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Ecological Base-Conditioned Preparation of Dipeptides Using Unprotected α-Amino Acids Containing Hydrophilic Side Chains

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Nobuyuki Imai was born in 1959. He graduated from Shizuoka College of Pharmacy in 1982 and obtained his Ph.D. from Shizuoka College of Pharmacy under Professor Kazuo Achiwa in 1987. After postdoctoral work at University of Kentucky (with Professor David S. Watt), Harvard University (with Professor E. J. Corey), and Sagami Chemical Research Institute (with Dr. Susumu Kobayashi), he joined Okayama University of Science as an assistant professor. He is currently a professor at Chiba Institute of Science.

Abstract

The coupling reactions of 3-phenylpropanoic acid and *N*-carboxybenzyl α-amino acids with unprotected α-amino acids containing hydrophilic side chains such as aliphatic alcohol, aromatic alcohol, thiol, carboxylic acid, and amide afforded the corresponding amides in 66–96% yield without racemization via the corresponding mixed carbonic carboxylic anhydrides under basic conditions through an ecological green synthetic method.

1. Introduction

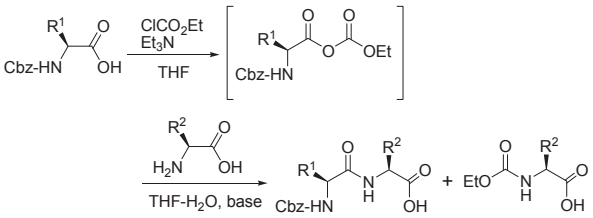
Development of convenient and cheap synthetic methods of peptides is quite important in industrial chemistry. α-Amino acids are generally categorized on the basis of the properties of their side chains into four groups, which are aliphatic, aromatic, acidic, and basic amino acids.[1] In particular, α-amino acids containing nucleophilic side chains such as hydroxy, mercapto, and carboxy groups also react easily with electrophiles in these side chains as undesired side reactions. Therefore, it is necessary for synthesis of peptides to protect not only the *N*-terminals of α-amino acids and the *C*-terminals of the other reactants but also the nucleophilic side chains in order to avoid undesired side reactions.

A number of useful peptide synthetic methods have recently been reported.[2–6] In these reports, protections of functional groups such as hydroxy, mercapto, amino, and carboxy groups in the corresponding α-amino acids are necessary to avoid generation of by-products in most of the peptide synthetic methods. Hofmann has reported that the synthesis of peptides related to α-melanocyte-stimulating hormone (α-MSH) and corticotropins.[7] In his study, Cbz-Met-Gln-OH was synthesized by the reaction of the mixed carbonic carboxylic anhydride of Cbz-Met-OH with aqueous solution of Gln, and Cbz-Ser-Tyr-OBn was prepared via the azidation of Cbz-Ser-OH with hydrazine hydrate and sodium nitrite under acidic conditions by the reaction with Tyr-OBn. However, the yields of these dipeptides were moderate. Furthermore, peptide syntheses using α-amino acids containing unprotected side chains also have been developed, and the native chemical ligation (NCL) method reported by Kent is quite efficient.[8] In NCL, the thioester at the *C*-terminal of a peptide reacts initially with the cysteine residue at the *N*-terminal of another peptide by ester transfer, followed by the replacement of sulfur with nitrogen to form the corresponding amide. Namely, the condensation by NCL is limited to the peptide fragment oriented cysteine residue at the *N*-terminal, and it is well known that peptides containing cysteine are rare.[9] In addition, the preparations of the thioesters in the *C*-terminals were obtained in poor yield in some cases.[10] Li also has reported the chemoselective synthesis of peptides using *O*-salicylaldehyde ester as a *C*-terminal fragment and L-serine or L-threonine ester possessing free side chain as an *N*-terminus via the corresponding *N*,*O*-benzylidene acetal.[11] These methods have problems in terms of atom economy and substrate generality.

Recently, we have reported a green synthetic method for dipeptides using unprotected α-amino acids via the mixed carbonic carboxylic anhydrides in aqueous organic solvent.[12a,12f,12g] In our method, dipeptides were synthesized from *N*-protected α-amino acids and unprotected α-amino acids in good yields in half aqueous organic solvent. Herein, we describe in detail the convenient condensation of *N*-protected α-amino acids with unprotected α-amino acids containing hydrophilic side chains under basic conditions via the mixed carbonic carboxylic anhydride under basic conditions as shown in Scheme 1.

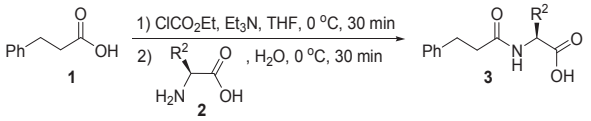
2. Results and Discussion

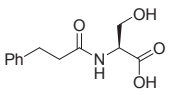
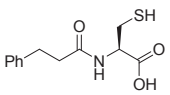
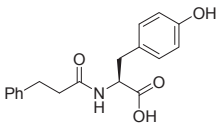
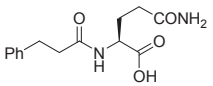
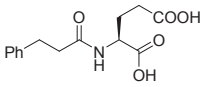
In a preliminary investigation, a clear solution of 3-phenylpropanoic acid (**1**) and 1.5 equiv of unprotected α-amino acids



Scheme 1. Convenient condensation of *N*-protected α-amino acids with unprotected α-amino acids containing hydrophilic side chains under basic conditions.

Table 1. Amidation of 3-phenylpropanoic acid (**1**) with unprotected α-amino acids **2a**–**2e**[a)]

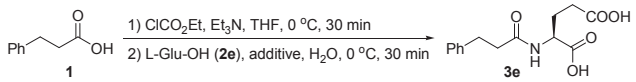


Entry	Amide **3**		Yield[b)]/%
1		**3a**	90
2		**3b**	87
3		**3c**	19
4		**3d**	85
5		**3e**	59

a) All reactions were carried out with 0.50 mmol of **1**, 0.70 mmol of ethyl chloroformate, and 1.5 mmol of triethylamine in 10 mL of the THF. After stirring for 30 min at 0 °C, 0.75 mmol of **2** in 10 mL of H_2O was added to the reaction mixtures. b) Isolated yields.

2a–**2e** containing another hydrophilic moiety as a side chain in aqueous tetrahydrofuran (THF) under neutral conditions was reacted to afford the corresponding amides **3a**–**3e** as indicated in Table 1. The reactions of **1** with unprotected α-amino acids **2a** and **2b** containing hydroxy and mercapto groups afforded the corresponding amides **3a** and **3b** in 90% and 87% yields, respectively (Entries 1 and 2). The amide **3c** was obtained by the reaction of **1** with **2c** containing aromatic hydroxy group in 19% yield due to low solubility of **2c** in H_2O (Entry 3). The acid **1** smoothly reacted with **2d** containing amide group to give the corresponding amide **3d** in 85% yield (Entry 4). In contrast, the coupling reaction of **1** with **2e** containing a carboxy group gave the corresponding amide **3e** in moderate yield (Entry 5). It is suggested that the amino group does not work well as a nucleophile due to protonation by the carboxy group of **2e**. Unprotected α-amino acids **2a**, **2b** and **2d** are easily dissolved in H_2O, but the solubility of **2c** and **2e** in H_2O is low

Table 2. Effect of additives on the amidation of 3-phenylpropanoic acid (**1**) with L-Glu-OH (**2e**)[a)]



Entry	Additive	pH[c)]	Yield[b)]/%
1	HCl	1.0	5
2	Free	4.5	59
3	$NaHCO_3$	6.5	90
4	NaOH	7.5	93
5	Na_2CO_3	8.0	92
6	K_2CO_3	9.0	93
7[d)]	K_2CO_3	12	36

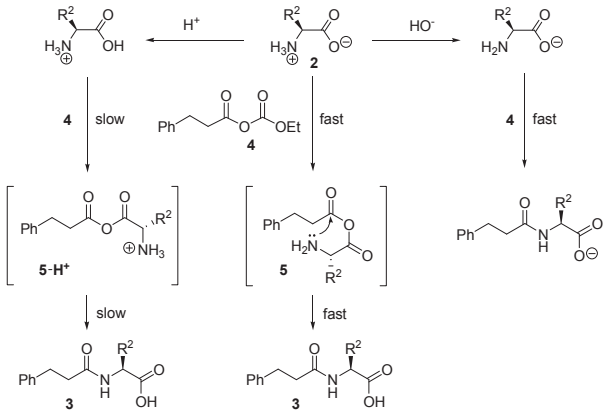
a) All reactions were carried out with 0.50 mmol of **1**, 0.70 mmol of ethyl chloroformate, and 1.5 mmol of triethylamine in 10 mL of THF. After stirring for 30 min at 0 °C, 0.75 mmol of L-Glu-OH (**2e**) and 0.75 mmol of an additive in 10 mL of H_2O were added at 0 °C to the reaction mixture. b) Isolated yields. c) The pH value of the solution of **2e** and additive in 10 mL of H_2O was measured with pH-test paper. d) The reaction was carried out with 20 mmol of K_2CO_3.

despite possession of hydrophilic side chains. A small amount of *N*-ethoxycarbonyl α-amino acids **2a′**–**2e′** were observed as a by-product on the basis of ^{1}H NMR analysis in all entries of Table 1.

