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Facile Stereoselective Synthesis of γ-Substituted γ-Amino Acids from the Corresponding α-Amino Acids

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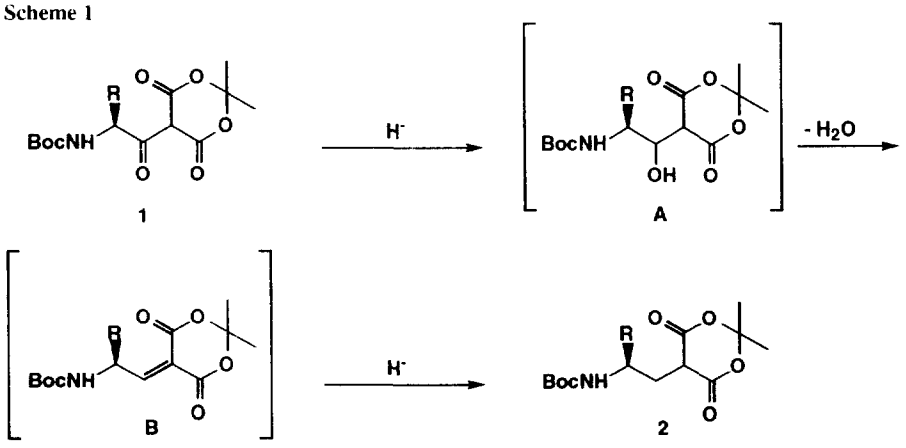
Abstract: A facile stereoselective method for the synthesis of γ-substituted, γ-amino acids from α-amino acids was developed. The key step of the procedure is complete reduction of the keto functionality of α-amino acyl Meldrum's acid by sodium acetoxyborohydride. The resulting amino alkyl Meldrum's acid undergoes thermal decarboxylative ring closure to a 5-substituted pyrrolidinone which yields the corresponding γ-amino acid after basic hydrolysis. The overall yield of the procedure ranges from 40 to 65%. © 1997 Elsevier Science Ltd.

INTRODUCTION

During repeated syntheses of 3-hydroxy-4-t-butoxycarbonylamino-5-phenyl pentanoic acid (BocAHPPA, **7a**) using a slight modification of the procedure of Jouin and Castro[1] (see Scheme 2, from **1** to **7**) we consistently observed a side product after sodium acetoxyborohydride mediated reduction of crude tetramic acid **5a**. The amount was inversely proportional to the purity of the starting tetramic acid and was negligible when recrystallized **5a** was used for the reaction. Analysis of the NMR spectra of the side product revealed three carbonyl groups and the acetonide moiety still present. It was thus assigned structure **2a**, resulting from complete reduction of the exocyclic carbonyl of **1a**. Unreacted **1a** present in crude **5a** apparently underwent reduction of its ketone functionality, followed by dehydration of the resulting ß-hydroxydiester **A** to unsaturated ester **B** which via Michael addition of hydride ion was further reduced to **2** (Scheme 1). A literature search revealed that the analogous reduction of acyl derivatives of Meldrum's acid and barbituric acid has been described,[2] but its synthetic potential remained almost unexplored.

Scheme 1



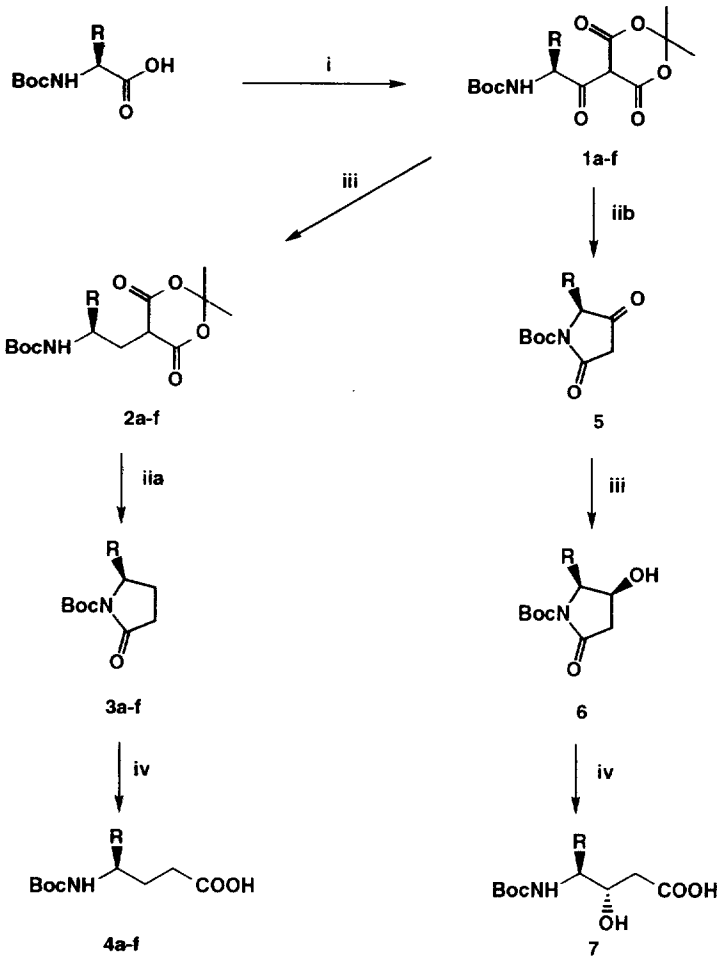
Decarboxylative ring closure of compound **2** forms the N-Boc-5-substituted pyrrolidinone **3**, precursor of the corresponding γ-substituted-γ-amino acid **4**. These functionalities are found in natural compounds[3,4,5] and have been used for peptide modification.[6,7] γ-Amino acids possess various biological activities, e.g. β-aminoadipic acid (aspartic acid analogue) binds to Glu and Asp receptors in brain,[8,9] 5-mercapto-4-aminopentanoic acid (cysteine analogue) is a potent inhibitor of glutamyl aminopeptidase[10] and 5-hydroxy-4-aminopentanoic acid (serine analogue) is an inhibitor of γ-amino butyric acid transaminase, an enzyme important in neurotransmission.[11] γ-Substituted, γ-amino acids could also serve as building blocks for combinatorial chemistry.

