Synthesis of optically Active α-Alkyl or α-Aryl Acids from
L-α-Amino Acids by the Use of Organocupper Reagents

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With an aim to further explore the utility of L-α-amino acids (I) in the synthesis of optically active compounds, the reaction of optically active α-tosyloxy acids and their derivatives (II) readily obtainable from I, with several types of organocupper reagents were studied.

Although there still remain some ambiguity in the formation of unusual reaction products such as the β-keto ester (dl-6) and the vicinal diol ((R)(+)-13) and in lower yields for the substitution products, it has become evident that when optically active α-tosyloxy acids prepared from L-phenylalanine, L-alanine, and L-leucine, respectively, are treated with lithium dialkyl- or diarylcuprates, the substitution reactions can proceed with almost full inversion to give corresponding optically active α-alkyl or α-aryl acids in max. 63% yield.

Keywords — optically active α-alkyl acids; optically active α-aryl acids; organocupper reagents; optically active α-tosyloxy acid esters; optically active α-tosyloxy acids; β-keto ester; vicinal-diol; inversion; deamination

Several kinds of L-α-amino acids (I) have been utilized as starting materials for the total syntheses of optically active natural products. Thus, various structural types of optically active isoquinoline alkaloids2) and some representatives of optically active Amaryllidaceae alkaloids3) have been elaborated from L-3,4-dihydroxyphenylalanine and L-tyrosine, respectively. The syntheses of optically active monosaccharides4), terpenes5), and piperidine and tropine alkaloids6) have been accomplished by using I such as L-glutamic acid, L-alanine, L-lysine, and D-phenylalanine, as starting materials.

In these total syntheses, I are incorporated into the synthetic schemes directly, or after they are first converted into the corresponding optically active α-hydroxy acids (II) and their derivatives. Optically active natural products having asymmetric centers which carry no heteroatoms such as nitrogen and oxygen, have never been constructed from I because of the lack of efficient methodology for replacing the α-amino functionality of I by alkyl or aryl group without a loss of stereochemical integrity.

Since optically active α-alkyl or α-aryl acids (IV: X=H) are considered quite useful for the preparation of optically active compounds including natural products such as phero-

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momones\textsuperscript{7}) and macrolides,\textsuperscript{8}) an efficient method which could produce IV(X=H) from I, was sought.

There have been no reported methods for substituting the amino group at asymmetric carbon with alkyl or aryl group except one reaction which can directly construct carbon-carbon bond from carbon-nitrogen bond by way of amino nitrene with partial retention of configuration.\textsuperscript{9}) Therefore, the preparation of IV(X=H) is attempted by allowing to react optically active \(\alpha\)-tosylxy acids and their derivatives (III), being easily accessible from I by way of II, with carbon nucleophiles. As sources of carbon nucleophiles, usual organo-

\[
\begin{aligned}
\text{COOH} & \quad \text{COOH} & \quad \text{COOX} & \quad \text{COOX} \\
\text{H}_2\text{N} & \quad \text{C} & \quad \text{H} & \quad \text{HO} & \quad \text{C} & \quad \text{H} & \quad \text{TosO} & \quad \text{C} & \quad \text{H} & \quad \text{LiCuR}^3 & \quad \text{H} & \quad \text{C} & \quad \text{R}^2 \\
\text{I} & \quad \text{II} & \quad \text{III} & \quad \text{IV} \\
\text{R}^1= & \text{C}_6\text{H}_5, \text{CH}_3, \text{CH}_2, \text{(CH}_3)_2\text{CHCH}_2, \text{etc.} \\
\text{R}^3= & \text{CH}_3, \text{C}_6\text{H}_5, \text{n-C}_6\text{H}_{13}, \text{etc.} \\
\text{X}= & \text{H,CH}_3, t-\text{C}_4\text{H}_9, \text{etc.}
\end{aligned}
\]

copper reagents\textsuperscript{10}) are chosen because it is well established that organocopper reagents substitute tosylxy group at asymmetric carbon with full retention\textsuperscript{10,11}) and are not prone to attack carbonyl groups\textsuperscript{10–13}) of ketones\textsuperscript{12a}) carboxylic acids,\textsuperscript{12b}) esters,\textsuperscript{12e,d}) and lactones\textsuperscript{12r}) without some exceptional cases.\textsuperscript{13})

Although III are seemingly quite racemizable under a basic condition because of their enhanced acidity of the asymmetric carbon, we have succeeded in substituting the \(\alpha\)-tosylxy group of III with almost full inversion by employing organocopper reagents.

This report describes our studies on the novel synthesis of IV(X=H) from I by way of II and III.

**Results and Discussion**

Among several possible substrates for the substitution reaction with organocopper reagents, (S)(\text{--})-ethyl 3-phenyl-2-tosylxypropionate ((S)(\text{--})-3) was first selected as a reaction substrate because of its ready accessibility, and was prepared from \(\text{L}\)-phenylalanine (1-1).

As shown in Chart 1, deamination of 1-1 according to the reported procedure,\textsuperscript{14}) gave (S)(\text{--})-2-hydroxy-3-phenylpropionic acid ((S)(\text{--})-2), \([\alpha]_b^{25} = 25.9^\circ \) (acetone), which on esterification\textsuperscript{14}) and tosylation, readily afforded optically pure (S)(\text{--})-3, \([\alpha]_b^{24} = -43.7^\circ \) (ethanol).

\textsuperscript{7}) R. Rossi, *Synthesis*, 1978, 413.


Reaction of (S)(−)-3 with lithium dimethylcuprate\(^{15}\) was found to give a complex reaction product from which desired (−)-ethyl 2-methyl-3-phenylpropionate((−)-4), \([r]_D^{20} = -31.9^\circ\) (chloroform), could be isolated by column chromatography. The yield of (−)-4 could be determined as 19% by gas-liquid chromatography (GLC). Since the optical purity and absolute configuration of (−)-4 thus obtained, was established as 89% and (R)-series, respectively, by comparing its optical rotation with that of (S)(+)-4. \([r]_D^{20} = +25.7^\circ\) (chloroform), prepared from(S)(+)-2-methyl-3-phenylpropionic acid((S)(+)-5), \(a_D^{24} + 0.384^\circ \) (\(l=0.02\), neat), 71% optically pure\(^{16,17}\) it became evident that the extent of inversion for the substitution reaction was 89%.

In addition to the desired product((R)(−)-4), another oily reaction product which was more polar than (R)(−)-4 and showed no optical activity, was isolated in 43% yield by the chromatographic separation. This oily sample also exhibited a reddish violet color characteristic to \(\beta\)-keto ester in contact with aqueous ferric chloride solution. The structure of this compound was verified as dl-ethyl 2-benzyl-3-oxo-5-phenylpentanoate (dl-6) by its chemical and spectral properties and by identification with an authentic sample prepared from ethyl acetocetate.\(^{18}\) Formation of dl-6 might be explained by the mechanism visualized in Chart 2. Thus, the copper enolate (7) derived directly from (S)(−)-3 or by way of the initial substitution product (8), might attack another molecule of (S)(−)-3 in the same manner as that for Claisen condensation, to produce the \(\beta\)-keto ester (9) which have a tosylxy group at the \(\gamma\) position. Further reaction of 9 with dimethylcuprate anion to expel the \(\gamma\)-tosyloxyl group, followed by protonation on aqueous workup, gives dl-6.\(^{19}\)

Next, improvement of the chemical yield for (R)(−)-4 was attempted using several tertiary amines and amides as additives\(^{20}\) because these compounds had been known to

\(^{15}\) Reactions with lithium dialkyl or diarylcuprate were all performed under complete argon atmosphere.


