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Regio- and stereoselective α-alkylation of N-terminal amino acid residue of peptides using a pyridoxal model compound with a chiral ansa-structure

Kazuyuki Miyashita, Hiroshi Iwaki, Kuninori Tai, Hidenobu Murafuji, Naoko Sasaki and Takeshi Imanishi*

Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka 565-0871, Japan

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Abstract—Regio- and stereoselective α-alkylation of N-terminal amino acid residue of peptides was achieved by Li^+-mediated alkylation of aldimines prepared from the peptides and a pyridoxal model compound having a chiral ansa-structure and an ethoxyethoxy group at C-3. The stereochemistry and stereoselectivity of the reaction were found to be influenced predominantly by the chirality of the model compound and Li^+, but little by the stereochemistry of the original peptides. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Peptides containing unnatural amino acid(s) have been receiving a great deal of attention because of their biochemical and medicinal properties. Such peptides are generally synthesized by sequential coupling of the respective amino acids prepared independently. As a consequence, much effort has been paid to the synthesis of unnatural amino acids.[1] In contrast, direct modification of peptides would be another choice and, in fact, several methods for this purpose have been reported.[2,3] However, most of these methods deal with the alkylation of peptides at sites other than the N-terminal position and, consequently, seem to lack generality. As both liquid- and solid-phase peptide

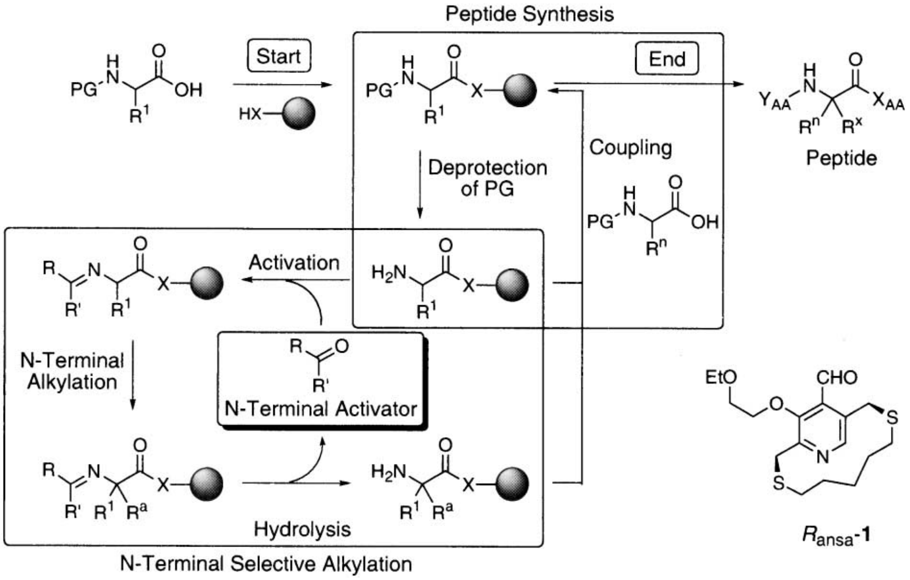

Figure 1. Unnatural peptide synthesis and structure of pyridoxal derivative R_{ansa}-**1**.

Keywords: peptide; alkylation; cyclophanes.

* Corresponding author. Tel.: +81-6-6879-8200; fax: +81-6-6879-8204; e-mail: imanishi@phs.osaka-u.ac.jp

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syntheses are generally achieved by sequential coupling from a C-terminal amino acid, N-terminal selective modification appears to be more useful, particularly when applied to construction of an unnatural peptide library in the field of combinatorial chemistry, because it is not necessary to synthesize the individual unnatural amino acids (Fig. 1). O'Donnell and coworkers reported an interesting method utilizing this idea: direct regioselective α-alkylation of peptides at the N-terminal position via imine formation, which appears to be very significant because this modification cycle was shown to be incorporated into general peptide synthesis.[3] The only problem with their method is the lack of stereoselectivity, because they use benzophenone as an N-terminal activator without any chiral elements excepting a substrate, peptide. If the α-alkylation takes place with predictable stereoselectivity, this method would be more useful and versatile. In previous papers, we reported asymmetric α-alkylation of α-amino esters using pyridoxal derivatives which have a chiral ionophore function and/or a chiral ansa-structure.[4] In this paper, we describe stereoselective and N-terminal selective α-alkylation of peptides employing our pyridoxal derivative R_{ansa}-**1**.[5]

2. Results and discussion

Taking account of application of the N-terminal selective alkylation not only to liquid-phase synthesis but also to solid-phase synthesis, we first examined the reaction conditions by employing L-Ala-NHBn **2a** in the presence of 3 equiv. of $LiClO_4$ and an organic base. The reaction with triethylamine, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, 4-dimethylaminopyridine or proton sponge did not proceed. Eventually, it was found that the reaction took place when DBU was employed (Table 1, run 1). The reaction rate of **2a** was, as expected, slower than that of the corresponding ester **2b** (run 1 vs. run 2). Interestingly, the stereoselectivity was found to depend on Li^+: *R*-stereoselectivity was obtained in the presence of Li^+ while *S*-stereoselectivity was obtained in the absence of Li^+ (run 3).[6] The stereoselectivity was determined by the ^1H NMR spectrum of the corresponding MTPA amide **5a** and the stereochemistry was assigned as shown by comparison of the ^1H NMR spectra with those of the corresponding ester **5b** (Table 2) (Scheme 1).[4]

Table 1. Alkylation of α-amino ester and amide

Run	2	X	M^+	Time (h)	Product **4**	
					Yield (%)	*R*/*S*
1	**a**	NH	$LiClO_4$	2	60	83:17
2	**b**	O	$LiClO_4$	1	72	87:13
3	**c**	NH	None	4.5	51	27:73

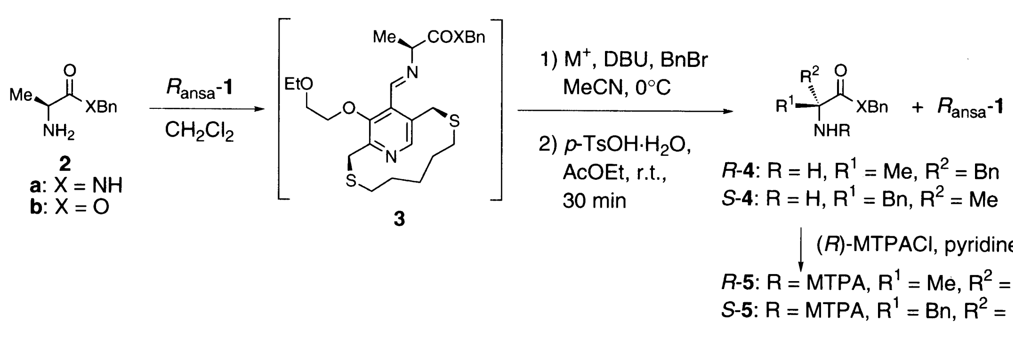
Encouraged by these findings, we studied the benzylation of dipeptides and a tripeptide **6** made from neutral amino acids under the conditions described above and the results are summarized in Table 3. The reactions, as expected, proceeded at the α-position of the N-terminal amino acid, regioselectively. Although stereoselectivities observed in these reactions with or without Li^+ were basically the same as that of the reaction of L-Ala-NHBn **2a**, the following were observed in the presence of Li^+. Changing the stereochemistry of the C-terminal amino acid from L- to D-configuration slightly lowered the stereoselectivity (run 1 vs. 2 and run 4 vs. 5), but did not reverse the stereoselectivity. It is also noted that the stereoselectivity of the reaction with L-Ala-Gly-NHBn **6b** is in the range of those with L- and D-amino acids at the C-terminal position (run 3). However, it is obvious that the bulkiness of the substituent at the C-terminal amino acid is not related to the stereoselectivity (run 1 vs. 4 and run 2 vs. 5). The reaction of the tripeptide **6d** also successfully took place with similar stereoselectivity.

