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GABA Receptor Agonists. Synthesis of Muscimol Analogues Including (*R*)- and (*S*)-5-(1-Aminoethyl)-3-isoxazolol and (*RS*)-5-Aminomethyl-2-isoxazolin-3-ol

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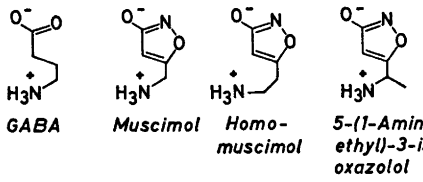
The muscimol analogues 4-methyl-5-(2-aminoethyl)-3-isoxazolol (*5a*), (*RS*)-5-(1-methyl-2-aminoethyl)-3-isoxazolol (*5b*), (*RS*)-4-methyl-5-(1-aminoethyl)-3-isoxazolol (*5c*), and (*RS*)-5-(2-aminopropyl)-3-isoxazolol (*17*) have been prepared. Furthermore the syntheses of (*S*)- and (*R*)-5-(1-aminoethyl)-3-isoxazolol (*18*) and (*19*) from (*S*)- and (*R*)-alanine and the synthesis of (*RS*)-5-aminomethyl-2-isoxazolin-3-ol hydrochloride (*24*) from (*RS*)-3-hydroxy-4-aminobutyric acid are described.

Various neurological diseases may be treated by γ-aminobutyric acid (GABA) replacement therapy based on drugs which mimic the central actions of GABA.[1–4] Consequently potent GABA receptor agonists like muscimol,[5–8] homomuscimol,[7,8] and 5-(1-aminoethyl)-3-isoxazolol[7,8] (Scheme 1) have pharmacological

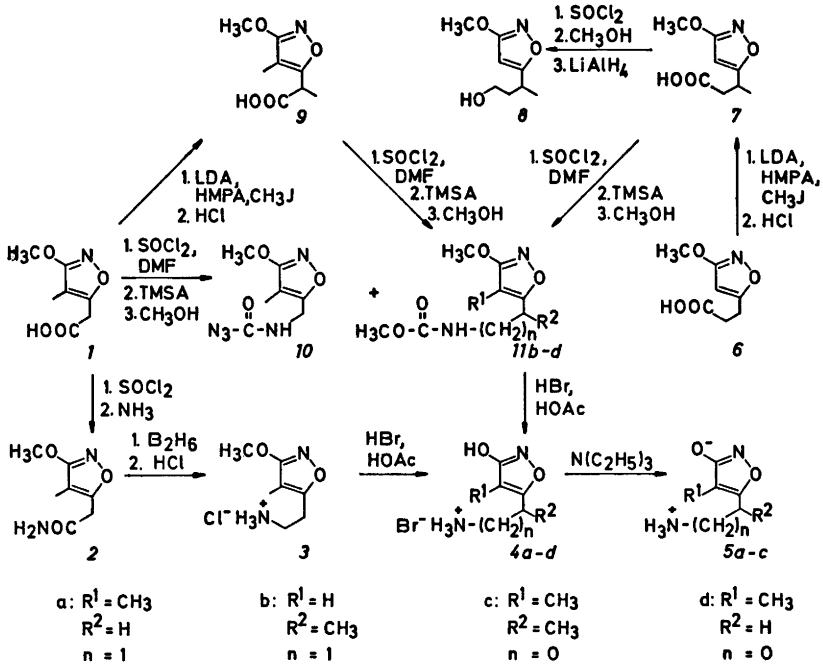


Scheme 1.

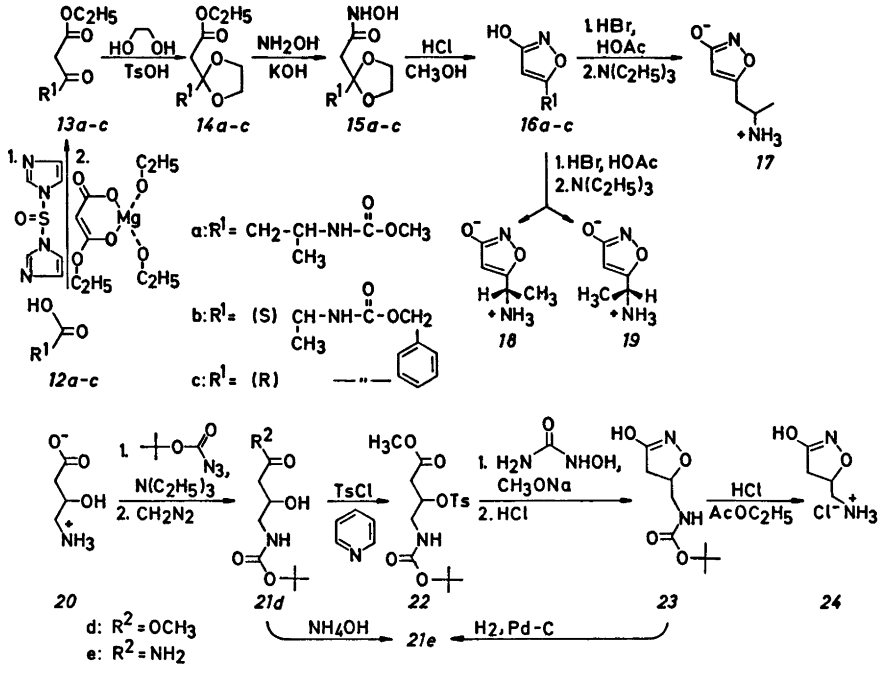
interest. The concentrations of homomuscimol, (*RS*)-5-(1-aminoethyl)-3-isoxazolol, and muscimol required for 50 % inhibition of binding of ^{3}H-GABA to GABA receptor sites on rat brain membranes[9] (IC_{50} values) are 10 μM, 7 μM, and 0.024 μM, respectively.[8] Based on this affinity binding test (*RS*)-4,5-dihydromuscimol (5-aminomethyl-2-isoxazolin-3-ol) hydrochloride (*24*) is equipotent with muscimol and (*S*)-(−)-5-(1-aminoethyl)-3-isoxazolol (*18*) is about forty times more potent than the (*R*)-form (*19*) (Scheme 3).[10] The muscimol analogues *4d*, *5a–c* (Scheme 2), and *17* (Scheme 3), however, are weak or inactive as GABA receptor agonists.[7,8] These findings indicate pronounced substrate specificity and stereoselectivity of the GABA receptors. This paper describes the syntheses of *5a–c*, *17*, *24*, and of *18* and *19* with known absolute configuration and an improved synthesis of *4d*.

