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Synthesis of Enantiomeric Pairs of *Vicinal*-Diols from L-α-Amino Acids by the Use of Organolithium Reagents: Its Application to optically Active Epoxyterpene Synthesis[1)]

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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 racemic[5)] and optically active[6)] 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.
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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. Billimoria 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° (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° (chloroform), could be obtained in 81% yield. On the other hand, the reaction of optically pure (*S*)(−)-ethyl

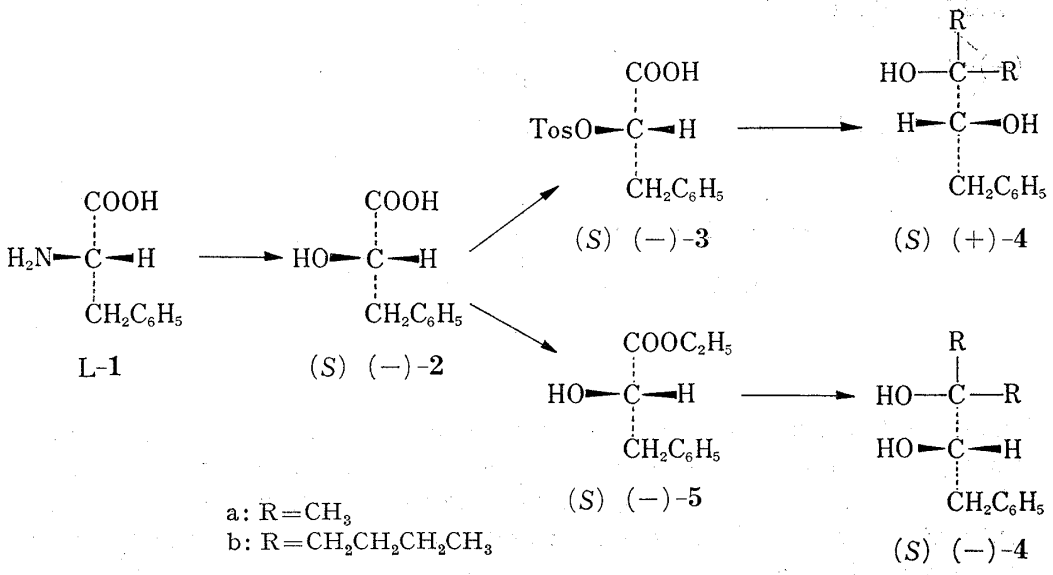


Chart 1

2-hydroxy-3-phenylpropionate((*S*)(−)-**5**),[3] $[\alpha]_D^{24}$ −21.4° (benzene), being also obtainable from **L-1**, with methyllithium, was found to give (−)-*vic*-diol((−)-**4a**), $[\alpha]_D^{20}$ −59.0° (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° (chloroform), and (−)-*vic*-diol((−)-**4b**), $[\alpha]_D^{20}$ −26.1° (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]