In contrast, stereoselectivities of the reactions in the absence of Li^+ were somewhat lower than those in the presence of Li^+ and were completely reversed as expected. The tendency of the stereoselectivity such as observed in the presence of Li^+ was not observed (runs 7–12), which could be attributable to the fact that the conformation in the absence of Li^+ is not so tightly restricted as that in the presence of Li^+.

Table 2. Chemical shifts (ppm) for α-CH_3 (δ_H) and CF_3 (δ_F) groups of **5a**,**b** and **15a**,**b**

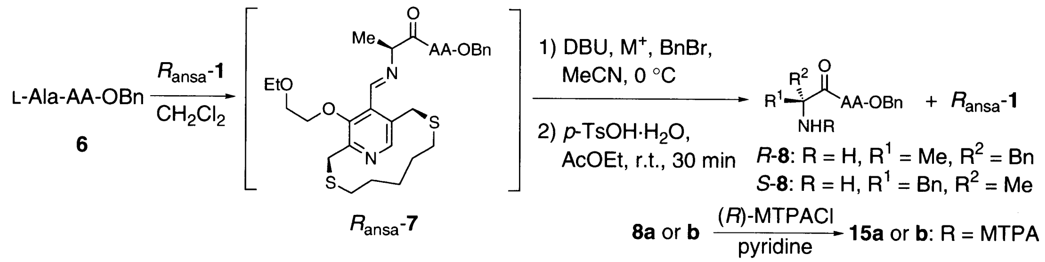
	5a	5b	15a	15b
α-CH_3	1.66 (1.72)	1.67 (1.68)	1.62 (1.67)	1.68 (1.70)
CF_3	−69.4 (−69.8)	−69.5 (−69.7)	−69.5 (−69.8)	−69.5 (−69.7)

Values in the parentheses are for *S*-isomers.



Scheme 1.

Table 3. Benzylation of peptides **6** in the presence and absence of Li^+



Run	Peptide **6**	AA	M^+	Time (h)	Benzylated peptide **8**	
					Yield (%)[a]	*R*/*S*
1	**a**	L-Ala	$LiClO_4$	4	51	86:14
2	**a′**	D-Ala	$LiClO_4$	4	49	74:26
3	**b**	Gly	$LiClO_4$	4	46	83:17
4	**c**	L-Val	$LiClO_4$	4.5	50	88:12
5	**c′**	D-Val	$LiClO_4$	5	51	73:27
6	**d**	L-Ala-L-Ala	$LiClO_4$	5	48	86:14
7	**a**	L-Ala	None	6	38	24:76
8	**a′**	D-Ala	None	7	38	21:79
9	**b**	Gly	None	7	36	33:67
10	**c**	L-Val	None	7	37	20:80
11	**c′**	D-Val	None	8	38	35:65
12	**d**	L-Ala-L-Ala	None	8	37	23:77

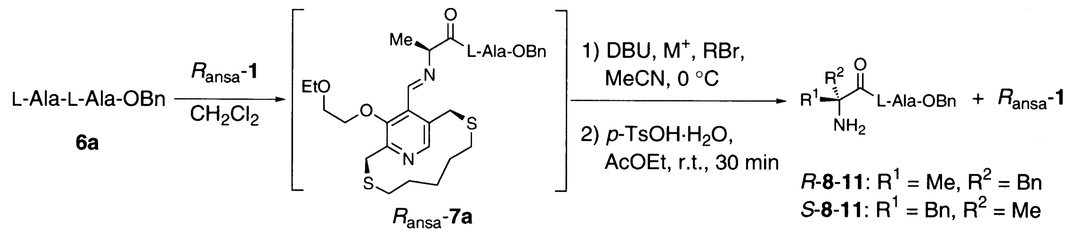
[a] Isolated yield based on the peptides **6**.

Although slight differences in stereoselectivity between the peptides examined were observed in the reactions with or without Li^+ as described above, these findings totally show that the stereochemistry and the size of the substituent at the C-terminal amino acid do not significantly affect the stereoselectivity of the alkylation. In other words, the stereoselectivity of the alkylation predominantly depends on the chirality of the pyridoxal derivative R_{ansa}-**1** and the reaction condition whether Li^+ is employed or not.

Alkylation of **6a** with other alkyl bromides also took place under the same conditions as shown in Table 4, giving alkylated dipeptides **8a** and **9–11** with similar stereoselectivity. Reactions with allyl bromide in the presence and absence of Li^+ afforded a somewhat lower stereoselectivity than those with other alkyl bromides, which could be attributable to the S_N2' character of the allylating agent.

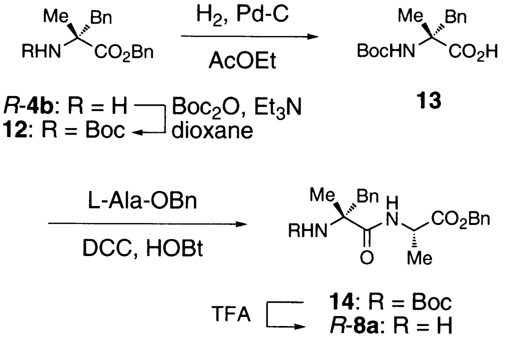
The reaction product *R*-**8a**, which was shown to be a mixture of two diastereomers (*R*/*S*=86:14), was treated with (*R*)-MTPACl to give the MTPA amide **15a**, which was also shown to be a mixture of only two diastereomers in the same ratio by its ^1H- and ^{19}F NMR data.[7] This result shows that isomerization at the α-position of the C-terminal amino ester does not proceed under the conditions of the α-alkylation. The stereochemistry of the alkylated peptide **8a** was established by a sequential peptide coupling method, as shown in Scheme 2, from optically active amino ester

Table 4. Alkylation of **6a** in the presence and absence of Li^+



Run	R	M^+	Time (h)	Alkylated peptide		
				Product	Yield (%)[a]	*R*/*S*
1	Bn–	$LiClO_4$	4	**8a**	51	86:14
2	4-$O_2NC_6H_4CH_2$–	$LiClO_4$	4	**9**	50	85:15
3	$HC{\equiv}CCH_2$–	$LiClO_4$	4.5	**10**	56	84:16
4	$H_2C{=}CHCH_2$–	$LiClO_4$	4.5	**11**	48	73:24
5	Bn–	None	7	**8a**	38	24:76
6	4-$O_2NC_6H_4CH_2$–	None	7	**9**	39	24:76
7	$HC{\equiv}CCH_2$	None	6	**10**	46	26:74
8	$H_2C{=}CHCH_2$–	None	6	**11**	42	31:69

[a] Isolated yield based on the peptide, L-Ala-L-Ala-OBn **6a**.