The preparation of *5a* from *1* through a series of conventional reactions is outlined in Scheme 2. In the synthesis of *9* from *1* dimethylation of the side chain of *1* was avoided by using only slight excess of base and methyl iodide. Under similar reaction conditions, described to give α-methylated carboxylic acids,[11,12] *6* was methylated regiospecifically at the carbon atom α to the isoxazole ring to give *7*. The urethanes *11b,c*, prepared from *7* and *9* by a modified Curtius rearrangement,[13] were converted into *5b,c*. The synthesis of *11d* from *1*, however, was accompanied by the formation of the carbamoyl azide *10*. The mechanism for the formation of *10* under these conditions is unknown, but the yield of *11d* was optimized by using equivalent amounts of trimethylsilyl azide (TMSA). The route from *1* to *4d via 11d* represents an improved synthesis of *4d*.[14]

The 3-isoxazolol zwitterions *17–19* were prepared from the appropriate *N*-protected amino acids *12a–c* as shown in Scheme 3, *18* and *19* having the same absolute con-



Scheme 2.



Scheme 3.

figuration as (*S*)- and (*R*)-alanine, respectively. Racemization of *13b,c* under the reaction conditions described was not observed. In one experiment for the preparation of *14b*, however, pH of the reaction mixture containing *13b* was adjusted to *ca.* 0 instead of 3. Further reactions with this sample of *14b* gave almost completely racemized products of *16b* and *18*.

Compound *22*, obtained by stepwise protection of (*RS*)-3-hydroxy-4-aminobutyric acid (*20*), was treated with hydroxyurea under basic conditions to give the 2-isoxazolin-3-ol derivative *23*, deprotection of which gave *24*. The conversion of *22* into *23* may involve elimination of 4-toluenesulfonate from *22* followed by nucleophilic addition, and subsequent cyclization reactions between the α,β-unsaturated intermediate formed and the hydroxyurea anion in analogy with the reaction described for the preparation of 2-isoxazolin-3-ols from α,β-unsaturated esters.[15]

The structure determinations of the new compounds *2*, *3*, *4a–c*, *5*, *7–12a,c*, *13–19*, and *21–24* were based on elemental analyses, IR and ^{1}H NMR spectroscopy, in the case of the isoxazole derivatives supported by UV spectroscopy. The structure of *7* was determined by conversion into *8*. The depicted position of the methyl group in *8* was established by the presence of a triplet at δ 3.7 in the ^{1}H NMR spectrum. Crude products of *13a–c* and *15a–c*, which were not isolated in a pure state, were analyzed by thin-layer chromatography(TLC) using pertinent spraying reagents (*cf.* EXPERIMENTAL). Based on optical rotation measurements and comparisons of the identical IR-spectra of *18* and *19* with the quite different spectrum of (*RS*)-5-(1-aminoethyl)-3-isoxazolol[16] *18* and *19* were optically pure. The constitution of *23* was established by hydrogenolysis of *23* to give *21e*, which was identical with *21e* obtained by ammonolysis of *21d*. The extent to which the respective isoxazolidin-3-one tautomers contribute to the structures of *23* and *24* could not be decided on the basis of the spectroscopic studies carried out.

EXPERIMENTAL

Melting points, determined in capillary tubes, are corrected. Elemental analyses were made by Mr. P. Hansen, Chemical Laboratory II, University of Copenhagen. A Perkin-Elmer grating infrared spectrophotometer model 247, a Perkin-Elmer ultraviolet-visible spectrophotometer model 402, a JEOL JMN-C-60HL (60 MHz) ^{1}H NMR instrument, and a Perkin-Elmer polarimeter 141 were used. ^{1}H NMR spectra were recorded by using TMS as an internal standard and those of compounds dissolved in D_2O by using sodium 3-(trimethylsilyl)propanesulfonate. TLC and column chromatography (CC) were accomplished by using silica gel F_{254} plates (Merck) and silica gel (Woelm 0.063–0.1 mm), respectively. Columns were developed by stepwise gradient elution. The β-oxoesters *13a–c* were visualized on TLC plates by using a 2,4-dinitrophenylhydrazine (DNP) spraying reagent. The same spraying agent followed by heating of the TLC plates to 100 °C for 5 s was used to visualize the ketals *14a–c*, whereas an iron(III) chloride spraying agent was used to visualize *15a–c* on TLC plates. The pK_A values were determined as earlier described.[13]

(3-Methoxy-4-methylisoxazol-5-yl)acetamide (2). To a stirred suspension of *1*[14] (3.65 g; 21.3 mmol) in thionyl chloride (15 ml) was added *N,N*-dimethylformamide (DMF) (200 μl). Stirring was continued for 3 min. The solution was evaporated *in vacuo* and the oily residue extracted with ether (3 × 100 ml). The combined ether phases were saturated with gaseous ammonia at 0 °C and left at 25 °C for 18 h. Upon addition of acetone (50 ml) and stirring for 30 min the mixture was filtered. The filtrate was evaporated *in vacuo* and the crystalline residue recrystallized (benzene) to give *2* (2.45 g; 68 %), m.p. 126.0–127.0 °C. Anal. $C_7H_{10}N_2O_3$: C, H, N. IR (KBr): 3380 (s), 3190 (s), 2890–2780 (m, several bands), 1670 (s), 1610 (m), 1530 (s). UV [methanol (log ε)]: 217 (3.82) nm. ^{1}H NMR (60 MHz, $CDCl_3$): δ 6.5–5.6 (2 H, broad signal), 3.88 (3 H, s), 3.52 (2 H, s), 1.83 (3 H, s).

2-(3-Methoxy-4-methylisoxazol-5-yl)ethylammonium chloride (3). To a solution of *2* (2. 38 g; 14 mmol) in dry tetrahydrofuran (THF) (175 ml) was added diborane, externally generated[17] from sodium borohydride (2.86 g; 75.6 mmol) in dry diglyme (80 ml) and boron trifluoride etherate (11.5 g; 81.2 mmol) in dry diglyme (70 ml). The solution was refluxed for 19 h and after cooling to 25 °C hydrochloric acid (25 ml; 4 M) was added. The solution was evaporated to dryness *in vacuo* and upon addition of an aqueous solution of potassium hydroxide (20 ml; 25 %) the mixture was extracted with ether (4 × 50 ml). The combined and dried (K_2CO_3) ether phases were evaporated *in vacuo*. To a solution of the oily residue in ether (25 ml) was added methanolic hydrogen chloride (25 ml; 7 %) and *3* (1.42 g; 53 %) crystallized, m.p. 143.5–144.0 °C. Anal. $C_7H_{13}ClN_2O_2$: C, H, Cl, N. IR (KBr): 3600–3300 (m), 3300–2300 (s), 2050 (w), 1660 (s), 1530 (s), 1465 (s) cm^{-1}. UV [methanol (log ε)]:

216 (3.81) nm. ^{1}H NMR (60 MHz, DMSO-d_6): δ 8.8–7.8 (3 H, broad signal), 3.85 (3 H, s), 3.03 (4 H, s), 1.80 (3 H, s).

