[Chem. Pharm. Bull. 26(1) 178—184 (1978)]

UDC 547.587.42.04 : 541.63.04

Stereochemical Studies. LII.[1] Studies on the Stereochemical Courses in Deaminative Bromination of 3,5-Dichloro-L-tyrosine and in Amination of the Corresponding α-Bromo Acid. Existence of Strong Neighboring "Phenoxide" Group Participation

KENJI KOGA, TZUOH MIIN JUANG, and SHUN-ICHI YAMADA

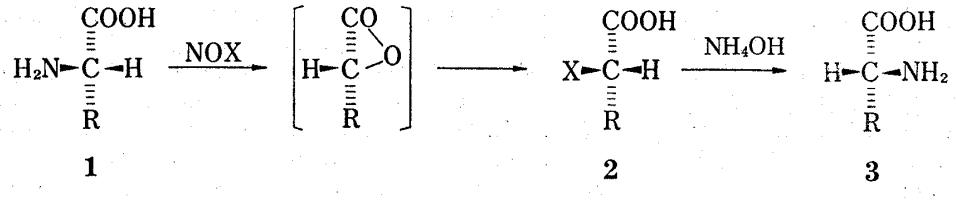
Faculty of Pharmaceutical Sciences, University of Tokyo[2]

(Received June 3, 1977)

It has become apparent that deaminative bromination of 3,5-dichloro-L-tyrosine (L-**4**) to the corresponding α-bromo acid ((−)-**5**) occurs with retention of configuration, and that amination of this bromo acid to the starting amino acid (L-**4**) occurs also with retention of configuration. The unusual stereochemical course in this amination step was found to be due to the strong neighboring aryl group participation as a phenoxide form.

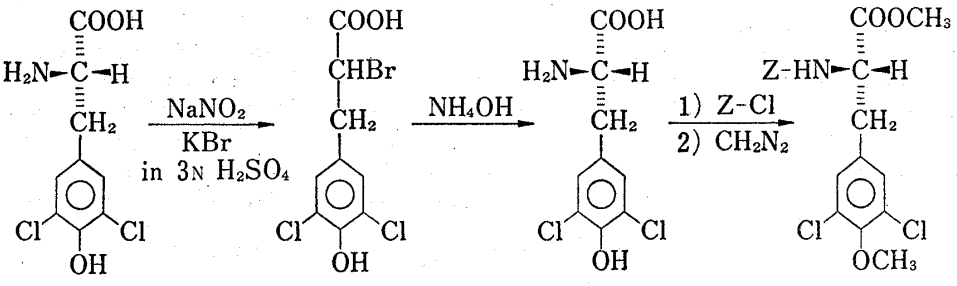
Keywords——deaminative bromination; 3,5-dichloro-L-tyrosine; amination; amino acid; neighboring group participation; stereochemistry; solvolysis; substitution reaction; retention of configuration

Deaminative halogenation of optically active α-amino acids followed by amination of the resulting α-halo acids is known as one of the methods for D-L interconversion of many optically active α-amino acids, and the stereochemical courses of this method are generally explained[3] as shown in Chart 1. The reaction of nitrosyl halides on optically active α-amino acids (**1**) having a hydrogen and having no aryl group at the asymmetric carbon atom leads to the corresponding α-halo acids (**2**) with retention (by two inversion processes) due to the participation of the neighboring carboxylate group,[4] and the amination of this α-halo acids (**2**) with ammonia leads to α-amino acids (**3**) with inversion.



1 **2** **3**

Chart 1



L-**4** (−)-**5** L-**4** L-(−)-**6**

Chart 2

Z = C_6H_5–CH_2–O–CO

1) Part LI: Y. Murakami, K. Koga, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **25**, 307 (1977).
2) Location: *7-3-1, Hongo, Bunkyo-ku, Tokyo 113, Japan.*
3) *a*) A. Neuberger, "Advances in Protein Chemistry," Vol. 4, ed. by M.L. Anson and J.T. Edsall, Academic Press, New York, 1948, p. 327; *b*) N. Izumiya, *Bull. Chem. Soc. Japan*, **72**, 26 (1951).
4) P. Brewster, F. Hiron, E.D. Hughes, C.K. Ingold, and P.A.D.S. Rao, *Nature*, **166**, 179 (1950).

One of the exceptions to this method of D-L interconversion was reported by Warburton, who recognized that deaminative bromination of 3,5-dichloro-L-tyrosine (L-**4**) followed by amination of the corresponding α-bromo acid ((—)-**5**) afforded the starting L-**4**.[5] This abnormal result of net retention of configuration means that the stereochemical courses of deaminative bromination from L-**4** to (—)-**5** and amination of (—)-**5** to L-**4** should be both retention or inversion. Determination of the configuration of (—)-**5** is expected to clarify the stereochemical courses of this abnormal result. From kinetical experiments on the reaction of (—)-**5** with sodium azide and from the configurational correlation of the resulting α-azido acid with α-amino acid by reduction, Warburton concluded that amination of (—)-**5** afforded L-**4** with inversion, and therefore, deaminative bromination of L-**4** to (—)-**5** should proceed also with inversion.[5]

Judging from our detailed examinations on nitrous acid deamination of optically active α-amino acids and their derivatives,[6] however, it is highly unlikely that deamination reaction of L-**4** occurs with inversion in the presence of

