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Stereoselective syntheses of tri- and tetrapeptide analogues by dynamic resolution of α-halo amides in nucleophilic substitution

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Abstract—Dynamic resolution of α-bromo and α-chloro acetamides in nucleophilic substitution with amine nucleophiles in the presence of TBAI has been investigated for stereoselective syntheses of tri- and tetrapeptide analogues. Mechanistic investigations suggest that primary pathway of the asymmetric induction is a dynamic kinetic resolution and real intermediate for the substitution is α-iodo acetamides. Also, application of this mild and simple methodology to stereoselective preparations of *N*-carboxyalkyl, *N*-aminoalkyl and *N*-hydroxyalkyl peptide analogues is demonstrated.

1. Introduction

Stereospecific nucleophilic substitution (S_N2) reaction of optically pure α-halo or α-sulfonyloxy acetamides with an amine nucleophile is widely used for stereoselective preparation of peptidomimetics.[1] However, most of optically pure α-halo or α-sulfonyloxy acetamides are made from natural amino acids and, consequently, this synthetic method seems to lack generality. Since various α-halo amides can be easily obtained in racemic form and configurational lability of them is readily induced, dynamic resolution of *N*-(α-haloacetyl) peptides in the substitution reaction would be more attractive strategy for asymmetric syntheses of peptide analogues. Recently, it has been shown from our group that the chiral information of adjacent amino acid residue is efficiently transferred to the new C–N bond formation at α-bromo carbon center for asymmetric syntheses of dipeptide analogues.[2] Herein we describe our recent progress to extend the scope of the methodology to tri- and tetrapeptide analogues via dynamic resolution of α-chloro or α-bromo acetamides with various amine nucleophiles. Application of this methodology to highly stereoselective N-terminal functionalization of peptides is also presented.

2. Results and discussion

We have previously reported that the treatment of *N*-(α-bromo-α-phenylacetyl)-*L*-leucine methyl ester **1** with dibenzylamine (1.2 equiv, Bn_2NH), tetrabutylammonium iodide (1.0 equiv, TBAI) and diisopropylethylamine (1.0 equiv, DIEA) in CH_2Cl_2 at rt provided the dipeptide analogues **14** in 83% yield with 93:7 diastereomeric ratio (dr, α*R*:α*S*) as shown in Table 1, entry 1.[2a] The chiral information of *L*-leucine is transferred to the substitution at α-bromo carbon center via dynamic kinetic resolution in the nucleophilic substitution with dibenzylamine. In order to assess the effect of the additional C-terminal amino acid residues on stereoselectivity, a series of *N*-(α-bromo-α-phenylacetyl)-*L*-leucine derivatives was initially examined as shown in Table 1. No stereoselectivity was observed in the reaction of glycine-*L*-leucine derivative **2**, where the C-terminal *L*-leucine was positioned apart from the reaction center (entry 2). In all cases of *N*-(α-bromoacetyl) *L*-leucine derivatives **3**–**5** having an additional C-terminal amino acid residue in **1**, tripeptide analogues **16**, **17** and **18** were obtained with lower selectivities (87:13–80:20 drs) compared to the reaction of **1** as shown in Table 1, entries 3–5. It is also noteworthy that chirality of the additional amino acid residue affects the stereoselectivity as replacing *L*-Ala in **4** with *D*-Ala gives rise to loss of asymmetric induction (entries 4 and 5).

In the reaction of *N*-(α-bromo-α-phenylacetyl)-*L*-proline derivative **7** having an additional C-terminal glycine in **6**, the stereoselectivity was lower compared to the reaction of **6** as shown in entries 6 and 7. Under the same reaction

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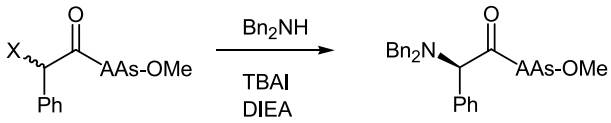
Table 1. Effect of additional C-terminal amino acid residues



Entry	X	AA (S.M.)[a]	% Yield[b,c] (product)	dr[d] (αR:αS)
1	Br	*L*-Leu (**1**)	83 (**14**)	93:7
2	Br	Gly-*L*-Leu (**2**)	69 (**15**)	50:50
3	Br	*L*-Leu-Gly (**3**)	69 (**16**)	81:19
4	Br	*L*-Leu-*L*-Ala (**4**)	64 (**17**)	87:13
5	Br	*L*-Leu-*D*-Ala (**5**)	75 (**18**)	80:20
6	Br	*L*-Pro (**6**)	93 (**19**)	>99:1
7	Br	*L*-Pro-Gly (**7**)	91 (**20**)	95:5
8	Cl	*L*-Pro-Gly (**8**)	84 (**20**)	95:5
9	Br	*L*-Pro-*L*-Leu (**9**)	85 (**21**)	>99:1
10	Cl	*L*-Pro-*L*-Leu (**10**)	82 (**21**)	>99:1
11	Cl	*L*-Pro-*D*-Leu (**11**)	77 (**22**)	96:4
12	Cl	*L*-Pro-*L*-Leu-*L*-Ala (**12**)	71 (**23**)	81:19
13	Cl	*L*-Pro-*L*-Leu-*D*-Ala (**13**)	68 (**24**)	76:24

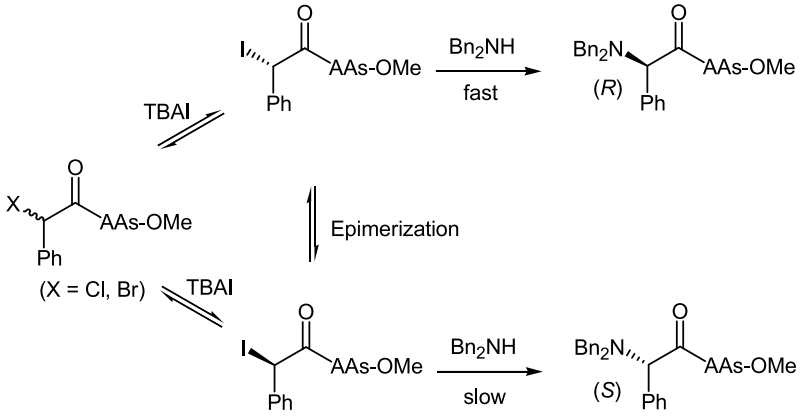
[a] Initial drs of **1**–**13** are approximately 50:50.
[b] All reactions were carried out in CH_2Cl_2 for 24 h at rt.
[c] Isolated yields.
[d] The drs are determined by ^{1}H NMR of reaction mixture using the authentic products prepared from racemic phenylglycine as a standard.

