Synthesis of (2*S*,3*S*,4*S*)-4-Amino-2,3-dihydroxyhexanedioic Acid Derivatives from (*R*)-Pyroglutamic Acid[1)]

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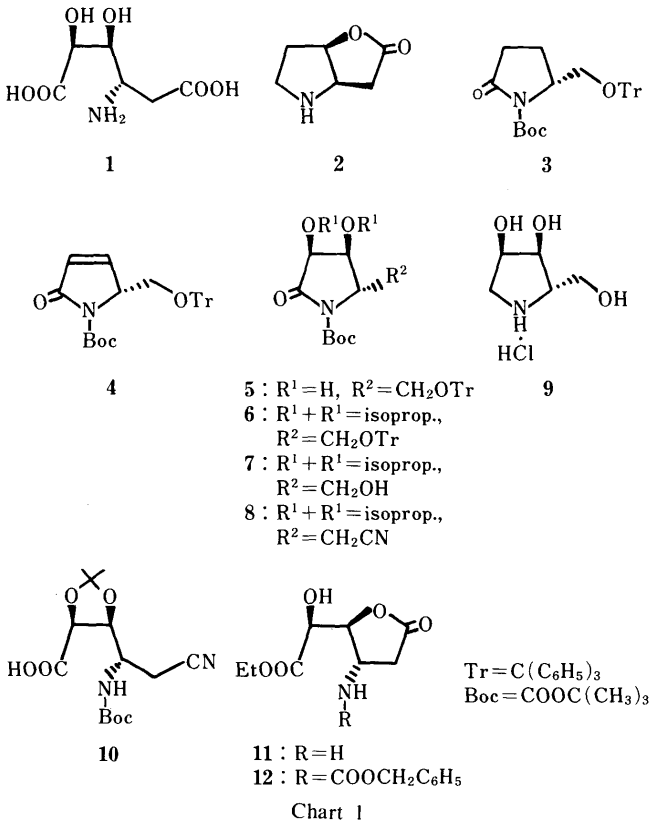
(2*S*,3*S*,4*S*)-4-Amino-2,3-dihydroxyhexanedioic acid derivatives (11 and 12) were synthesized from an (*R*)-pyroglutamic acid derivative (3) by *cis*-dihydroxylation of the α,β-unsaturated lactam (4) as the key reaction.

Keywords AI-77-B; chiral synthesis; (2*S*,3*S*,4*S*)-4-amino-2,3-dihydroxyhexanedioic acid; *cis*-dihydroxylation; α,β-unsaturated lactam; (*R*)-pyroglutamic acid

In the previous communications, we reported the synthesis of (−)-swainsonine and its stereoisomers,[2)] and the Geissman–Waiss lactone (**2**),[3)] in which trihydroxylated 2-pyrrolidinones derived from (*S*)-pyroglutamic acid were important intermediates. Recently, Shioiri *et al.*[4)] reported a facile synthesis of a gastroprotective substance AI-77-B,[5)] in which (2*S*,3*S*,4*S*)-4-amino-2,3-dihydroxyhexanedioic acid (**1**), a component of AI-77-B, was synthesized from (*R*)-pyroglutamic acid. In a continuation of our work on the utility of chiral pyroglutamic acid derivatives for natural product synthesis, we describe here our synthesis of (2*S*,3*S*,4*S*)-4-amino-2,3-dihydroxyhexanedioic acid derivatives (**11** and **12**) from (*R*)-pyroglutamic acid.

