lution was stirred at room temperature for 7 min and then 4 mL of anhydrous ether and 10 mL of cyclohexane were added to precipitate the product. The solvents were removed by evaporation under high vacuum. The tan residue was triturated with three 10-mL portions of anhydrous ether and dried to an off-white powder. The powder was dissolved in 4 mL of water and filtered through a cotton plug to remove insoluble impurities. The filtrate was adjusted to pH 2.5, causing precipitation of the product as a white powder: 22 mg, 67%; mp 211-214 °C dec (lit.[1] mp 214-216 °C dec); $[\alpha]^{23}_D = -148°$ $c = 1$, 1% aqueous $NaHCO_3$) [lit.[1] $[\alpha]_D = -146°$ ($c = 1.0$, 1% aqueous $NaHCO_3$); ^1H NMR (D_2O + NaOD) δ 7.36 (2 H, d, $J = 8.9$ Hz, Ar), 7.06 (2 H, d, $J = 8.6$ Hz, Ar), 6.99 (2 H, d, $J = 8.6$ Hz, Ar), 6.60 (2 H, d, $J = 8.9$ Hz, Ar), 5.20 (1 H, s, H-5), 5.03 (1 H, dd, $J = 5$, 1.8 Hz, H-3), 4.16 (2 H, t, $J = 6.5$ Hz, H-7'), 3.82 (1 H, t, $J = 5,5$ Hz, H-9'), 3.44 (1 H, t, $J = 5.5$ Hz, H-4α), 3.30 (1 H, dd, $J = 2$, 4 Hz, H-4β), 2.14 and 1.99 (2 H, 2 cm, H-8').

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Registry No. **1**, 39391-39-4; **2**, 60134-71-6; **2** trifluoroacetate, 123004-78-4; **3**, 59511-12-5; **4**, 61425-17-0; **4** trifluoroacetate, 123004-81-9; **5**, 63555-59-9; **6**, 63598-46-9; **7**, 65309-11-7; **12**, 111216-46-7; **13**, 110207-46-0; **14**, 123004-73-9; **15** (R = H), 27460-85-1; **16** (R = H), 110207-48-2; **27** (R = R' = *t*-Bu; X = OH), 110207-49-3; **27** (R = R' = *t*-Bu; X = Br), 123004-74-0; **28** (R = CH_2Ph), 26787-75-7; **29**, 123004-75-1; **30**, 123004-79-5; **31** (R = Me), 110207-50-6; **31** (R = H), 110207-53-9; **32** (R = CH_2Ph), 123004-76-2; **32**·HCl (R = H), 123004-77-3; **33**, 110269-45-9; **34**, 123004-80-8; **37**, 15206-55-0; **38**, 110207-51-7; **39**, 110207-52-8; D-[*p*-(benzyloxy)phenyl]glycine, 69489-40-3; D-[*p*-(benzyloxy)phenyl]glycine *tert*-butyl ester toluenesulfonate salt, 123004-72-8; L-Ox-serine dicyclohexylammonium salt, 48201-16-7; D-(*p*-hydroxyphenyl)glycine, 22818-40-2; *α-tert*-butyl *N*-(*tert*-butoxycarbonyl)-D-aspartate, 77004-75-2; sodium (*p*-hydroxybenzoyl)formate, 54537-30-3.

Asymmetric Alkylations of a Phenylalanylglycinate Equivalent. Novel Route to Dipeptides Bearing α-Alkyl-α-amino Acid Residues

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Abstract: Asymmetric single and double alkylations of chiral β-lactam acetate **1**, which is a chiral glycinate as well as a phenylalanylglycinate equivalent, are studied. First, the sequential asymmetric double alkylation of **1a** is performed to give the corresponding doubly alkylated β-lactam esters **3** (>99% de) in high yields, which can readily be converted to the corresponding dipeptides (**4**) via dissolving metal reduction in good yield. The salient advantage of this method is that a quaternary chiral center of desired configuration can be created just by changing the order of the addition of two alkyl halides used ($R^1 \neq R^2$). Remarkable effect of temperature on stereoselectivity is observed in the asymmetric single alkylation of **1a**, e.g., in the lithium enolate formation and alkylation of **1a** with allyl bromide; the observed stereoselectivities (R/S) are 7.6/1 at −95 °C, >50/1 at −78 °C, 7.9/1 at −50 °C, and 4.4/1 at −30 °C. Similar dependence of stereoselectivity on the reaction temperature is also observed for the reactions with methyl iodide and benzyl bromide. When ethyl bromoacetate was used as an electrophile, the reaction gave the highest stereoselectivity at −97 °C (>50/1) rather than at −78 °C, and the stereoselectivity decreased along with the increase of temperature. A rationale for the observed effect of temperature on stereoselectivity is proposed. The single alkylation products can be readily converted to the corresponding dipeptides through dissolving metal reduction and then to amino acids by hydrolysis; hence this asymmetric single alkylation serves as a new and effective method for the synthesis of enantiomerically pure non-protein amino acids and their dipeptides. Finally, the sequential asymmetric triple alkylation of **1a** with methyl iodide, allyl bromide, and methyl iodide is successfully achieved to give **5a-1** with virtually complete stereoselectivity. Deprotection of the *tert*-butyl ester of **5a-1** followed by the cleavage of β-lactam ring as well as the removal of *N*-protection with $Li/NH_3/THF/t$-BuOH at −78 °C gave enantiomerically pure (S)-α-methylphenylalanyl-(R)-α-allylalanine (**6a-1**) after purification on an ion-exchange column.

The significance of non-protein amino acids has recently been recognized in connection with design and synthesis of enzyme inhibitors as potential pharmaceutical drugs and also for the study of enzymatic reaction mechanisms.[2-5] In particular, α-alkyl-α-amino acids have been attracting medicinal and biochemical interests, i.e., (a) those amino acids which are known to be powerful enzyme inhibitors for e.g., dopa,[2] ornithine,[3] glutamate,[3] *S*-adenosylmethionine (SAM) decarboxylases,[4] and aspartate aminotransferase[5] and (b) those amino acids which act as conformational modifiers for physiologically active peptides.[6] α-Alkyl-α-amino acids also provide a challenging synthetic problem for chemists since the α-alkyl-α-amino acids have chiral quaternary carbons, and thus conventional enzymatic optical resolution technology cannot be applied effectively, viz., no racemization can take place at the chiral α-carbons, and thus D isomers cannot be recycled to the optical resolution process.[7] Therefore, the asymmetric synthesis of optically pure α-alkyl-α-amino acids is

(1) Reseach Fellow, 1988-1989, on leave from Central Glass Co., Ltd., Tokyo Research Center, Kawagoe, Saitama, Japan.