Subsequently, we tried to resolve the problems in Entries 3 and 5 of Table 1. The amidation of 3-phenylpropanoic acid (**1**) with L-Glu-OH (**2e**) was examined under acidic and basic conditions and the results are summarized in Table 2. The reaction of **1** with **2e** in aqueous HCl gave the corresponding amide **3e** in 5% yield, which was obviously decreased (Entry 1). In contrast, **1** reacted with **2e** under basic conditions in the presence of $NaHCO_3$ to afford **3e** in 90% yield (Entry 3). The amide **3e** was obtained in 93% yield by the reaction using NaOH as a base (Entry 4). The amidations in the presence of Na_2CO_3 and K_2CO_3, which are stronger bases than $NaHCO_3$, gave **3e** in 92% and 93% yields, respectively (Entries 5 and 6). In the presence of an excess amount of K_2CO_3, the reaction of **1** with **2e** proceeded in 36% yield (Entry 7). We judged that $NaHCO_3$ is better among these bases in the reaction by considering safety and handling.

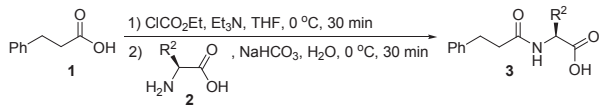
A possible pathway of the amidation via the mixed carbonic carboxylic anhydride **4** is shown in Scheme 2. The carboxylic anhydride intermediate **5** is generated under the neutral conditions from the corresponding mixed carbonic carboxylic anhydride **4** by the nucleophilic attack of α-amino acid **2**. The free amine of **5** works as a good nucleophile and the corresponding product **3** is formed by the intramolecular reaction of **5** via the five-membered transition state (Entries 3–6 in Table 2). The reaction rate is very slow under the acidic conditions due to the protonation of the nitrogen atom of **5-H**$^+$ (Entry 1 in Table 2). Then, the mixed carbonic carboxylic anhydride **4** reacts directly under the basic conditions with the amine part of **2** to give the corresponding product **3**.

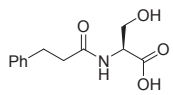
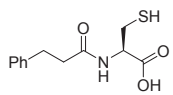
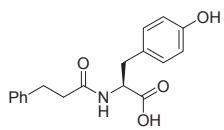
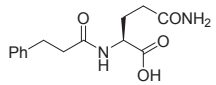
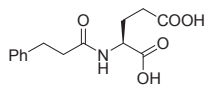
Next, we tried to synthesize the amides **3** using 3-phenylpropanoic acid (**1**) with several kinds of unprotected α-amino acids **2a**–**2e** in an aqueous $NaHCO_3$ solution as collected in



Scheme 2. Possible pathway of the amidation via the mixed carbonic carboxylic anhydride **5**.

Table 3. Amidation of 3-phenylpropanoic acid (**1**) with unprotected α-amino acids **2a**–**2e** under the basic conditions using $NaHCO_3$[a)]



Entry	Amide **3**		Yield[b)]/%
1		**3a**	93
2		**3b**	96
3		**3c**	25 (86)[c)]
4		**3d**	83
5		**3e**	90

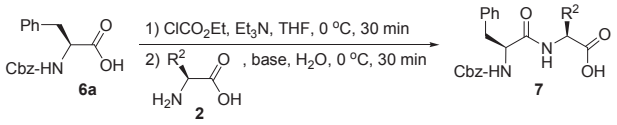
a) All reactions were carried out with 0.50 mmol of **1**, 0.70 mmol of ethyl chloroformate, and 1.5 mmol of triethylamine in 10 mL of THF. After stirring for 30 min at 0 °C, 0.75 mmol of unprotected α-amino acids **2** and 0.75 mmol of $NaHCO_3$ in 10 mL of H_2O were added at 0 °C to the reaction mixtures. b) Isolated yields. c) NaOH was used instead of $NaHCO_3$.

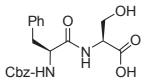
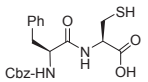
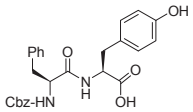
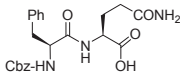
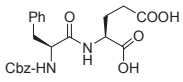
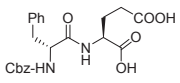
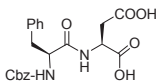
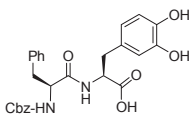
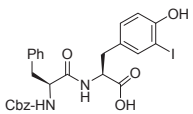
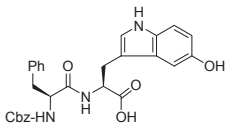
Table 3. The coupling reaction of **1** with L-Ser-OH (**2a**) proceeded smoothly to give the corresponding amide **3a** in 93% yield (Entry 1). L-Cys-OH (**2b**) was converted to the corresponding amide **3b** in 96% yield (Entry 2). Although the amidation of **1** with L-Tyr-OH (**2c**) afforded the corresponding amide **3c** in 25% yield under the basic conditions using $NaHCO_3$ (Entry 3), **2c** reacted efficiently with **1** to give **3c** in 86% yield under the basic conditions using NaOH (parentheses of Entry 3). In the case of using $NaHCO_3$ as a base, **2c** is hardly dissolved in H_2O as well as the neutral conditions. It is suggested that the solubility of **2c** is improved by the production of sodium phenoxide in an aqueous NaOH solution, and that **2c** works as a good nucleophile in the second step of the reaction. The amide **3d** was prepared from **1** with L-Gln-OH (**2d**) in 83% yield (Entry 4), which is similar to that of the reaction under the neutral conditions (Entry 4 of Table 1).

Then, we attempted to prepare dipeptides from Cbz-L-Phe-OH (**6a**) and various unprotected α-amino acids **2** and these results are displayed in Table 4. L-Asp-OH (**2f**), L-Tyr(3-OH)-OH (**2g**), L-Tyr(3-I)-OH (**2h**), and L-Trp(5-OH)-OH (**2i**) were added to the substrates containing aromatic alcohols as a side chain. The dipeptide **7aa** was synthesized from **6a** and L-Ser-OH (**2a**) containing a hydroxy group in 82% yield (Entry 1). The reaction of **6a** with L-Cys-OH (**2b**) containing a mercapto group proceeded sufficiently to give the corresponding dipeptide **7ab** in 86% yield (Entry 2). L-Tyr-OH (**2c**) containing a phenolic hydroxy group reacted with the activated form of **6a** to afford **7ac** in 73% yield (Entry 3). L-Gln-OH (**2d**) is most soluble in H_2O among them and was converted to produce **7ad** in 83% yield (Entry 4). Absence of racemization under the reaction conditions was investigated using Cbz-L-Phe-OH (**6a**) and Cbz-D-Phe-OH (**6a′**) as follows. The dipeptides **7ae** and **7a′e** were synthesized as a single diastereomer by the reactions of **6a** and **6a′** with L-Glu-OH (**2e**) containing a carboxy group in 87% and 85% yields, respectively (Entries 5 and 6). The coupling reaction of **6a** with L-Asp-OH (**2f**) gave the corresponding dipeptide **7af** in 74% yield (Entry 7), which is caused by slightly lower solubility of **2f** in H_2O than that of **2e**. Both α-amino acids **6a** and **2g** containing a 3,4-dihydroxyphenyl moiety condensed to give **7ag** in 68% yield (Entry 8). The formations of the dipeptides **7ah** and **7ai** by the reactions of **6a** from **2h** containing 4-hydroxy-3-iodophenyl moiety and **2i** containing 5-hydroxyindole moiety succeeded via the activation of **6a** by isobutyl chloroformate in 74% and 76% yields, respectively (Entries 9 and 10). The dipeptides **7ah** and **7ai** were easily separated from the *N*-isobutyloxycarbonyl by-products **2h″** and **2i″** by silica gel chromatography. In the case of using ethyl chloroformate for the activating agent, it was difficult to isolate from the mixtures of the dipeptides **7ah**, **7ai** and the *N*-ethoxycarbonyl derivatives **2h′**, **2i′**, respectively.