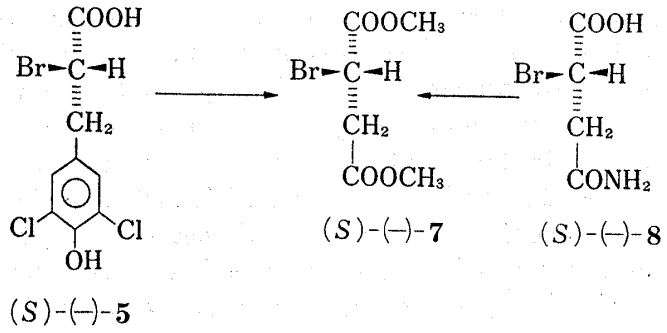


Chart 3

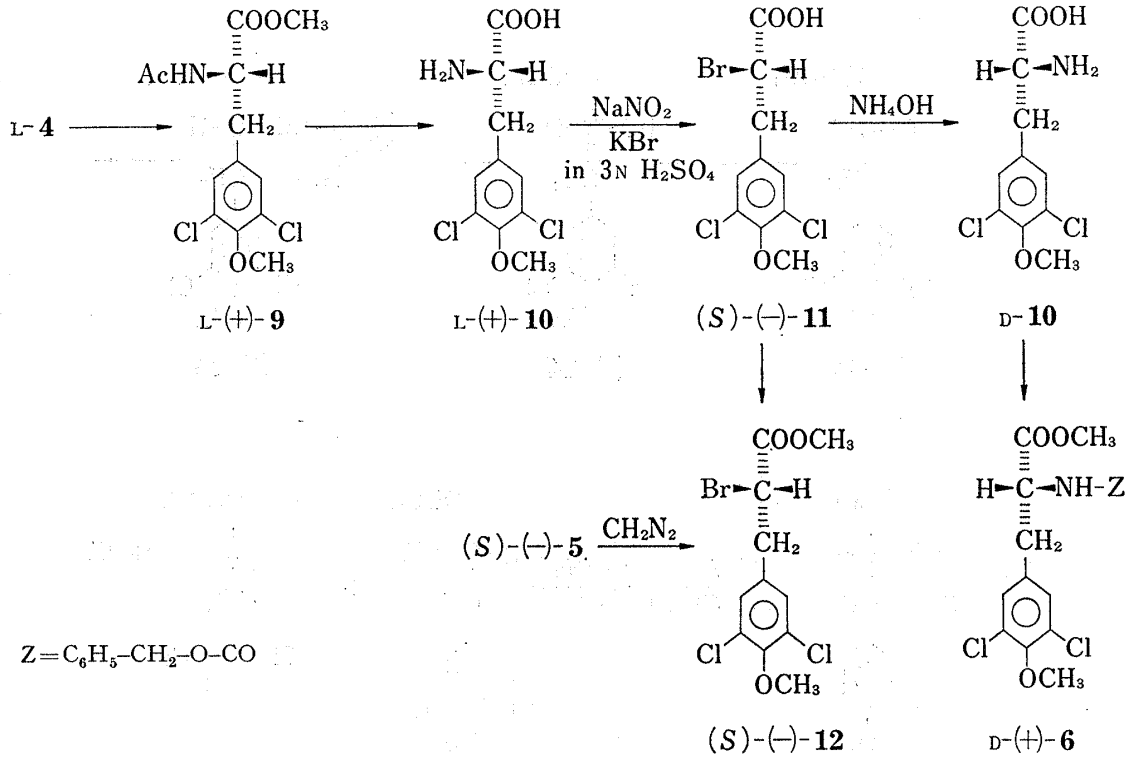


Chart 4

5) W.K. Warburton, *J. Chem. Soc.*, **1961**, 2651.
6) *a*) S. Yamada, T. Kitagawa, and K. Achiwa, *Tetrahedron Lett.*, **1967**, 3007; *b*) S. Yamada, M. Taniguchi, and K. Koga, *ibid.*, **1969**, 25; *c*) K. Koga, C.C. Wu, and S. Yamada, *ibid.*, **1971**, 2283; *d*) *Idem*, *ibid.*, **1971**, 2287; *e*) *Idem*, *Chem. Pharm. Bull.* (Tokyo), **20**, 1272 (1972); *f*) *Idem*, *ibid.*, **20**, 1282 (1972); *g*) M. Taniguchi, K. Koga, and S. Yamada, *ibid.*, **20**, 1438 (1972); *h*) M. Kobayashi, K. Koga, and S. Yamada, *ibid.*, **20**, 1898 (1972); *i*) M. Yoh, K. Koga, and S. Yamada, *ibid.*, **20**, 2017 (1972); *j*) Y. Murakami, K. Koga, and S. Yamada, *ibid.*, **26**, 307 (1978).

bromide ion as a nucleophile. Therefore, unequivocal determination of the absolute configuration of (—)-**5** was performed by chemical correlation as shown in Chart 3.

The configuration of dimethyl (*S*)-bromosuccinate ((*S*)-(—)-**7**) was already correlated chemically[7] with (*S*)-2-bromosuccinamic acid ((*S*)-(—)-**8**), whose absolute configuration had been determined by X-ray diffraction method.[8] In the present study, (—)-**5** obtained from L-**4** by the reported method[5] was oxidized with ozone in acetic acid followed by 30% aqueous hydrogen peroxide to a mixture of products, from which, after treatment with diazomethane, (*S*)-(—)-**7** was isolated. It has now become apparent that (—)-**5** has (*S*)-configuration. This means that deaminative bromination of L-**4** to (—)-**5** occurs with 88% retention, amination of (—)-**5** to L-**4** occurs also with almost complete retention, and therefore, stereochemical abnormality exists at the step of amination. Investigation was also made on the O-methyl derivative (L-(+)-**10**) prepared from L-**4** *via* L-(+)-**9** as shown in Chart 4. Deaminative bromination of L-(+)-**10** was found to occur with almost complete retention to give α-bromo acid (*S*)-(—)-**11**), whose absolute configuration was correlated with (*S*)-(—)-**5** *via* (*S*)-(—)-**12**. Amination of (*S*)-(—)-**11** was found to occur with 80% inversion to give D-**10**, which was characterized as its derivative (D-(+)-**6**), an enantiomer of L-(—)-**6** obtained previously as shown in Chart 2. Similar successful D-L interconversion is also reported for phenylalanine,[9] O-methyltyrosine,[10] *etc.*[3,5] The present result on the stereochemistry of amination of (*S*)-(—)-**5** and (*S*)-(—)-**11** to give their corresponding α-amino acids, with retention in the former case while inversion in the latter case, clearly suggests that free phenolic hydroxyl group on the aromatic ring is responsible for the abnormal stereochemistry in the former case.