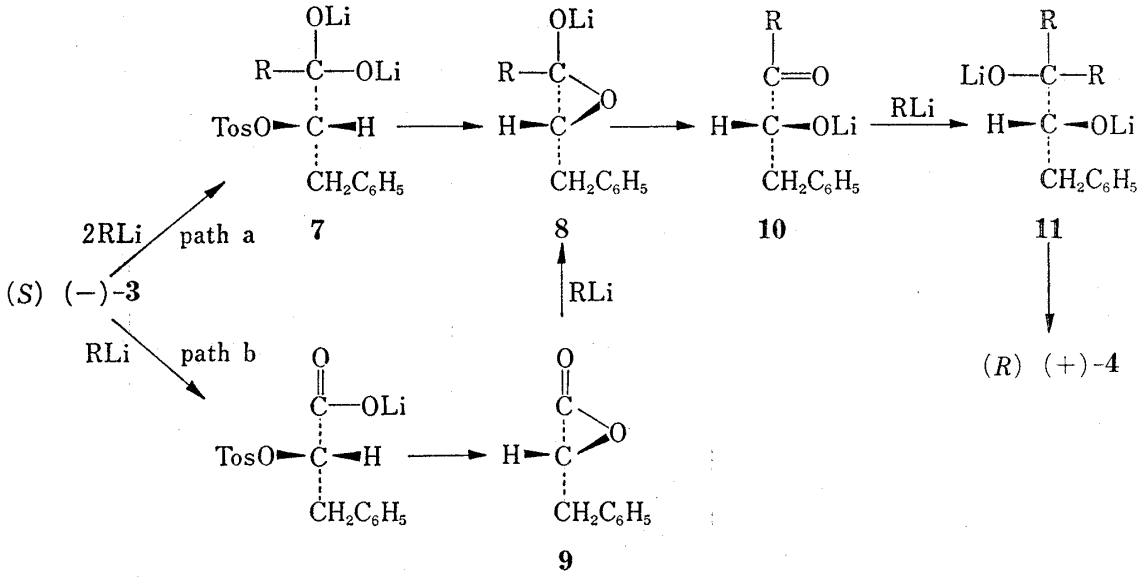
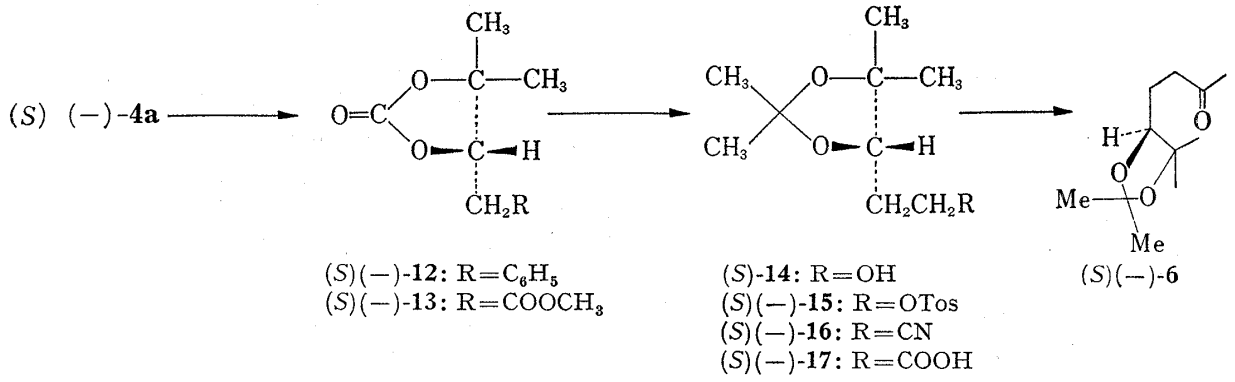


Chart 2

Although the two types of reactions were carried ont 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 Epoxyterpene 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



(*S*)(−)-**12**: R=C_6H_5
(*S*)(−)-**13**: R=$COOCH_3$

(*S*)-**14**: R=OH
(*S*)(−)-**15**: R=OTos
(*S*)(−)-**16**: R=CN
(*S*)(−)-**17**: R=COOH

(*S*)(−)-**6**

Chart 3

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° (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° (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° (chloroform), in 89% yield, which was transformed into (*S*)(−)-cyanide ((*S*)(−)-**16**), $[\alpha]_D^{20}$ −29.6° (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° (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° (chloroform) and $[\alpha]_D^{27}$ −14.8° (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° (chloroform) for (*R*)(+)-**6**[8] and $[\alpha]_D^{27}$ −14.1° (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**).

Experimental[12]

