[Chem. Pharm. Bull.
32(6)2126—2139(1984)]

Syntheses of Substituted L- and D-Tryptophans

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(Received September 2, 1983)

Several 5-substituted N_b-methoxycarbonyl-L- and -D-tryptophan derivatives were synthesized from proline by a new route involving electrochemical oxidation, as well as by the known procedures. Removal of the N_b-methoxycarbonyl group was accomplished by treatment with Me_3SiI in refluxing chloroform, then alkaline hydrolysis of the methyl esters afforded 5-substituted L- and D-tryptophans with high optical purities.

Keywords——L-tryptophan 5-substituted; D-tryptophan 5-substituted; anodic oxidation; *N*-methoxycarbonyl group deprotection; Fischer indole synthesis; iodotrimethylsilane

5-Substituted L- and D-tryptophans are of potential interest from a medical viewpoint, based on the important roles of tryptophan in the living body and as a biosynthetic precursor of indole alkaloids. There are two conventional methods to synthesize optically active tryptophan derivatives; one is to synthesize the racemic compounds and subsequently resolve them into each enantiomer, and the other is to transform an easily available optically active amino acid into tryptophan derivatives with retention of the pre-existing chirality.[1] We have achieved the synthesis of L- and D-tryptophan derivatives by the latter method, that is to say, through a new route starting from proline by utilization of electrochemical oxidation,[2] and the known procedures reported by Yamada *et al.*[3] and by Hino *et al.*[4] We also examined the deblocking reaction of optically active N_b-methoxycarbonyl tryptophans with Me_3SiI.

Syntheses of N_b-Protected L- and D-Tryptophan Derivatives

It is well known that anodic oxidation of lactams and *N*-acyl or *N*-alkoxycarbonyl cyclic

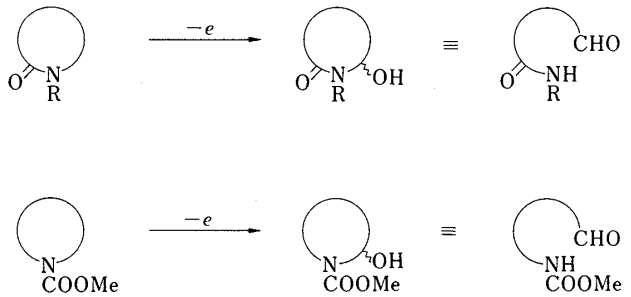
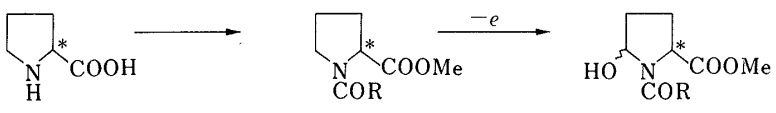


Chart 1



1

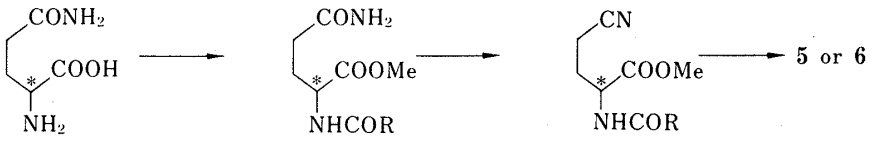
2 : R=Me
3 : R=OMe
4 : R=OCH_2Ph

5 : R=Me
6 : R=OMe
7 : R=OCH_2Ph

Chart 2

amines in aqueous acetonitrile gives hydroxy derivatives which are ring tautomers of aldehydes and possess reactivity similar to that of an aldehyde group[5,6] (Chart 1).

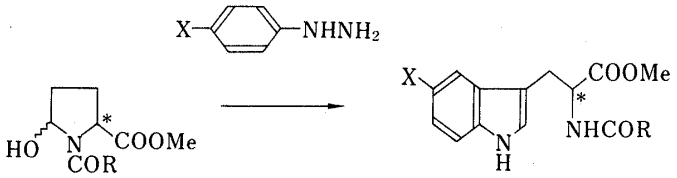
In order to obtain hydroxyproline derivatives as aldehyde equivalents, we attempted the anodic oxidation of L-proline derivatives. *N*-Acetyl and *N*-methoxycarbonyl-L-proline methyl esters (**2** and **3**) were electrolyzed in aqueous acetonitrile using Pt electrodes at constant current to furnish the desired hydroxy derivatives (**5** and **6**, respectively) in good yields. With the *N*-benzyloxycarbonyl derivative (**4**), however, anodic oxidation under the above conditions gave the hydroxy derivative (**7**) only in poor yield, and most of the starting material was recovered unchanged.[7]



8 9 : R=Me 10 : R=OMe 11 : R=Me 12 : R=OMe

Chart 3

The hydroxyprolines (**5**, **6** and **7**) thus obtained are equilibrium mixtures of 5-α- and 5-β-hydroxy isomers and are identical with the corresponding mixtures derived from *N*-acetyl or *N*-methoxycarbonyl glutamine methyl ester (**9** or **10**) according to Yamada's method (Chart 3).[3]



5–7 13–15

Chart 4

By using the 5-hydroxyprolines (**5**—**7**) as aldehyde equivalents, the Fischer indole synthesis with substituted phenylhydrazines was performed to give N_b-protected L-tryptophans (**13**—**15**). The results are summarized in Table I.

However, the above method used for the L-series is not practical for the preparation of the D-series of compounds, since D-proline is expensive and not available in quantity in our laboratory. Thus, substituted D-tryptophans were mainly synthesized from D-tryptophan by Hino's method, which consists of formation of a cyclic tautomer (**19**) and introduction of a substituent at the 5-position, followed by ring opening to yield 5-substituted D-tryptophans (D-**14b**, **c**, **f**, **i** and **j**) as illustrated in Chart 5. The 5-benzyloxy-D-tryptophan derivative (D-**14g**) was prepared by Fischer indole synthesis from the hydroxyproline (D-**6**) derived from D-glutamine according to Chart 3.

