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4-(Dimethylamino)pyridine *N*-oxide (DMAPO): An Effective Nucleophilic Catalyst in the Peptide Coupling Reaction with 2-Methyl-6-nitrobenzoic Anhydride

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Dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday

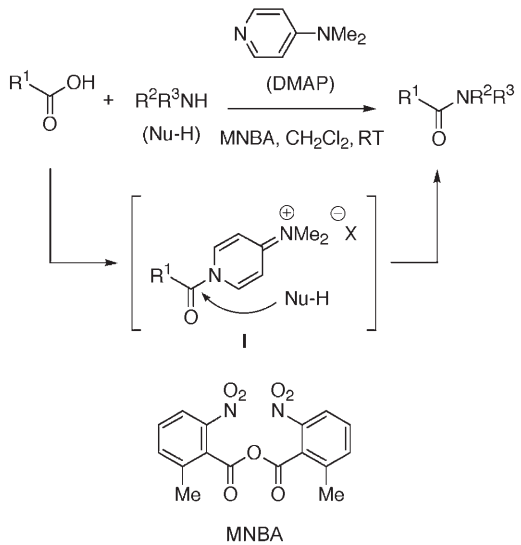
Abstract: Various carboxamides or peptides were synthesized from the corresponding carboxylic acids and amines or α-amino acids in high yields by the catalysis of 4-(dimethylamino)-pyridine *N*-oxide (DMAPO) with 2-methyl-6-nitrobenzoic anhydride (MNBA). Because the segment-coupling reaction of α-amino acids proceeds through the effective activation of the carboxylic acid moieties with DMAPO in the presence of tertiary amines under mild conditions, undesired racemization was hardly observed in the synthesis of oligopeptides such as Z-Gly-Phe-Val-OMe, Z-Phe-Val-Ala-OMe, and Bz-Val-Val-OMe.

Keywords: carboxamides · oligopeptides · peptide coupling · peptides · synthetic methods

Introduction

The carboxamide moiety is one of the most important ingredients in natural bioactive compounds such as peptides, β-lactams, and macrolactams. A new and useful method for the synthesis of these components under mild reaction conditions is now required. Although many coupling reagents for producing carboxamides have been investigated,[1] there remains the significant problem that racemization frequently occurs during the segment-coupling reaction of α-amino acids for providing oligopeptides.

Recently, we reported several useful methods for the synthesis of carboxylic acid derivatives by using substituted benzoic anhydrides under acidic or basic conditions.[2–4] For example, nearly equimolar amounts of carboxylic acids and alcohols or ω-hydroxycarboxylic acids react in the presence of 2-methyl-6-nitrobenzoic anhydride (MNBA) with nucleophilic catalysts such as 4-(dimethylamino)pyridine (DMAP) or 4-(dimethylamino)pyridine *N*-oxide (DMAPO) to produce the corresponding carboxylic esters or lactones in high yields.[3] The intermediary mixed anhydride, which functions as a reactive acylating reagent for alcohols to produce the desired carboxylic esters in high yields with high product selectivities, was formed during the initial part of the reaction with MNBA. Furthermore, when amines were used as nucleophiles instead of alcohols in the above reaction catalyzed by DMAP, the corresponding carboxamides were produced in high yields (Scheme 1)[5] through the formation of the



Scheme 1. Carboxamide-forming reaction with DMAP and MNBA.

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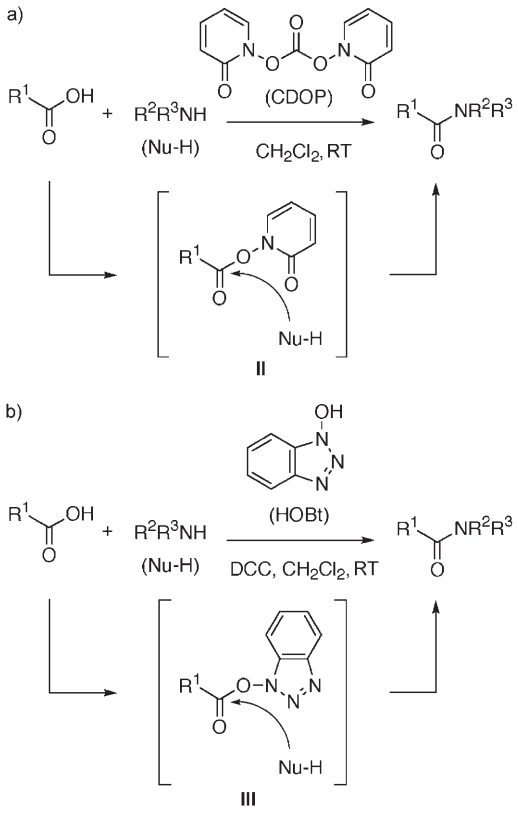
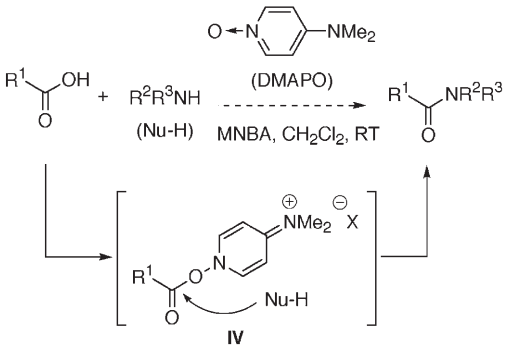
classically definitive pyridinium salt intermediates **I**. The last amidation smoothly proceeded to form the desired carboxamides and dipeptides; however, this method is not applicable to the synthesis of oligopeptides because significant racemization of the α-amino acids occurs via formation of the oxazolone intermediates generated from **I**.[6]

On the other hand, we investigated an effective method for the synthesis of carboxamides or oligopeptides in high yields without any loss of chirality of the starting carboxylic acids by using 1,1′-carbonyldioxydi[2(1*H*)-pyridone] (CDOP) in the absence of base (Scheme 2a).[7] In this synthesis, the assumed intermediate **II** functions as a reactive electrophile that can be attacked by amine nucleophiles. We noticed that the structure of this intermediate is similar to that of the intermediate **III** formed in situ during the effective peptide-forming reaction when 1-hydroxybenzotriazole (HOBt)[8] is used as an additional promoter combined with other coupling reagents (Scheme 2b).[1f]



Scheme 2. Carboxamide-forming reaction with CDOP or HOBt and DCC.

