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Synthesis of 2′-*epi*-Distichonic Acid A, an Iron-Chelating Amino Acid Derivative

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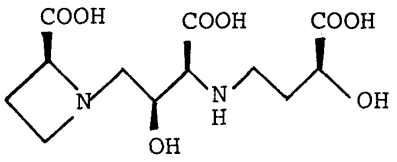
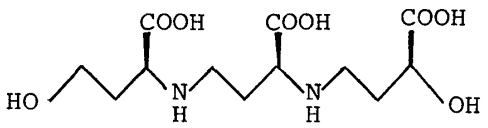
2′-*epi*-Distichonic acid A (**4b**), an iron-chelating amino acid derivative was synthesized starting from L-vinylglycine epoxide (**6b**). Reaction of **6b** with glycine ester **17** afforded a β-hydroxy amino acid derivative (**18**). Reductive coupling of **21** derived from **18** with L-malic-β-semialdehyde (**25**) gave 2′-*epi*-distichonic acid A (**4b**) after deprotection.

Keywords——iron-chelating amino acid; mugineic acid; 2′-*epi*-distichonic acid A; vinylglycine; vinylglycine epoxide; β-hydroxy-α-amino acid; malaldehydic acid; glycine

A number of amino acids in which amino acid moieties are linked by an *N*-alkyl bond have been isolated and characterized in recent years.[1-3] As representative examples, mugineic acid (**1**) and avenic acid A (**2**) have received considerable attention because of their characteristic iron-chelating activities (Chart 1). Among these amino acid derivatives, 2′-deoxymugineic acid (**3**) and avenic acid A (**2**), constructed from simple C-4 α-amino and α-hydroxy acids, have been synthesized by a reductive amination method using sodium cyanoborohydride ($NaBH_3CN$).[4,5]



1



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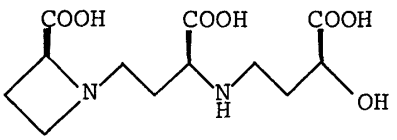

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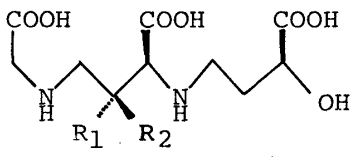
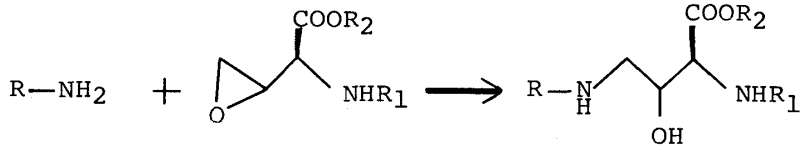


4a : R_1=H, R_2=OH
4b : R_1=OH, R_2=H

Chart 1



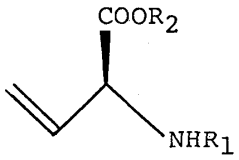
5 **6** **7**

Chart 2

Since relatively little work[6] has been reported on the synthesis of mugineic acid (**1**) and distichonic acid A (**4a**),[7] in which a β-hydroxy-α-amino acid moiety is contained as a partial structure, we planned to synthesize these compounds. As shown in Chart 2, vinylglycine epoxide (2-amino-3,4-epoxybutanoic acid)[8] seemed to provide a suitable building block to synthesize the β-hydroxy amino acid fragment: reaction of vinylglycine epoxide with an amine would result in the coupling of two amino acid fragments with an *N*-alkyl bond, accompanied with the introduction of a hydroxy group at the β-position.[9] In this paper, we report the preparation of vinylglycine epoxides and the synthesis of an iron-chelating amino acid, 2′-*epi*-distichonic acid A (**4b**).

The key intermediates, vinylglycine epoxides, were prepared by a *m*-chloroperbenzoic acid (mCPBA) oxidation of L-vinylglycine derivatives.[10] For the preparation of large amounts of L-vinylglycines,[11] the protected L-methionine sulfoxides were refluxed in xylene. L-Vinylglycines (**11a—c**) obtained by this procedure showed partial racemization of up to 13% (Table I). The optical purity of the products was investigated by high performance liquid

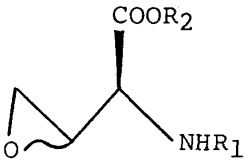
Table I



11

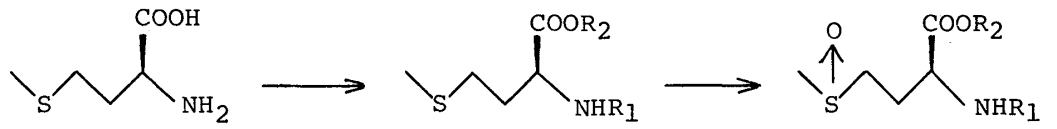
	2*S*/2*R*
11a	17/1
11b	7/1
11c	20/1

Table II

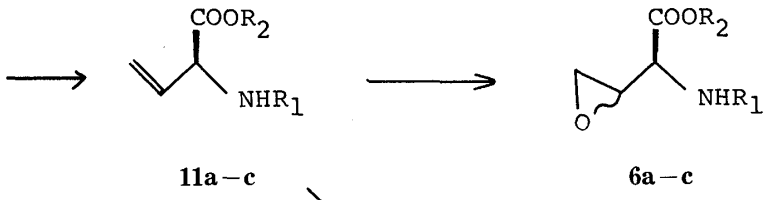


6

	threo/*erythro*
6a	4 /1
6b	4.7/1
6c	4 /1



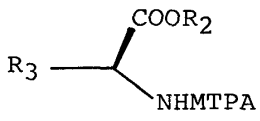
8 **9a—c** **10a—c**



11a—c **6a—c**

a : R_1=Z, R_2=Me
b : R_1=Z, R_2=*t*Bu
c : R_1=Boc, R_2=Bzl
d : R_2=Me, R_3=Et
e : R_2=*t*Bu, R_3=Et
f : R_2=Bzl, R_3=vinyl

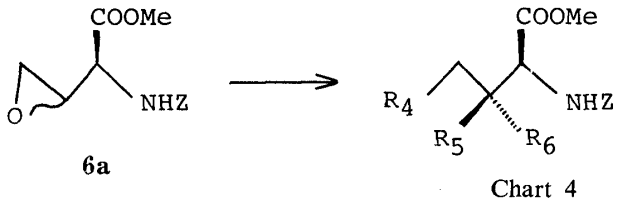
*t*Bu : *tert*-butyl



12d—f

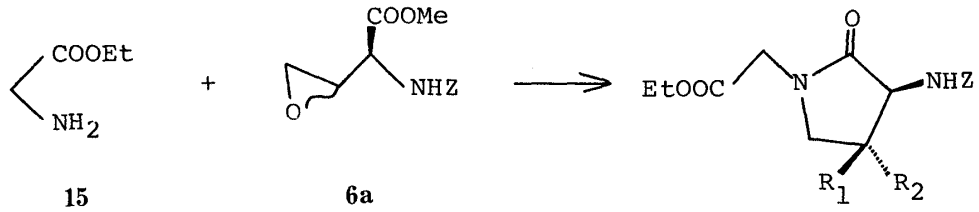
Chart 3

chromatography (HPLC) analysis of the α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) amides (**12d—f**) prepared from the L-vinylglycines (**11a—c**) after removal of the amino protecting groups.

