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Convenient green preparation of dipeptides using unprotected α-amino acids

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ABSTRACT

Dipeptides and amides were obtained in high yields from *N*-carbobenzyloxy α-amino acids and 3-phenylpropanoic acid with unprotected α-amino acids via the corresponding mixed carbonic carboxylic anhydrides using ethyl chloroformate and triethylamine by an ecological and convenient method in which the protection of *C*-terminals is not needed.

1. Introduction

Peptides are one of the most important human components and induce various physiological activities as an element of proteins.[1–3] Therefore, various types of convenient peptide syntheses have been developed in chemical and biomedical research.[4–6] Recently, solvent-free syntheses of peptide using ball-milling were reported by Lamaty et al.[7] and Juaristi et al.[8] Generally, condensations between carboxylic acids and amines need activation of the corresponding carbonyl group with an activating reagent such as thionyl chloride, phosphoryl chloride, oxalyl chloride, diphenylphosphoryl azide, carbonyldiimidazole, or alkyl chloroformate.[9] Among them, the mixed carbonic carboxylic anhydrides prepared from the corresponding carboxylic acids are relatively stable and efficiently reactive with nucleophiles.[10] They have been commonly used as a reactive intermediate for amidation of carboxylic acids with amines. Furthermore, it is well known that the functional groups such as hydroxy, amino, and carboxy group on α-amino acids should be protected in order to avoid production of undesired by-products in the synthesis of peptides.[11] However, the methods using protecting groups are not environmentally friendly (see Scheme 1).

Recently, we reported the convenient amidation of the mixed carbonic carboxylic anhydrides with unprotected α-amino acids under neutral or basic conditions to afford the corresponding dipeptides easily by crystallization.[12d,e] In addition, we have just developed an amidation using ammonium chloride or aniline derivatives as a nucleophile in the presence of water.[12a–c]

Herein, we describe in detail the condensation of carboxylic acids **1** and **5** with α-amino acids **2** via the corresponding mixed carbonic carboxylic anhydrides activated with alkyl chloroformate in the presence of triethylamine as shown in Scheme 2.[12e]

2. Results and discussion

In a preliminary investigation, the reaction of 3-phenylpropanoic acid **1** with 1.5 equiv of L-phenylalanine **2a** in the presence of 1.4 equiv of ethyl chloroformate and 3.0 equiv of triethylamine in tetrahydrofuran (THF)-H_2O afforded the corresponding amide **3a** in 97% yield as indicated in entry 2 of Table 1. The solvent effect of the reaction was examined as shown in Table 1. The reaction of **1** and **2a** in ether was monitored by TLC in both steps; the second step did not proceed at 0 °C. Therefore, the second step was performed at rt to afford the corresponding amide **3a** in 87% yield (see entry 1). In the case of using dimethyl sulfoxide (DMSO) and *N*,*N*-dimethylformamide (DMF) as the solvent, the yield of **3a** decreased to 4% and 59%, respectively as shown in entries 4 and 5. The reactions using 1,4-dioxane, DMSO, and DMF as the solvent were carried out at rt in order to avoid freezing. Amidation of **1** with **2a** proceeded in THF, 1,4-dioxane, acetone, and acetonitrile to give **3a** in 93–97% yields. A small amount of *N*-ethoxycarbonyl-L-phenylalanine **4a** was detected as a by-product on the basis of ^{1}H NMR analysis in all entries of Table 1. It is assumed that **4a** is mainly produced by the reaction of **2a** with the remaining ethyl chloroformate (see Scheme 2).

Next, the effect of the quantity of ethyl chloroformate on the amidation was examined and the results are summarized in Table 2. Carboxylic acid **1** was efficiently coupled with **2a** to afford **3a** in 94–97% yields, and a small amount of the by-product **4a** was detected by ^{1}H NMR analysis in all entries of Table 2. The optimized conditions for preparing **3a** were the treatment of **1** with 1.4 equiv of ethyl chloroformate and 3.0 equiv of triethylamine in

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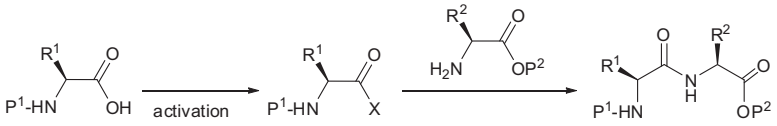
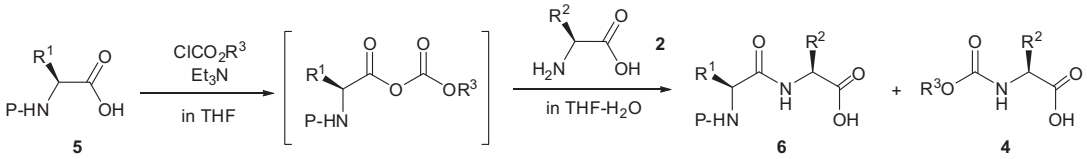
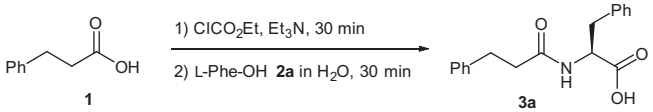


Scheme 1. General synthetic methods of dipeptides.



Scheme 2. Convenient synthetic method of dipeptides via the mixed carbonic carboxylic anhydrides.

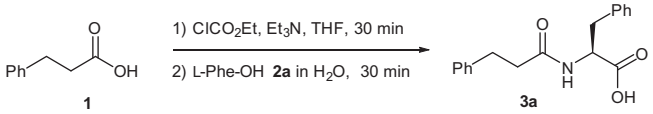
Table 1
Solvent effect on the amidation of 3-phenylpropanoic acid **1** with L-phenylalanine **2a** in the presence of ethyl chloroformate[a]



Entry	Solvent	Reaction Temp.		Yield[b]/%
		Step 1)	Step 2)	
1	Ether	0 °C	rt[c]	87
2	THF	0 °C	0 °C	97
3	1,4-Dioxane	rt	rt	95
4	DMSO	rt	0 °C to rt	4
5	DMF	rt	0 °C to rt	59
6	Acetone	0 °C	0 °C	96
7	Acetonitrile	0 °C	0 °C	93

[a] All reactions were carried out with 0.5 mmol of **1**, 0.7 mmol of ethyl chloroformate, and 1.5 mmol of triethylamine in 10 mL of the solvent. After stirring for 30 min, 0.75 mmol of **2a** in 10 mL of H_2O was added to the reaction mixtures.
[b] Isolated yields.
[c] The reaction time was 3 h.

Table 2
Effect of the quantity of ethyl chloroformate on the amidation of 3-phenylpropanoic acid **1** with L-phenylalanine **2a**[a]



Entry	$ClCO_2Et$	Reaction Temp.		Yield[b]/%
		Step 1)	Step 2)	
1	1.1 eq	0 °C	0 °C	96
2	1.4 eq	0 °C	0 °C	97
3	2.0 eq	0 °C	0 °C	97
4	1.4 eq	0 °C	0 °C to rt	94
5	1.4 eq	0 °C to rt	0 °C to rt	95

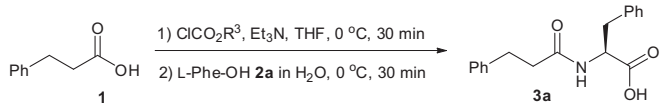
[a] All reactions were carried out with 0.5 mmol of **1**, ethyl chloroformate, and 1.5 mmol of triethylamine in 10 mL of THF. After stirring for 30 min, 0.75 mmol of **2a** in 10 mL of H_2O was added to the reaction mixtures.
[b] Isolated yields.

THF at 0 °C, followed by the addition of 1.5 equiv of **2a** in H_2O at 0 °C (see entry 2 of Table 2).