We thus sought to explore the utility of this method of converting α-amino acids into γ-amino acids by two carbon extension. Interestingly, there are apparently only two general methods described in the literature for obtaining enantiomerically pure γ-amino acids from the obvious precursors, the α-amino acids. The first method employs the well established Arndt-Eistert elongation that must be done twice;[12,13] the second method uses alkylation of diethylmalonate by substituted N-tosyl aziridines prepared *in situ* from N,O-ditosylates of amino alcohols derived from α-amino acids.[14] The product of alkylation is then subjected to 17 h reflux in 47% HBr to remove the N-tosyl protecting group and yield the unprotected γ-amino acid. Both methods suffer from severe drawbacks. The method based on the Arndt-Eistert procedure is not suitable for scaleup since it is lengthy and requires the use of hazardous diazomethane; the second method is not compatible with any side chain protection or sensitive functionality. Probably the most practical synthesis of γ-amino acids is based on multistep derivatization of the α-carboxy function of glutamic acid using alkyl cuprates.[15] A major limitation is incompatibility of cuprates with many functionalities. Recently a Wittig based homologation of α-amino aldehydes was published, but the paper lacks any experimental details.[19]

RESULTS AND DISCUSSION

In our method (Scheme 2) the N-t-butoxycarbonyl (Boc) protected amino acid is coupled with Meldrum's acid at 0 °C in dichloromethane using dicyclohexylcarbodiimide (DCC) and 4-dimethylamino-pyridine (DMAP) for activation. The precipitated dicyclohexyl urea is filtered off and DMAP removed by bisulfate extraction. The CH_2Cl_2 solution is dried with $MgSO_4$ and used directly for the sodium acetoxyborohydride reduction which gives **2**, typically in 60 to 90% overall yield. The intermediates **2** are stable and easy to purify. To obtain pure samples for characterization column chromatography was used (see experimental). However, since all compounds with the exception of **2c** are crystalline the chromatography is usually not necessary and a single crystallization is sufficient for preparative purposes. The decarboxylative ring closure of **2a-f** does not proceed as easily as in the case of their oxo-derivatives **1a-f**. Therefore the temperature was increased from 77 to 110 °C and the reaction time extended. Under these conditions the reaction proceeds smoothly and gives the 5-substituted pyrrolidinones **3a-f** in high yields and sufficient purity to be used for the next step. The final basic hydrolysis gives the N-Boc-γ-amino acids **4a-f** in almost quantitative yield. Not surprisingly, the benzyl ester moiety of aspartic acid analogue **3f** was partially (approx. 30%) saponified to (R)-3-t-butoxycarbonylamino hexanedioic acid (**8f**). The convenience of the present method is best shown by its comparison with the published procedure based on alkylation of diethylmalonate.[14] Our method is shorter, yields directly the N-Boc protected γ-amino acid, and because the reaction conditions in all steps are mild, is compatible with most common side chain protecting groups and sensitive functionalities.

Scheme 2



R= a) benzyl, b) i-propyl, c) i-butyl, d) benzyloxymethyl, e) benzylthiomethyl, f) benzyloxycarbonyl methyl
i) Meldrum's acid, DCC, DMAP, CH_2Cl_2, 0°C, 12h; iia) toluene, reflux, 3h; iib) ethyl acetate, reflux, 2h; iii) $NaBH_4$, AcOH, CH_2Cl_2, -5°C, 8h; iv) NaOH, acetone, water, 0.5h

Since the above mentioned synthesis of statines[1] was reported to be stereoselective, we expected the chirality of the original α-amino acid to be preserved in our synthesis. Among the compounds reported here only two Boc-γ-amino acids (**4c** and **4d**)[6,7] and three N-Boc-pyrrolidinones (**3a**, **3b** and **3d**)[5,17,18] were previously mentioned in the literature and their analytical data were sometimes incomplete. We compared the optical rotations of the above compounds with literature values where they were available (**3a**, **3b**, **3d** and **4d**). All measured values were slightly higher or identical with those in the literature exept for **3d** where the value was lower [$[\alpha]_D$ +60.5° (c 3.4; $CHCl_3$) vs.-77° (c 1; $CHCl_3$) reported for S enantiomer[17]]. However the

optical rotation of **4d** that was obtained from **3d** by hydrolysis in 90% yield matched the literature value.[6] To get a direct proof of enantiomeric purity of the product γ-amino acids we first prepared (S)-**4a** ((S)-BocAPPA) from D-phenylalanine and then coupled both (S)-**4a** and (R)-**4a** with (R)-1-phenyl ethylamine. Unfortunately both derivatives had identical retention time on RP-HPLC. Therefore, we deprotected both compounds and coupled them with Boc-(S)-valine. The obtained Boc-(S)-Val-(S)-APPA-(R)-phenethylamide and Boc-(S)-Val-(R)-APPA-(R)-phenethylamide were separable by RP-HPLC (see experimental). Neither of the compounds showed any detectable contamination by the other.