Scheme 2.

R-**4a** prepared according to our previous paper.[4] The stereochemistries of the other alkylated peptides **8c–d** and **9–11** were assigned by comparison of the ^{1}H NMR data with those of *R*- and *S*-**8a**: the chemical shifts for the N-terminal α-methyl hydrogens of the major isomers (*R*-isomers) obtained in the presence of Li^+ always appeared at slightly lower field than those of minor isomers (*S*-isomers) (see Section 3). The stereochemistry of **8b** was tentatively assigned as shown by comparison of the ^{1}H- and ^{19}F NMR spectra of its MTPA amide **15b** with those of **5a** and **b** (see Table 2 in Section 2).

We studied the conformation of the aldimine R_{ansa}-**7a** in the absence and presence of Li^+ to clarify the reaction mechanism. In a previous paper dealing with the α-alkylation of α-amino esters, we found that the conformation of the imino ester moiety is restricted in the direction of the C-5 position in the absence of Li^+ to avoid steric repulsion between the imino ester moiety and the ethoxyethoxy group at C-3, while the addition of Li^+ induces rotation of the C-4–C-4′ bond to the direction of the C-3 position to capture Li^+ between the imino ester moiety and the ethoxyethoxy group.[8] ^{1}H NMR study of R_{ansa}-**7a** in the absence and presence of Li^+ revealed that this phenomenon takes place in the case of peptide-aldimine as well (Fig. 2 and Table 5), and the C-terminal Ala moiety was shown to be positioned apart from the reaction center.

From the result mentioned above, the stereochemical outcome observed in the alkylation of the peptides appears to be attributable to this conformational change induced by Li^+. Taking account of this conformational behavior and the stereoselectivities observed in the absence and the presence of Li^+, it is obvious that the alkylating agent approaches from the same side of the ansa-chain in both cases with and without Li^+. The stereoselectivity observed in the presence of Li^+ would be explained by a similar transition state **B** to that of α-alkylation of α-amino ester, which we proposed in a previous paper: the ansa-chain works as a steric barrier to

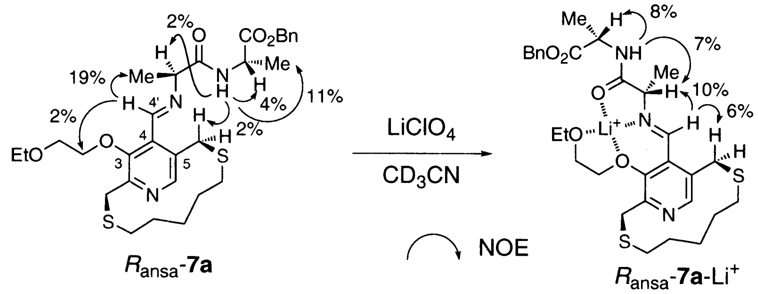


Figure 2. Selected NOE data for R_{ansa}-**7a** and R_{ansa}-**7a**-Li^+ and conformational change induced by Li^+.

Table 5. ^{1}H NMR data for R_{ansa}-**7a** and R_{ansa}-**7a**-Li^+ measured in CD_3CN

	R_{ansa}-**7a**	R_{ansa}-**7a**-Li^+
2-CH_2S-	3.59, 4.32 (each 1H, d, *J*=13.0 Hz)	3.67, 4.67 (each 1H, d, *J*=13.0 Hz)
4-C*H*=N-	8.85 (s)	8.76 (s)
5-CH_2S–	3.67, 4.67 (each 1H, d, *J*=13.0 Hz)	3.76, 4.34 (each 1H, d, *J*=13.0 Hz)
3-side chain H		
Me$CH_2O(CH_2)_2O$–	1.16 (t, *J*=7.0 Hz)	1.24 (t, *J*=7.0 Hz)
MeCH_2O$(CH_2)_2$O–	3.52 (q, *J*=7.0 Hz)	3.65 (q, *J*=7.0 Hz)
EtOCH_2CH$_2$O-	3.68 (m)	3.67, 3.85 (each 1H, m)
EtOCH$_2$CH_2O–	4.04 (m)	3.97, 4.05 (each 1H, m)
Ansa-chain H		
–SCH_2-$(CH_2)_3$-CH_2S–	2.09–2.18, 2.32–2.250 (each 2H, m)	1.90–2.08, 2.45–2.56 (each 2H, m)
–SCH$_2$-(CH_2)$_3$-CH$_2$S–	0.38 (1H, m), 0.66–0.92 (5H, m)	0.39 (1H, m), 0.61–0.89 (4H, m), 0.96 (1H, m)
N-terminal Ala		
α-*Me*	1.41 (d, *J*=7.0 Hz)	1.47 (d, *J*=7.0 Hz)
α-*H*	4.01 (q, *J*=7.0 Hz)	4.29 (q, *J*=7.0 Hz)
C-terminal Ala		
Amide N*H*	7.44 (br d, *J*=7.5 Hz)	7.70 (br d, *J*=7.5 Hz)
α-*Me*	1.40 (d, *J*=7.5 Hz)	1.44 (d, *J*=7.5 Hz)
α-*H*	4.51 (qn, *J*=7.5 Hz)	4.54 (qn, *J*=7.5 Hz)
COOCH_2Ph	5.06–5.13 (AB type)	5.12–5.18 (AB type)
COOCH$_2$*Ph*	7.30–7.37 (m)	7.34–7.40 (m)

Concentration: 0.1 M R_{ansa}-**7a** in CD_3CN; 0.1 M R_{ansa}-**7a** and 0.5 M $LiClO_4$ in CD_3CN.

