# Synthesis of 2(1*H*)-Pyrimidinone-Containing α-Amino Acid Derivatives by Chemical Modification of L-Glutamic Acid

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**A commercially available L-glutamic acid γ-methyl ester was converted into the corresponding urea-containing α-amino acid *via* the hydrazide, the azide, and then the isocyanate. The condensation of the urea-containing α-amino acid with β-diketones under acidic conditions afforded 2(1*H*)-pyrimidinone-containing α-amino acid derivatives in reasonable yields. The $^1$H-NMR analysis of the dipeptide indicated that no detectable racemization had occurred during the chemical modification of L-glutamic acid.**

**Keywords** α-amino acid derivative; 2(1*H*)-pyrimidinone; chemical modification; L-glutamic acid

Unnatural α-amino acids are important not only in designing pharmacologically active peptides but also in elucidating structure–biological activity relationships. In addition, techniques have been developed to incorporate unnatural α-amino acids into proteins.[1] As a consequence, much effort has been devoted to the design and synthesis of unnatural α-amino acids,[2] and heterocycle-containing unnatural α-amino acids have been found to show enhanced biological activities compared with the corresponding natural α-amino acids.[3] There are two approaches to the synthesis of heterocycle-containing α-amino acid derivatives: (i) the synthesis of racemic amino acids and subsequent optical resolution of them,[4] and (ii) the chemical modification of the ω-functional groups in natural α-amino acids.[3b,c] The second approach has been little used so far. 2(1*H*)-Pyrimidinone was selected here as a heterocycle, because its synthesis and reactions have been extensively investigated in our laboratory.[5]

In this paper we describe the synthesis of 2(1*H*)-pyrimidinone-containing α-amino acid derivatives by reaction of β-diketones with a urea-containing α-amino acid obtained by chemical modification of the γ-carboxyl group in L-glutamic acid.

## Results and Discussion

The synthetic procedure for 2(1*H*)-pyrimidinone-containing α-amino acid derivatives is depicted in Chart 1. *tert*-Butyl and methyl groups were adopted as protecting groups for α- and γ-carboxyl, respectively. The hydrazide **2** was obtained from a commercially available L-glutamic acid γ-methyl ester (**1**) *via* three steps according to the literature.[6] The isocyanate **3** was prepared by the Curtius rearrangement of the corresponding azide formed by treatment of the hydrazide **2** with $NaNO_2$ in the presence of 1 M HCl at 4 °C in $CHCl_3$–$H_2O$. The conversion was followed by monitoring the absorption bands at 2150 and 2250 $cm^{-1}$ due to the azide and isocyanate groups, respectively.[7] The absorption band of the azide completely disappeared after the $CHCl_3$ solution has been kept standing overnight, followed by reflux for 10 min. The urea-containing α-amino acid **4** was obtained in 55% overall yield by passing dry $NH_3$ gas into a solution of the isocyanate **3** in $CHCl_3$. When a mixture of compound **4** and 4,4-dimethoxy-2-butanone in 2% *tert*-butanolic HCl solution was heated at 70 °C for 6 h, the *N*-substituted urea-containing α-amino acid **5** was isolated in a 40% yield. The $^1$H-NMR spectrum shows a signal at 11.01 ppm, indicating that a strong intramolecular hydrogen bonding between NH and CO exists in $CDCl_3$ solution. An attempt to cyclize compound **5** was unsuccessful even under more forcing conditions. On the other hand, compound **4** was treated with 2,4-pentanedione under the same conditions to afford the desired product, *tert*-butyl 2-(benzyloxycarbonyl)amino-4-(4,6-dimethyl-2-oxo-1,2-dihydropyrimidin-1-yl)butyrate (**6a**), in 47% yield. The product showed the following data; IR: 3400 (N–H), 1712 (urethane and ester CO), 1660 (N–CO–N) $cm^{-1}$; $^{13}$C-NMR: 106.2 (d), 156.1 (s), 157.0 (s), 174.7 (s), which are very similar to the chemical shifts of the ring carbons of 1,4,6-trimethyl-2(1*H*)-pyrimidinone.[8] The reaction of the urea-containing α-amino acid **4** with other β-diketones in a similar fashion gave the corresponding α-amino acid derivatives **6b**—**e**. In the case of 1-phenyl-1,3-butanedione, the structural isomers **6d** and **6e**, which are separable by silica gel column chromatography, were obtained in 8 and 15% yields, respectively. The structures of **6d** and **6e** were easily assigned by means of the $^1$H-NMR spectroscopy. Compound **6e** showed the benzoyl pattern at δ 7.27—7.51 and at δ 8.04—8.20.[9] Further, the signal of the olefinic proton at the 5-position of the pyrimidinone ring was shifted 0.58 ppm to lower magnetic field compared with that of compound **6a** due to the anisotropic effect of the benzene ring at the 4-position.[9]

