A Charge-Transfer Effect in Solid Phase Peptide Synthesis: Unusually High Reactivity in Peptide Bond Formation between *p*-Nitrobenzophenone Oxime Resin Ester and Amino Acid 4-(Methylthio)phenyl Ester

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Unusually high reactivity was found in peptide bond formation between *p*-nitrobenzophenone oxime resin (**I**) ester and amino acid 4-(methylthio)phentyl (MTP) esters. A charge-transfer complex between the two phenyl rings of the oxime resin (**I**) and the incoming amino acid MTP esters was considered to be responsible to accelerate the aminolysis reaction of the peptide oxime resin ester. Several di-, tri-, and pentapeptide fragments for preparing enkephalin and glutathione oligomers were successfully prepared in short times.

Introduction

The merits of fragment condensation strategy in the solid phase synthesis of large size peptide have been well documented[1]. An oxime resin of type **I** has proved to be one of the ideal solid matrixes for this object.[2] Different from the conventional Merrifield peptide resin, **I** is suitable for the syntheses of protected peptide intermediates. The peptide chain linked to **I** can be released by aminolysis reaction with amino acid or peptide esters yielding fully protected peptide fragments without any side reactions. For the better use of peptide fragments in the syntheses of large size peptides, the carboxyl terminal of the fragment need to be blocked with a proper protecting group which can be easily modified or removed for further peptide bond formation. From this point of view, recovery of the pepide fragment from **I** as a form of peptide alkyl ester has a drawback.

As an alternative to that, Kaiser and Nakagawa[3] have obtained protected peptide acid fragments from **I** via peptide 1-piperidyl esters. However, 1-piperidyl ester turned out to be neither good protecting group nor proper activating group, and this result confirmed that novel orthogonal carboxyl protecting groups are necessary for the successful syntheses of large size peptides from the peptide fragments which are constructed with **I**.

Recently, amino acid pentammine cobalt(III) complexes[4] have been successfully exploited in our group[5] in the synthesis of Met-enkephalin derivative with **I**. Several other carboxyl protected amino acids were tested for the syntheses of peptide fragments from **I** including amino acid 4-(methylthio)phenyl (MTP) esters[6] which possess "safety-catch" type carboxyl protecting group. During these series of experiments, we have found that the amino acid derivatives with different carboxyl protecting groups showed remarkable differences in reactivity toward aminolysis reactions.[7] For example, it took more than 20 hours for glycine cobalt (III) complex to cleave the oxime resin ester bond, while glycine MTP ester finished the same job in less than 5 minutes.

We now wish to report that the charge-transfer interaction[8] between the two phenyl rings of the MTP group and the *p*-nitrobenzophenone oxime group may play an important role in such a high reactivity in peptide bond formation.

Results and Discussion

I was prepared from polystyrene 1%-divinylbenzene copolymer by the known procedure.[2] The oxime content of the resin was determined as 1.0 mmol/g resin by nitrogen analysis. For the easy comparison of the reactivity differences in peptide bond formation, series of phenylalanine containing dipeptide derivatives were chosen. After Boc-phenylalanine