2-(3-Hydroxy-4-methylisoxazol-5-yl)ethylammonium bromide (4a). A solution of *3* (1.12 g; 5.8 mmol) in a solution of hydrogen bromide in glacial acetic acid (10 ml; 43 %) was refluxed for 5 min. Upon evaporation to dryness *in vacuo* the residue was treated with the same reagent (10 ml) for a further 5 min. Evaporation to dryness *in vacuo* and recrystallization (methanol–ether) gave *4a* (1.07 g; 84 %), m.p. 198–200 °C (decomp.). Anal. $C_6H_{11}BrN_2O_2$: C, H, Br, N. IR (KBr): 3600–3300 (m), 3300–2300 (s), 2005 (w), 1670 (s), 1550 (s), 1500 (s), 1465 (s) cm^{-1}. UV (methanol): <210 nm. ^{1}H NMR (60 MHz, DMSO-d_6): δ 8.4–7.6 (3 H, broad signal), 3.2–2.7 (4 H, broad s), 1.80 (3 H, s).

4-Methyl-5-(2-aminoethyl)-3-isoxazolol zwitterion (5a). To a solution of *4a* (400 mg; 1.8 mmol) in water (1.5 ml) was added a solution of triethylamine (192 mg; 1.9 mmol) in ethanol (1.5 ml). The mixture was left at 5 °C for 16 h to give crude *5a*. Recrystallization (water–ethanol) gave *5a* (123 mg; 48 %), m.p. 142–144 °C (decomp.). Anal. $C_6H_{10}N_2O_2$: C, H, N. IR (KBr): 3600–3300 (m), 3300–2000 (s), 2150 (m), 1670 (s), 1655 (s), 1565 (s), 1555 (s), 1485 (s) cm^{-1}. UV [methanol (log ε)]: 212 (3.83) nm. ^{1}H NMR (60 MHz, D_2O): δ 3.5–2.7 (4 H, m), 1.72 (3 H, s). pK_A values (H_2O, 25 °C): 5.26 ± 0.03, 9.74 ± 0.03.

(RS)-3-(Methoxyisoxazol-5-yl)butyric acid (7). To a solution of diisopropylamine (9.55 g; 94.6 mmol) in dry THF (60 ml) kept under nitrogen at −70 °C was added with stirring a solution of butyllithium in hexane (47.3 ml; 90.3 mmol) and subsequently a solution of *6* [18] (7.35 g; 43 mmol) in dry THF (30 ml). During the latter addition the temperature of the solution did not exceed −70 °C. The mixture was stirred for 30 min at −70 °C. Upon addition of hexamethylphosphoramide (HMPA) (17.2 ml; 94.6 mmol) stirring was continued for 30 min at −70 °C, after which methyl iodide (6.72 g; 47.3 mmol) was added. The solution was stirred at 25 °C for 90 min, cooled to 0 °C, and upon addition of hydrochloric acid (30 ml; 4 M) extracted with ether (4 × 100 ml). The combined ether phases were evaporated *in vacuo*, and CC of the residue [silica gel: 580 g; eluents: benzene containing ethyl acetate (33–43 %) and formic acid (1 %)] followed by ball-tube distillation at 30 Pa (oven temperature 135 °C) gave *7* (4.85 g; 61 %) as an oil, which slowly crystallized, m.p. 41–43 °C. Anal. $C_8H_{11}NO_4$: C, H, N. IR (KBr): 3600–2400 (several bands, m–s), 1710 (s), 1610 (s), 1515 (s), 1465 (s) cm^{-1}. UV (methanol): <210 nm. ^{1}H NMR (60 MHz), $CDCl_3$): δ 10.9 (1 H, s), 5.63 (1 H, s), 3.92 (3 H, s), 3.5–3.0 (1 H, m), 2.7–2.5 (2 H, m), 1.32 (3 H, d, *J* 7 Hz).

(RS)-3-(3-Methoxyisoxazol-5-yl)butanol-1 (8). A solution of *7* (278 mg; 1.5 mmol) in thionyl chloride (1.5 ml) was kept at 25 °C for 5 min. Evaporation of the solution *in vacuo* gave an oil, which was mixed with methanol (2 ml). The solution was evaporated *in vacuo*. An ether solution (5 ml) of the residue was dried (Na_2SO_4), and upon addition of lithium aluminium hydride (35.6 mg; 0.94 mmol) the mixture was refluxed for 2 h. After cooling of the reaction mixture to 25 °C hydrochloric acid (1.5 ml; 4 M) was added. The ether phase was isolated, dried (Na_2SO_4), and evaporated *in vacuo*. Ball-tube distillation of the residue at 65 Pa (oven temperature 110 °C) gave *8* (187 mg; 73 %) as an oil. Anal. $C_8H_{13}NO_3$: C, H, N. IR (film): 3550–3200 (s), 2950–2820 (several bands, m–s), 1615 (s), 1520 (s), 1470 (s), 1415 (s) cm^{-1}. UV [methanol (log ε)]: 212 (3.88) nm. ^{1}H NMR (60 MHz, $CDCl_3$): δ 5.63 (1 H, s), 3.99 (3 H, s), 3.7 (2 H, t, *J* 6 Hz), 3.3–2.8 (1 H, m), 2.36 (1 H, s), 2.1–1.7 (2 H, m), 1.31 (3 H, d, *J* 7 Hz).

(RS)-3-Methoxy-5-(N-methoxycarbonyl-1-methyl-2-aminoethyl)isoxazole (11b). A solution of *7* (2.22 g; 12 mmol) in thionyl chloride (10 ml) was kept at 25 °C for 5 min. Evaporation of the solution *in vacuo* gave an oil, which was dissolved in tetrachloromethane (10 ml). Trimethylsilyl azide (TMSA) (1.52 g; 13.2 mmol) was added and the solution refluxed for 2 ½ h. After cooling to 25 °C methanol (1.92 g; 60 mmol) was added and the solution refluxed for 90 min. Evaporation of the solution *in vacuo* and ball-tube distillation of the oily residue at 40 Pa (oven temperature 135 °C) gave *11b* (2.13 g; 83 %) as an oil. Anal. $C_9H_{14}N_2O_4$: C, H, N. IR (film): 3325 (s), 3130 (w), 2975 (s), 2945 (s), 1720 (s), 1705 (s), 1610 (s), 1515 (s) cm^{-1}. UV [methanol (log ε)]: 210 (3.89) nm. ^{1}H NMR [60 MHz, $CDCl_3$-CCl_4 (1:1)]: δ 5.67 (1 H, s), 5.6–5.3 (1 H, broadened t), 3.92 (3 H, s), 3.66 (3 H, s), 3.5–3.3 (2 H, broadened t), 3.2–2.7 (1 H, m), 1.29 (3 H, d, *J* 5 Hz).