Subsequently, we checked the effect of various activating reagents on the amidation of **1** with **2a** and the results are shown in Table 3. The reaction of **1** with **2a** using methyl chloroformate afforded the corresponding amide **3a** in 82% yield (see entry 1). In contrast, **2a** reacted with the mixed carbonic carboxylic anhydrides prepared from **1** and ethyl, isopropyl or isobutyl chloroformate to give the corresponding amide **3a** in 97%, 96%, and 94% yields, respectively (see entries 2–4). We decided to use ethyl chloroformate as the activating reagent because the yield of **3a** in the reaction with ethyl chloroformate was similar to those with isopropyl and isobutyl chloroformates, while ethyl chloroformate is less expensive than isopropyl and isobutyl chloroformates.

Then, Table 4 shows the results of the reactions of **1** with several types of α-amino acids **2a–2j**. We selected L-Phe-OH **2a**,

Table 3
Effect of activating reagents on the amidation of 3-phenylpropanoic acid **1** with L-phenylalanine **2a**[a]



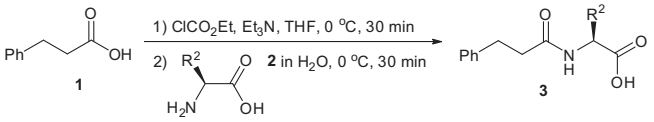
Entry	R^3	Yield[b]/%
1	Me	82
2	Et	97
3	*i*-Pr	96
4	*i*-Bu	94

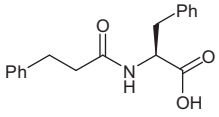
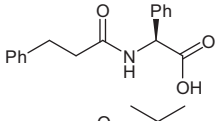
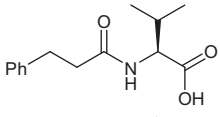
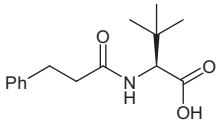
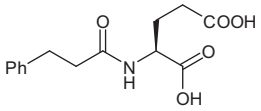
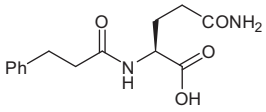
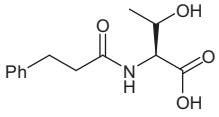
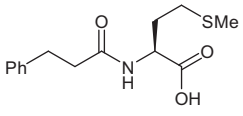
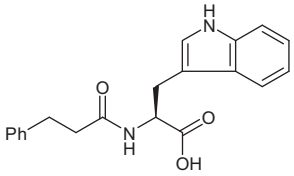
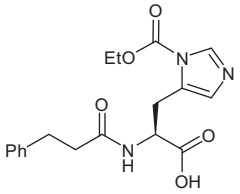
[a] All reactions were carried out with 0.5 mmol of **1**, 0.7 mmol of alkyl chloroformate, and 1.5 mmol of triethylamine in 10 mL of THF. After stirring for 30 min, 0.75 mmol of **2a** in 10 mL of H_2O was added to the reaction mixtures.
[b] Isolated yields.

L-Phg-OH **2b**, L-Trp-OH **2i** and L-His-OH **2j** as aromatic α-amino acids, L-Val-OH **2c** and L-*tert*-Leu-OH **2d** as chain-branched α-amino acids, and L-Glu-OH **2e**, L-Gln-OH **2f**, L-Thr-OH **2g** and L-Met-OH **2h** as α-amino acids containing another functional group. The amidation of **1** with **2a** proceeded efficiently to give the corresponding amide **3a** in excellent yield (see entry 1). Amide **3b** was obtained in 89% yield by the reaction of **1** with **2b** (see entry 2). Amino acids **2c** and **2d** were reacted with the activated **1** to afford the corresponding amides **3c** and **3d** in excellent yields in spite of sterically hindered side-chain such as isopropyl and *tert*-butyl groups (see entries 3 and 4). The coupling reaction of **1** and **2e** containing the carboxy group gave the corresponding amide **3e** in lower yield with the recovered **1** because of the solubility in the reaction solution (see entry 5). In contrast, the amidation of **1** with **2f** containing the amide group proceeded smoothly to afford the corresponding amide **3f** in 85% yield because **2f** is highly soluble in water (see entry 6). Amides **3g** and **3h** were prepared in 85% and 87% yields from **2g** containing a hydroxy group and **2h** containing a sulfide group, respectively (see entries 7 and 8). Amino acid **2i** possessing indole moiety was converted into the corresponding amide **3i** in 86% yield (see entry 9). The reaction with **2j** gave *N*-ethoxycarbonylimidazolylamide **3j** in 19% yield due to the nucleophilic nitrogen atom on the imidazole moiety (see entry 10).

Next, the results of the condensation of *N*-protected L-phenylalanines **5a**–**5c** with several types of unprotected α-amino acids **2a** and **2c**–**2j** via the corresponding mixed carbonic carboxylic anhydrides are shown in Table 5. We examined the effect of the protecting group on the *N*-terminal of the starting α-amino acids. We selected benzyl carbamate (Cbz), *tert*-butyl carbamate (Boc), and 9-fluorenylmethyl carbamate (Fmoc) as protecting groups for the starting α-amino acids **5a**, **5a**′, and **5a**″, respectively. The reaction of Cbz-L-Phe-OH **5a** with L-Val-OH **2c** afforded the corresponding dipeptide **6ac** in 75% yield (see entry 1), and Boc-L-Phe-OH **5a**′ was reacted with **2c** to give the corresponding dipeptide **6a**′**c** in 82% yield (see entry 2). The dipeptide **6a**″**c** was obtained by the reaction of Fmoc-L-Phe-OH **5a**″ with **2c** in 77% yield (see entry 3). Generally, the Boc group was cleaved by strong acids such as HCl, trifluoroacetic acid (TFA), or *p*-toluenesulfonic acid (TsOH), providing *t*-BuOH or isobutylene and CO_2 as the by-products. It is well known that *tert*-butylation generated from deprotection of Boc group react readily with electron rich side-chain of α-amino acids (Cys, Met, Thr, Ser, and Trp).[13] We were concerned about racemization under basic conditions although the Fmoc group is cleaved by weak bases such as $NaHCO_3$, piperidine, and morpholine. On the other hand, deprotection of the Cbz group is usually carried out with hydrogenation using H_2/Pd-C under mild conditions. Hence, we decided to check the variety of the reaction using Cbz group.

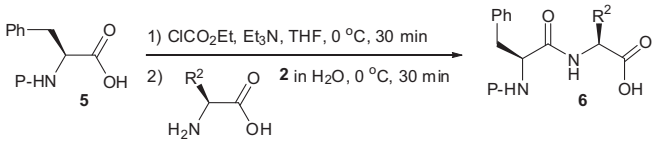
Table 4
Amidation of 3-phenylpropanoic acid **1** with α-amino acids **2** without protection of *C*-terminals[a]



Entry	Amide **3**		Yield[b]/%
1		**3a**	97
2		**3b**	89
3		**3c**	89
4		**3d**	Quant.
5		**3e**	59
6		**3f**	85
7		**3g**	85
8		**3h**	87
9		**3i**	86
10		**3j**	19[c]

[a] All reactions were carried out with 0.5 mmol of **1**, 0.7 mmol of ethyl chloroformate, and 1.5 mmol of triethylamine in 10 mL of THF. After stirring for 30 min, 0.75 mmol of **2** in 10 mL of H_2O was added to the reaction mixtures.
[b] Isolated yields.
[c] The *N*-ethoxycarbonyl derivative was obtained.