Finally, we examined application to synthesis of various dipeptides **7ba**–**7dc** under the reaction conditions, and the results are shown in Table 5. Cbz-L-Ala-OH (**6b**), Cbz-L-Val-OH (**6c**) and Cbz-L-Met-OH (**6d**) were selected as a *N*-protected α-amino acid. The reaction of Cbz-L-Ala-OH (**6b**) with L-Ser-OH (**2a**) was carried out to afford the corresponding dipeptide **7ba** in 79% yield (Entry 1). The reaction of **6b** with L-Cys-OH (**2b**) efficiently proceeded to give **7bb** in 89% yield (Entry 2). The dipeptide **7bc** was synthesized from **6b** and L-Tyr-OH (**2c**) in 71% yield (Entry 3), which was slightly lower than those of **7ba** and **7bb**. Cbz-L-Val-OH (**6c**) possessing a branched side chain reacted with **2a**, **2b**, and **2c** to provide the corresponding dipeptides **7ca**, **7cb**, and **7cc** in 81%, 75%, and 71% yields, respectively (Entries 4–6). Cbz-L-Met-OH (**6d**) containing a mercapto group as a side chain was converted by the reactions of unprotected α-amino acids **2a**, **2b**, and **2c** to the corresponding dipeptides **7da**, **7db**, and **7dc** in 77%, 78%, and 66% yields, respectively (Entries 7–9). Then, we attempted to synthesize the corresponding dipeptide from *N*-protected α-amino

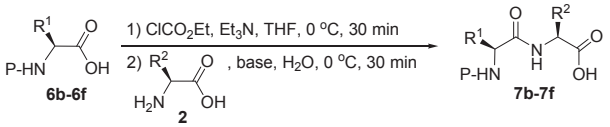
Table 4. Synthesis of dipeptides **7** with Cbz-L-Phe-OH (**6a**) and unprotected α-amino acids **2a**–**2i** under the basic conditions[a)]

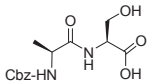
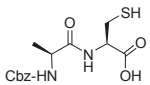
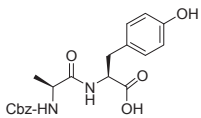
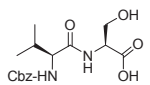
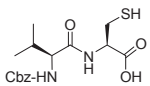
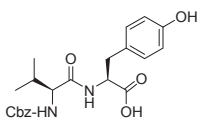
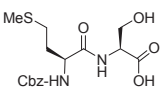
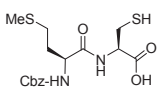
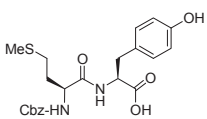
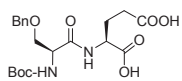
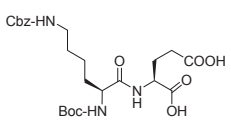


Entry	Base	Dipeptide **7**		Yield[b)]/%
1	$NaHCO_3$		**7aa**	82
2	$NaHCO_3$		**7ab**	86
3	NaOH		**7ac**	73
4	$NaHCO_3$		**7ad**	83
5	$NaHCO_3$		**7ae**	87 (81)[e)]
6[c)]	$NaHCO_3$		**7a′e**	85
7	$NaHCO_3$		**7af**	74
8	NaOH		**7ag**	68
9[d)]	NaOH		**7ah**	74
10[d)]	NaOH		**7ai**	76

a) All reactions were carried out with 0.50 mmol of Cbz-L-Phe-OH (**6a**), 0.70 mmol of ethyl chloroformate, and 1.5 mmol of triethylamine in 10 mL of THF. After stirring for 30 min at 0 °C, 0.75 mmol of unprotected α-amino acids **2** and 0.75 mmol of base in 10 mL of H_2O were added at 0 °C to the reaction mixtures. b) Isolated yields. c) This reaction was carried out with Cbz-D-Phe-OH (**6a′**). d) Isobutyl chloroformate was used instead of ethyl chloroformate. e) 5.0 mmol (1.5 g) of **6a** was used.

Table 5. The coupling reaction of *N*-protected α-amino acids **6b**–**6f** and unprotected α-amino acids **2a**–**2c** and **2e** under the basic conditions[a)]



Entry	Base	Dipeptide **7**		Yield[b)]/%
1	$NaHCO_3$		**7ba**	79
2	$NaHCO_3$		**7bb**	89
3	NaOH		**7bc**	71
4	$NaHCO_3$		**7ca**	81
5	$NaHCO_3$		**7cb**	75
6	NaOH		**7cc**	71
7	$NaHCO_3$		**7da**	77
8	$NaHCO_3$		**7db**	78
9	NaOH		**7dc**	66
10	$NaHCO_3$		**7ee**	76
11	$NaHCO_3$		**7fe**	84

a) All reactions were carried out with 0.50 mmol of *N*-protected α-amino acids **6b**–**6f**, 0.70 mmol of ethyl chloroformate, and 1.5 mmol of triethylamine in 10 mL of THF. After stirring for 30 min at 0 °C, 0.75 mmol of unprotected α-amino acids **2** and 0.75 mmol of base in 10 mL of H_2O were added at 0 °C to the reaction mixtures. b) Isolated yields.

acids containing hydrophilic side chains as the starting materials with L-Glu-OH (**2e**). The dipeptide **7ee** was synthesized from *N*-Boc-*O*-Bn-L-Ser-OH (**6e**) and **2e** under basic conditions in 76% yield (Entry 10). N^{α}-Boc-N^{ε}-Cbz-L-Lys-OH (**6f**) containing bulky side chain was effectively converted into the corresponding dipeptide **7fe** in 84% yield (Entry 11).

3. Conclusion

We have found that the dipeptides **7aa**–**7ai** were conveniently synthesized in 68–87% yield from Cbz-L-Phe-OH (**6a**) and unprotected α-amino acids **2a**–**2i** containing other hydrophilic moieties under the basic conditions. Additionally, we

have also succeeded in the preparation of the dipeptides **7ba**–**7fe** in 66–89% yields without racemization by the reactions of *N*-protected α-amino acids **6b**–**6f** with unprotected α-amino acids **2a**–**2c** and **2e** by the ecological green synthetic method.

4. Experimental

General Information. All reagents were used without any purification. The ^{1}H NMR and ^{13}C NMR spectra were measured with a Bruker Ultrashield TM 400 Plus (400 MHz) spectrometer. The chemical shifts are expressed in parts per million downfield from tetramethylsilane ($\delta = 0.00$) in MeOD-d^4 or dimethyl sulfoxide-d^6 ($\delta = 2.50$) as an internal standard. ^{13}C NMR spectra were calibrated with tetramethylsilane ($\delta = 0.00$) in MeOD-d^4 or dimethyl sulfoxide-d^6 ($\delta = 39.5$). Chemical shifts (δ) are reported in ppm, and spin–spin coupling constants (J) are given in hertz. Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). The high-resolution mass spectra (HRMS) of the compounds with a high molecular weight were recorded using a Waters LCT Premier (ESI-TOF-MS) spectrometer. Reactions were monitored using thin-layer chromatography with silica gel 60 F_{254}. Purification of the products was carried out by column chromatography using silica gel (64–210 mesh). Melting points were determined with a hot plate apparatus. Optical rotations were measured on a digital polarimeter with a sodium lamp at room temperature. Infrared (IR) spectra were recorded on HORIBA FT-IR Fourier transform infrared spectrophotometer.

A Typical Procedure for the Amidation of 3-Phenylpropanoic Acid (1) Using Ethyl Chloroformate is as Follows. To a colorless solution of 75 mg (0.50 mmol) of 3-phenylpropanoic acid (**1**) in 10 mL of THF were added at 0 °C 67 µL (0.70 mmol, 1.4 equiv) of ethyl chloroformate and 209 µL (1.5 mmol, 3.0 equiv) of triethylamine. After stirring for 30 min at 0 °C, a solution of 110 mg (0.75 mmol, 1.5 equiv) of L-Glu-OH (**2e**) and 63 mg (0.75 mmol, 1.5 equiv) of $NaHCO_3$ in 10 mL of H_2O was added at 0 °C to the colorless suspension. The mixture was stirred for 30 min at 0 °C and the resulting colorless clear solution was concentrated in vacuo. The residue was adjusted to pH 2 by addition of a 1.0 M aqueous solution of HCl. The resulted suspension was diluted with 30 mL of EtOAc. The aqueous layer was extracted with 20 mL of EtOAc. The combined organic layer was washed with 10 mL of brine, and dried over anhydrous $MgSO_4$. The crude product was chromatographed on silica gel with EtOAc containing 1% AcOH to afford 126 mg (90% yield) of *N*-(3-phenylpropanoyl)-L-Glu-OH (**3e**).

