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Oxazepines and Thiazepines, XXIV [1] Synthesis of Optically Active 2,3-Dihydro-2-methyl-1,5-benzoxazepin-4(5 *H*)-ones

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Summary. 2,3-Dihydro-2(*R*)-methyl-1,5-benzoxazepin-4(5*H*)-one [(*R*)-**3**] and its enantiomer (*S*)-**3** have been synthesized via the optical resolution and subsequent chemical transformations of (±)-3-(2-nitrophenoxy)butyric acid (**1**). Compounds (*R*)-**3** and (*S*)-**3** were converted into optically active 1,5-benzoxazepines (*R*)-**7**–(*R*)-**14** and (*S*)-**15**–(*S*)-**32**.

Keywords. Optical resolution; Catalytic hydrogenation; Ring closure of aminocarboxylic acids; Determination of optical purity; Determination of absolute configuration.

Oxazepine und Thiazepine, XXIV:
Darstellung optisch aktiver 2,3-Dihydro-2-methyl-1,5-benzoxazepin-4(5 *H*)-one

Zusammenfassung. 2,3-Dihydro-2(*R*)-methyl-1,5-benzoxazepin-4(5*H*)-on [(*R*)-**3**] und sein Enantiomeres (*S*)-**3** wurden durch Racemattrennung und weitere chemische Umsetzungen von (±)-3-(2-Nitrophenoxy)buttersäure (**1**) dargestellt. Die Verbindungen (*R*)-3 und (*S*)-3 wurden in die optisch aktiven 1,5-Benzoxazepine (*R*)-**7** bis (*R*)-**14** und (*S*)-**15** bis (*S*)-**32** übergeführt.

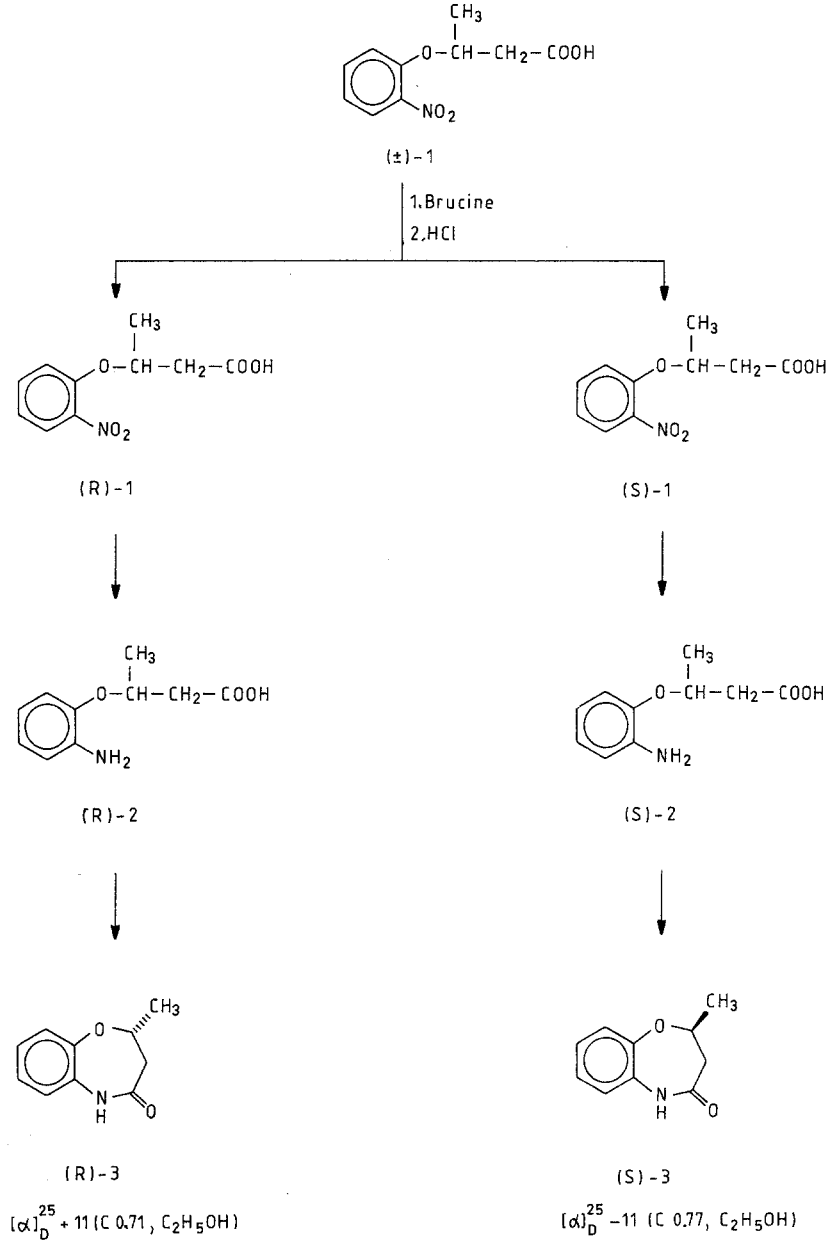
Introduction

Optically active 1,5-benzothiazepines are wellknown compounds [2–8] and some of them are the active ingredient of important drugs. However, their oxygen analogues, the appropriate benzoxazepines have hitherto attracted less attention. A first representative of the optically active benzoxazepines was synthesized by the reaction of a sugar derivative with 2-aminophenol [9]. Later, a series of optically active 1,5-benzoxazepine carboxylic acids possessing angiotensin converting enzyme inhibitor activity was prepared [10]. Recently Schultz et al. [11, 12] described the synthesis of optically active 1,4-benzoxazepine derivatives. In the present paper the synthesis of optically active 2,3-dihydro-2-methyl-1,5-benzoxazepin-4(5*H*)-ones is reported.

Results and Discussion

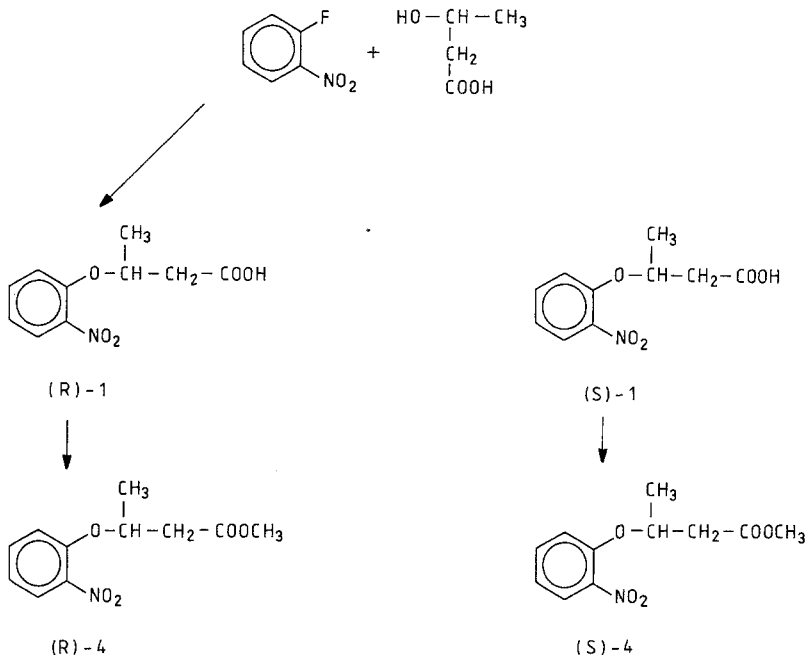
Starting material for the synthesis (Scheme 1) was (±)-3-(2-nitrophenoxy)butyric acid (**1**) described earlier [1]. Optical resolution of (±)-**1** with (−)-brucine gave

(*R*)-**1** and (*S*)-**1** which were then reduced to the appropriate aminocarboxylic acids (*R*)-**2** and (*S*)-**2**. Compounds (*R*)-**2** and (*S*)-**2** were converted into 2,3-dihydro-2(*R*)-methyl-1,5-benzoxazepin-4(5*H*)-one [(*R*)-**3**] and its enantiomer (*S*)-**3** in anhydrous dichloromethane with 1,3-dicyclohexylcarbodiimide.



