Synthesis of Peptides Related to Immunoglobulin E (IgE) and the Examination of Their Pharmacological Activity[1)]

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Five kinds of oligopeptides H-Asp-Ser-Asp-OH (1), H-Asp-Gly-Lys-OH (2), H-Ser-Asp-Gly-Lys-OH (3), H-Asp-Ser-Asp-Gly-Lys-OH (4), and H-Ala-Asp-Ser-Asp-Gly-Lys-OH (5) related to immunoglobulin E (IgE) were synthesized by the conventional solution method with the objective of obtaining a new type of antiallergic agent. Their pharmacological activity was examined by measuring the inhibition of the production of IgE and relaxation of the smooth muscle contraction of rabbit aorta. H-Ala-Asp-Ser-Asp-Gly-Lys-OH (5) displayed potent inhibition against the production of IgE antibody (69.6%) and relaxation against the contraction of rabbit aorta.

Keywords immunoglobulin E related oligopeptide; chemical synthesis; inhibition; immunoglobulin E antibody production; relaxation; aorta

Introduction

In 1968, Stanworth, *et al.*[2)] reported the immunoglobulin E-fragment crystalline (IgE-Fc) fragment bound to the IgE receptor and that the IgE-Fc fragment was involved in an allergic reaction. In 1974, Bennich and Johansson[3)] determined the amino acid sequence of IgE, which consisted of 547 amino acid residues. Futhermore, in 1975, Hamburger[4)] found that the IgE-Fc fragment (H–Asp–Ser–Asp–Pro–Arg–OH, positions 330—334) blocked the allergic response, and some other low molecular weight polypeptides also exhibited the inhibition of the allergic reaction. In 1976, Suzuki, *et al.*[5)] synthesized the Hamburger pentapeptide by the solution and solid phase methods.

The purpose of the present study is the synthesis of oligopeptides related to IgE and characterization of their chemical and pharmacological properties. We synthesized small peptides related to IgE, namely five kinds of oligopeptide H–Asp–Ser–Asp–OH (IgE-Fc fragment positions, 330—332) (**1**), H–Asp–Gly–Lys–OH (**2**), H–Ser–Asp–Gly–Lys–OH (**3**), H–Asp–Ser–Asp–Gly–Lys–OH (**4**), and H–Ala–Asp–Ser–Asp–Gly–Lys–OH (**5**), by the solution method and examined their pharmacological properties.

Materials and Methods

1) Peptide Synthesis The melting points are uncorrected. Optical rotations were measured with an automatic polarimeter model DIP-360 (Japan Spectroscopic Co., Ltd.). Amino acid compositions of acid hydrolysates (6 N HCl, 110 °C, 24 h) was determined with an amino acid analyzer K-101 AS (Kyowa Seimitsu Co., Ltd.). Thin-layer chromatography (TLC) was performed on 6060 Silica gel (Eastman Chromatogram Sheet) using the following solvent systems; Rf^1, $CHCl_3$–MeOH–H_2O (8 : 3 : 1, lower phase); Rf^2, *n*-BuOH–AcOH–H_2O (4 : 1 : 5, upper phase); Rf^3, *n*-BuOH–Py–AcOH–H_2O (1 : 1 : 1 : 1).

Boc-Ser-Asp(OBzl)-OBzl [I] H–Asp(OBzl)–OBzl·TosOH (4.86 g) was dissolved in DMF (25 ml) containing Et_3N (1.4 ml) under cooling with an ice-bath. Boc–Ser–OH (2.05 g), DCC (2.47 g) and HOBt (1.62 g) were added. The reaction mixture was stirred at 0 °C for 4 h, and then at room temperature for 4 h. After removal of dicyclohexylurea, the mixture was diluted with AcOEt (200 ml), which was washed with 8% Na_2CO_3, NaCl–H_2O, 8% citric acid and NaCl–H_2O. The organic layer was dried over Na_2SO_4 and evaporated down. Petroleum ether was added to the residue to afford crystalline material, which was collected by filtration and recrystallized from AcOEt and petroleum ether; yield 3.65 g (73.0%), mp 109—111 °C, $[\alpha]_D^{26}$ −16.1° (*c* = 1.0, DMF), Rf^1 0.71. Amino acid ratios in an acid hydrolysate: Asp 1.0 (1); Ser 1.0 (1). *Anal.* Calcd for $C_{26}H_{32}N_2O_8$: C, 62.39; H, 6.44; N, 5.60. Found: C, 62.39; H, 6.62; N, 5.67.