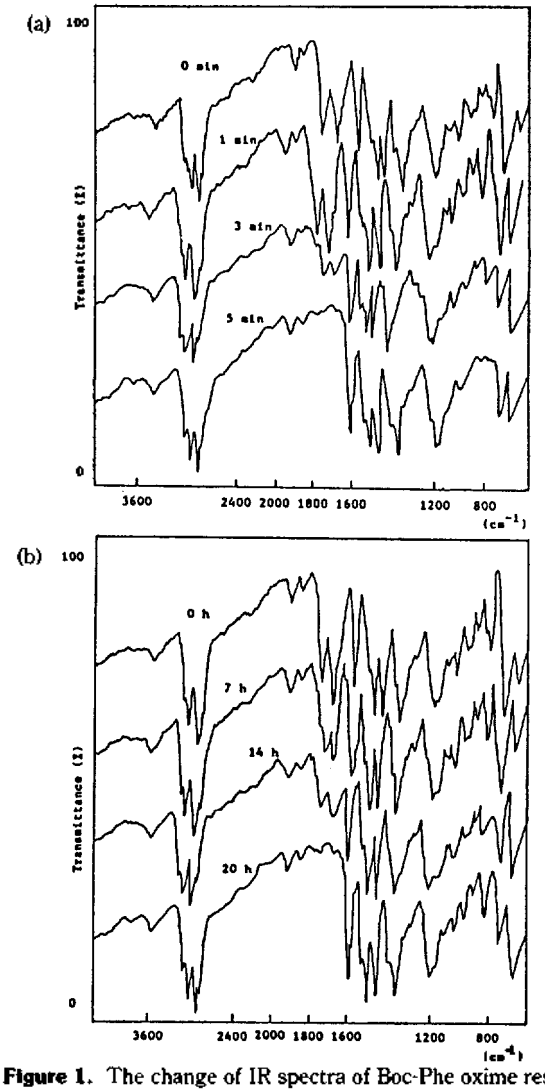


Figure 1. The change of IR spectra of Boc-Phe oxime resin during aminolysis reaction with (a) Gly-OMTP and (b) [Gly-Co(III)$(NH_3)_5$] $(ClO_4)_3$.

Table 1. Physical data of each coupling reaction[10]

Entry	Peptide Derivatives[a]	Reaction Times (min)		Yield[b](%)	mp(°C)	Rf(TLC)[c]	$[\alpha]_D^{30}$
		CH_2Cl_2	DMF				
1	Boc-Phe-Gly-OMTP	5	300	88	148-149	0.59(A)	7.0(c = 1, AcOH)
2	Boc-Phe-Gly-OMe	20	20	90	oil	0.55(A)	-1.40(c = 1, $CHCl_3$)
3	Boc-Phe-Gly-OPh	60	200	65	122-123	0.60(A)	-6.0(c = 1, AcOH)
4	Boc-Phe-Gly-O-t-Bu	60	60	91	82-83	0.60(A)	19.0(c = 1, $CHCl_3$)
5	Boc-Phe-Gly-OBzl	95	60	88	132-134	0.61(A)	-4.0(c = 1, $CHCl_3$)
6	Boc-Phe-Gly-Co(III)	*d*	1140	85	*e*		
7	Boc-Phe-β-Ala-OMTP	7	60	89	137-139	0.62(A)	15.0(c = 1, $CHCl_3$)
8	Boc-Phe-Leu-OMTP	90	500	89	121-122	0.76(A)	-20.0(c = 1, AcOH)
9	Boc-Phe-ε-ACA-OMTP	120	300	74	114-115	0.69(A)	0.80(c = 1, $CHCl_3$)

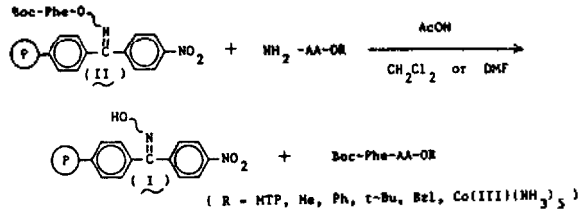
[a] Each run was performed at room temperature under identical conditions. [b] All the yields are isolation yields in methylene chloride except entry 6. [c] Solvent systems are described in experimental section. [d] Gly-Co(III) complex was in perchlorate form, and not soluble in methylene chloride. [e] Characterized after removing Co(III) from the C-terminus. All physical data were identical with the literature alue[11].

Table 2. Elemental analyses of peptide derivatives

Entry[a,b]	Calcd(%)			Found(%)		
	C	H	N	C	H	N
1	62.14	6.36	6.30	62.67	6.19	6.64
2	60.70	7.19	8.33	60.97	7.49	8.57
3	66.30	6.58	7.03	65.94	6.49	7.49
4	63.47	7.99	7.40	63.23	7.77	7.56
5	66.97	6.84	6.84	67.38	6.59	6.78
7	62.86	6.59	6.11	63.00	6.61	6.12
8	64.77	7.25	5.06	65.49	7.25	5.45
9	64.77	7.25	5.60	64.49	7.76	5.71

[a] Each entry number is correspondent to that indicated in Table 1. [b] For entry 6, elemental analysis is avoided for fear of its explosibility. After removing its C-terminal protecting group, resulted peptide was characterized. All physical data were satisfactory.

was anchored to **I**, series of dipeptide derivatives were prepared by the following scheme.



Scheme

In a typical experiment, **II** was swelled with CH_2Cl_2 in a reaction vessel.[9] After 3 equiv of carboxyl-protected amino acid in CH_2Cl_2 was added and neutralized with DIEA, 3 equiv of AcOH was added as a catalyst, and the resin mixture was shaken. Aliquot of the resin were taken out of reaction vessel periodically, and the IR spectra were taken to monitor the progress of the reaction. Figure 1 shows the oxime ester peak at 1780 cm^{-1} rapidly disappeared in 5 min as the coupling reaction of Boc-Phe-Gly-OMTP proceeded. In case of Boc-Phe-Gly-Co (III), the same peak was slowly diminished and disappeared in 20 h. The reaction times and analytical data for the peptide derivatives were summarized in Table 1 and Table 2. All the reactions were in >95% complete within the reaction times specified in Table 1, and upon subsequent workup the desired peptides were obtained in high yields.