(RS)-2-(3-Hydroxyisoxazol-5-yl)propylammonium bromide (4b). *4b* was prepared as described for *4a* by using *11b* (1.28 g; 6 mmol). Recrystallization of crude *4b* (ethanol-ether) gave *4b* (755 mg; 56 %) m.p. 140–142 °C (decomp.). Anal. $C_6H_{11}BrN_2O_2$: C, H, Br, N. IR (KBr): 3530–3300 (m), 3300–2300 (several bands, m–s), 1630 (s), 1550 (s), 1505 (s) cm^{-1}. UV [methanol (log ε)]: 210 (3.90) nm. ^{1}H NMR (60 MHz, DMSO-d_6): δ 8.8–7.5 (3 H, m), 5.93 (1 H, s), 3.8–2.8 (3 H, m), 1.30 (3 H, d, *J* 6 Hz).

(RS)-5-(1-Methyl-2-aminoethyl)-3-isoxazolol zwitterion (5b). *5b* was prepared as described for *5a* by using *4b* (223 mg; 1 mmol) dissolved in water (0.5 ml) and triethylamine (111 mg; 1.1 mmol) dissolved in ethanol (5 ml). *5b* (115 mg; 81 %) crystallized, m.p. 186–187 °C (decomp.). Anal. $C_6H_{10}N_2O_3$: C, H, N. IR (KBr): 3600–3300 (m), 3300–2000 (several bands, m–s), 2195 (m), 1615 (s), 1570 (s),

1520–1460 (several bands, s) cm^{-1}. UV [methanol (log ε)]: 210 (3.87) nm. ^1H NMR (60 MHz, D_2O): δ 5.63 (1 H, s), 3.3–2.7 (3 H, m), 1.30 (3 H, d, J 7 Hz). pK_A values (H_2O, 20 °C): 5.08 ± 0.06, 9.34 ± 0.06.

(RS)-2-(3-Methoxy-4-methylisoxazol-5-yl)propionic acid (9). *9* was prepared as described for *7* by using diisopropylamine (4.4 g; 44 mmol) dissolved in dry THF (40 ml), a solution of butyllithium in hexane (24.8 ml; 42 mmol), *1*[14] (3.42 g; 20 mmol), HMPA (8.0 ml; 44 mmol), and methyl iodide (2.98 g; 21 mmol). Upon addition of hydrochloric acid (30 ml; 4 M) the reaction mixture was extracted with ether (4 × 100 ml). The combined ether phases were extracted with aqueous sodium hydroxide (2 × 50 ml; 1 M). The combined aqueous phases were acidified with hydrochloric acid (30 ml; 4 M) and extracted with ether (3 × 100 ml). The combined and dried (Na_2SO_4) ether phases were evaporated *in vacuo* and the residue recrystallized (ethyl acetate–light petroleum) to give *9* (3.12 g; 84 %), m.p. 118.0–120.0 °C. Anal. $C_6H_{11}NO_4$: C, H, N. IR (KBr): 3600–2400 (several bands, m–s), 1740 (s), 1655 (s), 1540 (s) cm^{-1}. UV [methanol (log ε)]: 214 (3.82) nm. ^1H NMR (60 MHz, $CDCl_3$): δ 10.96 (1 H, s), 3.90 (3 H, s), 3.8 (1 H, q, J 7 Hz), 1.78 (3 H, s), 1.5 (3 H, d, J 7 Hz).

(RS)-3-Methoxy-4-methyl-5-(N-methoxycarbonyl-1-aminoethyl)isoxazole (11c). *11c* was prepared as described for *11b* by using *9* (1.85 g; 10 mmol), thionyl chloride (8 ml), TMSA (1.27 g; 11 mmol), and methanol (1.60 g; 50 mmol). Ball-tube distillation of the crude reaction product at 53 Pa (oven temperature 135 °C) gave *11c* (1.67 g; 78 %) as an oil. Found: C 49.95; H 6.72; N 12.90. Calc. for $C_9H_{14}N_2O_4$: C 50.46; H 6.59; N 13.08. IR (film): 3320 (s), 2985 (s), 2955 (s), 2875 (m), 1725 (s), 1710 (s), 1655 (s), 1530 (s) cm^{-1}. UV [methanol (log ε)]: 212 (3.81) nm. ^1H NMR (60 MHz, $CDCl_3$): δ 5.3 (1 H, broadened d, J 8 Hz), 5.1–4.6 (1 H, m), 3.89 (3 H, s), 3.59 (3 H, s), 1.85 (3 H, s), 1.4 (3 H, d, J 7 Hz).

(RS)-1-(3-Hydroxy-4-methylisoxazol-5-yl)-ethylammonium bromide (4c). *4c* was prepared as described for *4a* by using *11c* (1.28 g; 6 mmol). Recrystallization of crude *4c* (ethanol–ether) gave *4c* (930 mg; 70 %), m.p. 229–230 °C (decomp.). Anal. $C_6H_{11}BrN_2O_2$: C, H, Br, N. IR (KBr): 3550–3300 (m), 3300–2400 (several bands, m–s), 1655 (m), 1550 (s), 1510 (s) cm^{-1}. UV (methanol: < 210 nm. ^1H NMR (60 MHz, DMSO-d_6): δ 12.0–11.3 (1 H, broad signal), 9.0–8.2 (3 H, broad signal), 4.6 (1 H, q, J 7 Hz), 1.87 (3 H, s), 1.5 (3 H, d, J 7 Hz).

(RS)-4-Methyl-5-(1-aminoethyl)-3-isoxazolol zwitterion (5c). *5c* was prepared as described for *5a* by using *4c* (223 mg; 1 mmol) dissolved in water (0.5 ml) and triethylamine (111 mg; 1.1 mmol) in ethanol (5 ml). *5c* (130 mg; 92 %) crystallized, m.p. 245–246 °C (decomp.). Found: C 50.25; H 7.24; N 19.48. Calc. for $C_5H_{10}N_2O_2$: C 50.69; H 7.09; N 19.71. IR (KBr): 3600–3200 (m), 3200–2000 (several bands, m–s), 2205 (s), 1660 (s), 1550 (m), 1520–1440 (several bands, s) cm^{-1}. UV [methanol (log ε)]: 213 (3.74) nm. pK_A values (H_2O, 25 °C): 4.63 ± 0.03, 8.58 ± 0.02.