The extent of racemization during the chemical modification of L-glutamic acid was estimated by $^1$H-NMR spectral examination of the dipeptides. Compound **6a** was treated with 0.03 M HCl in formic acid at room temperature to give the corresponding acid **7**. Compound **7** was coupled with L-Ala–OMe and D-Ala–OMe by the *N*-ethyl-*N'*-dimethylaminopropylcarbodiimide hydrochloride (WSC·HCl)–1-hydroxybenzotriazole (HOBt) method to afford the diastereomeric dipeptides **8** and **9**, respectively (Chart 2). The chemical shifts of the methine proton of the 2(1*H*)-pyrimidinone-containing α-amino acid moiety and the two amide protons were clearly different in the two molecules, indicating that no detectable racemization had occurred during the chemical

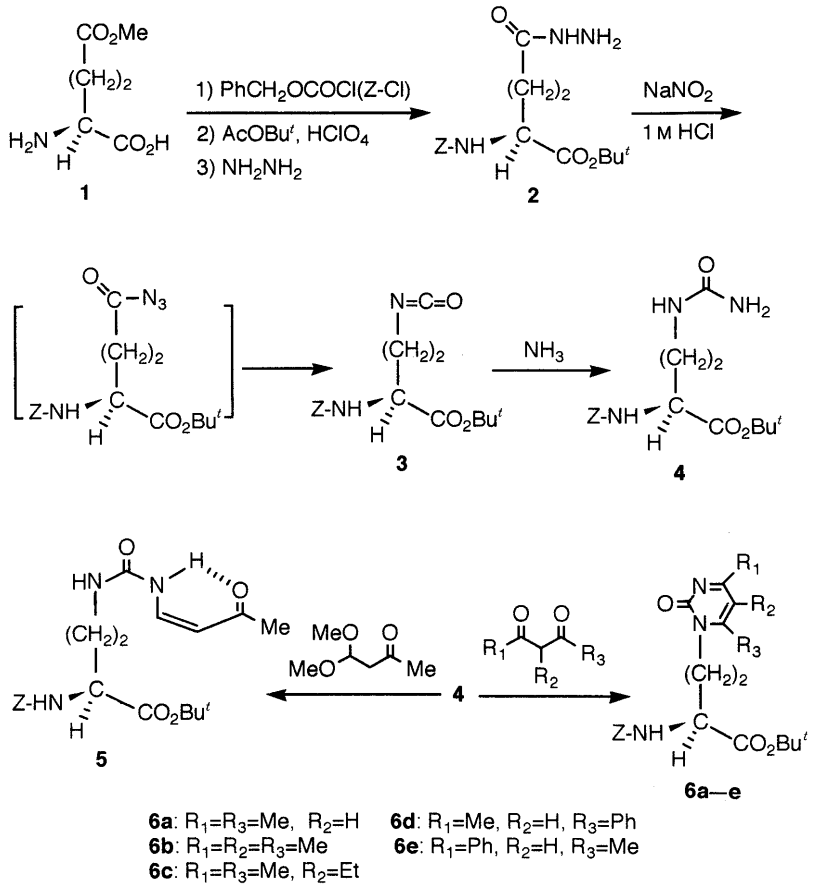


Chart 1

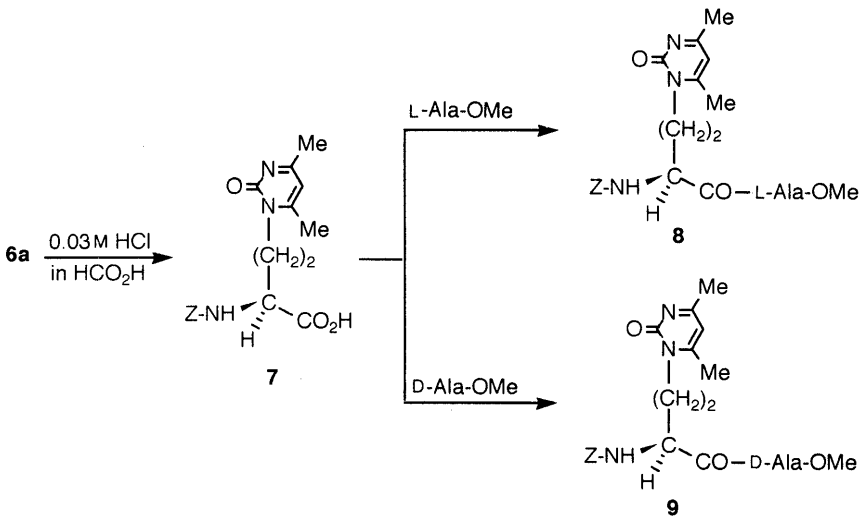


Chart 2

modification.

In conclusion, synthesis of 2(1*H*)-pyrimidinone-containing α-amino acid derivatives has been accomplished by the chemical modification of the γ-carboxyl group of L-glutamic acid without detectable racemization.

## Experimental

**General Notes** Melting points were measured on a Mel-Temp apparatus in open capillaries and are uncorrected. IR spectra were obtained with a JASCO A-100 infrared spectrophotometer. $^1$H- and $^{13}$C-NMR spectra were recorded on a JEOL GX-270 NMR spectrometer using $Me_4Si$ as an internal standard. FAB mass spectra were taken on a JEOL DX303 with a DA 5000 data system by using a Xe beam at 6 keV and a nitrobenzyl alcohol matrix. Specific rotations were recorded on a JASCO DIP-370 digital polarimeter. Thin layer chromatographic (TLC) analysis was performed on Silica gel 60F-254 with 0.2 mm layer thickness. Column chromatography was done with Merck Kieselgel 60 (230—400 mesh). Combustion analyses were performed on a Yanaco MT-3 CHN corder.

