**Synthesis of Enantiomeric Pairs of Vicinal-Diols from L- α -Amino Acids by
the Use of Organolithium Reagents: Its Application to
optically Active Epoxyterpene Synthesis¹⁾**

SHIRO TERASHIMA,^{2a)} CHUNG CHYI TSENG, MASAJI HAYASHI,
and KENJI KOGA³⁾

Faculty of Pharmaceutical Sciences, University of Tokyo²⁾

(Received October 31, 1978)

Reaction of (S)(-)- α -tosyloxy acid ((S)(-)-3) with methyl- or n-butyllithium was found to afford (R)(+)-vicinal(vic)-diol ((R)(+)-4) in an excellent yield with almost full inversion. On the other hand, when (S)(-)- α -hydroxy acid ester ((S)(-)-5) was allowed to react with methyl- or n-butyllithium, (S)(-)-vic-diol ((S)(-)-4) was obtained in an excellent yield with full retention. Since (S)(-)-3 and (S)(-)-5 are both derivable from L-phenylalanine (L-1), it has become possible to obtain an enantiomeric pair of vic-diols from L-1.

Plausible formation mechanism for (R)(+)-4 from (S)(-)-3 was proposed.

The utility of optically active vic-diols in natural product synthesis was also visualized by preparing the novel synthetic intermediate for epoxyterpene synthesis ((S)(-)-6) from (S)(-)-4a.

Keywords—enantiomeric pairs of vicinal-diols; optically active α -tosyloxy acids; optically active α -hydroxy acid esters; organolithium reagents; inversion; retention; optically active epoxyterpenes; 2-oxo-1,3-dioxolanes; ozonolysis; deamination

In the previous studies directed towards the synthesis of optically active α -alkyl or α -aryl acids from L- α -amino acids,³⁾ it was found that treatment of (S)(-)-3-phenyl-2-tosyloxypropionic acid ((S)(-)-3) with lithium di-n-butylcuprate gave (+)-3-n-butyl-1-phenyl-2,3-heptanediol((+)-4b) as the sole isolable reaction product in place of the desired substitution product. Since the formation of the unusual vicinal(vic)-diol((+)-4) could be construed by the assumption that lithium di-n-butylcuprate behaved in complete the same manner as n-butyllithium(*vide infra*), we paid much attention to the possible reaction of alkyllithiums with optically active α -tosyloxy acids.

Although the reaction of carboxylic acids with organolithium reagents constitutes a simple method for the synthesis of ketones,⁴⁾ and several applications of this method to racemic⁵⁾ and optically active⁶⁾ α -hydroxy acids have been reported to afford corresponding racemic and optically active α -hydroxy ketones, the use of optically active α -tosyloxy acids having excellent leaving group at the α -position as reaction substrates, has never been attempted.

We have now found that when optically active α -tosyloxy acid is allowed to react with organolithium reagent, optically active vic-diol can be produced in an excellent yield with almost full inversion at the asymmetric center. Since the reaction of optically active

- 1) This has been a subject of the preliminary communication: S. Terashima, M. Hayashi, C.C. Tseng, and K. Koga, *Tetrahedron Lett.*, 1978, 1763.
- 2) Location: Hongo, Bunkyo-ku, Tokyo 113, Japan; a) To whom all correspondence should be addressed.
- 3) S. Terashima, C.C. Tseng, and K. Koga, *Chem. Pharm. Bull.* (Tokyo), 27, 747 (1979).
- 4) M.J. Jorgenson, "Organic Reactions," Vol. 18, John-Wiley and Sons, Inc., New York, London, Sydney, Toronto, 1970, p. 1.
- 5) J.D. Billmoria and N.F. MacLagen, *J. Chem. Soc.*, 1951, 3067.
- 6) a) D.J. Cram and K.R. Kopecky, *J. Am. Chem. Soc.*, 81, 2748 (1959); b) H. Mizuno, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), 19, 227 (1971); c) S. Terashima, S.-s. Jew, and K. Koga, *Tetrahedron Lett.*, 1977, 4507; d) *Idem, ibid.*, 1978, 4937.

α -hydroxy acid ester and organolithium reagent can proceed with full retention at the asymmetric center to afford optically active *vic*-diol, and both optically active α -tosyloxy acid and α -hydroxy acid ester can be readily prepared from L- α -amino acid by way of optically active α -hydroxy acid, it is now possible to prepare an enantiomeric pair of *vic*-diols from L- α -amino acid.