Table 5
Synthesis of dipeptides **6** without protection of *C*-terminals in α-amino acids **2**[a]



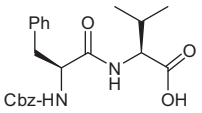
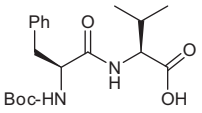
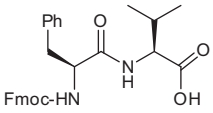
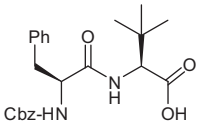
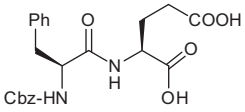
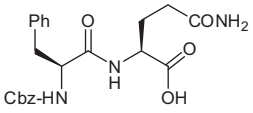
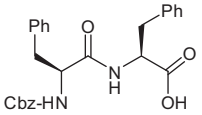
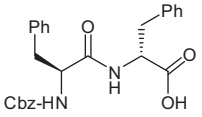
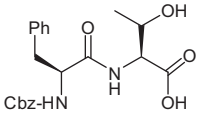
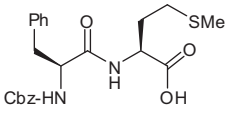
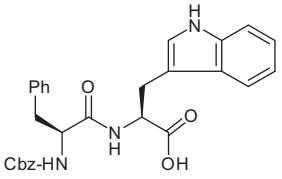
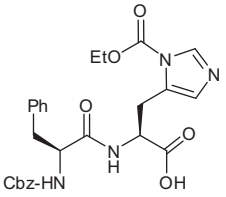
Entry	P	5	Dipeptide 6		Yield[b]/%
1	Cbz	**5a**		**6ac**	75
2	Boc	**5a′**		**6a′c**	82
3	Fmoc	**5a″**		**6a″c**	77
4	Cbz	**5a**		**6ad**	68
5	Cbz	**5a**		**6ae**	36
6	Cbz	**5a**		**6af**	87
7	Cbz	**5a**		**6aa**	80
8	Cbz	**5a**		**6aa′**	81
9	Cbz	**5a**		**6ag**	81
10	Cbz	**5a**		**6ah**	65
11	Cbz	**5a**		**6ai**	78

Table 5 (*continued*)

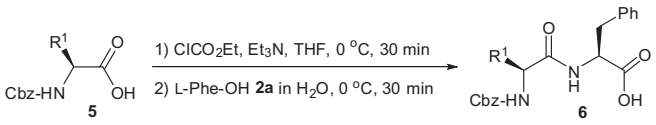
Entry	P	**5**	Dipeptide **6**		Yield[b]/%
12	Cbz	**5a**		**6aj**	21[c]

[a] All reactions were carried out with 0.5 mmol of **5**, 0.7 mmol of ethyl chloroformate, and 1.5 mmol of triethylamine in 10 mL of THF. After stirring for 30 min, 0.75 mmol of **2** in 10 mL of H_2O was added to the reaction mixtures.
[b] Isolated yields.
[c] The *N*-ethoxycarbonyl derivative was obtained.

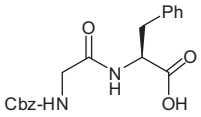
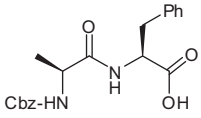
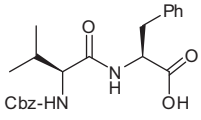
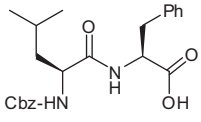
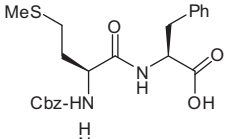
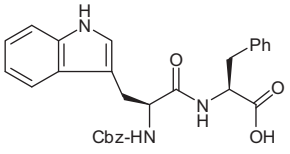
The yield of dipeptide **6ad** was slightly lower due to bulky side-chain on L-*tert*-Leu **2d** as indicated in entry 4. The reaction of **5a** with L-Glu-OH **2e** did not proceed well because of the solubility (see entry 5); while the dipeptide **6af** was synthesized from **5a** and L-Gln-OH **2f** in 87% yield (see entry 6). The two ^{1}H NMR spectra of the diastereomers **6aa** and **6aa′** prepared from the reactions of **5a** with the enantiomers L-Phe-OH **2a** and D-Phe-OH **2a′** in 80% and 81% yield, respectively, showed no epimerization under the optimized reaction conditions (see entries 7 and 8). Subsequently, we tried to run the reactions of L-Thr-OH **2g**, L-Met-OH **2h**, and L-Trp-OH **2i**. The amino acid **5a** reacted with **2g** and **2i** to afford the corresponding dipeptides **6ag** and **6ai** in 81% and 78% yields, respectively (see entries 9 and 11). The yield of the dipeptide **6ah** synthesized from **5a** and **2h** containing sulfide group was 65% (see entry 10). In the case of L-His-OH **2j** containing the imidazole moiety, the reaction gave *N*-ethoxycarbonyl dipeptide **6aj** in 21% yield as indicated in entry 12 of Table 5.

Finally, we applied this method to various *N*-Cbz α-amino acids **5b**–**5g**, and the results are shown in Table 6. The reaction of Cbz-Gly-OH **5b** with L-Phe-OH **2a** proceeded to afford the correspond-

Table 6
Application to synthesis of various dipeptides **6** with *N*-Cbz α-amino acids **5** and L-phenylalanine **2a**[a]



5 6

Entry	**5**	Dipeptide **6**		Yield [b]/%
1	**5b**		**6ba**	75
2	**5c**		**6ca**	79
3	**5d**		**6da**	71
4	**5e**		**6ea**	76
5	**5f**		**6fa**	70
6	**5g**		**6ga**	85

[a] All reactions were carried out with 0.5 mmol of **5**, 0.7 mmol of ethyl chloroformate, and 1.5 mmol of triethylamine in 10 mL of THF. After stirring for 30 min, 0.75 mmol of **2a** in 10 mL of H_2O was added to the reaction mixtures.
[b] Isolated yields.

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ing dipeptide **6ba** in 75% yield (see entry 1), and Cbz-L-Ala-OH **5c** reacted with **2a** to provide the corresponding dipeptide **6ca** in 79% yield (see entry 2). Cbz-L-Val-OH **5d** and Cbz-L-Leu **5e** as chain-branched α-amino acids were converted to the corresponding dipeptides **6da** and **6ea** in 71% and 76% yields, respectively (see entries 3 and 4). Dipeptide **6fa** was synthesized from Cbz-L-Met-OH **5f** and **2a** in 70% yield (see entry 5). The activated Cbz-L-Trp-OH **5g** coupled easily with **2a** to produce the dipeptide **6ga** in 85% yield because of the intramolecular π-π stacking interaction[14] between phenyl and indole moieties in **5g** (see entry 6).

3. Conclusions

We have developed an environmentally friendly and convenient synthetic method to dipeptides without protection of *C*-terminals, in which the dipeptides **6aa**, **6aa′**, **6a′c**, **6a″c**, and **6ac**–**6aj** were obtained in 36–81% yields from the corresponding α-amino acids. Additionally, we succeeded to synthesizing various dipeptides **6ba**–**6ga** in 70–85% yields using the corresponding α-amino acids **5a**–**5g** protected by Cbz group on *N*-terminal and L-Phe-OH **2a**. The main by-products are triethylamine hydrochloride, carbon dioxide, and the corresponding alcohols and racemization was not observed in our method.

4. Experimental

4.1. General

All reagents were used without further purification. The ^{1}H NMR and ^{13}C NMR spectra were measured with a Bruker Ultrashield™ 400 Plus spectrometer. The chemical shifts are expressed in parts per million downfield from tetramethylsilane ($\delta = 0.00$) as an internal standard. 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 reaction 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.

4.2. Typical procedure for amidation of 3-phenylpropanoic acid 1 with L-phenylalanine 2a

To a colorless solution of 75 mg (0.50 mmol) of **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 at 0 °C for 30 min, a solution of 124 mg (0.75 mmol, 1.5 equiv) of **2a** in 10 mL of H_2O was added at 0 °C to the colorless suspension. The mixture was stirred at 0 °C for 30 min and concentrated in vacuo. To the residue was added a 1.0 M aqueous HCl solution to adjust to pH 2. The resulting suspension was extracted with 50 mL of EtOAc, washed with 10 mL of brine, and dried over $MgSO_4$. The crude product was chromatographed on silica gel with a 2:1 mixture of hexane and EtOAc containing 1% AcOH to afford 145 mg (97% yield) of *N*-(3-phenylpropanoyl)-L-Phe-OH **3a**.