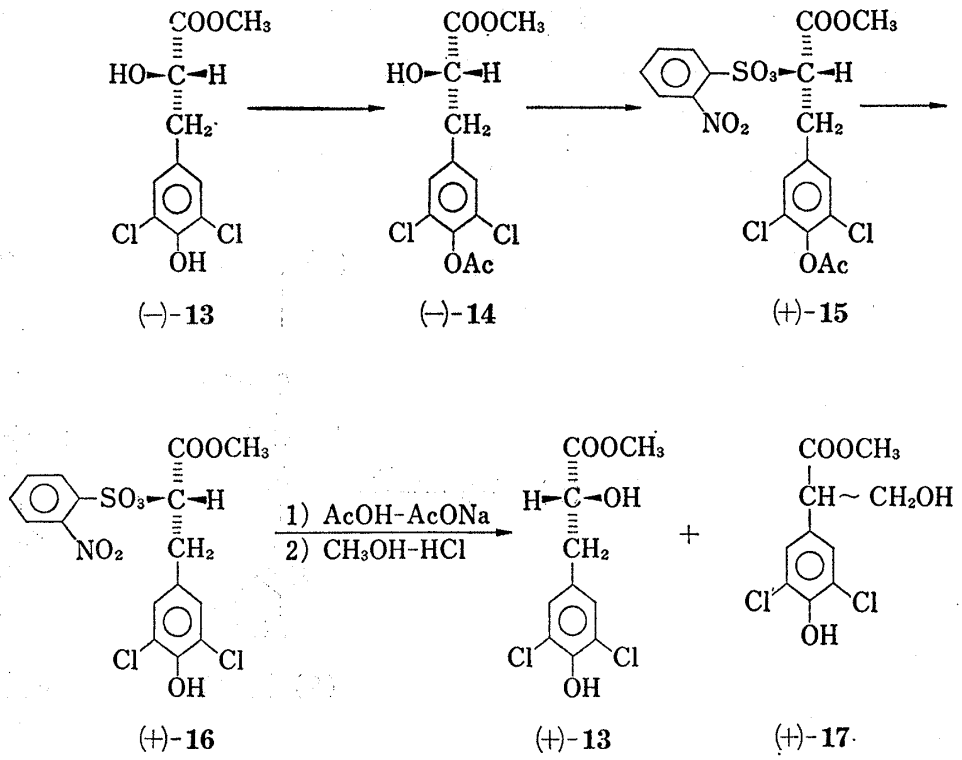


Chart 5

7) *a*) P. Walden, *Ber.*, **28**, 2766 (1895); *b*) L.J. Andrews and J.E. Hardwicke, *J. Am. Chem. Soc.*, **74**, 3582 (1952).
8) Y. Murakami and Y. Iitaka, *Chem. Pharm. Bull.* (Tokyo), **17**, 2397 (1969).
9) E. Fischer and H. Carl, *Ber.*, **39**, 3996 (1906).
10) R. Pitt-Rivers and J. Lerman, *J. Endocrinol.*, **5**, 223 (1948) [*C.A.*, **42**, 4141*f* (1948)].

Stereochemical investigation on the solvolysis reaction of the corresponding sulfonate ((+)-**16**)[11] was next undertaken[12] for the purpose to evaluate the neighboring effect of the aryl group on the reaction. As shown in Chart 5, acetolysis of (+)-**16** followed by treatment of the product with methanol and hydrochloric acid afforded the corresponding substitution product ((+)-**13**)[11] with 76% inversion, accompanied by aryl migration product ((+)-**17**). Previously, it was reported that acetolysis of the sulfonate having phenyl group instead of 3,5-dichloro-4-hydroxyphenyl group in (+)-**16** afforded the corresponding substitution product with 93% inversion.[13] The present results means that 3,5-dichloro-4-hydrophenyl group does not show so strong neighboring group participation as to alter the stereochemical course of the substitution reaction under the present acetolysis condition.

Under basic condition, however, 3,5-dichloro-4-hydroxyphenyl group exists as a dissociated "phenoxide" form, which is expected to show highly stronger neighboring group participation than that of the undissociated "phenol" form.[14] This consideration was confirmed by the fact that amination of α-bromo acid ((*S*)-(−)-**20**) having 4-hydroxyphenyl group afforded tyrosine (L-**21**) with 46% retention determined as its ester (L-(+)-**22**) as shown on Chart 6.