**Benzyloxycarbonyl-L-glutamic Acid α-*tert*-Butyl Ester γ-Hydrazide (2)** The hydrazide **2** was prepared from a commercially available L-glutamic acid γ-methyl ester (**1**) according to the literature,[6] mp 111 °C (lit. mp 110 °C), $[\alpha]_D^{22}$ −19° ($c$=0.58, MeOH). IR ($CHCl_3$): 3400—3300,

1730, 1670, 740, 700 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.45 (9H, s), 2.0—2.3 (4H, m), 3.4 (2H, br s), 4.0—4.3 (1H, m), 5.05 (2H, s), 7.25 (5H, s), 7.3 (1H, br s).

***N*-[3-(Benzyloxycarbonyl)amino-3-*tert*-butoxycarbonylpropyl]urea (4)** The hydrazide **2** (2.27 g, 6.5 mmol) was dissolved in 1 M HCl (19 ml) and $CHCl_3$ (30 ml), and cooled to 4 °C, then a solution of $NaNO_2$ (0.45 g, 6.5 mmol) in $H_2O$ (7 ml) was added dropwise. After vigorous stirring for 30 min, further $CHCl_3$ (25 ml) was added to the mixture. The $CHCl_3$ layer was washed with 5% $NaHCO_3$ (30 ml × 2), dried over anhydrous $Na_2SO_4$, kept standing overnight and then refluxed for 10 min to give the isocyanate **3**, which was used in the next reaction without purification.

Dry $NH_3$ gas was introduced into a solution of isocyanate **3** in $CHCl_3$ on an ice bath. The solution was stirred for 3 h at room temperature, then the solvent was evaporated off under reduced pressure. The residue was chromatographed on silica gel with AcOEt as an eluant to give the urea **4** (1.25 g) in 55% overall yield as an oil, $[\alpha]_D^{22}$ −32° ($c$=1.0, MeOH). IR ($CHCl_3$): 3400—3200, 1700, 1670, 740, 698 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.45 (9H, s), 1.8 (1H, m), 2.0 (1H, m), 3.0 (1H, m), 3.45 (1H, m), 4.3 (1H, m), 4.75 (2H, br s), 5.1 (2H, s), 5.65 (1H, br s), 5.8 (1H, br s), 7.4 (5H, s). $^{13}$C-NMR ($CDCl_3$) $\delta$: 27.9 (q), 32.0 (t), 37.3 (t), 52.7 (d), 66.9 (t), 127.3 (d), 129.1 (d), 136.3 (s), 146.3 (s), 159.4 (s), 172.8 (s). *Anal.* Calcd for $C_{17}H_{25}N_3O_5 \cdot 0.2H_2O$: C, 57.52; H, 7.16; N, 11.84. Found: C, 57.49; H, 7.16; N, 11.45.