Deblocking of N_b-Methoxycarbonyl L- and D-Tryptophan Derivatives by Use of Me_3SiI

For the preparation of optically active tryptophans, it is important to select an adequate protecting group for the amino group of the starting amino acids; the group must be stable during the reactions involved in the proposed synthetic scheme and also be readily removable without racemization. Of three possible *N*-protecting groups (acetyl, methoxycarbonyl, and

TABLE I. Fischer Indole Syntheses of L-Hydroxyproline Derivatives (**5**, **6**, **7**) with Substituted Phenylhydrazines

No.	L-Hydroxy-proline	Substituted phenylhydrazine	Reaction conditions[a,c]	Yield of L-tryptophan deriv. (%)[b]		
1	**5**	*p*-Methoxy	A	**13f**	5-Methoxy	60
2	**5**	*p*-Benzyloxy	A	**13g**	5-Benzyloxy	79
3	**5**	*p*-Nitro	B[d]	**13i**	5-Nitro	29
4	**6**	*p*-Chloro	C	**14b**	5-Chloro	36
5	**6**	*p*-Bromo	C	**14c**	5-Bromo	28
6	**6**	*p*-Methyl	C	**14d**	5-Methyl	41
7	**6**	*p*-Methoxy	A	**14f**	5-Methoxy	50
8	**6**	*p*-Benzyloxy	A	**14g**	5-Benzyloxy	66
9	**6**[e]	*p*-Benzyloxy	A	**14g**[e]	5-Benzyloxy	61
10	**6**	*p*-Methylthio	C	**14h**	5-Methylthio	51
11	**7**	*p*-Methyl	D	**15**	5-Methyl	55

a) The reaction conditions are not necessarily optimum.
b) Isolated yield.
c) A, AcOH–H_2O at 80—90 °C; B, PPA–xylene–dioxane at 80—110 °C; C, 1 N HCl–H_2O at 80—90 °C; D, 1 N HCl–H_2O–dioxane at 80—90 °C.
d) The *p*-nitrophenylhydrazone of **5** was isolated as crystals, which were used in this reaction.
e) D-Isomer.

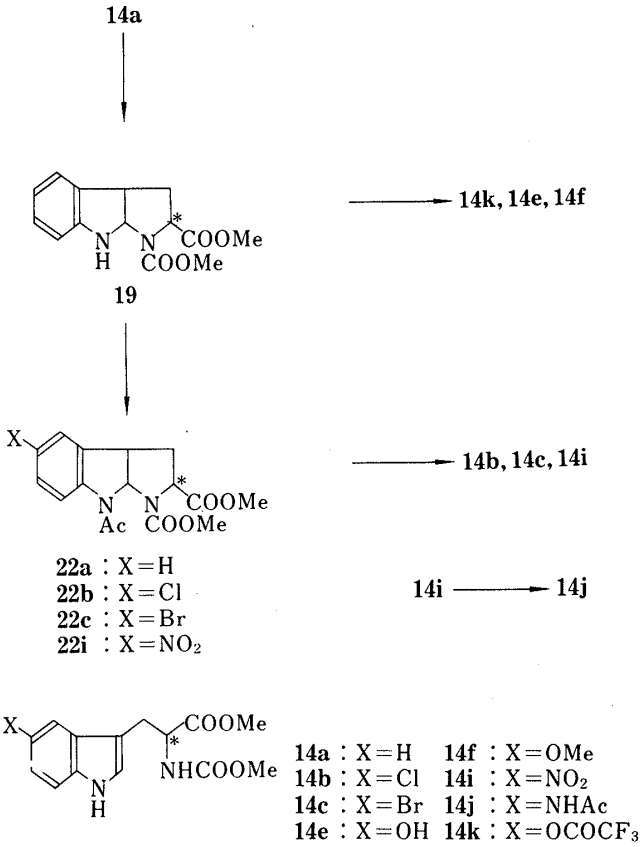


Chart 5

benzyloxycarbonyl), the methoxycarbonyl group seems to be the most suitable for our present purpose because of its stability and high yield in most of the reactions used in the preceding section. Although the benzyloxycarbonyl group is commonly used in peptide synthesis, the yield in anodic oxidation to the hydroxyproline (**7**) was unsatisfactory in our synthesis, and

Hino *et al.* also reported that, compared with the methoxycarbonyl group, the benzyloxycarbonyl group was unfavorable for their synthesis of tryptophan derivatives *via* a cyclic tautomer.[4] With N_b-acetyl derivatives, it is often easy to remove the *N*-acetyl group of L-derivatives by treatment with acylase, but this enzymatic method is not applicable to the deacylation of D-derivatives, and a chemical method may not give a good result with optically active amino acids. In fact, acid hydrolysis of **16e** and **16f** provided the corresponding tryptophans (L-**18e**, L-**18f**), but in poor yields in our experiments.

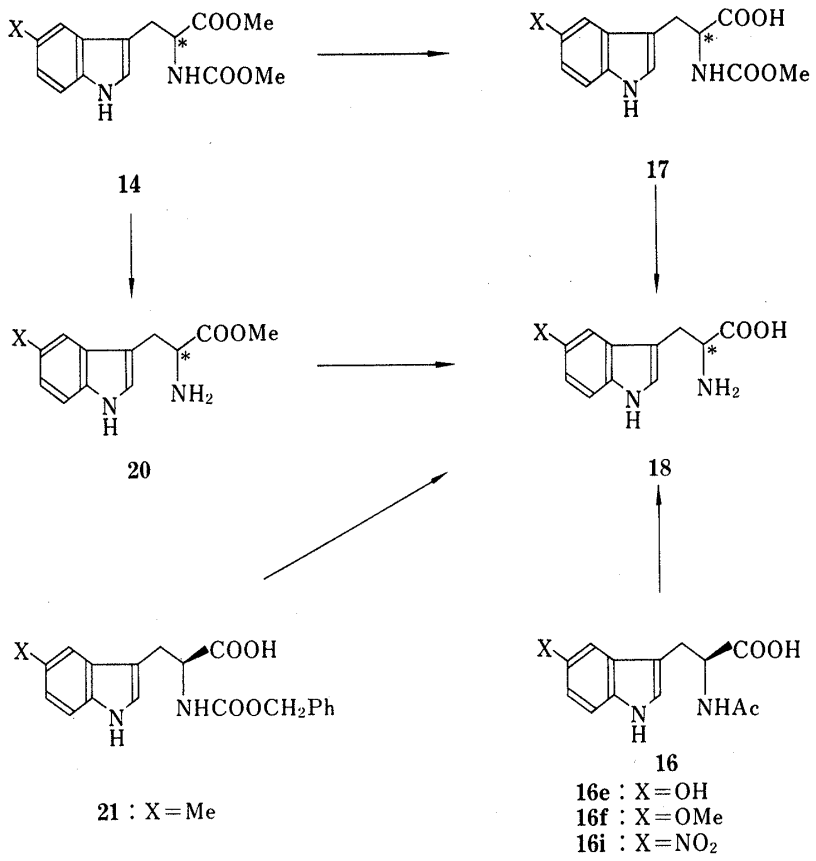


Chart 6

Then, with the N_b-methoxycarbonyl L- and D-tryptophan derivatives in hand, we investigated the removal of the *N*-protective group. It is well known that Me_3SiI is a good reagent for the removal of the *N*-methoxycarbonyl group under neutral and mild conditions,[8,9] but as far as we know, there is no report on the deblocking of optically active *N*-methoxycarbonyl amino acids with this reagent. We examined the two routes illustrated in Chart 6: alkaline hydrolysis of the methyl ester followed by deblocking of the N_b-methoxycarbonyl group (route A), and deblocking of the *N*-protective group followed by hydrolysis of the ester (route B). The experimental results are summarized in Tables II and III.