On the basis of the above hypothesis, it was anticipated that DMAPO,[9] an effective nucleophilic catalyst of our lactonization, would promote the coupling reaction of α-amino acids via the formation of the acyloxypyridinium intermediate **IV** (Scheme 3). Furthermore, we assumed that the structural nature of **IV**, with C–O–N bonds similar to those in **II** and **III**, might prevent the racemization process from occurring through the formation of oxazolone intermediates during the peptide-coupling reaction.



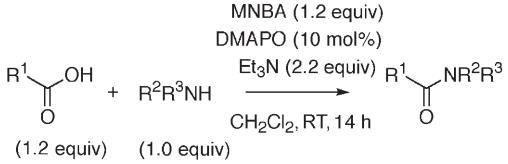
Scheme 3. Synthetic plan of carboxamides with MNBA and DMAPO.

In this paper, we describe a novel method for the synthesis of carboxamides with DMAPO instead of DMAP in the presence of MNBA and tertiary amines. As this reaction proceeds rapidly under mild reaction conditions, it can be applied to the segment coupling of several α-amino acids for the formation of oligopeptides without loss of the chirality of the acid parts.

Results and Discussion

A simple amidation reaction was chosen as a model case for the first stage of the present research. 3-Phenylpropylamine (**3**; 1.0 equiv) was added to the reaction mixture of MNBA (1.2 equiv), DMAPO (10 mol%), triethylamine (2.2 equiv), and 3-phenylpropanoic acid (**1**; 1.2 equiv) in dichloromethane at room temperature; the corresponding amide **7** was then obtained in an 81% yield (Table 1, entry 1). The reaction of **1** with other amines, such as 1-phenylethylamine (**4**), benzylmethylamine (**5**), and piperidine (**6**), also proceeded smoothly to form the corresponding coupling products **8**–**10** in high yields (Table 1, entries 2–4). 2-Phenylpropanoic acid (**2**), a 2-branched carboxylic acid, also reacted with **3** to

Table 1. Synthesis of a variety of carboxamides **7**–**14** with MNBA/DMAPO.



Entry	Carboxylic acid	Amine	Product	Yield[a] [%]
1	$Ph(CH_2)_2COOH$ (**1**)	$Ph(CH_2)_3NH_2$ (**3**)	**7**	81
2	**1**	$PhCHMeNH_2$ (**4**)	**8**	87
3	**1**	$PhCH_2NHMe$ (**5**)	**9**	81
4	**1**	piperidine (**6**)	**10**	78
5	PhCHMeCOOH (**2**)	$Ph(CH_2)_3NH_2$ (**3**)	**11**	71
6	**2**	$PhCHMeNH_2$ (**4**)	**12**	75
7	**2**	$PhCH_2NHMe$ (**5**)	**13**	76
8	**2**	piperidine (**6**)	**14**	69

[a] Yield of isolated product.

form the desired 2-phenyl-*N*-(3-phenylpropyl)propanamide (**11**) in high yield (Table 1, entry 5). The amidation of **2** with other typical amines **4**–**6**, including bulky ones, gave the corresponding carboxamides **12**–**14** in good yields with very high product selectivities (Table 1, entries 6–8).

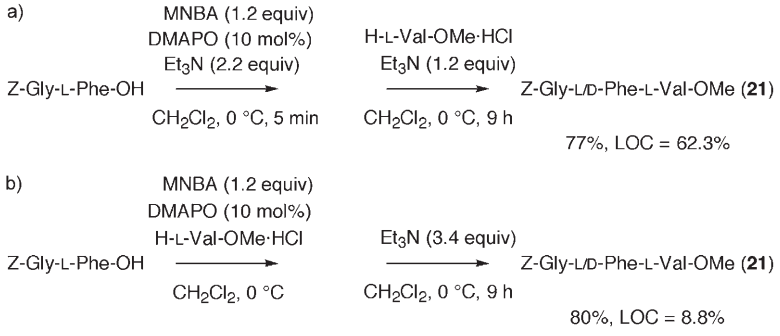
Next, we applied this protocol to the synthesis of the di- and tripeptides. After the treatment of several Z-amino acids with MNBA and DMAPO in the presence of triethylamine to produce the corresponding mixed anhydrides in situ, H-Gly-OEt·HCl was added to the mixture with an equal amount of triethylamine (Table 2, entries 1–6). All the reactions proceeded smoothly to afford the desired dipeptides **15**–**20** in good yields, and the optical purities of the products were not decreased during successive reactions.

Table 2. Synthesis of a variety of dipeptides **15**–**20** with MNBA/DMAPO.[a]

Entry	Acid	Amine	Product	Yield[b] [%]
1	Z-L-Ala-OH	H-Gly-OEt·HCl	**15**	62[c,d]
2	Z-L-Phe-OH	H-Gly-OEt·HCl	**16**	58[e]
3	Z-L-Val-OH	H-Gly-OEt·HCl	**17**	68[f]
4	Z-L-Leu-OH	H-Gly-OEt·HCl	**18**	57[g]
5	Z-L-Met-OH	H-Gly-OEt·HCl	**19**	49[h]
6	Z-L-Pro-OH	H-Gly-OEt·HCl	**20**	54[i]

[a] Conditions: MNBA (1.2 equiv), DMAPO (10 mol%), Et_3N (3.4 equiv), CH_2Cl_2, 0°C, 9 h. [b] Yield of isolated product. Acid (1.2 equiv) and amine (1.0 equiv) were used. [c] >99% *ee* (determined by HPLC with CHIRALCEL OD-H). [d] $[\alpha]_D^{21}=-22.2$ ($c=2.43$, EtOH); reference [15]: −22.10.[15] [e] $[\alpha]_D^{27}=-17.1$ ($c=0.57$, EtOH); reference [16]: −16.90.[16] [f] $[\alpha]_D^{23}=-25.2$ ($c=0.62$, EtOH); reference [17]: −25.30.[17] [g] $[\alpha]_D^{22}=-26.3$ ($c=1.68$, EtOH); reference [18]: −26.40.[18] [h] $[\alpha]_D^{22}=-19.4$ ($c=2.19$, EtOH); reference [19]: −19.80.[19] [i] $[\alpha]_D^{22}=-60.4$ ($c=2.43$, AcOEt); reference [20]: −60.4.[20]

We then attempted to develop a segment-coupling reaction of Z-Gly-Phe-OH with H-Val-OMe·HCl to form the corresponding tripeptide **21** by using MNBA, DMAPO, and triethylamine (Scheme 4). Typically, facile racemization has been observed during the synthesis of peptides from Z-Gly-Phe-OH with several amino acids by using conventional coupling reagents; the assessment for this is called the Anteunis test.[1f,h,j–m,10] Unfortunately, considerable racemization occurred when the usual stepwise-addition method was employed (Scheme 4a). In that method, a mixture of Z-Gly-Phe-OH, MNBA, DMAPO, and triethylamine in dichloromethane was stirred for 5 min at 0°C, then a solution of H-Val-OMe·HCl and triethylamine in dichloromethane was added to the reaction mixture to provide **21** with a significant loss of chirality (LOC=62.3). On the other hand, we showed that racemization diminished when all of the triethylamine was added at once after the mixed anhydride was generated without the tertiary amine (Scheme 4b). These results prompted us to survey the optimized reaction conditions and a suitable structure for a base that would function as an effective desalting reagent for the peptide coupling.