The α,β-unsaturated lactam (**4**) was prepared in 63% yield from (*R*)-1-(*tert*-butoxycarbonyl)-5-trityloxymethyl-2-pyrrolidinone (**3**) by the selenenylation–deselenenylation procedure.[2,6)] *cis*-Dihydroxylation of **4** with a catalytic amount of OsO_4 in the presence of *N*-methylmorpholine *N*-oxide (NMO) in aqueous acetone provided **5** in 88% yield as a single diastereomer. The configurations of **5** were confirmed by the conversion of **6** into the hydrochloride of (2*S*,3*S*,4*R*)-3,4-dihydroxy-2-hydroxymethylpyrrolidine (**9**) (mp 119—120 °C, $[\alpha]_D$ −53.9° (H_2O), lit.[2)] for (2*R*,3*R*,4*S*)-isomer: mp 121 °C, $[\alpha]_D$ +54.8° (H_2O)) by reduction with borane-dimethyl sulfide followed by acidic hydrolysis. After protection of the *cis*-diol in **5** with an isopropylidene group (88% yield), acidic treatment of **6** (concentrated HCl : MeOH = 1 : 25, 30—35 °C) afforded a mixture of **5** and **7** (**5** : **7** = 1 : 10 determined by proton nuclear magnetic resonance (^{1}H-NMR)) in 38% yield with 41% recovery of the starting **6**. Since **5** and **7** were not separated by column chromatography, a mixture of **5** and **7** was subjected to elongation of the carbon chain without further purification. After conversion of the primary hydroxy group of **7** into a nitrile **8** (Bu_3P/CCl_4/KCN/18-crown-6/CH_3CN,[7)] 43% yield), treatment of **8** with aqueous LiOH in tetrahydrofuran (THF)[8)] to open the pyrrolidinone ring gave an acid **10** in 85% yield. Esterification of the carboxylic acid, conversion of the cyano function into a carboxylic group, and the removal of the *N*-*tert*-butoxycarbonyl and isopropylidene groups of **10** in a single step (HCl/EtOH, 0 °C→room temperature) afforded a corresponding γ-lactone **11** (mp 169—171 °C, $[\alpha]_D$ −10.1° (H_2O)) in 78% yield as the hydrochloride salt. The *N*-benzyloxycarbonyl (Z) derivative (**12**) (mp 129—130 °C, $[\alpha]_D$ −30.9° ($CHCl_3$)) was also obtained in 75% yield from the hydrochloride of **11** by treatment with ZCl in saturated aqueous $NaHCO_3$. Thus, the selective *cis*-dihydroxylation of **4** resulted in the facile preparation of (2*S*,3*S*,4*S*)-4-amino-2,3-dihydroxyhexanedioic acid derivatives (**11** and **12**). Further synthetic studies utilizing the hydroxylated pyrrolidinone derivatives are in progress.



1 2 3 4 9 10

5 : R¹=H, R²=CH₂OTr
6 : R¹+R¹=isoprop., R²=CH₂OTr
7 : R¹+R¹=isoprop., R²=CH₂OH
8 : R¹+R¹=isoprop., R²=CH₂CN

11 : R=H
12 : R=COOCH₂C₆H₅

Chart 1

Experimental[9)]

***(R)*-1-(*tert*-Butoxycarbonyl)-5-trityloxymethyl-2-pyrrolidinone (3)** A mixture of (*R*)-5-trityloxymethyl-2-pyrrolidinone (5.2 g, 14.6 mmol, mp 159 °C, $[\alpha]_D^{20}$ −13.1° (*c*=3, $CHCl_3$), lit.[10)] for (*S*)-isomer, mp 165.5—166 °C, $[\alpha]_D^{20}$ +13.7° ($CHCl_3$)), triethylamine (2 ml, 14.6 mmol), di-*tert*-butyl dicarbonate (6.34 g, 29 mmol), and 4-(dimethylamino)pyridine (1.78 g, 14.5 mmol) in CH_2Cl_2 (40 ml) was stirred at room temperature for 16 h. After removal of the volatiles *in vacuo*, a residue was purified by column chromatography (silica gel, AcOEt : hexane = 1 : 3) to afford **3** (5.47 g, 82% yield) as crystals, mp 108 °C (AcOEt–hexane). $[\alpha]_D^{20}$ +37.5° (*c*=0.7, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 1776, 1695. ^{1}H-NMR ($CDCl_3$): 1.4 (9H, s, 3×CH_3), 1.7—2.9 (4H, m, 2×CH_2), 3.1 (1H, dd, *J*=2.8, 10 Hz, CH_2OTr), 3.5 (1H, dd, *J*=4.3, 10 Hz, CH_2OTr), 4—4.3 (1H, m, C_5-H), 7.1—7.4 (15H, m, aromatic protons). ^{13}C-NMR ($CDCl_3$): 22.2 (t), 27.8 (q), 32.0 (t), 57.4 (d), 64.0 (t), 82.5 (d), 86.7 (d), 126.9, 127.7, 128.3, 143.3 (s), 149.4 (s), 174.7 (s). *Anal.* Calcd for $C_{29}H_{31}N_1O_4$: C, 76.12; H, 6.83: N,