***N*-[3-(Benzyloxycarbonyl)amino-3-*tert*-butoxycarbonylpropyl]-*N'*-(3-oxo-1-butenyl)urea (5)** A mixture of **4** (350 mg, 1 mmol) and 4,4-dimethoxy-2-butanone (120 mg, 1.2 mmol) in 2% *tert*-butanolic HCl (2.8 ml) was heated at 70 °C for 6 h. After evaporation of the solvent, the residue was dissolved in $H_2O$ (10 ml). The aqueous solution was adjusted to pH 10 with 1 M NaOH, extracted with $CH_2Cl_2$ (50 ml), and dried over anhydrous $MgSO_4$. The residue was chromatographed on silica gel with $CHCl_3$–acetone–EtOH (100 : 10 : 2) mixture to give **5** (173 mg) in 40% yield, $[\alpha]_D^{25}$ −43.1° ($c$=0.4, MeOH). $^1$H-NMR ($CDCl_3$) $\delta$: 1.40 (9H, s), 1.80 (1H, m), 2.05 (1H, m), 2.10 (3H, s), 3.14 (1H, m), 3.53 (1H, m), 4.29 (1H, m), 5.09 (2H, s), 5.37 (1H, d, $J$=6.8 Hz), 5.70 (1H, d, $J$=8.1 Hz), 6.58 (1H, m), 7.35 (5H, s), 7.46 (1H, dd, $J$=6.5, 6.8 Hz), 11.01 (1H, d, $J$=6.5 Hz). *Anal.* Calcd for $C_{21}H_{29}N_3O_6 \cdot H_2O$: C, 57.66; H, 7.09; N, 9.61. Found: C, 57.53; H, 6.82; N, 9.37.

**General Procedure for Preparation of 2(1*H*)-Pyrimidinone-Containing α-Amino Acid Derivatives. A Typical Example: *tert*-Butyl 2-(Benzyloxycarbonyl)amino-4-(4,6-dimethyl-2-oxo-1,2-dihydropyrimidin-1-yl)-butyrate (6a)** A mixture of **4** (850 mg, 2.4 mmol) and 2,4-pentanedione (307 mg, 2.9 mmol) in 2% *tert*-butanolic HCl (6.6 ml) was heated at 70°C for 12 h. After evaporation of the solvent, $H_2O$ (50 ml) was added to the residue. The aqueous solution was neutralized with 1 M NaOH to pH 10, and extracted with $CH_2Cl_2$ (100 ml). The $CH_2Cl_2$ layer was dried over anhydrous $Na_2SO_4$ and then evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with $CHCl_3$–acetone–EtOH (100 : 10 : 5) mixture to give **6a** (472 mg) in 47% yield as an amorphous solid, $[\alpha]_D^{22}$ −9.3° ($c$=1.1, MeOH). IR ($CHCl_3$): 3400, 1712, 1660, 730, 670 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.45 (9H, s), 2.2 (2H, m), 2.3 (6H, s), 4.0 (2H, m), 4.3 (1H, m), 5.1 (2H, s), 5.95 (1H, d, $J$=8 Hz), 6.05 (1H, s), 7.35 (5H, s). $^{13}$C-NMR ($CDCl_3$) $\delta$: 19.7 (q), 25.0 (q), 27.9 (q), 30.4 (t), 42.2 (t), 52.7 (d), 66.9 (t), 82.9 (s), 106.2 (d), 128.1 (d), 128.2 (d), 128.5 (d), 136.3 (s), 156.1 (s), 157.0 (s), 170.4 (s), 174.7 (s). *Anal.* Calcd for $C_{22}H_{29}N_3O_5 \cdot 0.8\ H_2O$: C, 61.45; H, 7.0; N, 9.78. Found: C, 61.27; H, 7.07; N, 9.67.