Table 1 shows that the rate of the coupling reactions are quite different as the carboxyl protecting groups of amino acid are changed.

Several factors can be drawn for the big rate differences in reactivity of the peptide bond formation. First, hydrophobic interaction between the amino acid ester moiety and the polymer matrix may play an important role in the heterogeneous reaction condition. The polystyrene polymer backbone is very hydrophobic intrinsically. Therefore, amino acid derivatives with hydrophilic moiety such as Co(III) complex will not interact with the polymer chain and have less chances to react with the oxime ester bond. Second, steric factor will be another one (compare entries 2-6). Glycine methyl ester, owing to its small size, reacted faster than its corresponding phenyl, t-butyl, or benzyl ester, and Co(III) complex. This factor seems to be more important than hydrophobicity. But to our surprise, glycine MTP ester (enrty 1) which possesses about the same bulkiness as glycine benzyl ester showed the highest reactivity in CH_2Cl_2. The rate of aminolysis reaction of the oxime resin ester with the glycine MTP ester is even faster than that of hydrazinolyses which were reported to be finished in 10 min.[2] This is striking if we compare the nucleophilicity of hydrazine with that of α-amino group which will mainly exists as an acetate salt form.

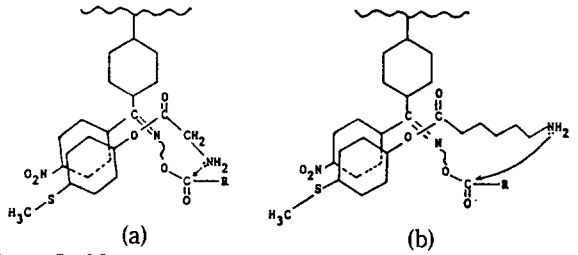
Series of experiments with homologous amino acid (β-alanine, or ε-aminocaproic acid) and bulkyl α-amino acid (leucine) MTP esters revealed that the reactivity of the peptide bond formation depends not only on the bulkiness of the side chains of the incoming amino acid derivatives, but on the distance between the MTP group and the reacting amino groups. Thus, ε-aminocaproic acid MTP ester (entry 9) and leucine MTP ester (entry 8) cleaved Boc-Phe-**I** ester in 120 and 90 min respectively. However, only 5 and 7 min were needed for the same job with glycine MTP ester and β-alanine MTP ester respectively. In previously reported aminolysis reactions with amino acid alkyl ester or peptide alkyl ester, the reactivity did not show any dependence on the distance between the carboxyl protecting group and the reacting amino group[2].

These results strongly suggest that some kind of charge-transfer interaction[12] exists, and it is responsible for the high reactivity of amino acid MTP ester toward the oxime ester bond. The charge-transfer complex can be formed between

Table 3. Physical data of each coupling reaction.

Peptide Derivatives[a]	Reaction Times (min)	Yield (%)	mp(°C)	Rf(TLC)[b]	$[\alpha]_D^{20}$
Boc-Tyr(OBzl)↓Gly-OMTP	10	95	104-105	0.75(B)	3.8(c = 1, AcOH)
Boc-Gly-Phe-Leu-Tyr(OBzl)↓Gly-OMTP	10	86	178-180	0.83(B)	-1.88(c = 1, AcOH)
Boc-Gly-Phe↓Leu-OMTP	120	88	138-139	0.77(B)	-4.66(c = 1, AcOH)
Z-γ-Glu(α-OEt)-Cys(SBzl)↓Gly-OMTP	15	75	153-155	0.58(A)	-19.0(c = 1, $CHCl_3$)

[a] Arrows indicate the positions of newly formed peptide bonds between the oxime resin ester and the amino acid esters. Each run was performed under identical reaction conditions. [b] Solvent systems are described in the experimental section.