Z-Asp(OBzl)-Ser-Asp(OBzl)-OBzl [II] A solution of [I] (2.00 g) in a mixture of TFA–anisole (5 ml–0.5 ml) was stored at room temperature for 1 h. Ether (50 ml) and petroleum ether (50 ml) were added to the solution to give a precipitate, N^{α}-deprotected peptide, which was collected by filtration and dried over NaOH pellets *in vacuo* for 3 h. To a solution of this product in DMF (10 ml) and Et_3N (0.63 ml) was added Z–Asp(OBzl)–OH (1.57 g), HOBt (0.65 g) and DCC (0.99 g) in DMF (10 ml). The mixture was stirred at 4 °C for 16 h. After removal of dicyclohexylurea, AcOEt (200 ml) was added to the mixture, which was washed with 8% Na_2CO_3, NaCl–H_2O, 0.1 N HCl and NaCl–H_2O. The organic layer was dried over Na_2SO_4 and then evaporated down. Upon trituration of the residue with ether the product was solidified and recrystallized from AcOEt and ether; yield 1.99 g (67.5%), mp 108—110 °C, $[\alpha]_D^{26}$ −11.7° (*c* = 0.76, DMF), Rf^1 0.82. Amino acid ratios in an acid hydrolysate: Asp 2.0 (2); Ser 0.9 (1). *Anal.* Calcd for $C_{40}H_{41}N_3O_{11}$: C, 64.9; H, 5.59; N, 5.68. Found: C, 64.8; H, 5.73; N, 5.78.

Z-Asp(OBzl)-Gly-Lys(Z)-OBzl [III] A solution of Z–Asp(OBzl)–OH (1.50 g) in DMF (10 ml), pre-activated for 3 h at 0 °C, with DCC (0.95 g) and HOBt (0.62 g) was mixed with a solution of TFA/anisole-treated Boc–Gly–Lys(Z)–OBzl[6)] (2.24 g) in DMF (10 ml) neutralized with Et_3N (0.59 ml). The reaction mixture was processed as described above [II]. Upon trituration of the residue with petroleum ether the product was solidified and reprecipitated from AcOEt–petroleum ether; yield 1.71 g (52.3%), mp 60—61 °C, $[\alpha]_D^{26}$ −16.3° (*c* = 0.93, DMF), Rf^1 0.82. Amino acid ratios in an acid hydrolysate: Asp 0.9 (1); Gly 0.8 (1); Lys 1.0 (1). *Anal.* Calcd for $C_{42}H_{46}N_4O_{10}\cdot 1/2H_2O$: C, 65.0; H, 6.11; N, 7.22. Found: C, 65.1; H, 6.13; N, 7.41.

Boc-Asp(OBzl)-Gly-Lys(Z)-OBzl [IV] A solution of Boc–Asp(OBzl)–OH (8.41 g) in DMF (20 ml), pre-activated for 3 h at 0 °C, with DCC (5.98 g) and HOBt (3.92 g) was mixed with a solution of TFA/anisole-treated Boc–Gly–Lys(Z)–OBzl[6)] (13.98 g) in DMF (15 ml) neutralized with Et_3N (3.64 ml). The reaction mixture was processed as described above and the product was purified by precipitation from AcOEt–petroleum ether; yield 14.75 g (76.9%), mp 70—72 °C, $[\alpha]_D^{26}$ −19.0° (*c* = 1.0, DMF), Rf^1 0.8. Amino acid ratios in an acid hydrolysate: Asp 0.8 (1): Gly 0.8 (1); Lys 1.0 (1). *Anal.* Calcd for $C_{39}H_4O_{10}\cdot 1/2H_2O$: C, 63.1; H, 6.66; N, 7.55. Found: C, 63.1; H, 6.64; N, 7.72.