EXPERIMENTAL

Materials and Equipment. Melting points were measured on an Electrothermal IA 9000 series digital melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer digital polarimeter model 241 with an error of $< \pm 0.3°$. ^{1}H- and ^{13}C-NMR spectra were recorded either on a Varian VXR-S-500 (500 MHz) or a Varian Gemini 200 (200 MHz) in $CDCl_3$ or DMSO solutions at 25 °C with TMS as internal reference. The high resolution mass spectra were measured on a VG 70-250HF double focusing mass spectrometer (70 eV, 6 kV) using a direct inlet probe. FAB spectra were recorded on a VG ZAB-2F Mass Spectrometer with a LS/MS Cs^+ gun (5 kV) in a dithiothreitol matrix. The Boc amino acids were purchased from Advanced ChemTech and ChemImpex International. Yields refer to isolated product showing one spot on TLC and no impurities detectable in the NMR spectra.

Typical procedure for step 1: 20 mmol of Boc-protected L-amino acid was dissolved with 22 mmol Meldrum's acid (3.02 g), and 31 mmol DMAP (3.85 g) in 100 mL CH_2Cl_2. The reaction mixture was cooled to -5 °C and a solution of 22 mmol DCC (4.74 g) in 50 mL CH_2Cl_2 was added dropwise over 1 hour. The mixture was left at < 0 °C overnight, during which time tiny crystals of dicyclohexylurea precipitated. After filtration the reaction mixture was washed 4x with 5% $KHSO_4$, 1x with brine and dried in the refrigerator with $MgSO_4$ for 5 hours. This solution was used for the second step without characterization or further purification.

Typical procedure for step 2: The solution of **1(a-f)** from the previous reaction was cooled to -5 °C and 13.3 mL (220 mmol) of 98% AcOH was added. Then 1.85 g (50 mmol) of $NaBH_4$ was added in small portions while stirring over 1 hour. The reaction mixture was left in the refrigerator overnight and then washed 3x with brine and 2x with water. Organic phase was dried with $MgSO_4$, filtered and evaporated to dryness. Products were purified by column chromatography through a 50 g pad of silica gel. The mobile phase for **2a** and **2b** was hexane/ethyl acetate 1:1; for **2c** and **2d** hexane/ethyl acetate/acetic acid 3:1:0.1; for **2e** hexane/ethyl acetate 2:1 and for **2f** hexane/ethyl acetate/acetic acid 2:1:0.1.

Typical procedure for step 3: Pure **2(a-f)** from the previous step was refluxed in 50 mL of toluene. TLC in ethyl acetate/hexane 2:1 indicated complete conversion after 3 hours. After evaporation of solvent, the compound was pure enough for the final step.

Typical procedure for step 4: Pyrrolidinone **3(a-f)** (8 mmol) was dissolved in 15 mL of acetone and 24 mL of 1M aqueous NaOH was added. The reaction mixture was stirred at 22 °C for 30 minutes. Acetone was removed under reduced pressure and the reaction mixture was acidified with 6M HCl to pH 2. All compounds **4(a-f)** precipitated as solids, were filtered off, washed 2x with water and recrystallized from a mixture of ethyl acetate/hexane.

Proof of stereochemical integrity : The (R)-BocAPPA was activated using TBTU and coupled with 1.5 molar excess of (R)-2-phenylethylamine in DMF. After evaporation of solvent, the product was precipitated by addition of 5% solution $NaHCO_3$. The precipitate was washed with 5% $NaHCO_3$, 5% $KHSO_4$ and water and dried in vacuo, yield > 95%. The product was then deprotected by trifluoroacetic acid (TFA) and the obtained trifluoroacetate coupled overnight with 1.5 molar excess of Boc-(S)-Val-ONSu. Aminoethylmorpholine was then added to the mixture, which was then concentrated in vacuo and worked up as described above, yield > 95%. The obtained Boc-(S)-Val-(R)-APPA-(R)-phenethylamide exhibited a peak at 17.1 min on reverse phase HPLC, column VYDAC C-18, 4.6x250 mm, flow 1.0 mL/min, gradient 50 - 100% MeOH (0.05% TFA) in 25 min. The same procedure was used to prepare the Boc-(S)-Val-(S)-APPA-(R)-phenethylamide, which exhibited a peak at 18.0 min under the same conditions.

(R)-5-[(2-t-Butoxycarbonylamino-3-phenyl)-propyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (2a)[16] Yield: 76%; m.p. 127-127.5 °C; (Found: C, 63.78; H, 7.39; N, 3.81. $C_{20}H_{27}NO_6$ requires C, 63.64; H, 7.21; N, 3.71%); $[\alpha]_D$ +3.8° (c 2; EtOH); ^1H NMR ($CDCl_3$) δ 1.36 (s, 9 H), 1.74 (s, 3 H), 1.78 (s, 3 H), 2.04-2.38 (m, 2 H), 2.72-2.99 (m, 2 H), 3.9 (bs, 1 H), 4.1-4.35 (m, 1 H), 4.36-4.55 (m, 1 H), 7.17-7.37 (m, 5 H); ^{13}C NMR δ 26.0 (q), 28.2 (q), 28.5 (q), 31.4 (t), 41.8 (t), 44.2 (d), 49.9 (d), 79.6 (s), 105.0 (s), 126.7 (d), 128.6 (d), 129.3 (d), 137.2 (s), 156.4 (s), 165.6 (s), 165.8 (s).

