)-1-phenylethylamine. Unfortunately, the resolution method proved to be unsuccessful with compounds bearing a substituent bound to the aromatic ring.[5] Therefore, we sought an efficient stereoselective synthesis of the enantiomers of **5**, possibly from a common readily available chiral precursor. Recently, we briefly communicated the enantioselective synthesis of (*R*)- and (*S*)-2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamides **7** by cyclization of (*R*)-monomethyl 2-methyl-2-(2-nitrophenoxy)malonates **3**.[6] Now we report full

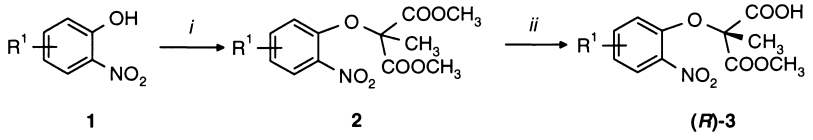
* Corresponding author. Fax: +386-61-125-80-31; e-mail: danijel.kikelj@ffa.uni-lj.si

0957-4166/99/$ - see front matter
PII: S0957-4166(98)00485-6

details of our studies on the stereoselective synthesis of (*R*)- and (*S*)-2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylic acids **5**, -carboxylates **4** and -carboxamides **7** based on selective cyclization of (*R*)-monomethyl 2-methyl-2-(2-nitrophenoxy)malonates **3** with the participation of the carboxy and the methoxycarbonyl group, respectively.

2. Results and discussion

The enantiomers of the title compounds were prepared starting from common chiral precursors, (*R*)-monomethyl 2-methyl-2-(2-nitrophenoxy)malonates **3**, most of which were prepared by us previously in a 69–81% enantiomeric excess by pig liver esterase (PLE) catalyzed hydrolysis of prochiral dimethyl 2-methyl-2-(2-nitrophenoxy)malonates **2** in a phosphate buffer (pH 7)/DMSO system.[7] Interestingly, we have found that if the enzymatic hydrolysis is performed in a phosphate buffer (pH 7):*N*,*N*-dimethylformamide (8:2) mixture, the (*R*)-monomethyl malonates **3** are obtained in a higher (73–88%) enantiomeric excess. The novel 3-methyl derivative **3b** was prepared from 3-methyl-2-nitrophenol **1b** using the alkylation method described by us previously[7] and PLE-catalyzed hydrolysis of the diester **2b** in the improved phosphate buffer/DMF system (Scheme 1).

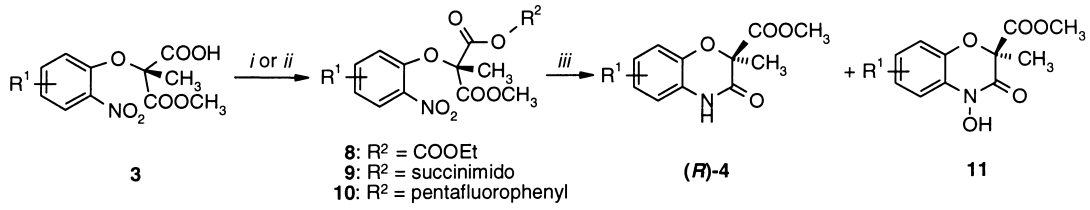


1-3	R1	Product 3 e.e.
a	H	87
b	3-Me	73
c	4-Me	85
d	5-Me	83
e	5-F	82
f	4-OMe	88

Scheme 1. i: $Br(CH_3)C(COOMe)_2$, KF, DMF, 60°C, 6 h; ii: PLE, buffer (pH 7):DMF (8:2), room temp., 24 h

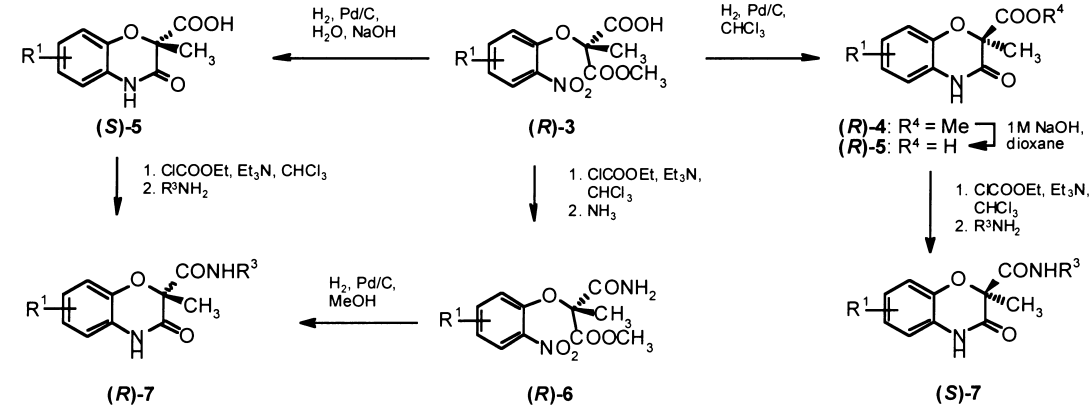
Initially, we anticipated that after reduction of the nitro group in (*R*)-**3** the expected more reactive ester moiety would participate in the cyclization to afford carboxylic acids (*S*)-**5**. However, the hydrogenolytic reduction of the chiral intermediates (*R*)-**3** in methanol, using palladium on charcoal as a catalyst after in situ cyclization, unexpectedly consistently afforded almost equimolar mixtures of carboxylic acids (*S*)-**5** and esters (*R*)-**4**. Therefore, we reasoned that for the selective cyclization over the methoxycarbonyl group, the carboxy group of (*R*)-**3** should be deactivated and, consequently, we found that a straightforward transformation of the chiral intermediates (*R*)-**3** to carboxamides (*R*)-**7A** is possible via conversion of the carboxylic acids (*R*)-**3** to carboxamides (*R*)-**6** using the mixed anhydride method,[8] reduction of the nitro group, and subsequent in situ cyclization of the resulting amine with participation of the ester group. For the synthesis of the opposite enantiomers, i.e. carboxamides (*S*)-**7A**, we tried to activate the carboxy group of (*R*)-**3** as mixed anhydride **8** and active ester with *N*-hydroxysuccinimide (**9**) or pentafluorophenol (**10**) to achieve sufficient difference in reactivity between the methoxycarbonyl and the activated carboxy group in the cyclization step. Unfortunately, in a very unclean reaction the 4-hydroxy derivatives **11** were always formed as major by-products after reduction and following in situ cyclization of the activated derivatives **8**, **9** and **10**. They were easily identified in the proton NMR spectra by the presence of a broad signal (N–OH) at ca. 11.0 ppm, accompanying the signal of the 4-NH proton of (*R*)-**4** at ca. 10.8 ppm.† The formation of these major by-products could be explained by the high reactivity of the activated carboxy group which can trap the 2-hydroxyamino intermediate[9] formed during reduction of the nitro group (Scheme 2).

† **11a** (R^1=H): ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.75 (s, 3H, CH_3), 3.65 (s, 3H, $COOCH_3$), 7.00–7.10 (m, 3H, Ar–H), 7.22 (d, 1H, *J*=7.3 Hz, Ar–H), 11.03 (s broad, 1H, NOH); MS (70 eV, EI): *m*/*z*=237 (M^+, 68%), 178 (100%).



Scheme 2. i: ClCOOEt, Et_3N, CH_2Cl_2; ii: *N*-hydroxysuccinimide or pentafluorophenol, DCC; iii: H_2, Pd/C (10%)

With the aim of obtaining the carboxamides (*S*)-**7A** our attention was focused on our earlier observation that, contrary to expectations based on the generally known reactivity of carboxylic acid derivatives, upon the reduction of (*R*)-**3** in methanol, a mixture of the ester (*R*)-**4** and carboxylic acid (*S*)-**5** was obtained. A systematic study of the catalytic hydrogenation of (*R*)-**3** in different solvents (chloroform, ethanol, methanol, isopropanol, acetic acid, tetrahydrofuran, water) was initiated with the purpose of finding a solvent pair in which selective cyclization of (*R*)-monomethyl 2-methyl-2-(2-aminophenoxy)malonates with the participation of the carboxy and methoxycarbonyl group, respectively, would be possible. As a result of these efforts we found that in situ cyclization of the aromatic amines obtained by hydrogenolytical reduction of (*R*)-**3** in chloroform afforded (*R*)-methyl 2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates **4** in a 60–80% yield, accompanied by small amounts of the corresponding (*S*)-2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylic acids **5** which could be easily separated simply by extraction. In contrast, when the reduction of (*R*)-**3** and in situ cyclization was performed in water in the presence of an equivalent amount of 0.1 N sodium hydroxide, the methoxycarbonyl group selectively participated in the cyclization step and (*S*)-2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylic acids **5** were obtained in good yields. The carboxylates (*R*)-**4** were efficiently transformed to carboxamides (*S*)-**7A** using standard chemistry by hydrolysis, subsequent activation of the resulting carboxylic acids (*R*)-**5** and reaction with amines. Similarly, carboxamides (*R*)-**7A** were obtained from carboxylic acids (*S*)-**5** (Scheme 3).