condition α-chloro acetamide **8** produced **20** in 84% yield with same selectivity as in the reaction of α-bromo acetamide **7** (entry 8). This is somewhat surprising considering the low reactivity of α-chloro acetamide and hence inefficient epimerization for dynamic resolution. This interesting fact was further supported by the reactions of α-bromo acetamide **9** and α-chloro acetamide **10**, where both reactions gave tripeptide analogue **21** with >99:1 dr in high yields (entries 9 and 10). While the additional C-terminal *L*-leucine in **6** did not affect the stereoselectivity, the selectivity was reduced with the additional C-terminal *D*-leucine (entry 11). Moreover, nucleophilic substitutions of both *N*-(α-chloroacetyl) tripeptides **12** and **13** were found to be less stereoselective compared to those of **10** and **11** (entries 12 and 13). It is also interesting to note here that chirality of third amino acid residue affects the stereoselectivity as replacing *L*-Ala in **12** with *D*-Ala gives rise to loss of asymmetric induction. The absolute configurations of major isomers of **14**–**24** were assigned as α*R* by comparison to the ^{1}H NMR of authentic epimers individually prepared from the coupling of *L*-leucine and *L*-proline derivatives and *N*,*N*-dibenzyl (*S*)- or (*R*)-phenylglycine.

To understand the reaction pathway and the origin of stereoselectivity, we carried out a series of reactions as shown in Table 2, focusing on epimerization process and transition state energy difference which may have a profound role in dictating the stereoselectivity of the substitution.[3] Two *N*-(α-bromoacetyl) dipeptides **3** and **5** were initially chosen for detailed study of their moderate stereoselectivities. When the mixture of two epimers of **3** (78:22 dr) was allowed to reach thermodynamic equilibrium in the presence of TBAI and DIEA, the epimeric ratio of recovered **3** was determined to be 52:48 (entry 1). The result indicates that α-bromo amide **3** is configurationally labile under the reaction condition and the thermodynamic stabilities of two epimers are almost same. Reaction of same population of two epimers with a deficient amount of nucleophile will give rise to a dr that reflects the intrinsic difference in activation energies between substitution reactions of each epimer.[4] In the reaction of **3** (49:51 dr) with 0.2 equiv of dibenzylamine in the absence of TBAI, the product **16** with 81:19 dr was obtained in 13% yield (entry 2). At rt, this dr of 81:19 corresponds to a difference in free energies of activation of about 0.9 kcal/mol. When **3** of 15:85 dr was treated with 1.2 equiv of dibenzylamine in the presence of both TBAI and DIEA, the reaction gave the product **16** with 81:19 dr as shown in entry 3. The dr is identical to the dr of both reactions of **3** in entry 3 (Table 1) and entry 2 (Table 2). This could be taken to suggest that the stereoselectivity depend mainly on the difference in the epimeric transition states energies and the primary pathway of the asymmetric induction is a dynamic kinetic resolution. However, with reversed diastereomeric enrichment of **3** (85:15 dr) slightly diminished dr of product **16** (73:27) was observed in the reaction of **3** (entry 4). The results indicate that the epimerization of **3** is not fast enough to get to complete thermodynamic equilibrium with respect to the substitution. As shown in entries 5–8, a series of reactions of *L*-leucine-*D*-alanine derivative **5** showed same tendency of stereochemical outcome as the reactions of *L*-leucine-glycine derivative **3**.

As expected, the reaction of α-chloro acetamide **8** does not produce the substitution product in the absence of TBAI (entry 9). In the presence of TBAB, the reactions of α-chloro acetamide **8** and α-bromo acetamide **10** gave the products **20** and **21**, respectively, with same stereoselectivities observed in the reaction with TBAI (Table 1, entries 8 and 10). However, the rate of the substitution is substantially decreased compared to the reactions with TBAI and require longer reaction time (60 h) to obtain moderate yields shown in entries 10 and 11. In addition, as shown in Table 2, entries 12 and 13, the reactions of α-bromo acetamides **3** and **4** in the presence of TBAB gave **16** and **18** with much lower stereoselectivities (55:45 and 64:36 dr) compared to the reactions with TBAI (Table 1, entries 3 and 4). The lower selectivity of the reaction of **3** than the selectivity estimated by the reaction with 0.2 equiv

Table 2. Dynamic kinetic resolution of α-bromo and α-chloro acetamides



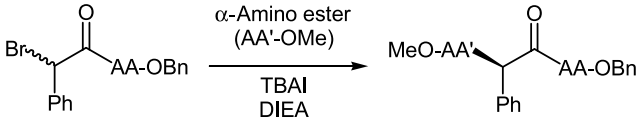
Entry	X	AA	S.M. (dr)[a]	Condition[b]	% Yield[c] (product)	dr[d] (α*R*:α*S*)
1	Br	*L*-Leu-Gly	**3** (78:22)	TBAI, DIEA	67 (**3**)	52:48
2	Br	*L*-Leu-Gly	**3** (49:51)	Bn_2NH (0.2 equiv)	13 (**16**)	81:19
3	Br	*L*-Leu-Gly	**3** (15:85)	TBAI, DIEA, Bn_2NH	74 (**16**)	81:19
4	Br	*L*-Leu-Gly	**3** (85:15)	TBAI, DIEA, Bn_2NH	83 (**16**)	73:27
5	Br	*L*-Leu-*D*-Ala	**5** (94:4)	TBAI, DIEA	85 (**18**)	53:47
6	Br	*L*-Leu-*D*-Ala	**5** (47:53)	Bn_2NH (0.2 equiv)	11 (**18**)	84:16
7	Br	*L*-Leu-*D*-Ala	**5** (19:81)	TBAI, DIEA, Bn_2NH	59 (**18**)	84:16
8	Br	*L*-Leu-*D*-Ala	**5** (83:17)	TBAI, DIEA, Bn_2NH	85 (**18**)	80:20
9	Cl	*L*-Pro-Gly	**8** (50:50)	DIEA, Bn_2NH	N.R.	—
10	Cl	*L*-Pro-Gly	**8** (50:50)	TBAB, DIEA, Bn_2NH	77 (**20**)	95:5
11	Br	*L*-Pro-*L*-Leu	**10** (48:52)	TBAB, DIEA, Bn_2NH	70 (**21**)	>99:1
12	Br	*L*-Leu-Gly	**3** (49:51)	TBAB, DIEA, Bn_2NH	48 (**16**)	55:45
13	Br	*L*-Leu-*L*-Ala	**4** (44:56)	TBAB, DIEA, Bn_2NH	51 (**18**)	64:36

[a] dr of S.M. before the reaction.
[b] All reactions were carried out in CH_2Cl_2 at rt.
[c] Isolated yields.
[d] The drs are determined by ^1H NMR of reaction mixture using the authentic products prepared from racemic phenylglycine as a standard.

of nucleophile (Table 2, entry 2) may be explained by less efficient epimerization process in the presence of TBAB. Although it is not exactly clear how iodide exerts its rate-accelerating effects on the substitution, these results in entries 9–13 can be taken to suggest that real intermediate for the substitution in the presence of TBAI is α-iodo acetamide rather than α-bromo and α-chloro acetamides.