Scheme 4. Synthesis of Z-Gly-Phe-Val-OMe with MNBA and DMAPO under different conditions.

Several bases and reaction temperatures were screened for the reaction of Z-Gly-Phe-OH with H-Val-OMe·HCl promoted by DMAPO (Table 3). When the reaction was carried out with 3.4 molar equivalents of triethylamine in the absence of DMAPO, the desired product was not obtained at all (Table 3, entry 1). Employment of a catalytic amount of DMAPO with several tertiary amines, such as triethylamine, diisopropylethylamine (DIEA), *N*-methylpiperidine (NMP), and *N*-methylmorpholine (NMM), afforded fairly good results by producing excellent yields of Z-Gly-Phe-Val-OMe (**21**) with fairly good optical purities (Table 3, entries 2–5). On the other hand, the yield of **21** was dramatically decreased to 17% by the use of DMAPO together with pyridine as a base (Table 3, entry 6). It was found

Table 3. Optimization of reaction conditions for peptide-coupling reaction.

Z-Gly-L-Phe-OH (1.2 equiv) + H-L-Val-OMe·HCl (1.0 equiv) → MNBA (1.2 equiv), DMAPO (10 mol%), then Base (3.4 equiv), CH_2Cl_2, *T* → Z-Gly-L/D-Phe-L-Val-OMe (**21**)

Entry	Base	*T* [°C]	*t* [h]	Yield[b] [%]	LOC[c,d] [%]
1[a]	Et_3N	0	1	0	–
2	Et_3N	0	1	88	10.5
3	DIEA	0	1	94	8.1
4	NMP	0	1	86	7.5
5	NMM	0	1	83	3.7
6	pyridine	0	1	17	2.6
7	Et_3N	−23	3	79	0.6
8	DIEA	−23	3	89	0.4

[a] The reaction was carried out in the absence of DMAPO. [b] Yield of isolated product **21**. [c] LOC=(diastereomeric excess of acid)−(diastereomeric excess of product). [d] Diastereomeric excess of product determined by HPLC analysis.

that the desired tripeptide **21** was obtained in excellent yield with high purity when the reaction was performed at −23 °C due to the efficient inhibition of the rapid racemization of the acid moiety (Table 3, entry 7). Finally, we determined that the optimized conditions for preparing the L,L form of **21** without formation of the D,L isomer are to use MNBA and DMAPO with a bulky base, such as DIEA, at −23 °C (Table 3, entry 8).

In Table 4, the yields and LOCs for the synthesis of peptides **21**–**23** with conventional coupling reagents such as dicyclohexylcarbodiimide (DCC) and *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) are shown for comparison with the results obtained by our recently developed original protocols. First, the Anteunis test was used to check for the reaction promoted by DCC combined with triethylamine under the standard conditions, and it was found that significant racemization occurred (LOC = 14.6; Table 4, entry 1). TBTU,[1f] an advanced uronium salt type reagent generated from carbodiimide and 1-hydroxybenzotriazole (HOBt), is comparatively effective and provided the desired tripeptide **21** in satisfactorily pure form (LOC = 3.0; Table 4, entry 2). These results indicate that the TBTU-promoted reaction is superior to the former in inhibiting the racemization of Z-Gly-Phe-OH during the coupling process. Compared with these results, we found that the present new protocol, which uses MNBA and a catalytic amount of DMAPO, is more suitable for the preparation of tripeptide **21** without increasing the loss of chirality (LOC = 0.4; Table 4, entry 3), as shown in the preceding experiments (see above).

Table 4. Synthesis of several peptides and their LOC values.

Entry	Acid	Amine	Product	Yield [%]	LOC[i] [%]
1[a]	Z-Gly-L-Phe-OH	H-L-Val-OMe·HCl	**21**	46[g]	14.6[j]
2[b]	Z-Gly-L-Phe-OH	H-L-Val-OMe·HCl	**21**	62[g]	3.0[j]
3[c]	Z-Gly-L-Phe-OH	H-L-Val-OMe·HCl	**21**	89[g]	0.4[j]
4[c]	Z-L-Phe-L-Val-OH	H-L-Ala-OMe·HCl	**22**	71[g]	5.0[j]
5[c]	Bz-L-Val-OH	H-L-Val-OMe·HCl	**23**	51[h]	< 0.1[k]
6[d]	Z-Gly-L-Phe-OH	H-L-Val-OMe·HCl	**21**	58[g]	0.8[j]
7[d]	Z-L-Phe-L-Val-OH	H-L-Ala-OMe·HCl	**22**	32[g]	9.3[j]
8[d]	Bz-L-Val-OH	H-L-Val-OMe·HCl	**23**	14[g]	12.0[k]
9[e]	Z-Gly-L-Phe-OH	H-L-Val-OMe·HCl	**21**	78[g]	< 0.1[j]
10[e]	Z-L-Phe-L-Val-OH	H-L-Ala-OMe·HCl	**22**	89[g]	< 0.1[j]
11[e]	Bz-L-Val-OH	H-L-Val-OMe·HCl	**23**	74[g]	22.4[k]
12[f]	Z-Gly-L-Phe-OH	H-L-Val-OMe·HCl	**21**	76[g]	96.0[j]

[a] DCC (1.1 equiv), Et_3N (1.1 equiv), CH_2Cl_2, 18 °C, 1 h. [b] TBTU (1.1 equiv), DIEA (2.0 equiv), *N*,*N*-dimethylformamide (DMF), −18 °C, 1 h. [c] MNBA (1.2 equiv), DMAPO (10 mol %), DIEA (3.4 equiv), CH_2Cl_2 −23 °C, 3 h. [d] MNBA (1.2 equiv), DMAP (10 mol %), DIEA (3.4 equiv), CH_2Cl_2, 0 °C, 1 h. [e] CDOP (1.8 equiv), CH_2Cl_2, −18 °C, 1 h. [f] DPC (1.1 equiv), DMAP (10 mol %), CH_2Cl_2, room temperature, 2.5 h; then Et_3N (1.1 equiv), −18 °C, 2 h. [g] Yield of isolated product. Acid (1.2 equiv) and amine (1.0 equiv) were used. [h] Yield of isolated product. Acid (2.0 equiv), amine (1.0 equiv), and DIEA (5.0 equiv) were used. [i] LOC = (diastereomeric excess of acid) − (diastereomeric excess of product). [j] Diastereomeric excess of product determined by HPLC analysis of **21** and **22**. [k] Diastereomeric excess of product determined by ^1H NMR spectroscopy of **23**.