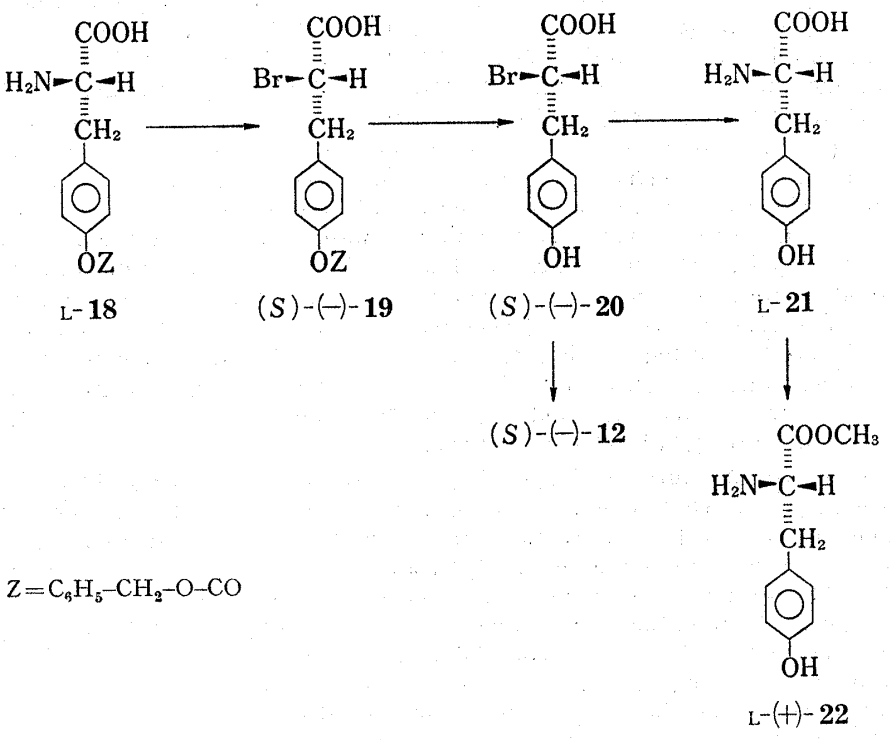


Chart 6

In conclusion, the failure of D-L interconversion of L-**4** by deaminative bromination followed by amination is found to be due to the strong neighboring 3,5-dichloro-4-hydroxyphenyl group participation as a dissociated "phenoxide" form to make the substitution reaction retention in the amination step.

11) The absolute configuration of this compound is not yet known. In the present study, relative configurations of optically active **13**, **14**, **15**, and **16** were established as in Chart 5. The stereostructures in Chart 5 are tentative.
12) This sulfonate was used because of the poor reactivity of (*S*)-(−)-**5** toward solvolysis.
13) S. Yamada, K. Koga, T.M. Juang, and K. Achiwa, *Chem. Letters*, **1976**, 927.
14) R. Baird and S. Winstein, *J. Am. Chem. Soc.*, **85**, 567 (1963).

Experimental[15]

(*S*)-α-Bromo-β-(3,5-dichloro-4-hydroxyphenyl)propionic Acid ((*S*)-(−)-**5**)——To a solution of L-**4**[16] (10.0 g, 40 mmol) and KBr (19.0 g, 160 mmol) in 3 N H_2SO_4 (160 ml) was added a solution of $NaNO_2$ (8.76 g, 120 mmol) in water (15 ml) under stirring at −8——10° during 2.5 hr, and the whole was stirred at 0° for 30 min. The precipitates were collected by filtration, washed well with water and dried to give a solid (9.5 g, 76%) of mp 70—80°, $[\alpha]_D^{20}$ −24.8° (c=2.32, dioxane) (corresponding to be 88% optically pure based on the data of purified material below). Three recrystallizations from benzene afforded colorless cubes of mp 85—86°, $[\alpha]_D^{20}$ −28.2° (c=1.88, dioxane) (reported[5] mp 85.5—86.5°, $[\alpha]_D^{20}$ −28.3° (c=3.0, dioxane)). Further recrystallizations did not change physical constants. IR ν_{max}^{KBr} cm^{-1}: 3450 (OH), 1700 (COOH). NMR ($CDCl_3$) δ: 3.13 and 3.30 (total 2H, ABX-octet, J_{AB}=15 Hz, J_{AX}=J_{BX}=7 Hz, Ar–C<u>H</u>$_2$–CH), 4.32 (1H, t, J_{AX}=J_{BX}=7 Hz, Ar–CH_2–C<u>H</u>), 7.18 (2H, s, C_6<u>H_2</u>). *Anal.* Calcd. for $C_9H_7BrCl_2O_3$: C, 34.43; H, 2.25. Found: C, 34.13; H, 2.18.

N-Carbobenzyloxy-O-methyl-3,5-dichloro-L-tyrosine Methyl Ester (L-(−)-**6**)——a) From L-**4**: To a solution of optically pure L-**4** (0.60 g, 2.4 mmol) in satd. aq. $NaHCO_3$ (20 ml) was added benzyloxycarbonyl chloride (0.49 g, 2.88 mmol) gradually under ice-cooling, and the whole was stirred for 6 hr. The reaction mixture was washed with ether, acidified with 10% aq. HCl, and then extracted with AcOEt. The extracts were combined, washed with satd. aq. NaCl, dried over $MgSO_4$, and evaporated to dryness to give a colorless solid. Treatment of this solid with excess diazomethane in ether in the usual way afforded a solid, which was purified by column chromatography on silica gel with hexane-ether (3: 1) to give L-(−)-**6** (0.44 g, 44%) as a colorless solid of $[\alpha]_D^{20}$ −47.8° (c=2.642, DMF). Recrystallization from hexane afforded colorless needles of mp 103—104°, $[\alpha]_D^{20}$ −47.7° (c=1.54, DMF). IR ν_{max}^{KBr} cm^{-1}: 3280 (NH), 1750 ($COOCH_3$), 1685 (CONH). NMR ($CDCl_3$) δ: 2.90 (2H, m, Ar–C<u>H</u>$_2$–CH), 3.62 and 3.80 (total 6H, two s, Ar–OC<u>H</u>$_3$, COOC<u>H</u>$_3$), 4.45 (1H, m, Ar–CH_2–C<u>H</u>), 5.00 (2H, s, C_6H_5–C<u>H</u>$_2$–O), 5.38 (1H, d, J=8 Hz, N<u>H</u>), 6.92 (2H, s, C_6<u>H_2</u>), 7.18 (5H, s, C_6<u>H_5</u>). *Anal.* Calcd. for $C_{19}H_{16}Cl_2NO_5$: C, 55.35; H, 4.65; N, 3.40. Found: C, 55.54; H, 4.75; N, 3.30.

b) From (*S*)-(−)-**5**: A solution of (*S*)-(−)-**5** ($[\alpha]_D^{20}$ −28.0° (dioxane)) (2.51 g) in conc. aq. NH_4OH (50 ml) was left standing in a stoppered flask for 7 days at room temperature, and then the whole was evaporated to dryness. The residue was dissolved in water, and the whole was passed through a column of Amberlite IR-120 (H-form) (40 ml). After washing the column with water until neutral, the amino acid fraction was eluted with dil. aq. NH_4OH. The eluates were combined and evaporated to dryness to give a yellow solid (2.13 g). This solid afforded L-(−)-**6** by the method identical with that described in a) as a colorless solid of mp 95—98°, $[\alpha]_D^{20}$ −47.8° (c=1.406, DMF) after purification by column chromatography. This sample was shown to be identical with the sample prepared in a) by IR, NMR, TLC, as well as mixed mp test.