Within the frame of a broad project aimed at asymmetric syntheses of various N-terminal functionalized peptide analogues, the scope of the methodology was examined with α-amino ester nucleophiles for the preparation of *N*-carboxyalkyl peptide analogues as shown in Table 3. Several *N*-carboxyalkyl peptides are known inhibitors of various metalloproteinases and angiotensin converting enzymes (ACE).[5] Treatment of *N*-(α-bromo-α-phenylacetyl)-*L*-leucine benzyl ester with glycine methyl ester hydrochloride (1.0 equiv), TBAI (1.0 equiv) and DIEA (2.2 equiv) in CH_2Cl_2 at rt provided the tripeptide analogue **25** in 99% yield with 86:14 dr (α*R*:α*S*) as shown in Table 3,

Table 3. Stereoselective syntheses of *N*-carboxyalkyl peptide derivatives

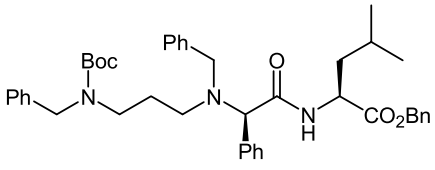


Entry[a,b]	AA′-OMe	AA-OBn	Product	Yield[c] (%)	dr[d] (α*R*:α*S*)
1	Gly-OMe	*L*-Leu-OBn	**25**	99	86:14
2	*L*-Ala-OMe	*L*-Leu-OBn	**26**	84	88:12
3	*D*-Ala-OMe	*L*-Leu-OBn	**27**	83	91:9
4	*L*-Leu-OMe	*L*-Leu-OBn	**28**	80	89:11
5	*D*-Leu-OMe	*L*-Leu-OBn	**29**	63	93:7
6	*L*-Phe-OMe	*L*-Leu-OBn	**30**	36	87:13
7	*D*-Phe-OMe	*L*-Leu-OBn	**31**	49	92:8
8	*L*-Leu-OMe	*L*-Pro-OBn	**32**	44	93:7

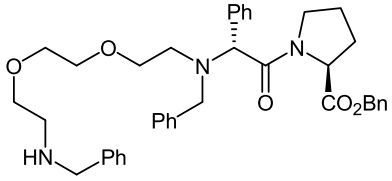
[a] Initial drs of S.M. are approximately 50:50.
[b] All reactions were carried out in CH_2Cl_2 for 24–48 h at rt.
[c] Isolated yields.
[d] The drs are determined by ^1H NMR of reaction mixture and HPLC analysis.

entry 1.[6] When two enantiomers of alanine methyl esters were used as nucleophiles, moderate double stereodifferentiation is observed as shown in entries 2 and 3. *N*-(α-Bromo-α-phenylacetyl)-*L*-leucine benzyl ester experienced matching with *D*-alanine methyl esters to afford tripeptide analogue **27** in a ratio of 91:9 (α*R*:α*S*) and mismatching with *L*-leucine amino ester to provide **26** in a 88:12 (α*R*:α*S*) ratio.[6,7] Furthermore, we found that this tendency of stereodifferentiation was also observed in both reactions of leucine and phenylalanine methyl ester nucleophiles (entries 4–7). As shown in Table 3, even mismatched cases (entries 2, 4 and 6) gave still high stereoselectivities, which allows us to have easy access to diverse *N*-carboxyalkyl peptide analogues. The substitution of *N*-(α-bromo-α-phenylacetyl)-*L*-proline benzyl ester with *L*-leucine methyl ester gave the tripeptide analogue **32** in 44% yield with 93:7 dr as shown in entry 8.

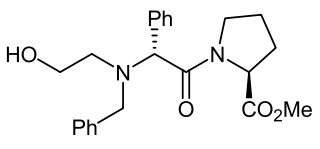
Finally, we were very pleased to demonstrate that this methodology is also efficient for the substitution with *N*-aminoxyalkyl and *N*-hydroxyalkyl amines, affording *N*-(aminoalkyl) peptides **33**–**34** and *N*-(hydroxyalkyl) peptide **35** with high selectivities and good yields as shown in Scheme 1. For example, when *N*-Boc *N*,*N*′-dibenzyl 1,3-propanediamine was used as a nucleophile for the reaction with *N*-(α-bromo-α-phenylacetyl)-*L*-leucine benzyl ester, the product **33** was formed in 63% yield with 96:4 dr. Also, treatment of *N*-(α-bromo-α-phenylacetyl)-*L*-proline benzyl ester with *N*,*N*′-dibenzyl 2,2′-(ethylenedioxy)diethyleneamine produced the mono substituted product **34** in 70% yield with 90:10 dr. Furthermore, we attempted the substitution reaction of *L*-proline methyl ester derivative with 2-(benzylamino)ethanol and found that the amino substituted product **35** was produced in 69% yield with 93:7 dr. For stereoselective preparation of various *N*,*N*-dialkyl substituted arylglycine peptide analogues, this methodology has potential advantages over *N*-alkylation of optically active arylglycine analogues in simplicity and cost. The products **33**–**35** should serve as versatile intermediates not only for the sequential asymmetric construction of non-natural oligopeptides but also for the asymmetric preparation of a variety of chiral ligands.



33 (63% yield, 96:4 dr)



34 (70% yield, 90:10 dr)



35 (69% yield, 93:7 dr)

Scheme 1.

3. Conclusion

We have shown that dynamic kinetic resolution of α-bromo and α-chloro amides in nucleophilic substitution reaction with dibenzylamine can be successfully applied towards the preparation of tri- and tetrapeptide analogues. Mechanistic investigations suggest that α-iodo acetamides is real intermediate for the nucleophilic substitutions of both α-bromo and α-chloro amides in the presence of TBAI. The methodology has also been successful for the N-terminal functionalization of peptides, affording a generalized and practical method for the asymmetric syntheses of *N*-carboxyalkyl, *N*-aminoalkyl and *N*-hydroxyalkyl peptide analogues. This mild and practical chemistry requires no special precautions and can be run on a multigram scale. The methodology of the present work should also be applicable to stereoselective syntheses of a number of related peptide analogues, now being used for the asymmetric syntheses of chiral ligands and macrocycles.

4. Experimental

4.1. General procedure for the preparation of 1–13

For α-bromo acetamides. Dipeptide or tripeptide alkyl ester (1.0 equiv), racemic α-bromo phenylacetic acid (1.0 equiv), DCC (1.0 equiv), Et_3N (2.2 equiv) and DMAP (0.2 equiv) were dissolved in CH_2Cl_2 and stirred at rt for 3 h. The precipitate was filtered off and the organic phase was washed with water. The organic phase was dried over $MgSO_4$, filtered and concentrated to provide the crude product that was purified by column chromatography on silica gel.