(2) E.g.: (a) Saari, W. S.; Halczenko, W.; Cochran, D. W.; Dobrinska, M. R.; Vincek, W. C.; Titus, D. G.; Gaul, S. L.; Sweet, C. S. *J. Med. Chem.* **1984**, *27*, 713. (b) Saari, W. S.; Freedman, M. B.; Hartman, R. D.; King, S. W.; Raab, A. W.; Randall, W. C.; Engelhardt, E. L.; Hirschmann, R.; Rosegay, A.; Ludden, C. T.; Scriabine, A. *Ibid.* **1978**, *21*, 746.

(3) Jung, M. J. In *Chemistry and Biochemistry of Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: New York, 1985; p 227.

(4) Ramalingam, K.; Woodard, R. W. *Tetrahedron Lett.* **1985**, *26*, 1135.

(5) Walsh, J. J.; Metzler, D. E.; Powell, D.; Jacobson, R. A. *J. Am. Chem. Soc.* **1980**, *102*, 7136.

(6) Paul, P. K. C.; Sukumar, M.; Bardi, R.; Piazzesi, A. M.; Valle, G.; Toniolo, C.; Balaram, P. *J. Am. Chem. Soc.* **1986**, *108*, 6363 and references cited therein.

(7) For recent reports on enzymic resolution of α-alkyl-α-amino acids: (a) Kruizinga, W. H.; Bolster, J.; Kellog, R. M. *J. Org. Chem.* **1988**, *53*, 1826. (b) Keller, J. W.; Hamilton, B. J. *Tetrahedron Lett.* **1986**, *27*, 1249.

0002-7863/90/1512-770$02.50/0

Scheme I

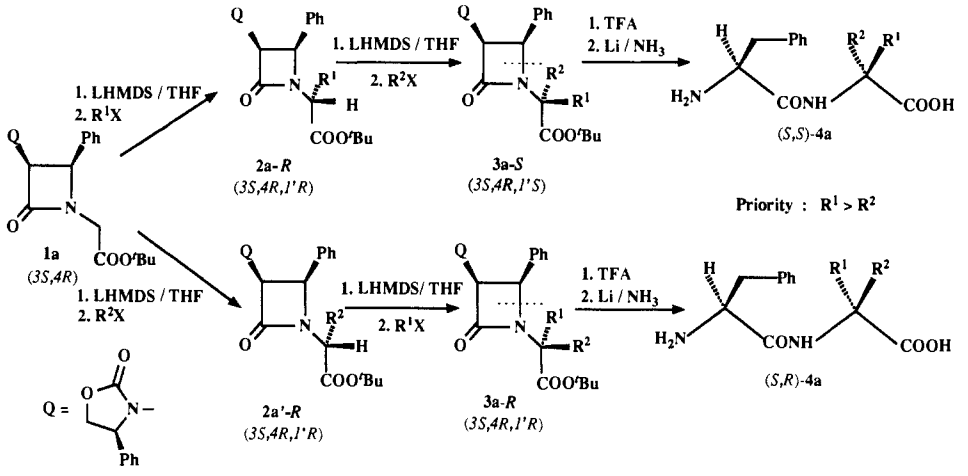


Table I. Asymmetric Single and Double Alkylations of β-Lactam Ester **1**[a]

			2				3		
entry	1	R^1X	yield (%)[b]	% de[c]	config[e]	R^2X	yield (%)[b]	% de[d]	config
1	**1a**	MeI	90			CH_2=$CHCH_2Br$	85	>99	3*S*,4*R*,1′*R*
2	**1b**	MeI	86			CH_2=$CHCH_2Br$	77	>99	3*R*,4*S*,1′*S*
3	**1b**	CH_2=$CHCH_2Br$	85			MeI	94	>99	3*R*,4*S*,1′*R*
4	**1b**	MeI	86			$PhCH_2Br$	79	>99	3*R*,4*S*,1′*S*
5	**1a**	MeI	89 (95)[c]	>96	*R*				
6	**1a**	CH_2=$CHCH_2Br$	80 (95)[c]	>96	*R*				
7	**1a**	$PhCH_2Br$	73 (93)[c]	>96	*R*				
8	**1a**	$BrCH_2COOEt$	79 (94)[c]	>96	*R*				

[a] All reactions were run with 0.1–0.2 mmol of **1**, 0.3–0.6 mmol of alkyl halides (3 equiv) in THF (7.5–15 mL) by adding LHMDS (1.0 equiv) in THF/hexane to the solution of **1** in THF. [b] Isolated yield unless otherwise noted. [c] Determined by ^1H NMR analysis. [d] Determined by HPLC analysis. [e] Configuration of substituted glycinate moiety.

the method of choice.[7-13] We will describe here effective new methods for the asymmetric synthesis of dipeptides bearing α-alkyl-α-amino acid residues through an application of the "β-lactam synthon method".[13-16]

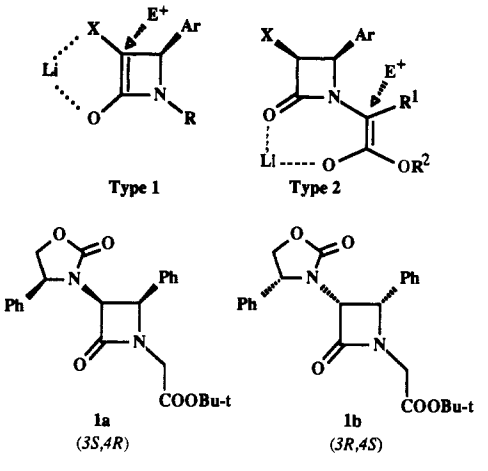
Table II. Dependence of Stereoselectivity on Reaction Temperature in Asymmetric Single Alkylation

	2a-*R*/2a-*S* (% yield)[a]			
RX	−97 °C	−78 °C	−50 °C	−30 °C
CH_2=$CHCH_2Br$	7.6/1 (94)	>50/1 (95)	7.9/1 (95)	4.4/1 (92)
$PhCH_2Br$	17/1 (93)	>50/1 (93)	36/1 (93)	8.4/1 (92)
MeI	37/1 (94)	>50/1 (95)	12/1 (94)	8.0/1 (93)
$EtOCOCH_2Br$	>50/1 (94)	40/1 (95)	18/1 (92)	6.0/1 (90)

[a] Determined by ^1H NMR analysis. **2a-*R*/2a-*S*** = (3*S*,4*R*,1′*R*)-**2a**/(3*S*,4*R*,1′*S*)-**2a**.