4.2.1. *N*-(3-Phenylpropanoyl)-L-Phe-OH 3a

145 mg (97%), colorless powder; mp: 167–169 °C; $[\alpha]_D^{23} = +1.4$ (c 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4): δ 2.45 (ddd, J = 1.0, 7.6, 7.6 Hz, 1H, CH_ACO), 2.45 (ddd, J = 1.0, 8.0, 8.0 Hz, 1H, CH_BCO), 2.79 (dd, J = 7.6, 8.0 Hz, 2H, $CH_2CH_2C_6H_5$), 2.91 (dd, J = 8.9, 13.8 Hz, 1H, $CHCH_AC_6H_5$), 3.15 (dd, J = 5.0, 13.8 Hz, 1H, $CHCH_BC_6H_5$), 4.64 (dd, J = 5.0, 8.9 Hz, 1H, CHCO), 7.13–7.17, 7.18–7.26 (m, m, 5H, 5H, C_6H_5 ×2); ^{13}C NMR (100 MHz, MeOD-d^4): δ 30.5, 36.2, 36.4, 52.9, 124.9, 125.4, 127.1, 127.1, 127.2, 128.0, 136.3, 139.9, 172.7, 172.8; HRMS (ESI-TOF): Calcd for $C_{18}H_{19}NO_3Na$ $(M+Na)^+$: 320.1257, found: 320.1283; IR (KBr, ν_{max}/cm^{-1}) = 3307 (OH), 1708 (CO_2), 1600 (CON).

4.2.2. *N*-(3-Phenylpropanoyl)-L-Phg-OH 3b

126 mg (89%), colorless powder; mp: 152–153 °C; $[\alpha]_D^{27} = +108.4$ (c 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4):δ 2.57 (ddd, J = 1.5, 7.6, 7.6 Hz, 1H, CH_ACO), 2.57 (ddd, J = 1.5, 8.0, 8.0 Hz, 1H, CH_BCO), 2.90 (dd, J = 7.6, 8.0 Hz, 2H, $CH_2C_6H_5$), 5.41 (s, 1H, CHCO), 7.12–7.24, 7.30–7.34 (m, m, 5H, 5H, C_6H_5 ×2); ^{13}C NMR (100 MHz, MeOD-d^4):δ 32.8, 38.5, 58.2, 127.2, 128.8, 129.3, 129.5, 129.5, 129.8, 138.2, 142.2, 173.8, 174.8; HRMS (ESI-TOF): Calcd for $C_{17}H_{17}NO_3Na$ $(M+Na)^+$: 306.1101, found: 306.1086; IR (KBr, ν_{max}/cm^{-1}) = 3338 (OH), 1698 (CO_2), 1616 (CON).

4.2.3. *N*-(3-Phenylpropanoyl)-L-Val-OH 3c

111 mg (89%), colorless powder; mp: 141–143 °C; $[\alpha]_D^{21} = -22.9$ (c 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4):δ 0.87 (d, J = 6.8 Hz, 6H, $(CH_3)_2$), 2.06–2.14 (m, 1H, $CH(CH_3)_2$), 2.57 (ddd, J = 3.9, 7.6, 7.6 Hz, 1H, CH_ACO), 2.58 (ddd, J = 3.9, 7.7, 7.7 Hz, 1H, CH_BCO), 2.91 (dd, J = 7.6, 7.7 Hz, 2H, $CH_2C_6H_5$), 4.28 (d, J = 5.7 Hz, 1H, CHCO), 7.13–7.17, 7.20–7.27 (m, m, 1H, 4H, C_6H_5); ^{13}C NMR (100 MHz, MeOD-d^4):δ 18.3, 19.6, 31.7, 32.9, 59.1, 127.2, 129.5, 129.5, 142.2, 175.1, 175.4; HRMS (ESI-TOF): Calcd for $C_{14}H_{19}NO_3Na$ $(M+Na)^+$: 272.1257, found: 272.1243; IR (KBr, ν_{max}/cm^{-1}) = 3338 (OH), 1699 (CO_2), 1616 (CON).

4.2.4. *N*-(3-Phenylpropanoyl)-L-*tert*-Leu-OH 3d

132 mg (Quant), colorless powder; mp: 183–185 °C; $[\alpha]_D^{26} = -9.7$ (c 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4):δ 0.94 (s, 9H, $(CH_3)_3C$), 2.59 (ddd, J = 6.5, 7.7, 7.7 Hz, 1H, CH_ACO), 2.59 (ddd, J = 6.5, 7.7, 7.7 Hz, 1H, CH_BCO), 2.91 (dd, J = 7.7, 7.7 Hz, 2H, $CH_2C_6H_5$), 4.25 (s, 1H, CHCO), 7.13–7.17, 7.20–7.26 (m, m, 1H, 4H, C_6H_5); ^{13}C NMR (100 MHz, MeOD-d^4):δ 27.2, 32.9, 34.8, 38.5, 62.2, 127.2, 129.5, 142.2, 174.4, 175.2; HRMS (ESI-TOF): Calcd for $C_{15}H_{21}NO_3Na$ $(M+Na)^+$: 286.1414, found: 286.1386; IR (KBr, ν_{max}/cm^{-1}) = 3348 (OH), 1699 (CO_2), 1610 (CON).

4.2.5. *N*-(3-Phenylpropanoyl)-L-Glu-OH 3e

83 mg (59%), colorless powder; mp: 131–134 °C; $[\alpha]_D^{23} = -28.4$ (c 1.00, MeOH); ^{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_2-CH), 2.54 (dd, J = 7.4, 8.0 Hz, 2H, CH_2CO), 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); ^{13}C NMR (100 MHz, MeOD-d^4):δ 27.9, 31.2, 32.8, 38.7, 53.0, 127.3, 129.5, 129.5, 142.2, 175.0, 175.4, 176.4; HRMS (ESI-TOF): Calcd for $C_{14}H_{17}NO_5Na$ $(M+Na)^+$: 302.0999, found: 302.1010; IR (KBr, ν_{max}/cm^{-1}) = 3276 (OH), 1716 (CO_2), 1653 (CON).

4.2.6. *N*-(3-Phenylpropanoyl)-L-Gln-OH 3f

74 mg (53%), colorless powder; mp: 141–144 °C; $[\alpha]_D^{22} = -19.2$ (c 1.00, MeOH); ^{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 (dd, J = 7.5, 8.1 Hz, 2H, CH_2CO), 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); ^{13}C NMR (100 MHz, MeOD-d^4):δ 28.6, 32.7, 32.8, 38.7, 53.3, 127.3, 129.5, 129.5, 142.2, 175.0, 175.4, 177.7; HRMS (ESI-TOF): Calcd for $C_{14}H_{18}N_2O_4Na$ $(M+Na)^+$: 301.1159, found:

301.1184; IR (KBr, ν_{max}/cm^{-1}) = 3292 (OH), 1724 (CO_2), 1646 (CON).

4.2.7. *N*-(3-Phenylpropanoyl)-L-Thr-OH 3g

107 mg (85%), colorless oil; $[\alpha]_D^{22} = -7.0$ (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4):δ 1.06 (d, *J* = 6.4 Hz, 3H, CH_3), 2.61 (dd, *J* = 7.4, 8.2 Hz, 2H, CH_2CO), 2.94 (dd, *J* = 7.4, 8.2 Hz, 2H, $CH_2C_6H_5$), 4.24–4.29 (m, 1H, $CHCH_3$), 4.41 (d, *J* = 3.0 Hz, 1H, CHCO), 7.13–7.20, 7.21–7.27 (m, m, 1H, 4H, C_6H_5); ^{13}C NMR (100 MHz, MeOD-d^4):δ 20.4, 32.8, 38.7, 59.1, 68.4, 127.2, 129.5, 129.5, 142.2, 173.9, 175.7; HRMS (ESI-TOF): Calcd for $C_{13}H_{17}NO_4Na$ $(M+Na)^+$: 274.1050, found: 274.1040; IR (NaCl, ν_{max}/cm^{-1}) = 3325 (OH), 1732 (CO_2), 1653 (CON).