4,5,7	a	b	c	d	e	f
R^1	H	5-Me	6-Me	7-Me	7-F	6-OMe

7	Series A	Series B
R^3	H	(*R*) -CH(Bn)COOBn

Scheme 3.

The crude diastereomeric amides **7B** obtained by coupling of the carboxylic acids (*R*)-**4** and (*S*)-**4** with D-phenylalanine benzyl ester displayed a single set of signals in their ^1H NMR spectra, which, in

addition to the specific rotation values, confirmed the high enantiomeric purity of the products of this stereoselective synthesis.

In conclusion, the enantiomers of methyl 2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates **4a–f**, 2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylic acids **5a–f** and 2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamides **7aA–fA** with different substituents on the aromatic ring were efficiently prepared from common chiral precursors (*R*)-monomethyl 2-methyl-2-(2-nitrophenoxy)malonates **3**, employing a strategy of solvent- and derivatization-based reactivity manipulation of the carboxy group of **3**. The application of these compounds as building blocks for the construction of peptidomimetics will be reported elsewhere.

3. Experimental

Melting points were taken on a Reichert hot-stage microscope and are uncorrected. IR spectra were recorded on a Perkin–Elmer 1600 Series FTIR spectrometer as KBr discs for solids and neat films for oils. Optical rotations were measured on a Perkin–Elmer 1241 MC polarimeter. The reported values for specific rotation are average values of 10 successive measurements using an integration time of 10 s. Elemental analyses were performed at the Faculty of Chemistry and Chemical Engineering, University of Ljubljana on a Perkin–Elmer C, H, N-Analyzer 240 C. Mass spectra were obtained on an Autospec Q, VG-Analytical mass spectrometer using EI or FAB ionization. NMR spectra were obtained on a Bruker Avance DPX 300 instrument operating at 300.13 MHz for protons with tetramethylsilane as an internal standard. Pig liver esterase suspension in 3.2 M ammonium sulfate solution (activity 130 U/mg protein) was obtained from Fluka. The enzyme used in all experiments was from the same Fluka lot, no. 46063. Phosphate buffer (pH 7.00) was obtained from Merck. Enantiomeric excess determinations by the ^{1}H NMR method using (*R*)-1-methylbenzylamine as a chiral solvating agent were performed as described previously.[7] D-Phenylalanine benzyl ester *p*-toluenesulfonate[10] was synthesized according to a published procedure.

3.1. *Dimethyl 2-methyl-2-(3-methyl-2-nitrophenoxy)malonate* ***2b***

Dimethyl 2-bromo-2-methylmalonate[7] (20.25 g, 90 mmol) was added to a stirred suspension of potassium fluoride (13.07 g, 0.225 mol) in dry *N*,*N*-dimethylformamide (60 ml). After stirring for 15 min at room temperature, 3-methyl-2-nitrophenol (13.78 g, 90 mmol) was added. The resulting mixture was stirred for 6 h at 60°C, cooled to room temperature and poured into crushed ice/water (250 g). After dissolution of the ice, the aqueous solution was extracted with ether (3×200 ml), the ether phase was washed successively with 0.1 N sodium hydroxide (3×50 ml) and 0.1 N hydrochloric acid (3×50 ml), dried over sodium sulfate, filtered and evaporated in vacuo to give 23.0 g (86%) of **2b** as orange crystals, mp 84–86°C; IR (film): ν 2960, 1771, 1745, 1618, 1582, 1532, 1473, 1375, 1283, 1140, 967, 852, 770 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.77 (s, 3H, CH_3), 2.33 (s, 3H, Ar–CH_3), 3.84 (s, 6H, 2×$COOCH_3$), 6.91 (d, 1H, *J*=9.0 Hz, Ar–H), 6.98 (d, 1H, *J*=7.2 Hz, Ar–H), 7.25 (dd, 1H, Ar–H) ppm; MS (70 eV, EI): *m/z*=297 (M^+, 7%), 113 (100%). Anal. calcd for $C_{13}H_{15}NO_7$: C 52.56%, H 5.05%, N 4.71%. Found: C 52.58%, H 4.86%, N 4.62%.

3.2. (R)-(−)-Monomethyl 2-methyl-2-(3-methyl-2-nitrophenoxy)malonate (R)-3b. General procedure for PLE-catalyzed hydrolysis of 2a–f in a phosphate buffer:DMF (80:20) mixture

A buffer solution (pH=7, 150 ml) containing 0.6 ml of PLE suspension was added to a solution of dimethyl 2-methyl-2-(3-methyl-2-nitrophenoxy)malonate **2b** (1.48 g, 5 mmol) in DMF (40 ml). The mixture was stirred for 48 h at room temperature. During this time the pH remained constant. Then the reaction mixture was made alkaline by the addition of a saturated aqueous $NaHCO_3$ solution (25 ml) and washed with ether (3×50 ml). The aqueous phase was acidified with 4 M hydrochloric acid to pH 2–3 and extracted with ether (2×40 ml), saturated with NaCl and extracted again with ether (2×30 ml). The ether phase was washed with a saturated aqueous NaCl solution (2×25 ml), water (3×30 ml), dried over $MgSO_4$, filtered and evaporated in vacuo to afford 1.2 g (86%) of (*R*)-**3b** as a yellow oil; $[\alpha]_D^{20}=-1.40$ (c=0.63, methanol); IR (film): ν 3536, 2958, 1749, 1584, 1534, 1476, 1372, 1278, 1128 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.84 (s, 3H, CH_3), 2.35 (s, 3H, Ar–CH_3), 3.85 (s, 3H, $COOCH_3$), 5.45 (s broad, 1H, COOH), 6.86 (d, 1H, *J*=8.3 Hz, Ar–H), 7.01 (d, 1H, *J*=7.9 Hz, Ar–H), 7.27 (dd, 1H, Ar–H) ppm; MS (70 eV, EI): *m/z*=283 (M^+, 6%), 146 (100%). Anal. calcd for $C_{12}H_{13}NO_7 \cdot 0.25H_2O$: C 50.09%, H 4.69%, N 4.87%. Found: C 49.94%, H 4.35%, N 4.86%.

3.3. (R)-(−)-Methyl 2-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylate (R)-4a. General procedure for the synthesis of carboxylates (R)-4a–f

(*R*)-Monomethyl 2-methyl-2-(2-nitrophenoxy)malonate (*R*)-**3a** (538 mg, 2 mmol) was dissolved in ethanol free $CHCl_3$ (200 ml) and hydrogenated over 10% Pd/C (54 mg) for 24 h at normal pressure and room temperature. The catalyst was filtered off, the filtrate was extracted with saturated $NaHCO_3$ solution (3×50 ml), dried over $MgSO_4$ and evaporated in vacuo. The crude product was recrystallized from MeOH to constant specific rotation value;‡ yield: 0.36 g (81%), white crystals; mp 150–152°C (from MeOH), $[\alpha]_D^{20}$ (crude product)=−41.5 (c=0.53, MeOH); $[\alpha]_D^{20}$ (recrystallized product)=−41.8 (c=0.40, MeOH), Lit.:[5] $[\alpha]_D^{20}=-43.6$ (c=0.50, MeOH); IR (KBr): ν 3248, 1750, 1710, 1613, 1506, 1429, 1380, 1239, 1153, 1124, 974, 767, 750, 578, 529 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.69 (s, 3H, CH_3), 3.64 (s, 3H, $COOCH_3$), 6.88–7.03 (m, 4H, Ar–H), 10.92 (s broad, 1H, NH); MS (70 eV, EI): *m/z*=221 (M^+, 10%), 162 (100%). Anal. calcd for $C_{11}H_{11}NO_4$: C 59.73%, H 5.01%, N 6.33%. Found: C 60.10%, H 4.96%, N 6.00%.