Z-Ser-Asp(OBzl)-Gly-Lys(Z)-OBzl [V] A solution of Z–Ser–OH (0.84 g) in DMF (10 ml), pre-activated for 3 h at 0 °C, with DCC (0.83 g) HOBt (0.54 g), was mixed with a solution of TFA/anisole-treated compound [IV] (2.40 g) in DMF (10 ml) neutralized with Et_3N (0.49 ml). The reaction mixture was processed as described above and the product was purified by precipitation from AcOEt–petroleum ether; yield 1.20 g (43.0%), mp 70—72 °C, $[\alpha]_D^{26}$ −16.8° (*c* = 0.75, DMF), Rf^1 0.83. Amino acid ratios in an acid hydrolysate: Asp 0.9 (1); Ser 1.1 (1); Gly 0.8 (1); Lys 1.0 (1). *Anal.* Calcd for $C_{45}H_{51}N_5O_{12}\cdot H_2O$: C, 61.99; H, 6.12; N, 8.03. Found: C, 61.99; H, 5.99; N, 8.30.

Boc-Ser-Asp(OBzl)-Gly-Lys(Z)-OBzl [VI] A solution of Boc–Ser–OH (2.87 g) in DMF (20 ml), pre-activated for 3 h at 0 °C with DCC (3.30 g) and HOBt (2.16 g), was mixed with a solution of TFA/anisole-treated compound [IV] (10.0 g) in DMF (20 ml) neutralized with Et_3N (1.96 ml). The reaction mixture was processed as described above and the product was purified by precipitation from AcOEt–petroleum ether; yield 5.83 g (52.0%), mp 57—60 °C, $[\alpha]_D^{26}$ −23.5° (*c* = 0.54, DMF), Rf^1 0.83. Amino acid ratios in an acid hydrolysate: Asp 0.9 (1); Ser 1.1 (1); Gly 0.8 (1); Lys 1.0 (1). *Anal.* Calcd for $C_{42}H_{53}N_5O_{12}\cdot 1/2H_2O$: C, 59.6; H, 6.66; N, 8.27. Found: C, 59.4; H, 6.64; N, 8.58.

Z-Asp(OBzl)-Ser-Asp(OBzl)-Gly-Lys(Z)-OBzl [VII] A solution of Z-Asp(OBzl)-OH (1.04 g) in DMF (10 ml), pre-activated for 3 h at 0 °C with DCC (0.66 g) and HOBt (0.43 g), was mixed with a solution of TFA/anisole-treated compound [VI] (2.17 g) in DMF (10 ml) neutralized with Et_3N (0.41 ml). The reaction mixture was processed as described above and the product was purified by precipitation from AcOEt–petroleum ether; yield 0.85 g (31.0%), mp 58 °C, $[\alpha]_D^{26}$ −20.5° (c=0.90, DMF), Rf^1 0.63. Amino acid ratios in an acid hydrolysate: Asp 2.0 (2); Ser 1.0 (1); Gly 0.8 (1); Lys 0.9 (1). *Anal.* Calcd for $C_{56}H_{62}N_6O_{15}\cdot H_2O$: C, 62.4; H, 5.99; N, 7.80. Found: C, 62.0; H, 5.69; H, 7.81.

Boc-Asp(OBzl)-Ser-Asp(OBzl)-Gly-Lys(Z)-OBzl [VIII] A solution of Boc-Asp(OBzl)-OH (0.60 g) in DMF (10 ml), pre-activated for 3 h at 0 °C with DCC (0.41 g) and HOBt (0.27 g) was mixed with a solution of TFA/anisole-treated compound [VI] (1.31 g) in DMF (10 ml) neutralized with Et_3N (0.27 ml). The reaction mixture was processed as descibed above and the product was purified by precipitation from AcOEt–petroleum ether; yield 0.75 g (46.0%), mp 49—51 °C, $[\alpha]_D^{26}$ −22.0° (c=0.75, DMF), Rf^1 0.78. Amino acid ratios in an acid hydrolysate: Asp 2.1 (2); Ser 1.0 (1); Gly 0.8 (1); Lys 1.0 (1). *Anal.* Calcd for $C_{53}H_{64}N_6O_{15}\cdot 2H_2O$: C, 60.0; H, 6.59; N, 7.92. Found: C, 59.7; H, 6.28; N, 7.81.