This report concerns with the efficient synthesis of an enantiomeric pair of *vic*-diols and with its application to optically active epoxyterpene synthesis.

Results and Discussion

A. Preparation of Enantiomeric Pairs of *Vic*-Diols from L- α -Amino Acids

As shown in Chart 1, when optically pure ((*S*)(-)-3),³⁾ $[\alpha]_D^{20} -46.9^\circ$ (chloroform), which was prepared from commercially available L-phenylalanine (L-1) by way of (*S*)(-)-2-hydroxy-3-phenylpropionic acid ((*S*)(-)-2) according to the synthetic scheme exploited in the previous study,³⁾ was treated with methyllithium, (+)-*vic*-diol((+)-4a), $[\alpha]_D^{20} +58.9^\circ$ (chloroform), could be obtained in 81% yield. On the other hand, the reaction of optically pure (*S*)(-)-ethyl

Chart 1

2-hydroxy-3-phenylpropionate((*S*)(-)-5),³⁾ $[\alpha]_D^{24} -21.4^\circ$ (benzene), being also obtainable from L-1, with methyllithium, was found to give (-)-*vic*-diol((-)-4a), $[\alpha]_D^{20} -59.0^\circ$ (chloroform), in 90% yield. It is quite clear that (-)-4a can be produced with full retention of the configuration because the alcoholic function of (*S*)(-)-5 might be immediately converted to the lithium alkoxide when (*S*)(-)-5 is treated with methyllithium. Therefore, the absolute configuration of (+)- and (-)-4a could be assigned as (*R*)- and (*S*)-series, respectively. This assignment was further ascertained by the successful synthesis of (*S*)(-)-ketone ((*S*)(-)-6), a key intermediate of optically active epoxyterpene synthesis, from (-)-4a (*vide infra*).

In a similar manner, when *n*-butyllithium was used in place of methyllithium, (+)-*vic*-diol((+)-4b), $[\alpha]_D^{20} +24.8^\circ$ (chloroform), and (-)-*vic*-diol((-)-4b), $[\alpha]_D^{20} -26.1^\circ$ (chloroform), were obtained from (*S*)(-)-3 and (*S*)(-)-5 in 92% and 97% yields, respectively. Considering the similarity of the reaction with methyllithium to that with *n*-butyllithium, the absolute configurations of (+)- and (-)-4b were determined as (*R*)- and (*S*)-series. The former *vic*-diol((*R*)(+)-4b) was completely identical with the sample previously obtained by the reaction of (*S*)(-)-3 with lithium di-*n*-butylcuprate,³⁾ by spectral comparisons and mixed melting point measurement.

Formation of the inverted $(R)(+)$ -4 from $(S)(-)$ -3 might be rationalized by the two possible paths shown in Chart 2. Thus, addition of two moles of organolithium to $(S)(-)$ -3 directly gives the dilithium salt (7) in which S_N2 type substitution of the adjacent tosyloxy group by the intramolecular alkoxide anion occurs to give the epoxy alkoxide (8) (path a). Formation of the same intermediate (8) is also possible by the stepwise addition of organolithium to $(S)(-)$ -3 by way of the α -lactone (9) (path b). The epoxy alkoxide (8) can isomerize to the α -keto alkoxide (10) and the addition of organolithium to 10 would produce the inverted dilithium salt (11), from which $(R)(+)$ -4 can be liberated on acidic workup. Operation of the same reaction mechanism is also expected for the reaction of $(S)(-)$ -3 with lithium di-*n*-butylcuprate.³⁾

Although the two types of reactions were carried out using limited numbers of organolithium reagents, and both $(S)(-)$ -3 and $(S)(-)$ -5 which had been prepared from L-1, were only employed as reaction substrates, it might be foreseen that the same reactions could proceed with other organolithium reagents and with various structural types of optically active α -tosyloxy acids and α -hydroxy acid esters obtainable from L- α -amino acids other than L-1.