(R)-N-t-Butoxycarbonyl-5-benzyl-2-pyrrolidinone (3a)[16] Yield: 96%; oil; $[\alpha]_D$ +53.4° (c 3.8; EtOH) (lit[5] $[\alpha]_D$ +48.5° (c 1.5; EtOH)) NMR data see lit.[5]; HRMS (FAB) *m/z* 276 ($(MH)^+$, calcd. for $C_{16}H_{22}NO_3$: 276.1600, found 276.1630).

(R)-4-t-Butoxycarbonylamino-5-phenyl-pentanoic acid (4a)[16] Yield: 86%; m.p. 114-114.5 °C; (Found: C, 65.30; H, 8.00; N, 4.63. $C_{16}H_{23}NO_4$ requires C, 65.51; H, 7.90; N, 4.77%); $[\alpha]_D$ -0.7° (c 4.5; EtOH); ^1H NMR ($CDCl_3$) δ 1.38 (s, 9 H), 1.54-1.98 (m, 2 H), 2.40 (dd, *J* = 6.8 Hz, 6.8 Hz, 2 H), 2.65-2.88 (m, 2 H), 3.64-4.00 (m, 1 H), 4.44 (d, *J* = 7.7 Hz, 1 H), 7.13-7.34 (m, 5 H); ^{13}C NMR δ 28.2 (q), 29.4 (t), 31.0 (t), 41.7 (t), 51.2 (d), 79.5 (s), 126.5 (d), 128.4 (d), 129.4 (d), 137.7 (s), 155.8 (s), 178.2 (s); FAB *m/z* 316 (MNa^+), 294 (MH^+); HRMS (CI) *m/z* (%) 294 ($(MH)^+$,1.4, calcd. for $C_{16}H_{24}NO_4$: 294.1705, found 294.1753).

(R)-5-[(2-t-Butoxycarbonylamino-3-methyl)-butyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (2b) Yield: 58%; m.p. 122 °C; (Found: C, 58.44; H, 8.47; N, 4.20. $C_{16}H_{27}NO_6$ requires C, 58.34; H, 8.26; N, 4.25%); $[\alpha]_D$ +12.3° (c 3; EtOH); ^1H NMR ($CDCl_3$) δ 0.94 (d, *J* = 3.4 Hz, 3 H), 0.98 (d, *J* = 3.4 Hz, 3 H), 1.41 (s, 9 H), 1.76 (d, *J* = 0.5 Hz, 3 H), 1.80 (d, *J* = 0.6 Hz, 3 H), 1.62-1.92 (m, 1 H), 2.00-2.35 (m, 2 H), 3.66-3.84 (m, 1 H), 3.90-4.01 (dd, *J* = 6.5 Hz, 2.8 Hz, 1 H), 4.48 (d, *J* = 9.6 Hz, 1 H); ^{13}C NMR δ 17.8 (q), 19.0 (q), 25.8 (q), 28.2 (q), 28.5 (q), 29.1 (t), 32.6 (d), 44.5 (d), 54.4 (d), 79.4 (s), 104.9 (s), 156.9 (s), 165.7 (s), 166.1 (s).

(R)-N-t-Butoxycarbonyl-5-isopropyl-2-pyrrolidinone (3b) Yield: 94%; oil; $[\alpha]_D$ +77.4° (c 1.4; $CHCl_3$) (lit[18] $[\alpha]_D$ +57.6° (c 1; $CHCl_3$)) ^1H NMR see lit.;[18] ^{13}C NMR δ 15.7 (q), 18.0 (t), 19.0 (q), 27.9 (q), 30.5 (d), 32.2 (t), 62.4 (d), 82.7 (s), 150.3 (s), 174.9 (s). HRMS (EI) *m/z* (%) 227 ($(M)^{+\bullet}$, 0.05 calcd. for $C_{12}H_{21}NO_3$: 227.1521 , found 227.1526), 184 (81), 171 (59), 154 (65), 140 (5), 128 (22), 111 (52), 84 (100)); HRMS (FAB) *m/z* 250 ($(MNa)^+$, calcd. for $C_{12}H_{21}NO_3Na$: 250.1419, found 250.1416).

(R)-4-t-Butoxycarbonylamino-5-methyl-hexanoic acid (4b) Yield: 75%; m.p. 103-105 °C; (Found: C, 58.71; H, 9.29; N, 5.46. $C_{12}H_{23}NO_4$ requires C, 58.75; H, 9.45; N, 5.71%); $[\alpha]_D$ +2.9° (c 4.0; EtOH); ^{1}H NMR (DMSO) δ 0.79 (d, *J* = 2.7 Hz, 3 H), 0.82 (d, *J* = 2.7 Hz, 3 H), 1.38 (s, 9 H), 1.32-1.76 (m, 3 H), 2.08-2.28 (m, 2 H), 3.10-3.30 (m, 1 H), 6.54 (d, *J* = 9.4 Hz, 1 H), 11.98 (bs, 1 H); ^{13}C NMR δ 18.2 (q), 19.0 (q), 26.5 (t), 28.2 (q), 30.7 (t), 31.9 (d), 54.7(d), 77.2 (s), 155.9 (s), 174.5 (s); HRMS (EI) *m/z* (%) 245 ((M)$^{+\bullet}$, 0.03 calcd. for $C_{12}H_{23}NO_4$: 245.1627 , found 245.1619), 202 (76), 190 (68), 172 (59), 154 (34), 146 (76), 128 (100), 84 (76).