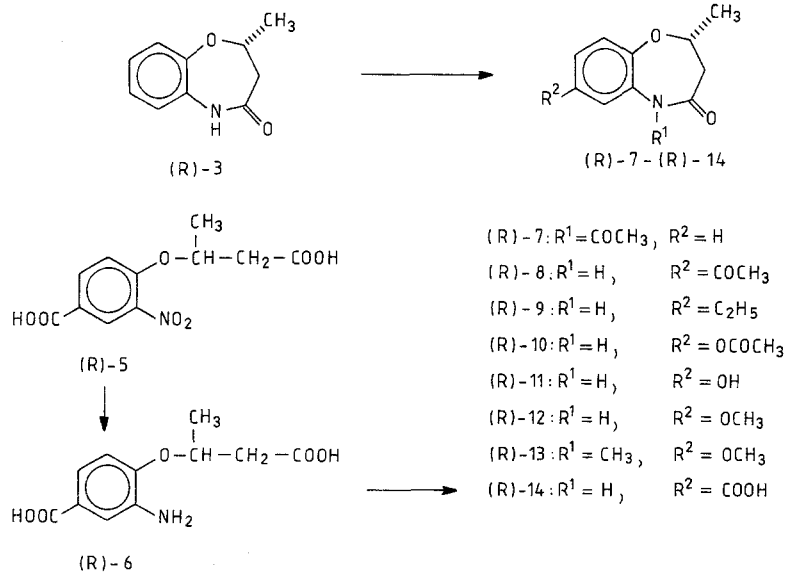
Scheme 1

The absolute configuration of the centre of chirality of (*R*)-**3** and (*S*)-**3** and their optically active intermediates have been determined by means of a so-called "chiral pool" synthesis. 3(*R*)-Hydroxybutyric acid was allowed to react with 2-nitrofluorobenzene to afford 3(*R*)-(2-nitrophenoxy)butyric acid [(*R*)-**1**] by retention (Scheme 2) which can then be used as reference substance for the determination of the absolute configuration of all related compounds.



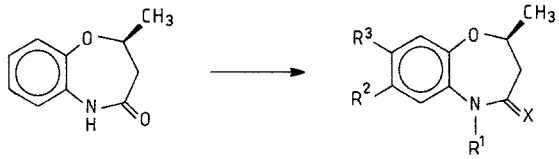
Scheme 2

The optical purities of all compounds prepared were established by the NMR shift reagent technique using tris-[3-(heptafluoropropylhydroxymethylene)-*D*-camphorato]-europium(III). As in the case of related 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones [8], methyl esters of the optically active nitrocarboxylic acid intermediates [(*R*)-**4** and (*S*)-**4** in Scheme 2] have been used for this purpose with both the methyl ester CH_3-singlet and the doublet of the other methyl group as monitors. The enantiomeric purities of all ompounds were higher than 99%.



Scheme 3

(*R*)-**3** and (*S*)-**3** are convenient intermediates for the preparation of various substituted optically active 2,3-dihydro-1,5-benzoxazepines: N-Acetylation of (*R*)-**3** gave the N-acetyl derivative (*R*)-**7**. Friedel-Crafts acylation of (*R*)-**3** with acetyl chloride afforded 7-acetyl-2,3-dihydro-2(*R*)-methyl-1,5-benzoxazepin-4(5H)-one [(*R*)-**8**] which was then used as starting material for the preparation of compounds (*R*)-**9** to (*R*)-**13**. 7-Carboxy-2,3-dihydro-2(*R*)-methyl-1,5-benzoxazepin-4(5H)-one [(*R*)-**14**] was obtained by ring closure of (*R*)-**6**. (*R*)-**6** was prepared by reduction of 3(*R*)-(4-carboxy-2-nitrophenoxy)butyric acid [(*R*)-**5**] synthesized by reaction of 3(*R*)-hydroxybutyric acid with 4-fluoro-3-nitrobenzoic acid.
Various chemical transformations of (*S*)-**3** afforded 2,3-dihydro-2(*S*)-methyl-1,5-benzoxazepin-4(5H)-ones and -thiones (*S*)-**15** to (*S*)-**32**.



(S)-3 (S)-15-(S)-32

Scheme 4

(*S*)-**15**: $X=O$, $R^1=CH_3$, $R^2=R^3=H$
(*S*)-**16**: $X=O$, $R^1=C_2H_5$, $R^2=R^3=H$
(*S*)-**17**: $X=O$, $R^1=C_6H_5CH_2$, $R^2=R^3=H$
(*S*)-**18**: $X=S$, $R^1=R^2=R^3=H$
(*S*)-**19**: $X=S$, $R^1=CH_3$, $R^2=R^3=H$
(*S*)-**20**: $X=O$, $R^1=R^3=H$, $R^2=C(CH_3)_3$
(*S*)-**21**: $X=S$, $R^1=R^3=H$, $R^2=C(CH_3)_3$
(*S*)-**22**: $X=O$, $R^1=R^3=H$, $R^2=NO_2$
(*S*)-**23**: $X=O$, $R^1=R^3=H$, $R^2=NH_2$
(*S*)-**24**: $X=O$, $R^1=R^3=H$, $R^2=NHCH(CH_3)_2$
(*S*)-**25**: $X=O$, $R^1=R^3=H$, $R^2=Cl$
(*S*)-**26**: $X=O$, $R^1=R^2=H$, $R^3=NO_2$
(*S*)-**27**: $X=O$, $R^1=R^2=H$, $R^3=NH_2$
(*S*)-**28**: $X=O$, $R^1=R^2=H$, $R^3=NHCH(CH_3)_2$
(*S*)-**29**: $X=O$, $R^1=R^2=H$, $R^3=NHCOCH_3$
(*S*)-**30**: $X=O$, $R^1=R^2=H$, $R^3=Cl$
(*S*)-**31**: $X=O$, $R^1=R^2=H$, $R^3=Br$
(*S*)-**32**: $X=O$, $R^1=CH_3$, $R^2=H$, $R^3=NO_2$

Structure elucidation of all compounds described has been performed by IR, ^1H- and ^{13}C-NMR and mass spectroscopy; the spectral data are shown in the Exp. Part. Circular dichroism studies of optically active substances described in this paper are in progress and their results will be published in a separate paper.

Experimental Part

Melting points were determined with a Kofler hot stage apparatus and are uncorrected. ^1H and, ^{13}C-NMR spectra were recorded on Bruker WP-80 and AM-400 instruments. Infrared spectra were

measured on a Perkin-Elmer 1310 spectrometer. Mass spectra were obtained on Varian MAT CH-5 and CH-7 instruments at 70 eV. Optical rotation was measured on a Perkin-Elmer 141 apparatus. Thin-layer chromatography was performed on Kieselgel 60 F_{254} (Merck) layer using various developing mixtures.