Z-Ala-Asp(OBzl)-Ser-Asp(OBzl)-Gly-Lys(Z)-OBzl [IX] A solution of Z-Ala-OH (0.21 g) in DMF (3 ml), pre-activated for 3 h at 0 °C with DCC (0.25 g) and HOBt (0.16 g), was mixed with a solution of TFA/anisole-treated compound [VIII] (0.4 g) in DMF (10 ml) neutralized with Et_3N (0.07 ml). The reaction mixture was processed as described above and the product was purified by precipitation from AcOEt–petroleum ether; yield 0.28 g (64%), mp 59—60 °C, $[\alpha]_D^{26}$ −23.0° (c=0.79, DMF), Rf^2 0.80. Amino acid ratios in an acid hydrolysate: Asp 2.0 (2); Ser 0.9 (1); Gly 0.8 (1); Ala 1.1 (1); Lys 0.9 (1). *Anal.* Calcd for $C_{59}H_{67}N_7O_{16}\cdot 1/2H_2O$: C, 62.2; H, 6.01; N, 8.61. Found: C, 62.6; H, 6.70; N, 9.59.

Total Deprotection and Purification The protected peptide of compound [II] (400 mg) in MeOH (10 ml), AcOH (4 ml) and H_2O (6 ml) was hydrogenated for 7 h in the presence of 5% Pd–C (400 mg). After removal of Pd–C, H_2O was added to the reaction mixture and then evaporated to a small volume. The residue was washed with ether. H_2O was added and evaporated to a small volume (2 ml), which was chromatographed on a Sephadex G-10 column (2.5 × 42 cm) and eluted with 0.5% AcOH. Individual fractions of 4 g each were collected. The desired fractions (tube Nos. 22—28) were collected and lyophilized.

Other protected peptides of [III] (400 mg), [V] (400 mg), [VII] (400 mg) and [IX] (150 mg) were deprotected by the same way. Yield, $[\alpha]_D^{26}$ value, Rf value and analytical data are shown in Table I.

2) Examination of Pharmacological Activity The pharmacological effects on IgE antibody formation *in vivo* and on the contraction of vascular smooth muscle *in vitro* of five kinds of synthetic peptides were examined. These activities were compared with that of the Hamburger pentapeptide (SIGMA Chem. Co.).

Effects on the IgE Antibody Formation in Mice Male BALB/c mice of 7 weeks of age were used for the formation of the antibody. This experiment used dinitrophenylated *ascaris* extract (DNP-As: COSMOBIO. Chem. Co.) as an antigen and aluminium hydroxide gel (alum) as an adjuvant for the mice. Alum was prepared by the method of Levine and Vaz.[7] Each mouse was immunized i.p. with 10 μg of DNP-As and 2 mg of alum (the primary immunization). They were bled at appropriate intervals, and their serums were separated and stored at −20 °C until the assay. Test compounds were dissolved in physiological saline (1 mg/ml), and injected in two separated groups of mice. One group was injected 3 times before or after immunization. These mice were bled at 14 d. The other group was injected at 7, 14 and 21 d from immunization. These mice were bled at 28 d. Serum IgE antibody levels were evaluated by passive cutaneous anaphylaxis (PCA) according to the technique described by Mota.[8] Briefly, two fold serially diluted serum samples were injected intradermally into the shaved backs of normal male rats. After 48 h, PCA was elicited by an intravenous injection of 1 ml of 0.5% Evans blue containing 1 mg of DNP-As. These rats were sacrificed after 30 min, and the PCA tite was measured. The results are shown in Tables III and IV.

Effects on the Contraction in the Smooth Muscle of Rabbit Aorta According to the method of Karaki *et al.*,[9] male albino rabbits (weight 2—3 kg) were stunned by a blow on the head and exsanguinated. The thoracic aorta was quickly removed and the surrounding tissues were cleaned. The segments of aorta were cut into helical strips of approximately 25—30 mm in length and 2—4 mm in width. The preparation for study of the contractile response to KCl or norepinephrine (NE) was suspended in a glass organ bath filled with 10 ml of Tyrode buffer solution, which consisted of the following materials (mM): NaCl, 136.9; KCl, 5.4; $CaCl_2$, 1.5; $MgCl_2$, 1.0; $NaHCO_3$, 23.8 and glucose, 5.5. The muscle strip was attached to a holder under a resting tension of 0.5 g and equilibrated in the bathing solution for 60—90 min before examination. Each test compound was added to the bath 20—30 min after the application of KCl (104 mM) or NE (10^{-6} M). The results are summarized in Table V.