Results and Discussion

We have reported highly efficient asymmetric alkylations of β-lactams (type 1) and β-lactam esters (type 2) in the previous papers.[13-15] We have extended the type 2 alkylation to the asymmetric single and double alkylations of chiral β-lactam acetate **1** which is a chiral glycinate as well as a phenylalanylglycinate equivalent.



(8) E.g.: (a) Schöllkopf, U. *Pure Appl. Chem.* **1983**, *55*, 1799. (b) Hartwig, W.; Schöllkopf, U. *Liebigs Ann. Chem.* **1982**, 1952. (c) Groth, U.; Chiang, Y.-C.; Schöllkopf, U. *Ibid.* **1982**, 1756. (d) Groth, U.; Schöllkopf, U.; Chiang, Y.-C. *Synthesis* **1982**, 864. (e) Groth, U.; Schöllkopf, U. *Ibid.* **1983**, 37.

(9) E.g.: (a) Polt, R.; Seebach, D. *J. Am. Chem. Soc.* **1989**, *111*, 2622. (b) Fitzi, R.; Seebach, D. *Tetrahedron* **1988**, *44*, 5277. (c) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390. (d) Naef, R.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 135. (e) Seebach, D.; Aebi, J. D.; Gander-Coquoz, M.; Naef, R. *Ibid.* **1987**, 70, 1194. (f) Weber, T.; Aeschimann, R.; Maetzke, T.; Seebach, D. *Ibid.* **1986**, *69*, 1365. (g) Aebi, J. D.; Seebach, D. *Ibid.* **1985**, *68*, 1507.

(10) (a) Karady, S.; Amato, J. S.; Weistock, L. M. *Tetrahedron Lett.* **1984**, *25*, 4337. (b) Fadel, A.; Salaün, J. *Tetrahedron Lett.* **1987**, 28, 2243. (c) Belokon, Y. N.; Bakhmutov, V. I.; Chernoglazova, N. I.; Kochetkov, K. A.; Vitt, S. V.; Garbalinskaya, N. S.; Belikov, V. M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 305.

(11) Sinclair, P. J.; Zhai, D.; Reibenspies, J.; Williams, R. M. *J. Am. Chem. Soc.* **1986**, *108*, 1103.

(12) (a) Georg, G. I.; Guan, X.; Kant, J. *Tetrahedron Lett.* **1988**, *29*, 403.

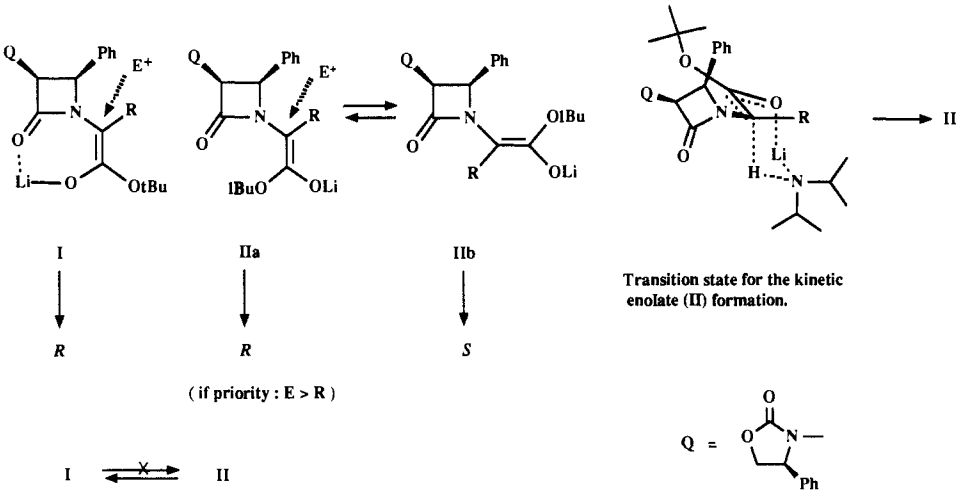
(13) (a) Ojima, I.; Chen, H.-J. C. *J. Chem. Soc., Chem. Commun.* **1987**, 625. (b) Ojima, I.; Shimizu, N.; Qiu, X.; Chen, H.-J. C.; Nakahashi, K. *Bull. Soc. Chim. Fr.* **1987**, 649.

(14) (a) Ojima, I.; Qiu, X. *J. Am. Chem. Soc.* **1987**, *109*, 6537. (b) Ojima, I.; Chen, H.-J. C.; Nakahashi, K. *J. Am. Chem. Soc.* **1988**, *110*, 278.

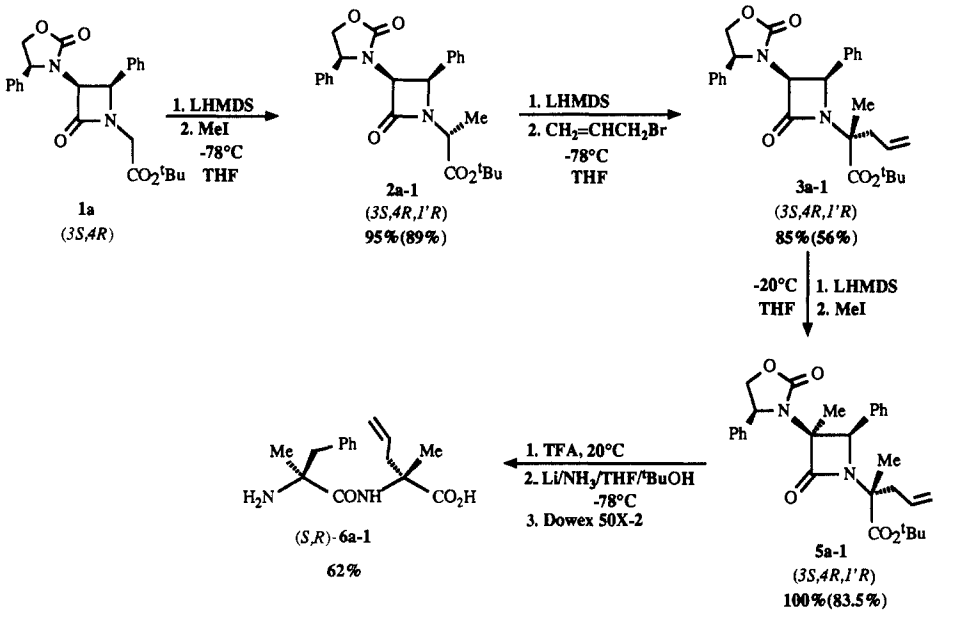
(15) Ojima, I.; Chen, H.-J. C.; Qiu, X. *Tetrahedron* **1988**, *44*, 5307.