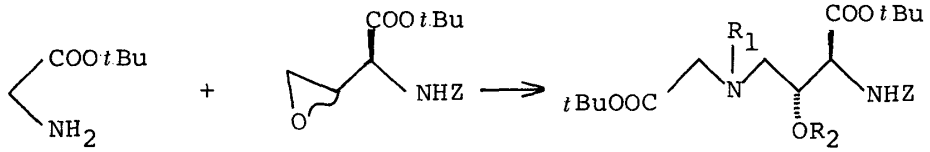


13a : R_4=Br, R_5=H, R_6=OH
13b : R_4=Br, R_5=OH, R_6=H
14a : R_4=H, R_5=H, R_6=OAc
14b : R_4=H, R_5=OAc, R_6=H

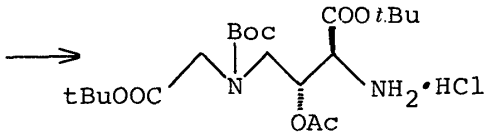
Chart 4



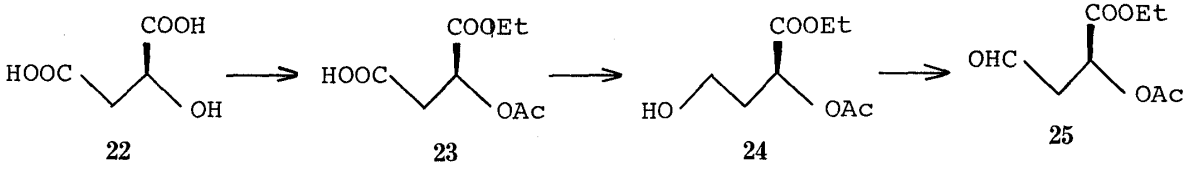
16a : R_1=H, R_2=OH
16b : R_1=OH, R_2=H



18 : R_1=H, R_2=H
19 : R_1=Boc, R_2=H
20 : R_1=Boc, R_2=Ac



21



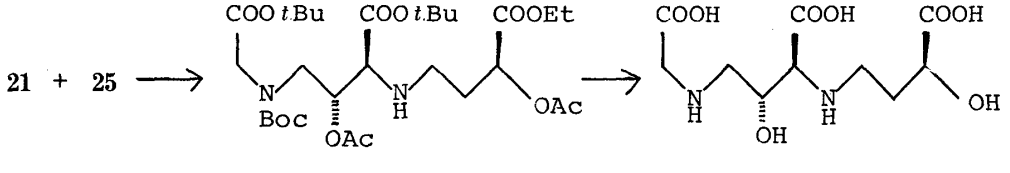


Chart 5

Oxidation of **11a** with mCPBA gave epoxides as a diastereomeric mixture at C-3 in the ratio of 4:1 (Table II). The assignment of the stereochemistry was confirmed as follows (Chart 4). Treatment of the mixture of epoxides (**6a**) with 48% HBr yielded a bromohydrin (**13a**) as a major product after recrystallization. Protection of the hydroxy group of **13a** and dehalogenation of the resulting acetate with tributyltin hydride (Bu_3SnH) gave the L-threonine derivative (**14a**), which was identical with a sample prepared from L-threonine. The L-allothreonine derivative (**14b**) was obtained from the minor product through the same sequence of reactions. Consequently, oxidation of L-vinylglycine gave the (*R*)-epoxide stereoselectively. Oxidation of other L-vinylglycines (**11b, c**) gave predominantly (*R*)-epoxides (**6b, c**) as determined by comparison of the proton nuclear magnetic resonance (^{1}H-NMR) spectra with that of **6a** (Table II).

Unfortunately, reaction of the epoxide mixture (**6a**) with glycine ethyl ester (**15**) resulted in the formation of a lactam (**16a**) as the major product. When the *tert*-butyl ester of glycine (**17**) was employed in place of the ethyl ester (**15**), lactamization was suppressed and a crude amino alcohol was formed, which upon protection provided the desired **18** as the major product. This compound was considered to be a suitable intermediate for the synthesis of distichonic acid A (**4a**), where the configuration at C-2′ of **19** should be inverted. Since trials to invert the configuration of C-2′ with the Mitsunobu procedure (DEAD–PPh_3–RCOOH, R = C_6H_5, CH_3 and H)[12] resulted in a recovery of the starting **19**, the synthesis of 2′-*epi*-distichonic acid A (**4b**) which is expected to be an iron chelator was carried out in the following manner (Chart 5). Protection of the hydroxy group followed by catalytic hydrogenation of **20** gave an amine (**21**). Reductive amination of **21** with L-malaldehydic acid (**25**)[4] in the presence of $NaBH_3CN$[13] gave the desired coupling product **26** in 58% yield. Finally, removal of the protecting groups with 1 N HCl and 1% KOH yielded 2′-*epi*-distichonic acid A (**4b**) ($[\alpha]_D$ −13.3° (*c* = 0.09), mp 215—217 °C (dec.)). The iron-chelating activity of **4b** was observed by the *o*-phenanthroline method.[14]

As mentioned above, vinylglycine is a useful intermediate for the synthesis of *threo*-β-hydroxy-α-amino acids and the synthesis of other biologically active β-hydroxy amino acid derivatives *via* vinylglycine epoxide is under investigation.

Experimental

General Procedure——Melting points were determined on a micro melting point apparatus (Yanagimoto Seisakusho) and are uncorrected. Optical rotations were determined on JASCO DIP-4 and JASCO DIP-340 spectrometers. The circular dichroism (CD) spectrum was recorded on a JASCO J-400X spectrometer. Low-resolution electron impact mass spectra (LRMS) were recorded on a Hitachi M-52G spectrometer, and high-resolution electron impact mass spectra (HRMS) and field desorption mass spectra (FDMS) were recorded on a JEOL JMS-01 SG-2 spectrometer. ^{1}H- and ^{13}C-NMR spectra were taken on Perkin-Elmer R-20, JEOL PMX60 SI, and JEOL JNM FX100 spectrometers. Chemical shifts are reported in δ units downfield from internal tetramethylsilane. Infrared (IR) spectra were recorded on Shimadzu IR-27G, JASCO A-100S and JASCO IRA-2 spectrometers. For the analysis of MTPA amide derivatives (**12d—f**), HPLC was carried out on an instrument (Hitachi 635A) equipped with a ultraviolet (UV) detector (Gilson, model 111B) set at 254 nm. A stainless steel column packed with Lichrosorb SI 60 was used and eluted with a hexane–ethyl acetate solvent system (described in each case) at a rate of 1 ml/min. For the analysis of 2′-*epi*-distichonic acid A (**4b**), HPLC was carried out on an instrument (JASCO TRIROTAR) equipped with a refractive index detector (Shodex RI SE-31). A stainless steel column packed with Hitachi gel #2618 (cation exchange resin) was eluted with ammonia formate buffer at a rate of 0.5 ml/min.