(S)-5-[(2-t-Butoxycarbonylamino-4-methyl)-pentyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (2c) Yield: 73%; oil; (Found: C, 59.59; H, 8.85; N, 4.21. $C_{17}H_{29}NO_6$ requires C, 59.46; H, 8.51; N, 4.08%); $[\alpha]_D$ +13.3° (c 1.3; EtOH); ^{1}H NMR ($CDCl_3$) δ 0.91 (d, *J* = 6.5, 3H), 0.98 (d, *J* = 6.0, 3H), 1.45 (s, 3H), 1.46 (s, 3H), 1.55 (s, 9H), 1.24-2.40 (m, 5H), 3.89-4.45 (m, 2H), 4.91 (d, *J* = 7.5, 1H). ^{13}C NMR δ 21.7 (q), 22.8 (q), 24.7 (q), 24.9 (q), 28.2 (q), 28.6 (d), 32.3 (t), 41.4 (t), 45.2 (d), 47.9 (d), 79.5 (s), 104.9 (s), 165.7 (s), 177.6 (s);

(R)-N-t-Butoxycarbonyl-5-(2-methyl-propyl)-2-pyrrolidinone (3c) Yield: 75%; oil; $[\alpha]_D$ +65.3° (c 1.5; $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.94 (s, 3 H), 0.97 (s, 3 H), 1.53 (s, 9 H), 1.36-1.86 (m, 6 H), 1.96-2.22 (m, 1 H), 2.41 (ddd, *J* = 17.6 Hz, 9.1 Hz, 2.6 Hz, 1 H), 2.60 (ddd, *J* = 17.6 Hz, 11.4 Hz, 8.8 Hz, 1 H), 4.09-4.23 (m, 1 H), 4.9 (d, *J* = 6.7 Hz, 1 H); ^{13}C NMR δ 21.4 (q), 22.6 (t), 23.8 (q), 25.2 (q), 28.0 (q), 31.1 (t), 42.4 (t), 56.6 (d), 82.7 (s), 149.9 (s), 174.7 (s); HRMS (FAB) *m/z* 264 ((MNa)$^+$, calcd. for $C_{12}H_{21}NO_3Na$: 264.1575, found 264.1600).

(R)-4-t-Butoxycarbonylamino-6-methyl-heptanoic acid (4c) Yield: 73%; m.p. 109.5-111.5 °C (lit.[7] 91-92 °C, lit.[15] 115-117 °C); (Found: C, 60.25; H, 9.80; N, 5.29. $C_{13}H_{25}NO_4$ requires C, 60.21; H, 9.72; N, 5.40%); $[\alpha]_D$ -10.7° (c 2.9; EtOH); ^{1}H NMR ($CDCl_3$) δ 0.89 (s, 3H), 0.92 (s, 3H), 1.44 (s, 9H), 1.10 - 1.51 (m, 2H), 1.51 - 2.02 (m, 3H), 2.41 (dd, *J* = 7.3, 7.3, 2H), 3.51 - 3.82 (m, 1H), 4.31 (d, *J* = 9.1, 1H), 9.85 (bs, 1H); ^{13}C NMR δ 22.9 (q), 24.8 (q), 28.3 (q), 30.9 (t), 31.2 (t), 45.0 (t), 48.4 (d), 79.4 (s), 156.0 (s), 178.6 (s); FAB 282 (MNa$^+$), 260 (MH$^+$); HRMS (EI) *m/z* (%) 259 ((M$^{+\bullet}$), 0.1, calcd. for $C_{13}H_{25}NO_4$: 259.1784, found 259.1778), 224 (1), 202 (29), 186 (31), 158 (24), 146 (61), 130 (84), 102 (100), 86 (98).

(R)-5-[(2-t-Butoxycarbonylamino-3-benzyloxy)-propyl-2,2-dimethyl-1,3-dioxane-4,6-dione (2d) Yield: 84%; m.p. 84-87 °C; (Found: C, 61.94; H, 7.26; N, 3.79. $C_{21}H_{29}NO_7$ requires C, 61.90; H, 7.17; N, 3.44%); $[\alpha]_D$ +16.4° (c 3.0; EtOH); ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9 H), 1.72 (s, 3 H), 1.75 (s, 3 H), 2.20 (ddd, *J* = 14.5 Hz, 10.5 Hz, 3.2 Hz, 1 H), 2.43 (ddd, *J* = 14.4 Hz, 10.5 Hz, 3.2 Hz, 1 H), 3.55 (d, *J* = 3.9 Hz, 2 H), 3.93-4.24 (m, 2 H), 4.48 (d, *J* = 11.9 Hz, 1 H), 4.55 (d, *J* = 11.9 Hz, 1 H), 5.02 (b d, *J* = 6.6 Hz, 1 H), 7.14-7.40 (m, 5 H); ^{13}C NMR δ 25.8 (q), 28.2 (q), 28.5 (q), 29.4 (t), 44.2 (d), 48.7 (d), 72.4 (t), 73.3 , 79.7 (s), 104.9 (s), 127.8 (d), 127.9 (d), 128.5 (d), 137.8 (s), 156.6 (s), 165.7 (s), 165.8 (s).