In route A, alkaline hydrolysis of the esters (**14**) was carried out at room temperature to give N_b-methoxycarbonyl tryptophans (**17**) in good yields, and heating of the latter compounds (**17**) in refluxing chloroform with 2.0—3.3 mol eq of Me_3SiI gave the corresponding tryptophans (**18**) in moderate yields as shown in Table II. A 1- or 2-fold molar excess of Me_3SiI was used, since the carboxylic and the phenolic hydroxyl groups also consume the reagent.

In route B, we used a slight excess of Me_3SiI for the deblocking of N_b-methoxycarbonyl tryptophan methyl esters (**14**) under conditions similar to those used with carboxylic acids

TABLE II. Deblocking of N_b-Protected Tryptophan Derivatives (Route A)

No.	Starting material	X	N_b-Protected tryptophans (yield, %)		$[\alpha]_D$ (MeOH)	Deblocking reagent	**18** (yield, %)		$[\alpha]_D^{20}$
1	L-**14a**	H	L-**17a**	90	+1.3	Me_3SiI (2.2 eq)	L-**18a**	63 (43)[a]	−32.6 (H_2O)
2	D-**14a**	H	D-**17a**	83	−1.2	Me_3SiI (2.2 eq)	D-**18a**	56	+31.0 (H_2O)
3	L-**13f**	OCH_3	L-**16f**	91	+16.0	Acylase	L-**18f**	76	−29.1 (H_2O)
4	L-**14f**	OCH_3	L-**17f**	79	−4.5	Me_3SiI (2.0 eq)	L-**18f**	48	−29.0 (H_2O)
5	L-**14g**	OCH_2Ph	L-**17g**	92	−7.9	Me_3SiI (3.0 eq)	L-**18e**	45[b]	−32.5 (H_2O)
6	D-**14g**	OCH_2Ph	D-**17g**	82	+7.0	Me_3SiI (3.3 eq)	D-**18e**	54[b]	+32.4 (H_2O)
7	L-**13i**	NO_2	L-**16i**	67	+23.4	Acylase	L-**18i**	77	+48.6 (1 N HCl)
8	L-**14i**	NO_2	L-**17i**	91	+1.5	Me_3SiI (2.3 eq)	L-**18i**	52	+52.1 (1 N HCl)
9	L-**14j**	NHAc	L-**17j**	98	−24.6	Me_3SiI (2.2 eq)	L-**18j**	57	+20.6 (1 N HCl)
10	L-**15**	CH_3	L-**21**	85	−20.8	H_2, Pd/C	L-**18d**	60	+10.6 (1 N HCl)

a) The figure given in parentheses is the deblocking yield with Me_3SiCl–NaI–acetonitrile.
b) Deblocking was conducted with **17e** after removal of the benzyl group of **17g** by catalytic hydrogenolysis using 10% Pd on carbon.

TABLE III. Deblocking of N_b-Methoxycarbonyl Tryptophan Derivatives (**14**) by Use of Me_3SiI (Route B)

No.	Starting material	X	**20** (yield, %)	$[\alpha]_D^{20}$ (MeOH)	**18** (yield, %)	$[\alpha]_D^{20}$
1	L-**14a**	H	88[a] (51)[b]	+37.0	83	−32.5 (H_2O)
2	D-**14a**	H	84	−38.0	72	+32.0 (H_2O)
3	L-**14b**	Cl	87	+51.2	56	+21.8 (1 N HCl)
4	D-**14b**	Cl	90	−51.6	50	−21.0 (1 N HCl)
5	L-**14c**	Br	78	+48.6	70	+23.4 (1 N HCl)
6	D-**14c**	Br	80	−49.2	53	−22.5 (1 N HCl)
7	L-**14d**	CH_3	93	+17.2	84	+11.2 (1 N HCl)
8	L-**14f**	OCH_3	79	+31.2	83	−28.9 (H_2O)
9	D-**14f**	OCH_3	58	−30.8	96	+28.8 (H_2O)
10	L-**14h**	SCH_3	71	+46.6	42	+30.0 (1 N HCl)
11	L-**14i**	NO_2	72	+78.8	64	+48.4 (1 N HCl)
12	D-**14i**	NO_2	79	−78.8	86	−49.0 (1 N HCl)
13	L-**14j**	NHAc	82	+47.2	80	+18.6 (1 N HCl)
14	D-**14j**	NHAc	72	−47.7	82	−19.0 (1 N HCl)

a) Me_3SiI (1.1—1.2 mol eq) was used in all the reactions.
b) The figure given in parentheses is the deblocking yield with Me_3SiCl–NaI–acetonitrile.

(**17**) in route A. The methyl group of the N_b-methoxycarbonyl group was selectively cleaved to give tryptophan methyl esters (**20**) in good yields. When too much of the reagent was used, the methyl group of the ester was also partially cleaved to give a mixture of **20** and **18**. Hydrolysis of **20** gave **18** without any difficulty.

Specific rotation values of the compounds (**18**) obtained by routes A and B were in good agreement with each other, and those of the 5-methoxy and 5-nitro derivatives (**18f**, **18i**) coincided with those of authentic samples derived from N_b-acetyl-L-tryptophans (**16f**, **16i**) by the enzymatic method. Although there is no great difference in total yields and optical purities of the final compounds (**18**), route B is preferable for the preparation of a large amount of **18** as regards economy of Me_3SiI and ease of work-up. The cleavage reaction using Me_3SiCl and NaI in place of Me_3SiI was also tried, but the reaction was generally slow and the yield was lower than those obtained with Me_3SiI.

Thus, the syntheses of substituted L- and D-tryptophans from L-proline, L- and D-glutamines, and D-tryptophan were accomplished through deprotection of the *N*-methoxycarbonyl group by use of Me_3SiI. These routes appear to provide practical methods for the preparation of optically active substituted tryptophans.