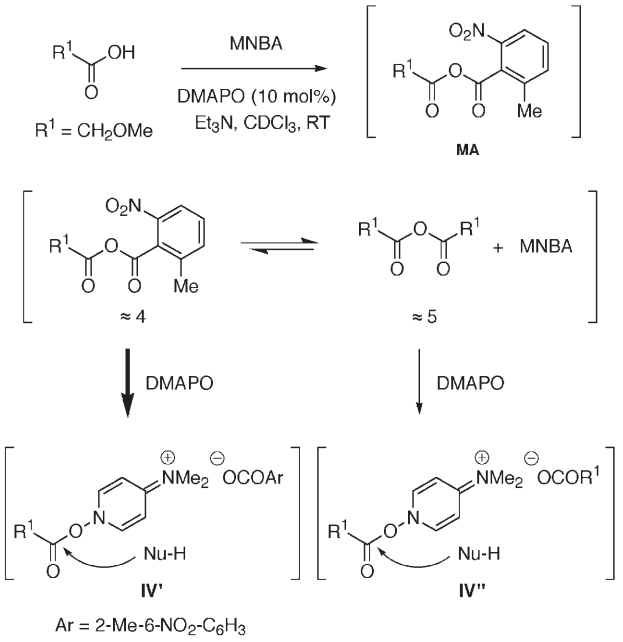
This reaction was next applied to the synthesis of Z-Phe-Val-Ala-OMe (**22**) from Z-Phe-Val-OH, with a hindered acid part, and H-Ala-OMe·HCl (Table 4, entry 4). It turned out that the desired L,L,L form of tripeptide **23** was preferentially obtained in good yield with only a slight loss of chirality. Finally, the reaction of Bz-Val-OH with H-Val-OMe·HCl, with MNBA in the presence of 10 mol % of DMAPO at −23 °C, was carried out as an additional assessment of the present peptide-coupling reaction under mild reaction conditions.[1g,11] ^1H NMR spectroscopic analysis of the crude product formed showed that the undesired D,L stereoisomer was not generated at all, and that only the desired L,L peptide **23**, which is quite bulky, was obtained (Table 4, entry 5).

We also applied the racemization test to other effective reagents that we developed for the formation of oligopeptides, and each LOC was determined, as shown in Table 4, entries 6–8 (MNBA/DMAP) and 9–11 (CDOP). When the recently established MNBA/DMAP combined method for the synthesis of the carboxamide was applied to the preparation of peptides **21**–**23**, we observed that the yields and purities of the coupling products apparently decreased to unacceptable levels (Table 4, entries 7 and 8), except for Table 4, entry 6.[5] On the other hand, the coupling between Z-Gly-Phe-OH and H-Val-OMe·HCl, or Z-Phe-Val-OH and H-Ala-OMe·HCl, accelerated by CDOP, efficiently produced the coupling products **21** and **22** in good yields with high optical purities (Table 4, entries 9 and 10); however, the reaction of Bz-Val-OH with H-Val-OMe·HCl promoted by CDOP produced a significant loss of chirality in product **23** (Table 4, entry 11).[7]

We initially reported an effective method for the synthesis of carboxamides or dipeptides in high yields from the corresponding carboxylic acids and amines or α-amino acids by the coupling reaction with di(2-pyridyl) carbonate (DPC) or its derivatives in the presence of a catalytic amount of DMAP.[12,13] It was revealed that the 2-pyridyl ester, a reactive acylating intermediate, was formed in situ from the carboxylic acids upon treatment with DPC by the catalysis of DMAP. However, these methods were not effective for preparing the tripeptide **21** derived from Z-Gly-Phe-OH and H-Val-OMe·HCl, as undesired racemization proceeded to form a mixture of nearly equal amounts of the L,L and D,L isomers (Table 4, entry 12). In this reaction, the pyridyl ester derived from Z-Gly-Phe-OH reacted with DMAP to form the more reactive intermediate **I** (Scheme 1), which caused racemization via the oxazolone intermediate.[6]

Notably, the segment-coupling reaction that uses the new combined system consisting of MNBA/DMAPO produces the corresponding peptides **21**–**23** in good yields with excellent optical purities by a very simple and facile procedure (Table 4, entries 3–5). This reaction takes place by the activation of the acid parts with DMAPO instead of DMAP; therefore, it is assumed that the generation of the pyridinium salt **I** to be formed in the DMAP-mediated coupling process is exclusively avoided.

The reaction pathway promoted by DMAPO was studied by ^{1}H NMR spectroscopy by using a mixture of stoichiometric amounts of carboxylic acid and MNBA (Scheme 5).



Scheme 5. Formation of the reactive intermediates of the present peptide-coupling reaction with MNBA and DMAPO.

When methoxyacetic acid was treated with MNBA and triethylamine in the presence of 10 mol% of DMAPO, we observed the formation of the mixed anhydride (**MA**) consisting of the methoxyacetic acid and 2-methyl-6-nitrobenzoic acid parts. The structure of **MA** was confirmed by comparison with the spectra of an authentic sample of **MA** independently generated from methoxyacetyl chloride with 2-methyl-6-nitrobenzoic acid in the presence of triethylamine. It was further found that there is an equilibrium between the mixed anhydride and methoxyacetic anhydride (≈4:5) determined from the ratio of the integrals of the ^{1}H NMR peaks at 4.32 and 4.19 ppm. Therefore, it is postulated that the activated intermediate **IV′** (or **IV″**) is formed by the reaction of the mixed anhydride or homogeneous methoxyacetic anhydride with DMAPO, and the successive rapid nucleophilic attack of amines on the pyridinium salt gives the desired peptides in high yields without racemization.