4.2.8. *N*-(3-Phenylpropanoyl)-L-Met-OH 3h

123 mg (87%), yellow powder; mp: 73–75 °C; $[\alpha]_D^{21} = -28.9$ (*c* 0.98, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4):δ 1.80–1.89 (m, 1H, CH_ACH_2S), 2.01–2.10 (m, 1H, CH_BCH_2S), 2.03 (s, 3H, CH_3), 2.27–2.41 (m, 2H, CH_2CH_2S), 2.54 (dd, *J* = 7.4, 7.9 Hz, 2H, CH_2CO), 2.91 (dd, *J* = 7.4, 7.7 Hz, 2H, $CH_2C_6H_5$), 4.48–4.51 (m, 1H, CHCO), 7.14–7.27 (m, 5H, C_6H_5); ^{13}C NMR (100 MHz, MeOD-d^4):δ 15.2, 31.2, 32.2, 32.8, 38.7, 52.6, 127.3, 129.5, 129.5, 142.2, 175.2, 175.4; HRMS (ESI-TOF): Calcd for $C_{14}H_{19}NO_3SNa$ $(M+Na)^+$: 304.0978, found: 304.0953; IR (KBr, ν_{max}/cm^{-1}) = 3302 (OH), 1705 (CO_2), 1647 (CON).

4.2.9. *N*-(3-Phenylpropanoyl)-L-Trp-OH 3i

111 mg (89%), colorless powder; mp: 160–162 °C; $[\alpha]_D^{27} = +1.3$ (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4):δ 2.44 (dd, *J* = 7.6, 8.0 Hz, 2H, CH_2CO), 2.78 (ddd, *J* = 3.1, 7.6, 7.6 Hz, 1H, $CH_AC_6H_5$), 2.78 (ddd, *J* = 3.1, 8.0, 8.0 Hz, 1H, $CH_BC_6H_5$), 3.11 (dd, *J* = 8.0, 14.8 Hz, 1H, CH_ACH), 3.30 (dd, *J* = 5.0, 14.8 Hz, 1H, CH_BCH), 4.71 (dd, *J* = 5.0, 8.0 Hz, 1H, CHCO), 6.96, 7.00, 7.06–7.21, 7.32, 7.53 (s, t, m, d, d, *J* = 7.4, 7.8, 7.8 Hz, 1H, 1H, 6H, 1H, 1H, indole, C_6H_5); ^{13}C NMR (100 MHz, MeOD-d^4):δ 28.6, 32.7, 38.8, 54.7, 111.1, 112.3, 119.3, 119.8, 122.4, 124.4, 127.2, 128.9, 129.4, 129.5, 138.1, 142.2, 175.1, 175.3; HRMS (ESI-TOF): Calcd for $C_{20}H_{20}N_2O_3Na$ $(M+Na)^+$: 359.1366, found: 359.1348; IR (KBr, ν_{max}/cm^{-1}) = 3410 (OH), 1734 (CO_2), 1655 (CON).

4.3. Typical procedure for amidation of Cbz-L-phenylalanine 5a with L-valine 2c

To a colorless solution of 150 mg (0.50 mmol) of **5a** 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 at 0 °C for 30 min, a solution of 88 mg (0.75 mmol, 1.5 equiv) of **2c** in 10 mL of H_2O was added at 0 °C to the colorless suspension. The mixture was stirred at 0 °C for 30 min, and concentrated in vacuo. To the residue was added a 1.0 M aqueous HCl solution to adjust to pH 2. The resulted suspension was extracted with 50 mL of EtOAc, washed with 10 mL of brine, and dried over $MgSO_4$. The crude product was chromatographed on silica gel with a 1:1 mixture of hexane and EtOAc containing 1% AcOH to afford 149 mg (75% yield) of Cbz-L-Phe-L-Val-OH **6ac**.

4.3.1. Cbz-L-Phe-L-Val-OH 6ac

149 mg (75%), colorless powder; mp; 140–143 °C; $[\alpha]_D^{25} = -7.7$ (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$):δ 0.84 (d, *J* = 6.8 Hz, 3H, CH_3), 0.89 (d, *J* = 6.8 Hz, 3H, CH_3), 2.13–2.21 (m, 1H, $CH(CH_3)_2$), 3.08 (dd, *J* = 7.0, 7.3 Hz, 2H, $CHCH_2C_6H_5$), 4.46–4.49 (m, 2H, CHCO ×2), 5.07 (d, *J* = 12.3 Hz, 1H, $OCH_AC_6H_5$), 5.11 (d, *J* = 12.3 Hz, 1H, $OCH_BC_6H_5$), 5.45 (br s, 1H, NH), 6.36 (br s, 1H, NH), 7.18–7.37 (m, 10H, C_6H_5 ×2); ^{13}C NMR (100 MHz, $CDCl_3$):δ 17.6, 18.8, 30.9, 38.2, 56.3, 57.2, 67.2, 127.1, 128.1, 128.3, 128.6, 128.8, 129.3, 136.1, 156.1, 171.2, 174.7; HRMS (ESI-TOF): Calcd for $C_{22}H_{27}N_2O_5$ $(M+H)^+$: 399.1914, found: 399.1918; IR (KBr, ν_{max}/cm^{-1}) = 3307 (OH), 1697 (CO_2), 1635 (CON).

4.3.2. Boc-L-Phe-L-Val-OH 6a′c

149 mg (82%), colorless powder; mp; 64–67 °C; $[\alpha]_D^{27} = -5.3$ (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4):δ 0.96 (d, *J* = 6.8 Hz, 6H, $(CH_3)_2$), 1.34 (s, 9H, $(CH_3)_3C$), 2.13–2.21 (m, 1H, $CH(CH_3)_2$), 2.80 (dd, *J* = 4.2, 13.9 Hz, 1H, $CH_AC_6H_5$), 3.12 (dd, *J* = 4.9, 13.9 Hz, 1H, $CH_BC_6H_5$), 4.32–4.37 (m, 2H, CHCO ×2), 7.17–7.26 (m, 5H, C_6H_5); ^{13}C NMR (100 MHz, MeOD-d^4):δ 18.3, 19.6, 28.7, 32.1, 39.0, 57.3, 58.9, 80.7, 127.7, 129.4, 130.4, 138.7, 157.7, 174.4, 174.5; HRMS (ESI-TOF): Calcd for $C_{19}H_{28}N_2O_5Na$ $(M+Na)^+$: 387.1890, found: 387.1901; IR (KBr, ν_{max}/cm^{-1}) = 3309 (OH), 1716 (CO_2), 1652 (CON).

4.3.3. Fmoc-L-Phe-L-Val-OH 6a″c

187 mg (77%), colorless powder; mp; 93–95 °C; $[\alpha]_D^{25} = -19.6$ (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4):δ 0.96 (d, *J* = 6.8 Hz, 6H, CH_3 ×2), 2.13–2.21 (m, 1H, $CH(CH_3)_2$), 2.85 (dd, *J* = 9.8, 13.9 Hz, 1H, $CH_AC_6H_5$), 3.12 (dd, *J* = 4.9, 13.9 Hz, 1H, $CH_BC_6H_5$), 4.11–4.36 (m, 4H, $CHCH(CH_3)_2$, CH_2O, $CHCH_2O$), 4.45–4.51 (m, 1H, $CHCH_2C_6H_5$), 7.16–7.30, 7.37, 7.55–7.58, 7.78 (m, t, m, d, *J* = 7.6, 7.6 Hz, 7H, 2H, 2H, 2H, C_6H_5, Fmoc); ^{13}C NMR (100 MHz, MeOD-d^4):δ 18.3, 19.6, 32.0, 39.0, 57.7, 59.0, 59.1, 68.1, 121.0, 126.3, 126.3, 127.8, 128.2, 128.8, 129.5, 130.4, 138.7, 142.6, 145.2, 158.3, 174.3, 174.5; HRMS (ESI-TOF): Calcd for $C_{29}H_{30}N_2O_5Na$ $(M+Na)^+$: 509.2047, found: 509.2039; IR (KBr, ν_{max}/cm^{-1}) = 3301 (OH), 1718 (CO_2), 1691 (CON), 1656 (CON).