Results and Discussion

Table I shows the physical and analytical data of five synthetic peptides. These peptides contained on Asp–Ser or Asp–Gly sequence. It is well known that aspartyl peptides such as –Asp–Ser– and –Asp–Gly– are a troublesome sequence. Especially the β-benzyl-asparatyl peptides have a great tendency to form aminosuccinyl derivatives as byproducts.[10] However, the above data indicate that the synthetic peptides were highly purified products without any aspartylimide formation. Furthermore, high performance liquid chromatography (HPLC) analysis supported the homogeneity of the above peptides (Column, YMC-PAC A-3020DS (4.6 × 150 mm); solvent, H_2O–CH_3CN (90 : 10) containing 0.05% TFA; absorbance, 220 nm; flow rate, 0.5 ml/min).

Table II shows the inhibitory effect of test compounds on primary IgE antibody formations in mice. H–Asp–Gly–Lys–OH (**2**) (48.2%) and H–Ala–Asp–Ser–Asp–Gly–Lys–OH (**5**) (40.9%) inhibited potently primary IgE antibody formation in comparison with the control group.

Table III shows the inhibitory effect of test compounds

TABLE I. Physical and Analytical Data of Synthetic Peptides

Peptides	Yield[a] (mg) (%)	$[\alpha]_D^{26}$ (°) c=0.16 H_2O	Rf^3	Amino acid ratios	Formula	Analysis (%) Calcd (Found) C	H	N
H–Asp–Ser–Asp–OH (**1**)	166.3 92	−8.6	0.51	Asp 2.00, Ser 0.95 88.3%	$C_{11}H_{17}N_3O_9\cdot 1/2AcOH\cdot 2H_2O$	36.1 (35.8	5.8 5.4	10.5 10.7)
H–Asp–Gly–Lys–OH (**2**)	47.1 28	+13.6	0.63	Asp 1.00, Gly 0.86, Lys 1.00, 87.3%	$C_{12}H_{22}N_4O_6\cdot 1/2AcOH\cdot 3H_2O$	39.0 (38.9	7.1 7.3	14.0 14.1)
H–Ser–Asp–Gly–Lys–OH (**3**)	60.8 32	−8.6	0.53	Asp 0.92, Ser 0.87, Gly 0.84, Lys 1.00 84.5%	$C_{15}H_{27}N_5O_8\cdot 1/2AcOH\cdot 3(1/2)H_2O$	38.7 (38.8	7.3 7.1	14.2 14.1)
H–Asp–Ser–Asp–Gly–Lys–OH (**4**)	103.6 52	−18.6	0.49	Asp 2.16, Ser 0.96, Gly 0.78, Lys 1.00 86.6%	$C_{19}H_{32}N_6O_{11}\cdot 1/2AcOH\cdot 3H_2O$	38.7 (39.3	6.7 6.3	13.9 13.5)
H–Ala–Asp–Ser–Asp–Gly–Lys–OH (**5**)	28.2 40	−35.6	0.50	Asp 2.00, Ser 0.83, Gly 0.84, Ala1.10, Lys 1.00 98.9%	$C_{22}H_{37}N_7O_{12}\cdot 2AcOH\cdot 7H_2O$	37.6 (37.1	7.2 6.8	11.8 11.9)

a) Yield is in the final deprotection stage.

TABLE II. Inhibition of Synthetic Peptides on Primary IgE Antibody Formation in Mice

Compounds		Dose (mg/kg, i.p.)	n	PCA titer (mean ± S.E.)	Inhibition (%)
Control		—	6	469 ± 43	—
H–Asp–Ser–Asp–OH	(1)	1	5	410 ± 63	12.7
H–Asp–Gly–Lys–OH	(2)	1	5	243 ± 77[a)]	48.2
H–Ser–Asp–Gly–Lys–OH	(3)	1	5	365 ± 98	22.3
H–Asp–Ser–Asp–Gly–Lys–OH	(4)	1	5	333 ± 77	29.1
H–Ala–Asp–Ser–Asp–Gly–Lys–OH	(5)	1	6	277 ± 82	40.9
H–Asp–Ser–Asp–Pro–Arg–OH		1	5	461 ± 51	1.8
Cyclophosphamide		1	5	461 ± 51	1.8

Compounds were administered intraperitoneally at 1 mg/kg/d, i.p. for 3 d before or after immunization. The mice were held 14 d after immunization. Each value represented the mean ± S.E. *a)* $p < 0.05$, significantly different from the control.