Starting material (±)-**1** was prepared as described earlier [1].

Optical Resolution of Compound (±)-**1**

A mixture of (±)-**1** (66.6 mmol) and (−)-brucine · 2 H_2O (66.6 mmol) was dissolved in hot ethanol (400 ml) and the solution was allowed to cool down overnight. The precipitated crystals were filtered off and recrystallized several times to afford brucine salt of (*R*)-1, yield 65% (calculated for one diastereomer), $[\alpha]_D^{25} = -41$ ($c = 1.0$, CH_3OH). The mother liquor was evaporated under reduced pressure and the residue crystallized to obtain the brucine salt of (*S*)-**1**, yield 43% (calculated for one diastereomer), $[\alpha]_D^{25} = +5$ ($c = 1.0$, CH_3OH).

Decomposition of the Brucine Salts

Brucine salts of (*R*)-**1** and (*S*)-**1** were dissolved in a mixture of acetone and hydrochloric acid of *pH* 1, then the free acids extracted with dichloromethane. The solution was dried with $MgSO_4$ and the solvent evaporated. The crude products were purified by column chromatography to afford pure optically active nitrocarboxylic acids [(*R*)-**1** ($[\alpha]_D^{25} = -55$ ($c = 0.50$, C_2H_5OH)] and (*S*)-**1** ($[\alpha]_D^{25} = +55$ ($c = 0.51$, C_2H_5OH)) in almost quantitative yield. IR (chloroform): 3 500 − 2 500, 1 720, 1 610, 1 525, 1 360, 1 280 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.41 (d, 3 H), 2.64 (dd, 1 H), 2.88 (dd, 1 H), 4.93 (m, 1 H), 7.00 (m, 1 H), 7.15 (dd, 1 H), 7.48 (m, 1 H), 7.73 (dd, 1 H); ^{13}C-NMR ($CDCl_3$): δ 19.4 (CH_3), 40.9 (CH_2), 72.7 (CH), 116.3 (CH), 120.8 (CH), 125.2 (CH), 133.7 (CH), 140.9 (C), 150.5 (C), 176.6 (C=O); MS *m*/e (% relative intensity): 225 (6, M^+), 139 (100), 122 (6, $C_6H_4NO_2^+$), 109 (34), 93 (8, $C_6H_5O^+$), 51 (11, $C_4H_3^+$), 41 (45, $C_3H_5^+$).

Reduction of Compounds (*R*)-**1** *and* (*S*)-**1**

Compounds (*R*)-**1**, (*S*)-**1** (25.0 g) were hydrogenated in ethanolic solution (150 ml) in the presence of Pd/C (10%) catalyst to afford (*R*)-**2** and (*S*)-**2** in almost quantitative yield. Aminocarboxylic acids obtained were used for ring closure without purification.

2,3-Dihydro-2(R)-methyl-1,5-benzoxazepin-4(5H)-one [(*R*)-**3**] *and*
2,3-Dihydro-2(S)-methyl-1,5-benzoxazepin-4(5H)-one [(*S*)-**3**]

A mixture of (*R*)-**2** (17.0 mmol), 1,3-dicyclohexylcarbodiimide (17.0 mmol), and anhydrous dichloromethane (150 ml) was stirred overnight at room temperature, then a small amount of acetic acid and ethanol was added and the precipitate filtered off. The solvent was evaporated and the residue purified by column chromatography to afford (*R*)-**3**, m.p. 140 − 141°C, $[\alpha]_D^{25} = -11$ ($c = 0.77$, C_2H_5OH) and (*S*)-**3**, m.p. 140 − 141°C, $[\alpha]_D^{25} = +11$ ($c = 0.71$, C_2H_5OH). IR (KBr): 3 190, 3 130, 3 070, 1 685, 1 590, 1 500, 1 220 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.42 (d, 3 H), 2.57 (dd, 1 H), 2.72 (dd, 1 H), 4.79 (m, 1 H), 7.03 (m, 4 aromatic protons); ^{13}C-NMR ($CDCl_3$): δ 21.2 (CH_3), 41.9 (CH_2), 78.3 (CH), 122.0 (CH), 123.2 (CH), 124.1 (CH), 125.7 (CH), 130.7 (C), 147.8 (C), 172.5 (C=O); MS *m*/e (% relative intensity): 177 (76, M^+), 149 (2, *M*-CO), 135 (30), 120 (17), 109 (96), 69 (100, $C_4H_5O^+$), 41 (38, $C_3H_5^+$).

3(R)-(2-Nitrophenoxy)butyric Acid [(*R*)-**1**]

A mixture of 3(*R*)-hydroxybutyric acid (3.84 mmol), 55% NaH suspension (7.68 mmol) and anhydrous N,N-dimethylformamide (5.0 ml) was stirred at 0°C until the hydrogen formation ceased, then 2-

nitrofluorobenzene (3.84 mmol) dissolved in anhydrous N,N-dimethylformamide (5.0 ml) was added and the mixture was allowed to warm to room temperature and stirred at this temperature overnight. Dilute hydrochloric acid was added and the mixture extracted with diethyl ether. The ethereal solution was extracted with 9% $NaHCO_3$ solution which was then acidified to afford 0.227 g (34%) of (*R*)-**1** on purification by column chromatography. All spectral data were identical with those of a product prepared by optical resolution of (±)-**1**.

Methyl Ester of 3(R)-(2-Nitrophenoxy)butyric Acid [(*R*)-**4**]

A mixture of (*R*)-**1** (0.171 g), anhydrous methanol (10.0 ml), and concentrated sulfuric acid (1.0 ml) was refluxed for 1.5 h, the solvent evaporated under reduced pressure, the residue triturated with water, and extracted with dichloromethane. The organic phase was washed with 9% $NaHCO_3$ solution, dried with $MgSO_4$ to yield 0.158 g (87%) yellow oil, $[\alpha]_D^{25} = -45$ ($c = 0.98$, C_2H_5OH).

Methyl Ester of 3(S)-(2-Nitrophenoxy)butyric Acid [(*S*)-**4**]

(*S*)-**1** was esterified as described for the other enantiomer to afford yellow oil, $[\alpha]_D^{25} = +45$ ($c = 0.88$, C_2H_5OH). IR (chloroform): 3 030, 1 735, 1 610, 1 530, 1 490, 1 360, 1 280 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.39 (d, 3 H), 2.57 (dd, 1 H), 2.82 (dd, 1 H), 3.65 (s, 3 H), 4.94 (m, 1 H), 6.99 (m, 1 H), 7.15 (dd, 1 H), 7.48 (m, 1 H), 7.72 (dd, 1 H); ^{13}C-NMR ($CDCl_3$): δ 19.4 (CH_3), 40.7 (CH_2), 51.5 (OCH_3), 73.1 (CH), 116.2 (CH), 120.6 (CH), 125.1 (CH), 133.6 (CH), 140.8 (C), 150.6 (C), 170.7 (C=O); MS *m*/e (% relative intensity): 239 (6, M^+), 139 (44), 122 (8, $C_6H_4NO_2^+$), 101 (54, $C_5H_9O_2^+$), 69 (32, $C_4H_5O^+$), 59 (100, $C_2H_3O_2^+$).