For α-chloro acetamides. Dipeptide or tripeptide alkyl ester (1.0 equiv), racemic α-chloro α-phenylacetyl chloride (1.0 equiv) and Et_3N (2.2 equiv) were dissolved in CH_2Cl_2 and stirred at rt for 2 h. The mixture was treated with extractive work up and the organic phase was dried over $MgSO_4$. Filtration and concentration provided the crude product that was purified by column chromatography on silica gel.

4.1.1. *N*-(α-Bromo-α-phenylacetyl)-glycine-(*S*)-leucine, methyl ester (2). A colorless oil was obtained in 55% yield. ^1H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.61–7.27 (m, 6H), 6.91–6.89 (m, 1H), 5.45, 5.39 (s, 1H), 4.60–4.55 (m, 1H), 4.05–4.00 (m, 2H), 3.71 (s, 3H), 1.62–1.47 (m, 3H), 0.90–0.89 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.5, 168.7, 168.5, 168.4, 137.3, 129.4, 128.9, 128.8, 128.4, 128.3, 52.8, 51.3, 50.6, 44.1, 41.5, 25.2, 23.2, 22.2. HRMS calcd for $C_{17}H_{24}BrN_2O_4$ ($M^+ + 1$): 399.0919. Found: 399.0954.

4.1.2. *N*-(α-Bromo-α-phenylacetyl)-(*S*)-leucine-glycine, methyl ester (3). A colorless oil was obtained in 49% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.50–7.27 (m, 7H), 5.53, 5.50 (s, 1H), 4.75–4.73 (m, 1H), 3.98–3.94 (m, 1H), 3.77–3.71 (m, 1H), 3.67, 3.65 (m, 3H), 1.71–1.57 (m, 3H) 0.94–0.82 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.9, 170.3, 168.4, 137.3, 129.4, 129.2, 129.1, 128.9, 128.3, 52.6, 50.6, 49.8, 41.7, 41.5, 25.1, 23.2, 22.6. HRMS calcd for $C_{17}H_{24}BrN_2O_4$ ($M^+ + 1$): 399.0919. Found: 399.0883.

4.1.3. *N*-(α-Bromo-α-phenylacetyl)-(*S*)-leucine-(*S*)-alanine, methyl ester (4). A pale yellow oil was obtained in 66% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.48–7.27 (m, 6H), 7.02–6.81 (m, 1H), 5.44, 5.43 (s, 1H), 4.54–4.46 (m, 2H), 3.73, 3.72 (s, 3H), 1.68–1.62 (m, 3H), 1.34–1.24 (m, 3H), 0.92–0.86 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.4, 171.5, 168.2, 137.3, 129.5, 129.3, 128.8, 128.2, 128.1, 52.8, 52.5, 50.9, 48.5, 41.3, 25.3, 23.2, 22.5, 18.3. HRMS calcd for $C_{18}H_{26}BrN_2O_4$ ($M^+ + 1$): 413.1076. Found: 413.1084.

4.1.4. *N*-(α-Bromo-α-phenylacetyl)-(*S*)-leucine-(*R*)-alanine, methyl ester (5). A colorless oil was obtained in 45% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.48–7.27 (m, 6H), 7.02–6.81 (m, 1H), 5.44, 5.43 (s, 1H), 4.54–4.46 (m, 2H), 3.73, 3.72 (s, 3H), 1.68–1.62 (m, 3H), 1.34–1.24 (m, 3H), 0.92–0.86 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.4, 171.5, 168.2, 137.3, 129.5, 129.3, 128.8, 128.2, 128.1, 52.8, 52.5, 50.9, 48.5, 41.3, 25.3, 23.2, 22.5, 18.3. HRMS calcd for $C_{18}H_{26}BrN_2O_4$ ($M^+ + 1$): 413.1076. Found: 413.1071.

4.1.5. *N*-(α-Bromo-α-phenylacetyl)-(*S*)-proline-glycine, methyl ester (7). A colorless oil was obtained in 27% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.52–7.25 (m, 6H), 5.62, 5.61 (s, 1H), 4.69–4.59 (m, 1H), 4.10–3.94 (m, 2H), 3.76–3.68 (m, 4H), 3.57–3.33 (m, 1H), 2.30–1.86 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.4, 170.4, 167.6, 135.9, 129.7, 129.6, 129.4, 128.7, 128.6, 61.0, 59.5, 52.7, 47.8, 41.7, 28.1, 25.4. HRMS calcd for $C_{16}H_{20}BrN_2O_4$ ($M^+ + 1$): 383.0606. Found: 383.0587.

4.1.6. *N*-(α-Chloro-α-phenylacetyl)-(*S*)-proline-glycine, methyl ester (8). A colorless oil was obtained in 55% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.50–7.25 (m, 6H), 5.63, 5.62 (s, 1H), 4.68–4.59 (m, 1H), 4.04–3.93 (m, 2H), 3.75–3.32 (m, 5H), 2.28–2.26 (m, 1H), 2.03–1.85 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.5, 170.4, 167.6, 135.8, 129.6, 129.4, 129.3, 128.7, 128.6, 61.0, 59.5, 52.6, 47.8, 41.5, 28.2, 25.4. HRMS calcd for $C_{16}H_{20}ClN_2O_4$ ($M^+ + 1$): 339.1122. Found: 339.1120

4.1.7. *N*-(α-Bromo-α-phenylacetyl)-(*S*)-proline-(*S*)-leucine, methyl ester (9). A colorless oil was obtained in 43% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.52–7.23 (m, 6H), 5.58, 5.56 (s, 1H), 4.70–4.62 (m, 1H), 4.52–4.43 (m, 1H), 3.72–3.40 (m, 5H), 2.37–2.34 (m, 1H), 2.04–1.46 (m, 6H), 0.97–0.79 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.5, 170.7, 167.7, 135.7, 129.7, 129.6, 129.3, 128.7, 128.6, 61.9, 59.2, 52.6, 51.4, 47.8, 41.5, 27.4, 25.5, 25.2, 23.3, 22.2. HRMS calcd for $C_{20}H_{28}BrN_2O_4$ ($M^+ + 1$): 439.1232. Found: 439.1248

4.1.8. *N*-(α-Chloro-α-phenylacetyl)-(*S*)-proline-(*S*)-leucine, methyl ester (10). A colorless oil was obtained in 68% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.52–7.29 (m, 6H), 5.60, 5.57 (s, 1H), 4.71–4.61 (m, 1H), 4.55–4.40 (m, 1H), 3.72–3.37 (m, 5H), 2.35–2.32 (m, 1H), 2.03–1.48 (m, 6H), 0.97–0.80 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.5, 170.7, 167.7, 136.0, 135.7, 129.6, 129.4, 129.3, 128.7, 128.5, 60.9, 58.9, 52.6, 51.4, 47.8, 41.4, 27.4, 25.5, 25.2, 23.3, 22.2. HRMS calcd for $C_{20}H_{28}BrN_2O_4$ ($M^+ + 1$): 395.1738. Found: 395.1737.