***N*-Benzyloxycarbonyl-L-methionine Methyl Ester (9a)**——**9a** was obtained from L-methionine according to Ardakani and Rapoport.[11]

***N*-Benzyloxycarbonyl-L-methionine *tert*-Butyl Ester (9b)**——Liquid isobutene (60 ml) chilled to −78 °C was added to a solution of *N*-benzyloxycarbonyl-L-methionine (2.40 g, 8.48 mmol) prepared from L-methionine[11] in anhydrous methylene chloride (45 ml) and anhydrous dioxane (20 ml) in a 200 ml sealed tube. After addition of concentrated H_2SO_4 (1 ml), the tube was sealed and allowed to stand at room temperature for 2 d. The tube was opened with cooling, and the reaction mixture was poured into Na_2CO_3 solution (2.4 g in 60 ml of water). The organic

layer was separated, washed with brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on a silica gel column with hexane–ethyl acetate (5 : 1) to give **9b** (2.13 g, 6.29 mmol, 74.1%) as a colorless oil. $[\alpha]_D$ +14.0° (c=2.10, chloroform). LRMS m/z: 339 (M^+), 282 ($M-t$Bu)$^+$, 91 $(C_6H_5CH_2)^+$. IR ν_{max}^{neat} cm^{-1}: 3350 (N–H), 2950 (C–H), 2850 (C–H), 1720 (C=O), 1155 (C–O). ^{1}H-NMR (60 MHz, $CDCl_3$, TMS) δ: 1.41 (9H, s, $-C(CH_3)_3$), 1.20—2.38 (2H, m, $C_{(3)}$-H_2), 2.02 (3H, s, CH_3S–), 2.38—2.74 (2H, m, $C_{(4)}$-H_2), 4.37 (1H, m, $C_{(2)}$-H), 5.10 (2H, s, $-CH_2C_6H_5$), 5.85 (1H, d, J=13 Hz, –NH–), 7.32 (5H, s, $-CH_2C_6H_5$).

***N-tert*-Butoxycarbonyl-L-methionine Benzyl Ester (9c)**——Benzylation of *N-tert*-butoxycarbonyl-L-methionine obtained from L-methionine[15] according to Tilak's procedure[16] yielded **9c** as a colorless oil in a 61% yield from L-methionine. $[\alpha]_D$ +1.99° (c=1.29, chloroform). LRMS m/z: 282 ($M-C_4H_9$)$^+$, 147 ($M-C_4H_9-CH_2C_6H_5-CO_2$)$^+$. IR ν_{max}^{neat} cm^{-1}: 3350 (N–H), 2970 (C–H), 2930 (C–H), 1790 (C=O), 1162 (C–O). ^{1}H-NMR (60 MHz, $CDCl_3$, TMS) δ: 1.42 (9H, s, $-C(CH_3)_3$), 2.05 (3H, s, CH_3S–), 1.9–2.2 (2H, m, $C_{(3)}$-H_2), 2.3—2.7 (2H, m, $C_{(4)}$-H_2), 4.3—4.7 (1H, m, $C_{(2)}$-H), 5.21 (2H, s, $-CH_2C_6H_5$), 5.1—5.5 (1H, m, –NH–), 7.38 (5H, s, $-CH_2C_6H_5$).

Methionine Sulfoxides

General Procedure——L-Methionine sulfoxides (**10a—c**) were obtained from protected L-methionines by oxidation with sodium periodate.[11]

2(*S*)-Methyl *N*-Benzyloxycarbonyl-4-(methylsulfinyl)butanoate (10a)——mp 104—105 °C. $[\alpha]_D$ −44.5° (c=1.07, methanol). LRMS m/z: 313 (M^+), 249 ($M-CH_3SO$)$^+$. IR ν_{max}^{KBr} cm^{-1}: 3330 (N–H), 3020 (C–H), 2960 (C–H), 2920 (C–H), 1740 (–COO–), 1690 (–OCONH–). ^{1}H-NMR (60 MHz, $CDCl_3$, TMS) δ: 1.98—2.42 (2H, m, $C_{(3)}$-H_2), 2.49 (3H, s, CH_3S–), 2.59—2.95 (2H, m, $C_{(4)}$-H_2), 3.72 (3H, s, $-COOCH_3$), 4.50 (1H, m, $C_{(2)}$-H), 5.10 (2H, s, $-CH_2C_6H_5$), 6.05 (1H, m, –NH–), 7.34 (5H, s, $-CH_2C_6H_5$).

2(*S*)-*tert*-Butyl *N*-Benzyloxycarbonyl-4-(methylsulfinyl)butanoate (10b)——$[\alpha]_D$ −19.3° (c=1.34, methanol). LRMS m/z: 355 (M^+), 298 ($M-t$Bu)$^+$. IR ν_{max}^{KBr} cm^{-1}: 3350 (N–H), 2950 (C–H), 2850 (C–H), 1720 (C=O). ^{1}H-NMR (60 MHz, $CDCl_3$, TMS) δ: 1.41 (9H, s, $-C(CH_3)_3$), 2.28 (2H, m, $C_{(3)}$-H_2), 2.32 (3H, s, CH_3S–), 2.71 (2H, m, $C_{(4)}$-H_2), 4.25 (1H, m, $C_{(2)}$-H), 5.08 (2H, s, $-CH_2C_6H_5$), 6.06 (1H, m, –NH–), 7.31 (5H, s, $-CH_2C_6H_5$).

2(*S*)-Benzyl *N*-*tert*-Butoxycarbonyl-4-(methylsulfinyl)butanoate (10c)——$[\alpha]_D$ −22.6° (c=1.08, methanol). LRMS m/z: 356 $(M+H)^+$, 299 $(M-CH_2=C(CH_3)_3)^+$, 265 $(M-CH_2C_6H_5)^+$, 256 $(M-C_4H_9-CO_2)^+$. IR ν_{max}^{KBr} cm^{-1}: 3550 (N–H), 2900 (C–H), 2850 (C–H), 1730 (C=O), 1155 (C–O). ^{1}H-NMR (60 MHz, $CDCl_3$, TMS) δ: 1.42 (9H, s, $-C_4H_9$), 2.0—2.4 (2H, m, $C_{(3)}$-H_2), 2.51 (3H, s, CH_3S–), 2.5—3.0 (2H, m, $C_{(4)}$-H_2), 4.45 (1H, m, $C_{(2)}$-H), 5.20 (2H, s, $-CH_2C_6H_5$), 5.63 (1H, d, J=7.6 Hz, –NH–), 7.39 (5H, s, $-CH_2C_6H_5$).