\(^{17}\) The (S)(+)-acid ((S)(+)-5) showing \(a_D^{24} + 2.686^\circ \) (\(l=0.1\), neat), was assumed to be optically pure. See, S. Terashima, M. Nara, and S. Yamada, Chem. Pharm. Bull. (Tokyo), 18, 1124 (1970).


\(^{19}\) The loss of optical activity is quite reasonable when the \(\beta\)-keto ester functionality of dl-6 is taken into consideration.

\(^{20}\) 1,4-Diazabicyclo[2,2,2]octane (DABCO), 1,5-diazabicyclo[5,4,0]undec-5-ene (DBU), N,N,N,N-tetramethylethylenediamine (TMEDA), 1,8-bis(dimethylamino)naphthalene (Proton Sponge), and hexamethylphosphoramide (HMPA) were used as additives. See, experimental.
increase nucleophilicity of organometallic reagents. However, these operations were found to be completely useless for increasing the yield of \((R)(-)-4\).

Since the lower yield of the substitution product\( ((R)(-)-4) \) might be partially due to the reaction of dimethylcuprate anion with the ester group, it is quite reasonable to expect that \((S)-t\)-butyl 2-methyl-3-phenylpropionate\((S)(-)-10\) could afford a better yield of the substitution product\((R)(-)-11\) on treatment with lithium dimethylcuprate. This is because the steric hindrance of \(t\)-butyl group should protect the ester carbonyl group from the attack of dimethylcuprate anion. This expectation was found to be the case.

Thus, when \((S)(-)-10\) obtained from \((S)(-)-2\) by successive acetylation, esterification with isobutene, alkaline hydrolysis, and tosylation, was treated with lithium dimethylcuprate, the desired \((R)(-)-11\) was produced in 31\% yield (GLC). From this result, it appears that protection of the carbonyl group adjacent to the reaction site from the attack by dimethylcuprate anion, can improve the chemical yield of the desired substitution product. Therefore, the carboxylate anion which can be produced by the reaction of carboxylic acid with lithium dimethylcuprate, was selected as a protected form of carbonyl group.

22) Measurement of the optical rotation for this compound was not performed.
23) Although the structure of \((R)(-)-11\) was fully confirmed by its spectral data, its optical purity could not be determined since preparation of \((S)-11\) from \((S)(+)-5\) was not performed.
24) Examination on the reaction products other than \((R)(-)-11\) was not carried out in this case.
The reaction substrate, (S)(−)-3-phenyl-2-tosloyxopropionic acid ((S)(−)-12), was similarly prepared from (S)(−)-2. Esterification of (S)(−)-2 with benzyl alcohol gave the corresponding benzyl ester, which on tosylation and reductive cleavage of the benzyl ester, yield ed optically pure (S)(−)-12, $[\alpha]_D^{20} = -46.9^\circ$ (chloroform), in 84% yield from (S)(−)-2.

Reaction of (S)(−)-12 with lithium dimethyloxycuprate\(^{15}\) followed by the usual esterification with ethanol and thionyl chloride, afforded a 55—63% yield(GLC) of (R)(−)-4, $[\alpha]_D^{20} = -32.1^\circ$ (chloroform).\(^{16}\) The extent of inversion for the substitution reaction could be similarly calculated as 89% (vide supra).\(^{17}\)

In order to elucidate the full scope of the substitution reaction exploited here, similar substitution reactions were examined by employing different kinds of organocopper reagents and by utilizing several types of III(X=H) derived from I other than l-1, as reaction substrates.

When (S)(−)-12 was treated with lithium di-n-butylcuprate,\(^{15}\) the unexpected product, (R)(+)-3-n-butyl-1-phenyl-2,3-heptanediol ((R)(+)-13), was isolated as the sole isolable reaction product in 75% yield instead of the desired $\alpha$-alkyl acid ((R)(+)-14). Based on the studies described in detail in the accompanying paper,\(^{26}\) the structure of (R)(+)-13 including its absolute configuration, was clearly established. Formation of (R)(+)-13 from (S)(−)-12 might be rationalized by the reaction mechanism in which lithium di-n-butylcuprate behaves in complete the same manner as n-butyl lithium.\(^{26}\) The reason why lithium di-n-butylcuprate follows the reaction course being different from that for lithium dimethyloxycuprate, is obscure, but some delicate difference of steric and electronic nature between two sorts of organocopper reagents might account for the observed results.

On the other hand, when lithium di-n-butylcuprate was allowed to react\(^{15}\) with optically pure (S)(−)-2-tosloyxopropionic acid ((S)(−)-15),\(^{26}\) $[\alpha]_D^{20} = -43.4^\circ$ (chloroform), prepared from l-alanine by a similar method to that for (S)(−)-12, (S)(−)-2-methylhexanoic acid ((S)(−)-16),\(^{27}\) $[\alpha]_D^{20} = +20.0^\circ$ (ether) and $[\alpha]_D^{20} = +0.333^\circ$ (β = 0.02, neat), was obtained in 32% isolated yield\(^{28}\) with almost full inversion (92% or 98% based on calculation).\(^{28}\) Lithium diphenylldihydridophenol also reacted with (S)(−)-15,\(^{15}\) similarly giving (S)(+)-2-phenyloxypropionic acid ((S)(+)-17),\(^{30}\) $[\alpha]_D^{20} = +67.4^\circ$ (ether), in 12% isolated yield\(^{28}\) and with 95% inversion.\(^{31}\) In addition, reaction of (S)(−)-4-methyl-2-tosloyxypentanoic acid ((S)(−)-18), $[\alpha]_D^{20} = -47.6^\circ$ (chloroform), derived from l-leucine, with lithium dimethyloxycuprate\(^{15}\) was found to afford (R)(−)-2,4-dimethylpentanoic acid ((R)(−)-19),\(^{32}\) $[\alpha]_D^{20} = -21.1^\circ$ (ether), in 27% isolated yield\(^{28}\) and with almost full inversion (100% based on calculation).\(^{33}\)

Summing up the above results, it might be concluded that treatments of optically pure III(X=H) derived from I, with lithium dialkyl or diarylcuprate result in the formation of