3(R)-(4-Carboxy-2-nitrophenoxy)butyric Acid [(*R*)-**5**]

A mixture of 3(*R*)-hydroxybutyric acid (5.4 mmol), 55% NaH suspension (16.2 mmol), and 4-fluoro-3-nitrobenzoic acid (5.4 mmol) was allowed to react as described for compound (*R*)-**1** to afford 0.974 g of crystalline material (66%), m.p. 117.5°C. IR (KBr): 3 300 – 2 500, 1 720, 1 700, 1 535, 1 355, 1 220 cm^{-1}; ^{1}H-NMR (acetone-d_6): δ 1.46 (d, 3 H), 2.74 (dd, 1 H), 2.83 (dd, 1 H), 5.22 (m, 1 H), 7.56 (d, 1 H), 8.23 (dd, 1 H), 8.37 (d, 1 H); ^{13}C-NMR (acetone-d_6): δ 19.5 (CH_3), 41.0 (CH_2), 74.4 (CH), 116.6 (CH), 123.6 (C), 127.2 (CH), 135.6 (CH), 154.9 (C), 160.6 (C), 165.6 (C=O), 171.5 (C=O); MS *m*/e (% relative intensity): 269 (2, M^+), 183 (98), 166 (14), 69 (43, $C_4H_5O^+$), 51 (18, $C_4H_3^+$), 41 (100, $C_3H_5^+$).

3(R)-(2-Amino-4-carboxyphenoxy)butyric Acid [(*R*)-**6**]

(*R*)-**5** (2.6 mmol) was hydrogenated in ethanolic solution (20 ml) in the presence of Pd/C (10%) catalyst to afford an oil which was used for ring closure without purification.

5-Acetyl-2,3-dihydro-2(R)-methyl-1,5-benzoxazepin-4(5H)-one [(*R*)-**7**]

A mixture of (*R*)-**3** (0.463 mmol) and acetic anhydride (15.0 ml) was refluxed for 2 h, then the solvent evaporated under reduced pressure. The residue was dissolved in dichloromethane, the solution was washed with 9% $NaHCO_3$ solution and dried with $MgSO_4$. The solvent was evaporated and the residue crystallized from hexane to afford 0.075 g colourless crystals (75%), m.p. 97 – 98°C. IR (KBr): 1 715, 1 600, 1 490, 1 245 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.37 (d, 3 H), 2.40 (dd, 1 H), 2.65 (s, 3 H), 2.67 (dd, 1 H), 4.71 (m, 1 H), 7.10 – 7.20 (m, 4 aromatic protons); ^{13}C-NMR ($CDCl_3$): δ 20.1 (CH_3), 27.9 (CH_3), 42.8 (CH_2), 79.1 (CH), 123.7 (CH), 124.6 (CH), 128.5 (CH), 128.9 (CH), 132.4 (C), 149.0 (C), 171.1 (C=O), 172.5 (C=O); MS *m*/e (% relative intensity): 219 (6, M^+), 177 (82), 135 (34, $C_7H_5NO_2^+$), 109 (100), 69 (94, $C_4H_5O^+$), 43 (58, CH_3CO^+).

7-Acetyl-2,3-dihydro-2(R)-methyl-1,5-benzoxazepin-4(5H)-one [(*R*)-**8**]

A mixture of (*R*)-**3** (5.65 mmol), acetyl chloride (5.93 mmol), $AlCl_3$ (14.1 mmol), and anhydrous 1,2-dichloroethane (10.0 ml) was left to stand at 0°C for 1 h, then further amount of acetyl chloride (5.93 mmol) was added at room temperature and the reaction mixture was stirred at this temperature for 5 h. The mixture was cooled with ice and hydrolyzed with hydrochloric acid, then extracted with dichloromethane. The organic phase was washed with 9% $NaHCO_3$ solution, then with water and dried with $MgSO_4$. The solvent was evaporated and the residue crystallized from benzene to yield 0.797 g crystalline product (64%), m.p. 147°C. IR (KBr): 3 310, 3 210, 3 100, 1 675, 1 660, 1 610, 1 500, 1 245 cm^{-1}; ^{1}H-NMR (acetone-d_6): δ 1.42 (d, 3 H), 2.52 (s, 3 H), 2.60 (dd, 1 H), 2.74 (dd, 1 H), 4.83 (m, 1 H), 7.10 (d, 1 H), 7.70 (d, 1 H), 7.74 (d, 1 H), 8.90 (s, NH); ^{13}C-NMR (acetone-d_6): δ 21.5 (CH_3), 26.4 (CH_3), 42.7 (CH_2), 78.7 (CH), 122.8 (CH), 123.7 (CH), 126.0 (CH), 131.9 (C), 133.9 (C), 152.6 (C), 171.0 (C=O), 196.3 (C=O); MS *m*/e (% relative intensity): 219 (30, M^+), 204 (4, M-CH_3), 162 (37), 151 (20), 136 (21), 69 (100, $C_4H_5O^+$), 41 (38, $C_3H_5^+$).

2,3-Dihydro-7-ethyl-2(R)-methyl-1,5-benzoxazepin-4(5H)-one [(*R*)-**9**]

A mixture of (*R*)-**8** (0.457 mmol), acetic acid (10.0 ml), and catalytic amount of 70% perchloric acid was hydrogenated in the presence of Pd/C (10%) catalyst until the hydrogen consumption stopped. The catalyst was filtered off, the solvent evaporated and the residue dissolved in dichloromethane. The solution obtained was washed with water, dried with $MgSO_4$, the solvent evaporated and the residue crystallized from hexane to afford 0.062 g colourless crystals (65%), m.p. 157°C. IR (KBr): 3 200, 3 120, 1 675, 1 220 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.39 (t, 3 H), 1.40 (d, 3 H), 2.55 (m, 3 H), 2.69 (dd, 1 H), 4.78 (m, 1 H), 6.81 (d, 1 H), 6.89 (dd, 1 H), 6.95 (d, 1 H); ^{13}C-NMR ($CDCl_3$): δ 15.5 (CH_3), 21.1 (CH_3), 28.0 (CH_2), 41.8 (CH_2), 78.7 (CH), 121.3 (CH), 123.1 (CH), 125.1 (CH), 130.6 (C), 140.5 (C), 145.6 (C), 172.4 (C=O); MS *m*/e (% relative intensity): 205 (75, M^+), 163 (15), 148 (76), 137 (100), 122 (30), 69 (58, $C_4H_5O^+$), 41 (42, $C_3H_5^+$).

7-Acetoxy-2,3-dihydro-2(R)-methyl-1,5-benzoxazepin-4(5H)-one [(*R*)-**10**]

A mixture of (*R*)-**8** (0.457 mmol), 55% 3-chloroperoxybenzoic acid (5.0 moleqv.), catalytic amount of trifluoroacetic acid, and anhydrous dichloromethane (30.0 ml) was stirred overnight at room temperature, refluxed for 6 h, then washed with sodium dithionite, $NaHCO_3$ solution and water. The organic phase was dried with $MgSO_4$, the solvent evaporated and the residue crystallized from a mixture of benzene and petroleum ether to obtain 0.075 g colourless crystals (70%), m.p. 149 – 150°C. IR (KBr): 3 200, 3 110, 1 760, 1 670, 1 200 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.42 (d, 3 H), 2.27 (s, 3 H), 2.57 (dd, 1 H), 2.72 (dd, 1 H), 4.79 (m, 1 H), 6.73 (d, 1 H), 6.81 (dd, 1 H), 7.03 (d, 1 H); ^{13}C-NMR ($CDCl_3$): δ 21.0 (CH_3), 21.1 (CH_3), 41.7 (CH_2), 78.7 (CH), 115.1 (CH), 118.7 (CH), 123.9 (CH), 131.4 (C), 145.5 (C), 146.5 (C), 169.3 (C=O), 171.8 (C=O); MS *m*/e (% relative intensity): 235 (18, M^+), 193 (75), 151 (38), 125 (100), 69 (58, $C_4H_5O^+$), 43 (46, CH_3CO^+), 41 (34, $C_3H_5^+$).