***N*-(3-phenylpropanoyl)-L-Ser-OH (3a):** 111 mg (93%), colorless powder; mp: 119–123 °C; $[\alpha]_D^{28} = +6.70$ (c 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4): δ 2.72 (ddd, $J = 1.5$, 7.6, 7.6 Hz, 1H, CH_ACO), 2.72 (ddd, $J = 1.5$, 8.3, 8.3 Hz, 1H, CH_BCO), 2.92 (dd, $J = 7.6$, 8.3 Hz, 2H, $CH_2C_6H_5$), 3.77 (dd, $J = 4.3$, 11.2 Hz, 1H, CH_AOH), 3.86 (dd, $J = 4.8$, 11.2 Hz, 1H, CH_BOH), 4.48 (dd, $J = 4.3$, 4.8 Hz, 1H, $CHCH_2OH$), 7.14–7.18, 7.21–7.28 (m, m, 1H, 4H, C_6H_5); ^{13}C NMR (100 MHz, MeOD-d^4): δ 32.8, 38.8, 56.1, 63.0, 127.2, 129.4, 129.5, 142.3, 173.5, 175.4; HRMS (ESI-TOF): Calcd for $C_{12}H_{15}NO_4Na$ $(M+Na)^+$: 260.0893, found: 260.0894; IR (KBr, ν_{max}/cm^{-1}): 3305 (OH), 1716 (CO_2), 1648 (CON).

***N*-(3-phenylpropanoyl)-L-Cys-OH (3b):** 122 mg (96%), colorless powder; mp: 132–133 °C; $[\alpha]_D^{28} = -4.10$ (c 1.01, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4): δ 2.58 (ddd, $J = 1.2$, 7.6, 7.6 Hz, 1H, CH_ACO), 2.58 (ddd, $J = 1.2$, 7.7, 7.7 Hz, 1H, CH_BCO), 2.79 (dd, $J = 6.6$, 14.0 Hz, 1H, CH_ASH), 2.86 (dd, $J = 4.6$, 14.0 Hz, 1H, CH_BSH), 2.93 (dd, $J = 7.6$, 7.7 Hz, 2H, $CH_2C_6H_5$), 4.58 (dd, $J = 4.6$, 6.6 Hz, 1H, $CHCH_2SH$), 7.14–7.19, 7.21–7.28 (m, m, 1H, 4H, C_6H_5); ^{13}C NMR (100 MHz, MeOD-d^4): δ 26.8, 32.8, 38.6, 55.9, 127.3, 129.5, 129.5, 142.1, 173.1, 175.3; HRMS (ESI-TOF): Calcd for $C_{12}H_{16}NO_3S$ $(M+Na)^+$: 254.0854, found: 254.0856; IR (KBr, ν_{max}/cm^{-1}): 3353 (OH), 2563 (SH), 1720 (CO_2), 1589 (CON).

***N*-(3-phenylpropanoyl)-L-Tyr-OH (3c):** 135 mg (86%), colorless powder; mp: 164–167 °C; $[\alpha]_D^{28} = +16.8$ (c 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4): δ 2.46 (ddd, $J = 1.6$, 8.1, 8.1 Hz, 1H, CH_ACO), 2.46 (ddd, $J = 1.6$, 8.2, 8.2 Hz, 1H, CH_BCO), 2.81 (dd, $J = 8.1$, 8.2 Hz, 2H, $CH_2C_6H_5$), 2.82 (dd, $J = 8.8$, 13.9 Hz, 1H, $CH_AC_6H_4$), 3.05 (dd, $J = 5.1$, 13.9 Hz, 1H, $CH_BC_6H_4$), 4.58 (dd, $J = 5.1$, 8.8 Hz, 1H, $CHCH_2C_6H_4$), 6.67, 6.95 (d, d, $J = 8.6$, 8.6 Hz, 2H, 2H, C_6H_4), 7.13–7.16, 7.21–7.25 (m, m, 3H, 2H, C_6H_5); ^{13}C NMR (100 MHz, MeOD-d^4): δ 32.8, 37.7, 38.6, 55.3, 116.2, 127.2, 129.1, 129.4, 129.5, 131.3, 142.2, 157.3, 174.9, 175.1; HRMS (ESI-TOF): Calcd for $C_{18}H_{19}NO_4Na$ $(M+Na)^+$: 336.1206, found: 336.1187; IR (KBr, ν_{max}/cm^{-1}): 3309 (ArOH), 3197 (OH), 1745 (CO_2), 1592 (CON).

***N*-(3-phenylpropanoyl)-L-Gln-OH (3d):**[12a] 116 mg (83%), colorless powder; ^{1}H NMR (400 MHz, MeOD-d^4): δ 1.83–1.93 (m, 1H, CH_ACH), 2.07–2.24 (m, 3H, CH_BCH, CH_2CH_2CH), 2.55 (ddd, $J = 1.5$, 7.5, 7.5 Hz, 1H, CH_ACO), 2.55 (ddd, $J = 1.5$, 8.1, 8.1 Hz, 1H, CH_BCO), 2.92 (dd, $J = 7.5$, 8.1 Hz, 2H, $CH_2C_6H_5$), 4.37 (dd, $J = 4.5$, 9.4 Hz, 1H, CHCO), 7.14–7.18, 7.21–7.28 (m, m, 1H, 4H, C_6H_5).

***N*-(3-phenylpropanoyl)-L-Glu-OH (3e):**[12a] 126 mg (90%), colorless powder; ^{1}H NMR (400 MHz, MeOD-d^4): δ 1.80–1.90 (m, 1H, CH_ACH), 2.07–2.15 (m, 1H, CH_BCH), 2.22–2.26 (m, 2H, CH_2CH_2CH), 2.54 (ddd, $J = 1.4$, 7.4, 7.4 Hz, 1H, CH_ACO), 2.54 (ddd, $J = 1.4$, 8.0, 8.0 Hz, 1H, CH_BCO), 2.91 (dd, $J = 7.4$, 8.0 Hz, 2H, $CH_2C_6H_5$), 4.40 (dd, $J = 4.8$, 9.8 Hz, 1H, CHCO), 7.15–7.18, 7.20–7.27 (m, m, 1H, 4H, C_6H_5).

A Typical Procedure of the Amidation of Cbz-L-Phenylalanine (6a) Using Ethyl Chloroformate is as Follows. To a colorless solution of 150 mg (0.50 mmol) of Cbz-L-phenylalanine (**6a**) in 10 mL of THF were added at 0 °C 67 µL (0.70 mmol, 1.4 equiv) of ethyl chloroformate and 209 µL (1.5 mmol, 3.0 equiv) of triethylamine. After stirring for 30 min at 0 °C, a solution of 110 mg (0.75 mmol, 1.5 equiv) of L-Glu-OH (**2e**) and 63 mg (0.75 mmol, 1.5 equiv) of $NaHCO_3$ in 10 mL of H_2O was added at 0 °C to the colorless suspension. The mixture was stirred for 30 min at 0 °C and the resulting colorless clear solution was concentrated in vacuo. The residue was adjusted to pH 2 by addition of a 1.0 M aqueous solution of HCl. The colorless suspension was diluted with 10 mL of brine, extracted with 25 ml × 3 of a 4:1 mixture of EtOAc and MeOH, and dried over anhydrous $MgSO_4$. The crude product was chromatographed on silica gel with a 9:1 mixture of chloroform and MeOH containing 1% AcOH to afford 187 mg (87% yield) of Cbz-L-Phe-L-Glu-OH (**7ae**).

Cbz-L-Phe-L-Ser-OH (7aa): 158 mg (82%), colorless powder; mp; 156–159 °C; $[\alpha]_D^{30} = +4.82$ (c 1.00, MeOH);

^{1}H NMR (400 MHz, MeOD-d^4): δ 2.85 (dd, J = 9.8, 13.8 Hz, 1H, CH_AC$_6$H$_5$), 3.19 (dd, J = 4.7, 13.8 Hz, 1H, CH_BC$_6$H$_5$), 3.83 (dd, J = 3.8, 11.2 Hz, 1H, CH_AOH), 3.92 (dd, J = 4.5, 11.2 Hz, 1H, CH_BOH), 4.46 (dd, J = 4.7, 9.8 Hz, 1H, CHCH$_2$C$_6$H$_5$), 4.48 (dd, J = 3.8, 4.5 Hz, 1H, CHCH$_2$OH), 4.98 (d, J = 12.6 Hz, 1H, OCH_AC$_6$H$_5$), 5.03 (d, J = 12.6 Hz, 1H, OCH_BC$_6$H$_5$), 7.19–7.33 (m, 10H, C$_6$H$_5$ × 2); ^{13}C NMR (100 MHz, MeOD-d^4): δ 39.2, 56.2, 57.8, 63.0, 67.6, 127.8, 128.7, 129.0, 129.5, 129.5, 130.4, 138.2, 138.6, 158.4, 173.1, 174.2; HRMS (ESI-TOF): Calcd for $C_{20}H_{23}N_2O_6$ (M+H)$^+$: 387.1551, found: 387.1539; IR (KBr, ν_{max}/cm^{-1}): 3298 (OH), 1732 (CO$_2$), 1647 (CON).