Conversion to Vinylglycine

(Typical) 2(*S*)-*tert*-Butyl 2-*N*-Benzyloxycarbonylamino-3-butenoate (*N*-Benzyloxycarbonyl-L-vinylglycine *tert*-Butyl Ester) (11b)——Trimethylphosphite (1.83 ml, 15.5 mmol) was added to a solution of L-methionine sulfoxide (**10b**) (5.51 g, 15.5 mmol) in xylene (30 ml), and the mixture was heated under reflux for 24 h. After evaporation of the solvent, the residue was chromatographed on a silica gel column with hexane–ethyl acetate (10 : 1) to give L-vinylglycine (**15**) (940 mg, 3.23 mmol, 20%) as a colorless oil. Further elution with ethyl acetate–methanol (5 : 1) gave unchanged **10b** (3.99 g, 11.3 mmol). Recovered **10b** (3.99 g, 11.3 mmol) was heated under reflux under the same conditions to provide vinylglycine (**11b**) (1.13 g, 3.87 mmol, 34%) together with recovered of **10b** (856 mg, 2.41 mmol). $[\alpha]_D$ −16.5° (c=1.81, methanol). HRMS m/z: 291.1475 Calcd 291.1469 for $C_{16}H_{22}NO_4$. IR ν_{max}^{KBr} cm^{-1}: 3440 (N–H), 2990 (C–H), 2940 (C–H), 1720 (C=O), 1645 (C=C), 1155 (C–O). ^{1}H-NMR (60 MHz, $CDCl_3$, TMS) δ: 1.43 (9H, s, $-C(CH_3)_3$), 4.85 (1H, m, $C_{(2)}$-H), 5.12 (2H, s, $-CH_2C_6H_5$), 5.9 (1H, m, –NH–), 5.6—6.3 (3H, m, $C_{(3)}$-H and $C_{(4)}$-H_2), 7.34 (5H, s, $-CH_2H_6H_5$).

2(*S*)-Methyl 2-*N*-Benzyloxycarbonylamino-3-butenoate (11a)——$[\alpha]_D$ −9.76° (c=0.74, methanol). LRMS m/z: 249 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440 (N–H), 3000 (C–H), 2965 (C–H), 1750 (C=O), 1730 (C=O), 1655 (C=C), 1175 (C–O). ^{1}H-NMR (60 MHz, $CDCl_3$, TMS) δ: 3.72 (3H, s, $-COOCH_3$), 4.93 (1H, m, $C_{(2)}$-H), 5.11 (2H, s, $-CH_2C_6H_5$), 5.15 (1H, m, –NH–), 5.42 (2H, dt, J=8.5, 1.5 Hz, $C_{(4)}$-H_2), 5.6—6.4 (1H, m, $C_{(3)}$-H).

2(*S*)-Benzyl 2-*N*-*tert*-Butoxycarbonylamino-3-butenoate (11c)——$[\alpha]_D$ −10.4° (c=2.39, chloroform). LRMS m/z: 235 $(M+H-CH_2=C(CH_3)_2)^+$, 190 $(M-OCOC(CH_3)_3)^+$, 157 $(M+H-COOCH_2C_6H_5)^+$. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440 (N–H), 2980 (C–H), 2940 (C–H), 1790 (–COO–), 1710 (–OCONH–), 1640 (C=C), 1150 (C–O). ^{1}H-NMR (60 MHz, $CDCl_3$, TMS) δ: 1.38 (9H, s, $-C(CH_3)_3$), 4.80 (1H, m, $C_{(2)}$-H), 5.08 (2H, s, $-CH_2C_6H_5$), 4.97—5.42 (3H, m, –NH– and $C_{(4)}$-H_2), 5.53—6.13 (1H, m, $C_{(3)}$-H), 7.20 (5H, s, $-CH_2C_6H_5$).

2(*RS*)-*tert*-Butyl 2-*N*-[α-Methoxy-α-(trifluoromethyl)phenylacetyl]aminobutanoate (DL-12e)——A 1 N HCl solution (0.22 ml) and 5% Pd–$BaSO_4$ (25 mg) were added to a solution of DL-**11b** (63.9 mg, 0.220 mmol) in methanol (1 ml), and the mixture was stirred under a hydrogen atmosphere at room temperature for 4.7 h. After removal of the catalyst, the solvent was evaporated off to give an amine salt (36.3 mg, 0.19 mmol, 86%). The residual amine salt was added to a solution of α-methoxy-α-trifluoromethylphenylacetic acid (55.5 mg, 0.23 mmol) and dicyclohexylcarbodiimide (DCC) (42.5 mg, 0.208 mmol) in methylene chloride (3 ml), and the reaction mixture was stirred at room temperature for 16 h. The precipitate was removed by filtration, and the filtrate was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine successively, and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was chromatographed on a silica gel column with ethyl acetate to give MTPA amide (**12e**). LRMS m/z: 320 $(M+H-CH_2=C(CH_3)_2)^+$, 274 $(M-COOC_4H_9)^+$. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3410 (N–H), 2975 (C–H), 2940 (C–H), 2845

(C–H), 1730 (–COO–), 1695 (–OCONH–), 1160 (C–O). ^{1}H-NMR (60 MHz, $CDCl_3$, TMS) δ: 0.93 (3H, t, J=8.4 Hz, $C_{(4)}$-H_3), 1.47 (9H, s, $-C(CH_3)_3$), 1.6—2.1 (2H, m, $C_{(3)}$-H_2), 3.43 (3H, m, $-OCH_3$), 4.43 (1H, m, $C_{(2)}$-H), 7.1—7.5 (5H, m, $-C_6H_5$). HPLC (hexane–ethyl acetate (20 : 1)), t_R=13.0 and 14.6 min. MTPA amide prepared from **11b** showed two peaks at t_R=13.0 and 14.6 min in the ratio of 1 : 6.7 on HPLC.

2(*RS*)-Methyl 2-[α-Methoxy-α-(trifluoromethyl)phenyl]aminobutanoate (DL-12d)——**12d** was obtained in the same manner. LRMS m/z: 334 $(M+H)^+$, 302 $(M-OCH_3)^+$, 274 $(M-COOCH_3)^+$. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (N–H), 2950 (C–H), 2840 (C–H), 1740 (–COO–), 1695 (–CONH–), 1165 (C–O). ^{1}H-NMR (60 MHz, $CDCl_3$, TMS) δ: 0.93 (3H, t, J=8.4 Hz, $C_{(4)}$-H_3), 1.5—2.1 (2H, m, $C_{(3)}$-H_2), 3.40 (3H, m, $-OCH_3$), 3.71 (3H, s, $-COOCH_3$), 4.3—4.9 (1H, m, $C_{(2)}$-H), 7.2—7.8 (5H, m, $-C_6H_5$). HPLC (hexane–ethyl acetate (10 : 1)), t_R=16.0 and 19.3 min. MTPA amide formed from **11a** showed two peaks at t_R=16.0 and 19.3 min in the ratio of 1 : 17 on HPLC.