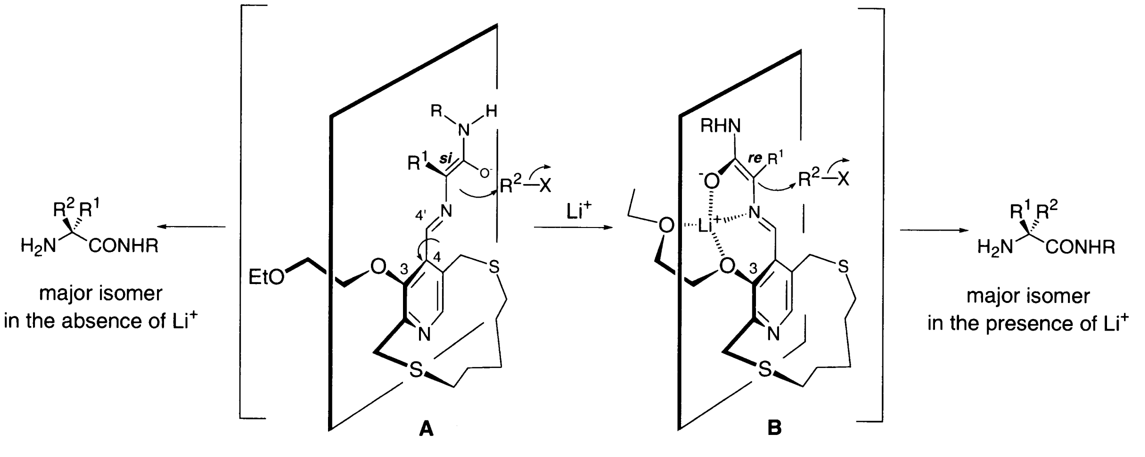


Figure 3. Possible transition states **A** and **B** for α-alkylation in the absence and presence of Li^+.

the formation of the chelation structure and not to the approach of the alkylating agent.[4b] As a consequence, the *si*-face appears to be blocked by the chelation structure formed in another side of the ansa-structure. In contrast, although the details are still not clear, the reversed stereoselectivity observed in the absence of Li^+ might be explained by the fact that the C-terminal amino ester moiety and/or the ethoxyethoxy group are most likely to occupy the other side of the ansa-chain to avoid the steric repulsion for the ansa-chain, which consequently could block the *re*-face as illustrated by the transition state **A** (Fig. 3).

In conclusion, we have demonstrated the first example of N-terminal selective and stereoselective α-alkylation of peptides. The present reaction has a characteristic feature in that the stereoselectivity depends on the chirality of the pyridoxal derivative and the reaction conditions whether Li^+ is employed or not, and not on the stereochemistry of the peptide, which means that both stereoisomers can be obtained with predictable stereoselectivity. Although in this paper we have examined the reaction of the peptides, which had been made from neutral amino acids, in a liquid-phase, this method would potentially be of great use for the synthesis of unnatural peptides, particularly for application to the construction of an unnatural peptide library.

3. Experimental

3.1. General

Melting points (mps) were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. Infrared spectra were measured on a JASCO FT/IR-200 Fourier-transfer infrared spectrometer. ^1H NMR spectra were measured on a JEOL GX-500 (500 MHz) or a Varian VXR-200 (200 MHz) spectrometer and tetramethylsilane (TMS) was used as an internal standard. ^{13}C NMR spectra were measured on a Varian VXR-200 (50.3 MHz) with $CDCl_3$ as an internal standard (77.0 ppm). Low and High resolution mass spectra (EI-MS and HR-MS) were obtained by use of a JEOL D-300 mass spectrometer. $[\alpha]_D$ values were obtained on a JASCO DIP-370 polarimeter. For silica gel column chromatography, E. Merck Kieselgel 60 (0.063–0.200 mm) was used. Pyridoxal derivative R_{ansa}-**1** was prepared according to our method.[4b]

3.2. Typical procedure for α-alkylation in the presence or absence of Li^+

Aldimines, **3** and **7**, were prepared from R_{ansa}-**1** (35.5 mg, 0.10 mmol) and amide **2a** or peptides **6** (0.10 mmol) according to the literature procedure[8] and were immediately used for the next reaction without purification. Their ^1H NMR spectra showed that the reaction had proceeded in almost quantitative yield and the aldimines were pure enough. ^1H NMR spectrum for aldimine R_{ansa}-**7a** is shown in Table 5 and those for R_{ansa}-**3a** and R_{ansa}-**7a′**–**d** measured in $CDCl_3$ are as follows: R_{ansa}-**3a** δ: 0.39 (1H, m, ansa chain H), 0.66–0.91 (5H, m, ansa chain H), 1.17 (3H, t, J=7.5 Hz, $MeCH_2O$–), 1.53 (3H, d, J=7.5 Hz, α-Me), 2.09–2.18, 2.33–2.49 (each 2H, m, ansa chain H), 3.51 (2H, q, J=7.5 Hz, $MeCH_2O$–), 3.57, 4.32 (each 1H, d, J=13.0 Hz, 2- or 5-CH_2S), 3.66, 4.70 (each 1H, d, J=13.5 Hz, 2- or 5-CH_2S), 3.67–3.70 (2H, m, $EtOCH_2CH_2O$), 4.00–4.06 (2H, m, $EtOCH_2CH_2O$), 4.10 (1H, q, J=7.5 Hz, α-H), 4.32–4.40 (2H, AB in ABX, J=4.4, 5.1 Hz, $NHCH_2Ph$), 7.16–7.30 (5H, m, aromatic H), 7.76 (1H, br m, amide H), 8.38 (1H, s, 6-H), 8.83 (1H, s, imine H); R_{ansa}-**7a′** δ: 0.32 (1H, m, ansa chain H), 0.72–0.98 (5H, m, ansa chain H), 1.18 (3H, t, J=7.0 Hz, $MeCH_2O$–), 1.42 (3H, d, J=7.0 Hz, N-terminal Ala α-Me), 1.48 (3H, d, J=7.0 Hz, C-terminal Ala α-Me), 1.96–2.22, 2.42–2.68 (each 2H, m, ansa chain H), 3.50 (2H, q, J=7.0 Hz, $MeCH_2O$–), 3.60, 3.62, 4.32, 4.76 (each 1H, d, J=13.0 Hz, 2- or 5-CH_2S), 3.61–3.69 (2H, m, $EtOCH_2CH_2O$), 3.99–4.07 (2H, m, $EtOCH_2CH_2O$), 4.07 (1H, q, J=7.0 Hz, N-terminal Ala α-H), 4.68 (1H, q, J=7.0 Hz, C-terminal Ala α-H), 5.16–5.22 (2H, AB type CH_2Ph), 7.25–7.31 (5H, m, aromatic H), 7.58 (1H, br d, J=7.5 Hz, amide H), 8.37 (1H, s, 6-H), 8.86 (1H, s, imine H); R_{ansa}-**7b** δ: 0.34 (1H, m, ansa chain H), 0.70–0.96 (5H, m, ansa chain H), 1.36 (3H, t, J=7.0 Hz, $MeCH_2O$–), 1.53 (3H, d, J=7.0 Hz, Ala α-Me), 1.90–2.18, 2.38–2.66 (each 2H, m, ansa chain H), 3.57 (2H, q, J=7.0 Hz, $MeCH_2O$–), 3.65, 3.68, 4.33, 4.77 (each 1H, d, J=13.5 Hz, 2- or 5-CH_2S), 3.60–3.70 (2H, m, $EtOCH_2CH_2O$), 4.06–4.13 (2H, m, $EtOCH_2CH_2O$), 4.08–4.12 (2H, AB in ABX, J=4.8, 5.5 Hz, Gly α-H), 4.14 (1H, q, J=7.0 Hz, Ala α-H), 5.17 (2H, s CH_2Ph), 7.26–7.40 (5H, m, aromatic H), 7.68