Cbz-L-Phe-L-Cys-OH (7ab): 173 mg (86%), colorless powder; mp; 121–122 °C; $[\alpha]_D^{29} = -9.32$ (c 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4): δ 2.87 (dd, J = 9.5, 13.9 Hz, 1H, CH_AC$_6$H$_5$), 2.88 (dd, J = 4.6, 14.0 Hz, 1H, CH_ASH), 2.97 (dd, J = 4.6, 14.0 Hz, 1H, CH_BSH), 3.16 (dd, J = 5.2, 13.9 Hz, 1H, CH_BC$_6$H$_5$), 4.44 (dd, J = 5.2, 9.5 Hz, 1H, CHCH$_2$C$_6$H$_5$), 4.60 (dd, J = 4.6, 4.6 Hz, 1H, CHCH$_2$SH), 5.01 (s, 2H, OCH_2C$_6$H$_5$), 7.17–7.33 (m, 10H, C$_6$H$_5$ × 2); ^{13}C NMR (100 MHz, MeOD-d^4): δ 26.8, 39.0, 56.0, 57.8, 67.6, 127.8, 128.7, 129.0, 129.5, 130.4, 138.2, 138.6, 158.3, 172.8, 174.2; HRMS (ESI-TOF): Calcd for $C_{20}H_{23}N_2O_5S$ (M+H)$^+$: 403.1322, found: 403.1296; IR (KBr, ν_{max}/cm^{-1}): 3309 (OH), 2568 (SH), 1716 (CO$_2$), 1656 (CON).

Cbz-L-Phe-L-Tyr-OH (7ac): 169 mg (73%), colorless powder; mp; 189–190 °C; $[\alpha]_D^{28} = -4.90$ (c 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4): δ 2.77 (dd, J = 9.9, 14.0 Hz, 1H, CH_AC$_6$H$_4$), 2.91 (dd, J = 8.0, 14.0 Hz, 1H, CH_AC$_6$H$_5$), 3.09 (dd, J = 5.0, 14.0 Hz, 1H, CH_BC$_6$H$_4$), 3.09 (dd, J = 5.3, 14.0 Hz, 1H, CH_BC$_6$H$_5$), 4.36 (dd, J = 5.0, 9.9 Hz, 1H, CHCH$_2$C$_6$H$_4$), 4.58 (dd, J = 5.3, 8.0 Hz, 1H, CHCH$_2$C$_6$H$_5$), 4.97 (d, J = 12.6 Hz, 1H, OCH_AC$_6$H$_5$), 5.03 (d, J = 12.6 Hz, 1H, OCH_BC$_6$H$_5$), 6.68, 7.02 (d, d, J = 8.4, 8.4 Hz, 2H, 2H, C$_6$H$_4$), 7.16–7.32 (m, 10H, C$_6$H$_5$ × 2); ^{13}C NMR (100 MHz, MeOD-d^4): δ 37.7, 39.0, 55.3, 57.8, 67.6, 116.3, 127.7, 128.7, 128.8, 129.0, 129.4, 129.5, 130.4, 131.5, 138.2, 138.6, 157.4, 173.9, 174.4; HRMS (ESI-TOF): Calcd for $C_{26}H_{27}N_2O_6$ (M+H)$^+$: 463.1864, found: 463.1862; IR (KBr, ν_{max}/cm^{-1}): 3433 (OH), 3334 (ArOH), 1734 (CO$_2$), 1684 (CON), 1653 (CON).

Cbz-L-Phe-L-Gln-OH (7ad):[12a] 177 mg (83%), colorless powder; ^{1}H NMR (400 MHz, MeOD-d^4): δ 1.91–1.98 (m, 1H, CH_ACH$_2$CO), 2.16–2.35 (m, 3H, CH_BCH$_2$CO, CH$_2$CO), 2.85 (dd, J = 9.7, 14.0 Hz, 1H, CH_AC$_6$H$_5$), 3.16 (dd, J = 4.9, 14.0 Hz, 1H, CH_BC$_6$H$_5$), 4.38–4.43 (m, 2H, CH × 2), 4.99 (d, J = 12.7 Hz, 1H, OCH_AC$_6$H$_5$), 5.03 (d, J = 12.7 Hz, 1H, OCH_BC$_6$H$_5$), 7.17–7.33 (m, 10H, C$_6$H$_5$ × 2).

Cbz-L-Phe-L-Glu-OH (7ae):[12a] 187 mg (87%), colorless powder; ^{1}H NMR (400 MHz, MeOD-d^4): δ 1.89–1.99 (m, 1H, CH_ACH$_2$CO), 2.15–2.23 (m, 1H, CH_BCH$_2$CO), 2.39 (dd, J = 7.6, 7.8 Hz, 2H, CH$_2$CO), 2.84 (dd, J = 9.6, 14.0 Hz, 1H, CH_AC$_6$H$_5$), 3.15 (dd, J = 5.0, 14.0 Hz, 1H, CH_BC$_6$H$_5$), 4.40–4.47 (m, 2H, CH × 2), 4.99 (d, J = 13.0 Hz, 1H, OCH_AC$_6$H$_5$), 5.03 (d, J = 13.0 Hz, 1H, OCH_BC$_6$H$_5$), 7.18–7.33 (m, 10H, C$_6$H$_5$ × 2).

Cbz-D-Phe-L-Glu-OH (7a′e): 182 mg (85%), colorless powder; mp; 169–172 °C; $[\alpha]_D^{28} = +0.82$ (c 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4): δ 1.79–1.88 (m, 1H, CH_ACH$_2$-CO), 2.04–2.18 (m, 3H, CH_BCH$_2$CO, CH$_2$CO), 2.88 (dd, J = 8.8, 13.7 Hz, 1H, CH_AC$_6$H$_5$), 3.09 (dd, J = 6.6, 13.7 Hz, 1H, CH_BC$_6$H$_5$), 4.38 (dd, J = 6.6, 8.8 Hz, 1H, CHCH$_2$C$_6$H$_5$), 4.40–4.44 (m, 1H, CHCH$_2$CH$_2$), 5.00 (d, J = 12.4 Hz, 1H, OCH_AC$_6$H$_5$), 5.05 (d, J = 12.4 Hz, 1H, OCH_BC$_6$H$_5$), 7.19–7.33 (m, 10H, C$_6$H$_5$ × 2); ^{13}C NMR (100 MHz, MeOD-d^4): δ 27.8, 31.0, 39.5, 53.1, 58.0, 67.7, 127.9, 128.8, 129.0, 129.5, 129.6, 130.4, 138.2, 138.4, 158.2, 174.0, 174.6, 176.3; HRMS (ESI-TOF): Calcd for $C_{22}H_{24}N_2O_7Na$ (M+Na)$^+$: 451.1476, found: 451.1488; IR (KBr, ν_{max}/cm^{-1}): 3299 (OH), 1716 (CO$_2$), 1670 (CON).

Cbz-L-Phe-L-Asp-OH (7af): 163 mg (74%), colorless powder; mp; 178–179 °C; $[\alpha]_D^{28} = -11.7$ (c 1.01, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4): δ 2.84 (dd, J = 9.7, 13.9 Hz, 1H, CH_AC$_6$H$_5$), 2.84 (d, J = 5.6 Hz, 2H, CH$_2$CO), 3.18 (dd, J = 4.8, 13.9 Hz, 1H, CH_BC$_6$H$_5$), 4.42 (dd, J = 4.8, 9.7 Hz, 1H, CHCH$_2$C$_6$H$_5$), 4.73 (t, J = 5.6 Hz, 1H, CHCH$_2$CO), 4.97 (d, J = 12.7 Hz, 1H, OCH_AC$_6$H$_5$), 5.02 (d, J = 12.7 Hz, 1H, OCH_BC$_6$H$_5$), 7.18–7.33 (m, 10H, C$_6$H$_5$ × 2); ^{13}C NMR (100 MHz, MeOD-d^4): δ 36.8, 39.1, 50.2, 57.8, 67.6, 127.7, 128.7, 128.9, 129.5, 130.4, 138.2, 138.6, 158.3, 173.7, 173.9, 174.0; HRMS (ESI-TOF): Calcd for $C_{21}H_{23}N_2O_7$ (M+H)$^+$: 415.1500, found: 415.1486; IR (KBr, ν_{max}/cm^{-1}): 3305 (OH), 1716 (CO$_2$), 1695 (CON), 1653 (CON).