B. Preparation of the Novel Synthetic Intermediate (($S)(-)$ -6) for optically Active Epoxy-terpene Synthesis

Aiming to definitely establish the absolute configurations of the optically active *vic*-diols-(($R)(-)$ - and $(S)(-)$ -4a) derived from $(S)(-)$ -3 and $(S)(-)$ -5, and moreover, to realize the

utility of the optically active *vic*-diols in natural product synthesis, preparation of the novel synthetic intermediate ((*S*)(-)-**6**) for optically active epoxyterpene synthesis, was examined by using (*S*)(-)-**4a**. Several versatile synthetic schemes to optically active epoxyterpenes such as epoxygeraniol, epoxyfarnesol, and squalene-2,3-oxide,^{7,8)} had been exploited from (*S*)(-)-**6**. Although partial racemization had been observed in the previous synthesis of (*S*)(-)-**6** from L-glutamic acid,⁷⁾ we succeeded in readily obtaining optically pure (*S*)(-)-**6** from (*S*)(-)-**4a** as shown in Chart 3.

Thus, protection of the *vic*-diol function of (*S*)(-)-**4a** as a cyclic carbonate afforded (*S*)(-)-1,3-dioxolane-2-one((*S*)(-)-**12**), $[\alpha]_D^{20} -75.2^\circ$ (chloroform), in a quantitative yield. Ozonolysis of (*S*)(-)-**12** in acetic acid, followed by oxidative workup and esterification with diazomethane, cleanly gave (*S*)(-)-ester((*S*)(-)-**13**), $[\alpha]_D^{20} -29.7^\circ$ (chloroform) in 69% yield with the recovery of (*S*)(-)-**12**. The yield of (*S*)(-)-**13** was calculated as 81% when corrected for the recovery of the starting material. Reduction of (*S*)(-)-**13** with lithium aluminum hydride and protection of the *vic*-diol functionality generated during the metal hydride reduction as an acetal, gave (*S*)-alcohol ((*S*)-**14**)⁹⁾ in 94% overall yield. Reaction of (*S*)-**14** with tosyl chloride in pyridine gave (*S*)(-)-tosylate((*S*)(-)-**15**),¹⁰⁾ $[\alpha]_D^{20} -17.6^\circ$ (chloroform), in 89% yield, which was transformed into (*S*)(-)-cyanide ((*S*)(-)-**16**), $[\alpha]_D^{20} -29.6^\circ$ (chloroform), in 99% yield on treatment with potassium cyanide in N,N-dimethylformamide. The cyanide ((*S*)(-)-**16**) was submitted to alkaline hydrolysis, giving (*S*)(-)-acid((*S*)(-)-**17**), $[\alpha]_D^{20} -10.1^\circ$ (chloroform), in 91% yield. Reaction of (*S*)(-)-**17** with an excess amount of methyllithium furnished the desired optically pure (*S*)(-)-**6**, $[\alpha]_D^{25} -12.1^\circ$ (chloroform) and $[\alpha]_D^{27} -14.8^\circ$ (methanol), in 85% yield. Spectral and chromatographic (TLC) properties of (*S*)(-)-**6** thus obtained were completely identical with those of (*S*)(-)-**6** previously prepared from L-glutamic acid.⁷⁾ Comparison of the optical rotation of our sample with those reported, $[\alpha]_D^{25} +10.4^\circ$ (chloroform) for (*R*)(+)-**6**⁸⁾ and $[\alpha]_D^{25} -14.1^\circ$ (methanol) for (*S*)(-)-**6**,^{7,11)} clearly disclosed that (*S*)(-)-**6** obtained here was optically pure and that the determination of the absolute configuration for the enantiomeric pair of *vic*-diols((*R*)(+)- and (*S*)(-)-**4a**) was correct.

Since (*R*)(+)-**6** can be prepared from (*R*)(+)-**4a** according to the synthetic schemes exploited here, it has become possible to produce optically pure (*R*)(+)- and (*S*)(-)-**6** from L-1 by way of (*S*)(-)-**2** and the enantiomeric pair of *vic*-diols((*R*)(+)- and (*S*)(-)-**4a**).

Experimental¹²⁾

(*R*)(+)-3-Methyl-1-phenyl-2,3-butanediol ((*R*)(+)-**4a**)—To an ethereal solution (4 ml) of (*S*)(-)-**3**³⁾ (640 mg, 2.0 mmol) cooled at -18° , was added a solution of methyllithium in ether (1.43 M solution, 7 ml,

7) S. Yamada, N. Oh-hashii, and K. Achiwa, *Tetrahedron Lett.*, **1976**, 2557 and 2561.