2(*RS*)-Benzyl 2-*N*-[α-Methoxy-α-(trifluoromethyl)phenyl]aminobutanoate (DL-12f)——Trifluoroacetic acid (TFA) (1 ml) was added to a mixture of DL-**11c** (45.3 mg, 0.156 mmol) and anisole (0.03 ml) at 0 °C, and stirred for 30 min. The TFA was evaporated off, then anisole was removed from the reaction mixture by silica gel column chromatography with hexane. Further elution with ethyl acetate–methanol (3 : 1) afforded an amine which was lead to MTPA amide DL-**12f**. LRMS m/z: 407 (M^+), 316 $(M-CH_2C_6H_5)^+$, 272 $(M-COOCH_2C_6H_5)^+$. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (N–H), 3020 (C–H), 2840 (C–H), 2815 (C–H), 1735 (–COO–), 1705 (–OCONH), 1700 (C=C), 1165 (C–O). ^{1}H-NMR(60 MHz, $CDCl_3$, TMS) δ: 3.40 (3H, m, $-OCH_3$), 4.93 (1H, m, $C_{(2)}$-H), 5.13 (2H, m, $-CH_2C_6H_5$), 5.10—5.47 (3H, m, –NH–, $C_{(4)}$-H_2), 5.53—6.13 (1H, m, $C_{(3)}$-H), 7.27 (5H, s, $-CH_2C_6H_5$), 7.1—7.7 (5H, m, $-C_6H_5$). HPLC (hexane–ethyl acetate (20 : 1)), t_R=35.6 and 38.2 min. MTPA amide formed from **11c** showed two peaks at t_R=35.6 and 38.2 min in the ratio of 1 : 20 on HPLC.

Epoxidation of Vinylglycine

(Typical) 2(*S*)-*tert*-Butyl 2-*N*-Benzyloxycarbonylamino-3,4-epoxybutanoate (6b)——mCPBA (511 mg, 2.07 mmol) was added to a solution of vinylglycine (**11b**) (309 mg, 1.06 mmol) in methylene chloride (9 ml), and refluxed for 4.5 h. The reaction mixture was poured into saturated aqueous $NaHSO_3$, and the organic layer was separated. The aqueous layer was extracted with methylene chloride, and the combined organic layer was washed with saturated aqueous $NaHCO_3$, water and brine and dried over anhydrous $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on a silica gel column with hexane–ethyl acetate (10 : 1) to give the epoxide (**6b**) (287 mg, 0.93 mmol, 88%). HRMS m/z: 307.1433 Calcd 307.1421 for $C_{16}H_{21}NO_5$. IR ν_{max}^{KBr} cm^{-1}: 3400 (N–H), 3050 (C–H), 1720 (C=O). ^{1}H-NMR (100 MHz, $CDCl_3$, TMS) δ: 1.47 (9H, s, $-C(CH_3)_3$), 2.57—2.80 (2H, m, $C_{(4)}$-H_2), 3.19 (1H, m, minor $C_{(3)}$-H), 3.40 (1H, m, major C_3-H), 4.39 (1H, minor C_2-H), 4.54 (1H, major $C_{(2)}$-H), 5.09 (2H, s, $-CH_2C_6H_5$), 5.23 (1H, d, major, –NH–), 5.46 (1H, d, minor,–NH–), 7.31 (5H, s, $-CH_2C_6H_5$); (*S*-epoxide): 1.47 (9H, s, $-C(CH_3)_3$), 2.62 (2H, m, $C_{(4)}$-H_2), 3.40 (1H, m, $C_{(3)}$-H), 4.54 (1H, dd, J=8.8, 2.0 Hz, $C_{(2)}$-H), 5.09 (2H, s, $-CH_2C_6H_5$), 5.23 (1H, d, J=8.8 Hz, –NH–), 7.35 (5H, s, $-CH_2C_6H_5$); (*R*-epoxide): 1.47 (9H, s, $-C(CH_3)_3$), 2.62 (2H, m, $C_{(4)}$-H_2), 3.19 (1H, m, $C_{(3)}$-H), 4.39 (1H, dd, J=8.0, 4.7 Hz, $C_{(2)}$-H), 5.09, 5.46 (1H, d, J=8.0 Hz, –NH–), 7.35.

2(*S*)-Methyl 2-*N*-Benzyloxycarbonylamino-3,4-epoxybutanoate (6a)——Yield 78%. LRMS m/z: 265 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430 (N–H), 3030 (C–H), 3010 (C–H), 2960 (C–H), 1750 (–COO–), 1725 (–OCONH–), 1165 (C–O). ^{1}H-NMR (100 MHz, $CDCl_3$, TMS) δ: ((*S*)-epoxide): 2.70 (2H, m, $C_{(4)}$-H_2), 3.40 (1H, m, $C_{(3)}$-H), 3.76 (3H, s, $-COOCH_3$), 4.66 (1H, dd, J=9.0, 1.9 Hz, $C_{(2)}$-H), 5.08 (2H, s, $-CH_2C_6H_5$), 5.35 (1H, d, J=9.0 Hz, –NH–), 7.29 (5H, s, $-CH_2C_6H_5$), 7.35 (5H, s, $-CH_2C_6H_5$); ((*R*)-epoxide): 2.70, 3.20 (1H, m, $C_{(3)}$-H), 3.76, 4.48 (1H, dd, J=7.8, 5.1 Hz, $C_{(2)}$-H), 5.08, 5.60 (1H, d, J=7.8 Hz, –NH–), 7.29.

2(*S*)-Benzyl 2-*N*-*tert*-Butoxycarbonylamino-3,4-epoxybutanoate (6c)——Yield 60%. LRMS m/z: 252 $(M-C(CH_3)_3)^+$, 172 $(M-COOCH_2C_6H_5)^+$. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440 (–OCONH–), 2980 (C–H), 2940 (C–H), 1745 (–COO–), 1715 (C=O), 1160 (C–O). ^{1}H-NMR (100 MHz, $CDCl_3$, TMS) δ: ((*S*)-epoxide): 1.42 (9H, s, $-C(CH_3)_3$), 2.72 (2H, m, $C_{(4)}$-H_2), 3.43 (1H, m, $C_{(3)}$-H), 4.64 (1H, dd, J=8.0, 1.5 Hz, $C_{(2)}$-H), 5.01 (1H, d, J=8.0 Hz, –NH–), 5.21 (2H, s, $-CH_2C_6H_5$), 7.52 (5H, s, $-CH_2C_6H_5$); ((*R*)-epoxide): 1.42, 2.72, 3.21 (1H, m, $C_{(3)}$-H), 4.46 (1H, m, $C_{(2)}$-H), 5.20 (1H, m, –NH–), 5.21, 7.52.