28) In this case, the reaction product was isolated without esterification. Examinations on the reaction products other than the normal substitution product were not carried out.
29) The [(S)(+)-17] and (R)(−)-1-acid ((S)(+)-17) and (R)(+)-16 showing $[\alpha]_D^{20} = +19.6^\circ$ (c=5.50, ether) and $[\alpha]_D^{20} = -18.7^\circ$ (neat), $d_2^0 = 0.909$, respectively, were assumed to be optically pure. P.A. Levene and L.W. Bass, J. Biol. Chem., 70, 211 (1926), and P.A. Levene and R.E. Marker, 98, 1 (1932).
31) The acid ((S)(+)-17) showing $[\alpha]_D^{20} = +81.1^\circ$ (c=3.108, ethanol), was assumed to be optically pure. H.S. Raper, J. Chem. Soc., 123, 2557 (1923).
32) The (+)-acid ((+)-19) is reported to have (S)-configuration. See, ref. 27a.
33) The (S)(+)-acid ((S)(+)-19) showing $[\alpha]_D^{20} = +19.4^\circ$ (c=5.23, ether) was assumed to be optically pure. P.A. Levene and L.W. Bass, J. Biol. Chem., 70, 211 (1926).
IV(X=H) with almost full inversion. Although there still remain some ambiguity in the formation of unusual reactin products such as \(dl-6\) and \((R)(+)\)-13 and in lower yields of the substitution products, the overall process developed here would further explore the utility of I in the synthesis of optically active compounds.

**Experimental**

\((S)(-)\)-2-Hydroxy-3-phenylpropionic Acid \((S)(-)\)-2 and Its Ester---Deamination of commercially available L-1 using sodium nitrite in 5% sulfuric acid according to the reported procedure,\(^{44}\) gave optically pure \((S)(-)\)-2, mp 126.5-128.5\(^\circ\) (recrystallized from petr. etherether), \([\alpha]_D^25\) = 25.9\(^\circ\) (c=3.24, acetone) (lit.,\(^{10}\) mp 126—127\(^\circ\), \([\alpha]_D^25\) = -27.8\(^\circ\) (c=3.78, acetone)).

Esterification of \((S)(-)\)-2\(^{45}\) with ethanol and \(p\)-toluenesulfonic acid monohydrate (catalytic amount), yielded the corresponding optically pure ethyl ester, bp 105—109\(^\circ\) (0.1 mm Hg), mp 47—49\(^\circ\), \([\alpha]_D^18\) = -21.4\(^\circ\) (c=4.61, benzene) (lit.,\(^{10}\) mp 40—47\(^\circ\), \([\alpha]_D^18\) = -22.6\(^\circ\) (c=4.33, benzene)).

\((S)(-)\)-Ethyl 3-Phenyl-2-tosyloxypropionate \((S)(-)\)-3---A pyridine solution (50 ml) of \((S)(-)\)-ethyl 2-hydroxy-3-phenylpropionic acid (20.0 g, 0.103 mol) was gradually added to a solution of tosyl chloride (29.5 g, 0.155 mol) in pyridine (50 ml) cooled in an ice bath. After stirring at room temperature overnight, the reaction mixture was poured onto a crushed ice (ca. 200 g). The aqueous mixture was extracted with ethyl acetate, and the combined ethyl acetate extracts were successively washed with 10% HCl, H\(_2\)O, satd. CuSO\(_4\), H\(_2\)O, satd. NaHCO\(_3\), and satd. NaCl. After drying over anhyd. MgSO\(_4\), filtration and evaporation \(in\ vacuo\) gave the crude product as a pale yellow oil (41.8 g). A half of the residual oil (20.9 g) was purified by column chromatography (silica gel, solvent petr. ether: hexane: ether: ethyl acetate 2:2:1:1) to give pure \((S)(-)\)-3 as a colorless oil (15.2 g, 85%), \([\alpha]_D^25\) = -43.7\(^\circ\) (c=6.53, ethanol). IR \(\nu_{max}\) cm\(^{-1}\): 1760 (ester), 1370, 1175 (SO\(_2\)). NMR (in CDCl\(_3\)): 1.13 (3H, t, J = 6 Hz, OCH\(_2\)CH\(_3\)), 2.31 (3H, s, CH\(_3\)CH\(_2\)CH\(_3\)), 2.75—3.40 (2H, m, C\(_6\)H\(_5\)CH\(_2\)CH\(_3\), 4.05 (2H, q, J = 6 Hz, OCH\(_2\)CH\(_3\)), 4.90 (1H, doubled, J = 6 Hz, CH\(_2\)CH\(_3\)), 5.70—7.30 (7H, m other aromatic protons). MS: m/e: 348 [M\(^+\)], 274, 176, 175, 154, 147, 130, 103, 91, 90. This oily ester gradually solidified as colorless crystals, mp 34—36\(^\circ\), when kept at —20\(^\circ\) for several days.

\((S)(+)\)-Ethyl 2-Methyl-3-phenylpropionate \((S)(+)\)-4---This was prepared by esterification of \((S)(+)\)-5,\(^{46}\) \(\alpha_2^2+0.384^\circ\) (l=0.02, neat), 71% optically pure,\(^{17}\) with ethanol and thionyl chloride. After usual workup, distillation gave pure \((S)(+)\)-4 as a colorless oil, bp 102—107 (7 mm Hg) (lit.,\(^{20}\) bp 90—95 (4.5 mm Hg) for \(dl-4\), \([\alpha]_D^25\) = +25.7\(^\circ\) (c=2.07, chloroform). IR \(\nu_{max}\) cm\(^{-1}\): 1735 (ester). NMR (in CDCl\(_3\)): 1.03 (3H, d, J = 6 Hz, CH\(_2\)CH\(_3\)), 1.05 (3H, t, J = 7 Hz, OCH\(_2\)CH\(_3\)), 2.30—3.25 (3H, m, C\(_6\)H\(_5\)CH\(_2\)CH\(_3\)), 3.98 (2H, q, J = 7 Hz, OCH\(_2\)CH\(_3\)), 7.06 (5H, s, C\(_6\)H\(_5\)). Since the optical purity of \((S)(+)\)-5 utilized here is 71%, the optical rotation of optically pure \((S)(+)\)-4 can be calculated as \([\alpha]_D^25+36^\circ\) (chloroform).