3.4. (R)-(−)-Methyl 2,5-dimethyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylate (R)-4b

Prepared from (*R*)-**3b** (566 mg, 2 mmol); yield: 0.22 g (47%), white crystals; mp 137–140°C (from MeOH), $[\alpha]_D^{20}$ (crude product)=−71.7 (c=0.45, MeOH); $[\alpha]_D^{20}$ (recrystallized product)=−90.3 (c=0.39, MeOH); IR (KBr): ν 3210, 1735, 1687, 1498, 1476, 1444, 1394, 1265, 1120, 779, 609 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.68 (s, 3H, CH_3), 2.22 (s, 3H, Ar–CH_3), 3.62 (s, 3H, $COOCH_3$), 6.80–6.88 (m, 3H, Ar–H), 10.41 (s broad, 1H, NH); MS (70 eV, EI): *m/z*=235 (M^+, 53%), 176 (100%). Anal. calcd for $C_{12}H_{13}NO_4$: C 61.27%, H 5.57%, N 5.95%. Found: C 61.57%, H 5.52%, N 5.95%.

‡ During recrystallization from a minimal volume of methanol, a product of lower enantiomeric excess (containing the opposite enantiomer) separated first from a saturated solution. After approximately 10% of the theoretical amount of the product crystallized from a saturated solution, the crystals were filtered off and from the filtrate a product of higher enantiomeric excess was slowly deposited. This process was repeated (usually 2–3 times) until a product of constant specific rotation value was obtained.

3.5. (R)-(−)-Methyl 2,6-dimethyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylate (R)-**4c**

Prepared from (*R*)-**3c** (566 mg, 2 mmol); yield: 0.37 g (78%), pale pink crystals; mp 135–138°C (from MeOH), $[\alpha]_D^{20}$ (crude product)=−59.7 (c=0.49, MeOH); $[\alpha]_D^{20}$ (recrystallized product)=−66.4 (c=0.43, MeOH); IR (KBr): ν 3236, 1760, 1693, 1608, 1518, 1485, 1374, 1247, 1121, 978, 819, 741, 538 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.66 (s, 3H, CH_3), 2.21 (s, 3H, Ar–CH_3), 3.63 (s, 3H, $COOCH_3$), 6.68 (d, 1H, *J*=1.9 Hz, Ar–H), 6.75 (ddd, 1H, *J*=8.3, 1.9, 0.8 Hz, Ar–H), 6.88 (d, 1H, *J*=8.3 Hz, Ar–H), 10.86 (s broad, 1H, NH); MS (70 eV, EI): *m/z*=235 (M^+, 39%), 176 (100%). Anal. calcd for $C_{12}H_{13}NO_4$: C 61.27%, H 5.57%, N 5.95%. Found: C 61.55%, H 5.53%, N 6.17%.

3.6. (R)-(−)-Methyl 2,7-dimethyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylate (R)-**4d**

Prepared from (*R*)-**3d** (566 mg, 2 mmol); yield: 0.34 g (73%), white crystals; mp 137–139°C (from MeOH), $[\alpha]_D^{20}$ (crude product)=−12.3 (c=0.50, MeOH); $[\alpha]_D^{20}$ (recrystallized product)=−13.7 (c=0.46, MeOH); IR (KBr): ν 3198, 3066, 1752, 1687, 1517, 1447, 1385, 1261, 1120, 987, 805, 579 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.67 (s, 3H, CH_3), 2.22 (s, 3H, Ar–CH_3), 3.64 (s, 3H, $COOCH_3$), 6.77 (s, 2H, Ar–H), 6.83 (s, 1H, Ar–H), 10.82 (s broad, 1H, NH); MS (70 eV, EI): *m/z*=235 (M^+, 49%), 176 (100%). Anal. calcd for $C_{12}H_{13}NO_4$: C 61.27%, H 5.57%, N 5.95%. Found: C 61.45%, H 5.60%, N 6.15%.

3.7. (R)-(−)-Methyl 7-fluoro-2-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylate (R)-**4e**

Prepared from (*R*)-**3e** (574 mg, 2 mmol); yield: 0.33 g (70%), pale pink crystals; mp 152–154°C (from MeOH), $[\alpha]_D^{20}$ (crude product)=−22.1 (c=0.51, MeOH); $[\alpha]_D^{20}$ (recrystallized product)=−24.6 (c=0.55, MeOH); IR (KBr): ν 3273, 2952, 1748, 1712, 1674, 1621, 1517, 1418, 1248, 1151, 1125, 995, 844, 752, 612, 526 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.70 (s, 3H, CH_3), 3.66 (s, 3H, $COOCH_3$), 6.81–6.99 (m, 3H, Ar–H), 10.97 (s broad, 1H, NH); MS (70 eV, EI): *m/z*=239 (M^+, 57%), 180 (100%). Anal. calcd for $C_{11}H_{10}FNO_4$: C 55.23, H 4.21, N 5.86. Found: C 55.03%, H 4.16%, N 6.00%.

3.8. (R)-(−)-Methyl 6-methoxy-2-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylate (R)-**4f**

Prepared from (*R*)-**3f** (598 mg, 2 mmol); yield: 0.40 g (80%), white crystals; mp 124–127°C (from MeOH), $[\alpha]_D^{20}$ (crude product)=−73.0 (c=0.51, MeOH); $[\alpha]_D^{20}$ (recrystallized product)=−88.0 (c=0.51, MeOH); IR (KBr): ν 3266, 2959, 1753, 1702, 1623, 1518, 1485, 1373, 1314, 1266, 1228, 1157, 1120, 1035, 977, 866, 758, 646, 529 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.62 (s, 3H, CH_3), 3.60 (s, 3H, $COOCH_3$), 3.66 (s, 3H, OCH_3), 6.42 (d, 1H, *J*=2.9 Hz, Ar–H), 6.49 (dd, 1H, *J*=8.6, 2.9 Hz, Ar–H), 6.90 (d, 1H, *J*=8.6 Hz, Ar–H), 10.81 (s broad, 1H, NH); MS (70 eV, EI): *m/z*=251 (M^+, 53%), 192 (100%). Anal. calcd for $C_{12}H_{13}NO_5$: C 57.37%, H 5.22%, N 5.58%. Found: C 57.10%, H 5.20%, N 5.44%.

3.9. (S)-(+)-2-Methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylic acid (S)-**5a**. General procedure for the synthesis of carboxylic acids (S)-**5a–f**

(*R*)-Monomethyl 2-methyl-2-(2-nitrophenoxy)malonate (*R*)-**3a** (538 mg, 2 mmol) was dissolved in water (50 ml). An equivalent amount of 0.1 M NaOH (20.0 ml, 20 mmol) was added and the mixture was hydrogenated over 10% Pd/C (54 mg) for 24 h at normal pressure and room temperature. The catalyst

was filtered off, the filtrate was acidified with 1 M HCl and extracted with ethyl acetate (4×30 ml), dried over $MgSO_4$ and evaporated in vacuo. The crude product was recrystallized from MeOH to constant specific rotation value;[‡] yield: 327 mg (79%), white crystals; mp 195–199°C (from MeOH), $[\alpha]_D^{20}$ (crude product)=+65.4 (c=0.45, MeOH); $[\alpha]_D^{20}$ (recrystallized product)=+71.3 (c=0.34, MeOH); IR (KBr): ν 3186, 3063, 1759, 1661, 1608, 1502, 1406, 1233, 1145, 968, 768, 653, 584 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.66 (s, 3H, CH_3), 6.86–7.00 (m, 4H, Ar–H), 10.78 (s broad, 1H, NH), 13.5 (s broad, 1H, COOH); MS (70 eV, EI): *m/z*=207 (M^+, 29%), 163 (100%). Anal. calcd for $C_{10}H_9NO_4$: C 58.00%, H 4.35%, N 6.76%. Found: C 57.98%, H 4.36%, N 6.73%.