3-Methoxy-4-methyl-5-(N-methoxycarbonylaminomethyl)isoxazole (11d) and 3-methoxy-4-methyl-5-(N-azidocarbonylaminomethyl)isoxazole (10). *To a stirred mixture of 1*[14] (2.56 g; 15 mmol) and thionyl chloride (12 ml) was added DMF (120 μl). The solution was stirred for a further 3 min and then evaporated *in vacuo*. The oily residue was extracted with ether (3 × 10 ml) and the combined ether phases evaporated *in vacuo* to give an oil. A solution of this crude acid chloride in tetrachloromethane (10 ml) was treated with TMSA (1.75 g; 15 mmol) and methanol (2.40 g; 75 mmol) as described for *11b* to give a mixture of *11d* and *10*. CC [silica gel: 200 g; eluents: dichloromethane containing ethyl acetate (15–40 %)] of the mixture and recrystallization of the separated components gave pure *11d* and *10*. *11d* (1.23 g; 42 %) had m.p. 84.5–85.0 °C (ether-light petroleum). Anal. $C_8H_{12}N_2O_4$: C, H, N. IR (KBr): 3325 (s), 2995 (m), 2950 (m), 1720 (s), 1695 (s), 1655 (s), 1530 (s), 1460 (s) cm^{-1}. UV [methanol (log ε)]: 215 (3.87) nm. ^1H NMR (60 MHz, $CDCl_3$): δ 5.5–5.0 (1 H, broad signal), 4.2 (2 H, d, J 6 Hz), 3.90 (3 H, s), 3.58 (3 H, s), 1.82 (3 H, s). *10* (220 mg; 7 %) had m.p. 91.5–92.0 °C (ether–light petroleum). Anal. $C_7H_9N_5O_3$: C, H, N. IR (KBr): 3260 (s), 3040 (m), 2960 (w), 2440 (w), 2145 (s), 1710 (s), 1655 (m), 1550 (s), 1530 (s) cm^{-1}. IR (CCl_4): 3445 (m), 3400–3150 (m), 3010–2800 (several bands, m–w), 2400 (w), 2150 (s), 1710 (s), 1655 (m), 1535–1500 (several bands, s) cm^{-1}. UV [methanol (log ε)]: 212 (4.09) nm. ^1H NMR (60 MHz, $CDCl_3$): δ 6.3–5.8 (1 H, broad signal), 4.4 (2 H, d, J 6 Hz), 3.98 (3 H, s), 1.91 (3 H, s).

(3-Hydroxy-4-methylisoxazol-5-yl)methylammonium bromide (4d). *4d* was prepared as described for *4a* by using *11d* (1.50 g; 7.5 mmol). Recrystallization of crude *4d* (methanol-benzene) gave *4d* (780 mg; 50 %), m.p. 220–221 °C (decomp.) [Ref. 14, m.p. 227–229 °C (decomp.)]. Anal. $C_5H_9BrN_2O_2$: C, H, Br, N. IR (KBr): 3600–3300 (m), 3300–2300 (several bands, m–s), 2050 (w), 1680 (m), 1600 (m), 1580 (s), 1575 (s), 1495 (s) cm^{-1}. UV [methanol (log ε)]: 211 (3.87) nm. ^1H NMR (60 MHz, DMSO-d_6): δ 11.0–10.0 (1 H, broad signal), 8.7–8.3 (3 H, broad signal), 4.02 (2 H, s), 1.84 (3 H, s). pK_A values (H_2O, 25 °C): 4.76 ± 0.03, 8.75 ± 0.01.

(RS)-N-Methoxycarbonyl-3-aminobutyric acid (12a). To a stirred solution of (*RS*)-3-aminobutyric acid (6.19 g; 60 mmol) and potassium carbonate (20.7 g; 150 mmol) in water (60 ml) was added at 0 °C methyl chloroformate (6.8 g; 72 mmol). After stirring for a further 30 min at 0 °C concentrated hydrochloric acid (25 ml)

was added, and the solution extracted with ether (7 × 50 ml). Evaporation of the combined and dried (Na_2SO_4) ether phases gave TLC-pure *12a* (5.76 g; 59 %) [R_F 0.62; eluent: ethyl acetate – methanol – formic acid (90:10:1)]. An analytical sample was recrystallized (ethyl acetate – toluene) to give *12a*, m.p. 93.0 – 94.0 °C. Anal. $C_6H_{11}NO_4$: C, H, N. IR (KBr): 3335 (s), 3200 – 2400 (several bands, w – m), 1710 – 1685 (s), 1540 (s) cm^{-1}. ^1H NMR [60 MHz, $CDCl_3$ – DMSO-d_6 (3:1)]: δ 11.0 (1 H, s), 5.7 – 5.3 (1 H, broad signal), 4.5 – 3.8 (1 H, m), 3.67 (3 H, s), 2.53 (2 H, d, J 6 Hz), 1.23 (3 H, d, J 6.5 Hz).

(RS)-Ethyl N-methoxycarbonyl-3-oxo-5-amino-hexanoate ethylene acetal (14a). To a stirred solution of *12a* (5.2 g; 32 mmol) in dry THF (25 ml) was added a solution of *N,N'*-thionyldiimidazole[19] (6.4 g; 35 mmol) in dry THF (140 ml). The solution formed was added to a stirred suspension of monoethyl malonate diethoxy magnesium enolate[19] (10.8 g; 70 mmol in dry THF (70 ml). Stirring was continued for 90 min and after addition of hydrochloric acid (61 ml; 4 M) (pH *ca.* 3) for a further 15 min. The solution was concentrated *in vacuo* to *ca.* 75 ml and extracted with ether (3 × 100 ml). The combined and dried (Na_2SO_4) ether phases were evaporated *in vacuo* to give crude *13a* (7.4 g) as an oil, characterized by TLC [R_F 0.32; eluent: dichloromethane – ethyl acetate (4:1)]. A mixture of crude *13a* (7.4 g), 4-toluenesulfonic acid (0.3 g), ethylene glycol (18 ml), and toluene (130 ml) was refluxed for 3 d using a Dean-Stark water separator. The mixture was washed with aqueous sodium carbonate (50 ml; 2 M) and saturated aqueous sodium chloride (50 ml). The dried (K_2CO_3) organic phase was evaporated *in vacuo* to give crude *14a* (6.8 g). CC [silica gel: 200 g; eluents: dichloromethane containing ethyl acetate (15 – 21 %)] gave *14a* (2.65 g; 30 % based on *12a*) as an oil. Found: C 51.85; H 7.41; N 5.09. Calc. for $C_{12}H_{21}NO_6$: C 52.35; H 7.69; N 5.09. IR (film): 3370 (s), 2980 (s), 2900 (s), 1735 – 1690 (s), 1540 (s) cm^{-1}. ^1H NMR (60 MHz, CCl_4): δ 5.3 – 5.0 (1 H, broad signal), 4.01 (q, J 7 Hz), 3.87 (s), and 4.2 – 3.6 (m) (a total of 7 H), 3.53 (3 H, s), 2.50 (2 H, s), 2.1 – 1.6 (2 H, m), 1.23 (t, J 7 Hz) and 1.15 (d, J 6.5 Hz) (a total of 6 H).