(a) (b)

Figure 2. Models of charge-transfer complexes between the oxime resin and (a) Gly-OMTP, (b) ε-aminocaproic acid MTP ester.

the two phenyl rings of the p-nitrobenzophenone oxime and the MTP ester. The former ring has an acceptor character due to the nitro group while the latter has a donor character due to the methyl sulfide moiety on the phenyl ring[13]. A molecular model study indicates that once the complex is formed, it provides such a nice geometry that the amino groups of the glycine and the β-alanine ester derivatives are kept in the vicinity of the oxime ester bond (Figure 2, (a)). In case of ε-aminocaproic acid MTP ester, long hydrocarbon chain makes the nucleophile difficult to approach the oxime ester even though the charge-transfer complex is formed (Figure 2, (b)). It is generally accepted that the stability of the charge-transfer complex diminishes with sterically hindered molecules, which is observed in case of leucine MTP ester. Moreover, much slower reaction rates in DMF (entries 1 and 7-9) are consistent with the general trend of the solvent effect on the charge-transfer complex formation.[14]

The possibility of any reactivity change or side reactions as the peptide chain gets longer in the polymer matrix was also examined. Thus, after Boc-Tyr(OBzl)-OH or Boc-Cys (SBzl) was loaded on **I**, the usual procedure[2] for the solid phase peptide elongation was followed to obtain Boc-Gly-Phe-Leu-Tyr(OBzl)-**I** and Z-γ-Glu(α-OEt)-Cys(SBZl)-**I** as well as Boc-Tyr(OBzl)-**I** and Boc-Gly-Phe-**I**. Treating them with glycine MTP ester or leucine MTP ester gave enkephalin oligomer segments, Boc-Tyr(OBzl)-Gly-OMTP, Boc-Gly-Phe-Leu-Tyr(OBzl)-Gly-OMTP, Boc-Gly-Phe-Leu-OMTP, and a glutathione derivative, Z-γ-Glu(α-OEt)Cys-(SBzl)-Gly-OMTP in high yields. The reaction times and the physical properties of the final peptide derivatives are listed in Table 3. The results showed that no substantial reactivity drop was found in the preparation of tri-, or pentapeptides under the same reaction conditions. These results verify again the existence and the predominant advantage of the charge-transfer complex in the course of peptide bond formation between the oxime resin ester and the amino acid MTP esters.

Until now, there have been little report which offerred an example of the reactivity differences in aminolysis reactions of peptide oxime resin esters with amino acid esters. DeGrado and Kaiser[2] have only reported such aminolysis reactions were usually finished in 12-18 h with 3 or 4 equiv of amino acid or peptide alkyl esters. Our results explained that the aminolysis reactions were affected by several factors and actually finished in much shorter times than normally expected if there is no charge-transfer interaction. The present paper offers some examples and rationale for the reactivity differences. Moreover, it suggests that charge-transfer complex mediated reactions can provide an environment to enhance reactivity in solid phase reactions. Works will be continued in our laboratory along this line to elucidate other factors which are affecting the reactivity in solid phase reactions.

In addition, preparation of enkephalin oligomers and glutathione oligomers using the resulting peptide fragments is now under study.

Experimental

Melting points were measured on a Yanaco MP-S5 and are not corrected. ^{1}H NMR spectra were obtained from a Jeol JNM-MH-100 NMR spectrophotometer. Optical rotations were measured with a Jasco DIP-360 polarimeter. Elemental analyses were performed with a Yanaco MT-2 CHN corder. IR spectra were recorded on a Jasco DS-710 infrared spectrophotometer using KBr pellets, and UV spectra were taken on a Shimadzu UV-200S double beam spectrometer. Amino acid analyses were performed at Reseach Center, Ginsco Corp., Seoul. Analytical thin layer chromatography was performed on silica gel plate (0.25mm, 60F-254 E. Merck) with the following solvent systems; A, chloroform/methanol (15:1); B, Chloroform/acetic acid (10:1). All solvents were in reagent grade and were purified by appropriate procedures.[15] All the amino acid derivatives were in L-configuration. Boc-amino acid derivatives and Gly-O-t-Bu were purchased from Chemical Dynamics Corp. and used without further purification. N,N-Dicyclohexylcarbodiimide (DCC) and 4-(methylthio)phenol were purchased from Aldrich. p-Nitrobenzophenone oxime resin was prepared from polystyrene-1%-divinylbenzene-copolymer (Bio beads S-X1, 200-400 mesh) according to the literature procedure.[2] The degree of substitution of the resin was determined by nitrogen analysis.