Experimental

Melting points were determined on a Yanaco MP-J2 hot stage microscope and with a Yamato MP-21 melting point apparatus. All melting points and boiling points are uncorrected. Infrared (IR) spectra were obtained using a Hitachi 260-10 or a FX-6200 FT-IR spectrophotometer (ANALECT Instruments). Nuclear magnetic resonance (^{1}H-NMR) spectra were determined with a JEOL JNM-PMX 60 spectrometer. Mass spectra (MS) were recorded on a Hitachi RMU-6M mass spectrometer. Ultraviolet (UV) spectra were taken on a Hitachi UV 323 recording spectrophotometer. Microanalyses (C, H, N) were determined with a Perkin-Elmer 240B elemental analyzer. Optical rotations were recorded with an automatic digital polarimeter PM-201 (Union Giken). Anodic oxidations were carried out with a Yanaco VE-8 controlled potential electrolyzer. Iodotrimethylsilane (Me_3SiI) utilized for deblocking of the *N*-methoxycarbonyl group was prepared by the procedures reported in Organic Synthesis **59**, 35—41 (1979). Thin layer chromatography was performed on 0.25 mm Merck precoated silica gel plates (60F-254). Column chromatography and flash chromatography were performed on silica gel 170—230 and 230—400 mesh (ASTM) obtained from Merck, respectively.

***N*-Acetyl-L-proline Methyl Ester (2)**——A mixture of L-proline (57.5 g, 0.5 mol), pyridine (13 ml), and H_2O (500 ml) was treated dropwise with Ac_2O (60 g, 0.6 mol) for 30 min under cooling with ice-water to 5—10 °C. The solution was stirred for a further 48 h at room temperature, then 100 ml of MeOH was added and the whole mixture was stirred for 20 min and evaporated *in vacuo* to leave a residue, which was purified by column chromatography on silica gel (500 g) eluted with $CHCl_3$–MeOH (10 : 1) to yield 45 g of *N*-acetyl-L-proline. Subsequent esterification of the *N*-acetyl derivative (38 g) was performed in MeOH (300 ml) containing a small amount of SO_2Cl_2 (1.5 g). The MeOH solution was stirred for 72 h at room temperature. The solvent was removed *in vacuo* to leave a crude product, which was chromatographed on silica gel with AcOEt–MeOH (10 : 1) as the eluent to provide 33 g (46%) of pure **2**: bp 100—104 °C (0.2 mmHg); $[\alpha]_D^{20}$ −105.9° (c = 1.6, MeOH); IR ν_{max}^{film} cm^{-1}: 2980, 2900, 1750, 1650. ^{1}H-NMR ($CDCl_3$) δ 1.7—2.4 (4H, m, CH_2CH_2), 2.18 (3H, s, $NHCOCH_3$), 3.4—3.8 (2H, m, NCH_2), 3.71, 3.76 (6H, d, $COOCH_3 \times 2$), 4.3—4.6 (1H, m, CH); MS m/z: 171 (M^+), 112 (100%), 70.

***N*-Methoxycarbonyl-L-proline Methyl Ester (3)**——Methyl chloroformate (47.3 g, 0.5 mol) and a solution of NaOH (20 g) in H_2O (100 ml) was added dropwise simultaneously to a mixture of L-proline (57.5 g, 0.5 mol), NaOH (20 g, 0.5 mol) and H_2O (200 ml) at 3—5 °C. After being stirred for 1 h, the solution was neutralized with conc. HCl (42.3 ml) and the mixture was concentrated *in vacuo* to leave a residue which was extracted with AcOEt–EtOH. Insoluble materials were removed by filtration, and the filtrate was dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to provide *N*-methoxycarbonyl proline as an oil. This oil was dissolved in MeOH (500 ml) containing 1.35 g (10 mmol) of SO_2Cl_2 and the mixture was stirred for 48 h at room temperature. After removal of the solvent, the residue was purified by column chromatography on silica gel (500 g) eluted with AcOEt–EtOH (10 : 1) to provide 80 g (83%) of pure **3**: bp 87 °C (0.3 mmHg); $[\alpha]_D^{20}$ −78.6° (c = 1.3, MeOH); IR ν_{max}^{film} cm^{-1}: 1740, 1700. ^{1}H-NMR ($CDCl_3$) δ 1.7—2.4 (4H, m, CH_2CH_2), 3.3—3.7 (2H, m, NCH_2), 3.68 (3H, s, $COOCH_3$), 3.72 (3H, s, $COOCH_3$), 4.2—4.5 (1H, m, CH); MS m/z: 187 (M^+), 128 (100%).

***N*-Benzyloxycarbonyl-L-proline Methyl Ester (4)**——Benzyl chloroformate (85.5 g, 0.5 mol) and a solution of NaOH (20 g) in H_2O (100 ml) were added dropwise simultaneously to a mixture of L-proline (57.7 g, 0.5 mol), NaOH (20 g, 0.5 mol) and H_2O (200 ml) at 3—5 °C. After being stirred for 1 h, the solution was neutralized with conc. HCl (42.3 ml). An oil separated and was extracted with AcOEt. Evaporation of the solvent gave *N*-benzyloxycarbonyl proline, which was subsequently methylated in MeOH (400 ml) containing 1.5 g of SO_2Cl_2. Work-up as described for the preparation of **3** furnished 99 g of **4**, which was purified by vacuum distillation to provide 81 g (60%) of pure **4**: bp 140—142 °C (0.15 mmHg); $[\alpha]_D^{20}$ −58.1° (c = 1.8, MeOH); IR ν_{max}^{film} cm^{-1}: 1750, 1710. ^{1}H-NMR ($CDCl_3$) δ 1.4—2.4 (4H, m, CH_2CH_2), 3.3—3.8 (5H, m), 4.1—4.5 (1H, m, CH), 5.14 (2H, s, $PhCH_2$), 7.32 (5H, s); MS m/z: 263 (M^+), 204, 160, 91 (100%).

Anodic Oxidation of 2——Compound **2** (6.85 g, 40 mmol), MeCN (67.5 ml), H_2O (7.5 ml) and Et_4NClO_4 (1.65 g, 7.5 mmol) as supporting electrolyte were added to a reaction vessel (undivided cell) equipped with Pt electrodes (3×10 cm^2 Pt wire gauze as the anode and Pt wire spiral as the cathode), and the whole mixture was made homogeneous by stirring with a magnetic stirrer. Anodic oxidation was carried out at room temperature with a constant current of 600 mA until 2.5 F/mol of electricity had passed through the solution. After removal of the solvent, the residue was dissolved in benzene, and insoluble materials were removed by filtration. The filtrate was concentrated *in vacuo* to yield a crude product, which was purified by column chromatography on silica gel (120 g) eluted with AcOEt–EtOH (20 : 1), providing 6.4 g (86%) of **5** as a mixture of 5-hydroxy epimers: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 3150, 1760, 1660. ^{1}H-NMR ($CDCl_3$) δ 1.98, 2.23 (3H, d, $NHCOCH_3$), 1.6—2.6 (4H, m, CH_2CH_2), 3.70, 3.77 (3H, d,

$COOCH_3$), 4.0—4.3 (1H, br, OH), 4.3—4.7 (1H, m, CH), 5.5, 5.8 (1H, br d, CHOH); MS *m/z*: 187 (M^+), 169, 144, 128, 86 (100%). These stereoisomers were separated into each 5-hydroxy epimer (**5a**, **5b**) by flash chromatography on silica gel eluted with hexane–AcOEt–MeOH (10 : 10 : 1).