*3.10. (S)-(+)-2,5-Dimethyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylic acid (S)-**5b***

Prepared from (*R*)-**3b** (566 mg, 2 mmol); yield: 358 mg (81%), white crystals; mp 197–200°C (from MeOH), $[\alpha]_D^{20}$ (crude product)=+82.9 (c=0.56, MeOH); $[\alpha]_D^{20}$ (recrystallized product)=+112.5 (c=0.39, MeOH); IR (KBr): ν 3219, 2496, 1730, 1654, 1481, 1440, 1372, 1264, 1225, 1152, 972, 778, 725, 605, 501 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.66 (s, 3H, CH_3), 2.22 (s, 3H, Ar–CH_3), 6.80–6.86 (m, 3H, Ar–H), 10.28 (s broad, 1H, NH), 13.45 (s broad, 1H, COOH); MS (70 eV, EI): *m/z*=221 (M^+, 28%), 177 (100%). Anal. calcd for $C_{11}H_{11}NO_4$: C 59.76% H 4.98% N 6.33%. Found: C 59.62%, H 5.07%, N 6.23%.

*3.11. (S)-(+)-2,6-Dimethyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylic acid (S)-**5c***

Prepared from (*R*)-**3c** (566 mg, 2 mmol); yield: 371 mg (84%), white crystals; mp 181–183°C (from MeOH), $[\alpha]_D^{20}$ (recrystallized product)=+85.1 (c=0.52, MeOH);[§] IR (KBr): ν 3254, 1737, 1677, 1608, 1519, 1491, 1396, 1237, 1130, 865, 822, 740, 691, 533 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.64 (s, 3H, CH_3), 2.21 (s, 3H, Ar–CH_3), 6.68 (d, 1H, *J*=1.8 Hz, Ar–H), 6.73 (dd, 1H, *J*=7.9, 1.8 Hz, Ar–H), 6.86 (d, 1H, *J*=7.9 Hz, Ar–H), 10.72 (s broad, 1H, NH), 13.4 (s broad, 1H, COOH); MS (70 eV, EI): *m/z*=221 (M^+, 2.6%), 177 (100%). Anal. calcd for $C_{11}H_{11}NO_4$: C 59.76%, H 4.98%, N 6.33%. Found: C 59.64%, H 4.80%, N 6.45%.

*3.12. (S)-(+)-2,7-Dimethyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylic acid (S)-**5d***

Prepared from (*R*)-**3d** (566 mg, 2 mmol); yield: 407 mg (92%), white crystals; mp 180–183°C (from MeOH), $[\alpha]_D^{20}$ (crude product)=+21.4 (c=0.51, MeOH); $[\alpha]_D^{20}$ (recrystallized product)=+28.2 (c=0.02, MeOH);[§] IR (KBr): ν 3237, 1739, 1669, 1518, 1383, 1302, 1241, 1210, 1139, 976, 814, 719 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.64 (s, 3H, CH_3), 2.22 (s, 3H, Ar–CH_3), 6.76 (s, 1H, Ar–H), 6.77 (s, 1H, Ar–H), 6.81 (s, 1H, Ar–H), 10.68 (s broad, 1H, NH), 13.45 (s broad, 1H, COOH); MS (70 eV, EI): *m/z*=221 (M^+, 28%), 177 (100%). Anal. calcd for $C_{11}H_{11}NO_4 \cdot 0.25H_2O$: C 58.57%, H 5.10%, N 6.21%. Found: C 58.91%, H 4.97%, N 6.22%.

*3.13. (S)-(+)-7-Fluoro-2-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylic acid (S)-**5e***

Prepared from (*R*)-**3e** (574 mg, 2 mmol); yield: 396 mg (88%), white crystals; mp 168–170°C (from MeOH); $[\alpha]_D^{20}$ (recrystallized product)=+34.9 (c=0.41, MeOH); IR (KBr): ν 3178, 1741, 1654, 1521,

[§] Not recrystallized further due to a limited quantity of substance.

1429, 1276, 1151, 956, 851, 806, 764 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.67 (s, 3H, CH_3), 6.78–6.90 (m, 2H, Ar–H), 6.94 (dd, 1H, *J*=2.6, 9.8 Hz, Ar–H), 10.83 (s broad, 1H, NH), 13.4 (s broad, 1H, COOH). MS (70 eV, EI): *m/z*=225 (M^+, 37%), 181 (100%). Anal. calcd for $C_{10}H_8FNO_4$: C 53.37%, H 3.55%, N 6.22%. Found: C 53.15%, H 3.75%, N 6.11%.

*3.14. (S)-(+)-6-Methoxy-2-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylic acid (S)-**5f***

Prepared from (*R*)-**3f** (598 mg, 2 mmol); yield: 388 mg (82%), white crystals; mp 175–182°C (from MeOH); $[\alpha]_D^{20}$ (recrystallized product)=+82.0 (c=0.12, MeOH); IR (KBr): ν 3219, 2938, 1734, 1669, 1515, 1233, 1032 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.62 (s, 3H, CH_3), 3.68 (s, 3H, OCH_3), 6.45 (d, 1H, *J*=2.9 Hz, Ar–H), 6.50 (dd, 1H, *J*=8.7, 2.9 Hz, Ar–H), 6.91 (d, 1H, *J*=8.7 Hz, Ar–H), 10.70 (s broad, 1H, NH), 13.50 (s broad, 1H, COOH); MS (70 eV, EI): *m/z*=237 (M^+, 25%), 193 (100%). Anal. calcd for $C_{11}H_{11}NO_5$: C 55.70%, H 4.67%, N 5.90%. Found: C 55.82%, H 5.03%, N 5.98%.

*3.15. (R)-(−)-2-Methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylic acid (R)-**5a**. General procedure for hydrolysis of methyl esters (R)-**4a–f***

A solution of (*R*)-**4a** (221 mg, 1 mmol) and 1 M NaOH (1.2 ml, 1.2 mmol) in dioxane (5 ml) was stirred at room temperature overnight and then evaporated in vacuo. The residue was dissolved in water (6 ml), the solution was acidified to pH 1–2 with 1 M HCl and the precipitated product was isolated by filtration; yield: 184 mg (89%); $[\alpha]_D^{20}$ (crude product)=−68.8 (c=0.50, MeOH). The product was in all other respects identical to (*S*)-**5a** obtained by cyclization from (*R*)-**3a**.

*3.16. (R)-(−)-2,5-Dimethyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylic acid (R)-**5b***

Prepared from (*R*)-**4b** (235 mg, 1 mmol); yield: 210 mg (95%); $[\alpha]_D^{20}$ (crude product)=−109.8 (c=0.321, MeOH). The product was in all other respects identical to (*S*)-**5b** obtained by cyclization from (*R*)-**3b**.

*3.17. (R)-(−)-2,6-Dimethyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylic acid (R)-**5c***

Prepared from (*R*)-**4c** (235 mg, 1 mmol); yield: 206 mg (93%); $[\alpha]_D^{20}$ (crude product)=−79.6 (c=0.35, MeOH); $[\alpha]_D^{20}$ (recrystallized product)=−93.5 (c=0.37, MeOH). The product was in all other respects identical to (*S*)-**5c** obtained by cyclization from (*R*)-**3c**.

*3.18. (R)-(−)-2,7-Dimethyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylic acid (R)-**5d***

Prepared from (*R*)-**4d** (235 mg, 1 mmol); yield: 206 mg (93%); $[\alpha]_D^{20}$ (crude product)=−29.6 (c=0.40, MeOH); $[\alpha]_D^{20}$ (recrystallized product)=−30.9 (c=0.44, MeOH). The product was in all other respects identical to (*S*)-**5d** obtained by cyclization from (*R*)-**3d**.

*3.19. (R)-(−)-7-Fluoro-2-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylic acid (R)-**5e***

Prepared from (*R*)-**4e** (239 mg, 1 mmol); yield: 211 mg (94%); $[\alpha]_D^{20}$ (crude product)=−30.2 (c=0.42, MeOH). The product was in all other respects identical to (*S*)-**5e** obtained by cyclization from (*R*)-**3e**.

3.20. (R)-(−)-6-Methoxy-2-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylic acid (R)-5f

Prepared from (*R*)-**4f** (251 mg, 1 mmol); yield: 215 mg (91%); $[\alpha]_D^{20}$ (recrystallized product)=−83.4 (c=1.0, MeOH). The product was in all other respects identical to (*S*)-**5f** obtained by cyclization from (*R*)-**3f**.