4.1.9. *N*-(α-Chloro-α-phenylacetyl)-(*S*)-proline-(*R*)-leucine, methyl ester (11). A colorless oil was obtained in 25% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.55–7.08 (m, 6H), 5.63, 5.59 (s, 1H), 4.75–4.64 (m, 2H), 3.76–3.61 (m, 3H), 3.58–3.41 (m, 2H), 2.36, 2.35 (m, 1H), 2.17–1.96 (m, 3H), 1.67–1.58 (m, 3H), 0.96–0.90 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.2, 170.6, 167.9, 135.5, 129.6, 129.5, 129.1, 128.8, 128.6, 61.0, 59.0, 52.6, 51.3, 47.8, 41.6, 27.5, 25.4, 25.2, 23.2, 22.2. HRMS calcd for $C_{20}H_{28}ClN_2O_4$ ($M^+ + 1$): 395.1738. Found: 395.1766.

4.1.10. *N*-(α-Chloro-α-phenylacetyl)-(*S*)-proline-(*S*)-leucine-(*S*)-alanine, methyl ester (12). A colorless oil was obtained in 49% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.49–7.04 (m, 7H), 5.60, 5.59 (s, 1H), 4.55–4.32 (m, 3H), 3.72–3.58 (m, 4H), 3.57–3.26 (m, 1H), 2.18–1.71 (m, 4H), 1.69–1.34 (m, 6H), 0.94–0.78 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.5, 172.4, 171.6, 167.6, 135.7, 129.7, 129.4, 129.3, 129.1, 128.6, 61.3, 59.3, 52.7, 52.4, 48.5, 47.9, 40.8, 28.4, 25.5, 25.4, 23.3, 22.1, 18.2. HRMS calcd for $C_{23}H_{33}ClN_3O_5$ ($M^+ + 1$): 466.2109. Found: 466.2101.

4.1.11. *N*-(α-Chloro-α-phenylacetyl)-(*S*)-proline-(*S*)-leucine-(*R*)-alanine, methyl ester (13). A colorless oil was obtained in 17% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.55–6.99 (m, 7H), 5.61 (s, 1H), 4.54–4.47 (m, 3H), 3.73–3.67 (m, 4H), 3.66–3.31 (m, 1H), 2.28–1.38 (m, 10H), 0.94–0.78 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.6, 171.9, 171.5, 168.0, 135.5, 129.8, 129.7, 129.6, 129.2, 128.7, 61.7, 59.3, 52.7, 52.1, 48.6, 48.0, 40.4, 28.7, 25.5, 25.3, 23.5, 21.9, 17.9. HRMS calcd for $C_{23}H_{33}ClN_3O_5$ ($M^+ + 1$): 466.2109. Found: 466.2080.

4.2. General procedure for asymmetric preparation of peptide analogues 14–35

To a solution of (α*RS*)-α-bromo or α-chloro acetamides in dry CH_2Cl_2 (ca. 0.1 M) at rt was added amine nucleophile (1.2 equiv), TBAI or TBAB (1.0 equiv) and DIEA (1.0 or 2.2 equiv). The resulting reaction mixture was stirred at rt for 24 h. The solvent in mixture was evaporated and the crude product was purified by column chromatography on silica gel.

4.2.1. *N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl]-glycine-(*S*)-leucine, methyl ester (15). A colorless oil was obtained in 69% yield (two diastereomers). ^{1}H NMR ($CDCl_3$, 400 MHz) 8.07–8.06 (m, 1H), 7.40–7.21 (m, 15H), 7.03–7.01 (d, J=8.2 Hz, 1H) 4.64–4.52 (m, 1H), 4.44 (s, 1H), 4.13–4.08 (m, 2H), 3.84 (m, 2H), 3.67 (m, 3H), 3.27 (d, J=13.7 Hz, 2H), 1.53–1.49 (m, 2H), 1.26–1.22 (m, 1H),

0.87–0.80 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.5, 172.8, 169.1, 138.8, 134.3, 130.7, 129.4, 129.3, 129.0, 128.7, 128.6, 128.4, 127.8, 68.4, 55.1, 52.6, 51.2, 43.7, 41.4, 25.4, 23.2, 22.2. HRMS calcd for $C_{31}H_{38}N_3O_4$ ($M^+ + 1$): 516.2862. Found: 516.2841.

4.2.2. *N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl]-(*S*)-leucine-glycine, methyl ester (16). A colorless oil was obtained in 69% yield (two diastereomers). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.80 (d, J=6.4 Hz, 1H), 7.41–7.24 (m, 15H), 6.86 (m, 1H), 4.56 (m, 1H), 4.44 (s, 1H), 3.94–3.84 (m, 4H), 3.69 (s, 3H), 3.23 (d, J=14.0 Hz, 2H), 1.78–1.59 (m, 3H), 0.95–0.88 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.6, 172.5, 170.4, 138.8, 133.8, 131.0, 129.4, 129.1, 129.0, 128.7, 128.6, 128.4, 127.8, 67.7, 54.9, 52.6, 51.8, 41.6, 41.4, 25.2, 23.5, 22.4. HRMS calcd for $C_{31}H_{38}N_3O_4$ ($M^+ + 1$): 516.2862. Found: 516.2887.

4.2.3. *N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl]-(*S*)-leucine-(*S*)-alanine, methyl ester (17). A colorless oil was obtained in 64% yield (two diastereomers). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.87 (d, J=7.5 Hz, 1H), 7.37–7.25 (m, 15H), 6.78 (d, J=7.3 Hz, 1H), 4.57–4.51 (m, 2H), 4.42 (s, 1H), 4.11 (d, J=13.7 Hz, 2H), 3.71 (s, 3H), 3.27 (d, J=13.7 Hz, 2H), 1.73–1.56 (m, 3H), 1.28–1.23 (m, 3H), 0.93–0.87 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.5, 172.3, 171.9, 138.7, 134.1, 130.8, 129.3, 129.0, 128.6, 68.0, 54.9, 52.8, 51.9, 48.4, 41.6, 25.2, 23.4, 22.3, 18.4. HRMS calcd for $C_{32}H_{40}N_3O_4$ ($M^+ + 1$): 530.3019. Found: 530.3043.