3.06. Found: C, 76.06; H, 6.72; N, 3.12.

(*R*)-1-(*tert*-Butoxycarbonyl)-2-oxo-5-trityloxymethyl-3-pyrroline (4) Butyl lithium (12.2 ml of a 1.03 M solution in hexane) was added to a solution of diisopropylamine (1.75 ml, 12.5 mmol) in THF (15 ml) at −78 °C. The mixture was stirred at −78 °C for 10 min, followed by addition of a solution of **3** (5.0 g, 10.9 mmol) in THF (20 ml). Then, the mixture was stirred at −78 °C for 10 min, at −20 °C for 5 min, and then −78 °C for 15 min. After addition of a solution of PhSeBr (3.09 g, 13.1 mmol) in THF (15 ml) at −78 °C, the mixture was stirred at −78 °C for 10 min, then 20 ml of 10% aqueous NH_4Cl was added. After dilution with AcOEt, the organic layer was separated and washed with H_2O and saturated aqueous NaCl. Drying followed by evaporation *in vacuo* gave a residue, which was chromatographed (silica gel, AcOEt : hexane = 4 : 1) to afford 3-selenopyrrolidinone (5.3 g, yield 79%) as a mixture of diastereomers. Less polar diastereomer: mp 133—134 °C (AcOEt–hexane). $[\alpha]_D^{20}$ +66.9° (*c* = 0.6, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 1781, 1706, 1652. ^{1}H-NMR ($CDCl_3$): 1.4 (9H, s, 3 × CH_3), 1.9—2.4 (2H, m, CH_2), 3.0 (1H, dd, *J* = 2.5, 10 Hz, C<u>H</u>$_2$OTr), 3.5 (1H, dd, *J* = 4.3, 10 Hz, C<u>H</u>$_2$OTr), 3.9—4.1 (1H, m, C_5-H), 4.3 (1H, t, *J* = 8.5 Hz, PhSeC<u>H</u>CH$_2$), 7—7.7 (20H, m, aromatic protons). ^{13}C-NMR: 27.8 (q), 30.0 (t), 41.9 (d), 56.1 (d), 63.8 (t), 82.8 (s), 86.9 (s), 126.9, 127.7, 128.3, 128.9, 134.8 (s), 143.2 (s), 149.0 (s), 172.9 (s). Polar diastereomer: oil, $[\alpha]_D^{20}$ −6.6° (*c* = 0.5, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 1.4 (9H, s, 3 × CH_3), 2.1—2.7 (2H, m, CH_2), 3.25 (1H, t, *J* = 8.5 Hz, PhSeC<u>H</u>CH$_2$), 3.5 (1H, dd, *J* = 3, 10 Hz, C<u>H</u>$_2$OTr), 3.85 (1H, dd, *J* = 3, 10 Hz, C<u>H</u>$_2$OTr), 4.15—4.4 (1H, m, C_5-H), 7.0—7.7 (20H, m, aromatic protons). ^{13}C-NMR ($CDCl_3$): 27.7 (q), 28.1 (t), 39.7 (d), 55.9 (d), 63.6 (t), 82.8 (s), 86.6 (s), 126.9, 127.6, 128.4, 128.8, 134.3 (d), 143.3 (s), 149.2 (s), 173.2 (s). A solution of 3-selenopyrrolidinone (5.0 g, 8.17 mmol) in AcOEt (60 ml) was treated with 30% H_2O_2 (15 ml) at 0 °C, and the mixture was stirred at 15—20 °C for 30 min, then AcOEt layer was separated and washed with H_2O, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. Drying followed by concentration *in vacuo* gave a residue, which was purified by column chromatography (silica gel, AcOEt : hexane = 3 : 2) to provide **4** (2.98 g, yield 80%) as crystals, mp 105—106 °C (AcOEt–hexane). $[\alpha]_D^{20}$ +150° (*c* = 2, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 1774, 1695, 1655. ^{1}H-NMR ($CDCl_3$): 1.38 (9H, s, 3 × CH_3), 3.2 (1H, dd, *J* = 6, 10 Hz, C<u>H</u>$_2$OTr), 3.6 (1H, dd, *J* = 4, 10 Hz, C<u>H</u>$_2$OTr), 5.6—5.8 (1H, m, C_5-H), 6.15 (1H, dd, *J* = 1.5, 6 Hz, vinyl proton), 7.0—7.5 (16H, m, vinyl and aromatic protons). ^{13}C-NMR ($CDCl_3$): 27.8 (q), 62.0 (d), 62.5 (t), 82.6 (s), 86.4 (s), 126.7, 126.9, 127.7, 128.2, 143.1 (s), 149.2 (d), 164.2 (s), 169.2 (s). *Anal.* Calcd for $C_{29}H_{29}N_1O_4$: C, 76.46; H, 6.42; N, 3.07. Found: C, 76.30; H, 6.33; N, 3.01.