\(dl\)-Ethyl 2-Benzyl-3-oxo-5-phenylpentanoate \((dl-6)\)---To a stirred suspension of sodium hydride (50% oily suspension) (0.54 g, 11 mmol) in anhyd. tetrahydrofuran (20 ml) was added ethyl acetocacetate (1.30 g, 10 mmol) at —5—0\(^\circ\). After stirring at the same temperature for 20 min, an ethereal solution of \(n\)-butyl-lithium (2.01 m solution, 5.2 ml, 10.5 mmol) was added to the reaction mixture at —20\(^\circ\), and the stirring was continued for 1 hr at —20—0\(^\circ\). To the solution of the diion prepared above,\(^{19}\) was gradually added benzyl bromide (5.13 g, 30 mmol) at —10—0\(^\circ\). After the addition was over, the cooling bath was removed to raise the temperature of the reaction mixture to room temperature, then the whole mixture was refluxed for 45 hr. The reaction was quenched by adding a mixture of conc. HCl (3 ml) and satd. NH\(_4\)Cl (10 ml), and the upper organic phase was separated. After saturated with NaCl, the aqueous layer was further extracted with ether and ethyl acetate. The combined organic extracts were washed with satd. NaCl, and dried over anhyd. MgSO\(_4\). Filtration and evaporation \(in\ vacuo\) gave a brown oil (4.21 g), a part of which (1.00 g) was purified by column chromatography (silica gel, solvent hexane: benzene: ether 8:1:1), giving \(dl-6\) as a brown oil (272 mg, 37%). This was further submitted to fractional distillation to afford pure \(dl-6\) as a faint yellow oil, bp 178—180 (1 mm Hg). IR \(\nu_{max}\) cm\(^{-1}\): 1750, 1720, 1645 (weak) (\(\beta\)-keto ester). NMR (in CDCl\(_3\)): 1.10 (3H, t, J = 7 Hz, OCH\(_2\)CH\(_3\)), 2.75 (4H, m, 2\(\times\)C\(_6\)H\(_5\)CH\(_2\)CH\(_3\)), 3.10 (2H, m, C\(_6\)H\(_5\)CH\(_2\)CH\(_3\)), 3.75 (1H, doubled d, J = 7 and 8 Hz, C\(_6\)H\(_5\)CH\(_2\)CH\(_3\)), 4.10 (2H, q, J = 7 Hz, OCH\(_2\)CH\(_3\)), 7.15 (10H, two singlets, 2\(\times\)C\(_6\)H\(_5\)). MS:

34) All melting and boiling 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 (\(\delta\) 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 (MS) were taken with a JEOL JMS SG-2 Mass Spectrometer. GLC analyses were performed using a Hitachi Gas Chromatograph 023.

Reaction of (S)-(-)-Ethyl 3-Phenyl-2-toslypropionate ((S)(-)-3) with Lithium Dimethylcuprate.

To a stirred mixture of cuprous iodide (1.52 g, 8.0 mmol) and dibenzyl (282 mg, 1.27 mmol, internal standard for GLC analysis) in ether (20 ml) was added dropwise an ethereal solution of methyl lithium (1.67 M solution, 9.6 ml, 16 mmol) at -10 to 0°C, to afford a solution of lithium dimethylcuprate.

An ethereal solution (4 ml) of (S)(-)-3 (1.39 g, 4.0 mmol) was gradually added to the solution of lithium dimethylcuprate in ether at -10 to 0°C, then the whole mixture was stirred at the same temperature for 3 hr. The reaction was quenched by the addition of a mixture of 10% HCl (4 ml) and satd. NH4Cl (36 ml), and the whole was extracted with ethyl acetate. The combined organic extracts were washed with satd. NaCl, then dried over anhyd. MgSO4. Filtration and evaporation in vacuo gave a yellow oil (923 mg), which was submitted to quantitative GLC analysis (30% SE-30 on Diastold L, 1 m, 110°C, 1 kg/cm2; (R)(-)-4, retention time 11 min; dibenzyl, retention time 24 min). The GLC analysis disclosed that the evaporation residue (923 mg) contained 151 mg (19%) of (R)(-)-4. Separation of the evaporation residue by column chromatography (silica gel, solvent, petr. ether: hexane:ethyl acetate 10:10:1) gave (R)(-)-4 as a colorless oil (154 mg, 19%), \[\frac{x}{D} = 31.9° (c=0.216, chloroform).\] Since (S)(-)-4 showing \[\frac{x}{D} = +36° (chloroform)\] is assumed to be optically pure, the optical purity of (R)(-)-4 and the extent of inversion for the substitution reaction can be calculated as 89%. Spectral (IR) and chromatographic (TLC) properties of (R)(-)-4 so obtained were superimposable on those of (S)(-)-4.

Further elution of the chromatogram with the same solvent system afforded dl-6 as one of the side reaction products (266 mg, 45%). This oily sample showed a reddish violet color in contact with aqueous ferric chloride solution and no optical activity. Spectral (IR, NMR, mass) properties of this oil were identical with those of an authentic sample independently prepared from ethyl acetate.

When the same substitution reaction was attempted in the presence of additives (1.0 equivalent to lithium dimethylcuprate) such as DABCO, DBU, TMEDA, Proton Sponge, and HMPA, the following yields of (R)(-)-4 were obtained by GLC analysis: 3.5% (DABCO); 12% (DBU); 14% (TMEDA); 17% (Proton Sponge); 3.5% (HMPA).

(S)-t-Butyl 3-Phenyl-2-toslypropionate ((S)-10) — a) (S)-2-Acetoxy-3-phenylpropionic Acid: A mixture of (S)(-)-2 (0.70 g, 4.2 mmol) and acetic anhydride (2.5 ml) was stirred at 100°C (bath temperature) for 2 hr. After addition of H2O (5 ml) to the reaction mixture, the whole was further stirred at room temperature for 3 hr, and extracted with ether. After being washed with H2O, the combined ethereal layers were then extracted with satd. NaHCO3. The aqueous bicarbonate extracts were then acidified (pH<2) with conc. HCl, then extracted with ether. The combined ethereal layers were washed with H2O and dried over anhyd. MgSO4. Filtration and evaporation in vacuo gave (S)-2-acetoxy-3-phenylpropionic acid \[\text{as a pale yellow oil (925 mg, 71%), bp } 150^\circ\text{C (3 mmHg).} \] IR \[\frac{\text{cm}^{-1}}{\text{m}^{-1}}\] 1750 (ester and acid). NMR (in CDCl3): 2.00 (3H, s, COCH3), 2.70—3.50 (2H, m, C6H5CH2CH3), 5.24 (1H, doubled d, J=5 and 7 Hz, C6H5-CH2-CH3), 7.20 (5H, s, C6H5), 10.75 (1H, s, COOH). This sample was immediately used for the next esterification.

b) (S)-t-Butyl 2-Acetoxy-3-phenylpropionate: A methylene chloride solution (75 ml) of (S)-2-acetoxy-3-phenylpropionic acid (25.0 g, 0.12 mol), isobutene (13.5 g, 0.24 mol), and conc. H2SO4 (2.5 ml) was kept at -5 to -4°C overnight, then was added to satd. NaHCO3 (75 ml) cooled in an ice bath. The organic layer separated was successively washed with satd. NaCl, satd. NaHCO3 and satd. NaCl after diluted with ether. The ethereal solution so obtained was dried over anhyd. MgSO4. Filtration and evaporation in vacuo gave a crude residue \[\text{as a pale yellow oil (725 mg, 71%), bp } 150^\circ\text{C (3 mmHg).} \] IR \[\frac{\text{cm}^{-1}}{\text{m}^{-1}}\] 1750 (ester). NMR (in CDCl3): 1.40 (9H, s, C(CH3)3), 2.01 (3H, s, C=OCH3), 2.90—3.30 (2H, m, C6H5CH2CH3), 5.06 (1H, doubled d, J=7 and 8 Hz, C6H5-CH2CH3), 7.19 (5H, s, C6H5). This sample was directly submitted to the next hydrolysis.