4.3.4. Cbz-L-Phe-L-*tert*-Leu-OH 6ad

140 mg (68%), colorless powder; mp; 164–167 °C; $[\alpha]_D^{25} = -14.3$ (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4):δ 1.00 (s, 9H, CH_3 ×3), 2.83 (dd, *J* = 9.6, 13.8 Hz, 1H, $CH_AC_6H_5$), 3.11 (dd, *J* = 5.3, 13.8 Hz, 1H, $CH_BC_6H_5$), 4.29 (s, 1H, $CHC(CH_3)_3$), 4.48 (dd, *J* = 5.3, 9.6 Hz, 1H, $CHCH_2C_6H_5$), 5.09 (s, 2H, $OCH_2C_6H_5$), 7.17–7.32 (m, 10H, C_6H_5 ×2); ^{13}C NMR (100 MHz, MeOD-d^4):δ 27.1, 35.2, 38.9, 57.8, 61.9, 67.6, 127.6, 128.7, 129.0, 129.5, 130.4, 138.2, 138.5, 158.3, 173.8, 174.0; HRMS (ESI-TOF): Calcd for $C_{23}H_{28}N_2O_5Na$ $(M+Na)^+$: 435.1890, found: 435.1890; IR (KBr, ν_{max}/cm^{-1}) = 3327 (OH), 1699 (CO_2), 1635 (CON).

4.3.5. Cbz-L-Phe-L-Glu-OH 6ae

78 mg (36%), colorless powder; mp; 149–152 °C; $[\alpha]_D^{27} = -12.1$ (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4):δ 1.89–1.99 (m, 1H, CH_ACH_2CO), 2.15–2.23 (m, 1H, CH_BCH_2CO), 2.39 (dd, *J* = 7.6, 7.8 Hz, 2H, CH_2CO), 2.84 (dd, *J* = 9.6, 14.0 Hz, 1H, $CH_AC_6H_5$), 3.15 (dd, *J* = 5.0, 14.0 Hz, 1H, $CH_BC_6H_5$), 4.40–4.47 (m, 2H, CH × 2), 4.99 (d, *J* = 13.0 Hz, 1H, $OCH_AC_6H_5$), 5.03 (d, *J* = 13.0 Hz, 1H, $OCH_BC_6H_5$), 7.18–7.33 (m, 10H, C_6H_5 ×2); ^{13}C NMR (100 MHz, MeOD-d^4):δ 28.0, 31.1, 39.0, 53.1, 57.8, 67.6, 127.8, 128.8, 129.0, 129.5, 130.4, 138.2, 138.6, 158.3, 174.2, 174.6, 176.4; HRMS (ESI-TOF): Calcd for $C_{22}H_{25}N_2O_7$ $(M+H)^+$: 429.1656, found: 429.1672; IR (KBr, ν_{max}/cm^{-1}) = 3286 (OH), 1716 (CO_2), 1660 (CON).

4.3.6. Cbz-L-Phe-L-Gln-OH 6af

187 mg (87%), colorless powder; mp; 179–182 °C; $[\alpha]_D^{28} = -10.2$ (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4):δ 1.91–1.98 (m, 1H, CH_ACH_2CO), 2.16–2.35 (m, 3H, CH_BCH_2CO, CH_2CO), 2.85 (dd, *J* = 9.7, 14.0 Hz, 1H, $CH_AC_6H_5$), 3.16 (dd, *J* = 4.9, 14.0 Hz, 1H, $CH_BC_6H_5$), 4.38–4.43 (m, 2H, CH × 2), 4.99 (d, *J* = 12.7 Hz, 1H, $OCH_AC_6H_5$), 5.03 (d, *J* = 12.7 Hz, 1H, $OCH_BC_6H_5$), 7.17–7.33 (m, 10H, C_6H_5 ×2); ^{13}C NMR (100 MHz, MeOD-d^4):δ 28.8, 32.7, 39.0, 53.2, 57.8, 67.6, 127.8, 128.7, 129.0, 129.5, 129.5, 130.4, 138.2, 138.6, 158.3, 174.3, 174.6, 177.8; HRMS (ESI-TOF): Calcd for $C_{22}H_{25}N_3O_6Na$ $(M+Na)^+$: 450.1636, found: 450.1606; IR (KBr, ν_{max}/cm^{-1}) = 3309 (OH), 1716 (CO_2), 1654 (CON).

4.3.7. Cbz-L-Phe-L-Phe-OH 6aa

178 mg (80%), colorless powder; mp; 148–151 °C; $[\alpha]_D^{24} = -10.5$ (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-*d*^{4}):δ 2.76 (dd, *J* = 9.7, 14.0 Hz, 1H, C*H*$_A$C$_6$H$_5$), 3.00 (dd, *J* = 8.2, 13.8 Hz, 1H, C*H*$_{A'}$C$_6$H$_5$), 3.08 (dd, *J* = 5.0, 14.0 Hz, 1H, C*H*$_B$C$_6$H$_5$), 3.19 (dd, *J* = 5.2, 13.8 Hz, 1H, C*H*$_{B'}$C$_6$H$_5$), 4.36 (dd, *J* = 5.0, 9.7 Hz, 1H, CH), 4.65 (dd, *J* = 5.2, 8.2 Hz, 1H, CH′), 4.97 (d, *J* = 12.6 Hz, 1H, OC*H*$_A$C$_6$H$_5$), 5.01 (d, *J* = 12.6 Hz, 1H, OC*H*$_B$C$_6$H$_5$), 7.15–7.33 (m, 15H, C$_6$H$_5$ ×3); ^{13}C NMR (100 MHz, MeOD-*d*^{4}):δ 38.5, 39.1, 55.0, 57.7, 67.6, 127.7, 127.8, 128.7, 128.9, 129.4, 129.5, 130.4, 130.5, 138.2, 138.6, 158.2, 173.9, 174.2; HRMS (ESI-TOF): Calcd for $C_{26}H_{27}N_2O_5$ (M+H)$^+$: 447.1914, found: 447.1890; IR (KBr, ν_{max}/cm^{-1}) = 3307 (OH), 1716 (CO$_2$), 1695 (CON), 1660 (CON).

4.3.8. Cbz-L-Phe-D-Phe-OH 6aa′

181 mg (81%), colorless powder; mp; 109–112 °C; $[\alpha]_D^{27} = -19.2$ (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-*d*^{4}):δ 2.67 (dd, *J* = 9.5, 14.0 Hz, 1H, C*H*$_A$C$_6$H$_5$), 2.92–2.98 (m, 2H, C*H*$_{A'}$C$_6$H$_5$, C*H*$_B$C$_6$H$_5$), 3.16 (dd, *J* = 5.0, 13.6 Hz, 1H, C*H*$_{B'}$C$_6$H$_5$), 4.37 (dd, *J* = 5.4, 9.5 Hz, 1H, CH), 4.66 (dd, *J* = 5.0, 8.4 Hz, 1H, CH′), 4.96 (d, *J* = 12.8 Hz, 1H, OC*H*$_A$C$_6$H$_5$), 5.02 (d, *J* = 12.8 Hz, 1H, OC*H*$_B$C$_6$H$_5$), 7.08–7.33 (m, 15H, C$_6$H$_5$ ×3); ^{13}C NMR (100 MHz, MeOD-*d*^{4}):δ 38.4, 39.3, 54.9, 57.7, 67.6, 127.7, 127.9, 128.7, 129.0, 129.4, 129.5, 129.6, 130.4, 130.4, 138.2, 138.5, 158.1, 173.8, 174.3; HRMS (ESI-TOF): Calcd for $C_{26}H_{26}N_2O_5Na$ (M+Na)$^+$: 469.1734, found: 469.1726; IR (KBr, ν_{max}/cm^{-1}) = 3307 (OH), 1716 (CO$_2$), 1652 (CON).