Dimethyl (*S*)-Bromosuccinate ((*S*)-(−)-**7**) a) From (*S*)-Bromosuccinic Acid[6j,7]; Prepared according to the reported method[6j,7] as colorless liquid of bp 78—79° (2 mmHg), $[\alpha]_D^{18}$ −67.1° (c=1.34, benzene) (reported[6j] bp 89—90° (5 mmHg), $[\alpha]_D^{12}$ −70.3° (c=1.208, benzene)).

b) From (*S*)-(−)-**5**: A solution of (*S*)-(−)-**5** ($[\alpha]_D^{20}$ −24.8° (dioxane)) (2.0 g, 8 mmol) in AcOH (20 ml) was bubbled with oxygen gas containing ozone at 10° for 1 hr and at room temperature for 3 hr. 30% aq. H_2O_2 (1.1 g, 10 mmol) was added to the reaction mixture and the whole was allowed to stand at room temperature for 2 hr. After decomposing excess H_2O_2 by addition of Pt, the whole was filtered. The filtrate was evaporated, and the residue was extracted with ether three times. The ethereal extracts were combined and dried over $MgSO_4$. Evaporation of the ether left an oil (2.6 g), which was chromatographed on silica gel with hexane–ether (1: 3). The fractions containing bromosuccinic acid (checked by TLC) were combined and evaporated to give a residue (167 mg), which was treated with excess diazomethane in ether in the usual manner. The crude ester thus obtained was chromatographed on silica gel with hexane–ether (19: 1) to give (*S*)-(−)-**7** (42 mg, 3.3%) as a colorless liquid of $[\alpha]_D^{18}$ −62.0° (c=0.64, benzene). This sample was identified with the sample obtained in a) by IR and NMR. MS m/e: 226, 224 (M^+).

N-Acetyl-O-methyl-3,5-dichloro-L-tyrosine Methyl Ester (L-(+)-**9**)——To a suspension of N-acetyl-3,5-dichloro-L-tyrosine of $[\alpha]_D^{20}$ +83.8° (c=4.83, dioxane) (reported[17] $[\alpha]_D^{20}$ +83.0° (dioxane)) in ether was added a solution of diazomethane in ether until the reaction mixture became clear, and the whole was allowed standing. The crystals deposited again were collected, and recrystallized from benzene to colorless fine needles of mp 119—119.5°, $[\alpha]_D^{20}$ +58.3° (c=1.56, dioxane). IR ν_{max}^{Nujol} cm^{-1}: 3320 (NH), 1730 ($COOCH_3$), 1640 (CONH). NMR ($CDCl_3$) δ: 2.00 (3H, s, C<u>H</u>$_3$CONH), ~3.05 (2H, m, Ar–C<u>H</u>$_2$), 3.78 and 3.90 (total 6H, two s, COOC<u>H</u>$_3$

15) All melting and boiling points are uncorrected. Infrared (IR) spectra were recorded with a JASCO DS-402G or a JASCO IRA-1 Spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded with a JNM PS-100 (100 MHz) or a Hitachi R-24 (60 MHz) Spectrometer using TMS as an internal standard. Optical rotations were measured with a Yanaco OR-50 Automatic Polarimeter. Mass spectra (MS) were recorded with a JOEL JMS-01 SG-2 Mass Spectrometer.

16) K.B. Brody and R.P. Spencer, *J. Org. Chem.*, 33, 1665 (1968).

17) A. Dibbo, L. Stephenson, T. Walker, and W.K. Warburton, *J. Chem. Soc.*, **1961**, 2645.

and Ar–OC$\underline{H}_3$), ~4.85 (1H, m, Ar–CH_2–C$\underline{H}$), 6.55 (1H, d, J=8 Hz, N$\underline{H}$), 7.10 (2H, s, $C_6\underline{H}_2$). MS *m/e*: 320 (M^+). *Anal.* Calcd. for $C_{13}H_{15}Cl_2NO_4$: C, 48.77; H, 4.72; N, 4.37. Found: C, 48.48; H, 4.65; N, 4.39.

O-Methyl-3,5-dichloro-L-tyrosine (L-(+)-10)——A mixture of L-(+)-**9** (8.0 g) and 10% aq. HCl (150 ml) was heated to reflux for 2 hr, and then evaporated to dryness. The residue was dissolved in water, and the resulting solution was adjusted to pH 6 by addition of 5% aq. NH_4OH. The precipitates were collected by filtration, washed with water, and dried to give crude L-(+)-**10** (5.64 g, 86%). Recrystallization from water–MeOH (3: 7) afforded colorless powder (3.45 g, 52%) of mp 218—220° (dec.), $[\alpha]_D^{20}$ +6.7° (c=1.064, 3 N HCl). *Anal.* Calcd. for $C_{10}H_{11}Cl_2NO_3$: C, 45.46; H, 4.20; N, 5.31. Found: C, 45.12; H, 4.39; N, 4.96.