3.21. General procedure for the synthesis of carboxamides 6 and 7 from carboxylic acids 3 and 5

To a stirred solution of a carboxylic acid **3** or **5** (1 mmol) in ethanol free $CHCl_3$ (15 ml) cooled to −15°C were added, successively, Et_3N [0.172 ml (1.25 mmol) for the reaction with ammonia or 0.348 ml (2.50 mmol) for the reaction with phenylalanine benzyl ester *p*-toluenesulfonate)] and ethyl chloroformate (0.109 ml, 1.15 mmol). After 0.5 h a slow stream of ammonia was passed through the mixture for 20 min, whereby the temperature of the mixture was not allowed to exceed 10°C, and phenylalanine benzyl ester *p*-toluenesulfonate (427 mg, 1 mmol) was added. The mixture was stirred for 1 h whereupon the solvent was evaporated in vacuo and the residue dissolved in ethyl acetate (50 ml). The solution was washed successively with 1 N HCl (3×20 ml), water (3×20 ml) and brine (20 ml), dried over $MgSO_4$, filtered and evaporated in vacuo. The crude product was used as such (**6**), recrystallized from methanol (unsubstituted carboxamides **7A**) or triturated with hexane and when necessary purified by column chromatography (phenylalanine derivatives **7B**).

3.22. (R)-(−)-Methyl 2-carbamoyl-2-(2-nitrophenoxy)propanoate (R)-6a

Prepared from (*R*)-**3a** (1.076 g, 4 mmol); yield: 0.804 g (75%), yellow oil; $[\alpha]_D^{20}$=−21.6 (c=0.82, MeOH); IR (KBr): ν 3463, 1748, 1704, 1606, 1525, 1484, 1349, 1277, 1127, 746 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.69 (s, 3H, CH_3), 3.73 (s, 3H, $COOCH_3$), 7.02 (dd, 1H, *J*=8.5, 1.0 Hz, Ar–H), 7.25–7.30 (ddd, 1H, *J*=8.1, 7.4, 1.0 Hz, Ar–H), 7.45 (s broad, 1H, $CONH_2$), 7.67 (ddd, 1H, *J*=8.5, 7.4, 1.7 Hz, Ar–H), 7.92 (s broad, 1H, $CONH_2$), 7.99 (dd, 1H, *J*=8.1, 1.7 Hz, Ar–H); MS (70 eV, EI): *m/z*=269 (MH^+, 1%), 123 (100%). Anal. calcd for $C_{11}H_{12}N_2O_6 \cdot 0.25H_2O$: C 48.44%, H 4.58%, N 10.27%. Found: C 48.55%, H 4.44%, N 9.74%.

3.23. (R)-(−)-Methyl 2-carbamoyl-2-(4-methyl-2-nitrophenoxy)propanoate (R)-6c

Prepared from (*R*)-**3c** (1.132 g, 4 mmol); yield: 0.96 g (85%), white crystals, mp 115–117°C (from MeOH); $[\alpha]_D^{20}$=−15.2 (c=0.44, MeOH); IR (KBr): ν 3442, 3246, 2957, 1749, 1677, 1533, 1393, 1342, 1277, 1248, 1120, 980, 828, 780 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.64, 3H, CH_3), 2.33 (s, 3H, Ar–CH_3), 3.72 (s, 3H, $COOCH_3$), 6.92 (d, 1H, *J*=8.6 Hz, Ar–H), 7.43 (s broad, 1H, $CONH_2$), 7.47 (dd, 1H, *J*=8.6, 2.2 Hz, Ar–H), 7.81 (d, 1H, *J*=2.2 Hz, Ar–H), 7.89 (s broad, 1H, $CONH_2$). MS (70 eV, EI): *m/z*=283 (MH^+, 1.5%), 136 (100%). Anal. calcd for $C_{12}H_{14}N_2O_6$: C 51.06%, H 5.00%, N 9.93%. Found: C 50.76%, H 5.08%, N 9.98%.

3.24. (R)-(+)-Methyl 2-carbamoyl-2-(5-methyl-2-nitrophenoxy)propanoate (R)-**6d**[¶]

Prepared from (*R*)-**3d** (1.128 g, 4 mmol); yield: 0.871 g (77%), white crystals, mp 141–144°C (from MeOH); $[\alpha]_D^{20}$=+4.8 (c=0.36, MeOH); IR (KBr): ν 3420, 3161, 1751, 1701, 1590, 1508, 1388, 1273, 1121, 927, 817 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.69 (s, 3H, CH_3), 2.37 (s, 3H, Ar–CH_3), 3.73 (s, 3H, $COOCH_3$), 6.76 (s, 1H, Ar–H), 7.07–7.10 (m, 1H, Ar–H), 7.45 (s broad, 1H, $CONH_2$), 7.90–7.93 (m, 2H, Ar–H, $CONH_2$); MS (70 eV, EI): *m/z*=283 (MH^+, 1%), 236 (100%).

3.25. (R)-(−)-Methyl 2-carbamoyl-2-(5-fluoro-2-nitrophenoxy)propanoate (R)-**6e**

Prepared from (*R*)-**3e** (1.148 g, 4 mmol); yield: 0.938 g (82%), white crystals, mp 148–151°C (from MeOH); $[\alpha]_D^{20}$=−22.8 (c=0.43, MeOH); IR (KBr): ν 3429, 3249, 1750, 1703, 1592, 1522, 1342, 1283, 1136, 988, 859, 608 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.76 (s, 3H, CH_3), 3.76 (s, 3H, $COOCH_3$), 6.84 (dd, 1H, *J*=10.3, 2.5 Hz, Ar–H), 7.16 (ddd, 1H, *J*=9.2, 7.8, 2.5 Hz, Ar–H), 7.55 (s broad, 1H, $CONH_2$), 7.94 (s broad, 1H, $CONH_2$), 8.13 (dd, 1H, *J*=9.2, 6.0 Hz, Ar–H); MS (70 eV, EI): *m/z*=287 (MH^+, 2%), 141 (100%). Anal. calcd for $C_{11}H_{11}FN_2O_6$: C 46.16%, H 3.87%, N 9.78%. Found: C 46.58%, H 3.70%, N 10.17%.

3.26. (R)-(−)-Methyl 2-carbamoyl-2-(4-methoxy-2-nitrophenoxy)propanoate (R)-**6f**

Prepared from (*R*)-**3f** (1.196 g, 4 mmol); yield: 0.953 g (80%), white crystals, mp 114–115°C (from MeOH); $[\alpha]_D^{20}$=−9.9 (c=0.42, MeOH); IR (KBr): ν 3377, 3210, 1700, 1618, 1509, 1336, 1158, 990, 808, 606 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.57 (s, 3H, CH_3), 3.72 (s, 3H, $COOCH_3$), 3.80 (s, 3H, OCH_3), 7.01 (d, 1H, *J*=9.2 Hz, Ar–H), 7.25 (dd, 1H, *J*=9.2, 3.2 Hz, Ar–H), 7.46 (s, 1H, $CONH_2$), 7.51 (d, 1H, *J*=3.2 Hz, Ar–H), 7.85 (s broad, 1H, $CONH_2$); MS (70 eV, EI): *m/z*=298 (M^+, 15%), 169 (100%). Anal. calcd for $C_{12}H_{14}N_2O_7$: C 48.32%, H 4.73%, N 9.39%. Found: C 48.16%, H 4.35%, N 9.55%.

3.27. (R)-(+)-2-Methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-2-carboxamide (R)-**7aA**

Prepared from (*S*)-**5a** (207 mg, 1 mmol); yield: 115 mg (56%), white crystals; mp 222–225°C (from MeOH); $[\alpha]_D^{20}$ (recrystallized product)=+81.6 (c=0.13, MeOH); IR (KBr): ν 3374, 3222, 1701, 1613, 1503, 1356, 1235, 1153, 756 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.63 (s, 3H, CH_3), 6.84–6.87 (m, 1H, Ar–H), 6.92–6.96 (m, 2H, Ar–H), 7.05–7.08 (m, 1H, Ar–H), 7.35 (s broad, 1H, $CONH_2$), 7.55 (s broad, 1H, $CONH_2$), 10.65 (s broad, 1H, NH); MS (70 eV, EI): *m/z*=206 (M^+, 10%), 162 (100%). Anal. calcd for $C_{10}H_{10}N_2O_3$: C 58.25%, H 4.89%, N 13.59%. Found: C 58.24%, H 4.94%, N 13.47%.