Conclusions

We have developed a new reaction that produces carboxamides and peptides in high yields by using MNBA and DMAPO in the presence of tertiary amines. This reaction proceeds rapidly through the formation of reactive acyloxypyridinium intermediates to produce the target compounds, and undesired racemization is effectively prevented during the peptide-segment-coupling process. Notably, the experimental procedure is quite simple, and nearly pure carboxamides and peptides are obtained by simply mixing the substrates, MNBA, and DMAPO, followed by the addition of a base. Further studies of the reaction with DMAPO and other applications of the present protocol for the synthesis of useful complex molecules are now in progress.

Experimental Section

General

All reactions were carried out under argon atmosphere in dried glassware. Dichloromethane was distilled from diphosphorus pentoxide then calcium hydride and dried over 4-Å molecular sieves. Thin-layer chromatography was performed on Wakogel B5F. All melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with tetramethylsilane (TMS) or chloroform (in [D]chloroform) as internal standard.

Starting Materials

All reagents were purchased from Tokyo Kasei Kogyo Co., Ltd., Kanto Chemical Co., Inc., Aldrich Chemical Co., Inc., or Bachem AG and used without further purification, unless otherwise noted. MNBA was purchased from Tokyo Kasei Kogyo Co., Ltd. (TCI, M1439) or synthesized from 2-methyl-6-nitrobenzoic acid.[3c]

Syntheses

DMAPO: Synthesized from DMAP according to the literature method with some modifications.[14] 3-Chloroperoxybenzoic acid (*m*-CPBA; 65%, 5.20 g, 19.6 mmol) was added to a solution of DMAP (2.00 g, 16.4 mmol) in dichloromethane (50 mL) at 0°C. After the reaction mixture was stirred for 3 h at room temperature, it was passed through a column of anion-exchange resin (DIAION-SA11A, Mitsubishi Chemical Co., Ltd.) with methanol, and the filtrate was concentrated by evaporation of the solvent to afford the crude product. The crude DMAPO in the residue was dissolved with ethyl acetate at reflux, and the mixture was filtered without cooling to remove the unreacted DMAP. The resulting solid was washed with hot ethyl acetate three times. After evaporation of the solvent, the crude product was recrystallized from acetone, and the precipitates were sublimed (190°C, 10 mmHg) to afford DMAPO as a white solid. It can be stored under argon atmosphere for several months.

Typical procedure for the amidation reaction: A typical experimental procedure is described for the reaction of 3-phenylpropanoic acid (**1**) with 3-phenylpropylamine (**3**). A solution of MNBA (82.4 mg, 0.239 mmol) and **1** (35.9 mg, 0.239 mmol) in dichloromethane (1.5 mL) was added to a solution of triethylamine (44.5 mg, 0.440 mmol) and DMAPO (2.7 mg, 0.020 mmol) in dichloromethane (0.5 mL) at room temperature. After the reaction mixture was stirred for 30 min at room temperature, a solution of **3** (26.7 mg, 0.198 mmol) in dichloromethane (0.5 mL) was added. The reaction mixture was stirred for 14 h at room temperature, and then saturated aqueous sodium hydrogencarbonate was added at 0°C. The mixture was extracted with dichloromethane, and the organic layer was washed with water and brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by preparative TLC on silica gel (hexane/

ethyl acetate = 1:1) to afford 3-phenyl-*N*-(3-phenylpropyl)propanamide (**7**; 42.4 mg, 81%) as a white solid.

7:[5] 3-Phenyl-*N*-(3-phenylpropyl)propanamide: M.p.: 57 °C; IR (KBr): $\tilde{\nu}$ = 3260, 1640, 1540 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.35–7.10 (m, 10H), 5.46 (br s, 1H), 3.15 (dt, J = 6.2, 7.0 Hz, 2H), 2.85 (t, J = 7.7 Hz, 2H), 2.48 (t, J = 7.7 Hz, 2H), 2.34 (t, J = 7.7 Hz, 2H), 1.67 ppm (tt, J = 7.7, 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 172.0, 141.3, 140.7, 128.4, 128.3, 128.2, 128.2, 126.1, 125.8, 39.0, 38.3, 33.1, 31.6, 30.9 ppm; HRMS: *m*/*z* calcd for $C_{18}H_{22}NO$: 268.1701 $[M+H]^+$; found: 268.1700.

8:[12] 3-Phenyl-*N*-[(1*S*)-1-phenylethyl]propanamide (98% *ee*): M.p.: 92 °C; $[\alpha]_D^{21} = -63.6$ (c = 1.03, EtOH); IR (KBr): $\tilde{\nu}$ = 3280, 1640, 1560 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.21–7.00 (m, 10H), 5.90 (br s, 1H), 4.97 (quint, J = 7.6 Hz, 1H), 2.83 (t, J = 7.3 Hz, 2H), 2.35 (t, J = 7.3 Hz, 2H), 1.28 ppm (d, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 171.1, 143.1, 140.7, 128.4, 128.4, 128.3, 127.1, 126.1, 126.0, 48.4, 38.4, 31.7, 21.5 ppm; HRMS: *m*/*z* calcd for $C_{17}H_{20}NO$: 254.1545 $[M+H]^+$; found: 254.1542.

9:[5] *N*-Benzyl-*N*-methyl-3-phenylpropanamide (mixture of two stereoisomers A and B): IR (neat): $\tilde{\nu}$ = 1640 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.33–7.06 (m, 10H, A+B), 4.59 (s, 2aH, A), 4.45 (s, 2bH, B), 3.05–2.96 (m, 2H, A+B), 2.70–2.64 (m, 2H, A+B), 2.94 (s, 3bH, B), 2.84 ppm (s, 3aH, A); ^{13}C NMR ($CDCl_3$) δ = 172.5 (B), 172.2 (A), 141.3, 141.2, 137.3, 136.4, 128.8, 128.8, 128.5, 128.4, 127.9, 127.9, 127.5, 127.5, 127.2, 127.2, 126.1, 126.0, 53.1 (B), 50.8 (A), 35.3 (A), 34.9 (B), 34.7 (A), 33.9 (B), 31.5 (B), 31.3 ppm (A); HRMS: *m*/*z* calcd for $C_{17}H_{20}NO$: 254.1545 $[M+H^+]$; found: 254.1541.

10:[5] (3-Phenylpropanoylpiperidine): IR (neat): $\tilde{\nu}$ = 1640 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.24–7.11 (m, 5H), 3.55 (br t, J = 5.3 Hz, 2H), 3.32 (br t, J = 5.3 Hz, 2H), 2.96 (t, J = 8.0 Hz, 2H), 2.61 (t, J = 8.0 Hz, 2H), 1.65–1.45 ppm (br m, 6H); ^{13}C NMR ($CDCl_3$): δ = 170.2, 141.4, 128.3, 128.3, 125.9, 46.5, 42.6, 35.0, 31.5, 26.3, 25.4, 24.4 ppm.