(16) (a) Ojima, I.; Hatanaka, N. *J. Org. Chem. Syn., Jpn.* **1982**, *40*, 209. (b) Ojima, I. In *Asymmetric Reactions and Processes in Chemistry*; Eliel, E. L., Otsuka, S., Eds.; ACS Symp. Series 185; American Chemical Society: Washington, DC, **1982**; p 109. (c) Ojima, I.; Suga, S.; Abe, R. *Chem. Lett.* **1980**, 853. (d) Ojima, I.; Suga, S.; Abe, R. *Tetrahedron Lett.* **1980**, 3907. (e) Hatanaka, N.; Ojima, I. *Chem. Lett.* **1981**, 231. (f) Hatanaka, N.; Abe, R.; Ojima, I. *Ibid.* **1981**, 1297. (g) *Idem., J. Chem. Soc., Chem. Commun.* **1981**, 344. (h) Ojima, I.; Nakahashi, K.; Brandstadter, S. M.; Hatanaka, N. *J. Am. Chem. Soc.* **1987**, *109*, 1798. (i) Ojima, I.; Shimizu, N. *J. Am. Chem. Soc.* **1986**, *108*, 3100. (j) Ojima, I.; Yoda, N.; Abe, R.; Yatabe, M.; Hatanaka, N.; Yamashita, M. In *Peptide Chemistry 1982*; Sakakibara, S., Eds.; Protein Research Foundation: Japan, 1983; p 29. (k) Yamashita, M.; Abe, R.; Hatanaka, N.; Ojima, I. In *Peptide Chemistry 1982*; Sakakibara, S., Ed.; Protein Research Foundation: Japan, 1983; p 85.

Scheme II



Scheme III

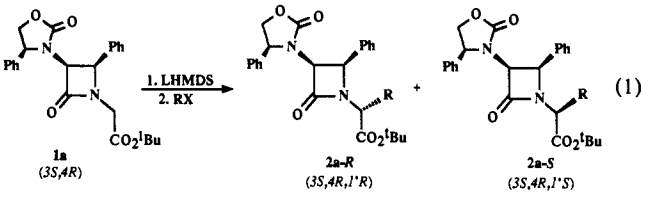


First, we performed sequential asymmetric double alkylation of a β-lactam ester (**1a**) (3*S*,4*R*), which was prepared through asymmetric [2 + 2] cycloaddition of (*S*)-(4-phenyloxazolidinyl)ketene[17] to *tert*-butyl *N*-benzylideneglycinate in 83% yield. As shown in Scheme I, the salient feature of this method is that a quaternary chiral center of desired configuration can be created just by changing the order of addition of two alkyl halides used ($R^1 \neq R^2$). Reactions were carried out with methyl iodide, allyl bromide, and benzyl bromide, and doubly alkylated β-lactam esters (**3**) were obtained in high yields. Results are shown in Table I. The doubly alkylated β-lactams (**3**) thus obtained can readily be converted to the corresponding dipeptides (**4**) in good yield via dissolving metal reduction (Li/NH_3/THF/*t*-BuOH, −78 °C).

As Table I shows, the stereoselectivity of the asymmetric double alkylation is extremely high (>99% de by HPLC analysis). As we reported previously,[14a] a chelated lithium ester enolate (I) must be formed through thermodynamic control in order to achieve high stereoselectivity (Scheme II), and the temperature of 0–5 °C is necessary for the smooth transformation of a kinetic enolate (II) of **2** (R^1 or R^2 = Me) to the corresponding chelated enolate (I). Thus, we employed 0–5 °C for the generation of chelated enolate in the second alkylation. For the first alkylation, however, we had to use a much lower temperature, typically -78 °C, since the lithium enolate generated from **1a** was found unstable at temperatures higher than −30 °C.

(17) Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3783.

Next, we looked at the efficiency of the asymmetric single alkylation of **1a** (eq 1) and found a remarkable effect of temperature on stereoselectivity. Results are summarized in Table II. As Table II shows, remarkable dependence of stereoselectivity on the reaction temperature was observed for the reactions with allyl bromide, methyl iodide, and benzyl bromide.



(1)

The best results for these alkyl halides (1'*R*/1'*S* = >50/1) were obtained at −78 °C. The results clearly indicate that (i) a kinetic enolate (non-chelated) is generated as major species at −95 °C, but a chelated enolate is formed at −78 °C (see Scheme II), and (ii) higher temperatures substantially attenuate stereoselectivity which may well be due to the large entropy term of this reaction. When ethyl bromoacetate was used as an electrophile, the reaction gave the highest stereoselectivity at −97 °C rather than at −78 °C, and the stereoselectivity decreased along with the increase of temperature. The results imply that the ester moiety of ethyl bromoacetate contributes to a facile conversion of the kinetic enolate to the chelated enolate.[14a] Consequently, it is found that the asymmetric single alkylation proceeds with extremely high

stereoselectivities as well. Since the single alkylation products can be readily converted to the corresponding dipeptides through dissolving metal reduction and then to amino acids by hydrolysis, this asymmetric single alkylation serves as a new and effective method for the synthesis of enantiomerically pure non-protein amino acids and their dipeptides.

Finally, we performed the sequential asymmetric triple alkylation of **1a** by the combination of type 1 and type 2 alkylations as exemplified in Scheme III. After the completion of asymmetric double alkylations of glycinate moiety with methyl iodide and allyl bromide, the side chain of the resulting β-lactam ester (**3a-*R*-1**) did not have any acidic protons. Thus, a type 1 enolate was generated and the third alkyl substitutent (methyl) was introduced to the C^3 position of **3a-*R*-1**; hence the whole process constitutes a unique and highly selective sequential asymmetric triple alkylation to give **5a-1**. It was found that the third alkylation also proceeded with virtually complete stereoselectivity.

Deprotection of the *tert*-butyl ester of **5a-1** by trifluoroacetic acid (TFA) in dichloromethane at 20 °C followed by the cleavage of β-lactam ring, as well as the removal of N-protection with $Li/NH_3/THF/t$-BuOH at −78 °C, gave (*S*)-α-methylphenylalanyl-(*R*)-α-allylalanine, (*S*,*R*)-**6a-1**, in 62% yield after purification on an ion-exchange column.

Further applications of these unique and efficient asymmetric single, double, and triple alkylations of β-lactam esters to the design and the synthesis of enzyme inhibitors and modified peptide hormones are actively in progress.