(R)-N-t-Butoxycarbonyl-5-benzyloxymethyl-2-pyrrolidinone (3d) Yield: 85%; oil; $[\alpha]_D$ +60.5° (c 3.4; $CHCl_3$) [lit. $[\alpha]_D$ -77° (c 1; $CHCl_3$ S-enantiomer)];[17] ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9 H), 2.00-2.13 (m, 2 H), 2.30-2.47 (m, 1 H), 2.74 (ddd, *J* = 20.8 Hz, 10.8 Hz, 10.1 Hz, 1 H), 3.57 (dd, *J* = 9.6 Hz, 3.0 Hz, 1 H), 3.68 (dd, *J* = 9.6 Hz, 4.8 Hz, 1 H), 4.21-4.33 (m, 1 H), 4.52 (s, 2 H), 7.24-7.40 (m, 5 H); ^{13}C NMR δ 21.3 (t), 27.9 (q), 32.0 (t), 57.4 (d), 70.7 (t), 73.4 (t), 82.8 (s), 127.5 (d), 127.8 (d), 128.5 (d), 137.9 (s), 149.9 (s), 175.0 (s), HRMS (EI) *m/z* (%) 305 (M$^{+\bullet}$, 0.01, calcd. for $C_{17}H_{23}NO_3$: 305.1627, found 305.1640), 249 (0.02), 205 (22), 158 (8), 143 (14), 114 (20), 99 (78), 91 (97), 84 (100).

(R)-4-t-Butoxycarbonylamino-5-benzyloxypentanoic acid (4d) Yield: 90%; m.p. 79-81 °C; (Found: C, 63.03; H, 7.90; N, 4.24. $C_{17}H_{25}NO_5$ requires C, 63.14; H, 7.79; N, 4.33%); $[\alpha]_D$ +21.8° (c 3.2; EtOH) [lit. oil; $[\alpha]_D$ -22.2° (c 5.1; MeOH, S-enantiomer)];[6] ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9 H), 1.76-1.98 (m, 2 H), 2.41 (dd, *J* = 7.4 Hz, 7.4 Hz, 2 H), 3.43 (d, *J* = 3.6 Hz, 2 H), 3.70-3.88 (m, 1 H), 4.47 (d, *J* = 12.0 Hz, 1 H), 4.55 (d, *J* = 12.0 Hz, 1 H), 4.86 (d, *J* = 8.8 Hz, 1 H), 7.27-7.37 (m, 5 H); ^{13}C NMR δ 27.5 (t), 28.3 (q), 30.8 (t), 49.8 (d), 72.0 (t), 73.2 (t), 79.6 (s), 127.7 (d), 127.8 (d), 128.4 (d), 138.0 (s), 156.0 (s), 178.4 (s); FAB 346 (MNa$^+$), 324 (MH$^+$); HRMS (EI) *m/z* (%) 323 (M$^{+\bullet}$, 0.3, calcd. for $C_{17}H_{25}NO_5$: 323.1733, found 323.1727), 267 (16), 250 (16), 202 (63), 161 (49), 146 (73), 102 (96), 91 (100).

(R)-5-[(2-t-Butoxycarbonylamino-3-benzylthio)propyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (2e) Yield: 66%; m.p. 99-101.5 °C; (Found: C, 59.02; H, 7.06; N, 3.32; S, 7.84. $C_{21}H_{29}NO_6S$ requires C, 59.55; H, 6.90; N, 3.31; S, 7.57%); $[\alpha]_D$ -17.8° (c 1.8; EtOH); ^{1}H NMR (DMSO) δ 1.38 (s, 9 H), 1.66 (s, 3 H), 1.77 (s, 3 H), 1.95-2.28 (m, 2 H), 2.44-2.52 (m, 2 H), 3.73 (s, 2 H), 3.88-4.10 (m, 1 H), 4.12-4.22 (m, 1 H), 6.67 (d, J = 9.0 Hz, 1 H), 7.18-7.34 (m, 5 H); ^{13}C NMR δ 25.7 (q), 27.9 (q), 28.1 (q), 30.4 (t), 34.8 (t), 35.5 (t), 43.3 (d), 47.1 (d), 77.8 (s), 104.6 (s), 126.8 (d), 128.4 (d), 128.9 (d), 138.4 (s), 155.8 (s), 165.7 (s).