11:[12] 2-Phenyl-*N*-(3-phenylpropyl)propanamide: M.p.: 93 °C; IR (KBr): $\tilde{\nu}$ = 3250, 1640, 1560 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.34–7.05 (m, 10H), 5.44 (br s, 1H), 3.50 (q, J = 7.3 Hz, 1H), 3.24–3.15 (m, 2H), 2.51 (br t, 2H), 1.76–1.69 (m, 2H), 1.50 ppm (d, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 174.1, 141.4, 141.3, 128.8, 128.3, 128.2, 127.5, 127.2, 125.9, 47.0, 39.1, 33.0, 31.0, 18.4 ppm. HRMS: *m*/*z* calcd for $C_{18}H_{21}NONa$: 290.1521 $[M+Na]^+$; found: 290.1495.

12a:[12] (2*R*,*S*)-2-Phenyl-*N*-[(1*S*,*R*)-1-phenylethyl]propanamide: M.p.: 127 °C; IR (KBr): $\tilde{\nu}$ = 3350, 1640, 1540 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.37–7.19 (m, 10H), 5.56 (br d, 1H), 5.09 (quint, J = 6.9 Hz, 1H), 3.53 (q, J = 7.1 Hz, 1H), 1.51 (d, J = 7.1 Hz, 3H), 1.34 ppm (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 173.2, 143.2, 141.4, 128.9, 128.6, 127.6, 127.2, 127.2, 126.0, 48.7, 47.1, 21.5, 18.6 ppm; HRMS: *m*/*z* calcd for $C_{17}H_{19}NONa$: 276.1365 $[M+Na]^+$; found: 276.1374.

12b:[12] (2*R*,*S*)-2-Phenyl-*N*-[(1*R*,*S*)-1-phenylethyl]propanamide: M.p.: 127 °C; IR (KBr): $\tilde{\nu}$ = 3240, 1640, 1540 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.34–7.17 (m, 8H), 7.08 (dd, J = 7.7, 1.2 Hz, 2H), 5.59 (d, J = 7.1 Hz, 1H), 5.08 (quint, J = 7.1 Hz, 1H), 3.57 (q, J = 7.3 Hz, 1H), 1.51 (d, J = 7.3 Hz, 3H), 1.39 ppm (d, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 173.1, 143.2, 141.3, 128.8, 128.5, 127.6, 127.2, 127.1, 125.7, 48.6, 47.1, 21.9, 18.4 ppm; HRMS: *m*/*z* calcd for $C_{17}H_{19}NONa$: 276.1365 $[M+Na]^+$; found: 276.1320.

13:[12] *N*-Benzyl-*N*-methyl-2-phenylpropanamide (mixture of two stereoisomers A and B): IR (neat): $\tilde{\nu}$ = 1640 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.31–7.15 (m, 8H, A+B), 7.01 (d, J = 7.3 Hz, 2H, A+B), 4.66 (d, J = 14.6 Hz, 1aH, A), 4.65 (d, J = 16.7 Hz, 1bH, B), 4.54 (d, J = 14.6 Hz, 1aH, A), 4.24 (d, J = 16.7 Hz, 1bH, B), 3.92 (q, J = 6.8 Hz, 1aH, A), 3.87 (q, J = 6.8 Hz, 1bH, B), 2.93 (s, 3bH, B), 2.79 (s, 3aH, A), 1.49 (d, J = 6.8 Hz, 3aH, A), 1.46 ppm (d, J = 6.8 Hz, 3bH, B); ^{13}C NMR ($CDCl_3$) δ = 174.1 (B), 173.7 (A), 141.9, 141.7, 137.4, 136.6, 128.8, 128.8, 128.8, 128.4, 127.8, 127.4, 127.3, 127.2, 127.1, 126.8, 126.7, 126.2, 52.9 (B), 51.1 (A), 43.4 (A), 43.1 (B), 34.7 (A), 34.2 (B), 20.9 (B), 20.8 ppm (A); HRMS: *m*/*z* calcd for $C_{17}H_{19}NONa$: 276.1365 $[M+Na]^+$; found: 276.1349.

14:[12] 2-Phenylpropanoylpiperidine: IR (neat): $\tilde{\nu}$ = 1640 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.33–7.19 (m, 5H), 3.88 (q, J = 6.8 Hz, 1H), 3.70–3.35 (br m, 4H), 1.52–1.37 (m, 6H), 1.44 ppm (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 171.7, 142.4, 128.8, 127.2, 126.6, 43.2, 43.2, 25.7, 24.5, 20.8 ppm. HRMS: *m*/*z* calcd for $C_{14}H_{19}NONa$: 240.1365 $[M+Na]^+$; found: 240.1377.

Typical procedure for the coupling to produce dipeptides: A typical experimental procedure is described for the synthesis of Z-Ala-Gly-OEt. DMAPO (2.8 mg, 0.020 mmol), H-Gly-OEt·HCl (28.5 mg, 0.204 mmol), and a solution of triethylamine (69.6 mg, 0.688 mmol) in dichloromethane (1.0 mL) were successively added to a solution of MNBA (82.8 mg, 0.240 mmol) and Z-Ala-OH (53.9 mg, 0.242 mmol) in dichloromethane (1.5 mL) at 0 °C. The reaction mixture was stirred for 9 h at 0 °C, and then iced brine was added. The mixture was extracted with dichloromethane, and the organic layer was washed with 1 M hydrochloric acid, water, and brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by preparative TLC on silica gel (hexane/ethyl acetate = 1:3) to afford Z-Ala-Gly-OEt (**15**; 39.3 mg, 62%) as a white solid.

15:[12,15] Z-L-Ala-Gly-OEt: HPLC (CHIRALCEL OD-H, hexane/*i*PrOH = 9:1, flow rate = 0.5 mL min^{-1}, detect 254 nm), t_R = 28.7 (L), 36.2 min (D); ^1H NMR ($CDCl_3$): δ = 7.39–7.28 (m, 5H, Ph), 6.65 (br s, 1H, 2-NH), 5.40 (br d, J = 7.4 Hz, 1H, 2′-NH), 5.06 (d, J = 12.3 Hz, 1H, Bn), 5.00 (d, J = 12.3 Hz, 1H, Bn), 4.24 (br dq, J = 7.4, 6.9 Hz, 1H, 2′-H), 4.12 (q, J = 7.1 Hz, 2H, EtO), 3.92 (br d, J = 5.3 Hz, 2H, 2-H), 1.32 (d, J = 6.9 Hz, 3H, 3′-H), 1.19 ppm (t, J = 7.1 Hz, 3H, EtO); ^{13}C NMR ($CDCl_3$): δ = 172.6 (C1′), 169.6 (C1), 155.9 (Z-C), 136.1 (Ph), 128.5 (Ph), 128.1 (Ph), 128.0 (Ph), 67.0 (Bn), 61.5 (EtO), 50.4 (C2′), 41.2 (C2), 18.5 (C3′), 14.0 ppm (EtO).