(*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-hashi, 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.[1]
10) Spectral (IR and NMR) properties of this tosylate were identical with those of (*R*)(+)-**15**, $[\alpha]_D^{20}$ +17° (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**, $[\alpha]_D^{28}$ −8.7° (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°, $[\alpha]_D^{20}$ +56.4° (*c*=1.28, chloroform). Repeated recrystallizations from hexane gave an analytical sample as colorless long needles, mp 74—75°, $[\alpha]_D^{20}$ +58.9° (*c*=0.91, chloroform). IR ν_{max}^{Nujol} cm^{-1}: 3560, 3360 (OH). NMR (in $CDCl_3$): 1.23, 1.24 (6H, two s, $C(C\underline{H}_3)_2$), 2.00, 2.18 (2H, two br s, 2×O<u>H</u>), 2.54 (1H, doubled d, *J*=10 and 14 Hz, one of $C_6H_5C\underline{H}_2CH$), 2.88 (1H, doubled d, *J*=3 and 14 Hz, one of $C_6H_5C\underline{H}_2CH$), 3.59 (1H, doubled d, *J*=3 and 10 Hz, $C_6H_5CH_2C\underline{H}$), 7.20 (5H, s, $C_6\underline{H}_5$). Two broad singlets at 2.00 and 2.18 ppm disappeared on treatment with D_2O. *Anal.* Calcd. for $C_{11}H_{16}O_2$: 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 methyllithium (1.43 M solution, 7 ml, 10 mmol) was added to a stirred solution of (*S*)(−)-**5**[3] (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°, $[\alpha]_D^{20}$ −55.1° (*c*=0.93, chloroform). Repeated recrystallizations from hexane gave an analytical sample as colorless long needles, mp 74.5—75.5°, $[\alpha]_D^{20}$ −59.0° (*c*=0.86, chloroform). Spectral (IR and NMR) properties of this sample were completely identical with those of (*R*)(+)-**4a**. *Anal.* Calcd. for $C_{11}H_{16}O_2$: 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**[3] (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°——30° 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°, $[\alpha]_D^{20}$ +24.8° (*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°, $[\alpha]_D^{20}$ +25.8° (*c*=0.546, chloroform), prepared with lithium di-*n*-butylcuprate.[3] Measurement of the mixed melting point of this sample with that prepared previously[3] showed no depression, mp 108—109°.

(*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**[3] (222 mg, 1.14 mmol). After being stirred at −40°——30° 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°, $[\alpha]_D^{20}$ −26.1° (*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°) 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°, $[\alpha]_D^{20}$ −73.6° (*c*=1.02, chloroform). Further recrystallizations from the same solvent system afforded an analytical sample as colorless plates, mp 84—85.5°, $[\alpha]_D^{20}$ −75.2° (*c*=0.97, chloroform). IR ν_{max}^{Nujol} cm^{-1}: 1780 (2-oxo-1,3-dioxolane). NMR (in $CDCl_3$): 1.43, 1.47 (6H, two s, $C(C\underline{H}_3)_2$), 2.82 (1H, doubled d, *J*=6 and 15 Hz, one of $C_6H_5C\underline{H}_2CH$), 3.10 (1H, doubled d, *J*=9 and 15 Hz, one of $C_6H_5C\underline{H}_2CH$), 4.47 (1H, doubled d, *J*=6 and 9 Hz, $C_6H_5CH_2C\underline{H}$), 7.27 (5H, s, $C_6\underline{H}_5$). *Anal.* Calcd. for $C_{12}H_{14}O_3$: 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° (*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° (*c*=0.66, chloroform). IR ν_{max}^{Nujol} cm^{-1}: 1760 (2-oxo-1,3-dioxolane), 1740 (ester). NMR (in $CDCl_3$): 1.37, 1.56 (6H, two s, $C(C\underline{H}_3)_2$), 2.63 (1H, doubled d, *J*=7 and 17 Hz, one of $C_6H_5C\underline{H}_2CH$), 2.73 (1H, doubled d, *J*=7 and 17 Hz, one of $C_6H_5C\underline{H}_2CH$), 3.75 (3H, s, $OC\underline{H}_3$), 4.82 (1H, t, *J*=7 Hz, $C_6H_5CH_2C\underline{H}$). MS *m/e*: 188 [M^+], 173, 144. *Anal.* Calcd. for $C_8H_{12}O_5$: 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 H_2O (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. $NaHCO_3$. After drying over anhyd. $MgSO_4$, 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 ν_{max}^{film} cm^{-1}: 3400 (OH). NMR (in $CDCl_3$): 1.15, 1.30 (6H, two s, $\overset{O}{\underset{C}{>}}C(C\underline{H}_3)_2$), 1.38, 1.46 (6H, two s, $\overset{O}{\underset{O}{>}}C(C\underline{H}_3)_2$), 1.55—2.00 (2H, m, $OCHC\underline{H}_2CH_2OH$), 2.25 (1H, br s, O<u>H</u>), 3.70—4.02 (3H, m, $OC\underline{H}CH_2C\underline{H}_2OH$).