(RS)-5-(N-Methoxycarbonyl-2-aminopropyl)-3-isoxazolol (16a). To a stirred solution of hydroxylammonium chloride (2.57 g; 37 mmol) in methanol (14 ml) was added at 0 °C methanolic potassium hydroxide (8.5 ml; 5.0 M) and a solution of *14a* (2.59 g; 9.4 mmol) in methanol (5 ml). The mixture was left at 5 °C for 4 d. Upon addition of glacial acetic acid (3.6 ml) the mixture was filtered and evaporated *in vacuo* to give a very viscous mass. CC [silica gel: 125 g; eluents: ethyl acetate containing methanol (10 – 15 %) and formic acid (1 %)] gave TLC-pure *15a* (2.0 g) [R_F 0.28; eluent: ethyl acetate – methanol-formic acid (90:10:1)]. A solution of crude *15a* (2.0 g) in methanol – concentrated hydrochloric acid [12 ml; (1:1)] was heated at 75 °C for 20 min. The solution was concentrated *in vacuo* to 6 ml and upon addition of water (10 ml) extracted with chloroform (4 × 20 ml). The combined and dried (Na_2SO_4) chloroform phases were evaporated *in vacuo* and the residue recrystallized (ethanol – toluene) to give *16a* (670 mg; 37 %, based on *14a*), m.p. 135.0 – 136.5 °C. Anal. $C_8H_{12}N_2O_4$: C, H, N. IR (KBr): 3370 (s), 3200 – 2300 (several bands, s – m), 1690 (s), 1625 (s), 1550 (s), 1535 (s), 1460 (m) cm^{-1}. UV [methanol (log ε)]: 211 (3.86) nm. ^1H NMR (60 MHz, $CDCl_3$): δ 9.2 – 8.3 (1 H, broad signal), 6.5 – 6.2 (1 H, broadened d), 5.68 (1 H, s), 4.3 – 3.7 (1 H, m), 3.59 (3 H, s), 3.0 – 2.6 (2 H, m), 1.18 (3 H, d, J 7 Hz).

(RS)-5-(2-Aminopropyl)-3-isoxazolol zwitterion (17). *16a* (250 mg; 1.25 mmol) was treated with a solution of hydrogen bromide in glacial acetic acid (2 × 3 ml; 43 %) as described for *4a*. To a solution of the evaporated reaction product in water (150 µl) was added a solution of triethylamine (132 mg; 1.31 mmol) in ethanol (800 µl). The solution was left at 5 °C for 14 d. *17* (103 mg; 58 %) crystallized, m.p. 155 °C (decomp.). Anal. $C_6H_{10}N_2O_2$: C, H, N. IR (KBr): 3600 – 3150 (s), 3100 – 2200 (several bands, s – m), 2165 (w), 1625 (m), 1605 (s), 1500 – 1465 (s) cm^{-1}. UV (methanol): < 210 nm. ^1H NMR (60 MHz, D_2O): δ 5.60 (1 H, s), 3.9 – 3.5 (1 H, m), 2.92 (2 H, d, J 7 Hz), 1.33 (3 H, d, J 7 Hz).

(S)-Ethyl N-benzyloxycarbonyl-3-oxo-4-amino-valerate ethylene acetal (14b). *14b* was synthesized as described for *14a* by using *12b* (23.2 g; 104 mmol) {$[\alpha]_D^{28}$ – 14.9° (*c* 1.1, ethanol)}, *N,N'*-thionyldiimidazole[19] (21.1 g; 116 mmol), monoethyl malonate diethoxy magnesium enolate[19] (35.8 g; 232 mmol), and hydrochloric acid (203 ml; 4 M). Crude *13b* (30.3 g) was obtained and analyzed by TLC [R_F 0.61; eluent: dichloromethane – ethyl acetate (4:1)]. Crude *13b* (30.3 g) was acetalized by using ethylene glycol (32 ml), 4-toluenesulfonic acid (1.1 g), and toluene (450 ml). CC of crude *14b* [silica gel: 300 g; eluents: dichloromethane containing ethyl acetate (20 – 25 %)] gave *14b* (14.4 g; 41 %, based on *12b*) as an oil. Anal. $C_{17}H_{23}NO_6$: C, H, N. IR (film): 3450 (m), 3065 (w), 3040 (w), 2980 (s), 2895 (m), 1745 – 1705 (s), 1530 (s), 1520 (s), 1455 (s) cm^{-1}. ^1H NMR (60 MHz, CCl_4): δ 7.30 (5 H, s), 5.03 (s) and 5.2 – 4.8 (m) (a total of 3 H), 4.03 (q, J 7 Hz), 4.0 – 3.8 (m), and 4.4 – 3.7 (m) (a total of 7 H), 2.60 (2 H, s), 1.17 (d, J 6 Hz) and 1.13 (t, J 7 Hz) (a total of 6 H).

(S)-(–)-5-(N-Benzyloxycarbonyl-1-amino-ethyl)-3-isoxazolol (16b). *16b* was synthesized as described for *16a* by using *14b* (14.4 g; 43 mmol), hydroxylammonium chloride (12.0 g; 172 mmol), methanolic potassium hydroxide (35.2 ml; 5.5 M), and glacial acetic acid (16.5 ml). CC of the evaporated mixture [silica gel: 250 g;

eluents: ethyl acetate containing methanol (15 – 20 %) and formic acid (1 %)] gave crude *15b* (8.4 g) as an oil [R_F 0.32; eluent: ethyl acetate – methanol-formic acid (90:10:1)]. Crude *15b* (8.4 g) was converted into *16b* by treatment with methanol – concentrated hydrochloric acid [60 ml; (1:1)]. Crude *16b* was recrystallized (ethanol – benzene) to give *16b* (1.09 g; 10 %, based on *14b*), m.p. 133.0 – 134.0 °C. Anal. $C_{13}H_{14}N_2O_4$: C, H, N. $[\alpha]_D^{28}$ – 56.7° (*c* 1.1, ethanol). IR (KBr): 3600 – 3200 (s), 3310 (s), 3200 – 2400 (several bands, m – w), 1690 (s), 1620 (m), 1610 (m), 1545 (s), 1530 (s) cm^{-1}. UV (methanol): < 210 nm. ^1H NMR [60 MHz, $CDCl_3$ – DMSO-d_6 (9:1)]: δ 9.0 – 8.6 (1 H, broad signal), 7.30 (5 H, s), 6.6 – 6.3 (1 H, broadened d), 5.65 (1 H, s), 5.02 (s) and 5.1 – 4.5 (m) (a total of 3 H), 1.43 (3 H, d, *J* 7 Hz).