4.3.9. Cbz-L-Phe-L-Thr-OH 6ag

162 mg (81%), colorless powder; mp; 141–143 °C; $[\alpha]_D^{25} = -7.7$ (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, CDCl$_3$):δ 1.17 (d, *J* = 6.4 Hz, 3H, CH$_3$), 2.95 (dd, *J* = 8.0, 14.0 Hz, 1H, C*H*$_A$C$_6$H$_5$), 3.11 (dd, *J* = 5.5, 14.0 Hz, 1H, C*H*$_B$C$_6$H$_5$), 4.40–4.48 (m, 1H, C*H*OH), 4.60–4.69 (m, 2H, C*H*CH$_2$, C*H*CHOH), 4.92 (d, *J* = 12.2 Hz, 1H, OC*H*$_A$C$_6$H$_5$), 5.04 (d, *J* = 12.2 Hz, 1H, OC*H*$_B$C$_6$H$_5$), 5.46 (br s, 1H, NH), 7.09–7.11, 7.19–7.21, 7.28–7.31 (m, m, m, 11H, NH, C$_6$H$_5$ ×2); ^{13}C NMR (100 MHz, CDCl$_3$):δ 19.2, 38.6, 55.8, 57.3, 67.3, 68.6, 127.1, 128.0, 128.2, 128.5, 128.7, 129.3, 135.9, 156.4, 172.0, 172.8; HRMS (ESI-TOF): Calcd for $C_{21}H_{25}N_2O_6$ (M+H)$^+$: 401.1707, found: 401.1708; IR (KBr, ν_{max}/cm^{-1}) = 3294 (OH), 1701 (CO$_2$), 1658 (CON).

4.3.10. Cbz-L-Phe-L-Met-OH 6ah

140 mg (65%), colorless powder; mp; 103–104 °C; $[\alpha]_D^{26} = -16.1$ (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, CDCl$_3$):δ 1.92–2.04 (m, 1H, C*H*$_A$CH$_2$S), 2.04 (s, 3H, CH$_3$), 2.10–2.19 (m, 1H, C*H*$_B$CH$_2$S), 2.37–2.48 (m, 2H, CH$_2$S), 3.03–3.15 (m, 2H, C*H*$_2$C$_6$H$_5$), 4.43–4.55 (m, 1H, C*H*CH$_2$CH$_2$), 4.61–4.66 (m, 1H, C*H*CH$_2$C$_6$H$_5$), 5.08 (s, 2H, OC*H*$_2$-C$_6$H$_5$), 5.39 (br s, 1H, NH), 6.72 (br s, 1H, NH), 7.17–7.38 (m, 10H, C$_6$H$_5$ ×2); ^{13}C NMR (100 MHz, CDCl$_3$):δ 15.3, 29.8, 30.8, 38.2, 51.7, 56.1, 67.3, 127.2, 128.1, 128.3, 128.6, 128.8, 129.3, 136.0, 156.2, 171.5, 174.4; HRMS (ESI-TOF): Calcd for $C_{22}H_{26}N_2O_5SNa$ (M+Na)$^+$: 453.1455, found: 453.1440; IR (KBr, ν_{max}/cm^{-1}) = 3301 (OH), 1712 (CO$_2$), 1689 (CON), 1652 (CON).

4.3.11. Cbz-L-Phe-L-Trp-OH 6ai

189 mg (78%), colorless powder; mp; 141–144 °C; $[\alpha]_D^{27} = -3.3$ (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-*d*^{4}):δ 2.74 (dd, *J* = 9.7, 14.0 Hz, 1H, C*H*$_A$C$_6$H$_5$), 3.07 (dd, *J* = 5.0, 14.0 Hz, 1H, C*H*$_B$C$_6$H$_5$), 3.22 (dd, *J* = 7.2, 14.7 Hz, 1H, CH$_A$-indole), 3.34 (dd, *J* = 5.2, 14.7 Hz, 1H, CH$_B$-indole), 4.37 (dd, *J* = 5.0, 9.7 Hz, 1H, C*H*CH$_2$C$_6$H$_5$), 4.71 (dd, *J* = 5.2, 7.2 Hz, 1H, C*H*CH$_2$-indole), 4.94 (d, *J* = 12.8 Hz, 1H, OC*H*$_A$C$_6$H$_5$), 5.00 (d, *J* = 12.8 Hz, 1H, OC*H*$_B$C$_6$H$_5$), 6.99, 7.05–7.09, 7.14–7.32, 7.55 (t, m, m, d, *J* = 7.0, 7.9 Hz, 1H, 2H, 11H, 1H, C$_6$H$_5$ ×2, indole); ^{13}C NMR (100 MHz, MeOD-*d*^{4}):δ 28.5, 39.0, 54.7, 57.8, 67.6, 110.7, 112.3, 119.4, 119.9, 122.4, 124.6, 127.7, 128.7, 129.0, 129.4, 129.5, 130.4, 138.0, 138.2, 138.6, 158.2, 173.9, 174.9; HRMS (ESI-TOF): Calcd for $C_{28}H_{27}N_3O_5Na$ (M+Na)$^+$: 508.1843, found: 508.1836; IR (KBr, ν_{max}/cm^{-1}) = 3408 (NH), 3313 (OH), 1712 (CO$_2$), 1627 (CON).

4.3.12. Cbz-Gly-L-Phe-OH 6ba

133 mg (75%), colorless sticky oil; $[\alpha]_D^{28} = +25.1$ (*c* 0.98, MeOH); ^{1}H NMR (400 MHz, MeOD-*d*^{4}):δ 3.00 (dd, *J* = 7.6, 14.2 Hz, 1H, C*H*$_A$-C$_6$H$_5$), 3.18 (dd, *J* = 5.4, 14.2 Hz, 1H, C*H*$_B$C$_6$H$_5$), 3.72 (d, *J* = 17.0 Hz, 1H, C*H*$_A$CONH), 3.79 (d, *J* = 17.0 Hz, 1H, C*H*$_B$CONH), 4.67 (dd, *J* = 5.4, 7.6 Hz, 1H, C*H*CH$_2$C$_6$H$_5$), 5.09 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.16–7.27, 7.28–7.38 (m, m, 5H, 5H, C$_6$H$_5$ ×2); ^{13}C NMR (100 MHz, MeOD-*d*^{4}):δ 38.4, 44.8, 54.9, 67.9, 127.9, 128.9, 129.1, 129.5, 130.4, 138.1, 159.0, 171.9, 174.4; HRMS (ESI-TOF): Calcd for $C_{19}H_{20}N_2O_5Na$ (M+Na)$^+$: 379.1264, found: 379.1250; IR (KBr, ν_{max}/cm^{-1}) = 3326 (OH), 1732 (CO$_2$), 1662 (CON).

4.3.13. Cbz-L-Ala-L-Phe-OH 6ca

144 mg (79%), colorless powder; mp; 125–127 °C; $[\alpha]^{27}{}_D = +1.0$ (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-*d*^{4}):δ 1.27 (d, *J* = 7.1 Hz, 3H, CH$_3$), 3.01 (dd, *J* = 7.8, 13.9 Hz, 1H, C*H*$_A$C$_6$H$_5$), 3.18 (dd, *J* = 5.2, 13.9 Hz, 1H, C*H*$_B$C$_6$H$_5$), 4.13 (q, *J* = 7.1 Hz, 1H, C*H* CH$_3$), 4.64 (dd, *J* = 5.2, 7.8 Hz, 1H, C*H*CH$_2$C$_6$H$_5$), 5.06 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.16–7.26, 7.28–7.38 (m, m, 5H, 5H, C$_6$H$_5$ ×2); ^{13}C NMR (100 MHz, MeOD-*d*^{4}):δ 18.3, 38.4, 51.9, 54.9, 67.7, 127.8, 128.9, 129.0, 129.5, 129.5, 130.5, 138.2, 158.2, 174.3, 175.3; HRMS (ESI-TOF): Calcd for $C_{20}H_{22}N_2O_5Na$ (M+Na)$^+$: 393.1421, found: 393.1449; IR (KBr, ν_{max}/cm^{-1}) = 3330 (OH), 1736 (CO$_2$), 1714 (CON), 1691 (CON).