Cbz-L-Phe-L-Tyr(3-OH)-OH (7ag): 164 mg (68%), colorless powder; mp; 132–134 °C; $[\alpha]_D^{28} = -7.26$ (c 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4): δ 2.77 (dd, J = 9.8, 14.0 Hz, 1H, CH_AC$_6$H$_3$), 2.87 (dd, J = 7.7, 14.0 Hz, 1H, CH_AC$_6$H$_5$), 3.03 (dd, J = 5.5, 14.0 Hz, 1H, CH_BC$_6$H$_5$), 3.09 (dd, J = 4.9, 14.0 Hz, 1H, CH_BC$_6$H$_3$), 4.37 (dd, J = 4.9, 9.8 Hz, 1H, CHCH$_2$C$_6$H$_3$), 4.58 (dd, J = 5.5, 7.7 Hz, 1H, CHCH$_2$C$_6$H$_5$), 4.96 (d, J = 12.7 Hz, 1H, OCH_AC$_6$H$_5$), 5.03 (d, J = 12.7 Hz, 1H, OCH_BC$_6$H$_5$), 6.53, 6.65–6.67 (d, m, J = 8.0 Hz, 1H, 2H, C$_6$H$_3$), 7.16–7.32 (m, 10H, C$_6$H$_5$ × 2); ^{13}C NMR (100 MHz, MeOD-d^4): δ 37.9, 39.0, 55.2, 57.8, 67.7, 116.4, 117.5, 121.9, 127.7, 128.7, 128.9, 129.4, 129.5, 130.4, 138.2, 138.6, 145.3, 146.2, 158.3, 173.9, 174.5; HRMS (ESI-TOF): Calcd for $C_{26}H_{27}N_2O_7$ (M+H)$^+$: 479.1813, found: 479.1796; IR (KBr, ν_{max}/cm^{-1}): 3487 (ArOH), 3325 (ArOH), 3033 (OH), 1724 (CO$_2$), 1695 (CON), 1657 (CON).

Cbz-L-Phe-L-Tyr(3-I)-OH (7ah): 220 mg (74%), colorless powder; mp; 182–185 °C; $[\alpha]_D^{28} = -1.08$ (c 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4): δ 2.79 (dd, J = 9.7, 13.9 Hz, 1H, CH_AC$_6$H$_3$), 2.88 (dd, J = 7.9, 13.9 Hz, 1H, CH_AC$_6$H$_5$), 3.08 (dd, J = 5.1, 13.9 Hz, 1H, CH_BC$_6$H$_5$), 3.08 (dd, J = 5.1, 13.9 Hz, 1H, CH_BC$_6$H$_3$), 4.36 (dd, J = 5.1, 9.7 Hz, 1H, CHCH$_2$C$_6$H$_3$), 4.58 (dd, J = 5.1, 7.9 Hz, 1H, CHCH$_2$C$_6$H$_5$), 4.97 (d, J = 12.6 Hz, 1H, OCH_AC$_6$H$_5$), 5.03 (d, J = 12.6 Hz, 1H, OCH_BC$_6$H$_5$), 6.74, 7.03, 7.54 (d, d, s, J = 8.0 Hz, 1H, 1H, 1H, C$_6$H$_3$), 7.17–7.32 (m, 10H, C$_6$H$_5$ × 2); ^{13}C NMR (100 MHz, MeOD-d^4): δ 37.0, 39.2, 55.1, 57.9, 67.7, 84.6, 115.7, 127.7, 128.7, 128.9, 129.5, 129.5, 130.4, 131.0, 131.6, 138.2, 138.6, 141.0, 157.0, 174.0, 174.2; HRMS (ESI-TOF): Calcd for $C_{26}H_{26}IN_2O_6$ (M+H)$^+$: 589.0830, found: 589.0835; IR (KBr, ν_{max}/cm^{-1}): 3359 (ArOH), 3280 (OH), 1735 (CO$_2$), 1706 (CON), 1644 (CON), 1051 (ArI).

Cbz-L-Phe-L-Trp(5-OH)-OH (7ai): 192 mg (76%), colorless powder; mp; 107–110 °C; $[\alpha]_D^{28} = -14.2$ (c 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4): δ 2.72 (dd, J = 10.0, 14.0 Hz, 1H, CH_A-indole), 3.08 (dd, J = 4.7, 14.0 Hz, 1H, CH_B-indole), 3.14 (dd, J = 7.2, 14.1 Hz, 1H, CH_AC$_6$H$_5$), 3.28 (dd, J =

5.3, 14.1 Hz, 1H, CH_BC$_6$H$_5$), 4.37 (dd, J = 4.7, 10.0 Hz, 1H, CHCH$_2$-indole), 4.69 (dd, J = 5.3, 7.2 Hz, 1H, CHCH$_2$C$_6$H$_5$), 4.94 (d, J = 12.8 Hz, 1H, OCH_AC$_6$H$_5$), 5.01 (d, J = 12.8 Hz, 1H, OCH_BC$_6$H$_5$), 6.66, 6.95, 7.03, 7.13–7.29 (d, s, s, m, J = 8.6 Hz, 1H, 1H, 1H, 11H, indole, C$_6$H$_5$ × 2); ^{13}C NMR (100 MHz, MeOD-d^4): δ 28.6, 39.0, 54.7, 57.8, 67.6, 103.7, 110.0, 112.5, 112.8, 125.4, 127.7, 128.7, 128.9, 129.4, 129.5, 129.7, 130.3, 133.0, 138.2, 138.6, 151.3, 158.3, 174.0, 174.9; HRMS (ESI-TOF): Calcd for $C_{28}H_{28}N_3O_6$ (M+H)$^+$: 502.1973, found: 502.1957; IR (KBr, ν_{max}/cm^{-1}): 3566 (NH), 3396 (ArOH), 3324 (OH), 1704 (CO$_2$), 1654 (CON).

Cbz-L-Ala-L-Ser-OH (7ba): 122 mg (79%), colorless powder; mp; >300 °C; $[\alpha]_D^{28}$ = +33.9 (c 1.00, DMSO); ^{1}H NMR (400 MHz, DMSO-d^6): δ 1.22 (d, J = 7.3 Hz, 3H, CH$_3$), 3.40 (dd, J = 6.2, 9.9 Hz, 1H, CH_AOH), 3.60 (dd, J = 5.3, 9.9 Hz, 1H, CH_BOH), 3.79 (ddd, J = 5.3, 6.2, 6.2 Hz, 1H, CHCH$_2$OH), 4.04 (dd, J = 7.3, 7.6 Hz, 1H, CHCH$_3$), 5.01 (d, J = 12.6 Hz, 1H, OCH_AC$_6$H$_5$), 5.06 (d, J = 12.6 Hz, 1H, OCH_BC$_6$H$_5$), 5.34 (brs, 1H, OH), 7.31–7.38 (m, 5H, C$_6$H$_5$), 7.49 (d, J = 6.2 Hz, 1H, NHCHCH$_2$), 7.60 (d, J = 7.6 Hz, 1H, NHCHCH$_3$); ^{13}C NMR (100 MHz, DMSO-d^6): δ 18.3, 50.4, 55.2, 62.5, 65.4, 127.7, 127.8, 128.4, 137.0, 155.7, 171.7, 173.9; HRMS (ESI-TOF): Calcd for $C_{14}H_{18}N_2O_6Na$ (M+Na)$^+$: 333.1057, found: 333.1073; IR (KBr, ν_{max}/cm^{-1}): 3354 (OH), 3320 (OH), 1693 (CO$_2$), 1666 (CON).

Cbz-L-Ala-L-Cys-OH (7bb): 145 mg (89%), colorless powder; mp; 164–166 °C; $[\alpha]_D^{27}$ = −11.9 (c 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4): δ 1.36 (d, J = 7.2 Hz, 3H, CH$_3$), 2.90 (dd, J = 5.8, 14.0 Hz, 1H, CH_ASH), 2.98 (dd, J = 4.6, 14.0 Hz, 1H, CH_BSH), 4.21 (q, J = 7.2 Hz, 1H, CHCH$_3$), 4.61 (dd, J = 4.6, 5.8 Hz, 1H, CHCH$_2$SH), 5.09 (s, 2H, OCH_2C$_6$H$_5$), 7.26–7.37 (m, 5H, C$_6$H$_5$); ^{13}C NMR (100 MHz, MeOD-d^4): δ 18.2, 26.8, 52.0, 55.9, 67.7, 128.9, 129.1, 129.5, 138.2, 158.3, 173.0, 175.6; HRMS (ESI-TOF): Calcd for $C_{14}H_{18}N_2O_5SNa$ (M+Na)$^+$: 349.0829, found: 349.0847; IR (KBr, ν_{max}/cm^{-1}): 3346 (OH), 2565 (SH), 1733 (CO$_2$), 1637 (CON).