c) (S)-t-Butyl 2-Hydroxy-3-phenylpropionate: The acetate (480 mg, 1.8 mmol) obtained in b) was added to 70% aqueous methanol (10 ml) containing NaOH (87 mg, 2.2 mmol), and the whole was stirred at -10 to 0°C for 1 hr. After the reaction mixture was poured onto a mixture of ether (40 ml) and H2O (10 ml), the upper ethereal layer was separated. The ethereal solution was successively washed with satd. NaCl, an aqueous solution of citric acid, satd. NaCl, satd. NaHCO3, and satd. NaCl then dried over anhyd. MgSO4. Filtration and evaporation in vacuo gave the crude acid (253 mg, 63%, 90%) which was directly used for the next tosylation. IR \[\frac{\text{cm}^{-1}}{\text{m}^{-1}}\] 3450 (OH), 1740 (ester). NMR (in CDCl3): 1.32 (9H, s, C(CH3)3), 2.65—3.22 (2H, m, C6H5CH2CH3), 3.00 (1H, brs, OEt), 4.17 (1H, brm, CHO), 7.11 (5H, s, C6H5). On treatment with D2O, the signal at 3.00 ppm disappeared and that at 4.17 ppm changed to triplet (J=6 Hz).

d) (S)-t-Butyl 3-Phenyl-2-toslypropionate ((S)-10): Tosylation of (S)-t-butyl 2-hydroxy-3-phenylpropionate (1.6 g, 7.2 mmol) in a similar manner to that for the preparation of (S)(-)-3 gave crude (S)-10 after evaporation of the combined ethereal extracts. Purification of crude (S)-10 by column chromatography (silica gel, solvent, petr. ether: hexane: ether 1:1:1) afforded pure (S)-10 as a colorless oil (1.50 g, 54%). IR \[\frac{\text{cm}^{-1}}{\text{m}^{-1}}\] 1760 (ester), 1370, 1190, 1180, 1160 (SO4). NMR (in CDCl3): 1.32 (9H, s, C(CH3)3), 2.35 (3H, s, CH3C6H5), 3.00 (2H, d, J=6 Hz, C6H5CH2CH3), 4.67 (1H, t, J=6 Hz, CH3CHO), 6.95—7.25
(7H, m, other aromatic protons), 7.51 (2H, d, J = 8 Hz, aromatic protons ortho to SO₂). MS: m/z: 376 [M]⁺, 320, 302, 274, 203, 154, 147, 96, 56.

Reaction of (S)-t-Butyl 3-Phenyl-2-toslyoxypropionate ((S)-10) with Lithium Dimethylcuprate—To a stirred mixture of cuprous iodide (762 mg, 4.0 mmol) and dibenzyl (110 mg, 0.61 mmol, internal standard for GLC analysis) in ether (10 ml) was added an ethereal solution of methylthiium (1.36 M solution, 5.9 ml, 8.0 mmol) at -40—-30°C, to give an ethereal solution of lithium dimethylcuprate.

A solution of (S)-10 (753 mg, 2.0 mmol) in ether (2 ml) was gradually added to the ethereal solution of lithium dimethylcuprate prepared above, and the whole mixture was stirred at -10—0°C for 3 hr. The reaction mixture was poured onto satd. NH₄Cl (80 ml), and the aqueous mixture was extracted with ether. The combined ether extracts were successively washed with satd. NH₄Cl and satd. NaCl, then dried over anhyd. MgSO₄. Filtration and evaporation in vacuo gave a brown oil (448 mg). GLC analysis (30% SE-30 on Diasolid L, 1 m, 110°C, 1 kg/cm²; (R)(−)-11, retention time 16.5 min; dibenzyl, retention time 25 min) of the evaporation residue disclosed that the oily residue (448 mg) contained 138 mg (31%) of (R)(−)-11.

The evaporation residue was purified by column chromatography (silica gel, solvent, petr. ether: hexane: ether 10: 10: 1) to give pure (R)(−)-11[5,34] as a colorless oil (87 mg, 22%). IR νₘ₉ cm⁻¹: 1735 (ester). NMR (in CDCl₃): 1.10 (3H, d, J = 6 Hz, C₃H₃(CH)₂), 1.35 (9H, s, C(CH₃)₃), 2.42—3.00 (3H, m, C₃H₃CH₂CH₂), .13 (5H, m, C₆H₅H₂).

(S)(−)-3-Phenyl-2-toslyoxypropionic Acid ((S)(−)-12)—a) (S)-Benzy1 2-Hydroxy-3-phenylpropionate: A benzene solution (70 ml) of (S)(−)-2 (10.0 g, 60.2 mmol), benzy1 alcohol (7.8 g, 72.2 mmol), and toluenesulfonic acid monohydrate (0.95 g, 5.0 mmol) was heated at reflux for 1.5 hr using Cope's apparatus to remove the water produced. After being cooled, the benzene solution was successively washed with Na₂O and satd. NaCl, then dried over anhyd. MgSO₄. Filtration and evaporation in vacuo gave the crude ester (77 mg, 15.6%, 10.0 g, 93.0 mmol) cooled at -30°C. After being left in a freezer (−20°C) for 65 hr, the whole mixture was poured onto ice-water (300 ml) and extracted with ethyl acetate. The combined organic extracts were successively washed at 0° with H₂O, satd. CuSO₄, and H₂O then dried over anhyd. MgSO₄. Filtration and evaporation in vacuo afforded the crude product as a colorless solid (21.9 g, 89% from (S)(−)-2, mp 46—52°C. Recrystallizations from a mixture of hexane and ether gave an analytical sample as colorless long needles, mp 58—59°C, [α]D²⁰ = 36.1° (c = 1.47, chloroform).

IR νₘ₉ cm⁻¹: 1750 (ester), 1380, 1360, 1180 (SO₂). NMR (in CDCl₃): 2.36 (3H, s, C₃H₃(CH)₂), δ 3.0—3.18 (2H, m, C₃H₃CH₂CH₂), 4.80—5.12 (1H, m, CH₂CH₂O), 5.04 (2H, s, C₃H₃CH₂CH₂), 8.41—7.38 (12H, m, other aromatic protons), 7.50 (2H, d, J = 8 Hz, aromatic protons ortho to SO₂). Anal. Calcd. for C₆H₄O₂S: C, 67.30; H, 5.40. Found: C, 67.01; H, 5.34.

b) (S)(−)-Benzy1 3-Phenyl-2-toslyoxypropionate: A pyridine solution (40 ml) of the crude benzy1 ester (15.6 g, prepared in a) was added dropwise to a solution of tosyl chloride (17.2 g, 90.3 mmol) in pyridine (100 ml) cooled at -30°C. After being left in a freezer (−20°C) for 65 hr, the whole mixture was poured onto ice-water (300 ml) and extracted with ethyl acetate. The combined organic extracts were successively washed at 0° with H₂O, satd. CuSO₄, and H₂O then dried over anhyd. MgSO₄. Filtration and evaporation in vacuo afforded the crude product as a colorless solid (7.4 g, 95% and 84% from (S)(−)-2, mp 117—122°C. Recrystallizations from a mixture of petr. ether and ether gave an analytical sample as colorless crystals, mp 122—124°C, [α]D²⁰ = -46.9° (c = 1.45, chloroform).