(1H, br m, amide H), 8.38 (1H, s, 6-H), 8.89 (1H, s, imine H); R_{ansa}-**7c** δ: 0.40 (1H, m, ansa chain H), 0.69–0.96 (5H, m, ansa chain H), 0.89, 0.94 (each 3H, d, J=7.5 Hz, Val β-Me), 1.25 (3H, t, J=7.0 Hz, *Me*CH_2O–), 1.34 (3H, d, J=7.0 Hz, Ala α-Me), 2.00–2.26, 2.39–2.61 (each 2H, m, ansa chain H), 2.24 (1H, m, Val β-H), 3.57 (2H, q, J=7.0 Hz, $MeCH_2O$–), 3.59, 4.36 (each 1H, d, J=13.5 Hz, 2- or 5-CH_2S), 3.64, 4.74 (each 1H, d, J=13.0 Hz, 2- or 5-CH_2S), 3.63–3.67 (2H, m, $EtOCH_2CH_2O$), 4.09–4.16 (2H, m, $EtOCH_2CH_2O$), 4.12 (1H, q, J=7.0 Hz, Ala α-H), 4.59 (1H, dd, J=7.0, 7.5 Hz, Val α-H), 5.09–5.19 (2H, AB type, CH_2Ph), 7.18–7.36 (5H, m, aromatic H), 7.45 (1H, br d, J=7.0 Hz, amide H), 8.40 (1H, s, 6-H), 8.85 (1H, s, imine H); R_{ansa}-**7c′** δ: 0.38 (1H, m, ansa chain H), 0.65–0.96 (5H, m, ansa chain H), 0.90, 0.94 (each 3H, d, J=7.5 Hz, Val β-Me), 1.28 (3H, t, J=7.0 Hz, *Me*CH_2O–), 1.44 (3H, d, J=7.0 Hz, Ala α-Me), 2.00–2.21, 2.36–2.59 (each 2H, m, ansa chain H), 2.22 (1H, m, Val β-H), 3.54 (2H, q, J=7.0 Hz, $MeCH_2O$–), 3.59, 4.35 (each 1H, d, J=13.5 Hz, 2- or 5-CH_2S), 3.61, 4.79 (each 1H, d, J=13.0 Hz, 2- or 5-CH_2S), 3.61–3.68 (2H, m, $EtOCH_2CH_2O$), 4.05–4.12 (2H, m, $EtOCH_2CH_2O$), 4.16 (1H, q, J=7.0 Hz, Ala α-H), 4.70 (1H, dd, J=7.0, 7.5 Hz, Val α-H), 5.14–5.19 (2H, AB type, CH_2Ph), 7.15–7.35 (5H, m, aromatic H), 7.57 (1H, br d, J=7.0 Hz, amide NH), 8.39 (1H, s, 6-H), 8.88 (1H, s, imine H); R_{ansa}-**7d** δ: 0.42 (1H, m, ansa chain H), 0.65–0.92 (5H, m, ansa chain H), 1.17 (3H, t, J=7.5 Hz, *Me*CH_2O–), 1.38, 1.39, 1.42 (each 3H, d, J=7.0 Hz, Ala α-Me), 1.90–2.15, 2.34–2.49 (each 2H, m, ansa chain H), 3.52 (2H, q, J=7.5 Hz, $MeCH_2O$–), 3.59, 3.67, 4.32, 4.68 (each 1H, d, J=13.0 Hz, 2- or 5-CH_2S), 3.64–3.72 (2H, m, $EtOCH_2CH_2O$), 3.99–4.08 (2H, m, $EtOCH_2CH_2O$), 4.09, (1H, q, J=7.0 Hz, N-terminal Ala α-H), 4.39, 4.55 (each 1H, qn, J=7.0 Hz, Ala α-H), 5.08–5.13 (2H, AB type CH_2Ph), 6.81, 7.88 (each 1H, br d, J=7.0 Hz, amide H), 7.16–7.38 (5H, m, aromatic H), 8.35 (1H, s, 6-H), 8.86 (1H, s, imine H).

To a stirred MeCN (1 ml) solution of the aldimine R_{ansa}-**3** or R_{ansa}-**7** (0.10 mmol), were added $LiClO_4$ (32.2 mg, 0.30 mmol) and then DBU (30 μl, 0.20 mmol) under ice-cooling and the whole was stirred for 5 min at the same temperature. After addition of benzyl bromide (13.1 μl, 0.11 mmol), the reaction mixture was stirred under ice-cooling for the period indicated in Tables, then diluted with ethyl acetate (10 ml) and washed with H_2O and saturated NaCl solution. To the organic layer, *p*-TsOH·H_2O (38.6 mg, 0.20 mmol) was added and the whole was stirred for 30 min at room temperature. The reaction mixture was partitioned with ether and H_2O and the ethereal layer was extracted with H_2O. The organic layer was dried, concentrated under reduced pressure and purified by silica gel column chromatography (ethyl acetate–hexane=1:1) to give recovered pyridoxal derivative R_{ansa}-**1**. The aqueous phase was basified with saturated $NaHCO_3$ solution, saturated with NaCl and extracted with ethyl acetate. The organic layer was dried and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (ethyl acetate) to give benzylated product. Diastereomeric mixtures were unseparable under the conditions. The reaction in the absence of Li^+ was carried out according to the same procedure without the addition of $LiClO_4$ and alkylations with other alkyl halides were also carried out by the same procedure. Spectral properties for the alkylated products are shown below.

3.2.1. 2-Amino-2-methyl-3-phenylpropanoyl benzylamide (4a). A colorless oil (Table 1, run 1, R/S=83:17). $[\alpha]_D^{25}$=+19.5 (c 0.51, $CHCl_3$). IR ν (KBr): 3353, 1660, 1506 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ: 1.42 (3H, s, α-Me), 1.50 (2H, br s, NH_2), 2.63 (1H, d, J=13.4 Hz, α-CH_2Ph), 3.45 (1H, d, J=13.4 Hz, α-CH_2Ph), 4.33–4.44 (2H, AB in ABX, J=5.5, 6.1 Hz, $NHCH_2Ph$), 7.13–7.27 (10H, m, aromatic H), 7.79 (1H, br s, amide NH). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 28.1, 43.2, 46.8, 58.4, 126.8, 127.2, 127.6, 128.4, 128.5, 130.4, 137.0, 138.5, 176.2. EI-MS m/z (%): 269 (M^++H, 1.9), 134 (100). High-resolution MS calcd for $C_{17}H_{20}N_2O$ (M^++H): 269.1654, found: 269.1652.