(R)-N-t-Butoxycarbonyl-5-benzylthiomethyl-2-pyrrolidinone (3e) Yield: 77%; oil; $[\alpha]_D$ +77.6° (c 2.0; $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 9 H), 1.80-2.30 (m, 2 H), 2.41 (ddd, J = 17.4 Hz, 9.2 Hz, 3.0 Hz, 1 H), 2.59 (ddd, J = 17.4 Hz, 10.9 Hz, 9.5 Hz, 1 H), 2.59 (dd, J = 13.2 Hz, 9.0 Hz, 1 H), 2.86 (ddd, J = 13.2 Hz, 3.1 Hz, 0.8 Hz, 1 H), 3.75 (dd, J = 14.2 Hz, 13.3 Hz, 2 H), 4.26 (dddd, J = 9.0 Hz, 8.1 Hz, 3.0 Hz, 2.1 Hz, 1 H), 7.21-7.36 (m, 5 H); ^{13}C NMR δ 22.0 (t), 27.9 (q), 31.2 (t), 34.9 (t), 36.9 (t), 57.2 (d), 83.1 (s), 127.3 (d), 128.6 (d), 128.9 (d), 137.9 (s), 149.8 (s), 174.1 (s); HRMS (EI) *m/z* (%) 321 ($M^{+\bullet}$, 0.01, calcd. for $C_{17}H_{23}NO_3S$: 321.1398, found 321.1406), 265 (9), 221 (44), 138 (48), 130 (24), 99 (86), 91 (97), 84 (100).

(R)-4-t-Butoxycarbonylamino-5-benzylthiopentanoic acid (4e) Yield: 98%; m.p. 77-79 °C; (Found: C, 60.01; H, 7.53; N, 3.98; S, 9.63. $C_{17}H_{25}NO_4S$ requires C, 60.15; H, 7.42; N, 4.13; S, 9.45%); $[\alpha]_D$ -6.0° (c 2.3; EtOH); ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9 H), 1.50-2.04 (m, 2 H), 2.38 (dd, J = 7.4 Hz, 7.4 Hz, 2 H), 2.40-2.60 (m, 2 H), 3.71 (s, 2 H), 3.74-3.88 (m, 1 H), 4.60 (d, J = 8.7 Hz, 1 H), 7.20-7.33 (m, 5 H); ^{13}C NMR δ 20.7 (t), 28.3 (q), 29.1 (t), 30.8 (t), 36.6 (t), 49.4 (d), 79.7 (s), 127.1 (d), 128.6 (d), 129.0 (d), 138.0 (s), 155.8 (s), 178.7 (s); HRMS (EI) *m/z* (%) 339 ($M^{+\bullet}$, 0.4, calcd. for $C_{17}H_{25}NO_4S$: 339.1504, found 339.1514), 283 (16), 266 (4), 222 (18), 202 (6.5), 146 (20), 138 (24), 102 (75), 91 (100).

(R)-5-[(2-t-Butoxycarbonylamino-3-benzyloxycarbonyl)-propyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (2f) Yield: 92%; m.p. 114-116 °C; (Found: C, 60.64; H, 7.00; N, 3.46. $C_{22}H_{29}NO_8$ requires C, 60.68; H, 6.71; N, 3.22%); $[\alpha]_D$ +19.6° (c 1.8; $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9 H), 1.75 (s, 3 H), 1.80 (s, 3 H), 2.19 (ddd, J = 14.3 Hz, 7.3 Hz, 3.2 Hz, 1 H), 2.40 (ddd, J = 17.4 Hz, 11.1 Hz, 3.2 Hz, 1 H), 2.63 (dd, J = 16.0 Hz, 5.5 Hz, 1 H), 2.72 (dd, J = 16.0 Hz, 5.2 Hz, 1 H), 3.88-4.02 (m, 1 H), 4.20-4.42 (m, 1 H), 5.15 (s, 2 H), 5.22-5.38 (m, 1 H), 7.33-7.40 (m, 5 H); ^{13}C NMR δ 25.8 (q), 28.2 (q), 28.5 (q), 31.0 (t), 39.4 (t), 44.2 (d), 46.2 (d), 66.7 (t), 79.9 (s), 105.1 (s), 128.4 (d), 128.4 (d), 128.7 (d), 135.5 (s), 156.3 (s), 165.4 (s), 165.5 (s), 171.1 (s).

(R)-N-t-Butoxycarbonyl-5-benzyloxycarbonylmethyl-2-pyrrolidinone (3f) Yield: 82%; oil; $[\alpha]_D$ +13.5 (c 3.8; $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.52 (s, 9 H), 1.77-1.93 (m, 1 H), 2.13-2.69 (m, 4 H), 2.95 (dd, J = 15.5 Hz, 3.2 Hz, 1 H), 4.52 (dddd, J = 9.9 Hz, 8.2 Hz, 3.2 Hz, 2.1 Hz, 1 H), 7.36 (m, 5 H); ^{13}C NMR δ 22.9 (t), 27.9 (q), 30.9 (t), 38.2 (t), 54.5 (d), 66.6 (t), 83.3 (s), 128.4 (d), 128.5 (d), 128.6 (d), 135.5 (s), 149.8 (s), 170.3 (s), 173.7 (s); HRMS (FAB) *m/z* 334 ($(MH)^+$, calcd. for $C_{18}H_{24}NO_5$: 334.1655, found 334.1668).