Cbz-L-Ala-L-Tyr-OH (7bc): 137 mg (71%), colorless powder; mp; 148–152 °C; $[\alpha]_D^{28}$ = +10.6 (c 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4): δ 1.28 (d, J = 7.1 Hz, 3H, CH$_3$), 2.93 (dd, J = 7.5, 14.0 Hz, 1H, CH_AC$_6$H$_4$), 3.07 (dd, J = 5.4, 14.0 Hz, 1H, CH_BC$_6$H$_4$), 4.14 (q, J = 7.1 Hz, 1H, CHCH$_3$), 4.57 (dd, J = 5.4, 7.5 Hz, 1H, CHCH$_2$C$_6$H$_4$), 5.05 (d, J = 12.5 Hz, 1H, OCH_AC$_6$H$_5$), 5.09 (d, J = 12.5 Hz, 1H, OCH_BC$_6$H$_5$), 6.68, 7.02 (d, d, J = 8.3, 8.3 Hz, 2H, 2H, C$_6$H$_4$), 7.28–7.35 (m, 5H, C$_6$H$_5$); ^{13}C NMR (100 MHz, MeOD-d^4): δ 18.2, 37.6, 51.9, 55.2, 67.8, 116.2, 128.8, 128.9, 129.1, 129.5, 131.5, 138.2, 157.4, 158.2, 174.6, 175.3; HRMS (ESI-TOF): Calcd for $C_{20}H_{22}N_2O_6Na$ (M+Na)$^+$: 409.1370, found: 409.1386; IR (KBr, ν_{max}/cm^{-1}): 3401 (ArOH), 3300 (OH), 1733 (CO$_2$), 1687 (CON), 1653 (CON).

Cbz-L-Val-L-Ser-OH (7ca): 138 mg (81%), colorless powder; mp; 172–175 °C; $[\alpha]_D^{28}$ = −4.24 (c 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4): δ 0.94 (d, J = 6.8 Hz, 3H, CH$_3$), 0.99 (d, J = 6.8 Hz, 3H, CH$_3$), 2.05–2.14 (m, 1H, CH(CH$_3$)$_2$), 3.82 (dd, J = 4.2, 11.3 Hz, 1H, CH_AOH), 3.91 (dd, J = 4.5, 11.3 Hz, 1H, CH_BOH), 4.03 (d, J = 6.8 Hz, 1H, CHCH(CH$_3$)$_2$), 4.49 (dd, J = 4.2, 4.5 Hz, 1H, CHCH$_2$OH), 5.10 (s, 2H, OCH_2C$_6$H$_5$), 7.26–7.38 (m, 5H, C$_6$H$_5$); ^{13}C NMR (100 MHz, MeOD-d^4): δ 18.4, 19.8, 32.2, 56.1, 62.0, 63.1, 67.8, 128.9, 129.1, 129.5, 138.3, 158.7, 173.2, 174.3; HRMS (ESI-TOF): Calcd for $C_{16}H_{22}N_2O_6Na$ (M+Na)$^+$: 361.1370, found: 361.1388; IR (KBr, ν_{max}/cm^{-1}): 3546 (OH), 3307 (OH), 1733 (CO$_2$), 1645 (CON).

Cbz-L-Val-L-Cys-OH (7cb): 132 mg (75%), colorless powder; mp; 152–154 °C; $[\alpha]_D^{28}$ = −11.2 (c 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4): δ 0.96 (d, J = 7.0 Hz, 3H, CH$_3$), 0.98 (d, J = 7.0 Hz, 3H, CH$_3$), 2.03–2.12 (m, 1H, CH(CH$_3$)$_2$), 2.88 (dd, J = 6.4, 13.9 Hz, 1H, CH_ASH), 2.96 (dd, J = 4.6, 13.9 Hz, 1H, CH_BSH), 3.99 (d, J = 7.0 Hz, 1H, CHCH(CH$_3$)$_2$), 4.62 (dd, J = 4.6, 6.4 Hz, 1H, CHCH$_2$SH), 5.09 (s, 2H, OCH_2C$_6$H$_5$), 7.26–7.37 (m, 5H, C$_6$H$_5$); ^{13}C NMR (100 MHz, MeOD-d^4): δ 18.6, 19.8, 26.7, 31.9, 55.9, 62.2, 67.8, 128.9, 129.0, 129.5, 138.3, 158.7, 172.8, 174.4; HRMS (ESI-TOF): Calcd for $C_{16}H_{22}N_2O_5SNa$ (M+Na)$^+$: 377.1142, found: 372.1144; IR (KBr, ν_{max}/cm^{-1}): 3356 (OH), 2575 (SH), 1736 (CO$_2$), 1643 (CON).

Cbz-L-Val-L-Tyr-OH (7cc): 147 mg (71%), colorless powder; mp; 156–157 °C; $[\alpha]_D^{27}$ = −4.70 (c 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4): δ 0.88 (d, J = 7.1 Hz, 3H, CH$_3$), 0.89 (d, J = 7.1 Hz, 3H, CH$_3$), 1.96–2.01 (m, 1H, CH(CH$_3$)$_2$), 2.89 (dd, J = 8.2, 13.9 Hz, 1H, CH_AC$_6$H$_4$), 3.08 (dd, J = 5.3, 13.9 Hz, 1H, CH_BC$_6$H$_4$), 3.91 (d, J = 7.1 Hz, 1H, CHCH(CH$_3$)$_2$), 4.60 (dd, J = 5.3, 8.2 Hz, 1H, CHCH$_2$C$_6$H$_4$), 5.06 (d, J = 12.5 Hz, 1H, OCH_AC$_6$H$_5$), 5.11 (d, J = 12.5 Hz, 1H, OCH_BC$_6$H$_5$), 6.67, 7.03 (d, d, J = 8.4, 8.4 Hz, 2H, 2H, C$_6$H$_4$), 7.26–7.37 (m, 5H, C$_6$H$_5$); ^{13}C NMR (100 MHz, MeOD-d^4): δ 18.6, 19.7, 32.0, 37.8, 55.3, 62.1, 67.8, 116.2, 128.9, 129.0, 129.1, 129.6, 131.4, 138.3, 157.4, 158.6, 174.0, 174.6; HRMS (ESI-TOF): Calcd for $C_{22}H_{26}N_2O_6Na$ (M+Na)$^+$: 437.1683, found: 437.1685; IR (KBr, ν_{max}/cm^{-1}): 3301 (ArOH), 3307 (OH), 1716 (CO$_2$), 1695 (CON), 1654 (CON).

Cbz-L-Met-L-Ser-OH (7da): 142 mg (77%), colorless powder; mp; 158–161 °C; $[\alpha]_D^{28}$ = +8.16 (c 1.00, DMSO); ^{1}H NMR (400 MHz, MeOD-d^4): δ 1.87–1.96 (m, 1H, CH_ACH$_2$S), 2.04–2.13 (m, 1H, CH_BCH$_2$S), 2.08 (s, 3H, CH$_3$), 2.51–2.63 (m, 2H, CH$_2$S), 3.83 (dd, J = 3.9, 11.3 Hz, 1H, CH_AOH), 3.93 (dd, J = 4.3, 11.3 Hz, 1H, CH_BOH), 4.32 (dd, J = 5.3, 8.6 Hz, 1H, CHCH$_2$CH$_2$), 4.48 (dd, J = 3.9, 4.3 Hz, 1H, CHCH$_2$OH), 5.10 (s, 2H, OCH_2C$_6$H$_5$), 7.26–7.38, (m, 5H, C$_6$H$_5$); ^{13}C NMR (100 MHz, MeOD-d^4): δ 15.2, 31.1, 33.0, 55.5, 56.2, 62.9, 67.8, 128.9, 129.1, 129.5, 138.2, 158.5, 173.2, 174.4; HRMS (ESI-TOF): Calcd for $C_{16}H_{23}N_2O_6S$ (M+H)$^+$: 371.1271, found: 371.1262; IR (KBr, ν_{max}/cm^{-1}): 3289 (OH), 1743 (CO$_2$), 1722 (CON), 1680 (CON).