Prepared from (*R*)-**6a** (268 mg, 1 mmol); yield: 144 mg (70%); $[\alpha]_D^{20}$ (recrystallized product)=+77.7 (c=0.11, MeOH). The product was in all other respects identical to (*R*)-**7aA** described earlier.

[¶] Compound (*R*)-**6d** is the only compound in this carboxamide series which showed a positive specific rotation in methanol. However, there are several instances where closely related substances with the same absolute configuration rotate the plane of the plane-polarized light in different directions.[7,11]

*3.28. (S)-(−)-2-Methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-2-carboxamide (S)-**7aA***

Prepared from (*R*)-**5a** (207 mg, 1 mmol); yield: 146 mg (71%), white crystals; mp 224–226°C (from MeOH); $[\alpha]_D^{20}$ (crude product)=−69.6 (c=0.09, MeOH).§ The product was in all other respects identical to (*R*)-**7aA**.

*3.29. (R)-(+)-2,5-Dimethyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-2-carboxamide (R)-**7bA***

Prepared from (*S*)-**5b** (221 mg, 1 mmol); yield: 130 mg (59%), white crystals; mp 221–223°C (from MeOH); $[\alpha]_D^{20}$ (recrystallized product)=+116.2 (c=0.07, MeOH). The product was in all other respects identical to (*S*)-**7bA** described later.

*3.30. (S)-(−)-2,5-Dimethyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-2-carboxamide (S)-**7bA***

Prepared from (*R*)-**5b** (221 mg, 1 mmol); yield: 158 mg (72%), white crystals; mp 222–226°C (from MeOH); $[\alpha]_D^{20}$ (recrystallized product)=−113.9 (c=0.09, MeOH); IR (KBr): ν 3458, 2924, 2854, 1702, 1475, 1360, 1135, 1034, 973, 782, 727, 603, 502 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.63 (s, 3H, CH_3), 2.20 (s, 3H, Ar–CH_3), 6.79–6.87 (m, 2H, Ar–H), 6.93 (dd, 1H, Ar–H, *J*=7.5, 1.9 Hz), 7.32 (s broad, 1H, $CONH_2$), 7.52 (s broad, 1H, $CONH_2$), 10.16 (s broad, 1H, NH); MS (70 eV, EI): *m/z*=220 (M^+, 50%), 177 (100%); HRMS: calcd: 220.084792. Found: 220.085065.

*3.31. (R)-(+)-2,6-Dimethyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-2-carboxamide (R)-**7cA***

Prepared from (*R*)-**6c** (282 mg, 1 mmol); yield: 185 mg (84%); white crystals, mp 292–293°C (from MeOH); $[\alpha]_D^{20}$=+87.4 (c=0.16, MeOH). The product was in all other respects identical to (*S*)-**7cA** described later.

*3.32. (S)-(−)-2,6-Dimethyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-2-carboxamide (S)-**7cA***

Prepared from (*R*)-**5c** (221 mg, 1 mmol); yield: 154 mg (70%), white crystals; mp 302–304°C (from MeOH), $[\alpha]_D^{20}$=−87.6 (c=0.16, MeOH); IR (KBr): ν 3376, 3154, 1699, 1609, 1520, 1495, 1361, 1237, 1151, 814 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.61 (s, 3H, CH_3), 2.20 (s, 3H, Ar–CH_3), 6.65 (d, 1H, *J*=1.8 Hz, Ar–H), 6.72 (dd, 1H, *J*=8.1, 1.8 Hz, Ar–H), 6.94 (d, 1H, *J*=8.1 Hz, Ar–H), 7.32 (s broad, 1H, $CONH_2$), 7.51 (s broad, 1H, $CONH_2$) 10.58 (s broad, 1H, NH); MS (70 eV, EI): *m/z*=220 (M^+, 45%), 177 (100%). Anal. calcd for $C_{11}H_{12}N_2O_3$: C 59.99%, H 5.49%, N 12.72%. Found: C 59.72%, H 5.48%, N 12.59%.

*3.33. (S)-(−)-2,7-Dimethyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-2-carboxamide (S)-**7dA***

Prepared from (*R*)-**5d** (221 mg, 1 mmol); yield: 116 mg (53%), white crystals; mp 386–290°C (from MeOH), $[\alpha]_D^{20}$=−39.0 (c=0.10, MeOH); IR (KBr): ν 3375 3199, 1699, 1698, 1518, 1157, 807 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.62 (s, 3H, CH_3), 2.22 (s, 3H, Ar–CH_3), 6.72–6.88 (m, 2H, Ar–H), 6.88 (s, 1H, Ar–H), 7.33 (s broad, 1H, $CONH_2$), 7.50 (s broad, 1H, $CONH_2$) 10.54 (s broad, 1H, NH); MS (70 eV, EI): *m/z*=220 (M^+, 45%), 177 (100%). Anal. calcd for $C_{11}H_{12}N_2O_3$: C 59.99%, H 5.49%, N 12.72%. Found: C 60.01%, H 5.39%, N 12.88%.

*3.34. (*R*)-(+)-7-Fluoro-2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (*R*)-**7eA***

Prepared from (*R*)-**6e** (286 mg, 1 mmol); yield: 168 mg (75%), white crystals; mp 232–237°C (from MeOH); $[\alpha]_D^{20}$ (recrystallized product)=+34.7 (c=0.12, MeOH);§ IR (KBr): ν 3377, 3210, 1700, 1509, 1336, 1158, 992, 860, 808 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.64 (s, 3H, CH_3), 6.80–6.86 (m, 2H, Ar–H), 6.96 (dd, 1H, *J*=9.5, 2.3 Hz, Ar–H), 7.41 (s broad, 1H, $CONH_2$), 7.58 (s broad, 1H, $CONH_2$), 10.69 (s broad, 1H, NH); MS (70 eV, EI): *m/z*=224 (M^+, 35%), 181 (100%). Anal. calcd for $C_{10}H_9FN_2O_3$: C 53.58%, H 4.05%, N 12.50%. Found: C 53.60%, H 4.06%, N 12.45%.

*3.35. (*S*)-(−)-7-Fluoro-2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (*S*)-**7eA***

Prepared from (*R*)-**5e** (225 mg, 1 mmol); yield: 128 mg (57%), white crystals; mp 236–240°C (from MeOH); $[\alpha]_D^{20}$ (recrystallized product)=−36.9 (c=0.10, MeOH). The product was in all other respects identical to (*R*)-**7eA** described earlier.

*3.36. (*R*)-(+)-6-Methoxy-2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (*R*)-**7fA***

Prepared from (*R*)-**6f** (299 mg, 1 mmol); yield: 217 mg (92%), white crystals; mp 252–255°C (from MeOH); $[\alpha]_D^{20}$ (recrystallized product)=+81.3 (c=0.47, MeOH); IR (KBr): ν 3374, 3214, 1696, 1513, 643 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.60 (s, 3H, CH_3), 3.67 (s, 3H, CH_3), 6.42 (d, 1H, *J*=2.9 Hz, Ar–H), 6.50 (dd, 1H, *J*=8.8, 2.9 Hz, Ar–H), 6.99 (d, 1H, *J*=8.8 Hz, Ar–H), 7.33 (s broad, 1H, $CONH_2$), 7.54 (s broad, 1H, $CONH_2$), 10.56 (s broad, 1H, NH); MS (70 eV, EI): *m/z*=236 (M^+, 65%), 192 (100%). Anal. calcd for $C_{11}H_{12}N_2O_4$: C 55.93%, H 5.12%, N 11.86%. Found: C 55.94%, H 5.02%, N 11.90%.

*3.37. (*S*)-(−)-6-Methoxy-2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide (*S*)-**7fA***

Prepared from (*R*)-**5f** (237 mg, 1 mmol); yield: 206 mg (85%), white crystals; mp 254–258°C (from MeOH); $[\alpha]_D^{20}$ (recrystallized product)=−75.4 (c=0.29, MeOH).§ The product was in all other respects identical to (*R*)-**7fA** described earlier.