(3*S*,4*S*,5*S*)-1-(*tert*-Butoxycarbonyl)-3,4-dihydroxy-5-trityloxymethyl-2-pyrrolidinone (5) A mixture of **4** (2.33 g, 5.1 mmol), OsO_4 (64 mg, 0.26 mmol) and NMO monohydrate (860 mg, 6.38 mmol) in acetone (40 ml) and H_2O (15 ml) was stirred at room temperature for 20 h. After addition of sodium hydrosulfite (1.1 g), the acetone was removed *in vacuo*, and the mixture was extracted with CH_2Cl_2 (× 4). The combined CH_2Cl_2 extracts were washed with H_2O. Drying followed by concentration *in vacuo* gave a residue, which was purified by column chromatography (silica gel, AcOEt) to provide **5** (2.2 g, yield 88%) as crystals, mp 100—102 °C (AcOEt–hexane). $[\alpha]_D^{20}$ +12° (*c* = 0.6, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 3455, 3357, 1778, 1695. ^{1}H-NMR ($CDCl_3$): 1.40 (9H, s, 3 × CH_3), 3.21 (1H, dd, *J* = 2.5, 10 Hz, C<u>H</u>$_2$OTr), 3.41 (1H, br s, OH), 3.55 (1H, dd, *J* = 3.7, 10 Hz, C<u>H</u>$_2$OTr), 3.93 (1H, d, *J* = 4.5 Hz, OH), 4.1—4.3 (2H, m, C_5-H, C<u>H</u>OH), 4.78 (1H, dd, *J* = 4.5, 4.5 Hz, C<u>H</u>OH), 7.1—7.5 (15H, m, aromatic protons). ^{13}C-NMR ($CDCl_3$): 27.7 (q), 61.6 (t), 63.2 (d), 68.9 (d), 71.4 (d), 83.5 (s), 87.2 (s), 127.1, 127.8, 128.3, 142.9 (s), 149.2 (s), 174.0 (s). *Anal.* Calcd for $C_{29}H_{31}N_1O_6$: C, 71.15; H, 6.38; N, 2.86. Found: C, 71.47; H, 6.21; N, 2.95.