Experimental Section

General. Microanalyses were performed at M-H-W Laboratories, Phoenix, AZ. HPLC analyses were carried out using columns packed with Waters Resolve 5μ-Spherical Silica (normal phase), 5μ-Spherical C18, or μ-Bondapak C18 (reversed phase). (*S*)- and (*R*)-phenylglycine and glycine were generous gifts from Ajinomoto Co., Inc. (*S*)- and (*R*)-(4-phenyl-2-oxooxazolidinyl)acetic acid were prepared by the literature method.[17] *tert*-Butyl glycinate was prepared by the standard method.[18] Allyl bromide, benzyl bromide, ethyl bromoacetate, and methyl iodide were purchased from Aldrich Co. These materials were dried and distilled before use. Benzaldehyde, 1,1,1,3,3,3-hexamethyldisilazane (HMDS), and *tert*-butyl alcohol were purchased and distilled over activated 4-Å molecular sieves before use. Tetrahydrofuran (THF) used in this work was freshly distilled under nitrogen in the presence of sodium and benzophenone.

Preparation of *tert*-Butyl *N*-Benzylideneglycinate. A mixture of *tert*-butyl glycinate (300 mg, 2.29 mmol), benzaldehyde (243 mg, 2.29 mmol), 10 mL of benzene, and 500 mg of anhydrous sodium sulfate was stirred at room temperature overnight. After filtration, the filtrate was concentrated in vacuo to give *tert*-butyl *N*-benzylideneglycinate as a yellowish liquid (501 mg, 100% yield): ^1H NMR ($CDCl_3$) δ 1.50 (s, 9 H), 4.31 (d, J = 1.2 Hz, 2 H), 7.3–7.5 (m, 3 H), 7.75–7.85 (m, 2 H), 8.26 (s, 1 H).

Preparation of β-Lactam 1. To a solution of (*R*)-(4-phenyl-2-oxooxazolidinyl)acetic acid (456 mg, 2.06 mmol) in toluene (20 mL) were added oxalyl chloride (0.45 mL, 5.15 mmol) and two drops of DMF at room temperature with stirring, and the mixture was heated at 60 °C for 5 h. The removal of the solvent and excess oxalyl chloride in vacuo gave the corresponding acid chloride quantitatively. The acid chloride thus obtained was dissolved in dichloromethane (20 mL), and the solution was cooled to −78 °C. Triethylamine (0.43 mL, 3.09 mmol) was added to the acid chloride solution, and the mixture was stirred at −78 °C for 30 min. Then, a solution of *tert*-butyl *N*-benzylideneglycinate (479.9 mg, 2.19 mmol) in dichloromethane (10 mL) was added to the mixture at −78 °C with stirring. The reaction mixture was allowed to stir overnight with a gradual increase of temperature to room temperature. The reaction was quenched with methanol (2 mL). The dichloromethane layer was separated and washed with water, 5% HCl, water, brine, and dried over anhydrous sodium sulfate. The residue obtained by the removal of dichloromethane was charged on a silica gel column and eluted with chloroform. After recrystallization from AcOEt/hexane, pure (3*R*,4*S*)-1-[(*tert*-butoxycarbonyl)methyl]-3-[(*S*)-4-phenyloxazolidinyl]-4-phenylazetidin-2-one (**1b**) was obtained (718 mg, 83% yield) as a white solid.

1b: mp 199–200 °C; $[\alpha]^{19}_D$ −44.1° (*c* 1.61, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.40 (s, 9 H), 3.47 (d, J = 18.0 Hz, 1 H), 3.94 (dd, J = 7.6, 8.7 Hz, 1 H), 4.19 (t, J = 8.7 Hz, 1 H), 4.32 (dd, J = 7.6, 8.7 Hz, 1 H), 4.46 (d, J = 18.0 Hz, 1 H), 4.62 (d, J = 5.0 Hz, 1 H), 5.05 (d, J = 5.0 Hz, 1 H), 7.00–7.50 (m, 10 H); IR (KBr disk) 1765, 1747, 1730 cm^{-1}. Anal. Calcd for $C_{24}H_{26}N_2O_5$: C, 68.22; H, 6.21; N, 6.63. Found: C, 68.34; H, 6.39; N, 6.50.

In the same manner, (3*S*,4*R*)-1-[(*tert*-butoxycarbonyl)methyl]-3-[(*S*)-4-phenyloxazolidinyl]-4-phenylazetidin-2-one (**1a**) was prepared from (*S*)-(4-phenyl-2-oxooxazolidinyl)acetic acid, triethylamine, and *tert*-butyl *N*-benzylideneglycinate: mp 198–199 °C; $[\alpha]^{19}_D$ +44.4° (*c* 1.62, $CHCl_3$).

Single Asymmetric Alkylations of 1. Procedure for the single methylation of a β-lactam ester is described. To a solution of enantiomerically pure β-lactam ester **1a** (504 mg, 1.19 mmol) in THF (75 mL) was added LHMDS (2.3 mL of 0.5 M solution in THF/hexane; 1.0 equiv) at −78 °C under nitrogen, and the mixture was stirred for 30 min at the same temperature. To the enolate thus generated, methyl iodide (0.2 mL, 3.2 mmol; 3 equiv) was added. The reaction mixture was stirred at −78 °C for 5 h and quenched with a saturated aqueous NH_4Cl (10 mL) at the same temperature. The THF layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with saturated sodium bisulfite and brine and dried over anhydrous magnesium sulfate. The solvent was removed to give crude (3*S*,4*R*,1′*R*)-1-[1′-(*tert*-butoxycarbonyl)ethyl]-3-[(*S*)-4-phenyloxazolidinyl]-4-phenylazetidin-2-one (**2a-*R*-1**: R¹ = Me) in 95% yield by ^1H NMR. The formation of the other diastereomer, (3*S*,4*R*,1′*S*)-1-[1′-(*tert*-butoxycarbonyl)ethyl]-3-[(*S*)-4-phenyloxazolidinyl]-4-phenylazetidin-2-one (**2a-*S*-1**), was not detected by ^1H NMR analysis. After recrystallization with AcOEt/hexane, pure **2a-*R*-1** was obtained as colorless crystals (465 mg, 89% yield).

2a-*R*-1: mp 200–201 °C; $[\alpha]^{20}_D$ +28.7° (*c* 1.15, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.17 (d, J = 7.5 Hz, 3 H), 1.42 (s, 9 H), 3.90 (m, 1 H), 4.09 (m, 2 H), 4.48 (d, J = 5.1 Hz, 1 H), 4.58 (q, J = 7.5 Hz, 1 H), 5.05 (d, J = 5.1 Hz, 1 H), 7.2–7.6 (m, 10 H); IR (KBr disk) 1747, 1738, 1725 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{25}H_{28}N_2O_5$: C, 68.78; H, 6.48; N, 6.42. Found: C, 68.72; H, 6.62; N, 6.20.