5a: mp 101—104 °C (recrystallization from 2-PrOH–isoPr$_2$O); $[\alpha]_D^{18}$ −131.0° (*c*=1.1, H_2O) [lit.[1b] mp 99.0—102.0 °C; $[\alpha]_D^{20}$ −128.5° (H_2O)]; IR ν_{max}^{Nujol} cm^{-1}: 3400, 1740, 1625. ^{1}H-NMR (DMSO-d_6) δ 1.6—2.6 (4H, m, CH_2CH_2), 2.08 (3H, s, $NHCOCH_3$), 3.58 (3H, s, $COOCH_3$), 4.29 (1H, d, *J*=10 Hz, CH), 5.3—5.9 (1H, m, CHOH), 5.92 (1H, d, *J*=8 Hz, OH); MS *m/z*: 187 (M^+), 170, 169, 144, 128 (100%), 101, 86. *Anal.* Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48. Found: C, 51.37; H, 7.04; N, 7.41.

5b: mp 100—103 °C (recrystallization from 2-PrOH–isoPr$_2$O); $[\alpha]_D^{20}$ −91.0° (*c*=1.0, H_2O); IR ν_{max}^{Nujol} cm^{-1}: 3250, 1730, 1620. ^{1}H-NMR (DMSO-d_6) δ 1.7—2.4 (4H, m, CH_2CH_2), 2.06 (3H, s, $NHCOCH_3$), 3.58 (3H, s, $COOCH_3$), 4.0—4.3 (1H, m, CH), 5.3—5.5 (1H, m, CHOH), 5.87 (1H, d, *J*=6 Hz, OH); MS *m/z*: 187 (M^+), 170, 169, 144, 128 (100%), 101, 86. *Anal.* Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48. Found: C, 51.31; H, 7.09; N, 7.69.

Anodic Oxidation of 3——A homogeneous solution of **3** (7.5 g, 40 mmol) and Et_4NClO_4 (1.65 g, 7.5 mmol) in MeCN (67.5 ml) containing 7.5 ml of H_2O was electrolyzed at room temperature with a constant current of 600 mA. The reaction was completed after 2.6 F/mol of electricity had passed through the solution. After recovery of the electrolyte, purification of the crude product by flash chromatography on silica gel (150 g) eluted with AcOEt–hexane (3 : 2) afforded 6.95 g (86%) of **6** as a colorless oil: $[\alpha]_D^{20}$ −71.5° (*c*=1.2, MeOH); IR ν_{max}^{film} cm^{-1}: 3420, 2950, 1700. ^{1}H-NMR ($CDCl_3$) δ 1.6—2.9 (4H, m, CH_2CH_2), 3.4 (1H, br, OH), 3.6—3.9 (6H, m, $COOCH_3 \times 2$), 4.1—4.6 (1H, m, CH), 5.65 (1H, br s, $NHCOOCH_3$); MS *m/z*: 203 (M^+), 186, 144 (100%), 102.

Anodic Oxidation of 4——A homogeneous solution of **4** (10.5 g, 40 mmol) and Et_4NClO_4 (1.65 g, 7.5 mmol) in MeCN (67.5 ml) containing 7.5 ml of H_2O was electrolyzed at room temperature with a constant current of 600 mA until 4 F/mol of electricity had passed through the solution. After recovery of the electrolyte, separation of the crude product by flash chromatography on silica gel (100 g) eluted with AcOEt–hexane (2 : 3) afforded 2.82 g (25%) of **7** and 4.6 g (43.8%) of unreacted starting material: **7**: $[\alpha]_D^{20}$ −48.7° (*c*=1.7, MeOH); IR ν_{max}^{film} cm^{-1}: 3450, 2950, 1740, 1710. ^{1}H-NMR ($CDCl_3$) δ 1.6—2.6 (4H, m, CH_2CH_2), 3.10 (1H, br, OH), 3.62, 3.75 (3H, d, $COOCH_3$), 4.1—4.6 (1H, m, CH), 7.33 (5H, s, aromatic H), 5.14 (2H, br s, $PhCH_2$), 5.60 (1H, br s, CHOH); MS *m/z*: 279 (M^+), 277, 261, 220, 176, 158, 91.

***N*-Methoxycarbonyl-L- and -D-glutamine Methyl Esters (L- and D-10)**——Methyl chloroformate (13 g, 0.138 mol) and a solution of NaOH (5.5 g) in H_2O (30 ml) were added simultaneously to a mixture of L-glutamine (20 g, 0.137 mol), NaOH (5.5 g, 0.137 mol) and H_2O (40 ml) under cooling with ice-water to 5 °C. Stirring was continued for 2 h, then the solution was neutralized with conc. HCl (14 g) and evaporated *in vacuo*. The residue was extracted with EtOH and insoluble materials were removed by filtration. Drying of the filtrate over anhydrous Na_2SO_4 and evaporation provided 29.7 g of *N*-methoxycarbonyl-L-glutamine as a highly viscous oil. This oil, without purification, was dissolved in MeOH (200 ml) containing 500 mg (3.7 mmol) of SO_2Cl_2 and the mixture was stirred for 69 h at room temperature. After removal of the solvent, the residue was purified by silica gel column chromatography (SiO_2, 150 g) eluted with $CHCl_3$–MeOH (10 : 1) to furnish 25.8 g (86%) of L-**10** as crystals. Recrystallization from AcOEt gave pure L-**10** as colorless crystals: mp 88—90 °C; $[\alpha]_D^{20}$ −24.5° (*c*=1.4, MeOH); IR ν_{max}^{film} cm^{-1}: 3300, 2950, 1730, 1700, 1660. ^{1}H-NMR ($CDCl_3$) δ 1.9—2.6 (4H, m, CH_2CH_2), 3.69 (3H, s, $COOCH_3$), 3.75 (3H, s, $COOCH_3$), 4.1—4.6 (1H, m, CH), 5.7—6.4 (3H, br, $CONH_2$, $NHCOOCH_3$); MS *m/z*: 218 (M^+), 200, 169, 159 (100%), 142, 114.

D-**10**: 41% yield from D-glutamic acid; mp 93—94 °C (recrystallization from AcOEt); $[\alpha]_D^{20}$ +24.2° (*c*=1.2, MeOH).