Cbz-L-Met-L-Cys-OH (7db): 151 mg (78%), colorless powder; mp; 142–144 °C; $[\alpha]_D^{28}$ = −7.03 (c 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4): δ 1.88–1.97 (m, 1H, CH_ACH$_2$S), 2.03–2.12 (m, 1H, CH_BCH$_2$S), 2.07 (s, 3H, CH$_3$), 2.50–2.63 (m, 2H, CH$_2$CH_2S), 2.90 (dd, J = 6.0, 13.8 Hz, 1H, CH_ASH), 2.98 (dd, J = 4.5, 13.8 Hz, 1H, CH_BSH), 4.30 (dd, J = 5.5, 8.5 Hz, 1H, CHCH$_2$CH$_2$), 4.62 (dd, J = 4.5, 6.0 Hz, 1H, CHCH$_2$SH), 5.10 (s, 2H, OCH_2C$_6$H$_5$), 7.27–7.37 (m, 5H, C$_6$H$_5$); ^{13}C NMR (100 MHz, MeOD-d^4): δ 15.3, 26.7, 31.1, 32.8, 55.5, 55.9, 62.9, 67.8, 128.9, 129.1, 129.5, 138.2, 158.5, 172.8, 174.5; HRMS (ESI-TOF): Calcd for $C_{16}H_{23}N_2O_5S$ (M+H)$^+$: 387.1043, found: 387.1062; IR (KBr, ν_{max}/cm^{-1}): 3313 (OH), 2584 (SH), 1736 (CO$_2$), 1635 (CON).

Cbz-L-Met-L-Tyr-OH (7dc): 148 mg (66%), colorless powder; mp; 133–135 °C; $[\alpha]_D^{28} = +0.26$ (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4): δ 1.78–1.87 (m, 1H, CH_ACH$_2$S), 1.93–2.04 (m, 1H, CH_BCH$_2$S), 2.04 (s, 3H, CH$_3$), 2.41–2.54 (m, 2H, CH$_2$S), 2.92 (dd, $J = 8.0$, 14.0 Hz, 1H, CH_AC$_6$H$_4$), 3.09 (dd, $J = 5.1$, 14.0 Hz, 1H, CH_BC$_6$H$_4$), 4.23 (dd, $J = 5.7$, 8.7 Hz, 1H, C*H*CH$_2$CH$_2$), 4.59 (dd, $J = 5.1$, 8.0 Hz, 1H, C*H*CH$_2$C$_6$H$_4$), 5.06 (d, $J = 12.4$ Hz, 1H, OCH_AC$_6$H$_5$), 5.10 (d, $J = 12.4$ Hz, 1H, OCH_BC$_6$H$_5$), 6.68, 7.03 (d, d, $J = 8.4$, 8.4 Hz, 2H, 2H, C$_6$H$_4$), 7.28–7.35 (m, 5H, C$_6$H$_5$); ^{13}C NMR (100 MHz, MeOD-d^4): δ 15.2, 31.0, 32.8, 37.5, 55.2, 55.5, 67.8, 116.3, 128.8, 128.9, 129.1, 129.5, 131.4, 138.2, 157.4, 158.4, 174.1, 174.5; HRMS (ESI-TOF): Calcd for $C_{22}H_{27}N_2O_6S$ $(M+H)^+$: 447.1584, found: 447.1569; IR (KBr, ν_{max}/cm^{-1}): 3302 (OH), 1716 (CO$_2$), 1691 (CON), 1649 (CON).

***N*-Boc-*O*-Bn-L-Ser-L-Glu-OH (7ee):** 161 mg (76%), colorless sticky oil; $[\alpha]_D^{19} = -1.46$ (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4): δ 1.45 (s, 9H, CH$_3$ × 3), 1.89–1.98 (m, 1H, CH_ACH$_2$CO), 2.15–2.25 (m, 1H, CH_BCH$_2$CO), 2.36–2.42 (m, 2H, CH$_2$CO), 3.67 (dd, $J = 4.5$, 9.8 Hz, 1H, CH_AOCH$_2$C$_6$H$_5$), 3.74 (dd, $J = 5.2$, 9.8 Hz, 1H, CH_BOCH$_2$C$_6$H$_5$), 4.30 (dd, $J = 4.5$, 5.2 Hz, 1H, C*H*CH$_2$O), 4.47–4.50 (m, 1H, C*H*CH$_2$CH$_2$), 4.52 (d, $J = 11.5$ Hz, 1H, OCH_AC$_6$H$_5$), 4.55 (d, $J = 11.5$ Hz, 1H, OCH_BC$_6$H$_5$), 7.26–7.33 (m, 5H, C$_6$H$_5$); ^{13}C NMR (100 MHz, MeOD-d^4): δ 28.2, 28.7, 31.0, 53.0, 56.2, 71.1, 74.3, 81.0, 128.8, 129.0, 129.5, 139.3, 157.8, 172.9, 174.4, 176.4; HRMS (ESI-TOF): Calcd for $C_{20}H_{28}N_2O_8Na$ $(M+Na)^+$: 447.1743, found: 447.1756; IR (KBr, ν_{max}/cm^{-1}): 3329 (OH), 1716 (CO$_2$), 1652 (CON).

***N*$^{\alpha}$-Boc-*N*$^{\varepsilon}$-Cbz-L-Lys-L-Glu-OH (7fe):** 215 mg (84%), colorless sticky oil; $[\alpha]_D^{18} = -11.4$ (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4): δ 1.39–1.55 (m, 13H, CH$_3$ × 3, CH_2-(CH$_2$)$_2$N, CH_2CH$_2$N), 1.56–1.63 (m, 1H, CH_A(CH$_2$)$_3$N), 1.70–1.81 (m, 1H, CH_B(CH$_2$)$_3$N), 1.91–1.98 (m, 1H, CH_ACH$_2$CO), 2.14–2.23 (m, 1H, CH_BCH$_2$CO), 2.38–2.42 (m, 2H, CH$_2$CO), 3.09–3.1.3 (m, 2H, CH$_2$N), 3.99–4.03 (m, 1H, C*H*(CH$_2$)$_4$N), 4.42–4.44 (m, 1H, C*H*CH$_2$CH$_2$CO), 5.06 (s, 2H, OCH_2C$_6$H$_5$), 7.28–7.34 (m, 5H, C$_6$H$_5$); ^{13}C NMR (100 MHz, MeOD-d^4): δ 24.1, 28.0, 28.8, 30.5, 31.1, 32.9, 41.5, 52.9, 56.0, 67.4, 81.0, 128.8, 129.0, 129.5, 138.5, 157.9, 159.0, 174.6, 175.4, 176.4; HRMS (ESI-TOF): Calcd for $C_{24}H_{35}N_3O_9Na$ $(M+Na)^+$: 532.2276, found: 532.2278; IR (KBr, ν_{max}/cm^{-1}): 3329 (OH), 1716 (CO$_2$), 1685 (CON), 1655 (CON).

A Typical Procedure of the Amidation of Cbz-L-Phenylalanine (6a) in a Gram Scale is as Follows. To a colorless solution of 1.50 g (5.0 mmol) of Cbz-L-phenylalanine (**6a**) in 100 mL of THF were added at 0 °C 0.67 mL (7.0 mmol, 1.4 equiv) of ethyl chloroformate and 2.09 mL (15 mmol, 3.0 equiv) of triethylamine. After stirring for 30 min at 0 °C, a solution of 1.10 g (7.5 mmol, 1.5 equiv) of L-Glu-OH (**2e**) and 0.63 g (7.5 mmol, 1.5 equiv) of $NaHCO_3$ in 100 mL of H_2O was added at 0 °C to the colorless suspension. The mixture was stirred for 30 min at 0 °C and the resulting colorless clear solution was concentrated in vacuo. The residue was adjusted to pH 2 by addition of a 1.0 M aqueous solution of HCl. The colorless suspension was diluted with 100 mL of brine, extracted with 200 mL of a 9:1 mixture of EtOAc and MeOH. The aqueous layer was extracted with 100 mL × 2 of a 9:1 mixture of EtOAc and MeOH. The combined organic layer was dried over anhydrous $MgSO_4$. The crude product was recrystallized from 50 mL of a 1:4 mixture of toluene and hexane to afford a colorless solid, followed by recrystallization from 20 mL of a 4:1 mixture of EtOAc and hexane to afford 1.74 g (81% yield) of Cbz-L-Phe-L-Glu-OH (**7ae**).

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Supporting Information

^{1}H NMR and ^{13}C NMR spectra for all amides **3a**–**3e** and dipeptides **7aa**–**7fe** are available on http://dx.doi.org/10.1246/bcsj.20170035.

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