4.2.4. *N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl]-(*S*)-leucine-(*R*)-alanine, methyl ester (18). A colorless oil was obtained in 72% yield (two diastereomers). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.77 (d, J=8.2 Hz, 1H), 7.41–7.26 (m, 15H), 6.78 (d, J=7.4 Hz, 1H), 4.56–4.48 (m, 2H), 4.44 (s, 1H), 3.89–3.84 (m, 2H), 3.63 (s, 3H), 3.22 (d, J=13.6 Hz, 2H), 1.76–1.53 (m, 3H), 1.37–1.35 (m, 3H), 0.95–0.87 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.5, 172.6, 171.9, 138.7, 133.9, 131.0, 130.6, 129.4, 129.1, 129.0, 128.9, 128.7, 128.4, 127.8, 67.8, 54.8, 52.7, 51.7, 48.5, 25.2, 23.5, 22.3, 18.5. HRMS calcd for $C_{32}H_{40}N_3O_4$ ($M^+ + 1$): 530.3019. Found: 530.3011.

4.2.5. *N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl]-(*S*)-proline-glycine, methyl ester (20). A colorless oil was obtained in 91% yield (two diastereomers). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.77–7.71 (m, 1H), 7.39–7.19 (m, 16H), 4.77–4.74 (m, 1H), 4.64 (s, 1H), 4.18–4.09 (m, 2H), 3.95–3.86 (m, 4H), 3.76 (s, 3H), 2.96 (m, 1H), 2.75 (m, 1H), 2.35 (m, 1H), 2.03–1.66 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.7, 172.2, 170.5, 140.8, 136.8, 130.4, 129.7, 129.5, 129.2, 129.1, 129.0, 128.8, 128.7, 128.4, 128.3, 127.6, 127.3, 64.5, 60.1, 55.1, 52.7, 47.3, 41.8, 27.8, 25.2. HRMS calcd for $C_{30}H_{34}N_3O_4$ ($M^+ + 1$): 500.2549. Found: 500.2538.

4.2.6. *N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl]-(*S*)-proline-(*S*)-leucine, methyl ester (21). A colorless oil was obtained in 85% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.54 (d, J=7.6 Hz, 1H), 7.36–7.20 (m, 16H), 4.71–4.63 (m, 3H), 3.86 (s, 4H), 3.76 (s, 3H), 2.96, 2.95 (m, 1H), 2.76 (m, 1H), 2.34 (m, 1H), 1.97–1.90 (m, 2H), 1.79–1.67 (m, 4H), 1.02–0.99 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.7, 173.5, 171.7, 140.7, 136.7, 130.0, 129.6, 129.4, 129.2, 129.0, 128.9, 128.8, 128.7, 128.6, 128.4, 127.6, 127.4, 64.4, 60.3, 54.9, 52.7, 51.6, 47.4, 42.0, 27.7, 25.3, 25.2, 23.4, 22.4. HRMS calcd for $C_{34}H_{42}N_3O_4$ ($M^+ + 1$): 556.3175. Found: 556.3178.

4.2.7. *N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl]-(*S*)-proline-(*R*)-leucine, methyl ester (22). A colorless oil was obtained in 77% yield (two diastereomers). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.94 (d, J=7.8 Hz, 1H), 7.41–7.22 (m, 15H), 4.80 (d, J=6.6 Hz, 1H), 4.66 (m, 2H), 3.93–3.91 (m, 4H), 3.72 (s, 3H), 2.96 (m, 1H), 2.74 (m, 1H), 2.44 (m, 1H), 1.89–1.64 (m, 6H), 1.03–1.00 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 174.2, 173.5, 171.4, 140.8, 136.7, 129.4, 129.2, 129.0, 128.7, 128.5, 127.3, 64.5, 60.1, 54.9, 52.6, 51.5, 47.3, 42.0, 27.1, 25.3, 25.1, 23.4, 22.4. HRMS calcd for $C_{34}H_{42}N_3O_4$ ($M^+ + 1$): 556.3175. Found: 556.3162.

4.2.8. *N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl]-(*S*)-proline-(*S*)-leucine-(*S*)-alanine, methyl ester (23). A colorless oil was obtained in 71% yield (two diastereomers). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.41–7.22 (m, 16H), 6.96 (d, J=7.1 Hz, 1H), 4.68–4.58 (m, 4H), 3.90–3.82 (m, 4H), 3.74 (s, 3H), 2.98–2.70 (m, 2H), 2.25 (m, 1H), 1.91–1.75 (m, 6H), 1.47–1.42 (m, 3H), 1.03–0.91 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.6, 173.5, 172.0, 171.9, 140.6, 136.6, 129.7, 129.5, 129.3, 129.2, 129.1, 128.9, 128.7, 128.5, 127.4, 64.2, 60.4, 55.0, 54.9, 52.8, 52.5, 48.6, 47.4, 41.6, 28.3, 25.2, 23.6, 23.3, 18.6. HRMS calcd for $C_{37}H_{47}N_4O_5$ ($M^+ + 1$): 627.3546. Found: 627.3546.

4.2.9. *N*-[(*R*)-α-Phenyl-*N*,*N*-(dibenzyl)glycinyl]-(*S*)-proline-(*S*)-leucine-(*R*)-alanine, methyl ester (24). A colorless oil was obtained in 68% yield (two diastereomers). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.45–7.18 (m, 17H), 4.67–4.58 (m, 4H), 3.94–3.78 (m, 4H), 3.72–3.64 (m, 3H), 2.98–2.73 (m, 2H), 2.22 (m, 1H), 1.91–1.48 (m, 9H), 1.02–0.86 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.6, 173.4, 172.1, 172.0, 140.6, 136.5, 129.9, 129.8, 129.5, 129.3, 129.1, 128.9, 128.8, 128.7, 128.5, 127.7, 127.4, 64.6, 60.8, 54.9, 52.7, 52.3, 48.6, 47.5, 41.1, 28.7, 25.4, 23.6, 23.4, 22.2, 18.6. HRMS calcd for $C_{37}H_{47}N_4O_5$ ($M^+ + 1$): 627.3546. Found: 627.3536.

4.2.10. *N*-[1-(Methoxycarbonyl)methyl]-(*R*)-phenylglycine-(*S*)-leucine, benzyl ester (25). A colorless oil was obtained in 99% yield (two diastereomers). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.49 (d, J=8.6 Hz, 1H), 7.39–7.28 (m, 10H), 5.16–5.08 (m, 2H), 4.69 (m, 1H), 4.26 (s, 1H), 3.71 (s, 3H), 3.46 (m, 2H), 2.30 (br, 1H), 1.70–1.57 (m, 3H), 0.92–0.82 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.1, 172.8, 171.8, 138.8, 135.8, 129.3, 129.2, 128.9, 128.6, 128.5, 128.3, 128.1, 128.0, 127.9, 127.7, 67.6, 52.4, 51.0, 50.8, 41.8, 25.4, 25.3, 22.2. HRMS calcd for $C_{24}H_{31}N_2O_5$ ($M^+ + 1$): 427.2233. Found: 427.2207.