***N*-Methoxycarbonyl-4-cyano-L- and -D-2-aminobutyric Acid Methyl Esters (L-12 and D-12)**——*p*-Toluenesulfonyl chloride (21.1 g, 0.11 mol) was added portionwise to a solution of L-**10** (24.2 g, 0.11 mol) in pyridine (150 ml) and the mixture was stirred for 4 h at room temperature. After removal of the solvent, the residue was dissolved in AcOEt and stirred at 0—10 °C to generate a precipitate of the *p*-toluenesulfonium salt of pyridine, which was removed by filtration. The filtrate was concentrated *in vacuo* to provide the crude product, which was purified by silica gel column chromatography (SiO_2, 150 g) eluted with hexane–AcOEt (5 : 4) to furnish 19.5 g (88%) of L-**12** as a colorless oil: bp 145—150 °C (0.15 mmHg); $[\alpha]_D^{20}$ −36.7° (*c*=1.1, MeOH); IR ν_{max}^{film} cm^{-1}: 3350, 2950, 2250, 1720. ^{1}H-NMR ($CDCl_3$) δ 1.8—2.9 (4H, m, CH_2CH_2), 3.69 (3H, s, $COOCH_3$), 3.78 (3H, s, $COOCH_3$), 4.0—4.7 (1H, m, CH), 5.80 (1H, br d, *J*=8 Hz, $NHCOOCH_3$); MS *m/z*: 201 (M^+), 141 (100%), 109.

D-**12**: 92% yield from D-**10**, $[\alpha]_D^{20}$ +37.2° (*c*=1.3, MeOH).

***N*-Methoxycarbonyl-5-hydroxy-L- and -D-proline Methyl Esters (L- and D-6)**——Raney nickel, the catalytic activity of which had been reduced by addition of $Pb(OAc)_2$ $3H_2O$ (120 mg), was added to a solution of L-**12** (20 g, 0.1 mol) in H_2O (200 ml) containing 18 g of AcOH. The mixture was stirred vigorously under a hydrogen atmosphere at room temperature till 2250 ml of hydrogen had been absorbed. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* at low temperature. The residue was dissolved in $CHCl_3$ and dried over anhydrous Na_2SO_4. Evaporation *in vacuo* gave a crude product which was purified by column chromatography on silica gel (300 g) eluted with $CHCl_3$–MeOH (10 : 1) to furnish 14 g (70%) of L-**6** as a colorless viscous oil: $[\alpha]_D^{20}$ −73.1° (*c*=1.1, MeOH).

D-**6**: 69% yield from D-**12**: $[\alpha]_D^{20}$ +72.4° (*c*=1.9, MeOH).

5-Benzyloxy-N_b-acetyl-L-tryptophan Methyl Ester (L-13g)——A mixture of L-**5** (10 g, 53 mmol), *p*-benzyloxyphenylhydrazine HCl (13.3 g, 53 mmol), AcOH (200 ml) and H_2O (180 ml) was stirred at 80—90 °C under an argon atmosphere for 2 h. After removal of the solvent, the residue was dissolved in AcOEt and washed with water and then with saturated brine. Drying of the solution over anhydrous Na_2SO_4 and evaporation provided 22 g of a crude product, which was chromatographed on silica gel (150 g) eluted with AcOEt–hexane (4 : 1) to furnish 15.4 g (79%) of L-**13g** as a colorless solid. Recrystallization from hexane–CH_2Cl_2 provided pure L-**13g**: mp 95—96 °C; $[\alpha]_D^{20}$ −1.26° (c=1.1, MeOH); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3360, 3230, 1730, 1650. ^{1}H-NMR ($CDCl_3$) δ 1.90 (3H, s, $NHCOCH_3$), 3.25 (2H, d, J=6 Hz, CH_2), 3.65 (3H, s, $COOCH_3$), 4.7—5.2 (1H, m, CH), 5.08 (2H, s, $PhCH_2$), 6.05 (1H, br d, J=8 Hz, $NHCOCH_3$), 6.7—7.7 (9H, m, aromatic H), 8.25 (1H, br s, NH); MS m/z: 366 (M^+), 307, 236 (100%), 173, 145, 91.

5-Methoxy-N_b-acetyl-L-tryptophan Methyl Ester (L-13f)——This compound was prepared from **5** and *p*-methoxyphenylhydrazine in 60% yield by a procedure similar to that described for the preparation of **13g**: mp 112—113 °C (recrystallization from 2-PrOH); $[\alpha]_D^{20}$ +4.8° (c=1.0, MeOH); IR ν_{max}^{Nujol} cm^{-1}: 3400, 3310, 1730, 1650. ^{1}H-NMR ($CDCl_3$) δ 1.93 (3H, s, $NHCOCH_3$), 3.25 (2H, d, J=6 Hz, CH_2), 3.67 (3H, s, $COOCH_3$), 3.82 (3H, s, OCH_3), 4.7—5.1 (1H, m, CH), 6.10 (1H, br d, J=8 Hz, $NHCOCH_3$), 6.6—7.3 (4H, m, aromatic H), 8.35 (1H, br s, NH); MS m/z: 290 (M^+), 231 (100%), 160, 145, 117.

5-Nitro-N_b-acetyl-L-tryptophan Methyl Ester (L-13i)——A mixture of L-**5** (4 g, 21.4 mmol), *p*-nitrophenylhydrazine (3.3 g, 21.6 mmol) and EtOH (200 ml) was heated at reflux for 2.5 h. After removal of the solvent, the residue was dissolved in AcOEt. The solution was kept standing for several hours, and the precipitated yellow crystals were collected by filtration and dried in a vacuum desiccator to afford 5.06 g (70.5%) of the hydrazone: mp 168—172 °C, MS m/z: 322 (M^+). A mixture of PPA (polyphosphoric acid) (20 g) and xylene (100 ml) was heated at 80 °C. To this was added dropwise a solution of the hydrazone (4.4 g, 13.6 mmol) in dioxane (30 ml) and xylene (50 ml), and the mixture was stirred at 110 °C for 1.5 h. After removal of the solvent, the residue was poured into water and extracted with AcOEt. The extract was washed with saturated $NaHCO_3$ and then saturated brine. Evaporation of the solvent gave 3.67 g of the crude product which was purified by silica gel column chromatography eluted with AcOEt to furnish 1.23 g (29.5%) of L-**13i**: mp 214—217 °C (recrystallization from MeOH); $[\alpha]_D^{20}$ +15.3° (c=0.56, MeOH); IR ν_{max}^{Nujol} cm^{-1}: 3400, 3270, 1730, 1660. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ 3.35 (2H, d, J=6 Hz, CH_2), 1.95 (3H, s, $NHCOCH_3$), 3.70 (3H, s, $COOCH_3$), 4.85 (1H, q, J=7 Hz, CH), 7.30 (1H, d, J=2 Hz, C(2)–H), 7.45 (1H, J=9 Hz, C(7)–H), 8.05 (1H, dd, J=9, 2 Hz, C(6)–H), 7.75 (1H, br d, J=7 Hz, $NHCOCH_3$), 8.60 (1H, d, J=2 Hz, C(4)–H), 11.25 (1H, br s, NH); MS m/z: 305 (M^+), 287, 246, 215, 175 (100%), 129. *Anal.* Calcd for $C_{14}H_{14}N_3O_5$: C, 55.08; H, 4.95; N, 13.76. Found: C, 54.79; H, 5.03; N, 13.62.