(*S*)-α-Bromo-β-(3,5-dichloro-4-methoxyphenyl)propionic Acid ((*S*)-(−)-11)——To a solution of L-(+)-**10** (5.28 g, 20 mmol) and KBr (9.52 g, 80 mmol) in 3 N H_2SO_4 (80 ml) was added a solution of $NaNO_2$ (4.14 g, 60 mmol) in water (75 ml) under stirring at −10° during 2.5 hr, and the whole was stirred at 0° for 30 min. The precipitates were collected by filtration, washed with water and dried to give a solid, which was chromatographed on silica gel with AcOEt–MeOH (19: 1) to give (*S*)-(−)-**11** (5.9 g, 90%) as a pale yellow solid of mp 72—79°, $[\alpha]_D^{20}$ −30.5° (c=2.868, dioxane). Recrystallization from benzene afforded pale yellow needles of mp 82—84°, $[\alpha]_D^{20}$ −31.1° (c=2.174, dioxane). NMR ($CDCl_3$) δ: 3.21 (2H, m, Ar–C$\underline{H}_2$), 3.89 (3H, s, Ar–OC$\underline{H}_3$), 4.40 (1H, t, J=8 Hz, Ar–CH_2–C$\underline{H}$), 7.12 (2H, s, $C_6\underline{H}_2$). *Anal.* Calcd. for $C_{10}H_9BrCl_2O_3$: C, 36.62; H, 2.77. Found: C, 36.90; H, 2.87.

Methyl (*S*)-α-Bromo-β-(3,5-dichloro-4-methoxyphenyl)propionate ((*S*)-(−)-12)——a) From (*S*)-(−)-**5**: (*S*)-(−)-**5** ($[\alpha]_D^{20}$ −28.5° (c=2.06, dioxane)) was treated with diazomethane in ether in the usual way and the product was purified by column chromatography on silica gel with hexane–ether (2: 1) to give (*S*)-(−)-**12** as a pale yellow liquid of $[\alpha]_D^{20}$ −32.2° (c=1.416, dioxane), bp 162° (6 mmHg) (accompanied by racemization) in 63% yield. IR ν_{max}^{film} cm^{-1}: 2840 (OCH_3), 1750 ($COOCH_3$), NMR ($CDCl_3$) δ: 3.2 (2H, m, Ar–C$\underline{H}_2$), 3.72 and 3.84 (total 6H, two s, Ar–OC$\underline{H}_3$ and COOC$\underline{H}_3$), 4.33 (1H, t, J=7 Hz, Ar–CH_2–C$\underline{H}$), 7.10 (2H, s, $C_6\underline{H}_2$). *Anal.* Calcd. for $C_{11}H_{11}BrCl_2O_3$: C, 38.63; H, 3.24. Found: C, 39.14; H, 3.35.

b) From (*S*)-(−)-**11**: (*S*)-(−)-**11** ($[\alpha]_D^{20}$ −30.5° (dioxane)) was treated as in a) to give (*S*)-(−)-**12** as a pale yellow liquid of $[\alpha]_D^{20}$ −32.1° (c=1.95, dioxane). This sample showed identical IR and NMR spectra with those of the sample prepared in a).

c) From (*S*)-(−)-**20**: (*S*)-(−)-**20** ($[\alpha]_D^{20}$ −17.7° (dioxane)) was chlorinated as in the preparation of L-**4**[16] and then esterified as in a) above. The product was purified by column chromatography on silica gel with ether–hexane (1: 7) to give (*S*)-(−)-**12** in 50% yield as a pale yellow liquid of $[\alpha]_D^{20}$ −28.4° (c=2.18, dioxane), corresponding to be 88% optically pure based on the data in a), and therefore, optically pure (*S*)-(−)-**20** should have $[\alpha]_D^{20}$ −20.7° (dioxane). This sample showed identical IR and NMR spectra with those of the sample prepared in a).

N-Carbobenzyloxy-O-methyl-3,5-dichloro-D-tyrosine Methyl Ester (D-(+)-6)——A solution of (*S*)-(−)-**11** ($[\alpha]_D^{20}$ −30.5° (dioxane)) (2.0 g) in conc. aq. NH_4OH (40 ml) was treated as in the amination of (*S*)-(−)-**5** described above afforded crude amino acid (2.09 g) after purification by Amberlite IR-120 (H-form) resin. The reaction of this sample with benzyloxycarbonyl chloride followed by diazomethane as described in the preparation of L-(−)-**6** above afforded D-(+)-**6** as a colorless solid of $[\alpha]_D^{20}$ +37.1° (c=1.454, dioxane), corresponding to be 80% optically pure. This sample showed identical IR and NMR spectra with those of L-(−)-**6**.

(−)-β-(3,5-Dichloro-4-hydroxyphenyl)lactic Acid Methyl Ester ((−)-13)——To a solution of L-**4** (10.0 g, 40 mmol) in AcOH (200 ml) was added $NaNO_2$ (3.3 g, 48 mmol) in portions and the whole was stirred at room temperature for 4 hr. The AcOH was evaporated *in vacuo*, the residue was taken up in satd. aq. $NaHCO_3$, and the whole was washed with ether. The aq. layer was acidified with 10% aq. HCl, and then extracted with ether three times. The extracts were combined, washed with satd. aq. NaCl, dried over Na_2SO_4 and evaporated to a dark brown residue (10.7 g), which was taken up in 23% methanolic HCl (150 ml) and the whole was heated to reflux for 4 hr. Evaporation to dryness gave a residue, which was dissolved in AcOEt, and the whole was washed with satd. aq. NaCl. The dried (Na_2SO_4) AcOEt solution was evaporated to give a residue, which was chromatographed on silica gel with CH_2Cl_2–MeOH (97: 3) to (−)-**13** (5.43 g, 44%) as a pale yellow solid of mp 75—84°, $[\alpha]_D^{20.5}$ −8.2 (c=3.118, dioxane). Recrystallization from $CHCl_3$ afforded pale yellow needles of mp 124—127°, $[\alpha]_D^{20.5}$ −4.45° (c=3.506, dioxane). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH), 1740 ($COOCH_3$). NMR ($CDCl_3$) δ: 2.9 (2H, m, Ar–C$\underline{H}_2$), 3.76 (3H, s, COOC$\underline{H}_3$), 4.4 (1H, m, Ar–CH_2–C$\underline{H}$), 7.10 (2H, s, $C_6\underline{H}_2$). *Anal.* Calcd. for $C_{10}H_{10}Cl_2O_4$: C, 45.31; H, 3.80. Found: C, 45.21; H, 3.81.