2,3-Dihydro-7-hydroxy-2(R)-methyl-1,5-benzoxazepin-4(5H)-one [(*R*)-**11**]

A mixture of (*R*)-**10** (0.447 mmol), 16% NaOH solution (0.11 ml), and methanol (10.0 ml) was left to stand at room temperature for 1 h, then the solution was acidified and the solvent evaporated under reduced pressure. The residue was purified by column chromatography to yield 0.036 g colourless crystals (42%), m.p. 188 – 189°C. IR (KBr): 3 500 – 3 000, 1 660, 1 500, 1 225 cm^{-1}; ^{1}H-NMR (acetone-d_6): δ 1.32 (d, 3 H), 2.41 (dd, 1 H), 2.65 (dd, 1 H), 4.71 (m, 1 H), 6.55 – 6.88 (m, 3 aromatic protons); ^{13}C-NMR (acetone-d_6): δ 21.1 (CH_3), 42.1 (CH_2), 80.0 (CH), 109.3 (CH), 112.6 (CH), 124.5 (CH), 134.0 (C), 141.6 (C), 154.7 (C), 172.2 (C=O); MS *m*/e (% relative intensity): 193 (52, M^+), 151 (36), 136 (14), 125 (100), 69 (77, $C_4H_5O^+$), 41 (60, $C_3H_5^+$).

2,3-Dihydro-7-methoxy-2(R)-methyl-1,5-benzoxazepin-4(5H)-one [(*R*)-**12**]

A mixture of (*R*)-**11** (0.913 mmol), dimethyl sulfate (1.83 mmol), 16% NaOH solution (0.12 ml), and water (4.0 ml) was stirred for 5 h at room temperature, then extracted with dichloromethane. The organic phase was washed with water, dried with $MgSO_4$, the solvent evaporated and the residue purified by column chromatography to afford 0.073 g colourless substance (39%), m.p. 103°C. IR (chloroform): 3400, 3210, 1680, 1615, 1510, 1230 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.40 (d, 3H), 2.48 (dd, 1H), 2.68 (dd, 1H), 3.77 (s, 3H), 4.77 (m, 1H), 6.50 (d, 1H), 6.63 (dd, 1H), 6.98 (dd, 1H); ^{13}C-NMR ($CDCl_3$): δ 20.9 (CH_3), 41.5 (CH_2), 55.6 (OCH_3), 79.2 (CH), 107.4 (CH), 111.0 (CH), 123.9 (CH), 132.0 (C), 141.5 (C), 156.2 (C), 172.4 (C=O); MS *m*/e (% relative intensity): 207 (60, M^+), 165 (34), 150 (43), 139 (100), 124 (10), 69 (44, $C_4H_5O^+$), 41 (38, $C_3H_5^+$).

2,3-Dihydro-2(R),5-dimethyl-7-methoxy-1,5-benzoxazepin-4(5H)-one [(*R*)-**13**]

This substance (colourless oil) is a by-product of the synthesis of (*R*)-**12**. IR (chloroform): 1655, 1600, 1500, 1220 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.34 (d, 3H), 2.35 (dd, 1H), 2.60 (dd, 1H), 3.29 (s, 3H), 3.76 (s, 3H), 4.78 (m, 1H), 6.67–6.96 (m, 3 aromatic protons); ^{13}C-NMR ($CDCl_3$): δ 20.3 (CH_3), 34.5 (NCH_3), 41.1 (CH_2), 55.6 (CH_3), 81.0 (CH), 108.5 (CH), 110.8 (CH), 124.1 (CH), 138.7 (C), 141.7 (C), 156.5 (C), 170.2 (C=O); MS *m*/e (% relative intensity); 221 (100, M^+), 206 (14, *M*-CH_3), 191 (18), 179 (58), 164 (58), 153 (88), 138 (21), 123 (37), 69 (60, $C_4H_5O^+$), 41 (54, $C_3H_5^+$).

7-Carboxy-2,3-dihydro-2(R)-methyl-1,5-benzoxazepin-4(5H)-one [(*R*)-**14**]

Compound (*R*)-**6** (2.51 mmol) dissolved in toluene (60.0 ml) was refluxed for 3 h in the presence of Kieselgel 60 (1.5 g). The solid material was filtered off, the solvent evaporated, and the residue purified by column chromatography to yield 0.22 g colourless crystals (40%), m.p. 243–244°C. IR (KBr): 3200, 3000–2300, 1690, 1500, 1220 cm^{-1}; ^{1}H-NMR (*DMSO-d*$_6$): δ 1.33 (d, 3H), 2.51 (1H, overlapped by the solvent peak), 2.65 (dd, 1H), 4.76 (m, 1H), 7.06 (d, 1H), 7.59 (dd, 1H), 7.64 (d, 1H); ^{13}C-NMR (*DMSO-d*$_6$): δ 21.0 (CH_3), 41.8 (CH_2), 77.8 (CH), 122.8 (CH), 123.1 (CH), 125.8 (CH), 126.1 (C), 131.0 (C), 150.9 (C), 166.5 (C=O), 170.5 (C=O); MS *m*/e (% relative intensity): 221 (60, M^+), 179 (18), 162 (18), 153 (35), 135 (8), 69 (100, $C_4H_5O^+$).

2,3-Dihydro-2(S),5-dimethyl-1,5-benzoxazepin-4(5H)-one [(*S*)-**15**]

A mixture of (*S*)-**3** (0.847 mmol), KOH (3.39 mmol), iodomethane (1.69 mmol), and anhydrous dimethyl sulfoxide (4.0 ml) was stirred at room temperature for 20 min, then acidified with dilute hydrochloric acid and extracted with dichloromethane. The organic phase was washed with sodium dithionite solution and dried with $MgSO_4$. The solvent was evaporated and the residue purified by column chromatography to obtain 0.129 g oil (80%). IR (KBr): 1675, 1600, 1495, 1220 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.37 (d, 3H), 2.36 (dd, 1H), 2.61 (dd, 1H), 3.31 (s, 3H), 4.84 (m, 1H), 7.05–7.15 (m, 4 aromatic protons); ^{13}C-NMR ($CDCl_3$): δ 20.5 (CH_3), 34.6 (NCH_3), 41.0 (CH_2), 81.2 (CH), 122.4 (CH), 123.8 (CH), 124.8 (CH), 126.3 (CH), 138.2 (C), 148.1 (C), 170.0 (C=O); MS *m*/e (% relative intensity): 191 (74, M^+), 149 (41), 134 (25), 123 (100), 108 (10), 93 (25, $C_6H_6O^+$), 69 (70, $C_4H_5O^+$), 41 (46, $C_3H_5^+$).