***tert*-Butyl 2-(Benzyloxycarbonyl)amino-4-(4,5,6-trimethyl-2-oxo-1,2-dihydropyrimidin-1-yl)butyrate (6b)** Yield 37%, $[\alpha]_D^{25}$ −8.89° ($c$=1.0, MeOH). IR ($CHCl_3$): 3432, 1716, 1649, 737, 669 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.44 (9H, s), 2.03 (3H, s), 2.16 (2H, m), 2.29 (3H, s), 2.34 (3H, s), 4.05 (2H, m), 4.28 (1H, m), 5.11 (2H, s), 6.05 (1H, d, $J$=8 Hz), 7.34 (5H, s). $^{13}$C-NMR ($CDCl_3$) $\delta$: 13.9 (q), 16.0 (q), 24.5 (q), 27.9 (q), 29.6 (t), 42.8 (t), 52.8 (d), 66.8 (t), 82.6 (s), 111.0 (s), 128.0 (d), 128.4 (d), 136.5 (s), 152.8 (s), 156.2 (s), 170.5 (s), 174.2 (s). FAB-MS $m/z$: 430 $(M+1)^+$.

***tert*-Butyl 2-(Benzyloxycarbonyl)amino-4-(5-ethyl-4,6-dimethyl-2-oxo-1,2-dihydropyrimidin-1-yl)butyrate (6c)** Yield 45%, $[\alpha]_D^{25}$ −8.14° ($c$=1.07, MeOH). IR ($CDCl_3$): 3421, 1718, 1649, 735, 669 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.07 (3H, t, $J$=7.6 Hz), 1.44 (9H, s), 2.17 (2H, m), 2.31 (3H, s), 2.37 (3H, s ), 2.46 (2H, q, $J$=7.6 Hz), 4.06 (2H, m), 4.31 (1H, m), 5.11 (2H, s), 6.07 (1H, d, $J$=8 Hz), 7.34 (5H, s). $^{13}$C-NMR ($CDCl_3$) $\delta$: 13.9 (q), 15.4 (q), 21.3 (t), 23.7 (q), 27.1 (q), 30.4 (t), 42.0 (t), 52.8 (d), 66.9 (t), 82.7 (s), 117.2 (s), 128.0 (d), 128.5 (d), 136.4 (d), 152.8 (s), 156.1 (s), 156.2 (s), 170.5 (s), 174.0 (s). FAB-MS $m/z$: 444 $(M+1)^+$. *Anal.* Calcd for $C_{24}H_{33}N_3O_5 \cdot H_2O$: C, 62.47; H, 7.59; N, 9.11. Found: C, 62.70; H, 7.41; N, 8.97.

***tert*-Butyl 2-(Benzyloxycarbonyl)amino-4-(4-methyl-6-phenyl-2-oxo-1,2-dihydropyrimidin-1-yl)butyrate (6d) and *tert*-Butyl 2-(Benzyloxycarbonyl)amino-4-(6-methyl-4-phenyl-2-oxo-1,2-dihydropyrimidin-1-yl)-butyrate (6e)** The reaction of **4** with 1-phenyl-1,3-butanedione gave two structural isomers, which were separated by column chromatography on silica gel with $CHCl_3$–acetone–EtOH (100 : 10 : 5) mixture. The first fraction afforded **6d**, yield 8%, $[\alpha]_D^{25}$ −10.37° ($c$=0.75, MeOH). IR ($CHCl_3$): 3425, 1716, 1653, 733, 669 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.46 (9H, s), 2.0—2.21 (2H, m), 2.39 (3H, s), 3.87 (2H, m), 4.08 (1H, m), 5.03 (2H, s), 5.46 (1H, d, $J$=8 Hz), 6.10 (1H, s), 7.34—7.45 (10H, m). $^{13}$C-NMR ($CDCl_3$) $\delta$: 25.2 (q), 27.8 (q), 31.0 (t), 43.4 (t), 52.6 (d), 66.8 (t), 82.6 (s), 106.7 (d), 127.7 (d), 128.0 (d), 128.1 (d), 128.5 (d), 129.0 (d), 130.3 (s), 136.4 (s), 155.9 (s), 156.7 (s), 158.9 (s), 170.4 (s), 175.0 (s). FAB-MS $m/z$: 478 $(M+1)^+$. *Anal.* Calcd for $C_{27}H_{31}N_3O_5 \cdot H_2O$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.43; H, 6.65; N, 8.52. The second fraction afforded **6e**, yield 15%. $[\alpha]_D^{25}$ −3.29° ($c$=1.15, MeOH). IR ($CHCl_3$): 3427, 1718, 1657, 735, 669 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.46 (9H, s), 2.15—2.30 (2H, m), 2.39 (3H, s), 4.10 (2H, m), 4.32 (1H, m), 5.13 (2H, s), 5.95 (1H, d, $J$=8 Hz), 6.63 (1H, s), 7.27-7.51 (8H, m), 8.04—8.20 (2H, m). $^{13}$C-NMR ($CDCl_3$) $\delta$: 20.3 (q), 27.9 (q), 30.5 (t), 42.4 (t), 52.8 (d), 67.0 (t), 83.0 (s), 102.5 (d), 127.8 (d), 128.1 (d), 128.2 (d), 128.5 (d), 128.7 (d), 131.7 (s), 136.0 (s), 156.2 (s), 157.2 (s), 157.5 (s), 169.8 (s), 170.4 (s). FAB-MS $m/z$: 478 $(M+1)^+$. *Anal.* Calcd for $C_{27}H_{31}N_3O_5 \cdot H_2O$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.53; H, 6.81; N, 8.73.