16:[12,16] Z-L-Phe-Gly-OEt: ^1H NMR ($CDCl_3$): δ = 7.39–7.21 (m, 10H, Ph), 6.61 (br s, 1H, 2-NH), 5.55 (br d, J = 7.8 Hz, 1H, 2′-NH), 5.11 (d, J = 12.4 Hz, 1H, Bn), 5.06 (d, J = 12.4 Hz, 1H, Bn), 4.55 (br ddd, J = 7.8, 6.8, 6.6 Hz, 1H, 2′-H), 4.20 (q, J = 7.1 Hz, 2H, EtO), 4.03 (dd, J = 18.1, 5.4 Hz, 1H, 2-H), 3.92 (dd, J = 18.1, 4.8 Hz, 1H, 2-H), 3.16 (dd, J = 13.9, 6.6 Hz, 1H, 3′-H), 3.08 (dd, J = 13.9, 6.8 Hz, 1H, 3′-H), 1.29 ppm (t, J = 7.1 Hz, 3H, EtO); ^{13}C NMR ($CDCl_3$): δ = 171.2 (C1′), 169.4 (C1), 156.0 (Z-C), 136.3 (Ph), 136.0 (Ph), 129.2 (Ph), 128.6 (Ph), 128.5 (Ph), 128.1 (Ph), 127.9 (Ph), 127.0 (Ph), 67.0 (Bn), 61.5 (EtO), 56.0 (C2′), 41.2 (C2), 38.3 (C3′), 14.0 ppm (EtO).

17:[12,17] Z-L-Val-Gly-OEt: ^1H NMR ($CDCl_3$): δ = 7.41–7.28 (m, 5H, Ph), 6.63 (br dd, J = 5.4, 5.0 Hz, 1H, 2-NH), 5.47 (br d, J = 8.8 Hz, 1H, 2′-NH), 5.11 (d, J = 12.2 Hz, 1H, Bn), 5.07 (d, J = 12.2 Hz, 1H, Bn), 4.19 (q, J = 7.2 Hz, 2H, EtO), 4.09 (dd, J = 8.8, 6.6 Hz, 1H, 2′-H), 4.07 (dd, J = 18.2, 5.4 Hz, 1H, 2-H), 3.96 (dd, J = 18.2, 5.0 Hz, 1H, 2-H), 2.15 (qqd, J = 6.8, 6.8, 6.6 Hz, 1H, 3′-H), 1.27 (t, J = 7.2 Hz, 3H, EtO), 0.98 (d, J = 6.8 Hz, 3H, 4′-H), 0.93 ppm (d, J = 6.8 Hz, 3H, 4′-H); ^{13}C NMR ($CDCl_3$): δ = 171.7 (C1′), 169.6 (C1), 156.4 (Z-C), 136.1 (Ph), 128.4 (Ph), 128.1 (Ph), 127.9 (Ph), 66.9 (Bn), 61.4 (EtO), 60.2 (C2′), 41.2 (C2), 31.0 (C3′), 19.1 (C4′), 17.7 (C4′), 14.0 ppm (EtO).

18:[12,18] Z-L-Leu-Gly-OEt: ^1H NMR ($CDCl_3$): δ = 7.38–7.29 (m, 5H, Ph), 6.54 (br s, 1H, 2-NH), 5.17 (br d, J = 8.3 Hz, 1H, 2′-NH), 5.13 (d, J = 12.2 Hz, 1H, Bn), 5.09 (d, J = 12.2 Hz, 1H, Bn), 4.25–4.20 (m, 1H, 2′-H), 4.21 (q, J = 7.2 Hz, 2H, EtO), 4.04 (dd, J = 18.1, 4.4 Hz, 1H, 2-H), 3.99 (dd, J = 18.1, 4.9 Hz, 1H, 2-H), 1.73–1.63 (m, 1H, 4′-H), 1.69 (ddd, J = 16.2, 7.4, 7.0 Hz, 1H, 3′-H), 1.52 (ddd, J = 16.2, 9.2, 8.9 Hz, 1H, 3′-H), 1.28 (t, J = 7.2 Hz, 3H, EtO), 0.94 ppm (d, J = 6.1 Hz, 6H, 5′-H, 5′-H); ^{13}C NMR ($CDCl_3$): δ = 172.3 (C1′), 169.6 (C1), 156.2 (Z-C), 136.0 (Ph), 128.6 (Ph), 128.2 (Ph), 128.1 (Ph), 67.2 (Bn), 61.6 (EtO), 53.4 (C2′), 41.3 (C2), 41.3 (C3′), 24.6 (C4′), 22.9 (C5′), 21.9 (C5′), 14.1 ppm (EtO).

19:[12,19] Z-L-Met-Gly-OEt: ^1H NMR ($CDCl_3$): δ = 7.36–7.28 (m, 5H, Ph), 6.84 (br s, 1H, 2-NH), 5.70 (br d, J = 6.4 Hz, 1H, 2′-NH), 5.12 (d, J = 12.2 Hz, 1H, Bn), 5.08 (d, J = 12.2 Hz, 1H, Bn), 4.44 (br td, J = 6.7, 6.4 Hz, 1H, 2′-H), 4.19 (q, J = 7.2 Hz, 2H, EtO), 4.05 (dd, J = 18.0, 4.0 Hz, 1H, 2-H), 3.95 (dd, J = 18.0, 4.9 Hz, 1H, 2-H), 2.58 (t, J = 7.0 Hz, 2H, 4′-H), 2.11 (ddt, J = 14.1, 7.0, 6.7 Hz, 1H, 3′-H), 2.09 (s, 3H, MeS), 1.98 (ddt, J = 14.1, 7.0, 6.7 Hz, 1H, 3′-H), 1.26 ppm (t, J = 7.2 Hz, 3H, EtO); ^{13}C NMR ($CDCl_3$): δ = 171.5 (C1′), 169.5 (C1), 156.2 (Z-C), 136.1 (Ph), 128.5 (Ph), 128.2 (Ph), 128.0 (Ph), 67.1 (Bn), 61.5 (EtO), 53.7 (C2′), 41.3 (C2), 31.6 (C3′), 29.9 (C4′), 15.1 (MeS), 14.1 ppm (EtO).