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. $CuSO_4$ and satd. NaCl. After drying over anhyd. $MgSO_4$, 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° (*c*=0.99, chloroform) (lit.,[8] mp 67° and $[\alpha]_D^{20}$ +17.0° (*c*=1.0, chloroform) for (*R*)(+)-**15**). IR ν_{max}^{Nujol} cm^{-1}: 1380, 1360, 1190, 1170 (SO_2). NMR (in $CDCl_3$): 1.15, 1.22 (6H, two s, $\overset{O}{\underset{C}{>}}C(C\underline{H}_3)_2$), 1.27, 1.37 (6H, two s, $\overset{O}{\underset{O}{>}}C(C\underline{H}_3)_2$), 1.85 (2H, q, *J*=6 Hz, $OCHC\underline{H}_2CH_2O$), 2.43 (3H, s, $C\underline{H}_3C_6H_4$), 3.75 (1H, t, *J*=6 Hz, $OC\underline{H}CH_2CH_2O$), 4.20 (2H, t, *J*=6 Hz, $OCHCH_2C\underline{H}_2O$), 7.31 (2H, d, *J*=9 Hz, aromatic protons *ortho* to CH_3), 7.78 (2H, *J*=9 Hz, aromatic protons *ortho* to SO_2). *Anal.* Calcd. for $C_{16}H_{24}O_5S$: 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 H_2O (40 ml), the mixture was extracted with ether. The combined ethereal extracts were successively washed with satd. $NaHCO_3$ and satd. NaCl, then dried over anhyd. $MgSO_4$. 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° (*c*=0.98, chloroform). IR ν_{max}^{film} cm^{-1}: 2280 (CN). NMR (in $CDCl_3$): 1.12, 1.30 (6H, two s, $\overset{O}{\underset{C}{>}}C(C\underline{H}_3)_2$), 1.37, 1.41 (6H, two s, $\overset{O}{\underset{O}{>}}C(C\underline{H}_3)_2$), 1.50—2.25 (2H, m, $OCHC\underline{H}_2CH_2CN$), 2.55 (2H, t, *J*=7 Hz, $OCHCH_2C\underline{H}_2CN$), 3.78 (1H, doubled d, *J*=5 and 7 Hz, $OC\underline{H}CH_2CH_2CN$). 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 H_2O (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. $MgSO_4$. 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° (*c*=0.99, chloroform). IR ν_{max}^{Nujol} cm^{-1}: 1740 (acid). NMR (in $CDCl_3$): 1.12, 1.28 (6H, two s, $\overset{O}{\underset{C}{>}}C(C\underline{H}_3)_2$), 1.35, 1.42 (6H, two s, $\overset{O}{\underset{O}{>}}C(C\underline{H}_3)_2$), 1.50—2.10 (2H, m, $OCHC\underline{H}_2CH_2CO$), 2.40—2.75 (2H, m, $C\underline{H}_2CO$), 3.70 (1H, t, *J*=6 Hz, $OC\underline{H}CH_2CH_2CO$), 10.5 (1H, br s, COO<u>H</u>). *Anal.* Calcd. for $C_{10}H_{18}O_4$: 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%), $[\alpha]_D^{25}$ −12.1° (c=1.01, chloroform) and $[\alpha]_D^{27}$ −14.8° (c=1.35, methanol) (lit.,[8] $[\alpha]_D^{25}$ +10.1° (c=1.0, chloroform) for (*R*)(+)-**6**; lit.,[11] $[\alpha]_D^{27}$ −14.1° (c=1.31, methanol)). IR ν_{max}^{film} cm^{-1}: 1720 (ketone). NMR (in $CDCl_3$): 1.12, 1.28 (6H, two s, $\overset{O}{C}\rangle C(CH_3)_2$), 1.35, 1.42 (6H, two s, $\overset{O}{O}\rangle C(CH_3)_2$), 1.50—1.95 (2H, m, $OCHC\underline{H}_2CH_2CO$), 2.15 (3H, s, $C\underline{H}_3$), 2.45—2.80 (2H, m, $OCHCH_2C\underline{H}_2CO$), 3.59 (1H, doubled d, J=5 and 7 Hz, $OC\underline{H}$). These spectral properties were identical with those of the authentic sample independently prepared from L-glutamic acid.[11]

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