IR νₘ₉ cm⁻¹: 1740, 1720 (COOH), 1370, 1190, 1180 (SO₂). IR νₘ₉ cm⁻¹: 1740 (COOH), 1372, 1180, 1175 (SO₂). NMR (in CDCl₃): 2.29 (3H, s, C₃H₃(CH)₂), 3.02 (1H, doubled d, J = 9 and 19 Hz, one of C₃H₃CH₂CH₂), 3.16 (1H, doubled d, J = 5 and 19 Hz, one of C₃H₃CH₂CH₂), 4.91 (1H, doubled d, J = 5 and 9 Hz, C₃H₃CH₂CH₂), 6.83—7.22 (7H, m, other aromatic protons), 7.43 (2H, d, J = 8 Hz, aromatic protons ortho to SO₂), 9.85 (1H, s, COOH). The signal at 9.85 ppm disappeared on treatment with D₂O. Anal. Calcd. for C₆H₄O₂S: C, 59.99; H, 5.05. Found: C, 59.84; H, 5.02.

Reaction of (S)(−)-3-Phenyl-2-toslyoxypropionic Acid ((S)(−)-12) with Lithium Dimethylcuprate—To a stirred mixture of cuprous iodide (1.52 g, 8.0 mmol) and dibenzyl (128 mg, 0.703 mmol, an internal standard for GLC analysis) in ether (20 ml) was added an ethereal solution of methylthiium (1.95 M solution, 8.2 ml, 16 mmol) at -10°C, to give a solution of lithium dimethylcuprate in ether.

A solution of (S)(−)-12 (641 mg, 2.0 mmol) in ether (2 ml) was gradually added to the ethereal solution of lithium dimethylcuprate prepared above, and to −6°C, and the reaction mixture was stirred at ca. 0°C for 3 hr. The reaction was quenched by adding the reaction mixture to a mixture of 10% HCl (7 ml) and satd. NH₄Cl (26 ml), and the aqueous solution was extracted with ether. The ether extracts were washed with H₂O, then dried over anhyd. MgSO₄. Filtration and evaporation in vacuo gave a pale yellow oil (441 mg), to which was added ethanol (2 ml) and thioxyl chloride (297 mg, 2.5 mmol). The ethanolic solution was refluxed for 1 hr, then evaporated in vacuo to afford an oily residue which was dissolved in ethyl acetate. The ethyl acetate solution was washed with H₂O and satd. NaHCO₃, then dried over anhyd. MgSO₄. Filtration and evaporation in vacuo gave a brown oil (453 mg). The oily evaporation residue was submitted to GLC analysis in a manner similar to that for the reaction of (S)(−)-3 with lithium dimethylcuprate. The GLC analysis clearly showed that the oily residue (438 mg) contained 213 mg (55%) of (R)(−)-4.
In order to determine the optical rotation of \((R)(-)-4\), the evaporation residue was purified by preparative TLC (silica gel, solvent, petr. ether: hexane: ethyl acetate 1:1:1), giving pure \((R)(-)-4\) as a pale yellow oil (157 mg, 41%), \([\alpha]_b^{20} = -23.1^\circ \) (c=1.90, chloroform). Since \((S)(+)-4\) showing \([\alpha]_b^{20} +36^\circ\) (chloroform) is assumed to be optically pure, the optical purity of \((R)(-)-4\) and the extent of inversion for the substitution can be calculated as 89%. Spectral (IR) and chromatographic (TLC) behavior of this oil were completely identical with those of authentic \((S)(+)-4\).

When the substitution reaction was repeated three more times under almost the same condition as that described above, the following yields for \((R)(-)-4\) were recorded by GLC analysis: 58%, 59%, and 63%.

**Reaction of \((S)(-)-3-Phenyl-2-tosylxyproponic Acid ((S)(-)-12) with Lithium Di-n-butycuprate**

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A hexane solution of \(n\)-butyllithium (1.33 m solution, 12 ml, 16 mmol) was added to a stirred mixture of cuprous iodide (1.52 g, 8.00 mmol) in ether (15 ml) at -40\(^\circ\), to give a solution of lithium di-n-butycuprate in a mixture of hexane and ether.

An ethereal solution (4 ml) of \((S)(-)-12\) (641 mg, 2.0 mmol) was added dropwise to the solution of lithium di-n-butycuprate at -50\(^\circ\) to 35\(^\circ\), and the whole was stirred at the same temperature for 4 hr. The reaction was quenched by adding the reaction mixture to a mixture of 10% \(HCl\) (6 ml) and satd. \(NH_4Cl\) (20 ml), and the aqueous mixture was extracted with ether. The lower aqueous phase was further extracted with benzene after addition of 10% \(HCl\) (0.5 ml). The combined organic extracts were washed with \(H_2O\), then dried over anhyd. \(MgSO_4\). Filtration and evaporation in vacuo gave crude \((R)(+)-13\) as a yellow solid (308 mg, 75%). IR spectrum of this solid (in nujol) was almost the same as that of pure \((R)(+)-13\). A part of the solid (134 mg) was purified by column chromatography (silica gel, solvent: hexane: ether 1:1) to give pure \((R)(+)-13\) as a colorless solid (114 mg, 64%), \([\alpha]_b^{20} +25.0^\circ \) (c=1.04, chloroform). An analytical sample was obtained as long needles by recrystallization from hexane, mp 107.5—108.5\(^\circ\), \([\alpha]_b^{20} +25.8^\circ\) (c=0.546, chloroform).

**Reaction of \((S)(-)-2-Tosylxyproponic Acid ((S)(-)-15)\)**

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a) \((S)(-)-Acetoxypropionic Acid: This was prepared from commercially available l-alanine according to the reported procedure.**

b) (S)-Benzy1 2-Hydroxypropionate: Reflux of a benzene solution (70 ml) of \((S)(-)-2\)-acetoxypropionic acid (20.0 g, 0.15 mol), benzyl alcohol (35.7 g, 0.33 mol) and \(p\)-toluenesulfonyl acid monohydrate (3.6 g, 18 mmol) for 3.5 hr using Cope's apparatus to remove the water produced, followed by the same workup as that for the preparation of \((S)(-)-12\) gave the crude product as a yellow oil (53.0 g) with concomitant transesterification.