8) M.A. Abdallah and J.N. Shah, *J. Chem. Soc. Perkin I*, **1975**, 888.

9) This sample was erroneously expressed as (*R*)(-)-**14** in the preliminary communication.⁴⁾

10) Spectral (IR and NMR) properties of this tosylate were identical with those of (*R*)(+)-**15**, $[\alpha]_D^{20} +17^\circ$ (chloroform), prepared from (*R*)-2-hydroxy- γ -butyrolactone in the synthetic approach to optically active squalene-2,3-oxide performed by Abdallah, *et al.*⁸⁾ Although they synthesized (*R*)(+)-**6** from (*R*)(+)-**15** by using 2-lithio-2-methyl-1,3-dithiane to extend the carbon chain, we employed the reaction scheme being operationally simpler than that reported.⁸⁾

11) This sample was prepared from L-glutamic acid by removing racemic compound at the synthetic intermediate. Without this operation for purification, partially optically active (*S*)(-)-**6**, $[\alpha]_D^{25} -8.7^\circ$ (methanol), was obtained from L-glutamic acid (S. Yamada, N. Ohhashi, and K. Achiwa, unpublished results).

12) All melting points are uncorrected. Infrared (IR) spectra were recorded with a JASCO IRA-1 Grating Infrared Spectrometer. Nuclear magnetic resonance (NMR) spectra were measured with a JNM-PS 100 Spectrometer (100 MHz) and a Hitachi R-24 High Resolution NMR Spectrometer (60 MHz). All signals are expressed by the ppm downfield from tetramethylsilane used as an internal standard (δ value). Following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br). Measurements of optical rotations were carried out using a YANACO OR-50 Automatic polarimeter. Mass spectra measurements were performed with a JEOL JMS SG-2 Mass Spectrometer.

10 mmol). After being stirred at -10° for 3.5 hr, the reaction mixture was poured onto a mixture of 10% HCl (6 ml) and satd. NH_4Cl (20 ml). The aqueous mixture was extracted with a mixture of benzene (10 ml) and ether (10 ml). The lower aqueous phase was saturated with NaCl, and was extracted four times with a mixture of benzene and ether (1:1). The combined organic extracts were dried over anhyd. MgSO_4 . Filtration and evaporation *in vacuo* gave crude (*R*)(+)-**4a** as a brown solid (402 mg, 100%). A part of the solid (135 mg) was purified by column chromatography (silica gel, solvent, hexane: ether: acetic acid 120:120:7.5) to give pure (*R*)(+)-**4a** as a colorless solid (98 mg, 81%), mp $72-73.5^{\circ}$, $[\alpha]_D^{20} +56.4^{\circ}$ ($c=1.28$, chloroform). Repeated recrystallizations from hexane gave an analytical sample as colorless long needles, mp $74-75^{\circ}$, $[\alpha]_D^{20} +58.9^{\circ}$ ($c=0.91$, chloroform). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3560, 3360 (OH). NMR (in CDCl_3): 1.23, 1.24 (6H, two s, $\text{C}(\text{CH}_3)_2$), 2.00, 2.18 (2H, two br s, $2 \times \text{OH}$), 2.54 (1H, doubled d, $J=10$ and 14 Hz, one of $\text{C}_6\text{H}_5\text{CH}_2\text{CH}$), 2.88 (1H, doubled d, $J=3$ and 14 Hz, one of $\text{C}_6\text{H}_5\text{CH}_2\text{CH}$), 3.59 (1H, doubled d, $J=3$ and 10 Hz, $\text{C}_6\text{H}_5\text{CH}_2\text{CH}$), 7.20 (5H, s, C_6H_5). Two broad singlets at 2.00 and 2.18 ppm disappeared on treatment with D_2O . Anal. Calcd. for $\text{C}_{11}\text{H}_{16}\text{O}_2$: C, 73.30; H, 8.95. Found: C, 73.41; H, 8.98.