(−)-β-(4-Acetoxy-3,5-dichlorophenyl)lactic Acid Methyl Ester ((−)-14)——To a solution of (−)-**13** (mp 75—84°, $[\alpha]_D^{20.5}$ −8.2° (dioxane)) (2.284 g, 8.6 mmol) in pyridine (30 ml) was added Ac_2O (970 mg, 9.5 mmol) dropwise, and the whole was allowed to stand at room temperature for 2 hr. After dilution with ether, the reaction mixture was washed successively with 10% aq. HCl, 5% aq. $NaHCO_3$, satd. aq. NaCl, and dried over Na_2SO_4. Evaporation of the solvent left a yellow solid, which was chromatographed on silica gel (200 g) with benzene–hexane (2: 1) to give (−)-**14** (2.3 g, 87%) of mp 84—87°, $[\alpha]_D^{20}$ −12.1° (c=2.532, dioxane). Recrystallization from ether–hexane afforded pale yellow needles of mp 93—94.5°, $[\alpha]_D^{20}$ −14.9° (c=2.540, dioxane). IR ν_{max}^{Nujol} cm^{-1}: 1770 (Ar–OAc), 1750 ($COOCH_3$). NMR ($CDCl_3$) δ: 2.35 (3H, s, C$\underline{H}_3$–CO), 2.9 (2H, m, Ar–C$\underline{H}_2$–), 3.75 (3H, s, COOC$\underline{H}_3$), 4.3 (1H, m, Ar–CH_2–C$\underline{H}$), 7.25 (2H, s, $C_6\underline{H}_2$). *Anal.* Calcd. for $C_{12}H_{12}Cl_2O_5$: C, 46.95; H, 3.94. Found: C, 46.92; H, 4.13.

(+)-β-(4-Acetoxy-3,5-dichlorophenyl)lactic Acid Methyl Ester O-o-Nitrobenzenesulfonate ((+)-15)——To an ice-cooled solution of (−)-**14** (mp 84—87°, $[\alpha]_D^{20}$ −12.1° (dioxane)) (1.23 g, 4 mmol) and triethylamine (24 ml) in AcOEt (40 ml) was added *o*-nitrobenzenesulfonyl chloride (2.65 g, 12 mmol) in portions. After stirring at 0° for 4 hr, the reaction mixture was evaporated *in vacuo*. The residue was mixed with water, acidified with 10% aq. HCl, and the whole was extracted with AcOEt. The combined extracts were washed with 5% aq. $NaHCO_3$, satd. aq. NaCl, dried over Na_2SO_4, and evaporated to dryness to give a solid. Recrystallization from benzene afforded (+)-**15** (1.2 g, 62%) as colorless platelets of mp 138.5—139°, $[\alpha]_D^{20}$ +32.8° (c=2.976, dioxane). NMR ($CDCl_3$) δ: 2.32 (3H, s, C$\underline{H}_3$–CO), 3.1 (2H, m, Ar-C$\underline{H}_2$), 3.75 (3H, s, COOC$\underline{H}_3$), 5.2 (1H, m, Ar–CH_2–C$\underline{H}$), 7.14 (2H, s, $C_6\underline{H}_2$), 7.5—8.0 (4H, m, $C_6\underline{H}_4$). *Anal.* Calcd. for $C_{18}H_{15}Cl_2NO_9S$: C, 43.92; H, 3.07; N, 2.85. Found: C, 43.89; H, 3.02; N, 3.00.

(+)-β-(3,5-Dichloro-4-hydroxyphenyl)lactic Acid Methyl Ester O-o-Nitrobenzenesulfonate ((+)-16)——A solution of (+)-**15** ($[\alpha]_D^{20}$ +32.8° (dioxane)) (982 mg) in 19% methanolic HCl (20 ml) and CH_2Cl_2 (20 ml) was allowed to stand at room temperature overnight. The solvent was evaporated to dryness, and the residue was dissolved in AcOEt. The AcOEt solution was washed successively with satd. aq. NaCl and dried over $MgSO_4$. Evaporation of the solvent left a residue, which was recrystallized from benzene to (+)-**16** (720 mg, 80%) as colorless needles of mp 164—164.5°, $[\alpha]_D^{20}$ +40.5° (c=2.816, dioxane). IR ν_{max}^{Nujol} cm^{-1}: 3460 (OH), 1762 ($COOCH_3$), 1540, 1360 (NO_2). NMR (d_6-acetone) δ: 3.1 (2H, m, Ar-C$\underline{H}_2$), 3.70 (3H, s, COOC$\underline{H}_3$), 5.26 (1H, m, Ar–CH_2–C$\underline{H}$), 7.12 (2H, s, $C_6\underline{H}_2$), 7.85 (4H, m, $C_6\underline{H}_4$). MS m/e: 449 (M^+ for ^{35}Cl). *Anal.* Calcd. for $C_{16}H_{13}Cl_2NO_8S$: C, 42.68; H, 2.91; N, 3.11. Found: C, 42.79; H, 2.96; N, 3.10.