(3*S*,4*S*,5*S*)-1-(*tert*-Butoxycarbonyl)-3,4-isopropylidenedioxy-5-trityloxymethyl-2-pyrrolidinone (6) A mixture of **5** (2.2 g, 4.5 mmol) and 2,2-dimethoxypropane (8 ml) in acetone (20 ml) was stirred in the presence of a catalytic amount of *p*-TsOH · H_2O at room temperature for 2 h. After dilution with AcOEt, the mixture was washed with saturated aqueous $NaHCO_3$, H_2O, and saturated aqueous NaCl. Drying followed by concentration *in vacuo* gave a residue, which was subjected to column chromatography (silica gel, AcOEt : hexane = 1 : 3) to give **6** (2.1 g, yield 88%) as crystals, mp 144 °C (AcOEt–hexane). $[\alpha]_D^{20}$ +40.1° (*c* = 1.6, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 1768, 1713. ^{1}H-NMR ($CDCl_3$): 1.30 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.47 (9H, s, 3 × CH_3), 3.06 (1H, dd, *J* = 2.6, 10 Hz, C<u>H</u>$_2$OTr), 3.73 (1H, dd, *J* = 2.7, 10 Hz, C<u>H</u>$_2$OTr), 4.1—4.28 (2H, m, C_5-H, CH), 4.89 (1H, d, *J* = 5.4 Hz, CH), 7.1—7.4 (15H, m, aromatic protons). ^{13}C-NMR ($CDCl_3$): 25.6 (q), 27.1 (q), 27.9 (q), 60.6 (d), 61.7 (t), 75.7 (d), 78.3 (d), 83.6 (s), 87.4 (s), 112.0 (s), 127.3, 128.3, 142.9 (s), 149.5 (s), 171.4 (s). *Anal.* Calcd for $C_{32}H_{35}N_1O_6$: C, 72.57; H, 6.66; N, 2.64. Found: C, 72.36; H, 6.71; N, 2.65.

(2*S*,3*S*,4*R*)-3,4-Dihydroxy-2-hydroxymethylpyrrolidine Hydrochloride (9) Borane-dimethyl sulfide (0.12 ml) was added to a solution of **6** (250 mg, 0.47 mmol) in THF (3 ml). The solution was stirred at 70 °C for 2 h. After cooling to room temperature, the mixture was diluted with AcOEt, and quenched with saturated aqueous NH_4Cl. The organic layer was separated and washed with 5% aqueous HCl, saturated aqueous $NaHCO_3$, and H_2O. Drying followed by concentration *in vacuo* gave a residue, which was purified by column chromatography (silica gel, AcOEt : hexane = 1 : 3.5) to afford (2*S*,3*S*,4*R*)-1-(*tert*-butoxycarbonyl)-3,4-isopropylidenedioxy-5-trityloxymethylpyrrolidine (47 mg, yield 19%) as crystals, mp 123—125 °C. $[\alpha]_D^{20}$ +31° (*c* = 0.7, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 1693. ^{1}H-NMR ($CDCl_3$): 1.27, 1.34, 1.41, 1.47 (15H, 4 × s, 5 × CH_3), 2.88—3.40 (2H, m), 3.46—4.21 (3H, m), 4.55 (1H, d, *J* = 6 Hz, CH–O–), 4.73—4.99 (1H, m, CH–O–), 6.98—7.53 (15H, m, aromatic protons). A mixture of the above (2*S*,3*S*,4*R*)-pyrrolidine derivative (45 mg, 0.087 mmol), MeOH (2 ml), and 10% aqueous HCl (2 ml) was stirred at 70 °C for 3 h. After removal of the methanol *in vacuo*, the aqueous layer was washed with AcOEt, then evaporated *in vacuo* to dryness. The residue was crystallized from MeOH–ether to give **10** (10 mg, yield 77%) as needles, mp 119—120 °C. $[\alpha]_D^{20}$ −53.9° (*c* = 0.6, H_2O). Its spectral data were identical with those of the (2*R*,3*R*,4*S*)-isomer previously prepared.[2]