(S)-(–)-5-(1-Aminoethyl)-3-isoxazolol zwitterion (18). A solution of *16b* (300 mg; 1.14 mmol) in a solution of hydrogen bromide in glacial acetic acid (3 ml; 43 %) was heated to 100 °C for 7 min and then evaporated *in vacuo*. A solution of the residue in water (7 ml) was extracted with ether (3 × 10 ml). The aqueous phase was evaporated *in vacuo*. To a solution of the residue in water (0.5 ml) was added triethylamine (122 mg; 1.21 mmol) dissolved in ethanol (1.2 ml). The solution was left at 5 °C for 18 h. *18* (115 mg; 79 %) crystallized, m.p. 200 °C (decomp.). Anal. $C_5H_8N_2O_2$: C, H, N. $[\alpha]_D^{28}$ – 10.5°, $[\alpha]_{436}^{28}$ – 19.3° (*c* 1.2, water). IR (KBr): 3600 – 3300 (*m*), 3150 – 2350 (several bands, s – m), 2250 (s), 1640 (s), 1615 (s), 1565 (m), 1525 (s), 1515 (s), 1510 (s), 1495 (s), 1490 (s), 1450 (m) cm^{-1}. UV [methanol (log ε)]: 210 (3.74) nm. ^1H NMR (60 MHz, D_2O): δ 5.82 (1 H, s), 4.53 (1 H, q, *J* 7 Hz), 1.62 (3 H, d, *J* 7 Hz).

(R)-(+)-N-Benzyloxycarbonylalanine (12c). The procedure for the preparation of *12c* is analogous with that described for *12a*. The starting materials were (*R*)-(–)-alanine [4.46 g; 50 mmol; $[\alpha]_{546}^{20}$ – 17.5° (*c* 5.0, 5 M HCl)], benzyl chloroformate (11.1 g; 65 mmol), potassium carbonate (17.3 g; 125 mmol) and concentrated hydrochloric acid (20 ml). Recrystallization (toluene) of crude *12c* gave *12c* (10.3 g; 92 %), m.p. 80.0 – 82.0 °C. Anal. $C_{11}H_{13}NO_4$: C, H, N. $[\alpha]_D^{28}$ + 15.8° (*c* 0.97, ethanol). IR (KBr): 3340 (s), 3200 – 2500 (several bands, s – m), 1720 – 1680 (s), 1545 (s), 1540 (s), 1535 (s) cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$): δ 10.3 (1 H, s), 7.30 (5 H, s), 5.7 – 5.3 (1 H, broad signal), 5.11 (2 H, s), 4.7 – 4.3 (1 H, m), 1.42 (3 H, d, *J* 7 Hz).

(R)-Ethyl N-benzyloxycarbonyl-3-oxo-4-aminovalerate ethylene acetal (14c). *14c* was prepared as described for *14a* by using *12c* (9.37 g; 42 mmol), *N,N'*-thionyldiimidazole [19] (8.37 g; 46 mmol), monoethyl malonate diethoxy magnesium enolate [19] (14.2 g; 92 mmol), and hydrochloric acid (81 ml; 4 M). Crude *13c*, analysed as described for *13b*, was acetalized by using ethylene glycol (16 ml), 4-toluenesulfonic acid (0.45 g), and toluene (200 ml). CC of crude *14c* [silica gel: 200 g; eluents: dichloromethane containing ethyl acetate (20 – 30 %)] gave *14c* (3.6 g; 25 %, based on *12c*) as an oil. The IR spectrum was identical with that of *14b*.

(R)-(+)-5-(N-Benzyloxycarbonyl-1-aminoethyl)-3-isoxazolol (16c). *16c* was synthesized as described for *16a* by using *14c* (5.7 g; 17 mmol), hydroxylammonium chloride (4.70 g; 68 mmol), methanolic potassium hydroxide (15.4 ml; 4.95 M), and glacial acetic acid (6.5 ml). CC of the evaporated reaction mixture [silica gel: 200 g; eluents: ethyl acetate containing methanol (10 – 20 %) and formic acid (1 %)] gave crystalline *15c* (3.7 g), analysed as described for *15b*. *15c* (3.7 g) was converted into *16c* by treatment with methanol-concentrated hydrochloric acid [24 ml; (1:1)]. Crude *16c* was recrystallized (ethanol – benzene) to give *16c* (671 mg; 15 %, based on *14c*), m.p. 132.0 – 134.0 °C. $[\alpha]_D^{28}$ + 54.8° (*c* 0.91, ethanol). The IR spectrum was identical with that of *16b*.

(R)-(+)-5-(1-Aminoethyl)-3-isoxazolol zwitterion (19). *16c* (393 mg; 1.50 mmol) was converted into *19* as described for *18* by using a solution of hydrogen bromide in glacial acetic acid (2 ml) and triethylamine (159 mg; 1.58 mmol). *19* (122 mg; 64 %) crystallized, m.p. 193 °C (decomp.). $[\alpha]_D^{28}$ + 10.9°, $[\alpha]_{436}^{28}$ + 19.6° (*c* 0.92, water). The IR spectrum was identical with that of *18* and different from that of (*RS*)-5-(1-aminoethyl)-3-isoxazolol zwitterion.[16]