Determination of Configuration

2(*S*),3(*R*)-Methyl 2-*N*-Benzyloxycarbonylamino-4-bromo-3-hydroxybutanoate (13a)——A 48% solution of HBr was added to a solution of **6a** (184 mg, 0.692 mmol) in methylene chloride, and the mixture was stirred at room temperature for 2.5 h. After addition of anhydrous $NaHCO_3$, the reaction mixture was extracted with methylene chloride. The organic layer was washed with water and brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated off and the residue was recrystallized from hexane–chloroform to give the bromohydrin (**13a**) (133 mg, 0.385 mmol, 56%). mp 93—94 °C. $[\alpha]_D$ 15.9° (c=1.50, chloroform). HRMS 345.0169 Calcd 345.0211 for $C_{13}H_{16}BrNO_5$, 347.0169 Calcd for 347.0211 for $C_{13}H_{16}BrNO_5$. IR ν_{max}^{KBr} cm^{-1}: 3500 (O–H), 3330 (N–H), 3030 (C–H), 2950 (C–H), 1720 (–COO–), 1690 (–OCONH–), 1190 (C–O). ^{1}H-NMR (100 MHz, $CDCl_3$, TMS) δ: 3.3—3.6 (2H, m, $C_{(4)}$-H), 3.67 (3H, s, $-COOCH_3$), 4.38 (1H, m, $C_{(3)}$-H), 4.56 (1H, dd, J=9.0, 2.4 Hz, $C_{(2)}$-H), 5.11 (2H, s, $-CH_2C_6H_5$), 5.54 (1H, br d, J=9.0 Hz, –NH–), 7.32 (5H, s, $-CH_2C_6H_5$).

***O*-Acetyl-*N*-benzyloxycarbonyl-L-threonine Methyl Ester (14a)**——Acetic anhydride (1 ml) was added to a solution of **13a** (91.5 mg, 0.236 mmol) in pyridine (2 ml), and the mixture was allowed to stand at room temperature for 16 h, then poured into ice-cold water and extracted with ethyl acetate. The organic layer was washed with

saturated aqueous $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude acetate. Tributyltin hydride (0.32 ml, 1.18 mmol) in methylene chloride (1 ml) was added to a solution of the acetate in methylene chloride (3 ml). After being stirred at room temperature for 13.5 h, the reaction mixture was poured into ice-cold water. The organic layer was extracted with saturated aqueous $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$. The solvent was removed, and the residue was chromatographed on a silica gel column with hexane–ethyl acetate (1 : 1) to yield **14a** (63.8 mg, 0.21 mmol, 86% from 23). All spectral signals of the threonine derivative (**14a**) were superimposable on those an authentic sample derived from L-threonine. $[\alpha]_D$ +40.3° (c=1.09, chloroform). LRMS m/z: 309 (M^+), 250 $(M-COOCH_3)^+$. IR ν_{max}^{neat} cm^{-1}: 3330 (N–H), 3050 (C–H), 2980 (C–H), 2960 (C–H), 1730 (C=O), 1170 (C–O). ^{1}H-NMR (60 MHz, $CDCl_3$, TMS) δ: 1.30 (3H, d, J=6.4 Hz, $C_{(4)}$-H_3), 1.95 (3H, s, $C_{(2)}$-$OCOCH_3$), 3.68 (3H, s, $-COOCH_3$), 4.43 (1H, dd, J=10, 3.6 Hz, $C_{(3)}$-H), 5.10 (2H, s, $-CH_2C_6H_5$), 5.37 (1H, dq, J=6.4, 3.6 Hz, $C_{(2)}$-H), 5.48 (1H, d, J=10 Hz, –NH–), 7.26 (5H, s, $-CH_2C_6H_5$).

***O*-Acetyl-*N*-benzyloxycarbonyl-L-allothreonine Methyl Ester (14b)**——L-Allothreonine derivative (**14b**) was synthesized from the minor compound in the mother liquor of the bromohydrin (**13a**) through the same sequence of reactions. All spectral data were identical with those of an authentic sample prepared from L-allothreonine. LRMS m/z: 309 (M^+), 250 $(M-COOCH_3)^+$. IR ν_{max}^{neat} cm^{-1}: 3330 (N–H), 3050 (C–H), 2980 (C–H), 2920 (C–H), 1730 (C=O), 1170 (C–O). ^{1}H-NMR (60 MHz, $CDCl_3$, TMS) δ: 1.23 (3H, d, J=8.0 Hz, $C_{(4)}$-H_3), 1.93 (3H, s, $C_{(3)}$-$OCOCH_3$), 3.67 (3H, s, $-COOCH_3$), 4.58 (1H, dd, J=8.0, 4.8 Hz, $C_{(2)}$-H), 5.05 (2H, s, $-CH_2C_6H_5$), 5.10 (1H, dq, J=8.0, 4.8 Hz, $C_{(3)}$-H), 5.67 (1H, br d, J=8.0 Hz, –NH–), 7.23 (5H, s, $-CH_2C_6H_5$).

2′(*R*),3′(*S*)-*N*-(3-Benzyloxycarbonylamino-3-*tert*-butoxycarbonyl-2-hydroxypropyl)glycine *tert*-Butyl Ester (18)——Glycine *tert*-butyl ester (**17**) (534 mg, 4.08 mmol) was added to a solution of the epoxide (**6b**) (416 mg, 1.36 mmol) in dimethoxyethane (10 ml). The mixture was refluxed for 4 h, then concentrated, and the remaining oily residue was chromatographed on a silica gel column. Elution with hexane–ethyl acetate (1 : 2) and recrystallization from hexane–chloroform gave **18** (342 mg, 0.59 mmol, 43%). mp 106.5—107.0 °C. $[\alpha]_D$ 27.7° (c=1.12, chloroform). FDMS m/z: 439 $(M+H)^+$. IR ν_{max}^{KBr} cm^{-1}: 3440 (O–H), 3330 (N–H), 2980 (C–H), 2830 (C–H), 1740 (–COO–), 1725 (–OCONH–), 1155 (C–O). ^{1}H-NMR (100 MHz, $CDCl_3$, TMS) δ: 1.40 (s, 18H, $-C(CH_3)_3\times2$), 2.5—3.0 (2H, m, $C_{(1')}$-H_2), 3.23 (2H, s, $C_{(2)}$-H_2), 3.8—4.5 (2H, m, $C_{(2')}$-H and $C_{(3')}$-H), 5.05 (2H, s, $-CH_2C_6H_5$), 5.58 (1H, d, J=9.6 Hz, –NH–), 7.25 (5H, s, $-CH_2C_6H_5$).