(*S*)(-)-3-Methyl-1-phenyl-2,3-butanediol ((*S*)(-)-**4a**)—An ethereal solution of methylolithium (1.43 M solution, 7 ml, 10 mmol) was added to a stirred solution of (*S*)(-)-**5^a** (445 mg, 2.3 mmol) in ether (3 ml) cooled at -15° . After being stirred at -10° for 3.5 hr, the reaction mixture was worked up in a similar manner to the case for (*R*)(+)-**4a**, to give crude (*S*)(-)-**4a** as a yellow solid (396 mg, 95%) after evaporation of the combined organic extracts. A part of the solid (115 mg) was purified by the same manner as that for (*R*)(+)-**4a**, giving pure (*S*)(-)-**4a** as a colorless solid (108 mg, 90%), mp $73-74.5^{\circ}$, $[\alpha]_D^{20} -55.1^{\circ}$ ($c=0.93$, chloroform). Repeated recrystallizations from hexane gave an analytical sample as colorless long needles, mp $74.5-75.5^{\circ}$, $[\alpha]_D^{20} -59.0^{\circ}$ ($c=0.86$, chloroform). Spectral (IR and NMR) properties of this sample were completely identical with those of (*R*)(+)-**4a**. Anal. Calcd. for $\text{C}_{11}\text{H}_{16}\text{O}_2$: C, 73.30; H, 8.95. Found: C, 73.42; H, 8.99.

(*R*)(+)-3-*n*-Butyl-1-phenyl-2,3-heptanediol ((*R*)(+)-**4b**)—An ethereal solution (3 ml) of (*S*)(-)-**3^b** (320 mg, 1.0 mmol) was added to a cooled (-37°), stirred solution of *n*-butyllithium (1.43 M solution, 3.5 ml, 5.0 mmol) in hexane diluted with ether (7 ml). After stirring at $-40^{\circ}-30^{\circ}$ for 3 hr, the reaction mixture was poured onto a mixture of 10% HCl (3 ml) and satd. NH_4Cl (10 ml). The aqueous solution was extracted with a mixture of benzene and ether. The organic extract was washed with H_2O , then dried over anhyd. MgSO_4 . Filtration and evaporation *in vacuo* gave crude (*R*)(+)-**4b** as a colorless solid (242 mg, 92%). Recrystallizations from hexane afforded pure (*R*)(+)-**4b** (124 mg, 47%) as colorless needles, mp $109-112^{\circ}$, $[\alpha]_D^{20} +24.8^{\circ}$ ($c=2.44$, chloroform). Spectral (IR and NMR) and chromatographic (TLC) properties of this sample were identical with those of (*R*)(+)-**4b**, mp $107.5-108.5^{\circ}$, $[\alpha]_D^{20} +25.8^{\circ}$ ($c=0.546$, chloroform), prepared with lithium di-*n*-butylcuprate.³⁾ Measurement of the mixed melting point of this sample with that prepared previously³⁾ showed no depression, mp $108-109^{\circ}$.

(*S*)(-)-3-*n*-Butyl-1-phenyl-2,3-heptanediol ((*S*)(-)-**4b**)—To a cooled (-40°), stirred solution of *n*-butyllithium (1.43 M solution, 3.5 ml, 5.0 ml) in hexane diluted with ether (7 ml), was added an ethereal solution (3 ml) of (*S*)(-)-**5^b** (222 mg, 1.14 mmol). After being stirred at $-40^{\circ}-30^{\circ}$ for 5 hr, the reaction mixture was worked up in a similar manner to the case for (*R*)(+)-**4b**, to give crude (*S*)(-)-**4b** as a colorless solid (291 mg, 97%) after evaporation of the combined organic extracts. Repeated recrystallizations from hexane gave pure (*S*)(-)-**4b** as colorless needles (175 mg, 58%), mp $110-111^{\circ}$, $[\alpha]_D^{20} -26.1^{\circ}$ ($c=2.30$, chloroform). Spectral (IR) and chromatographic (TLC) behavior of this sample were completely identical with those of (*R*)(+)-**4b**.