20:[12,20] Z-L-Pro-Gly-OEt: ^1H NMR ($CDCl_3$): δ = 7.44–7.22 (m, 5H, Ph), 7.09 (br s, 1H, 2-NH in one of rotamers), 6.48 (br s, 1H, 2-NH in one of rotamers), 5.12 (d, J = 12.4 Hz, 1H, Bn), 5.04 (d, J = 12.4 Hz, 1H, Bn),

4.40–4.20 (br m, 1H, 2′-H), 4.10 (q, J=7.1 Hz, 2H, EtO), 4.06–3.42 (br m, 4H, 2-H, 5′-H), 2.36–1.85 (m, 4H, 3′-H, 4′-H), 1.27 ppm (t, J=7.1 Hz, 3H, EtO); ^{13}C NMR ($CDCl_3$): δ=171.9 (C1′), 169.5 (C1), 155.9 (Z-C), 136.3 (Ph), 128.3 (Ph), 127.9 (Ph), 127.8 (Ph), 67.1 (Bn), 61.2 (EtO), 60.4 (C2′), 46.9 (C2), 41.2 (C5′), 28.5 (C3′), 24.3 (C4′), 14.0 ppm (EtO).

Typical procedure for the segment coupling to produce tripeptides: A typical experimental procedure is described for the synthesis of Z-Gly-Phe-Val-OMe. Z-Gly-Phe-OH[21] (86.4 mg, 0.242 mmol), DMAPO (2.8 mg, 0.020 mmol), H-Val-OMe·HCl (34.2 mg, 0.204 mmol), and a solution of diisopropylethylamine (88.7 mg, 0.686 mmol) in dichloromethane (1.0 mL) were successively added to a solution of MNBA (82.7 mg, 0.240 mmol) in dichloromethane (1.5 mL) at −23 °C. The reaction mixture was stirred for 3 h at −23 °C, and then iced brine was added. The mixture was extracted with dichloromethane, and the organic layer was washed with 1 M hydrochloric acid, water, and brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by preparative TLC on silica gel (dichloromethane/methanol=10:1) to afford Z-Gly-Phe-Val-OMe (**21**; 85.3 mg, 89 %) as a white solid.

21:[1f,h,j–m,10] Z-Gly-L-Phe-L-Val-OMe: HPLC (Kromasil KR 100–10 C18 (4.6 mm×25 cm), CH_3CN/H_2O=40:60, flow rate=0.75 mL min^{-1}, detect 220 nm): t_R=25.5 (L,L), 28.7 min (D,L); ^{1}H NMR ($CDCl_3$): δ=7.29–7.08 (m, 10H, Ph), 6.97 (br d, J=7.6 Hz, 1H, 2′-NH), 6.61 (br d, J=8.4 Hz, 1H, 2-NH), 5.63 (br t, J=5.6 Hz, 1H, 2″-NH), 5.03 (s, 2H, Bn), 4.68 (br dt, J=7.6, 6.8 Hz, 1H, 2′-H), 4.35 (dd, J=8.4, 5.2 Hz, 1H, 2-H), 3.78 (br s, 2H, 2″-H), 3.59 (s, 3H, MeO), 2.97 (br d, J=6.8 Hz, 2H, 3′-H), 1.99 (dqq, J=5.2, 6.8, 6.8 Hz, 1H, 3-H), 0.77 (d, J=6.8 Hz, 3H, 4-H), 0.74 ppm (d, J=6.8 Hz, 3H, 4-H).

22:[22] Z-L-Phe-L-Val-L-Ala-OMe: HPLC (Cosmosil 5C18 (4.6 mm i.d. ×150 mm), MeOH/H_2O=60:40, flow rate=1.0 mL min^{-1}, detect 254 nm): t_R=29.2 (L,L,L), 34.5 min (L,D,L); ^{1}H NMR ($CDCl_3$): δ=7.37–7.15 (m, 10H), 6.43 (br d, J=7.9 Hz, 1H, 2′-NH), 6.38 (br d, J=7.0 Hz, 1H, 2-NH), 5.29 (br t, J=7.5 Hz, 1H, 2″-NH), 5.11 (d, J=12.0 Hz, 1H, Bn), 5.06 (d, J=12.0 Hz, 1H, Bn), 4.52 (dq, J=7.0, 7.2 Hz, 1H, 2-H), 4.44 (br dt, J=7.5, 6.8 Hz, 1H, 2″-H), 4.17 (dd, J=7.9, 6.0 Hz, 1H, 2′-H), 3.75 (s, 3H, MeO), 3.10 (d, J=6.8 Hz, 2H, 3″-H), 2.16–2.02 (m, 1H, 3′-H), 1.40 (d, J=7.2 Hz, 3H, 3-H), 0.88 (d, J=6.8 Hz, 3H, 4′-H), 0.83 ppm (d, J=6.8 Hz, 3H, 4′-H).

23:[23] Bz-L-Val-L-Val-OMe: L,L form of **23**: ^{1}H NMR ($CDCl_3$) δ=7.85–7.76 (m, 2H, Ph), 7.55–7.40 (m, 3H, Ph), 6.90–6.77 (m, 1H, 2-NH), 6.46 (d, J=8.4 Hz, 1H, 2′-NH), 4.58–4.50 (m, 2H, 2-H, 2′-H), 3.76 (s, 3H, MeO), 2.30–2.13 (m, 2H, 3-H, 3′-H), 1.04 (d, J=6.8 Hz, 3H, 4′-H), 1.03 (d, J=6.8 Hz, 3H, 4′-H), 0.91 (d, J=6.8 Hz, 3H, 4-H), 0.89 (d, J=6.8 Hz, 3H, 4-H). D,L form of **23**: ^{1}H NMR ($CDCl_3$): δ=7.80–7.76 (m, 2H, Ph), 7.55–7.38 (m, 3H, Ph), 6.88–6.83 (m, 1H, 2-NH), 6.61 (d, J=8.0 Hz, 1H, 2′-NH), 4.63–4.57 (m, 2H, 2-H, 2′-H), 3.70 (s, 3H, MeO), 2.30–2.12 (m, 2H, 3-H, 3′-H), 1.04 (d, J=7.2 Hz, 3H, 4′-H), 1.03 (d, J=7.2 Hz, 3H, 4′-H), 0.98 (d, J=7.2 Hz, 3H, 4-H), 0.94 ppm (d, J=7.2 Hz, 3H, 4-H).

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