2,3-Dihydro-5-ethyl-2(S)-methyl-1,5-benzoxazepin-4(5H)-one [(*S*)-**16**]

(*S*)-**3** (0.435 mmol) and ethyl bromide (0.87 mmol) were allowed to react as described for compound (*S*)-**15** to afford 0.020 g colourless oil (22%). IR (chloroform): 1660, 1600, 1495, 1230 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.13 (t, 3H), 1.37 (d, 3H), 2.33 (dd, 1H), 2.59 (dd, 1H), 3.85 (m, 2H), 4.84 (m, 1H), 7.05–7.70 (m, 4 aromatic protons); ^{13}C-NMR ($CDCl_3$): δ 13.4 (CH_3), 20.5 (CH_3), 41.1 (CH_2), 42.4 (CH_2), 81.4 (CH), 122.9 (CH), 123.9 (CH), 124.9 (CH), 126.6 (CH), 136.9 (C), 149.0 (C), 169.7

(C=O); MS *m*/e (% relative intensity): 205 (100, M^+), 190 (6, *M*-CH_3), 163 (16), 148 (44), 137 (70), 122 (56), 93 (6, $C_6H_5O^+$), 69 (58, $C_4H_5O^+$), 41 (16, $C_3H_5^+$).

5-Benzyl-2,3-dihydro-2(S)-methyl-1,5-benzoxazepin-4(5H)-one [(*S*)-**17**]

(*S*)-**3** (0.339 mmol) and benzyl chloride (0.678 mmol) were allowed to react as described for (*S*)-**15** to yield 0.067 g colourless crystals (74%), m.p. 97°C. IR (KBr): 3030, 1675, 1600, 1495, 1220 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.41 (d, 3 H), 2.48 (dd, 1 H), 2.72 (dd, 1 H), 4.92 (m, 1 H), 5.06 (s, 2 H), 7.00–7.20 (m, 9 aromatic protons); ^{13}C-NMR ($CDCl_3$): δ 20.5 (CH_3), 41.1 (CH_2), 50.5 (NCH_2), 81.4 (CH), 122.6 (CH), 124.0 (CH), 124.9 (CH), 126.7 (CH), 126.8 (CH), 127.0 (CH), 128.4 (CH), 137.2 (C), 137.3 (C), 148.5 (C), 170.2 (C=O); MS *m*/e (% relative intensity): 267 (44, M^+), 199 (21), 91 (100, $C_7H_7^+$), 69 (12, $C_4H_5O^+$), 65 (16, $C_5H_5^+$), 41 (13, $C_3H_5^+$).

2,3-Dihydro-2(S)-methyl-1,5-benzoxazepin-4(5H)-thione [(*S*)-**18**]

A mixture of (*S*)-**3** (0.564 mmol), Lawesson's Reagent (0.338 mmol), and toluene (3.0 ml) was heated at 85°C for 3 h, then extracted with dichloromethane. The extract was washed with water, dried with $MgSO_4$ and the solvent evaporated. The residue was purified by column chromatography to obtain 0.064 g product (60%), m.p. 160°C. IR (KBr): 3160, 3100, 1590, 1550, 1490, 1225 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.44 (d, 3 H), 2.92 (dd, 1 H), 3.18 (dd, 1 H), 4.92 (m, 1 H), 7.08–7.18 (m, 4 aromatic protons); ^{13}C-NMR ($CDCl_3$): δ 20.8 (CH_3), 49.7 (CH_2), 82.1 (CH), 121.9 (CH), 123.8 (CH), 124.3 (CH), 127.6 (CH), 131.5 (C), 148.5 (C), 202.1 (C=S); MS *m*/e (% relative intensity): 193 (100, M^+), 160 (66, *M*-HS), 151 (20), 133 (21), 120 (20), 109 (7), 85 (18, $C_4H_5S^+$), 41 (13, $C_3H_5^+$).

2,3-Dihydro-2(S),5-dimethyl-1,5-benzoxazepin-4(5H)-thione [(*S*)-**19**]

(*S*)-**15** (0.471 mmol) and Lawesson's Reagent (0.283 mmol) were allowed to react as described for compound (*S*)-**18** to yield 0.088 g product (90%), m.p. 85–86°C. IR (KBr): 1490, 1480, 1240 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.38 (d, 3 H), 2.86 (dd, 1 H), 3.15 (dd, 1 H), 3.78 (s, 3 H), 4.94 (m, 1 H), 7.06–7.22 (m, 4 aromatic protons); ^{13}C-NMR ($CDCl_3$): δ 20.0 (CH_3), 44.0 (NCH_3), 50.8 (CH_2), 83.8 (CH), 122.6 (CH), 124.1 (CH), 124.9 (CH), 128.0 (CH), 139.1 (C), 199.9 (C=S); MS *m*/e (% relative intensity): 207 (55, M^+), 192 (2, *M*-CH_3), 174 (100, *M*-HS), 134 (15), 123 (5), 85 (16, $C_4H_5S^+$).

2,3-Dihydro-2(S)-methyl-7-(tert-butyl)-1,5-benzoxazepin-4(5H)-one [(*S*)-**20**]

Anhydrous $FeCl_3$ (1.69 mmol) was added to a stirred mixture of (*S*)-**3** (1.23 mmol) and *tert*-butyl chloride (1.5 ml) at 0°C, then the mixture was stirred at room temperature for 3 h, treated with water, and extracted with dichloromethane. The extract was washed with $NaHCO_3$ solution, then with water and the solvent evaporated. The residue was purified by column chromatography to afford 0.076 g colourless crystals (29%), m.p. 170–171°C. IR (KBr): 3200, 3120, 1680, 1390, 1380, 1215 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.27 (s, 9 H), 1.41 (d, 3 H), 2.54 (dd, 1 H), 2.70 (dd, 1 H), 4.77 (m, 1 H), 6.95–7.08 (m, 3 aromatic protons); ^{13}C-NMR ($CDCl_3$): δ 21.1 (CH_3), 31.3 (CH_3), 34.3 (C), 41.8 (CH_2), 78.4 (CH), 119.0 (CH), 122.7 (CH), 122.8 (CH), 130.0 (C), 145.4 (C), 147.4 (C), 172.1 (C=O); MS *m*/e (% relative intensity): 233 (61, M^+), 218 (75, *M*-CH_3), 176 (58), 165 (30), 150 (100), 41 (64, $C_3H_5^+$).

2,3-Dihydro-2(S)-methyl-7-(tert-butyl)-1,5-benzoxazepin-4(5H)-thione [(*S*)-**21**]

(*S*)-**20** (0.258 mmol) and Lawesson's Reagent (0.16 mmol) were allowed to react as described for (*S*)-**16** to yield 0.032 g colourless substance (50%), m.p. 149°C. IR (KBr): 3180, 1540, 1500, 1270 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.28 (s, 9 H), 1.42 (d, 3 H), 2.93 (dd, 1 H), 3.19 (dd, 1 H), 4.88 (m, 1 H), 6.99 (m, 2 H), 7.19 (dd, 1 H); ^{13}C-NMR ($CDCl_3$): δ 20.8 (CH_3), 31.2 (CH_3), 34.3 (C), 49.8 (CH_2), 81.6

(CH), 118.9 (CH), 123.1 (CH), 124.6 (CH), 130.6 (C), 146.1 (C), 147.5 (C), 202.2 (C=S); MS *m/e* (% relative intensity): 249 (100, M^+), 234 (80, *M*-CH_3), 216 (63, *M*-HS), 201 (12), 192 (36), 176 (16), 150 (25), 133 (23), 85 (45, $C_4H_5S^+$), 41 (38, $C_3H_5^+$).