4.2.11. *N*-[1-(*S*)-(Methoxycarbonyl)ethyl]-(*R*)-phenylglycine-(*S*)-leucine, benzyl ester (26). A colorless oil was obtained in 84% yield (two diastereomers). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.36–7.23 (m, 10H), 5.18–5.08 (m, 2H), 4.67 (m, 1H), 4.31 (s, 1H), 3.69 (s, 3H), 3.26 (m, 1H), 2.25 (br, 1H), 1.66–1.53 (m, 3H), 1.30 (d, J=6.8 Hz, 3H), 0.90–0.85 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 175.3,

173.1, 172.2, 138.9, 135.8, 129.3, 129.2, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.3, 127.5, 77.5, 67.5, 54.6, 52.4, 51.1, 42.0, 25.3, 23.2, 22.2 19.1. HRMS calcd for $C_5H_{33}N_2O_5$ ($M^+ + 1$): 441.2389. Found: 441.2379.

4.2.12. *N*-[1-(*R*)-(Methoxycarbonyl)ethyl]-(*R*)-phenylglycine-(*S*)-leucine, benzyl ester (27). A colorless oil was obtained in 83% yield (two diastereomers). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.79 (d, $J=8.6$ Hz, 1H), 7.41–7.27 (m, 10H), 5.18 (m, 2H), 4.69 (m, 1H), 4.16 (s, 1H) 3.71 (s, 3H), 3.34 (m, 1H) 2.25 (br, 1H), 1.74–1.61 (m, 3H), 1.33 (d,, $J=$ 7.3 Hz, 3H), 0.96 (d, $J=6.4$ Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 175.8, 172.9, 172.1, 139.2, 135.8, 129.3, 129.2, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 129.3, 128.0, 67.5, 66.7, 56.4, 52.4, 51.0, 41.8, 25.6, 23.3, 22.2, 19.9. HRMS calcd for $C_{25}H_{33}N_2O_5$ ($M^+ + 1$): 441.2389. Found: 441.2420.

4.2.13. *N*-[1-(*S*)-(Methoxycarbonyl)-3-methylbutyl]-(*R*)-phenylglycine-(*S*)-leucine, benzyl ester (28). A colorless oil was obtained in 80% yield (two diastereomers). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.36–6.99 (m, 10H), 6.99 (d, $J=8.4$ Hz, 1H), 5.17 (m, 2H), 4.69 (m, 1H), 4.26 (m, 1H), 3.69 (S, 3H), 3.13 (br, 1H), 2.25 (br, 1H), 1.73–1.47 (m, 6H), 0.93–0.74 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) 175.7, 172.9, 171.8, 138.7, 135.8, 129.3, 129.2, 129.0, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 127., 67.4, 66.7, 57.6, 52.2, 51.1, 42.8, 41.9, 25.4, 25.3, 25.1, 25.0, 23.2, 22.2. HRMS calcd for $C_{28}H_{39}N_2O_5$ ($M^+ + 1$): 483.2859. Found: 483.2842.

4.2.14. *N*-[1-(*R*)-(Methoxycarbonyl)-3-methylbutyl]-(*R*)-phenylglycine-(*S*)-leucine, benzyl ester (29). A colorless oil was obtained in 63% yield (two diastereomers). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.81 (d, $J=8.8$ Hz, 1H), 7.38–7.25 (m, 10H), 5.13 (m, 2H), 4.72 (m, 1H), 4.11 (s, 1H), 3.71 (s, 3H), 3.34 (m, 1H), 2.09 (br, 1H), 1.89–1.47 (m, 6H), 0.97–0.86 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) 176.0, 172.9, 172.1, 129.5, 135.8, 129.2, 129.0, 128.9, 128.8, 128.6, 128.4, 128.3, 128.2, 128.1, 127.9, 67.5, 66.7, 59.8, 52.3, 50.9, 43.8, 42.2, 25.4, 25.3, 23.2, 23.1, 22.9, 22.2. HRMS calcd for $C_{28}H_{39}N_2O_5$ ($M^+ + 1$): 483.2859. Found: 483.2867.

4.2.15. *N*-[1-(*S*)-(Methoxycarbonyl)-2-phenylethyl]-(*R*)-phenylglycine-(*S*)-leucine, benzyl ester (30). A colorless oil was obtained in 36% yield (two diastereomers). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.35–7.09 (m, 16H), 5.16–5.07 (m, 2H), 4.60 (m, 1H), 4.24 (s, 1H), 3.65 (s, 3H), 3.40–3.39 (m, 1H), 3.05–3.00 (m, 1H), 2.90–2.79 (m, 1H), 2.27 (br, 1H), 1.66–1.46 (m, 3H), 0.90–0.74 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 174.4, 172.8, 171.8, 138.1, 137.2, 135.8, 130.2, 129.6, 129.2, 129.0, 128.9, 128.8, 128.7, 128.6, 128.4, 127.6, 127.3, 67.4, 65.9, 60.5, 52.3, 51.1, 41.7, 39.8, 25.3, 23.3, 22.2. HRMS calcd for $C_{31}H_{37}N_2O_5$ ($M^+ + 1$): 517.2702. Found: 517.2688.

4.2.16. *N*-[1-(*R*)-(Methoxycarbonyl)-2-phenylethyl]-(*R*)-phenylglycine-(*S*)-leucine, benzyl ester (31). A colorless oil was obtained in 49% yield (two diastereomers). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.37–7.25 (m, 16H), 5.10 (q, $J=$ 12.3 Hz, 2H), 4.47–4.44 (m, 1H), 4.09 (s, 1H), 3.73 (s, 3H), 3.41–3.39 (m, 1H), 3.03–2.68 (m, 2H), 2.17 (d, $J=$ 12.6, 1H), 1.39–1.36 (m, 2H), 1.01–0.84 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz) 175.0, 172.5, 171.7, 139.4, 138.0, 136.0, 130.0, 129.8, 129.3, 129.2, 129.0, 128.9, 128.8, 128.7, 128.1, 127.9, 127.4, 67.3, 66.5, 63.0, 52.6, 50.5, 41.3, 40.6, 25.3, 23.3, 22.0. HRMS calcd for $C_{31}H_{37}N_2O_5$ ($M^+ + 1$): 517.2702. Found: 517.2683.

4.2.17. *N*-[1-(*S*)-(Methoxycarbonyl)-3-methylbutyl]-(*R*)-phenylglycine-(*S*)-proline, benzyl ester (32). A colorless oil was obtained in 44% yield (two diastereomers). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.37–7.24 (m, 10H), 7.15 (m, 1H), 5.19 (m, 2H), 4.50 (m, 2H), 3.69 (s, 3H), 3.55 (m, 1H), 3.08 (m, 2H), 2.85 (br, 1H), 1.99–1.43 (m, 7H), 0.83 (d, $J=6.6$ Hz, 3H), 0.65 (d, $J=6.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 175.9, 172.3, 171.6, 138.2, 136.2, 129.5, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 67.1, 63.5, 59.9, 56.6, 52.1, 47.2, 427, 32.0, 29.4, 29.3, 25.2, 22.1, 22.0. HRMS calcd for $C_{27}H_{35}N_2O_5$ ($M^+ + 1$): 467.2546. Found: 467.2523.