(*S*)(-)-5-Benzyl-4,4-dimethyl-2-oxo-1,3-dioxolane ((*S*)(-)-**12**)—A mixture of (*S*)(-)-**4a** (9.0 g, 50 mmol), sodium ethoxide (0.60 g, catalytic amount), and diethyl carbonate (40 ml, 0.33 mol) was heated at reflux (bath temperature $170-180^{\circ}$) for 16 hr. The whole was evaporated *in vacuo* to afford an oily residue, which was dissolved in a mixture of ether (80 ml) and ethyl acetate (120 ml). The organic solution was successively washed with satd. NaHCO_3 and satd. NaCl, then dried over anhyd. MgSO_4 . Filtration and evaporation *in vacuo* gave crude (*S*)(-)-**12** as a yellow solid (10.4 g, 100%). Recrystallization from a mixture of hexane and ethyl acetate gave pure (*S*)(-)-**12** as colorless leaflets (9.67 g, 94%), mp $84-85.5^{\circ}$, $[\alpha]_D^{20} -73.6^{\circ}$ ($c=1.02$, chloroform). Further recrystallizations from the same solvent system afforded an analytical sample as colorless plates, mp $84-85.5^{\circ}$, $[\alpha]_D^{20} -75.2^{\circ}$ ($c=0.97$, chloroform). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1780 (2-oxo-1,3-dioxolane). NMR (in CDCl_3): 1.43, 1.47 (6H, two s, $\text{C}(\text{CH}_3)_2$), 2.82 (1H, doubled d, $J=6$ and 15 Hz, one of $\text{C}_6\text{H}_5\text{CH}_2\text{CH}$), 3.10 (1H, doubled d, $J=9$ and 15 Hz, one of $\text{C}_6\text{H}_5\text{CH}_2\text{CH}$), 4.47 (1H, doubled d, $J=6$ and 9 Hz, $\text{C}_6\text{H}_5\text{CH}_2\text{CH}$), 7.27 (5H, s, C_6H_5). Anal. Calcd. for $\text{C}_{12}\text{H}_{14}\text{O}_3$: C, 69.88; H, 6.84. Found: C, 69.72; H, 7.02.

(*S*)(-)-Methyl 4,4-Dimethyl-2-oxo-1,3-dioxolane-5-acetate ((*S*)(-)-**13**)—Ozone gas was bubbled through a solution of (*S*)(-)-**12** (2.0 g, 9.7 mmol) in acetic acid (50 ml) at room temperature for 12 hr. An aqueous solution of hydrogen peroxide (30%) (8 ml) was added to the reaction mixture, and the whole was stirred at room temperature overnight. Excess amount of hydrogen peroxide was decomposed by the addition of a small amount of platinum. After stirring at room temperature overnight, filtration and evaporation *in vacuo* gave an oily residue (2.58 g), which was dissolved in ether (10 ml). To the ethereal solution was added a solution of diazomethane in ether until the yellow color of diazomethane remained. The ethereal mixture was directly evaporated *in vacuo*, giving a yellow residue (2.39 g). This was submitted to column chromatography (silica gel, solvent, benzene: ethyl acetate 4:1) to afford the starting material ((*S*)(-)-**12**) as

a colorless solid (275 mg, 14% recovery), mp 84—85°, and pure (S)(-)-13 as a colorless oil (1.26 g, 69% and 81% corrected for the recovery of (S)(-)-12), $[\alpha]_D^{20} -25.1^\circ$ ($c=0.99$, chloroform). The latter colorless oil gradually solidified on standing. Repeated recrystallizations from a mixture of hexane and ether gave an analytical sample as colorless needles, mp 64—65°, $[\alpha]_D^{20} -29.7^\circ$ ($c=0.66$, chloroform). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1760 (2-oxo-1,3-dioxolane), 1740 (ester). NMR (in CDCl₃): 1.37, 1.56 (6H, two s, C(CH₃)₂), 2.63 (1H, doubled d, $J=7$ and 17 Hz, one of C₆H₅CH₂CH), 2.73 (1H, doubled d, $J=7$ and 17 Hz, one of C₆H₅CH₂CH), 3.75 (3H, s, OCH₃), 4.82 (1H, t, $J=7$ Hz, C₆H₅CH₂CH). MS m/e : 188 [M⁺], 173, 144. Anal. Calcd. for C₈H₁₂O₅: C, 51.06; H, 6.43. Found: C, 51.09; H, 6.40.

(S)(-)-2(2,2,4,4-Tetramethyl-1,3-dioxolan-5-yl)ethyl Tosylate ((S)(-)-15)—a (S)-2(2,2,4,4-Tetramethyl-1,3-dioxolan-5-yl)ethanol ((S)-14): To a stirred suspension of lithium aluminum hydride (1.16 g, 31 mmol) in tetrahydrofuran (60 ml) cooled at -23°, was gradually added a solution of (S)(-)-13 (1.17 g, 6.2 mmol) in tetrahydrofuran (30 ml). The reaction mixture was stirred under argon atmosphere at -23° for 2 hr, then at room temperature for 1.5 hr, and was finally heated at reflux for 2 hr. After cooling at 0°, addition of H₂O (9 ml) to the reaction mixture, followed by reflux for 2 hr, filtration, and evaporation *in vacuo* (azeotropic evaporation with benzene), gave an oily residue (1.24 g).