4.3.14. Cbz-L-Val-L-Phe-OH 6da

142 mg (71%), colorless powder; mp; 174–177 °C; $[\alpha]_D^{27} = -0.8$ (*c* 1.00, DMSO); ^{1}H NMR (400 MHz, MeOD-*d*^{4}):δ 0.87 (d, *J* = 6.8 Hz, 3H, CH$_3$), 0.89 (d, *J* = 6.8 Hz, 3H, CH$_3$), 1.93–2.00 (m, 1H, C*H*(CH$_3$)$_2$), 2.97 (dd, *J* = 8.6, 13.9 Hz, 1H, C*H*$_A$C$_6$H$_5$), 3.18 (dd, *J* = 5.2, 13.9 Hz, 1H, C*H*$_B$C$_6$H$_5$), 3.90 (d, *J* = 7.3 Hz, 1H, C*H*CH(CH$_3$)$_2$), 4.66 (dd, *J* = 5.2, 8.6 Hz, 1H, C*H*CH$_2$C$_6$H$_5$), 5.08 (s, 2H, OC*H*$_2$-C$_6$H$_5$), 7.13–7.22, 7.28–7.35 (m, m, 5H, 5H, C$_6$H$_5$ ×2); ^{13}C NMR (100 MHz, MeOD-*d*^{4}):δ 18.6, 19.7, 32.1, 38.5, 54.9, 62.1, 67.7, 127.8, 128.9, 129.1, 129.5, 129.5, 130.4, 138.3, 158.5, 174.0, 174.4; HRMS (ESI-TOF): Calcd for $C_{22}H_{26}N_2O_5Na$ (M+Na)$^+$: 421.1734, found: 421.1757; IR (KBr, ν_{max}/cm^{-1}) = 3342 (OH), 1734 (CO$_2$), 1635 (CON).

4.3.15. Cbz-L-Leu-L-Phe-OH 6ea

156 mg (76%), colorless powder; mp; 81–83 °C; $[\alpha]_D^{27} = -7.4$ (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-*d*^{4}):δ 0.89 (d, *J* = 6.6 Hz, 3H, CH$_3$), 0.92 (d, *J* = 6.6 Hz, 3H, CH$_3$), 1.44–1.48 (m, 2H, C*H*$_A$CH(CH$_3$)$_2$, C*H*(CH$_3$)$_2$), 1.58–1.66 (m, 1H, C*H*$_B$CH(CH$_3$)$_2$), 3.00 (dd, *J* = 8.4, 13.7 Hz, 1H, C*H*$_A$C$_6$H$_5$), 3.19 (dd, *J* = 5.2, 13.7 Hz, 1H, C*H*$_B$C$_6$-H$_5$), 4.14 (dd, *J* = 6.3, 6.3 Hz, 1H, C*H*CH$_2$CH), 4.65 (dd, *J* = 5.2, 8.3 Hz, 1H, C*H*CH$_2$C$_6$H$_5$), 5.07 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.15–7.24, 7.27–7.35 (m, m, 5H, 5H, C$_6$H$_5$ ×2); ^{13}C NMR (100 MHz, MeOD-*d*^{4}):δ 22.0, 23.4, 25.9, 38.4, 42.1, 54.9, 54.9, 67.7, 127.8, 128.8, 129.0, 129.5, 129.5, 130.5, 138.2, 158.4, 174.3, 175.1; HRMS (ESI-TOF): Calcd for $C_{23}H_{28}N_2O_5Na$ (M+Na)$^+$: 435.1890, found: 435.1909; IR (KBr, ν_{max}/cm^{-1}) = 3319 (OH), 1716 (CO$_2$), 1697 (CON), 1664 (CON).

4.3.16. Cbz-L-Met-L-Phe-OH 6fa

150 mg (70%), colorless powder; mp; 125–126 °C; $[\alpha]_D^{27} = -7.0$ (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, MeOD-*d*^{4}):δ 1.77–1.86 (m, 1H, C*H*$_A$CH$_2$S), 1.92–1.99 (m, 1H, C*H*$_B$CH$_2$S), 2.04 (s, 3H, CH$_3$), 2.40–2.53 (m, 2H, CH$_2$S), 3.00 (dd, *J* = 8.3, 13.9 Hz, 1H, C*H*$_A$C$_6$H$_5$), 3.19 (dd, *J* = 5.2, 13.9 Hz, 1H, C*H*$_B$C$_6$H$_5$), 4.22 (dd, *J* = 5.6, 8.5 Hz, 1H, C*H*CH$_2$CH$_2$), 4.66 (dd, *J* = 5.2, 8.3 Hz, 1H, C*H*CH$_2$C$_6$H$_5$), 5.07 (s, 2H, OC*H*$_2$C$_6$H$_5$), 7.15–7.26, 7.28–7.35 (m, m, 5H, 5H, C$_6$H$_5$ ×2); ^{13}C NMR (100 MHz, MeOD-*d*^{4}):δ 15.2, 31.0, 32.9, 38.3, 54.9, 55.5, 67.8, 127.9, 128.9, 129.1, 129.5, 129.5, 130.4, 138.2, 158.4, 174.1, 174.3; HRMS (ESI-TOF): Calcd for $C_{22}H_{26}N_2O_5SNa$ (M+Na)$^+$:

453.1455, found: 453.1454; IR (KBr, ν_{max}/cm^{-1}) = 3311 (OH), 1722 (CO_2), 1695 (CON), 1660 (CON).

4.3.17. Cbz-L-Trp-L-Phe-OH 6ga

207 mg (85%), colorless powder; mp; 70–72 °C; $[\alpha]_D^{28} = -18.1$ (*c* 0.99, MeOH); ^{1}H NMR (400 MHz, MeOD-d^4):δ 2.96 (dd, *J* = 7.8, 13.9 Hz, 1H, CH_AC$_6$H$_5$), 3.01 (dd, *J* = 8.4, 14.8 Hz, 1H, CH$_A$-indole), 3.14 (dd, *J* = 5.4, 13.9 Hz, 1H, CH_BC$_6$H$_5$), 3.20 (dd, *J* = 5.4, 14.8 Hz, 1H, CH$_B$-indole), 4.43 (dd, *J* = 5.4, 8.4 Hz, 1H, C*H*CH$_2$-indole), 4.64 (dd, *J* = 5.4, 7.8 Hz, 1H, C*H*CH$_2$C$_6$H$_5$), 5.00 (s, 2H, OCH_2C$_6$H$_5$), 6.96–7.33, 7.57 (m, d, *J* = 7.9 Hz, 14H, 1H, C$_6$H$_5$ ×2, indole); ^{13}C NMR (100 MHz, MeOD-d^4):δ 29.1, 38.4, 55.0, 57.2, 67.7, 111.0, 112.3, 119.4, 119.9, 122.4, 124.7, 127.8, 128.7, 128.8, 128.9, 129.4, 129.5, 130.5, 138.1, 158.2, 174.2; HRMS (ESI-TOF): Calcd for $C_{28}H_{27}N_3O_5Na$ $(M+Na)^+$: 508.1843, found: 508.1820; IR (KBr, ν_{max}/cm^{-1}) = 3402 (NH), 3313 (OH), 1716 (CO_2), 1662 (CON).

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