When the reaction was carried out at −30 °C, the formation of **2a-*S*-1** was detected by ^1H NMR: ($CDCl_3$) δ 1.40 (s, 9 H), 1.70 (d, J = 7.5 Hz, 3 H), 3.76 (q, J = 7.5 Hz, 1 H), 3.95 (dd, J = 7.5, 8.8 Hz, 1 H), 4.24 (t, J = 8.8 Hz, 1 H), 4.42 (dd, J = 7.5, 8.8 Hz, 1 H), 4.61 (d, J = 5.2 Hz, 1 H), 4.83 (d, J = 5.2 Hz, 1 H), 7.00–7.80 (m, 10 H).

In a manner similar to that described above, (3*S*,4*R*,1′*R*)-1-[1′-(*tert*-butoxycarbonyl)buten-3-yl]-3-[(*S*)-4-phenyloxazolidinyl]-4-phenylazetidin-2-one (**2a-*R*-2**: R¹ = allyl), (3*S*,4*R*,1′*R*)-1-[1′-(*tert*-butoxycarbonyl)-2′-phenylethyl]-3-[(*S*)-4-phenyloxazolidinyl]-4-phenylazetidin-2-one (**2a-*R*-3**: R¹ = benzyl), and (3*S*,4*R*,1′*R*)-1-[1′-(*tert*-butoxycarbonyl)-2′-(ethoxycarbonyl)ethyl]-3-[(*S*)-4-phenyloxazolidinyl]-4-phenylazetidin-2-one (**2a-4**: R¹ = CH_2COOEt) were obtained. Minor diastereomers, **2a-*S*-2** (3*S*,4*R*,1′*S*), **2a-*S*-3** (3*S*,4*R*,1′*S*), and **2a-*S*-4** (3*S*,4*R*,1′*S*), were identified by ^1H NMR analyses.

2a-*R*-2: white solid; mp 188–189 °C; $[\alpha]^{20}_D$ +42.9° (*c* 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.42 (s, 9 H), 2.28–2.52 (m, 2 H), 3.90 (m, 1 H), 4.09 (m, 2 H), 4.49 (t, J = 7.3 Hz, 1 H), 4.48 (d, J = 5.1 Hz, 1 H), 4.80–5.00 (m, 2 H), 5.04 (d, J = 5.1 Hz, 1 H), 5.50–5.70 (m, 1 H), 7.20–7.70 (m, 10 H); IR (KBr disk) 1744, 1723 ($\nu_{C=O}$) cm^{-1}; yield determined by ^1H NMR for the reaction at −78 °C was 95% and isolated yield after recrystallization from AcOEt/hexane was 80%. Anal. Calcd for $C_{27}H_{30}N_2O_5$: C, 70.11; H, 6.55; N, 6.06. Found: C, 69.89: H, 6.68; N, 5.80.

2a-*S*-2: ^1H NMR ($CDCl_3$) δ 1.38 (s, 9 H), 2.60–2.80 (m, 1 H), 2.90–3.20 (m, 1 H), 3.74 (dd, J = 5.7, 10.0 Hz, 1 H), 3.80–4.00 (m, 1 H), 4.21 (t, J = 8.8 Hz, 1 H), 4.39 (dd, J = 7.5, 8.8 Hz, 1 H), 4.61 (d, J = 5.2 Hz, 1 H), 4.80 (d, J = 5.2 Hz, 1 H), 5.10–5.30 (m, 2 H), 5.80–6.00 (m, 1 H), 7.00–7.60 (m, 10 H).

2a-*R*-3: white solid; mp 183–184 °C; $[\alpha]^{20}_D$ +56.8° (*c* 1.46, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.32 (s, 9 H), 2.88 (dd, J = 8.1, 14.2 Hz, 1 H), 3.06 (dd, J = 8.1, 14.2 Hz, 1 H), 3.89 (m, 1 H), 4.09 (m, 2 H), 4.40 (d, J = 5.1 Hz, 1 H), 4.53 (t, J = 8.1 Hz, 1 H), 4.71 (d, J = 5.1 Hz, 1 H), 7.1–7.4 (m, 15 H); IR (KBr disk) 1752, 1713 ($\nu_{C=O}$) cm^{-1}; yield determined by ^1H NMR for the reaction at −78 °C was 93% and isolated yield after recrystallization from AcOEt/hexane was 73%. Anal. Calcd for $C_{31}H_{32}N_2O_5$: C, 72.63; H, 6.31; N, 5.47. Found: C, 72.81; H, 6.39; N, 5.37.

2a-*S*-3: ^1H NMR ($CDCl_3$) δ 1.38 (s, 9 H), 3.27 (dd, J = 5.0, 13.5 Hz, 1 H), 3.67 (dd, J = 10.5, 13.5 Hz, 1 H), 3.80–3.95 (m, 2 H), 4.11 (t, J = 8.7 Hz, 1 H), 4.26 (dd, J = 7.1, 8.7 Hz, 1 H), 4.54 (d, J = 5.3 Hz, 1 H), 4.69 (d, J = 5.3 Hz, 1 H), 6.80–7.50 (m, 15 H).

2a-*R*-4: white solid; mp 178–179 °C; $[\alpha]^{20}_D$ +15.2° (*c* 1.32, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.97 (t, J = 7.1 Hz, 3 H), 1.41 (s, 9 H), 2.60 (dd, J = 4.6, 17.5 Hz, 1 H), 2.88 (dd, J = 5.7, 17.5 Hz, 1 H), 3.57 (m, 1 H), 3.77 (m, 1 H), 3.86 (m, 1 H), 4.03 (m, 2 H), 4.49 (d, J = 5.1 Hz, 1 H), 4.79 (dd, J = 4.6, 5.7 Hz, 1 H), 5.07 (d, J = 5.1 Hz, 1 H), 7.1–7.5 (m,

(18) Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis*; Springer-Verlag: New York, 1984; pp 48–50 and references cited therein.

10 H); IR (KBr disk) 1746, 1728, 1710 ($\nu_{C=O}$) cm^{-1}; yield determined by ^1H NMR for the reaction at −97 °C was 94% and isolated yield after recrystallization from AcOEt/hexane was 79%. Anal. Calcd for $C_{28}H_{32}N_2O_7$: C, 66.12; H, 6.34; N, 5.51. Found: C, 65.88; H, 6.39; N, 5.32.