This crude sample was directly used for the next tosylation.

c) (S)(-)-Benzy1 2-Tosylxypropionate: A part of the crude benzy1 ester (40.0 g) was tosylated according to the same procedure as that for the preparation of \((S)(-)-12\), to afford the crude tosylate as a pale yellow oil (43.4 g) after evaporation of the ethyl acetate extracts. Purification of a part of this crude oil by preparative TLC (silica gel, solvent, petr. ether: hexane: benzy1 ether 2:2:1:1) gave the pure sample as a pale yellow oil, \([\alpha]_b^{20} = -28.6^\circ\) (c=5.05, chloroform). IR \(\nu_{max}\) cm\(^{-1}\): 1763 (ester), 1372, 1192, 1184 (SO\(_3\)).

NMR (in CCl\(_4\)): 1.42 (3H, d, J=7 Hz, CH\(_3\)CH), 2.33 (3H, s, CH\(_3\)CH\(_2\)H), 4.90 (1H, q, J=7 Hz, CH\(_3\)CO), 5.00 (2H, s, CH\(_2\)CH\(_2\)O), 6.98—7.38 (7H, other aromatic protons), 7.73 (2H, d, J=9 Hz, aromatic protons ortho to SO\(_3\)).

d) \((S)(-)-2-Tosylxyproponic Acid ((S)(-)-15): The same treatment of the crude tosylate (40 g) obtained in c) as that for the preparation of \((S)(-)-12\) afforded a pale yellow oil after filtration of the catalyst and evaporation of the tetrahydrofuran filtrate. After addition of hexane, the oily residue was triturated, and the formed colorless solid was washed several times with hexane. Filtration and drying in vacuo gave crude \((S)(-)-15\) as a colorless solid (13.9 g, 55% from \((S)(-)-2\)-acetoxypropionic acid). Repeated recrystallizations from a mixture of hexane and ether gave an analytical sample as colorless plates, mp 110—111\(^\circ\), \([\alpha]_b^{20} = -43.4^\circ\) (c=5.27, chloroform) [lit.\(^{36}\) mp 108\(^\circ\), \([\alpha]_b^{20} +41.2^\circ\)] (c=4.97, chloroform) for \((R)\)-isomer).

IR \(\nu_{max}\) cm\(^{-1}\): 1732 (COOH), 1191, 1180 (SO\(_3\)).

NMR (in CDCl\(_3\)): 1.56 (3H, d, J=7 Hz, CH\(_3\)CH), 2.45 (3H, s, CH\(_3\)CH\(_2\)H), 4.98 (1H, q, J=7 Hz, CH\(_3\)CO), 7.35 (2H, d, J=8 Hz, aromatic protons ortho to CH\(_3\)CO), 7.85 (2H, d, J=8 Hz, aromatic protons ortho to SO\(_3\)).

Found: C, 49.34; H, 4.99.

**Reaction of \((S)(-)-2-Tosylxyproponic Acid ((S)(-)-15) with Lithium Di-n-butycuprate**

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To a stirred suspension of cuprous iodide (11.42 g, 60 mmol) in ether (30 ml) was added over 30 min an etheral

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36 Preliminary separation of this crude oil (300 mg) by preparative TLC (silica gel, solvent, hexane: ether 1:1) uncovered that this oil contained dibenzy1 ether (6 mg), benzyl acetate (the weight was not determined), benzyl alcohol (the weight was not determined), (S)-benzy1 2-acetoxypropionate (35 mg), and (S)-benzy1 2-hydroxypropionate (86 mg) [S. Terashima, C.C. Tseng, and K. Koga, unpublished results].
solution of n-butyl lithium (2.07 M solution, 48.4 ml, 100 mmol) at $-50^{\circ}$ to $-40^{\circ}$, and the mixture was stirred at the same temperature for 50 min.

To the solution of lithium di-n-butylcuprate so obtained was added an ethereal solution (20 ml) of (S)-(−)15 (2.93 g, 12 mmol) at $-50^{\circ}$ to $-40^{\circ}$, and the temperature of the reaction mixture was gradually raised to $-10^{\circ}$ over 5 hr with stirring. After further stirring at $-10^{\circ}$ to $0^{\circ}$ for 4 hr, the whole mixture was again cooled to $-40^{\circ}$ and was poured onto a mixture of conc. HCl (8 ml) and satd. NH$_4$Cl (20 ml) to quench the reaction. Extractive isolation in a similar manner to that for the reaction of (S)-(−)12 with lithium dimethylcuprate, followed by evaporation in vacuo, gave a yellow oil (1.53 g). The oily residue was twice purified by column chromatography (silica gel, solvent: hexane: ether 1:1) to afford pure (S)-(−)-172$^a$ as a pale yellow oil (565 mg, 32%), bp 109$^a$-110$^a$ (17 mmHg), $[\alpha]_D^{25} +20.0^a$ ($c=6.36$, ether) and $d_2^0 +0.333^a$ ($d=0.02$, neat).

The optical purity of (S)-(−)-16 and the extent of inversion for the substitution can be calculated as 102% or 98%.$^a$ IR $n_v$ cm$^{-1}$: 1715 (COOH), NMR (in CDC$_3$): 0.92 (3H, m, CH$_3$CH$_2$CH$_2$CH$_2$), 1.17 (3H, d, $J=7$ Hz, CH$_2$CHO), 1.07-2.00 (6H, m, CH$_3$CH$_2$CH$_2$CH$_2$), 2.37 (3H, m, CH$_3$CH$_2$), 11.64 (1H, s, COOH). MS: m/e: 130 [M$^+$], 112, 100, 86, 73.

Reaction of (S)-(−)-2-Tosyloxypropionic Acid (S)-(−)-15 with Lithium Diphenylcuprate$^b$—To a stirred suspension of cuprous iodide (3.43 g, 18 mmol) in ether (10 ml) was added over 30 min a solution of phenyllithium$^c$ in a mixture of ether and benzene (3:7) (1.44 M solution, 25 ml, 36 mmol) at $-20^{\circ}$ to $-10^{\circ}$, to give a solution of lithium diphenylcuprate.

A solution of (S)-(−)-15 (733 mg, 3.0 mmol) in ether (5 ml) was added over 30 min to the ether solution of lithium diphenylcuprate cooled at $-40^{\circ}$, and the whole was stirred at $-60^{\circ}$ to $-50^{\circ}$ for 2 hr, at $-20^{\circ}$ to $-10^{\circ}$ for 2.5 hr, and finally at $-10^{\circ}$ to $0^{\circ}$ for 3 hr. The reaction was quenched by adding the reaction mixture to a mixture of conc. HCl (8 ml) and satd. NH$_4$Cl (25 ml), and the upper organic layer was separated. The lower aqueous phase was further extracted with ethyl acetate, and the combined organic extracts were successively washed with H$_2$O, dil. Na$_2$SO$_4$, and H$_2$O, then dried over anhyd. MgSO$_4$. Filtration and evaporation in vacuo gave an oily residue which was contaminated with bromobenzene.$^d$ Therefore, the oily residue was dissolved in ether (20 ml), and the ether solution was extracted with satd. NaHCO$_3$. The combined bicarbonate extracts were washed with ether, and acidified with conc. HCl. The acidic aqueous solution was extracted with ether, and the combined etheral layers were dried over anhyd. MgSO$_4$. Filtration and evaporation in vacuo gave an oily residue (124 mg), which was purified by column chromatography (silica gel, solvent: hexane: ether 2:1) to afford pure (S)-(−)-172$^a$ as a colorless oil (54.6 mg, 12%), $[\alpha]_D^{25} +76.9^a$ ($c=1.09$, ethanol).