(3*S*,4*S*,5*S*)-1-(*tert*-Butoxycarbonyl)-5-hydroxymethyl-3,4-isopropylidenedioxy-2-pyrrolidinone (7) A mixture of **6** (1.03 g, 1.95 mmol) in MeOH (10 ml) and concentrated HCl (0.4 ml) was stirred at 30—35 °C for 5 h. After dilution with AcOEt, the mixture was washed with saturated aqueous $NaHCO_3$, H_2O, and saturated aqueous NaCl. Drying followed by concentration *in vacuo* gave a residue, which was subjected to column chromatography (silica gel, AcOEt : hexane = 1 : 1) to afford **6** (422 mg, 41% recovery) and **7** (oil, 213 mg, about 38% yield, contaminated with **5**). $[\alpha]_D^{20}$ +74° (*c* = 0.6, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3444, 1785, 1710. ^{1}H-NMR ($CDCl_3$): 1.33 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.50 (9H, s, 3 × CH_3), 3.2 (1H, br s, OH), 3.6—4.0 (2H, m, C<u>H</u>$_2$OH), 4.2 (1H, m, C_5-H), 4.60 (1H, d, *J* = 4 Hz, CH), 4.77 (1H, d, *J* = 4 Hz, CH). ^{13}C-NMR ($CDCl_3$): 25.5 (q), 26.9 (q), 27.9 (q), 61.1 (t), 62.1 (d), 75.4 (d), 78.0 (s), 83.8 (s), 111.7 (s), 149.6 (s), 172.2 (s). MS *m/z*: 287 (M^+).

(3*S*,4*S*,5*S*)-1-(*tert*-Butoxycarbonyl)-5-cyanomethyl-3,4-isopropylidenedioxy-2-pyrrolidinone (8) A mixture of **7** (384 mg, 1.34 mmol), potassium cyanide (260 mg, 4 mmol), and 18-crown-6 (88 mg, 0.33 mmol) in acetonitrile (3.5 ml) was stirred at room temperature for 15 min. Then, tributylphosphine (540 mg, 2.67 mmol) in acetonitrile (3 ml) was added, followed by the addition of a solution of carbon tetrachloride (411 mg, 2.67 mmol) in acetonitrile (1.5 ml) at 0 °C. The mixture was stirred at room temperature for 13 h, and then refluxed for 15 min. After dilution with AcOEt, the mixture was filtered and the filtrate was concentrated. The residue was purified by column chromatography (silica gel, AcOEt : hexane = 2 : 3) to provide **8** (170 mg, 43% yield) as a yellow oil. $[\alpha]_D^{20}$ +105° (*c* = 0.8, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 2254, 1789, 1722. ^{1}H-NMR ($CDCl_3$): 1.40 (3H, s, CH_3), 1.46 (3H, s, CH_3), 1.56 (9H, s, 3 × CH_3), 3.15—3.72 (2H, m, C<u>H</u>$_2$CN), 4.25—4.44 (1H, m, C_5-H), 4.57 (1H, d, *J* = 5.6 Hz, CH), 4.90 (1H, d, *J* = 5.5 Hz, CH). ^{13}C-NMR ($CDCl_3$): 21.2 (t), 25.5 (q), 26.9 (q), 27.9 (q), 56.6 (d), 75.2 (d), 76.7 (d), 85.0 (s), 113.0 (s), 115.9 (s), 149.3 (s), 172.8 (s). MS *m/z*: 297 ($(M+1)^+$).