2′(*R*),3′(*S*)-*N*-(3-Benzyloxycarbonylamino-3-*tert*-butoxycarbonyl-2-hydroxypropyl)-*N*-*tert*-butoxycarbonylglycine *tert*-Butyl Ester (19)——Di-*tert*-butyldicarbonate (150 mg, 0.69 mmol) was added to a solution of **18** (342 mg, 0.59 mmol) in methylene chloride (6 ml). The mixture was stirred at room temperature for 16 h, then poured into 10% citric acid, and the organic layer was separated. The aqueous layer was extracted with methylene chloride. The combined organic layer was washed with water, saturated aqueous $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$. After removal of the solvent by evaporation, the residue was chromatographed on a silica gel column with hexane–ethyl acetate (5 : 1) to give **19** (315 mg, 0.58 mmol, 99%). $[\alpha]_D$ +29.6° (c=1.06, chloroform). FDMS m/z: 541 $(M+H)^+$. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (N–H), 2970 (C–H), 2920 (C–H), 1730 (C=O), 1200 (C–O). ^{1}H-NMR (100 MHz, $CDCl_3$, TMS) δ: 1.43 (27H, m, $-COOC(CH_3)_3\times2$, N–$COOC(CH_3)_3$), 3.28 (2H, m, $C_{(1')}$-H_2), 3.69 (2H, m, $C_{(2)}$-H_2), 3.9—4.5 (2H, m, $C_{(2')}$-H and $C_{(3')}$-H), 4.93 (2H, s, $-CH_2C_6H_5$), 5.54 (1H, d, J=8.8 Hz, –NH–), 7.15 (5H, s, $-CH_2C_6H_5$).

2′(*R*),3′(*S*)-*N*-(2-Acetoxy-3-benzyloxycarbonylamino-3-*tert*-butoxycarbonylpropyl)-*N*-*tert*-butoxycarbonylglycine *tert*-Butyl Ester (20)——Acetic anhydride (1.5 ml) was added to a solution of **19** (315 mg, 0.58 mmol) in pyridine (3 ml). The mixture was stirred at room temperature for 4.5 h, then poured into ice-cold water and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. The solvent was removed, and the residue was chromatographed on a silica gel column with hexane–ethyl acetate (5 : 1) to give **20** (324 mg, 0.56 mmol, 95%). $[\alpha]_D$ +31.4° (c=1.70, chloroform). FDMS m/z: 581 $(M+H)^+$. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3240 (N–H), 2980 (C–H), 2930 (C–H), 1730 (–COO–), 1715 (–COO–), 1700 (–NHCOO–), 1150 (C–O). ^{1}H-NMR (100 MHz, $CDCl_3$, TMS) δ: 1.43 (27H, m, $-COOC(CH_3)_3\times2$, N–$COOC(CH_3)_3$), 1.98 (3H, s, $-OCOCH_3$), 3.2—3.6 (2H, m, $C_{(1')}$-H_2), 3.78 (2H, m, $C_{(2')}$-H), 4.43 (1H, m, $C_{(3')}$-H), 5.09 (2H, s, $-CH_2C_6H_5$), 5.2—5.8 (2H, m, $C_{(2')}$-H and –NH–), 7.32 (5H, s, $-CH_2C_6H_5$).

(*S*)-Ethyl 2-Acetoxy-3-carboxypropionate (23)——A mixture of L-malic acid (**22**) (8.00 g, 59.7 mmol) and acetyl chloride (21.6 ml) was stirred at 40 °C for 5 h. The reaction mixture was then concentrated under reduced pressure, and anhydrous ethanol (15.8 ml) was added to the residue. The mixture was stirred at 50 °C for 1 h. The solvent was evaporated off and the remaining oily residue was chromatographed on a silica gel column with hexane–ethyl acetate (2 : 1) to afford a half ester **23**, which was recrystallized from hexane–ethyl acetate to give a colorless crystalline product (9.93 g, 48.7 mmol, 80.1%). mp 53 °C. $[\alpha]_D$ −32.4° (c=0.5, chloroform). LRMS m/z: 204 (M^+), 186 (M^+-H_2O), 158 $(M^+-HCOOH)$, 130 $(M^+-HCOOCH_2CH_3)$. IR ν_{max}^{KBr} cm^{-1}: 3180 (O–H), 1750 (C=O), 1738 (C=O), 1722 (C=O). ^{1}H-NMR (60 MHz, $CDCl_3$, TMS) δ: 1.28 (3H, t, J=7.0 Hz, $-COOCH_2CH_3$), 2.12 (3H, s, $C_{(2)}$-$OCOCH_3$), 2.92 (2H, d, J=6.0 Hz, $C_{(3)}$-H_2), 4.20 (2H, q, J=7.0 Hz, $-COOCH_2CH_3$), 5.51 (1H, t, J=6.0 Hz, $C_{(2)}$-H).

(*S*)-Ethyl 2-Acetoxy-4-hydroxybutanoate (24)——Borane dimethylsulfide (9 ml of 10 M THF solution) was added to a solution of the half ester **23** (9.93 g, 48.7 mmol) in THF (40 ml) over a period of 30 min with stirring at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 20 min and at room temperature for 18 h.

Methanol (20 ml) was added and then the reaction mixture was stirred at 0 °C for 20 min. After removal of the solvent, the residue was chromatographed on a silica gel column with hexane–ethyl acetate (2 : 1) to give the alcohol **24** (8.32 g, 43.8 mmol, 89.9%) as a colorless oil. LRMS *m/z*: 190 (M^+), 172 ($M^+ - H_2O$), 144 ($M^+ - OCOCH_3$), 116 ($M^+ - HCOOCH_2CH_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (O–H), 2980 (C–H), 1736 (C=O). ^{1}H-NMR (60 MHz, $CDCl_3$, TMS) δ: 1.27 (3H, t, J=7.0 Hz, $COOCH_2C\underline{H}_3$), 2.06 (2H, q, J=6.0 Hz, $C_{(4)}$-H_2), 2.21 (3H, s, $C_{(2)}$-$OCOC\underline{H}_3$), 3.17 (1H, br s, –OH), 3.73 (2H, t, J=6.0 Hz, $C_{(4)}$-H_2), 4.21 (2H, q, J=7.0 Hz, $-COOC\underline{H}_2CH_3$), 5.15 (1H, t, J=6.0 Hz, $C_{(2)}$-H).