2,3-Dihydro-2(S)-methyl-7-nitro-1,5-benzoxazepin-4(5H)-one [(*S*)-**22**]

Compound (*S*)-**3** (1.13 mmol) was dissolved in trifluoroacetic acid (10.0 ml) and powdered anhydrous potassium nitrate (3.39 mmol) was added at 0°C. The mixture was allowed to warm to room temperature and 30 ml of water was added during 2.5 h. The precipitate was filtered off, washed with water and diethyl ether, then separated by column chromatography to obtain 0.087 g yellow material (35%), m.p. 198°C. IR (KBr): 3 210, 3 090, 1 665, 1 590, 1 520, 1 490, 1 340 cm^{-1}; ^{1}H-NMR (*DMSO-d_6*): δ 1.36 (d, 3 H), 2.67 (dd, 1 H), 2.75 (dd, 1 H), 4.80 (m, 1 H), 7.16 (d, 1 H), 7.86 (dd, 1 H), 7.95 (d, 1 H); ^{13}C-NMR (*DMSO-d_6*): δ 21.1 (CH_3), 42.2 (CH_2), 76.9 (CH), 116.9 (CH), 119.6 (CH), 123.2 (CH), 130.5 (C), 142.4 (C), 152.6 (C), 170.6 (C); MS *m/e* (% relative intensity): 222 (17, M^+), 180 (2), 165 (4), 154 (7), 69 (100, $C_4H_5O^+$), 51 (15, $C_4H_3^+$), 41 (44, $C_3H_5^+$).

7-Amino-2,3-dihydro-2(S)-methyl-1,5-benzoxazepin-4(5H)-one [(*S*)-**23**]

(*S*)-**22** (2.22 mmol) was hydrogenated in ethanolic solution (200 ml) in the presence of Pd/C (10%) catalyst to afford 0.362 g colourless crystals (85%), m.p. 212°C. IR (KBr): 3 450, 3 360, 3 180, 3 100, 1 680, 1 510, 1 225 cm^{-1}; ^{1}H-NMR (*DMSO-d_6*): δ 1.22 (d, 3 H), 2.22 (dd, 1 H), 2.48 (1 H, overlapped by the solvent signal), 4.59 (m, 1 H), 5.10 (bs, NH_2), 6.21 (d, 1 H), 6.22 (dd, 1 H), 6.69 (d, 1 H); ^{13}C-NMR (*DMSO-d_6*): δ 20.6 (CH_3), 41.2 (CH_2), 78.9 (CH), 107.1 (CH), 110.5 (CH), 123.3 (CH), 133.1 (C), 137.8 (C), 145.0 (C), 170.9 (C=O); MS *m/e* (% relative intensity): 192 (80, M^+), 150 (43), 135 (14), 124 (100), 69 (21, $C_4H_5O^+$), 41 (42, $C_3H_5^+$).

2,3-Dihydro-7-isopropylamino-2(S)-methyl-1,5-benzoxazepin-4(5H)-one [(*S*)-**24**]

(*S*)-**22** (1.0 mmol) was dissolved in acetone (50 ml) and hydrogenated in the presence of Pd/C (10%) catalyst to yield 0.179 g colourless material (93%), m.p. 146°C. IR (chloroform): 3 400, 1 670, 1 620, 1 510, 1 210 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.17 (d, 6 H), 1.38 (d, 3 H), 2.46 (dd, 1 H), 2.65 (dd, 1 H), 3.40 (s, NH), 3.51 (m, 1 H), 4.73 (m, 1 H), 6.16 (d, 1 H), 6.30 (dd, 1 H), 6.86 (d, 1 H), 7.40 (s, NH); ^{13}C-NMR ($CDCl_3$): δ 20.9 (CH_3), 22.9 (CH_3), 41.5 (CH_2), 44.6 (C), 79.2 (CH), 106.1 (CH), 110.5 (CH), 124.1 (CH), 132.1 (C), 138.9 (C), 144.6 (C), 172.3 (C=O); MS *m/e* (% relative intensity): 234 (95, M^+), 219 (50, *M*-CH_3), 192 (16), 191 (32), 177 (100), 166 (23), 151 (28), 134 (16), 69 (22, $C_4H_5O^+$), 41 (60, $C_3H_5^+$).

7-Chloro-2,3-dihydro-2(S)-methyl-1,5-benzoxazepin-4(5H)-one [(*S*)-**25**]

(*S*)-**23** (0.52 mmol) was added to a stirred mixture of anhydrous $CuCl_2$ (0.625 mmol), anhydrous acetonitrile (3.0 ml), and *n*-pentyl nitrite (0.781 mmol) at 0°C. The mixture was then stirred at room temperature for another 2 h and heated at 70°C for 10 min. Dilute hydrochloric acid was added and the reaction mixture extracted with dichloromethane. The organic phase was dried with $MgSO_4$, the solvent evaporated and the residue purified by column chromatography to obtain 0.054 g colourles crystals (49%), m.p. 179–180°C. IR (KBr): 3 200, 3 120, 1 690, 1 600, 1 490, 1 220 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.42 (d, 3 H), 2.56 (dd, 1 H), 2.73 (dd, 1 H), 4.78 (m, 1 H), 6.95–7.05 (m, 3 aromatic protons); ^{13}C-NMR ($CDCl_3$): δ 21.1 (CH_3), 41.8 (CH_2), 78.6 (CH), 121.8 (CH), 124.4 (CH), 125.7 (CH), 129.0 (C), 131.7 (C), 146.5 (C), 172.0 (C=O); MS *m/e* (% relative intensity): 211 (30, M^+), 169 (22), 154 (10), 143 (44), 69 (100, $C_4H_5O^+$), 51 (17, $C_4H_3^+$), 41 (40, $C_3H_5^+$).

2,3-Dihydro-2(S)-methyl-8-nitro-1,5-benzoxazepin-4(5H)-one [(*S*)-**26**]

Prepared as the second major product of the nitration of (*S*)-**3** [see (*S*)-**22**]. Yield 38%, m.p. 195°C. IR (KBr): 3180, 3100, 1690, 1590, 1520, 1490, 1335, 1225 cm^{-1}; ^{1}H-NMR (*DMSO-d*$_6$): δ 1.35 (d, 3H), 2.62 (dd, 1H), 2.75 (dd, 1H), 4.76 (m, 1H), 7.22 (d, 1H), 7.79 (d, 1H), 7.94 (dd, 1H); ^{13}C-NMR (*DMSO-d*$_6$): δ 20.7 (CH_3), 42.4 (CH_2), 77.6 (CH), 118.0 (CH), 119.4 (CH), 121.5 (CH), 138.2 (C), 143.0 (C), 146.8 (C), 170.7 (C=O); MS *m*/e (% relative intensity): 222 (16, M^+), 180 (1), 154 (4), 69 (100, $C_4H_5O^+$), 51 (10, $C_4H_3^+$), 41 (39, $C_3H_5^+$).