**2-(Benzyloxycarbonyl)amino-4-(4,6-dimethyl-2-oxo-1,2-dihydropyrimidin-1-yl)butyric Acid (7)** A solution of **6a** (500 mg, 1.2 mmol) in 0.03 M HCl in formic acid (30 ml) was stirred overnight at room temperature. After evaporation of the solvent, $CHCl_3$ (100 ml) was added to the residue. The $CHCl_3$ layer was washed with $H_2O$ (20 ml × 2) and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave the product **7** (310 mg) in 72% yield, $[\alpha]_D^{26}$ 5.3° ($c$=0.5, MeOH). $^1$H-NMR ($CDCl_3$) $\delta$: 2.18 (2H, m), 2.28 (3H, s), 2.33 (3H, s), 4.06 (2H, m), 4.33 (1H, m), 5.07 (2H, s), 6.09 (1H, s), 6.41 (1H, br s), 7.31 (4H, s).

**Synthesis of Diastereomeric Dipeptides 8 and 9 for Measurement of the Degree of Racemization** WSC·HCl (29 mg, 0.15 mmol) in $CH_2Cl_2$ (0.5 ml) was added to a mixture of **7** (50 mg, 0.14 mmol), L-Ala–OMe·HCl (21.4 mg, 0.15 mmol), *N*-methylmorpholine (15 mg, 0.15 mmol), and HOBt (42.8 mg, 0.28 mmol) in dry *N*,*N*-dimethylformamide (DMF) (2 ml) at −10°C. The mixture was stirred for 2 h at −10°C and then for 24 h at room temperature. After evaporation of the solvent, the residue was dissolved in $CHCl_3$ (50 ml). The $CHCl_3$ layer was successively washed with 5% $NaHCO_3$ (20 ml × 2), 5% citric acid (20 ml × 2), $H_2O$ (20 ml × 2), and brine (20 ml × 2), and then dried over anhydrous $MgSO_4$. After evaporation of the solvent, the $^1$H-NMR spectrum of the product (**8**) was measured. $^1$H-NMR ($CDCl_3$) $\delta$: 1.42 (3H, d, $J$=7.5 Hz), 2.12 (2H, m), 2.32 (3H, s), 2.35 (3H, s), 3.73 (3H, s), 3.91 (1H, m), 4.25 (1H, m), 4.29 (1H, m), 4.44 (1H, quintet, $J$=7.5 Hz), 5.12 (2H, s), 6.11 (1H, s), 6.51 (1H, d, $J$=7.4 Hz), 7.35 (5H, s), 7.58 (1H, d, $J$=7.5 Hz). $[\alpha]_D^{26}$ 3.0° ($c$=0.5, MeOH).

The coupling of compound **7** and D-Ala–OMe·HCl was carried out in the same manner to give the dipeptide **9**. $^1$H-NMR ($CDCl_3$) $\delta$: 1.44 (3H, d, $J$=7.4 Hz), 2.11 (2H, m), 2.32 (3H, s), 2.38 (3H, s), 3.71 (3H, s), 3.86 (1H, m), 4.31 (1H, m), 4.48 (1H, quintet, $J$=7.3 Hz), 4.61 (1H, m), 5.08 (2H, s), 6.15 (1H, s), 6.37 (1H, d, $J$=7.2 Hz), 7.33 (5H, s), 8.34 (1H, d, $J$=7.3 Hz). $[\alpha]_D^{26}$ −30.3° ($c$=1.0, MeOH).

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