3.2.2. Benzyl 2-amino-2-methyl-3-phenylpropanoate (4b). Colorless crystals, mp 45–46°C (AcOEt–hexane) (Table 1, run 2, R/S=87:13). $[\alpha]_D^{25}$=+25.2 (c 0.51, $CHCl_3$). IR ν (KBr): 3374, 1723, 1593 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ: 1.41 (3H, s, α-Me), 1.63 (2H, br s, NH_2), 2.79–3.14 (2H, AB type, α-CH_2Ph), 5.12 (2H, s, CO_2CH_2Ph), 7.02–7.42 (10H, m, aromatic H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 26.6, 46.8, 58.8, 66.8, 126.8, 128.3, 128.3, 128.3, 128.5, 129.9, 135.6, 136.4, 176.8. EI-MS m/z (%): 270 (M^++H, 0.1), 91 (100). High-resolution MS calcd for $C_{17}H_{20}NO_2$ (M^++H): 270.1495, found: 270.1495.

3.2.3. (2-Amino-2-methyl-3-phenylpropanoyl)-L-alanine benzyl ester (8a). A colorless oil (Table 3, run 1, R/S=86:14). $[\alpha]_D^{25}$=+35.1 (c 0.50, $CHCl_3$). IR ν (KBr): 3363, 1741, 1668, 1506 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) (R)-isomer δ: 1.33 (3H, s, N-terminal α-Me), 1.40 (3H, d, J=7.3 Hz, C-terminal α-Me), 1.52 (2H, br s, NH_2), 2.73 (1H, d, J=13.5 Hz, α-CH_2Ph), 3.25 (1H, d, J=13.5 Hz, α-CH_2Ph), 4.57 (1H, qn, J=7.3 Hz, α-H), 5.15 (2H, s, CO_2CH_2Ph), 7.12–7.40 (10H, m, aromatic H), 7.97 (1H, br s, amide NH). (S)-isomer δ: 1.30 (3H, d, J=7.3 Hz, C-terminal α-Me), 1.37 (3H, s, N-terminal α-Me), 1.52 (2H, br s, NH_2), 2.61 (1H, d, J=13.5 Hz, α-CH_2Ph), 3.36 (1H, d, J=13.5 Hz, α-CH_2Ph), 4.57 (1H, qn, J=7.3 Hz, α-H), 5.14–5.17 (2H, AB type, CO_2CH_2Ph), 7.12–7.40 (10H, m, aromatic H), 7.97 (1H, br s, amide NH). High-resolution MS calcd for $C_{17}H_{20}NO_2$ (M^++H): 341.1865, found: 341.1871.

3.2.4. (2-Amino-2-methyl-3-phenylpropanoyl)glycine benzyl ester (8b). A colorless oil (Table 3, run 3, R/S=83:17). $[\alpha]_D^{25}$=+14.5 (c 0.50, $CHCl_3$). IR ν (KBr): 3335, 1751, 1629, 1589 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ: 1.37 (3H, s, α-Me), 1.46 (2H, br s, NH_2), 2.69 (1H, d, J=13.4 Hz, α-CH_2Ph), 3.32 (1H, d, J=13.4 Hz, α-CH_2Ph), 3.91–4.15 (2H, AB in ABX, J=5.5, 6.1 Hz, Gly α-H), 5.16–5.17 (2H, AB type, CO_2CH_2Ph), 7.23–7.36 (10H, m, aromatic H), 7.98 (2H, br s, amide NH). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 27.7, 41.3, 46.4, 58.3, 67.0, 126.8, 127.6, 128.4, 128.5, 128.6, 130.3, 135.3, 136.8, 169.8, 177.0. EI-MS m/z (%): 327 (M^++H, 0.1), 91 (100). High-resolution MS calcd for $C_{17}H_{20}NO_2$ (M^++H): 327.1708, found: 327.1697.

3.2.5. (2-Amino-2-methyl-3-phenylpropanoyl)-L-valine benzyl ester (8c). A colorless oil (Table 3, run 4, R/S=

88:12). $[\alpha]_D^{25}=+39.2$ (*c* 0.52, $CHCl_3$). IR ν (KBr): 3366, 1741, 1671, 1586 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) (*R*)-isomer δ: 0.88, 0.91 (each 3H, d, *J*=7.0 Hz, Val β-Me), 1.35 (3H, s, α-Me), 1.47 (2H, br s, NH_2), 2.08 (1H, m, Val β-H), 2.71 (1H, d, *J*=13.2 Hz, α-CH_2Ph), 3.27 (1H, d, *J*=13.2 Hz, α-CH_2Ph), 4.53 (1H, dd, *J*=5.0, 7.0 Hz, α-H), 5.11–5.20 (2H, AB type, CO_2CH_2Ph), 7.12–7.38 (10H, m, aromatic H), 8.05 (1H, br s, amide NH). (*S*)-isomer δ: 0.74, 0.75 (each 3H, d, *J*=7.0 Hz, Val β-Me), 1.37 (3H, s, α-Me), 1.47 (2H, br s, NH_2), 2.08 (1H, m, Val β-H), 2.61 (1H, d, *J*=13.2 Hz, α-CH_2Ph), 3.41 (1H, d, *J*=13.2 Hz, α-CH_2Ph), 4.46 (1H, dd, *J*=4.9, 7.0 Hz, α-H), 5.11–5.20 (2H, AB type, CO_2CH_2Ph), 7.12–7.38 (10H, m, aromatic H), 8.05 (1H, br s, amide NH). High-resolution MS calcd for $C_{17}H_{20}NO_2$ (M^++H): 369.1940, found: 369.1949.

3.2.6. (2-Amino-2-methyl-3-phenylpropanoyl)-L-alanyl-L-alanine benzyl ester (8d). A colorless oil (Table 3, run 6, *R*/*S*=86:14). $[\alpha]_D^{25}=+29.3$ (*c* 0.50, $CHCl_3$). IR ν (KBr): 3363, 1751, 1672, 1589 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) (*R*)-isomer δ: 1.26 (3H, s, N-terminal α-Me), 1.35 (3H, d, *J*=7.3 Hz, α-Me), 1.38 (3H, d, *J*=6.6 Hz, C-terminal α-Me), 2.72 (1H, d, *J*=13.8 Hz, α-CH_2Ph), 3.28 (1H, d, *J*=13.8 Hz, α-CH_2Ph), 4.40 (1H, qn, *J*=7.3 Hz, α-H), 4.54 (1H, qn, *J*=6.6 Hz, C-terminal α-H), 5.16–5.18 (2H, AB type, CO_2CH_2Ph), 6.76 (1H, br s, amide NH), 7.14–7.39 (10H, m, aromatic H), 7.81 (1H, br s, amide NH). (*S*)-isomer δ: 1.22 (3H, d, *J*=6.6 Hz, C-terminal α-Me), 1.38 (3H, s, N-terminal α-Me), 1.41 (3H, d, *J*=7.3 Hz, α-Me), 2.64 (1H, d, *J*=13.8 Hz, α-CH_2Ph), 3.35 (1H, d, *J*=13.8 Hz, α-CH_2Ph), 4.40 (1H, qn, *J*=7.3 Hz, α-H), 4.54 (1H, qn, *J*=6.6 Hz, C-terminal α-H), 5.16–5.18 (2H, AB type, CO_2CH_2Ph), 6.78 (1H, br s, amide NH), 7.14–7.39 (10H, m, aromatic H), 7.81 (1H, br s, amide NH). EI-MS *m*/*z* (%): 412 (M^++H, 1.5), 91 (100). High-resolution MS calcd for $C_{17}H_{20}NO_2$ (M^++H): 412.2158, found: 412.2155.