A part of the residual oil (1.21 g) was dissolved in a mixture of acetone (40 ml) and petr. ether (40 ml) containing *p*-toluenesulfonic acid monohydrate (catalytic amount), and the whole solution was refluxed for 4 hr using Cope's apparatus to remove the water produced. The reaction mixture was diluted with ether (150 ml), and washed with satd. NaHCO₃. After drying over anhyd. MgSO₄, filtration and evaporation *in vacuo* gave the crude acetal ((S)-14) as a yellow oil (0.99 g, 94%).⁹ The crude product was directly used for the next tosylation. IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 3400 (OH). NMR (in CDCl₃): 1.15, 1.30 (6H, two s, $\text{C}(\text{CH}_3)_2$), 1.38, 1.46 (6H, two s, $\text{C}(\text{CH}_3)_2$), 1.55—2.00 (2H, m, OCHCH₂CH₂OH), 2.25 (1H, br s, OH), 3.70—4.02 (3H, m, OCHCH₂CH₂OH).

b) (S)(-)-2(2,2,4,4-Tetramethyl-1,3-dioxolan-5-yl)ethyl Tosylate ((S)(-)-15): Tosyl chloride (1.63 g, 8.5 mmol) was added dropwise over 30 min to a cooled (-20°), stirred solution of (S)-14 (0.98 g, 5.6 mmol) in pyridine (5 ml). The reaction mixture was stirred at 0° for 4 hr, then was diluted with ice-water. The aqueous mixture was extracted with ether, and the combined ethereal extracts were successively washed with satd. CuSO₄ and satd. NaCl. After drying over anhyd. MgSO₄, filtration and evaporation *in vacuo* gave crude (S)(-)-15 as a colorless solid (1.64 g, 89%). Repeated recrystallizations from petr. ether gave an analytical sample as colorless needles, mp 61.5—64.5°, $[\alpha]_D^{20} -17.6^\circ$ ($c=0.99$, chloroform) (lit.,⁸ mp 67° and $[\alpha]_D^{20} +17.0^\circ$ ($c=1.0$, chloroform) for (R)(+)-15). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1380, 1360, 1190, 1170 (SO₂). NMR (in CDCl₃): 1.15, 1.22 (6H, two s, $\text{C}(\text{CH}_3)_2$), 1.27, 1.37 (6H, two s, $\text{C}(\text{CH}_3)_2$), 1.85 (2H, q, $J=6$ Hz, OCHCH₂CH₂O), 2.43 (3H, s, CH₃C₆H₄), 3.75 (1H, t, $J=6$ Hz, OCHCH₂CH₂O), 4.20 (2H, t, $J=6$ Hz, OCHCH₂CH₂O), 7.31 (2H, d, $J=9$ Hz, aromatic protons *ortho* to CH₃), 7.78 (2H, $J=9$ Hz, aromatic protons *ortho* to SO₂). Anal. Calcd. for C₁₆H₂₄O₅S: C, 58.51; H, 7.37. Found: C, 58.78; H, 7.45.

(S)(-)-3(2,2,4,4-Tetramethyl-1,3-dioxolan-5-yl)propanonitrile ((S)(-)-16)—A mixture of (S)(-)-15 (0.40 g, 1.2 mmol), potassium cyanide (0.27 g, 4.2 mmol) in N,N-dimethylformamide (14 ml) was stirred at 60° for 4 hr. After being diluted with H₂O (40 ml), the mixture was extracted with ether. The combined ethereal extracts were successively washed with satd. NaHCO₃ and satd. NaCl, then dried over anhyd. MgSO₄. Filtration and evaporation *in vacuo* gave crude (S)(-)-16 as a yellow oil (220 mg, 99%). This was purified by column chromatography (silica gel, solvent, benzene) to afford pure (S)(-)-16 as a pale yellow oil (190 mg, 85%), $[\alpha]_D^{20} -29.6^\circ$ ($c=0.98$, chloroform). IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 2280 (CN). NMR (in CDCl₃): 1.12, 1.30 (6H, two s, $\text{C}(\text{CH}_3)_2$), 1.37, 1.41 (6H, two s, $\text{C}(\text{CH}_3)_2$), 1.50—2.25 (2H, m, OCHCH₂CH₂CN), 2.55 (2H, t, $J=7$ Hz, OCHCH₂CH₂CN), 3.78 (1H, doubled d, $J=5$ and 7 Hz, OCHCH₂CH₂CN). MS m/e : 183 [M⁺], 168, 149.