Preparation of Carboxyl Protected Amino Acid Derivatives. Boc amino acid MTP esters were prepared according to the following procedure. Boc-amino acid (40 mmol) and 4-methylthiophenol (40 mmol) were dissolved in 150 ml of CH_2Cl_2 and allowed to cool to 0 °C. After DCC (42 mmol) was added, the solution was stirred for 1 hr at 0 °C and then at room temperature overnight. DCU was filtered off and the filtrate was removed under reduced pressure to give an oily

residue. It was dissolved in 100 m*l* of EtOAc and washed with 5% $NaHCO_3$ (3 × 70 m*l*), 5% citric acid (3 × 70 m*l*), water (2 × 100 m*l*), and dried over Na_2SO_4. Evaporation of the solvent gave an oil which was crystallized from EtOAc-n-hexane. Boc-amino acid phenyl esters[16] were also prepared in the similar fashion. Amino acid MTP or phenyl ester hydrochlorides were obtained from corresponding Boc-derivatives by removing Boc-group with 2N HCl-dioxane/AcOH[17].

Amino acid methyl or benzyl esters were prepared directly from corresponding amino acids by the known procedures in the form of hydrochloride or p-toluenesulfonate respectively[18,19]. Glycine cobalt(III) complex were prepared according to Isied's method.[4]

Preparation of Boc-phenylalanine-I. Boc-phenylalanine (30 mmol) and DCC (30 mmol) were added to **I** (10 g) in CH_2Cl_2(100 m*l*). The mixture was shaken at room temperature for 1 day and filtered. The resin was washed with CH_2Cl_2(3 × 1 min), CH_2Cl_2/EtOH (2:1, v/v) (3 × 1 min), EtOH (3 × 1 min), CH_2Cl_2(3 × 1 min), and dried in vacuum over P_2O_5. The substitution level for the amino acid bound to the polymeric support was determined by amino acid analysis or picric acid titration method[20] after removing Boc-group.

General procedure for the syntheses of Boc-phenylalanine containing dipeptide derivatives. Boc-Phe-**I** was swelled in CH_2Cl_2 in a reaction vessel.[9] Into the reaction vessel was added 3 equiv of carboxyl protected amino acid derivative which was previously neutralized with DIEA. After glacial acetic acid was added as a catalyst, the mixture was shaken at room temperature. To monitor the progress of the reactions, small portions (10-20 mg) of the resin was taken out from the reaction vessel periodically, washed thoroughly with CH_2Cl_2 and/or DMF, MeOH and dried in vacuum over P_2O_5 for IR analyses. After the reaction was completed, the resin mixture was filtered, washed with CH_2Cl_2(4 × 1 min), EtOH/CH_2Cl_2(1:2, v/v) (2 × 1 min), CH_2Cl_2 (2 × 1 min). The filtrate and the first and the second washing were combined, washed with 5% citric acid (3×), 5% $NaHCO_3$ (1×), water (2×), and dried over Na_2SO_4. Evaporation of the organic solvent gave crude products, which were purified by crystallization from EtOAc-n-hexane.

In case of Boc-Phe-Gly-Co(III) complex, similar condition was taken except for the solvent. Due to the poor solubility of the amino acid Co(III) complexes in CH_2Cl_2, DMF was used as a solvent. After the reaction was finished, the resin was filtered and washed with DMF, MeOH, and the combined filtrate was concentrated in vacuum to give an oily residue, which was solidified with an appropriate amount of EtOH/ether. The product mixture was filtered, washed with dry ether, and dried in vacuo. Final product was purified by column chromatography on a Bio-Gel P-2 column (2.4 × 40 cm, flow rate = 1.4 m*l*/min) by eluting with water. The collected fraction was lyophilized to give solid in 85% yield. Elemental analysis was avoided for fear of explosion of the perchlorate moiety. Physical data of the dipeptide after removing Co(III) from the C-terminal agreed with the literature value[11].

Boc-Tyr(OBzl)-Gly-OMTP. Boc-Tyr(OBzl)-OH (6.3 g, 17 mmol) was loaded on 5 g(3.7 mmol) of **I** with DCC (3.5 g, 1.72 mmol) for 24 h as previously described. The substitution level was determined as 0.3 mmol/g resin by picric acid titration method. Boc-Tyr(OBzl)-**I**(1.0 g, 0.3 mmol) was treated with Gly-OMTP·HCl (210 mg, 0.9 mmol) by the same procedure for the dipeptide preparation as described before. Recrystallization of the crude product from EtOAc-n-hexane gave analytically pure product: yield 157 mg (95%); mp 104-105 °C; TLC one spot, Rf 0.82(A), 0.75(B); ^{1}H NMR($CDCl_3$) δ 1.5(s, 9H), 2.5(s, 3H), 2.7(d, 2H), 4.1(broad, 2H), 4.5(broad, 1H), 5.0(s, 2H), 7.0-7.7(m, 13H), 8.1(broad, 1H); $[\alpha]_D^{20}$ = 3.8 (c = 1, AcOH); Anal. Calcd. for $C_{30}H_{34}N_3O_3S$ (550.66): C, 65.43; H, 6.22; N, 5.09%. Found: C, 65.02; H, 6.70; N, 5.21%.