(R)-4-t-Butoxycarbonylamino-5-benzyloxycarbonyl pentanoic acid (4f) Yield: 80% crude, 53% pure; m.p. 95-96 °C; (Found: C, 61.51; H, 7.28; N, 3.82. $C_{18}H_{25}NO_6$ requires C, 61.52; H, 7.17; N, 3.99%); $[\alpha]_D$ -12.9° (c 2.8; EtOH); ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9 H), 1.75-1.92 (m, 2 H), 2.42 (dd, J = 7.3 Hz, 7.3 Hz, 2 H), 2.53-2.65 (m, 2 H), 3.87-4.09 (m, 1 H), 5.12 (s, 2 H), 5.08 (b s, 1H), 7.31-7.38 (m, 5 H); ^{13}C NMR δ 28.0 (t), 28.3 (q), 29.5 (t), 30.8 (t), 39.2 (t), 47.0 (d), 66.5 (t), 79.7 (s), 128.3 (d), 128.4 (d), 128.7 (d), 135.6 (s), 171.4 (s), 178.0 (s); FAB: 352 (MH^+); HRMS (EI) *m/z* (%) 351 ($M^{+\bullet}$, 0.3, calcd. for $C_{18}H_{25}NO_6$: 351.1682, found 351.1685), 295 (18), 250 (23), 222 (13), 178 (43), 160 (40), 102 (34), 91 (100).

(R)-3-t-Butoxycarbonylamino hexanedioic acid (8f) Yield: 80% crude, 20% pure; m.p. 162-164 °C; (Found: C, 50.23; H, 7.45; N, 5.12. $C_{11}H_{19}NO_6$ requires C, 50.57; H, 7.33; N, 5.36%); $[\alpha]_D$ +7.7° (c 2.6; EtOH); ^{1}H NMR (DMSO) δ 1.37 (s, 9 H), 1.47-1.79 (m, 2 H), 2.19 (t, *J* = 7.5 Hz, 2 H), 2.27 (dd, *J* = 15.3 Hz, 7.0 Hz, 1 H), 2.36 (dd, *J* = 15.3 Hz, 7.0 Hz, 1 H), 3.62-3.84 (m, 1 H), 6.70 (d, *J* = 7.7 Hz, 1 H), 12.06 (bs, 1 H); ^{13}C NMR δ 28.2 (q), 29.6 (t), 30.4 (t), 39.7 (t), 46.9 (d), 77.6 (s), 155.2 (s), 172.6 (s), 174.3 (s); FAB 328 (MNa_3^+), 306 (MNa_2^+), 284 (MNa^+); HRMS (EI) *m/z* (%) 261 ($M^{+\bullet}$, 0.1, calcd. for $C_{11}H_{20}NO_6$: 261.1212, found 261.1201), 205 (64), 188 (56), 170 (44), 160 (66), 146 (66), 132 (54), 102 (80), 88 (100).

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REFERENCES AND NOTES

1. Jouin, P., Castro, B., Nisato, D., *J. Chem. Soc. Perkin Trans.* I **1987**, 1177.
2. a) Nutaitis, C.F., Schultz, R.A., Obaza, J., Smith, F.X., *J. Org. Chem.* **1980**, *45*, 4606. b) Obaza, J., Smith, F.X., *Synth.Commun.* **1982**, *12*, 19. c) Rosowsky, A., Forsch, R., Uren, J., Wick, M., Kumar, A., Freisheim, J., *J. Med. Chem.* **1983**, *26*, 1719.
3. Harkin, S.A., Singh, O. and Thomas, E.J., *J. Chem. Soc. Perkin Trans.* I **1984**, 1489.
4. Craven, A.P., Dyke, H.J. and Thomas, E.J., *Tetrahedron* **1989**, *45*, 2417.
5. Ackermann, J., Matthes, M., Tamm, C., *Helv. Chim. Acta* **1990**, *73*, 122.
6. Rajashekhar, B. and Kaiser, E.T., *J. Biol. Chem.* **1986**, *261*, 13617.
7. a) Rich, D.H., Sun, E.T.O., *J. Med. Chem.* **1980**, *23*, 27. b) Rich, D.H., Sun, E.T.O., Singh, J. *Biochem. Biophys. Res. Commun.* **1977**, *74*, 762.
8. Robinson, M.B., Sinor, J.D., Dowd, L.A., Kerwin, J.F.,Jr. *J. Neurochem.* **1993**, *60*, 167.
9. Killinger, S., Blume, G.L., Bohart, L., Bested, A., Dias, L.S., Cooper, B., Allan, R.D., Balcar, V.J., *Neurosci . Lett.* **1996**, *216*, 101.
10. Wilk, S. and Thurston L.S., *Neuropeptides* **1990**, *16*, 163.
11. Silverman, R.B. and Levy, M.A., *J. Biol. Chem.* **1981**, *256*, 11565.
12. Chimiak, A., *Rocz. Chim.* **1969**, *43*, 299.
13. Buchschacher, P., Cassal, J.M., Furst, A.and Meier, W., *Helv. Chim. Acta* **1977**, *60*, 2747.
14. Tseng, C.C., Terashima, S. and Yamada, S., *Chem. Pharm. Bull.* **1977**, *25*, 29.
15. El Marini, A., Roumestant, M.L., Viallefont, Ph., Razafindramboa, D., Bonato, M., Follet, M., *Synthesis* **1992**, 1104.
16. (S)-enantiomers of **2a**, **3a** and **4a** prepared from D-phenylalanine exhibited identical physical properties except for opposite α_D values.
17. Katoh, T., Nagata, Y., Kobayashi, Y., Arai, K., Minami, J., Terashima, S., *Tetrahedron Lett.* **1993**, *34*, 5743.
18. Schmidt, U., Riedl, B., Haas, G., Griesser, H., Vetter, A., Weinbrenner, S., *Synthesis* **1993**, 216.
19. Hanessian, S. and Schaum, R., *Tetrahedron Lett.* **1997**,*38*, 163.

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