(2*S*,3*S*,4*S*)-3-(*tert*-Butoxycarbonyl)amino-5-cyano-2,3-isopropylidenedioxypentanoic Acid (10) A 1 N solution of lithium hydroxide (0.81 ml) was added to a solution of **8** (160 mg, 0.54 mmol) in THF (3 ml). The mixture was stirred at 0 °C for 15 min. After removal of THF *in vacuo*, the aqueous layer was acidified by the addition of aqueous citric acid and extracted with AcOEt. The AcOEt extracts were washed with saturated aqueous NaCl. Drying followed by concentration *in vacuo* gave a residue, which was crystallized from AcOEt–hexane to provide **10** (145 mg, 85% yield) as crystals, mp 120—122 °C, $[\alpha]_D^{20}$ +25.0° (*c* = 0.9, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 2615, 2262, 1691, 1655. ^{1}H-NMR ($CDCl_3$): 1.41 (3H, s, CH_3), 1.48 (9H, s, 3 × CH_3), 1.6 (3H, s, CH_3), 2.5—2.9 (2H, m, CH_2CN), 3.45—4.1 (1H, m, C_4-H), 4.60 (1H, dd, *J* = 6.4, 6.8 Hz, C_3-H), 4.75 (1H, d, *J* = 6.4 Hz, C_2-H), 5.46 and 7.0 (1H, NH), 9.6 (1H, br s, COOH). ^{13}C-NMR ($CDCl_3$): 21.1 (t), 25.0 (q), 26.4 (q), 27.9 (q), 47.5 and 48.5 (d), 75.3 (d), 76.7 (d), 80.5 and 82.8 (s), 111.2 (s), 117.0 (s), 154.7 (s), 172.8 (s). *Anal.* Calcd for $C_{14}H_{22}N_2O_6$: C, 53.49; H, 7.06; N, 8.91. Found: C, 53.60, H, 7.07; N, 8.76.

(3*S*,4*S*,5*S*)-3-Amino-5-ethoxycarbonyl-5-hydroxy-4-pentanolide Hydrochloride (Hydrochloride of 11) A solution of **10** (110 mg, 0.35 mmol) in EtOH (3 ml) was bubbled through with HCl gas at 0 °C for 5 min. Then, the mixture was stirred at room temperature for 11 h (a

mininum amount of EtOH was added to dissolve the precipitate). After addition of ether (3 ml), the precipitate was filtered off. Further addition of ether to the filtrate gave a solid, which was collected by filtration. Recrystallization from EtOH–ether gave **11** (65 mg, 78% yield) as crystals, mp 169—171 °C. $[\alpha]_D^{20}$ −10.1° (c=0.6, H_2O). IR ν_{max}^{Nujol} cm^{-1}: 3420, 1803 (γ-lactone), 1734 (ester). ^{1}H-NMR (D_2O, internal standard: dioxane δ=3.7): 1.25 (3H, t, J=7.1 Hz, CH_3), 2.75 (1H, dd, J=2.7, 19 Hz, CH_2CO), 3.26 (1H, dd, J=9, 19 Hz, CH_2CO), 4.02—4.43 (3H, m, CH_2CH_3, C_3-H), 4.66 (1H, d, J=2.9 Hz, C_5-H), 5.04 (1H, dd, J=2.3, 2.9 Hz, C_4-H). ^{13}C-NMR (D_2O, internal standard: dioxane δ=67.4): 14.1 (q), 34.4 (t), 48.7 (d), 64.2 (t), 71.8 (d), 83.8 (d), 171.8 (s), 177.1 (s). *Anal.* Calcd for $C_{28}H_{14}Cl_1N_1O_5$: C, 40.09; H, 5.89; N, 5.84. Found: C, 39.55, H, 5.72; N, 6.24.