(+)-β-(3,5-Dichloro-4-hydroxyphenyl)lactic Acid Methyl Ester ((+)-13)——A solution of (+)-**16** ($[\alpha]_D^{20}$ +37.7° (dioxane),prepared from (−)-**13** of $[\alpha]_D^{20.5}$ −8.2° (dioxane) using chromatography only for the purification method at each step) (900 mg, 2 mmol) and AcONa (164 mg, 2 mmol) in AcOH (35 ml) was refluxed for 35 hr. Evaporation of the AcOH left a residue, which was extracted with benzene. The benzene extracts were combined, washed with satd. aq. $NaHCO_3$, satd. aq. NaCl and dried over Na_2SO_4. Evaporation of the solvent left an oil, which was shown to be a mixture of monoacetates (having free phenolic group) and diacetates (having no free phenolic group). Column chromatography on silica gel with CH_2Cl_2–benzene (1: 1) afforded monoacetates fraction (314 mg), which was dissolved in 15% methanolic HCl and the whole was heated to reflux for 6 hr. Evaporation of the solvent left a residue, which was extracted with ether. The ethereal solution was washed with satd. aq. NaCl, dried over Na_2SO_4, and evaporated to give a residue. Preparative TLC on silica gel with CH_2Cl_2–ether (4: 1) afforded (+)-**13** (91 mg, 17%) as a solid of mp 92—100°, $[\alpha]_D^{19}$ +6.2° (c=1.166, dioxane), corresponding to be 76% inversion based on the specific rotation of (−)-**13** used, and (+)-**17** (43 mg, 8%) as a liquid of $[\alpha]_D^{19}$ +55.2° (c=0.862, dioxane), IR ν_{max}^{film} cm^{-1}: 3400 (OH), 1734 ($COOCH_3$), NMR ($CDCl_3$+D_2O) δ: 3.7—4.3 (3H, m, C$\underline{H}$–C$\underline{H}_2$OH), 3.72 (3H, s, COOC$\underline{H}_3$), 7.15 (2H, s, $C_6\underline{H}_2$), MS m/e: 264 (M^+ for ^{35}Cl), *Anal.* Calcd. for $C_{10}H_{10}Cl_2O_4$: C, 45.31; H, 3.80. Found: C, 45.06; H, 3.77.

(*S*)-(−)-α-Bromo-β-[4-(benzyloxycarbonyloxy)phenyl]propionic Acid ((*S*)-(−)-19)——Deaminative bromination of L-**18**[18] was performed as in the preparation of (*S*)-(−)-**5** described above. The reaction mixture was extracted with AcOEt, the extracts were combined, washed with water, satd. aq. NaCl, dried over $MgSO_4$, and then evaporated to dryness. The residual oil was chromatographed on silica gel with $CHCl_3$–AcOH (50: 1) to give (*S*)-(−)-**19** in 68% yield as a solid of mp 76—78°, $[\alpha]_D^{20}$ −6.7° (c=3.746, dioxane). Recrystallization from ether–hexane afforded colorless needles of mp 83°, $[\alpha]_D^{20}$ −9.7° (c=1.06, dioxane). NMR ($CDCl_3$) δ: 3.25 and 3.35 (total 2H, ABX-type octet, J_{AB}=15 Hz, J_{AX}=J_{BX}=7 Hz, Ar-C$\underline{H}_2$), 4.30 (1H, t, J_{AX}=J_{BX}= 7 Hz, Ar–CH_2–C$\underline{H}$), 5.20 (2H, s, C_6H_5–C$\underline{H}_2$–O), 7.0—7.5 (9H, m, $C_6\underline{H}_5$- and $C_6\underline{H}_4$–), 9.45 (1H, broad s, COO$\underline{H}$). *Anal.* Calcd. for $C_{17}H_{15}BrO_5$: C, 53.84; H, 3.99. Found: C, 53.80; H, 3.95.

(*S*)-(−)-α-Bromo-β-(4-hydroxyphenyl)propionic Acid ((*S*)-(−)-20)——A mixture of (*S*)-(−)-**19** ($[\alpha]_D^{20}$ −6.7° (dioxane)) (500 mg) and 10% Pd-C (200 mg) in AcOEt (25 ml) was stirred vigorously overnight in the atmosphere of H_2. The catalyst was filtered off, and the filtrate was evaporated to dryness to leave a solid, which was purified by preparative TLC to (*S*)-(−)-**20** (300 mg, 93%) as a solid of $[\alpha]_D^{20}$ −13.8° (c=2.244, dioxane). Recrystallization from $CHCl_3$ afforded colorless transparent leaflets of mp 113—115°, $[\alpha]_D^{20}$ −19.3° (c=2.002, dioxane). IR ν_{max}^{Nujol} cm^{-1}: 3200 (OH), 1700 (COOH). NMR (d_6-acetone) δ: 3.2 (2H, m, Ar-C$\underline{H}_2$), 4.4 (1H, m, Ar–CH_2–C$\underline{H}$), 6.70 and 7.15 (total 4H, AB-type q, J=10 Hz, $C_6\underline{H}_4$). MS m/e: 246, 244 (M^+). *Anal.* Calcd. for $C_9H_9BrO_3$: C, 44.11; H, 3.70. Found: C, 43.99; H, 3.60.

L-Tyrosine Methyl Ester (L-(+)-22)——Amination of (*S*)-(−)-**20** ($[\alpha]_D^{20}$ −19.3° (dioxane), corresponding to be 93% optically pure) was performed as in the preparation of L-**4** from (*S*)-(−)-**5** described above, and the product was isolated as methyl ester (L-(+)-**22**) in 48% yield as a solid of mp 112—120°, $[\alpha]_D^{20}$ +11.8° (c= 1.016, CH_3OH) (reported[19b] value for optically pure L-(+)-**22**: mp 135—136°, $[\alpha]_D^{20}$ +25.75° (CH_3OH)). This sample showed identical spectral data with those of the sample prepared by the reported method.[19] *Anal.* Calcd. for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.41; H, 6.70; N, 7.26.

18) B.G. Overell and V. Petrow, *J. Chem. Soc.*, **1955**, 232.

19) *a*) S. Drabarek and V. du Vigneaud, *J. Am. Chem. Soc.*, **87**, 3974 (1965); *b*) E. Fischer, *Ber.*, **41**, 850 (1908).