(*S*)-Ethyl 2-Acetoxy-3-formylpropionate (*O*-Acetylmalaldehydic Acid Ethyl Ester) (25)——The alcohol (**24**) (500 mg, 2.63 mmol) in methylene chloride (3 ml) was added to a suspension of pyridinium chlorochromate (850 mg), sodium acetate (650 mg) and celite (850 mg) in methylene chloride (4 ml). The mixture was stirred at room temperature for 40 min. The reaction mixture was diluted with ether (21 ml), and poured into a Florisil (60—100 mesh) column. The ether eluate was evaporated and the residue was chromatographed on a silica gel column with hexane–ethyl acetate (4 : 1) to give the aldehyde **25** (173 mg, 0.92 mmol, 35%). $[\alpha]_D$ −31.7° (c=0.5, chloroform). LRMS *m/z*: 189 (M^++1), 159 (M^+−CHO), 128 ($M^+ - HOCOCH_3$), 115 ($M^+ - COOCH_2C\underline{H}_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3030 (C–H), 2990 (C–H), 1738 (C=O), 1192 (C–O). ^{1}H-NMR (60 MHz, $CDCl_3$, TMS) δ: 1.27 (3H, t, J=7.0 Hz, $-COOCH_2C\underline{H}_3$), 2.11 (3H, s, $-OCOC\underline{H}_3$), 2.99 (2H, dd, J=1.0, 6.0 Hz, $C_{(3)}$-H_2), 4.23 (2H, q, J=7.0 Hz, $COOC\underline{H}_2CH_3$), 5.51 (1H, t, J=6.0 Hz, $C_{(2)}$-$\underline{H}$), 9.78 (1H, t, J=1.0 Hz, $-C\underline{H}O$).

2′(*R*),3′(*S*),3″(*S*)-*N*-[3-(3-Acetoxy-3-ethoxycarbonylpropyl)amino-3-*tert*-butoxycarbonyl-2-acetoxypropyl]-*N*-*tert*-butoxycarbonylglycine *tert*-Butyl Ester (26)——A 1 N HCl solution (0.56 ml) and 5% Pd–C were added to a methanol solution of **20** (324 mg, 0.56 mmol), and the mixture was stirred under a hydrogen atmosphere at room temperature for 2 h. The catalyst was removed by filtration and the filtrate was freed from the solvent *in vacuo* to give the amine **21** as the hydrochloride. $NaBH_3CN$ (35.3 mg) was added to a solution of **21** and the aldehyde (**25**) (210 mg) in methanol (2 ml), and the mixture was stirred at room temperature for 16 h. Water (10 ml) was added to the reaction mixture and the whole was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated off and the residue was chromatographed on silica gel with hexane–ethyl acetate (5 : 1) to afford protected 2′-*epi*-distichonic acid A (**26**) (201 mg, 0.33 ml, 58%). $[\alpha]_D$ +12.7° (c=0.297, chloroform). FDMS *m/z*: 619 $(M+H)^+$. IR ν_{max}^{neat} cm^{-1}: 3550 (N–H), 3450 (N–H), 3420 (N–H), 2980 (C–H), 2940 (C–H), 1750 (–COO–), 1710 (–OCONH–), 1160 (C–O), 1040. ^{1}H-NMR (100 MHz, $CDCl_3$, TMS) δ: 1.29 (3H, t, J=8.0 Hz), 1.43 (27H, m, -*t*Bu, *t*Bu, Boc), 1.99 (3H, s, $C_{(3'')}$-$OCOC\underline{H}_3$), 2.14 (3H, s, $C_{(2')}$-$OCOC\underline{H}_3$), 2.3—2.6 and 2.6—3.0 (2H, m, $C_{(2'')}$-H_2), 3.1—3.6 (5H, m, $C_{(1')}$-H_2, $C_{(3')}$-H and $C_{(1'')}$-H_2), 3.83 (2H, m, $C_{(2)}$-H_2), 4.19 (2H, q, J=8.0 Hz, $-OC\underline{H}_2CH_3$), 5.10 (1H, m, $C_{(3'')}$-H), 5.2—5.7 (2H, m, $C_{(2')}$-H and –NH–).

2′-*epi*-Distichonic Acid A (4b)——A 5 N HCl solution (1 ml) was added to a methanol solution (4 ml) of protected 2′-*epi*-distichonic acid A (**26**), and the mixture was stirred at room temperature for 20 h. The solvent was removed *in vacuo*, and water was added to the residue. The aqueous solution was applied to a Dowex 50W × 8 (H^+ form) column, and the column was washed with water, then eluted with 1 N NH_4OH, and the eluate was evaporated. Next, 2.5% KOH aqueous solution was added to an aqueous solution (8.3 ml) of the residue at 0 °C, and the solution was stirred at room temperature for 17 h. The reaction mixture was freed from alkali on an Amberlite IRC-50 (H^+) column and chromatographed on a Dowex 50W × 8 (H^+) column with pH 2.70 ammonium–formate buffer then on a Cellulophine GCL-25-m column to afford 2′-*epi*-distichonic acid A (**4b**) (46 mg, 40%) as a white powder. mp 215—217 °C (dec.). $[\alpha]_D$ −13.3° (c=0.09). CD (c=0.03, 1 N HCl) [θ] (nm): +2630 (208.5) (positive maximum). FDMS *m/z*: 295 $(M+H)^+$. IR ν_{max}^{KBr} cm^{-1}: 3400 (O–H), 2850 (C–H), 1600 (C=O), 1400, 1100 (C–O), 900, 770. ^{1}H-NMR (D_2O, 100 MHz, TMS) δ: 2.04 (2H, m, $C_{(2'')}$-H_2), 2.91—3.30 (4H, m, $C_{(1')}$-H_2, $C_{(1'')}$-H_2), 3.50 (1H, d, J=6.2 Hz, $C_{(3')}$-H_2), 3.60 (2H, s, $C_{(2)}$-H_2), 4.15 (1H, d, $C_{(3'')}$-H), 4.32 (1H, dd, J=6.2, 2.0 Hz, $C_{(2')}$-H); (100 MHz, DCl, TMS) δ: 2.0—2.6 (2H, m, $C_{(2'')}$-H_2), 3.2—3.8 (4H, m, $C_{(1')}$-H_2 and $C_{(1'')}$-H_2), 4.16 (2H, s, $C_{(2)}$-H_2), 4.36 (1H, d, J=6.0 Hz, $C_{(3')}$-H), 4.48—4.80 (2H, m, $C_{(2')}$-H and $C_{(3'')}$-H). ^{13}C-NMR (D_2O, 25 MHz, TMS) δ: 29.82 (sp^3, t), 46.09 (sp^3, t), 48.26 (sp^3, t), 50.43 (sp^3, t), 62.53 (sp^3, d), 64.93 (sp^3, d), 68.98 (sp^3, d), 169.97 (sp^2, s), 168.7 (sp^2, s), 176.48 (sp^2, s). PC: *Rf* 0.13 (phenol: H_2O: 28% NH_3 = 75 : 15 : 10). HPLC; t_R = 11 min. (NH_3–HCOOH pH 2.80, Asp. t_R = 14 min).

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