Boc-Gly-Phe-Leu-OMTP. The conventional chain lengthening method[3] was applied to 2.4 g (1.2 mmol) of Boc-Phe-**I**. After acetylation and deblocking step, the resin was coupled with Boc-Gly (1.26 g, 7.2 mmol) by symmetric anhydride method, yielding 2.7 g of Boc-Gly-Phe-**I**. The dipeptide resin was treated with Leu-OMTP·HCl (1.9g, 3.6 mmol) to give 0.4 g (61%) of Boc-Gly-Phe-Leu-OMTP: mp 138-139 °C; TLC one spot, Rf 0.77 (B); ^{1}H NMR($CDCl_3$) δ 0.9(s, 7H), 1.5(s, 9H), 1.7(s, 2H), 2.5(s, 3H), 3.1(s, 2H), 3.9(broad, 2H), 5.0(broad, 1H), 6.0(broad, 1H), 6.9-7.3(m, 10H), 8.0(broad, 1H); $[\alpha]_D^{20}$ = −4.66 (c = 1, AcOH); Anal. Calcd. for $C_{29}H_{39}N_3O_6S$ (557.69): C, 62.45; H, 7.05; N, 7.53%. Found: C, 62.17; H, 7.33; N, 8.00%.

Boc-Gly-Phe-Leu-Tyr(OBzl)-Gly-OMTP. The usual chain lengthening step was applied to Boc-Tyr(OBzl)-**I** (7.5 g, 2.25 mmol). Thus after acetylation, Boc-Leu, Boc-Phe, and Boc-Gly were successively coupled to the resin by symmetric anhydride method yielding 8.0 g of Boc-Gly-Phe-Leu-Tyr(OBzl)-**I**. It was treated with Gly-OMTP·HCl (1.6 g, 6.8 mmol) and routine workup was followed to give 1.10 g (86%) of Boc-Gly-Phe-Leu-Tyr(OBzl)-Gly-OMTP; mp 178-180 °C; TLC one spot, Rf 0.83(B); ^{1}H NMR($CDCl_3$) δ 0.85(s, 7H), 1.5(s, 3H), 1.85(s, 2H), 2.5(s, 3H), 3.0(broad, 4H), 4.3(s, 2H), 4.9(broad, 1H), 5.8(broad, 1H), 6.5-7.7(m, 18H); $[\alpha]_D^{20}$ = −1.88 (c = 1, AcOH); Anal. Calcd. for $C_{47}H_{57}N_5O_9S$ (868.06): C, 65.03; H, 6.62; N, 8.07%. Found: C, 64.63; H, 7.08; N, 8.49%.

Boc-γ-Glu(α-OEt)-Cys(SBzl)-Gly-OMTP. Boc-Cys (SBzl) (2.24 g, 2.4 mmol) was loaded on **I** in the usual manner with substitution level of 0.6 mmol/g resin. Conventional chain lengthening of Boc-Cys(SBzl)-**I** with Z-Glu(α-OEt) gave Z-γ-Glu(α-OEt)-Cys(SBzl)-**I**. Treating the peptide resin with Gly-OMTP·HCl under the usual reaction condition and crystallization from EtOAc-n-hexane gave 510 mg (75%) of Z-γ-Glu(α-OEt)-Cys(SBzl)-Gly-OMTP: mp 153-155 °C; TLC one spot, Rf 0.58 (A); ^{1}H NMR($CDCl_3$) δ 1.2(t, 3H), 1.9-2.4 (broad, 4H), 2.5(s, 3H), 2.9(d, 2H), 3.8(s, 2H), 4.1-4.3(m, 4H), 4.4(m, 1H), 5.2(s, 2H), 5.9(broad, 1H), 6.8(broad, 1H), 7.1-7.5(m, 14H), 7.8(broad, 1H); $[\alpha]_D^{20}$ = −19.0 (c = 1, $CHCl_3$); Anal. Calcd. for $C_{34}H_{39}N_3O_8S_2$(681.82): C, 59.89; H, 5.77; N, 6.16%. Found: C, 60.41; H, 5.32; N, 6.57%.

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