TABLE III. Inhibition of Synthetic Peptides on Going IgE Antibody Formation in Mice

Compounds		Dose (1 mg/kg, i.p.)	n	PCA titer (mean ± S.E.)	Inhibition (%)
Control		—	6	395 ± 78	—
H–Asp–Ser–Asp–OH	(1)	1	7	357 ± 68	9.6
H–Asp–Gly–Lys–OH	(2)	1	7	247 ± 53	37.5
H–Ser–Asp–Gly–Lys–OH	(3)	1	7	302 ± 124	23.5
H–Asp–Ser–Asp–Gly–Lys–OH	(4)	1	7	293 ± 37	25.8
H–Ala–Asp–Ser–Asp–Gly–Lys–OH	(5)	1	7	120 ± 40[a)]	69.6
H–Asp–Ser–Asp–Pro–Arg–OH		1	7	315 ± 132	20.3
Cyclophosphamide		1	6	133 ± 41[b)]	66.3

Compounds were administered intraperitoneally 3 times; 7, 14 and 21 d from immunization. Each value represented the mean ± S.E. *a)* $p < 0.01$, significantly different from the control. *b)* $p < 0.05$, significantly different from the control.

TABLE IV. Effect of Peptides on the Contraction of Aorta Induced by Norepinephrine

Compounds		n	Relaxation (%)				
			10^{-8}	10^{-7}	10^{-6}	10^{-5}	10^{-4} (M)
H–Asp–Ser–Asp–OH	(1)	4	0	0	12.1 ± 3.8	20.0 ± 1.8	43.8 ± 10.9
H–Asp–Gly–Lys–OH	(2)	4	0	0	6.6 ± 3.1	9.3 ± 2.9	40.3 ± 17.8
H–Ser–Asp–Gly–Lys–OH	(3)	4	1.7 ± 1.2	9.1 ± 5.3	17.7 ± 2.1	25.0 ± 4.7	52.6 ± 7.3
H–Asp–Ser–Asp–Gly–Lys–OH	(4)	4	2.2 ± 1.3	5.1 ± 2.1	7.7 ± 1.0	14.1 ± 3.2	58.2 ± 7.5
H–Ala–Asp–Ser–Asp–Gly–Lys–OH	(5)	4	3.0 ± 2.1	11.8 ± 4.3	36.1 ± 2.5	66.7 ± 1.9	81.8 ± 4.1
H–Asp–Ser–Asp–Pro–Arg–OH		4	0	0	0	4.9 ± 2.6	23.7 ± 8.1
Nitroprusside		4	16.1 ± 13.9	59.4 ± 10.2	86.0 ± 2.5	93.8 ± 1.7	98.8 ± 1.2

Compounds were added to the preparation 15 min after the maximal contractions induced by 10^{-6} M norepinephrine. Each value represents the mean ± S.E.

on ongoing IgE antibody formations in mice. Every synthetic peptide inhibited ongoing IgE antibody formations. H–Ala–Asp–Ser–Asp–Gly–Lys–OH (**5**) displayed the strongest inhibition against the production of IgE (69.6%).

Table IV shows the effects on the smooth muscle contraction of rabbit aorta. Synthetic peptides and the Hamburger peptide had no effect on the contractions induced by K^+ in rabbit aorta. On the contrary, these peptides had a dose-dependent relaxing effect on the norepinephrine-induced contraction in the rabbit aorta. The most relaxative peptide was H–Ala–Asp–Ser–Asp–Gly–Lys–OH (**5**) (81.8% at -10^{-4} M).

The present data prove that synthetic peptides, especially H–Ala–Asp–Ser–Asp–Gly–Lys–OH (**5**) inhibited the production of IgE antibody formation, and relaxed the norepinephrine-induced contraction of the blood vessel. These results suggest that H–Ala–Asp–Ser–Asp–Gly–Lys–OH (**5**) has both activities, the suppression of IgE antibody formation and relaxation of the contraction of the blood vessel, and is a new antiallergic agent candidate. A further experiment on the mechanisms of the action of this hexapeptide (**5**) is in progress in our laboratory.

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References and Notes

1) Amino acids used in this investigation are of the L-configuration except in the case of glycine. The following abbreviations are used: Z, benzyloxycarbonyl; Boc, *tert*-butyloxycarbonyl; B_zl, benzyl; DMF, dimethylformamide; DDC, dicyclohexylcarbodiimide; HOBt, 1-hydroxybenzotriazole; TFA, trifluoroacetic acid; Et_3N, triethyl amine.
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