3.38. N-*{[(2*S*)-2,5-Dimethyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-yl]carbonyl}-*D*-phenylalanine benzyl ester (2*S*)-**7bB***

Prepared from (*R*)-**5b** (221 mg, 1 mmol); yield: 394 mg (86%), white solid foam; mp 46–48°C, $[\alpha]_D^{20}$=−31.3 (c=0.10, MeOH); IR (KBr): ν 3412, 1705, 1498, 1376, 1277, 1175, 699 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.59 (s, 3H, CH_3), 2.16 (s, 3H, Ar–CH_3), 2.97 (ABX-system, 2H, J_{AB}=13.9 Hz, J_{AX}=9.8 Hz, J_{BX}=4.1 Hz, CHCH_2Ph), 4.32–4.40 (m, 1H, CH), 5.09 (AB-system, 2H, *J*=12.4 Hz, $COOCH_2$Ph), 6.80–6.82 (m, 2H, Ar–H), 6.84–6.93 (m, 3H, Ar–H), 7.05–7.14 (m, 3H, Ar–H), 7.28–7.42 (m, 5H, Ar–H), 8.45 (d broad, 1H, CONH, *J*=8.3 Hz), 10.16 (s broad, 1H, NH); MS (70 eV, EI): *m/z*=458 (M^+, 9%), 177 (100%); HRMS: calcd: 458.184172. Found: 458.184899. Anal. calcd for $C_{27}H_{26}N_2O_5 \cdot 0.6H_2O$: C 69.14%, H 5.80%, N 5.97%. Found: C 68.88%, H 5.20%, N 6.04%.

3.39. N-*{[(2*R*)-2,5-Dimethyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-yl]carbonyl}*-D-*phenylalanine benzyl ester (2*R*)-**7bB**

Prepared from (*S*)-**5b** (221 mg, 1 mmol); yield: 417 mg (91%), white solid foam; mp 46–49°C, $[\alpha]_D^{20}$=+85.6 (c=0.11, MeOH); IR (KBr): ν 3419, 1702, 1499, 1480, 1376, 1175, 1027, 749, 698 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.47 (s, 3H, CH_3), 2.16 (s, 3H, Ar–CH_3), 3.03 (ABX-system, 2H, J_{AB}=13.8 Hz, J_{AX}=9.7 Hz, J_{BX}=4.9 Hz, CHC*H*$_2$Ph), 4.44–4.51 (m, 1H, CH), 4.93 (AB-system, 2H, *J*=12.3 Hz, $COOCH_2$Ph), 6.76–6.86 (m, 3H, Ar–H), 7.10–7.13 (m, 2H, Ar–H), 7.18–7.23 (m, 5H, Ar–H), 7.32–7.36 (m, 3H, Ar–H), 8.35 (d broad, 1H, *J*=8.3 Hz, CONH), 10.19 (s broad, 1H, NH); MS (70 eV, EI): *m/z*=458 (M^+, 5%), 177 (100%); HRMS: calcd: 458.184172. Found: 458.185100.

3.40. N-*{[(2*S*)-2,6-Dimethyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-yl]carbonyl}*-D-*phenylalanine benzyl ester (2*S*)-**7cB**

Prepared from (*R*)-**5c** (221 mg, 1 mmol); yield: 408 mg (89%), white solid foam; mp 29–30°C, $[\alpha]_D^{20}$=−10.7 (c=0.10, MeOH); IR (KBr): ν 3410, 1705, 1519, 1453, 1377, 1231, 812, 744, 698 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.57 (s, 3H, CH_3), 2.20 (s, 3H, Ar–CH_3), 2.98 (ABX-system, 2H, J_{AB}=14.5 Hz, J_{AX}=8.1 Hz, J_{BX}=4.5 Hz, CHC*H*$_2$Ph), 4.34–4.42 (m, 1H, CH), 5.08 (AB-system, 2H, *J*=12.8 Hz, $COOCH_2$Ph), 6.59 (s, 1H, Ar–H), 6.87–6.95 (m, 3H, Ar–H), 7.09–7.14 (m, 3H, Ar–H), 7.31–7.38 (m, 7H, Ar–H), 8.44 (d broad, 1H, *J*=8.3 Hz, CONH), 10.59 (s broad, 1H, NH); MS (70 eV, EI): *m/z*=458 (M^+, 8%), 177 (100%); HRMS: calcd: 458.184172. Found: 458.183961. Anal. calcd for $C_{27}H_{26}N_2O_5 \cdot 0.4H_2O$: C 69.67%, H 5.76%, N 6.02%. Found: C 69.98%, H 5.67%, N 5.51%.

3.41. N-*{[(2*R*)-2,6-Dimethyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-yl]carbonyl}*-D-*phenylalanine benzyl ester (2*R*)-**7cB**

Prepared from (*S*)-**5c** (221 mg, 1 mmol); yield: 435 mg (95%), white solid foam; mp 44–48°C, $[\alpha]_D^{20}$=+65.8 (c=0.11, MeOH); IR (KBr): ν 3256, 3032, 1702, 1609, 1518, 1454, 1379, 1231, 1168, 1026, 811, 741, 697 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.46 (s, 3H, CH_3), 2.16 (s, 3H, Ar–CH_3), 3.03 (ABX-system, 2H, J_{AB}=13.7 Hz, J_{AX}=9.8 Hz, J_{BX}=5.3 Hz, CHC*H*$_2$Ph), 4.44–4.51 (m, 1H, CH), 4.95 (AB-system, 2H, *J*=12.4 Hz, $COOCH_2$Ph), 6.61–6.67 (m, 2H, Ar–H), 6.86 (d, 1H, *J*=8.3 Hz, Ar–H), 7.10–7.13 (m, 2H, Ar–H), 7.18–7.23 (m, 5H, Ar–H), 7.32–7.36 (m, 3H, Ar–H), 8.35 (d broad, 1H, *J*=8.3 Hz, CONH), 10.63 (s broad, 1H, NH); MS (70 eV, EI): *m/z*=458 (M^+, 10%), 177 (100%); HRMS: calcd: 458.184172. Found: 458.185200. Anal. calcd for $C_{27}H_{26}N_2O_5 \cdot 0.5H_2O$: C 69.40%, H 5.78%, N 5.99%. Found: C 69.61%, H 5.76%, N 5.86%.

3.42. N-*{[(2*R*)-2,7-Dimethyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-yl]carbonyl}*-D-*phenylalanine benzyl ester (2*R*)-**7dB**

Prepared from (*S*)-**5d** (221 mg, 1 mmol); yield: 330 mg (72%), white solid foam; mp 43–45°C, $[\alpha]_D^{20}$=+29.0 (c=0.09, MeOH); IR (KBr): ν 3410, 1705, 1517, 1260, 1025, 799 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.47 (s, 3H, CH_3), 2.15 (s, 3H, Ar–CH_3), 3.03 (ABX-system, 2H, J_{AB}=13.5 Hz, J_{AX}=9.0 Hz, J_{BX}=4.9 Hz, CHC*H*$_2$Ph), 4.42–4.50 (m, 1H, CH), 4.92 (AB-system, 2H, *J*=12.6 Hz, $COOCH_2$Ph), 6.72–6.82 (m, 3H, Ar–H), 7.08–7.15 (m, 2H, Ar–H), 7.20–7.32 (m, 5H, Ar–H), 7.35–7.45 (m, 3H, Ar–H), 8.32 (d broad, 1H, *J*=8.3 Hz, CONH), 10.61 (s broad, 1H, NH); MS (70 eV, EI):

m/z=458 (M^+, 10%), 177 (100%); HRMS: calcd: 458.184172. Found: 458.183074. Anal. calcd for $C_{27}H_{26}N_2O_5 \cdot 0.9H_2O$: C 68.35%, H 5.86%, N 5.90%. Found: C 68.69%, H 5.60%, N 5.49%.