The optical purity of (S)-(−)-17 and the extent of inversion for the substitution reaction can be calculated as 95%.$^a$ IR $n_v$ cm$^{-1}$: 1700 (COOH). NMR (in CCl$_4$): 1.47 (3H, d, $J=7$ Hz, CH$_3$CH$_2$), 3.66 (1H, q, $J=7$ Hz, CH$_2$CHO), 7.24 (5H, s, C$_6$H$_5$), 11.96 (1H, s, COOH).

(S)-(−)-4-Methyl-2-tosyloxypentanoic Acid (S)-(−)-18—a) (S)-(−)-2-Hydroxy-4-methylpentanoic Acid: This was prepared by deaminating commercially available L-leucine with sodium nitrite in 5% sulfuric acid. Recrystallization of the crude deamination product from a mixture of hexane and ether gave the optically pure acid as colorless needles, mp 78$^a$-81$^a$, $[\alpha]_D^{25} -11.3^a$ (c=5.72, H$_2$O) (lit.$^g$ mp 80$^a$-81$^a$, $[\alpha]_D^{25} -12.9^a$ (c=1, H$_2$O)).

b) (S)-(−)-Benzyloxy-2-Hydroxy-4-methylpentanoate: Esterification of (S)-(−)-2-hydroxy-4-methylpentanoic acid (13.1 g, 0.10 mol) with benzyl alcohol in a similar manner to that for the preparation of (S)-(−)-12 gave the (S)-(−)-benzyl ester as a pale yellow oil (21.9 g, 98%), bp 126$^a$ (5 mmHg), $[\alpha]_D^{25} -15.8^a$ ($c=3.09$, chloroform). IR $n_v$ cm$^{-1}$: 3470 (OH), 1735 (ester).

c) (S)-(−)-Benzyloxy-4-Methyl-2-tosyloxypentanoate: Treatment of the (S)-(−)-benzyl ester (10.0 g, 45 mmol) with tosyl chloride and pyridine in the same manner as that for the preparation of (S)-(−)-12 gave the crude product as a yellow oil (4.5 g, 86% and 84% from (S)-(−)-2-hydroxy-4-methylpentanoic acid) after evaporation of the ethyl acetate extract. A part of the crude product was purified by preparative TLC (silica gel, solvent, petr. ether: hexane: benzene: ether 2:2:1:1) to give the pure product as a pale yellow oil, $[\alpha]_D^{25} -35.5^a$ ($c=3.89$, chloroform). IR $n_v$ cm$^{-1}$: 1760 (ester), 1375, 1195, 1180 (SO$_2$). NMR (in CDC$_3$): 0.82, 0.86 (6H, two d, $J$=each 6 Hz, CH(CH$_3$)$_2$), 1.15-2.02 (3H, m, CH$_2$CH$_2$CH$_2$), 2.37 (3H, s, CH$_3$CH$_2$), 4.96 (1H, m, CH$_2$CH$_2$O), 4.92 (2H, s, CH$_3$CH$_2$O), 7.20 (2H, d, $J=8$ Hz, aromatic protons ortho to CH$_3$), 7.21 (2H, d, $J=8$ Hz, aromatic protons ortho to CH$_3$). NMR (in CDCl$_3$): 0.85, 0.95 (6H, two d, $J$=each 6 Hz, CH$_2$CH$_2$), 1.46-2.16 (3H, m, CH$_2$CH$_2$CH$_2$), 2.44 (3H, s, CH$_3$CH$_2$), 4.66-5.07 (1H, m, CH$_2$CH$_2$O), 7.33 (2H, d, $J=8$ Hz, aromatic protons ortho to CH$_3$), 7.82

37) A solution of phenyllithium purchased from Ventron Corporation, Alfa Products, U.S.A., was directly used for the reaction.

38) The phenyllithium solution contained bromobenzene as an impurity.

(2H, d, \( J = 8 \text{ Hz} \), aromatic protons \textit{ortho} to SO\(_2\)), 9.89 (1H, s, COOH). MS: \( m/e \) 285 [M\(^+\) - 1], 240, 156, 155, 154, 113, 91, 90. This sample was directly used for the reaction with lithium dimethyldicuprate.

\textbf{Reaction of (S)(--)\textsuperscript{4}Methyl-2-tosyloxypentanoic Acid ([S](--)\textsuperscript{18} with Lithium Dimethyldicuprate\textsuperscript{12}}---

To a stirred suspension of cuprous iodide (11.4 g, 60 mmol) in ether (10 ml) was added an ethereal solution of methyllithium (1.60 M solution, 75 ml, 120 mmol) at \(-20^\circ\), to give a solution of lithium dimethyldicuprate.

An ethereal solution (20 ml) of (S)(--)\textsuperscript{18} (3.44 g, 12 mmol) was gradually added over 40 min to the solution of lithium dimethyldicuprate prepared above, and the reaction mixture was stirred at \(-20--10^\circ\) for 1 hr, then at \(-10--0^\circ\) for 4 hr. The reaction was quenched by adding the reaction mixture to a mixture of conc. HCl (12 ml) and satd. NH\(_4\)Cl (25 ml). Similar extractive isolation with ethyl acetate to the reaction of (S)(--)\textsuperscript{12} with lithium dimethyldicuprate, followed by filtration and evaporation \emph{in vacuo}, gave a yellow oil. The oily evaporation residue was twice purified by column chromatography (silica gel, solvent, hexane: ether 1:1) to afford pure \(\langle R\rangle(\text{--})\textsuperscript{19,20}\) as a pale yellow oil (415 mg, 27%). Fractional distillation of this sample gave a colorless oil, bp 93--94° (11 mmHg), \([\alpha]_D^\text{25} = -21.1° (c = 5.79, ether)\) (lit. \ textsuperscript{10} bp 117° (17 mmHg), \([\alpha]_D^\text{25} + 19.4° (c = 5.23, ether)\) for (S)(\textsuperscript{+})\textsuperscript{19}.

The optical purity of \(\langle R\rangle(\text{--})\textsuperscript{19} and the extent of inversion for the substitution reaction can be calculated as 99.9%.\textsuperscript{13} IR \textsuperscript{CBOH} cm\(^{-1}\): 1715 (COOH). NMR (in CCl\(_4\)): 0.91 (6H, two d, \( J = 4 \text{ Hz} \), CH(CH\(_3\))\(_2\)), 1.18 (3H, d, \( J = 7 \text{ Hz} \), CH\(_3\)CHCO), 1.00--2.00 (3H, m, \( (\text{CH}_3)_2\text{CHCH}_2\)), 2.44 (1H, m, CHCO), 12.06 (1H, s, COOH). MS \textit{m/e}: 130 [M\(^+\)], 122, 86, 73, 72.

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