2a-*S*-4: ^1H NMR ($CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 3 H), 1.39 (s, 9 H), 3.17 (d, J = 7.1 Hz, 2 H), 3.91–3.96 (m, 1 H), 4.12–4.28 (m, 4 H), 4.32 (dd, J = 7.1 Hz, 8.7 Hz, 1 H), 4.57 (d, J = 5.2 Hz, 1 H), 4.91 (d, J = 5.2 Hz, 1 H), 7.1–7.5 (m, 10 H).

Sequential Asymmetric Double Alkylation of 1. A typical procedure is described for the synthesis of (3*R*,4*S*,1′*S*)-1-[1′-(*tert*-butoxycarbonyl)-1′-methylbuten-3-yl]-3-[(*R*)-4-phenyloxazolidinyl]-4-phenylazetidin-2-one (**3b-*S*-1**) via sequential double asymmetric alkylation of **1b**.

The first alkylation of **1b** with methyl iodide (3 equiv) was carried out in the same manner as mentioned above. After **2b-*S*-1** was isolated through a short silica gel column (silica gel 60) using AcOEt/hexane as the eluant and the purity of the product was checked by ^1H NMR, the product was submitted to the second alkylation with allyl bromide.

To a solution of β-lactam ester **2b-*S*-1** (100 mg, 0.229 mmol) in dry THF (15 mL) was added LHMDS (0.57 mL of 0.40 M solution in THF/hexane; 1.0 equiv) at 0–5 °C under nitrogen, and the mixture was stirred for 5 min at the same temperature. The reaction system was cooled to −78 °C, and allyl bromide (83.1 mg, 0.687 mmol; 3 equiv) was added. The mixture was stirred at −78 °C for 5 h and quenched with saturated NH_4Cl at the same temperature. The same workup as that described for the single alkylation, gave **3b-*S*-1** as the sole product. The ^1H NMR of the product showed the formation of only one diastereomer. After purification on a short silica gel column and recrystallization from AcOEt/hexane, pure **3b-1** was obtained as colorless crystals (84 mg, 77% yield).

3b-*S*-1: mp 210–211 °C; $[\alpha]^{19}_D$ −37° (c 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.46 (s, 9 H), 1.54 (s, 3 H), 2.37 (dd, J = 7.5, 13.9 Hz, 1 H), 2.45 (dd, J = 7.2, 13.9 Hz, 1 H), 3.90 (dd, J = 7.1, 8.5 Hz, 1 H), 4.13 (t, J = 8.5 Hz, 1 H), 4.23 (dd, J = 7.1, 8.5 Hz, 1 H), 4.43 (d, J = 5.2 Hz, 1 H), 4.80–5.10 (m, 2 H), 4.95 (d, J = 5.2 Hz, 1 H), 5.50–5.70 (m, 1 H), 7.00–7.70 (m, 10 H); IR (KBr disk) 1764, 1753, 1735 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{28}H_{32}N_2O_5$: C, 70.56; H, 6.78; N, 5.88. Found: C, 70.55; H, 7.00; N, 5.88.

In the same manner, (3*R*,4*S*,1′*R*)-1-[1′-(*tert*-butoxycarbonyl)-1′-methylbuten-3-yl]-3-[(*R*)-4-phenyloxazolidinyl]-4-phenylazetidin-2-one (**3b-*R*-2**) and (3*R*,4*S*,1′*S*)-1-[1′-(*tert*-butoxycarbonyl)-1′-methyl-2′-phenylethyl]-3-[(*R*)-4-phenyloxazolidinyl]-4-phenylazetidin-2-one (**3b-*S*-3**) were obtained.

3b-*R*-2: 94% yield; colorless crystals; mp 145–146 °C; $[\alpha]^{18}_D$ −1.3° (c 3.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.06 (s, 3 H), 1.41 (s, 9 H), 2.47 (dd, J = 7.9, 13.6 Hz, 1 H), 3.30 (dd, J = 6.2, 13.6 Hz, 1 H), 3.89 (dd, J = 6.2, 7.9 Hz, 1 H), 4.00–4.25 (m, 2 H), 4.47 (d, J = 5.3 Hz, 1 H), 4.88 (d, J = 5.3 Hz, 1 H), 5.00–5.30 (m, 2 H), 5.80–6.20 (m, 1 H), 7.00–7.60 (m, 10 H); IR (KBr disk) 1775, 1751, 1731 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{28}H_{32}N_2O_5$: C, 70.56; H, 6.78; N, 5.88. Found: C, 70.68; H, 6.95; N, 5.74.

3b-*S*-3: 79% yield; colorless crystals; mp 200–200.5 °C (lit.[15] mp 200–200.5 °C); ^1H NMR ($CDCl_3$) δ 1.31 (s, 3 H), 1.51 (s, 9 H), 2.93 (d, J = 13.4 Hz, 1 H), 3.29 (d, J = 13.4 Hz, 1 H), 3.90 (m, 1 H), 4.10 (m, 2 H), 4.23 (s, 2 H), 6.90–7.70 (m, 15 H).

Sequential Triple Alkylation of 1a. The procedure for the synthesis of (3*S*,4*R*,1′*R*)-1-[1′-(*tert*-butoxycarbonyl)-1′-methylbuten-3-yl]-3-methyl-3-[(*S*)-4-phenyloxazolidinyl]-4-phenylazetidin-2-one (**5a-1**) is as follows.

The first and second alkylations of **1a** with methyl iodide and allyl bromide, respectively, were carried out in the same manner as described above. After the second alkylation, (3*S*,4*R*,1′*R*)-1-[1′-(*tert*-butoxycarbonyl)-1′-methylbuten-3-yl]-3-[(*S*)-4-phenyloxazolidinyl]-4-phenylazetidin-2-one (**3a-*R*-1**) was obtained in 85% yield as a white solid: mp 209.5–210 °C; $[\alpha]^{19}_D$ +36.5° (c 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.47 (s, 9 H), 1.54 (s, 3 H), 2.37 (dd, J = 7.2, 13.9 Hz, 1 H), 2.45 (dd, J = 7.2, 13.9 Hz, 1 H), 3.90 (dd, J = 7.2, 8.3 Hz, 1 H), 4.13 (dd, J = 8.3, 8.7 Hz, 1 H), 4.22 (dd, J = 7.2, 8.7 Hz, 1 H), 4.43 (d, J = 5.2 Hz, 1 H), 4.95 (d, J = 5.2 Hz, 1 H), 4.87–5.02 (m, 2 H), 5.51–5.66 (m, 1 H), 7.1–7.4 (m, 10 H); IR (KBr disk) 1746, 1740, 1725 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{28}H_{32}N_2O_5$: C, 70.57; H, 6.77; N, 5.88. Found: C, 70.71; H, 6.78; N, 5.81.