5-Benzyloxy-N_b-methoxycarbonyl-L- and -D-tryptophan Methyl Esters (L-14g and D-14g)——A mixture of L-**6** (10 g, 49.3 mmol), *p*-benzyloxyphenylhydrazine HCl (12.5 g, 50 mmol), H_2O (165 ml) and AcOH (180 ml) was stirred at 80—90 °C under an argon atmosphere for 2 h. After removal of the solvent, the residue was dissolved in AcOEt and insoluble materials were removed by filtration. The filtrate was washed with saturated brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the crude product by silica gel column chromatography (SiO_2, 100 g) eluted with hexane–AcOEt (3 : 2) provided 12.5 g (66%) of L-**14g** as a highly viscous oil: $[\alpha]_D^{20}$ −8.9° (c=1.0, MeOH); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480, 3430, 1720. ^{1}H-NMR ($CDCl_3$) δ 3.25 (2H, d, J=5 Hz, CH_2), 3.65 (6H, s, $COOCH_3$ × 2), 4.3—4.9 (1H, m, CH), 5.10 (2H, s, $PhCH_2$), 5.20 (1H, br d, J=8 Hz, $NHCOOCH_3$), 6.7—7.6 (9H, m, aromatic H), 8.10 (1H, br s, NH); MS m/z: 382 (M^+), 350, 236 (100%), 145, 117, 91.

D-**14g**: 61% yield from D-**6**; $[\alpha]_D^{20}$ +8.2° (c=1.5, MeOH).

5-Methoxy-N_b-methoxycarbonyl-L-tryptophan Methyl Ester (L-14f)——This compound was obtained from L-**6** and *p*-methoxyphenylhydrazine in 47% yield by a procedure similar to that described for the preparation of L-**14g**: mp 99—101 °C (recrystallization from 2-PrOH–isoPr$_2$O); $[\alpha]_D^{20}$ −6.3° (c=1.1, MeOH); IR ν_{max}^{Nujol} cm^{-1}: 3330, 1720, 1710. ^{1}H-NMR ($CDCl_3$) δ 3.25 (2H, d, J=6 Hz, CH_2), 3.64 (3H, s, $COOCH_3$), 3.66 (3H, s, $COOCH_3$), 3.85 (3H, s, OCH_3), 4.5—4.9 (1H, m, CH), 5.30 (1H, br d, J=8 Hz, $NHCOOCH_3$), 6.7—7.1 (3H, m, aromatic H), 7.20 (1H, d, J=9 Hz, C(7)–H), 8.20 (1H, br s, NH); MS m/z: 306 (M^+), 274, 160 (100%), 145. *Anal.* Calcd for $C_{15}H_{18}N_2O_5$: C, 58.82; H, 5.92; N, 9.14. Found: C, 58.77; H, 5.93; N, 9.11.

5-Methoxy-N_b-Methoxycarbonyl-D-tryptophan Methyl Ester (D-14f)——This compound was prepared according to Hino's procedures with minor modifications.[4c] A solution of D-**14a** (11.04 g, 40 mmol) in CF_3COOH (100 ml) was stirred at room temperature for 2.5 h. This solution was added to a solution of $Pb(OAc)_4$ (42 g, 80 mmol) in CH_2Cl_2 (800 ml). The mixture was stirred for 5 min, then active zinc powder (22 g) was added. The mixture was stirred for a further 15 min and treated with saturated $(NH_4)_2SO_4$ (200 ml). The organic layer was separated and washed with water repeatedly. Evaporation of the solvent and trituration with hexane–AcOEt (2 : 1) containing a small amount of $CHCl_3$ gave 6.4 g (41%) of a white solid. This was found to be 5-trifluoroacetoxy-N_b-methoxycarbonyl-D-tryptophan methyl ester (D-**14k**). From the mother liquor, 1.1 g (9%) of a 5-hydroxy derivative (D-**14e**) was obtained as a powder after purification by silica gel column chromatography ($CHCl_3$–AcOEt, 2 : 1). The compound (D-**14k**) was quantitatively converted into D-**14e** by solvolysis with MeOH at room temperature for 30 min. The combined crops of D-**14e** (9.6 g, 32.9 mmol) were dissolved in AcOEt. This solution was treated with ethereal diazomethane generated from 40 g of nitrosomethylurea. After being kept standing for 4 d in a refrigerator, the solution was evaporated and

the residue was purified by silica gel chromatography (hexane–AcOEt–$CHCl_3$, 4:4:1) to give 7.6 g (76%) of the 5-methoxy derivative (D-**14f**) as crystals. Recrystallization from 2-PrOH–isoPr$_2$O gave a pure sample. The overall yield of D-**14f** from D-**14a** was 38%: mp 102—103 °C; $[\alpha]_D^{20}$ +7.6° (c=1.2, MeOH).

5-Chloro-N_b-methoxycarbonyl-L-tryptophan Methyl Ester (L-14b)——This compound was prepared from L-**6** and *p*-chlorophenylhydrazine in 36% yield by a procedure similar to that described for the preparation of L-**14h**: mp 108—110 °C (recrystallization from 2-PrOH–isoPr$_2$O); $[\alpha]_D^{20}$ −1.20° (c=1.0, MeOH); IR ν_{max}^{Nujol} cm^{-1}: 3380, 3300, 1740, 1700. ^{1}H-NMR ($CDCl_3$) δ 3.25 (2H, d, J=6 Hz, CH_2), 3.65 (3H, s, $COOCH_3$), 3.70 (3H, s, $COOCH_3$), 4.4—4.9 (1H, m, CH), 5.25 (1H, br d, J=8 Hz, $NHCOOCH_3$), 6.95 (1H, d, J=2 Hz, C(2)–H), 7.1—7.5 (3H, m, aromatic H), 8.30 (1H, br s, NH); MS *m/z*: 312, 310 (M^+), 166, 164 (100%), 129. UV λ_{max}^{MeOH} nm (ε): 228 (36000), 282 (6000), 290 (6400), 300 (5100). *Anal.* Calcd for $C_{14}H_{15}ClN_2O_4$: C, 54.12; H, 4.87; Cl, 11.41; N, 9.02. Found: C, 54.14; H, 4.85; Cl, 11.57; N, 9.03.