3.2.7. [2-Amino-2-methyl-3-(4-nitrophenyl)propanoyl]-L-alanine benzyl ester (9). A colorless oil (Table 4, run 2, *R*/*S*=85:15). $[\alpha]_D^{25}=+30.5$ (*c* 0.51, $CHCl_3$). IR ν (KBr): 3323, 1722, 1672, 1516 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) (*R*)-isomer δ: 1.40 (3H, s, N-terminal α-Me), 1.41 (3H, d, *J*=6.8 Hz, C-terminal α-Me), 1.62 (2H, br s, NH_2), 2.74 (1H, d, *J*=13.1 Hz, α-CH_2Ph), 3.48 (1H, d, *J*=13.1 Hz, α-CH_2Ph), 4.53 (1H, qn, *J*=6.8 Hz, α-H), 5.22–5.39 (2H, AB type, CO_2CH_2Ph), 7.12–7.40 (10H, m, aromatic H), 7.97 (1H, br s, amide NH). (*S*)-isomer δ: 1.29 (3H, d, *J*=6.8 Hz, C-terminal α-Me), 1.43 (3H, s, N-terminal α-Me), 1.62 (2H, br s, NH_2), 2.70 (1H, d, *J*=13.1 Hz, α-CH_2Ph), 3.53 (1H, d, *J*=13.1 Hz, α-CH_2Ph), 4.53 (1H, qn, *J*=6.8 Hz, α-H), 5.22–5.39 (2H, AB type, CO_2CH_2Ph), 7.12–7.40 (10H, m, aromatic H), 7.97 (1H, br s, amide NH). EI-MS *m*/*z* (%): 386 (M^++H, 0.9), 91 (100). High-resolution MS calcd for $C_{17}H_{20}NO_2$ (M^++H): 386.1638, found: 386.1636.

3.2.8. [2-Amino-2-methyl-3-pentynoyl]-L-alanine benzyl ester (10). A colorless oil (Table 4, run 3, *R*/*S*=84:16). $[\alpha]_D^{25}=+26.1$ (*c* 0.51, $CHCl_3$). IR ν (KBr): 3292, 2119, 1733, 1666, 1588 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) (*R*)-isomer δ: 1.36 (3H, s, N-terminal α-Me), 1.43 (3H, d, *J*=7.3 Hz, C-terminal α-Me), 1.52 (2H, br s, NH_2), 2.03 (1H, t, *J*=2.6 Hz, $CH_2C\equiv C\mathit{H}$), 2.50–2.66 (2H, AB in ABX, *J*=2.6, 15.9 Hz, $C\mathit{H}_2C\equiv CH$), 4.58 (1H, qn, *J*=7.1 Hz, α-H), 5.15–5.17 (2H, AB type, CO_2CH_2Ph), 7.12–7.40 (10H, m, aromatic H), 8.11 (1H, br s, amide NH). (*S*)-isomer δ: 1.35 (3H, s, N-terminal α-Me), 1.43 (3H, d, *J*=7.3 Hz, C-terminal α-Me), 1.52 (2H, br s, NH_2), 2.05 (1H, t, *J*=2.6 Hz, $CH_2C\equiv C\mathit{H}$), 2.47–2.75 (2H, AB in ABX, *J*=2.6, 16.7 Hz, $C\mathit{H}_2C\equiv CH$), 4.58 (1H, qn, *J*=7.1 Hz, α-H), 5.15–5.17 (2H, AB type, CO_2CH_2Ph), 7.12–7.40 (10H, m, aromatic H), 8.11 (1H, br s, amide NH). EI-MS *m*/*z* (%): 289 (M^++H, 1.1), 91 (100). High-resolution MS calcd for $C_{17}H_{20}NO_2$ (M^++H): 289.1474, found: 289.1475.

3.2.9. [2-Amino-2-methyl-3-pentenoyl]-L-alanine benzyl ester (11). A colorless oil (Table 4, run 4, *R*/*S*=73:27). $[\alpha]_D^{25}=+19.9$ (*c* 0.51, $CHCl_3$). IR ν (KBr): 3310, 1731, 1653, 1640, 1603 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) (*R*)-isomer δ: 1.33 (3H, s, N-terminal α-Me), 1.43 (3H, d, *J*=7.3 Hz, C-terminal α-Me), 1.57 (2H, br s, NH_2), 2.09 (1H, m, $C\mathit{H}_2CH{=}CH_2$), 2.52 (1H, m, $C\mathit{H}_2CH{=}CH_2$), 4.52–4.64 (2H, m, $CH_2CH{=}C\mathit{H}_2$), 4.58 (1H, qn, *J*=7.0 Hz, α-H), 5.17–5.22 (2H, AB type, CO_2CH_2Ph), 5.66–5.86 (1H, m, $CH_2C\mathit{H}{=}CH_2$), 7.12–7.40 (10H, m, aromatic H), 8.11 (1H, br s, amide NH). (*S*)-isomer δ: 1.32 (3H, s, N-terminal α-Me), 1.42 (3H, d, *J*=7.3 Hz, C-terminal α-Me), 1.57 (2H, br s, NH_2), 2.06 (1H, m, $C\mathit{H}_2CH{=}CH_2$), 2.70 (1H, m, $C\mathit{H}_2CH{=}CH_2$), 4.58 (1H, qn, *J*=7.0 Hz, α-H), 5.04–5.18 (2H, m, $CH_2CH{=}C\mathit{H}_2$), 5.17–5.22 (2H, AB type, CO_2CH_2Ph), 5.66–5.86 (1H, m, $CH_2C\mathit{H}{=}CH_2$), 7.12–7.40 (10H, m, aromatic H), 8.11 (1H, br s, amide NH). EI-MS *m*/*z* (%): 291 (M^++H, 2.2), 91 (100). High-resolution MS calcd for $C_{17}H_{20}NO_2$ (M^++H): 291.1630, found: 291.1633.