3.43. N-*{[(2*S*)-6-Methoxy-2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-yl]carbonyl}*-D-*phenylalanine benzyl ester (2*S*)-**7fB**

Prepared from (*R*)-**5f** (237 mg, 1 mmol); yield: 0.380 mg (80%), white solid foam; mp 44–47°C, $[\alpha]_D^{20}$=−10.3 (c=0.47, MeOH); IR (KBr): ν 3745, 1745, 1713, 1606, 1511, 1388, 1225, 1029, 800, 737 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.56 (s, 3H, CH_3), 3.00 (ABX-system, 2H, J_{AB}=13.5 Hz, J_{AX}=8.7 Hz, J_{BX}=4.5 Hz, CHCH_2Ph), 3.67 (s, 3H, OCH_3), 4.35–4.42 (m, 1H, CH), 5.09 (AB-system, 2H, *J*=12.5 Hz, $COOCH_2$Ph), 6.35 (d, 1H, *J*=2.9 Hz, Ar–H), 6.45 (dd, 1H, *J*=8.9 Hz, *J*=2.9 Hz, Ar–H), 6.92 (d, 1H, *J*=8.9 Hz, Ar–H), 6.93–6.97 (m, 2H, Ar–H), 7.07–7.13 (m, 3H, Ar–H), 7.29–7.41 (m, 5H, Ar–H), 8.47 (d broad, 1H, *J*=8.1 Hz, CONH), 10.56 (s broad, 1H, NH); MS (70 eV, EI): *m/z*=474 (M^+, 50%), 193 (100%). Anal. calcd for $C_{27}H_{26}N_2O_6$: C 68.35%, H 5.48%, N 5.90%. Found: C 68.08%, H 5.63%, N 6.06%.

3.44. N-*{[(2*R*)-6-Methoxy-2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-yl]carbonyl}*-D-*phenylalanine benzyl ester (2*R*)-**7fB**

Prepared from (*S*)-**5f** (237 mg, 1 mmol); yield: 400 mg (84%), white crystals; mp 44–48°C (from MeOH), $[\alpha]_D^{20}$=+58.9 (c=0.16, MeOH); IR (KBr): ν 3328, 2938, 1709, 1611, 1515, 1456, 1378, 1226, 1035, 741, 699 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.44 (s, 3H, CH_3), 3.03 (ABX-system 2H, J_{AB}=13.7 Hz, J_{AX}=9.7 Hz, J_{BX}=5.0 Hz, CHCH_2Ph), 3.63 (s, 3H, OCH_3), 4.52–4.44 (m, 1H, CH), 4.96 (AB-system, 2H, *J*=12.6 Hz, $COOCH_2$Ph), 6.35–6.47 (m, 2H, Ar–H), 6.90 (d, 1H, *J*=8.7 Hz, Ar–H), 7.10–7.16 (m, 2H, Ar–H), 7.18–7.25 (m, 5H, Ar–H), 7.31–7.38 (m, 3H, Ar–H), 8.39 (d broad, 1H, CONH, *J*=8.4 Hz), 10.60 (s broad, 1H, NH); HRMS: calcd: 474.180029. Found: 474.179087. Anal. calcd for $C_{27}H_{26}N_2O_6$: C 68.35%, H 5.48%, N 5.90%. Found: C 67.85%, H 5.55%, N 5.39%.

3.45. General procedure for the synthesis of mixed anhydrides ***8***

Ethyl chloroformate (0.38 ml, 4 mmol) was added dropwise at −15°C to a stirred solution of (*R*)-monomethyl 2-methyl-2-(2-nitrophenoxy)malonate (*R*)-**3** (4 mmol) in ethanol free $CHCl_3$ (20 ml). After 30 min, at which time thin layer chromatography (silica gel; $CHCl_3$:MeOH, 9:1) indicated a complete conversion of educt to the product **8**, the reaction mixture was filtered and the filtrate was evaporated in vacuo. The crude anhydride was almost pure on the basis of its proton NMR spectrum and was used immediately in a further reaction.

8a (R^1=H, R^2=$COOC_2H_5$): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.40 (t, 3H, *J*=7.1 Hz, CH_2CH_3), 1.88 (s, 3H, CH_3), 3.88 (s, 3H, $COOCH_3$), 4.38 (q, 2H, *J*=7.1 Hz, CH_2CH_3), 7.25 (ddd, 1H, *J*=8.4, 7.4, 0.9 Hz, Ar–H), 7.30 (dd, 1H, *J*=8.4, 0.9 Hz, Ar–H), 7.53 (ddd, 1H, *J*=8.1, 7.4, 1.7 Hz, Ar–H), 7.86 (dd, 1H, *J*=8.1, 1.7 Hz, Ar–H).

3.46. General procedure for the synthesis of N-*hydroxysuccinimide esters* ***9***

A solution of (*R*)-monomethyl 2-methyl-2-(2-nitrophenoxy)malonate (*R*)-**3** (5 mmol) in dry tetrahydrofuran (50 ml) was cooled in an ice-water bath, then dicyclohexylcarbodiimide (1.03 g, 5 mmol) was added with stirring and the mixture was kept at 0–5°C overnight. The separated *N*,*N*′-dicyclohexylurea

was removed by filtration and the solvent was evaporated in vacuo. The crude active ester was almost pure on the basis of its proton NMR spectrum and was used immediately in a further reaction.

9a (R^1=H, R^2=succinimido): ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.86 (s, 3H, CH_3), 2.84 (s, 4H, 2 CH_2), 3.84 (s, 3H, $COOCH_3$), 7.28 (d, 1H, *J*=8.4 Hz, Ar–H), 7.36 (ddd, 1H, *J*=8.1, 7.5, 1.0 Hz, Ar–H), 7.68 (ddd, 1H, *J*=8.4, 7.5, 1.6 Hz, Ar–H), 7.96 (dd, 1H, *J*=8.1, 1.6 Hz, Ar–H).

*3.47. General procedure for the synthesis of pentafluorophenyl esters **10***

Pentafluorophenol (920 mg, 5 mmol) was added to an ice-cold solution of (*R*)-monomethyl 2-methyl-2-(2-nitrophenoxy)malonate (*R*)-**3** (5 mmol) in ethyl acetate (8 ml) followed by the addition of dicyclohexylcarbodiimide (1.03 g, 5 mmol). The mixture was stirred for 6 h at −10°C and then kept at 0–5°C overnight. The separated *N*,*N*′-dicyclohexylurea was removed by filtration and the solvent was evaporated in vacuo. The crude active ester was almost pure on the basis of its proton NMR spectrum and was used immediately in a further reaction.

9a (R^1=H, R^2=C_6F_6): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.98 (s, 3H, CH_3), 3.92 (s, 3H, $COOCH_3$), 7.25–7.36 (m, 2H, Ar–H), 7.51–7.56 (m, 1H, Ar–H), 7.87–7.90 (dd, 1H, *J*=8.1, 1.7 Hz, Ar–H).

Acknowledgements

This work was supported financially by the Ministry of Science and Technology of the Republic of Slovenia. The authors thank the Faculty of Chemistry and Chemical Technology, University of Ljubljana for microanalyses, and the J. Stefan Institute for mass spectra.

References

1. Kikelj, D.; Rutar, A.; Suhadolc, E.; Pečar, S.; Urleb, U.; Leskovšek, V.; Ponču h, A.; Krbavčič, A.; Marc, G.; Sollner, M.; Serša, G.; Novakovič, S.; Povšič, L.; Štalc, A. *Eur. Patent EP 695308* (1998).
2. Kikelj, D.; Povšič, L.; Pristovšek, P.; Štalc, A.; Kidrič, J. *Med. Chem. Res*. **1996**, *6*, 118–127.
3. Goodman, M.; Ro, S. Peptidomimetics for drug design. In *Burger's Medicinal Chemistry and Drug Discovery*; Wolff, M. E., Ed.; John Wiley & Sons Inc.: New York, 1995; pp. 803–861.
4. Giannis, A.; Rübsam, F. *Advances in Drug Research* **1997**, *29*, 1–78.
5. Rutar, A.; Žbontar, U.; Kikelj, D.; Leban, I. *Chirality* **1998**, *10*, 791–799.
6. Breznik, M.; Mrcina, A.; Kikelj, D. *Tetrahedron: Asymmetry* **1998**, *9*, 1115–1116.
7. Breznik, M.; Kikelj, D. *Tetrahedron: Asymmetry* **1997**, *8*, 425–434.
8. Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis*; Springer: Berlin, 1994; pp. 89–95.
9. March, J. *Advanced Organic Chemistry — 4th Edition*; Wiley Interscience: New York, 1992; p. 1218.
10. Schwarz, H.; Arakawa, K. *J. Am. Chem. Soc*. **1959**, *81*, 5691–5696.
11. Parker, D.; Taylor, R. J. Analytical methods: determination of enantiomeric purity. In *Asymmetric Synthesis*; Aitken, R. A.; Kilényi, S. N., Eds; Blackie Academic & Professional: London, 1994; p. 36.