4.2.18. *N*-Benzyl-*N*-(*N*-Boc-*N*-benzyl-3-aminopropyl)-(*R*)-phenylglycine-(*S*)-leucine, benzyl ester (33). A colorless oil was obtained in 63% yield (two diastereomers). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.46–7.19 (m, 20H), 5.17 (m, 2H), 4.70 (m, 1H), 4.34 (m, 3H), 3.81 (m, 1H), 3.30–3.08 (m, 3H), 2.57 (m, 1H), 2.16 (m, 1H), 1.7–1.26 (m, 14H), 0.97–0.88 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.2, 171.9, 139.1, 135.9, 134.3, 131.6, 130.7, 129.2, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 80.1, 69.0, 67.4, 59.4, 51.0, 48.5, 45.1, 41.9, 28.9, 26.2, 25.4, 23.3, 22.2. HRMS calcd for $C_{43}H_{54}N_3O_5$ ($M^+ + 1$): 692.4063. Found: 692.4047.

4.2.19. *N*-Benzyl-*N*-[2-[2-(*N*-benzyl-2-aminoethoxy)-ethoxy]ethyl]-(*R*)-phenylglycine-(*S*)-leucine, benzyl ester (34). A colorless oil was obtained in 70% yield (two diastereomers). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.38–7.23 (m, 20H), 5.29 (m, 2H), 4.72 (m, 1H), 4.65 (m, 1H), 3.89–3.68 (m, 3H), 3.44–3.30 (m, 9H), 3.10–2.68 (m, 5H), 1.94–1.69 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.6, 172.0, 141.1, 140.0, 137.4, 136.3, 130.0, 129.8, 129.7, 129.6, 129.5, 129.4, 129.3, 129.2, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 128.2, 128.1, 127.3, 127.2, 127.0, 71.8, 70.7, 70.2, 67.9, 66.0, 59.3, 56.7, 53.0, 52.2, 51.3, 50.0, 46.9, 29.5, 25.3. HRMS calcd for $C_{40}H_{48}N_3O_5$ ($M^+ + 1$): 650.3594. Found: 650.3582.

4.2.20. *N*-Benzyl-*N*-(2-hydroxyethyl)-(*R*)-phenylglycine-(*S*)-proline, methyl ester (35). A colorless oil was obtained in 69% yield (two diastereomers). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.43–7.24 (m, 10H), 4.68 (s, 1H), 4.55 (m, 1H), 3.88 (m, 2H), 3.81 (s, 3H), 3.60 (m, 1H), 3.37 (m, 1H), 2.96 (m, 3H), 2.15–1.67 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.4, 171.8, 140.2, 13.6, 130.4, 130.0, 129.7, 129.5, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 65., 59.8, 59.3, 55.7, 52.8, 52.6, 46.8, 29.4, 25.2. HRMS calcd for $C_{23}H_{29}N_2O_4$ ($M^+ +$ 1): 397.2127. Found: 397.2125.

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References and notes

1. (a) Yuan, Z.; Blomberg, D.; Sethson, I.; Brickmann, K.; Ekholm, K.; Johansson, B.; Nilsson, A.; Kihlberg, J. *J. Med. Chem.* **2002**, *45*, 2512. (b) Fujisawa, T.; Igeta, K.; Odake, S.; Morita, Y.; Yasuda, J.; Morikawa, T. *Bioorg. Med. Chem.* **2002**, *10*, 2569. (c) Souers, A. J.; Ellman, J. A. *Tetrahedron* **2001**, *57*, 7431. (d) Haskell-Luevano, C.; Rosenquist, A.; Souers, A.; Khong, K. C.; Ellman, J. A.; Cone, R. D. *J. Med. Chem.* **1999**, *42*, 4380.
2. (a) Nam, J.; Chang, J.-Y.; Shin, E.-k.; Kim, H. J.; Kim, Y.; Jang, S.; Park, Y. S. *Tetrahedron* **2004**, *60*, 6311. (b) Nam, J.; Chang, J.-Y.; Hahm, K.-S.; Park, Y. S. *Tetrahedron Lett.* **2003**, *44*, 7727.
3. (a) Valenrod, Y.; Myung, J.; Ben, R. N. *Tetrahedron Lett.* **2004**, *45*, 2545. (b) Nam, J.; Lee, S.-k.; Park, Y. S. *Tetrahedron* **2003**, *59*, 2397. (c) Nam, J.; Lee, S.-k.; Kim, K. Y.; Park, Y. S. *Tetrahedron Lett.* **2002**, *43*, 8253. (d) Lee, S.-k.; Nam, J.; Park, Y. S. *Synlett* **2002**, 790. (e) Caddick, S.; Afonso, C. A. M.; Candeias, S. X.; Hitchcock, P. B.; Jenkins, K.; Murtagh, L.; Pardoe, D.; Santos, A. G.; Treweeke, N. R.; Weaving, R. *Tetrahedron* **2001**, *57*, 6589. (f) Lee, S.-k.; Lee, S. Y.; Park, Y. S. *Synlett* **2001**, 1941. (g) Ben, R. N.; Durst, T. *J. Org. Chem.* **1999**, *64*, 7700.
4. Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.
5. (a) Huffman, M. A.; Reider, P. J. *Tetrahedron Lett.* **1999**, *40*, 831. (b) Chapman, K. T.; Kopka, I. E.; Durette, P. L.; Esser, C. K.; Lanza, T. J.; Izquierdo-Martin, M.; Niedzwiecki, L.; Chang, B.; Harrison, R. K.; Kuo, D. W.; Lin, T.-Y.; Stein, R. L.; Hagmann, W. K. *J. Med. Chem.* **1993**, *36*, 4293–4301.
6. The absolute configurations of **25**, **26** and **27** were assigned as αR by comparison to the ^{1}H NMR of authentic epimers individually prepared from the coupling of *L*-leucine derivative and (*S*)- or (*R*)-phenylglycine derivative followed by N-alkylation with methyl α-bromo acetate or methyl (*S*)-α-bromo-α-methyl acetate. The absolute configurations of **28**–**32** are provisionally assigned by analogy to the formation of **25**, **26** and **27**.
7. In the substitution reactions of *L*-alanine methyl ester and *L*-leucine methyl ester with methyl α-bromo-α-phenyl acetate under the same condition, the (αS)-products were produced as major isomer with 65:35 and 70:30 dr, respectively. The absolute configurations of major (αS)-isomers were assigned by comparison to the ^{1}H NMR of authentic epimers individually prepared from the substitution of methyl (*R*)-α-bromo α-methyl or α-isobutyl acetate with (*S*)-phenylglycine methyl ester on the basis of inversion mechanism.