3.2.10. Benzyl (*R*)-2-(*tert*-Butoxycarbonylamino)-2-methyl-3-phenylpropanoate (12). To a stirred solution of the dialkyl amino ester *R*-**4a** (30.2 mg, 0.11 mmol) in dioxane (1 ml) were added triethylamine (34.2 μl, 0.11 mmol) and di-*tert*-butyl dicarbonate (48.8 mg, 0.22 mmol) and the whole mixture was stirred for 6 h at room temperature. The reaction mixture was diluted with ethyl acetate and washed with saturated NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (ethyl acetate–hexane, 1:2) to give **12** (40.6 mg, 98%) as colorless crystals, mp 89–90°C. $[\alpha]_D^{25}=+11.5$ (*c* 0.92, $CHCl_3$). IR ν (KBr): 3428, 1714, 1496 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ: 1.44 (9H, s, *t*-Bu), 1.58 (3H, s, α-Me), 3.19–3.38 (2H, AB type, α-CH_2Ph), 5.08 (1H, br s, NH), 5.16 (2H, s, CO_2CH_2Ph), 6.99–7.36 (10H, m, aromatic H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 23.7, 28.4, 41.6, 60.2, 67.3, 126.8, 128.1, 128.4, 128.5, 130.1, 135.4, 136.3, 154.3, 173.8. EI-MS *m*/*z* (%): 369 (M^++H, 2.3), 178 (100). High-resolution MS calcd for $C_{22}H_{27}NO_4$ (M^++H): 369.1940, found: 369.1949.

3.2.11. (*R*)-2-(*tert*-Butoxycarbonylamino)-2-methyl-3-phenylpropanoic acid (13). A mixture of **12** (40.6 mg, 0.11 mmol) and 10% Pd–C (50 mg) in ethyl acetate (1 ml) was stirred under atmospheric pressure of H_2 for 4 h at room temperature. After being filtered, the reaction mixture was concentrated and the residue was purified by aluminum oxide column chromatography (ethyl acetate–MeOH, 10:1) to give **13** (30.6 mg, quant.) as colorless crystals, mp 158–160°C (ethyl acetate). $[\alpha]_D^{24}=-6.16$ (*c* 1.72, $CHCl_3$). IR ν (KBr): 3421, 1713, 1453 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ: 1.48 (9H, s, *t*-Bu), 1.53 (3H, s, α-Me), 3.25–3.32 (2H, AB type, α-CH_2Ph), 4.99 (1H, br s, NH), 7.13–7.31 (5H, m, aromatic H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 23.5, 28.4, 41.3, 60.0, 127.0, 128.2, 130.3, 136.0, 154.8, 179.0. EI-MS *m/z* (%): 279 (M^++H, 5.7). High-resolution MS calcd for $C_{15}H_{21}NO_4$ (M^++H): 279.1470, found: 279.1467.

3.2.12. [(*R*)-2-(*tert*-Butoxycarbonylamino)-2-methyl-3-phenylpropanoyl]-L-alanine benzyl ester (14). To a stirred solution of **13** (30.6 mg, 0.11 mmol) and HOBt (29.6 mg, 0.22 mmol) in ethyl acetate (1 ml) were added DCC (44.8 mg, 0.22 mmol) and L-Ala-OBn (39.0 mg, 0.22 mmol) and the whole was stirred for 24 h at room temperature. After being filtered, the reaction mixture was successively washed with 5% HCl, saturated $NaHCO_3$ solution, water, and saturated NaCl solution, dried over Na_2SO_4 and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (ethyl acetate–hexane, 1:2) to give **14** as colorless crystals, mp 84–85°C (ethyl acetate–hexane). $[\alpha]_D^{24}=42.1$ (*c* 0.71, $CHCl_3$). IR ν (KBr): 3320, 1716, 1669, 1496 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ: 1.41 (3H, d, *J*=7.0 Hz, C-terminal α-Me), 1.45 (9H, s, *t*-Bu), 1.56 (3H, s, N-terminal α-Me), 3.08–3.33 (2H, AB type, α-CH_2Ph), 4.62 (1H, qn, *J*=7.0 Hz, α-H), 4.81 (1H, br s, NH), 5.17 (2H, s, CO_2CH_2Ph), 6.91 (1H, br d, *J*=7.0 Hz, NH), 7.11–7.35 (10H, m, aromatic H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 18.4, 23.6, 28.3, 41.6, 48.3, 59.8, 67.1, 80.2, 126.9, 128.1, 128.2, 128.4, 128.6, 130.5, 135.3, 136.0, 154.5, 172.7, 173.4. EI-MS *m/z* (%): 440 (M^+, 1.2), 349 (M^+-Bn, 25). High-resolution MS calcd for $C_{25}H_{32}N_2O_5$ (M^+): 440.2311, found: 440.2300.

3.2.13. [(*R*)-2-Amino-2-methyl-3-phenylpropanoyl]-L-alanine benzyl ester (*R*-8a). To a stirred solution of **14** (39.9 mg, 0.091 mmol) in CH_2Cl_2 (0.5 ml) was added trifluoroacetic acid (0.5 ml) under ice-cooling and the whole mixture was stirred for 3 h at the same temperature. After concentration under reduced pressure, the residue was dissolved in ethyl acetate and saturated $NaHCO_3$ solution. The organic phase was separated and the aqueous phase was extracted three times with ethyl acetate. The combined organic layer was washed with water and saturated NaCl solution, dried over Na_2SO_4 and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography to give *R*-**8a** (27.9 mg, 90%) as a colorless oil, $[\alpha]_D^{24}=+41.6$ (*c* 0.55, $CHCl_3$). ^1H NMR spectrum was identical with that of the major compound obtained by the direct benzylation of L-Ala-L-Ala-OBn.

3.3. Preparation of MTPA amide

To a solution of amino compound **4a**,**b** or **8a**,**b** (0.010 mmol) in dry pyridine (0.1 ml) containing a catalytic amount of DMAP was added (*R*)-MTPACl (2.2 μl, 0.012 mmol) and the whole was stirred at room temperature for 2 h. After being diluted with ethyl acetate, the reaction mixture was washed successively with saturated $NaHCO_3$ solution, 5% HCl, water and brine, dried over Na_2SO_4 and concentrated under reduced pressure to give the amide **5a**,**b** or **15a**,**b** in almost quantitative yield. The optical purities of these compounds were obtained by ^1H- and ^{19}F NMR analyses.

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6. The stereoselectivity of the reaction in the presence of 5 equiv. of $LiClO_4$ was the almost same as that in the presence of 3 equiv. of $LiClO_4$.
7. The ^1H and ^{19}F NMR spectra of **15a** showed a pair of signals in a ratio of 86:14 at δ_H 1.62 and 1.67 (N-terminal α-CH_3) and at δ_F −69.5 and −69.8, respectively. The corresponding MTPA amide obtained starting from L-Ala-DL-Ala-OBn by the same reaction procedures was shown to be a mixture of four isomers by the same spectra: δ_H 1.60, 1.62, 1.66, 1.67 (N-terminal α-CH_3) and δ_F −69.8, −69.5, −69.5, −69.4. This result shows that the pair of signals observed in the spectra of **15a** was due to a diastereomeric mixture, not due to a mixture of geometrical isomers of an amide bond, and, at the same time, that no racemization is involved in the alkylation procedure.
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