8-Amino-2,3-dihydro-2(S)-methyl-1,5-benzoxazepin-4(5H)-one [(*S*)-**27**]

(*S*)-**26** (2.11 mmol) was hydrogenated in ethanolic solution (200 ml) in the presence of Pd/C (10%) catalyst to yield 0.374 g product (92%), m.p. 215°C. IR (KBr): 3440, 3360, 3180, 3120, 1670, 1620, 1510, 1210 cm^{-1}; ^{1}H-NMR (*DMSO-d*$_6$): δ 1.26 (d, 3H), 2.26 (dd, 1H), 2.47 (1H, overlapped by the solvent signal), 4.66 (m, 1H), 5.12 (s, NH_2), 6.24 (d, 1H), 6.28 (dd, 1H), 6.66 (d, 1H); ^{13}C-NMR (*DMSO-d*$_6$): δ 21.0 (CH_3), 41.0 (CH_2), 78.6 (CH), 108.2 (CH), 109.8 (CH), 121.0 (C), 122.7 (CH), 146.3 (C), 148.2 (C), 170.3 (C=O); MS *m*/e (% relative intensity): 192 (77, M^+), 150 (13), 135 (10), 124 (100), 94 (22, $C_6H_6O^+$), 69 (16, $C_4H_5O^+$), 41 (25, $C_3H_5^+$).

2,3-Dihydro-8-isopropylamino-2(S)-methyl-1,5-benzoxazepin-4(5H)-one [(*S*)-**28**]

Compound (*S*)-**26** (0.613 mmol) was dissolved in acetone (50 ml) and hydrogenated in the presence of Pd/C (10%) catalyst to obtain 0.11 g product (76%), m.p. 148–149°C. IR (KBr): 3380, 3160, 1670, 1615, 1510, 1210 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.18 (dd, 6H), 1.40 (d, 3H), 2.49 (dd, 1H), 2.66 (dd, 1H), 3.48 (s, NH), 3.55 (m, 1H), 4.78 (m, 1H), 6.27–6.74 (m, 3 aromatic protons), 7.45 (s, NH); ^{13}C-NMR ($CDCl_3$): δ 21.2 (CH_3), 22.8 (CH_3), 22.9 (CH_3), 41.3 (CH_2), 44.4 (CH), 78.9 (CH), 107.3 (CH), 109.2 (CH), 120.3 (C), 123.0 (CH), 146.3 (C), 149.8 (C), 171.7 (C=O); MS *m*/e (% relative intensity): 234 (60, M^+), 219 (100, *M*-CH_3), 177 (16), 166 (6), 151 (24), 69 (10, $C_4H_5O^+$), 41 (18, $C_3H_5^+$).

8-Acetamido-2,3-dihydro-2(S)-methyl-1,5-benzoxazepin-4(5H)-one [(*S*)-**29**]

A mixture of (*S*)-**27** (0.417 mmol), acetic anhydride (1.0 ml) and anhydrous dichloromethane (2.0 ml) was stirred overnight at room temperature, then the precipitate filtered off and purified by column chromatography to afford 0.057 g material (60%), m.p. 246-248°C. IR (KBr): 3310, 3280, 1640, 1560 cm^{-1}; ^{1}H-NMR (*DMSO-d*$_6$): δ 1.29 (d, 3H), 2.00 (s, 3H), 2.36 (dd, 1H), 2.56 (dd, 1H), 4.71 (m, 1H), 6.90 (d, 1H), 7.18 (dd, 1H), 7.36 (d, 1H); ^{13}C-NMR (*DMSO-d*$_6$): δ 20.9 (CH_3), 23.9 (CH_3), 41.4 (CH_2), 78.4 (CH), 113.4 (CH), 114.5 (CH), 121.8 (CH), 126.9 (C), 136.3 (C), 147.2 (C), 168.0 (C=O), 170.3 (C=O); MS *m*/e (% relative intensity): 234 (58, M^+), 192 (23, *M*-CH_2CO), 166 (35), 150 (20), 135 (8), 124 (100), 69 (50, $C_4H_5O^+$), 43 (54, CH_3CO^+).

8-Chloro-2,3-dihydro-2(S)-methyl-1,5-benzoxazepin-4(5H)-one [(*S*)-**30**]

(*S*)-**27** (0.52 mmol) was converted into (*S*)-**30** under reaction conditions described for the preparation of compound (*S*)-**25**. Yield 38%, m.p. 191–193°C. IR (KBr): 3180, 3110, 1680, 1490, 1220 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.43 (d, 3H), 2.58 (dd, 1H), 2.73 (dd, 1H), 4.78 (m, 1H), 6.90 (d, 1H), 7.04 (m, 2H); ^{13}C-NMR ($CDCl_3$): δ 21.2 (CH_3), 41.9 (CH_2), 78.5 (CH), 122.6 (CH), 123.5 (CH), 124.2 (CH), 129.2 (C), 130.4 (C), 148.4 (C), 171.7 (C=O); MS *m*/e (% relative intensity): 211 (30, M^+), 169 (14), 143 (45), 69 (100, $C_4H_5O^+$), 51 (5, $C_4H_3^+$), 41 (34, $C_3H_5^+$).

8-Bromo-2,3-dihydro-2(S)-methyl-1,5-benzoxazepin-4(5H)-one [(*S*)-**31**]

(*S*)-**27** (0.812 mmol) was converted into (*S*)-**31** under reaction conditions described for (*S*)-**25** using $CuBr_2$ instead of $CuCl_2$. Yield 34%, m.p. 190–191°C. IR (KBr): 3180, 3110, 1690, 1495, 1230 cm^{-1};

^{1}H-NMR (acetone-d_6): δ 1.40 (d, 3H), 2.52 (dd, 1H), 2.71 (dd, 1H), 4.81 (m, 1H), 7.05 (d, 1H), 7.23 (m, 2H); ^{13}C-NMR (acetone-d_6): δ 21.3 (CH_3), 42.3 (CH_2), 79.9 (CH), 116.9 (C), 124.1 (CH), 126.8 (CH), 127.7 (CH), 132.7 (C), 149.8 (C), 170.8 (C=O); MS *m/e* (% relative intensity): 257 (45, $M^{81}Br^+$), 213 (12), 189 (34), 69 (100, $C_4H_5O^+$), 51 (15, $C_4H_3^+$), 41 (20, $C_3H_5^+$).

2,3-Dihydro-2(S),5-dimethyl-8-nitro-benzoxazepin-4(5H)-one [(*S*)-**32**]

A mixture of (*S*)-**26** (0.360 mmol), KOH (1.44 mmol), and iodomethane (0.721 mmol) was allowed to react as described for compound (*S*)-**15** to obtain 0.026 g yellow crystals (31%), m.p. 140°C. IR (chloroform): 1680, 1600, 1530, 1500, 1350, 1230 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.44 (d, 3H), 2.44 (dd, 1H), 2.70 (dd, 1H), 3.37 (s, 3H), 4.95 (m, 1H), 7.29 (d, 1H), 7.93 (d, 1H), 8.07 (dd, 1H); ^{13}C-NMR ($CDCl_3$): δ 20.5 (CH_3), 34.7 (CH_3), 41.0 (CH_2), 82.1 (CH), 119.6 (CH), 120.3 (CH), 122.2 (CH), 144.6 (C), 145.1 (C), 148.4 (C), 169.4 (C=O); MS *m/e* (% relative intensity): 236 (10, M^+), 179 (3), 168 (5), 133 (5), 69 (100, $C_4H_5O^+$), 51 (10, $C_4H_3^+$), 41 (45, $C_3H_5^+$).

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