To a solution of **3a-*R*-1** (100 mg, 0.21 mmol) in THF (30 mL) was added LHMDS (0.42 mL of 0.5 M solution in THF/hexane; 1.0 equiv) at −20 °C, and the mixture was stirred for 30 min at the same temperature. To this solution was added methyl iodide (0.13 mL, 2.1 mmol; 10 equiv), and the mixture was stirred at −20 °C for 4 h and quenched with saturated aqueous NH_4Cl at the same temperature. The usual workup (vide supra) gave **5a-1** (conversion was 100% by ^1H NMR). After purification on a short silica gel column, pure **5a-1** was obtained as a white solid (86 mg, 83.5% yield).

5a-1: mp 218–220 °C; $[\alpha]^{25}_D$ +5.32° (c 0.94, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.46 (s, 9 H), 1.52 (s, 3 H), 1.57 (s, 1 H), 2.23 (dd, J = 7.2, 13.7 Hz, 1 H), 2.33 (dd, J = 7.2, 13.7 Hz, 1 H), 3.5–3.9 (m, 2 H), 4.40 (m, 1 H), 4.81 (s, 1 H), 4.85–5.02 (m, 2 H), 5.47–5.63 (m, 1 H), 7.2–7.5 (m, 10 H); IR (KBr disk) 1759, 1735, 1723 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{29}H_{34}N_2O_5$: C, 71.00; H, 6.99; N, 5.71. Found: C, 70.84; H, 7.02; N, 5.57.

Synthesis of Dipeptide via Reductive Cleavage of Alkylated β-Lactam Esters 3 and 5. A typical procedure is described for the synthesis of (*S*)-α-methylphenylalanyl-(*R*)-α-allylalanine (**6a-1**) from **5a-1**.

The deprotection of *tert*-butyl ester moiety of **5a-1** was carried out by reacting **5a-1** (76.2 mg, 0.115 mmol) with TFA (0.5 mL) in dichloromethane (5 mL) at room temperature with stirring for 1 h. The removal of TFA and the solvent in vacuo gave the corresponding C-terminus-free compound in quantitative yield as a white powder: ^1H NMR ($CDCl_3$) δ 1.47 (s, 3 H), 1.66 (s, 3 H), 2.42 (dd, J = 7.2, 14.0 Hz, 1 H), 2.55 (dd, 7.2, 14.0 Hz, 1 H), 3.52 (m, 1 H), 3.81 (bs, 1 H), 4.22 (m, 1 H), 4.87 (s, 1 H), 4.93–5.12 (m, 2 H), 5.55–5.66 (m, 1 H), 7.2–7.7 (m, 10 H). To a dark blue solution of lithium (6.8 mg, 0.98 mmol) in liquid ammonia (10 mL) was added a solution of the C-terminus-free compound (62 mg, 0.143 mmol) and *t*-BuOH (0.10 mL) in THF (5 mL) at −78 °C, and the mixture was stirred for 5 min. Then the reaction was quenched with solid ammonium chloride (60 mg) at −78 °C. After the solvent was removed, the residue was dissolved in water (5 mL), acidified with 1 N HCl to pH 3, and washed with ether (3 × 6 mL). The aqueous layer was neutralized with 0.1 N ammonium hydroxide and charged to an ion-exchange column packed with Dowex Ag50-X2. After inorganic salts were washed out with water, (*S*,*R*)-**6a-1** was obtained from 0.1 N ammonium hydroxide elute, which was monitored by HPLC (Waters 5μ-Spherical C18 column, MeOH/0.1 NH_4OAc = 1/1 v/v; pH was adjusted to 5.0 with AcOH). Recrystallization from hot water gave pure (*S*,*R*)-**6a-1** (25.6 mg. 62%; >99.5% de).

(*S*,*R*)-**6a-1**: white solid; mp >250 °C; $[\alpha]^{23}_D$ +54.6° (c 1.08, DMSO); ^1H NMR (CD_3OD) δ 0.38 (s, 3 H), 1.46 (s, 3 H), 1.95 (dd, J = 7.9, 13.7 Hz, 1 H), 2.38 (dd, J = 6.5, 13.7 Hz, 1 H), 2.62 (d, J = 13.2 Hz, 1 H), 3.14 (d, J = 13.2 Hz, 1 H), 4.95–5.07 (m, 2 H), 5.46–5.62 (m, 1 H), 7.1–7.25 (m, 5 H); IR (KBr disk) 1660 ($\nu_{C=O}$) cm^{-1}. Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.19; H, 7.64; N, 9.65. Found: C, 66.14; H, 7.59; N, 9.87.

In a similar manner, (*S*)-phenylalanyl-(*R*)-α-methylphenylalanine [(*S*,*R*)-**4a-3**] and (*R*)-phenylalanyl-(*S*)-α-methylphenylalanine [(*R*,*S*)-**4b-3**] were obtained 76% and 81%, respectively.

(*S*,*R*)-**4a-3**: white solid; mp >250 °C; $[\alpha]^{25}_D$ −45.5° (c 1.0, MeOH); ^1H NMR (CD_3OD) δ 1.56 (s, 3 H), 2.77 (dd, J = 8.9, 14.2 Hz, 1 H), 2.87 (dd, J = 5.8, 14.2 Hz, 1 H), 3.26 (d, J = 13.3 Hz, 1 H), 3.35 (d, J = 13.3 Hz, 1 H), 3.99 (dd, J = 5.8, 8.9 Hz, 1 H), 7.0–7.5 (m, 10 H). Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.91; H, 6.80; N, 8.58. Found: C, 70.03; H, 6.71; N, 8.45.

(*R*,*S*)-**4a-3**: colorless needles; mp >250 °C; $[\alpha]^{25}_D$ +45° (c 1.5, MeOH); ^1H NMR (CD_3OD) δ 1.56 (s, 3 H), 2.77 (dd, J = 8.9, 14.2 Hz, 1 H), 2.87 (dd, J = 5.8, 14.2 Hz, 1 H), 3.26 (d, J = 13.3 Hz, 1 H), 3.35 (d, J = 13.3 Hz, 1 H), 3.99 (dd, J = 5.8, 8.9 Hz, 1 H), 7.0–7.5 (m, 10 H); ^{13}C NMR (CD_3OD) δ 24.32, 38.85, 42.72, 56.24, 63.78, 127.44, 128.57, 128.96, 130.02, 130.39, 131.15, 136.29, 139.23, 168.53, 179.07. Anal. Calcd for $C_{19}H_{22}N_2O_3.H_2O$: C, 66.26; H, 7.02; N, 8.13. Found: C, 65.46; H, 6.93; N, 8.16.

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