(RS)-Methyl N-tert-butyloxycarbonyl-3-hydroxy-4-aminobutyrate (21d). To a stirred solution of *20* (2.0 g; 16.8 mmol) in water (25 ml) was added at 0 °C triethylamine (5.1 g; 50.4 mmol) and subsequently a solution of *tert*-butyl azidoformate (3.3 g; 22.9 mmol) in dioxane (25 ml). Stirring was continued at 25 °C for 1 ½ h. The solution was concentrated *in vacuo* to 25 ml and extracted with ether (2 × 30 ml). The ether phases were discarded and upon addition of hydrochloric acid (20 ml; 1 M) the aqueous phase was extracted with ethyl acetate (3 × 30 ml). The combined and dried (Na_2SO_4) ethyl acetate phases were evaporated *in vacuo* to give crude (*RS*)-*N-tert*-butyloxycarbonyl-3-hydroxy-4-aminobutyric acid (2.45 g). To a mixture of this crude product (2.45 g; 12 mmol) and ether (250 ml) was added with stirring a solution of diazomethane (*ca.* 1 g; 24 mmol) [prepared from *N*-methyl-*N*-nitroso-4-toluenesulfonamide (5.4 g; 24 mmol)] in ether (60 ml). Excess of diazomethane was destroyed by addition of glacial acetic acid (0.5 ml). Evaporation of the reaction mixture *in vacuo* gave *21d* (2.57 g; 66 %, based on *20*) as an oil. Anal. $C_{10}H_{19}NO_5$: C, H, N. IR (film): 3700 – 3100 (m), 2970 (m), 2930 (m), 1740 – 1670 (several bands, s), 1525 (s), 1435 (s) cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$): δ 7.5 – 6.9 (1 H, m), 5.3 – 4.8 (1 H, m), 4.2 – 3.8 (1 H, m), 3.65 (3 H, s), 3.3 – 2.9 (2 H, m), 2.45 (2 H, d, *J* 6 Hz), 1.43 (9 H, s).

(RS)-Methyl N-tert-*butyloxycarbonyl-3-(4-toluenesulfonyloxy)-4-aminobutyrate (22).* To a solution of *21d* (16.0 g; 69 mmol) in pyridine (140 ml) was added 4-toluenesulfonyl chloride (13.1 g; 69 mmol). Upon standing at 5 °C for 4 d ice water (400 ml) was added and the mixture extracted with chloroform (3 × 250 ml). The combined chloroform phases were washed with water (300 ml), dried (Na_2SO_4) and evaporated *in vacuo*. Recrystallization (toluene – light petroleum) of the crude product gave *22* (16.8 g; 63 %), m.p. 79.0 – 80.0 °C. Anal. $C_{17}H_{25}NO_7S$: C, H, N, S. IR (KBr): 3420 (m), 2980 (m), 2930 (m), 1735 (s), 1695 (s), 1595 (m), 1515 (s), 1440 (m) cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$): δ 7.9 – 7.1 (4 H, m), 5.1 – 4.5 (2 H, m), 3.6 – 3.2 (5 H, m), 2.58 (2 H, d, J 6 Hz), 2.40 (3 H, s), 1.40 (9 H, s).

(RS)-N-tert-Butyloxycarbonyl-5-aminomethyl-2-isoxazolin-3-ol (23). To a stirred solution of sodium (2.1 g; 91.6 mmol) in methanol (32 ml) was added hydroxyurea (3.2 g; 41.6 mmol) and subsequently a solution of *22* (16.1 g; 41.6 mmol) in methanol (90 ml). The reaction mixture was left at 40 °C for 2 h and at 25 °C for 20 h. Upon filtration, pH of the mixture was adjusted to 3 with hydrochloric acid (1 M) and the mixture was evaporated *in vacuo*. The residue was taken up in water (100 ml) and extracted with ethyl acetate (3 × 100 ml). The combined, dried (Na_2SO_4), and concentrated organic phases were submitted to CC [silica gel: 450 g; eluents: toluene containing ethyl acetate (75 – 90 %) and formic acid (1 %)] to give crude *23* (3.3 g; 37 %). Recrystallization (benzene – light petroleum) of an analytical sample gave *23*, m.p. 87 – 92 °C. Anal. $C_9H_{16}N_2O_4$: C, H, N. IR (KBr): 3500 – 3100 (m), 2975 (m), 2930 (m), 1710 (s), 1670 (s), 1640 (m), 1530 (m) cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$): δ 9.4 – 9.0 (1 H, m), 5.4 – 4.8 (1 H, m), 4.8 – 4.3 (1 H, m), 3.7 – 3.1 (2 H, m), 2.7 – 2.1 (2 H, m), 1.46 (9 H, s).

(RS)-5-Aminomethyl-2-isoxazolin-3-ol hydrochloride (24). To a solution of hydrogen chloride in ethyl acetate (11 ml; 3.4 M) was added dropwise at 0 °C a solution of *23* (400 mg; 1.85 mmol) in ethyl acetate (14.5 ml). Upon standing *24* (256 mg; 91 %) precipitated as very hygroscopic crystals. Recrystallization (DMF – acetonitrile) of an analytical sample gave *24*, m.p. 163 – 164 °C (decomp.). Found: C 31.85; H 6.12; Cl 22.25; N 18.37. Calc. for $C_4H_9ClN_2O_2$: C 31.46; H 5.95; Cl 23.24; N 18.36. IR (KBr): 3600 – 3275 (m), 3275 – 2500 (s), 1675 (s), 1620 (m), 1605 (m) cm^{-1}. ^1H NMR (60 MHz, D_2O): δ 5.3 – 4.8 (1 H, m), 3.8 – 3.3 (2 H, m), 3.3 – 2.5 (2 H, m). pK_A values (H_2O, 24 °C): 5.75 ± 0.04, 9.25 ± 0.04.

(RS)-N-tert-Butyloxycarbonyl-3-hydroxy-4-aminobutyramide (21e). a. To aqueous ammonia (8 ml; ϱ 0.87) was added *21d* (300 mg; 1.3 mmol), and the solution was left for 17 h. The solution was evaporated *in vacuo* and the residue submitted to CC [silica gel: 35 g; eluents: dichloromethane containing ethyl acetate (20 %) and methanol (10 – 20 %)] to give crude *21e* (276 mg; 98 %). Recrystallization (ethanol – toluene) of an analytical sample gave *21e*, m.p. 103.5 – 104.5 °C. Anal. $C_9H_{18}N_2O_4$: C, H, N. IR (KBr): 3370 (s), 3200 (s), 2980 (m), 2930 (m), 1680 (s), 1655 (s), 1530 (s) cm^{-1}. ^1H NMR [60 MHz, $CDCl_3$ – DMSO-d_6 (4:1)]: δ 7.4 – 7.0 (1 H, m), 6.7 – 6.3 (1 H, m), 6.3 – 5.8 (1 H, m), 5.0 – 4.7 (1 H, m), 4.1 – 3.8 (1 H, m), 3.3 – 2.9 (2 H, m), 2.28 (2 H, d, J 6 Hz), 1.45 (9 H, s).

b. To a solution of *23* (100 mg; 0.46 mmol) in methanol (10 ml) was added Pd-black catalyst (40 mg). To the stirred mixture was continuously added hydrogen for 3 h. The reaction mixture was filtered and evaporated *in vacuo* to give pure crystalline *21e* (96 mg; 96 %). The IR spectrum was identical with that of *21e* prepared from *21d*.

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