(S)(-)-3(2,2,4,4-Tetramethyl-1,3-dioxolan-5-yl)propionic Acid ((S)(-)-17)—A mixture of (S)(-)-17 (0.65 g, 3.6 mmol) and 20% aqueous NaOH (0.83 ml, 7.1 mmol) in ethanol (2 ml) was refluxed for 10 hr, then was diluted with H₂O (30 ml). After being washed with ether, the aqueous solution was made acidic (pH≈3) with oxalic acid, and extracted with ether. The combined ethereal extracts were washed with satd. NaCl, and dried over anhyd. MgSO₄. Filtration and evaporation *in vacuo* gave crude (S)(-)-17 as a colorless oil (655 mg, 91%) which gradually solidified when kept at room temperature, mp 54—59°. Recrystallization from petr. ether afforded an analytical sample as colorless needles, mp 57—59°, $[\alpha]_D^{20} -10.1^\circ$ ($c=0.99$, chloroform). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1740 (acid). NMR (in CDCl₃): 1.12, 1.28 (6H, two s, $\text{C}(\text{CH}_3)_2$), 1.35, 1.42 (6H, two s, $\text{C}(\text{CH}_3)_2$), 1.50—2.10 (2H, m, OCHCH₂CH₂CO), 2.40—2.75 (2H, m, CH₂CO), 3.70 (1H, t, $J=6$ Hz, OCHCH₂CH₂CO), 10.5 (1H, br s, COOH). Anal. Calcd. for C₁₀H₁₈O₄: C, 59.39; H, 8.97. Found: C, 59.15; H, 8.82.

(S)(-)-4(2,2,4,4-Tetramethyl-1,3-dioxolan-5-yl)butan-2-one ((S)(-)-6)—A solution of methyllithium (0.80 M solution, 6.55 ml, 5.2 mmol) was added over 25 min to a cooled (0°), stirred ethereal solution of (S)(-)-

17 (530 mg, 2.6 mmol) under argon atmosphere. After being stirred at room temperature for 4 hr, the reaction mixture was poured onto ice-water (60 ml). The aqueous mixture was extracted with ether, and the combined ethereal extracts were washed with satd. NaCl. After drying over anhyd. MgSO_4 , filtration and evaporation *in vacuo* afforded a yellow oil (620 mg), which was purified by column chromatography (silica gel, solvent, benzene: ethyl acetate 9:1) to give pure (S)(-)-6 as a pale yellow oil (445 mg, 85%), $[\alpha]_{\text{D}}^{25} -12.1^\circ$ ($c=1.01$, chloroform) and $[\alpha]_{\text{D}}^{27} -14.8^\circ$ ($c=1.35$, methanol) (lit.,⁸⁾ $[\alpha]_{\text{D}}^{25} +10.1^\circ$ ($c=1.0$, chloroform) for (R)(+)-6; lit.,¹¹⁾ $[\alpha]_{\text{D}}^{27} -14.1^\circ$ ($c=1.31$, methanol)). IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 1720 (ketone). NMR (in CDCl_3): 1.12, 1.28 (6H, two s, $\text{O} \begin{smallmatrix} \text{O} \\ \diagup \end{smallmatrix} \text{C}(\text{CH}_3)_2$), 1.35, 1.42 (6H, two s, $\text{O} \begin{smallmatrix} \text{O} \\ \diagup \end{smallmatrix} \text{C}(\text{CH}_3)_2$), 1.50—1.95 (2H, m, $\text{OCHCH}_2\text{CH}_2\text{CO}$), 2.15 (3H, s, CH_3), 2.45—2.80 (2H, m, $\text{OCHCH}_2\text{CH}_2\text{CO}$), 3.59 (1H, doubled d, $J=5$ and 7 Hz, OCH). These spectral properties were identical with those of the authentic sample independently prepared from L-glutamic acid.¹¹⁾

Acknowledgement The authors are indebted to the Central Analysis Room of this faculty for elemental analyses and spectra measurements.