(3*S*,4*S*,5*S*)-3-(Benzyloxycarbonyl)amino-5-ethoxycarbonyl-5-hydroxy-4-pentanolide (12) A mixture of the hydrochloride of **11** (18 mg, 0.075 mmol), ZCl (26 mg, 0.15 mmol) in saturated aqueous $NaHCO_3$ (1.5 ml) and AcOEt (0.5 ml) was stirred at 0 °C for 6 h, then extracted with AcOEt. The organic layer was washed with H_2O and saturated aqueous NaCl. Drying followed by evaporation and chromatography (silica gel, AcOEt: $CHCl_3$=1:2) afforded **12** (19 mg, yield 75%) as crystals, mp 129—130 °C (AcOEt–hexane). $[\alpha]_D^{20}$ −30.9° (c=0.56, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 3446, 3330, 1778 (γ-lactone), 1741 (ester), 1687 (CONH). ^{1}H-NMR ($CDCl_3$): 1.31 (3H, t, J=7.1 Hz, CH_3), 2.48 (1H, dd, J=4, 18 Hz, CH_2CO), 3.09 (1H, dd, J=9, 18 Hz, CH_2CO), 3.41 (1H, d, J=4.2 Hz, OH), 4.1—4.5 (3H, m, CH_2CH_3, C_3-H), 4.56 (1H, dd, J=2, 4.2 Hz, C_5-H), 4.78 (1H, m, CH), 5.12 (2H, s, CH_2Ph), 5.34 (1H, d, J=7 Hz, NH), 7.37 (5H, s, aromatic protons). ^{13}C-NMR ($CDCl_3$): 13.9 (q), 35.3 (t), 48.0 (d), 62.8 (t), 67.1 (t), 71.0 (d), 85.9 (d), 128.1, 128.3, 128.5, 135.8 (s), 155.3 (s), 170.7 (s), 174.5 (s). *Anal.* Calcd for $C_{16}H_{19}N_1O_7$: C, 56.97; N, 5.68; N, 4.15. Found: C, 56.91; H, 5.70; N, 4.28.

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References and Notes

1) A part of this work was presented at the Japanese-United States Congress of Pharmaceutical Sciences, Honolulu, Hawaii, December 1987. Abstract papers, S234.
2) N. Ikota and A. Hanaki, *Chem. Pharm. Bull.*, **35**, 2140 (1987); *idem*, *Heterocycles*, **26**, 2369 (1987).
3) N. Ikota and A. Hanaki, *Heterocycles*, **27**, 2535 (1988).
4) O. Hara, A. Kawai, Y. Kohno, Y. Hamada and T. Shioiri, Abstracts of Papers, The 108th Annual Meeting of the Pharmaceutical Society of Japan, Hiroshima, April 1988, p. 49.
5) Y. Shimojima, H. Hayashi, T. Ooka, M. Shibukawa and Y. Iitaka, *Tetrahedron Lett.*, **23**, 5435 (1982).
6) Y. Ohfune and M. Tomita, *J. Am. Chem. Soc.*, **104**, 3511 (1982).
7) A. Mizuno, Y. Hamada and T. Shioiri, *Synthesis*, **1980**, 1007.
8) D. L. Flynn, R. E. Zell and P. A. Grieco, *J. Org. Chem.*, **48**, 2424 (1983).
9) Melting points were measured on a hot stage apparatus and are uncorrected. Infrared (IR) spectral measurements were performed with a JASCO IRA-1 grating IR spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were measured with a JNM-FX-100 (100 MHz) spectrometer. Data are recorded in parts per million (ppm) downfield from internal tetramethylsilane unless otherwise described. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Optical rotations were determined with a JASCO DIP-360. Mass spectra (MS) were recorded with a JEOL JMS-DS302 mass spectrometer. The organic solvents were dried over $MgSO_4$ before vacuum evaporation.
10) K. Tomioka, T. Suenaga and K. Koga, *Tetrahedron Lett.*, **27**, 369 (1986).