5-Methylthio-N_b-methoxycarbonyl-L-tryptophan Methyl Ester (14h)——A solution of L-**6** (2.1 g, 10 mmol) in H_2O (5 ml) was added dropwise to a solution of *p*-methylthiophenylhydrazine HCl (1.9 g, 10 mmol) in H_2O (20 ml) containing 1 ml of 1 N HCl at 90 °C under an argon atmosphere. The mixture was stirred for 1.5 h at the same temperature, then cooled to room temperature and extracted with AcOEt. The extract was washed with saturated brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue which was dissolved in MeOH (50 ml) and treated with excess diazomethane. The solution was concentrated *in vacuo* to leave a residue, which was purified by flash chromatography (SiO_2, 40 g) eluted with AcOEt–hexane (2:3) to furnish 1.65 g (51%) of **14h** as a colorless solid: mp 95—97 °C (recrystallization from 2-PrOH–isoPr$_2$O); $[\alpha]_D^{20}$ −8.0° (c=1.0, MeOH); IR ν_{max}^{Nujol} cm^{-1}: 3380, 3300, 1740, 1710. ^{1}H-NMR ($CDCl_3$) δ 2.50 (3H, s, SCH_3), 3.25 (2H, d, J=6 Hz, CH_2), 3.65 (3H, s, $COOCH_3$), 3.70 (3H, s, $COOCH_3$), 4.5—4.9 (1H, m, CH), 5.25 (1H, br d, J=8 Hz, $NHCOOCH_3$), 6.95 (1H, d, J=2 Hz, C(2)–H), 7.22 (2H, br s, C(6), (7)–H), 7.54 (1H, br s, C(5)–H), 8.35 (1H, br s, NH); MS *m/z*: 322 (M^+), 290, 176 (100%), 161. UV λ_{max}^{MeOH} nm (ε): 231 (27500), 252 (sh), (12500), 287 (4400). *Anal.* Calcd for $C_{15}H_{18}N_2O_4S$: C, 55.89; H, 5.89; N, 8.69; S, 9.94. Found: C, 55.72; H, 5.62; N, 8.55; S, 9.96.

5-Bromo-N_b-methoxycarbonyl-L-tryptophan Methyl Ester (L-14c)——This compound was prepared from L-**6** and *p*-bromophenylhydrazine in 28% yield: mp 113—115 °C (recrystallization from 2-PrOH–isoPr$_2$O); $[\alpha]_D^{20}$ −1.0° (c=1.0, MeOH); IR ν_{max}^{Nujol} cm^{-1}: 3380, 3290, 1730, 1700. ^{1}H-NMR ($CDCl_3$) δ 3.30 (2H, d, J=6 Hz, CH_2), 3.65 (3H, s, $COOCH_3$), 3.70 (3H, s, $COOCH_3$), 4.4—4.9 (1H, m, CH), 5.20 (1H, br d, J=8 Hz, $NHCOOCH_3$), 6.90 (1H, d, J=2 Hz, C(2)–H), 7.1—7.3 (2H, m, C(6), (7)–H), 7.60 (1H, br s, C(5)–H), 8.30 (1H, br s, NH); MS *m/z*: 356, 354 (M^+), 324, 322, 297, 295, 281, 279, 210, 208 (100%), 129. UV λ_{max}^{MeOH} nm (ε): 227 (36000), 283 (5500), 290 (5700), 299 (4400). *Anal.* Calcd for $C_{14}H_{15}BrN_2O_4$: C, 47.34; H, 4.26; Br, 22.50; N, 7.89. Found: C, 47.65; H, 4.26; Br, 22.66; N, 7.80.

5-Methyl-N_b-methoxycarbonyl-L-tryptophan Methyl Ester (L-14d)——This compound was prepared from L-**6** and *p*-tolylhydrazine in 41% yield: mp 108—110 °C (recrystallization from 2-PrOH–isoPr$_2$O); $[\alpha]_D^{20}$ −7.6° (c=1.0, MeOH); IR ν_{max}^{Nujol} cm^{-1}: 3370, 1740, 1720. ^{1}H-NMR ($CDCl_3$) δ 2.45 (3H, s, CH_3), 3.25 (2H, d, J=6 Hz, CH_2), 3.61 (3H, s, $COOCH_3$), 3.64 (3H, s, $COOCH_3$), 4.4—4.9 (1H, m, CH), 5.25 (1H, br d, J=8 Hz, $NHCOOCH_3$), 6.85 (1H, d, J=2 Hz, C(2)–H), 7.0—7.4 (3H, m, aromatic H), 8.25 (1H, br s, NH); MS *m/z*: 290 (M^+), 144 (100%). UV λ_{max}^{MeOH} nm (ε): 224 (30000), 279 (5500), 286 (5500), 297 (4100).

5-Nitro-N_b-methoxycarbonyl-L- and -D-tryptophan Methyl Esters (L-14i and D-14i)——According to the procedures reported for the preparation of racemic **14i** by Hino and Taniguchi,[4b] L- and D-**14i** were prepared through two steps (nitration of **22a** followed by acid treatment) in 81 and 91% yields, respectively. L-**14i**: mp 144—145 °C (recrystallization from MeOH); $[\alpha]_D^{20}$ +2.98° (c=1.6, MeOH); IR ν_{max}^{Nujol} cm^{-1}: 3350 (sh), 3300, 1730, 1690. ^{1}H-NMR ($CDCl_3$) δ 3.35 (2H, d, J=6 Hz, CH_2), 3.65 (3H, s, $COOCH_3$), 3.70 (3H, s, $COOCH_3$), 4.4—4.9 (1H, m, CH), 7.20 (1H, d, J=2 Hz, C(2)–H), 5.75 (1H), 7.40 (1H, d, J=9 Hz, C(7)–H), 8.05 (1H, dd, J=9, 2 Hz, C(6)–H), 8.50 (1H, d, J=2 Hz, C(4)–H), 10.55 (1H, br s, NH); MS *m/z*: 321 (M^+), 246, 175 (100%), 145, 129.

D-**14i**: mp 142.5—143.5 °C (recrystallization from MeOH); $[\alpha]_D^{20}$ −2.90° (c=1.0, MeOH).

5-Acetamido-N_b-methoxycarbonyl-L- and -D-tryptophan Methyl Esters (L-14j and D-14j)——A mixture of L-**14i** (3.0 g, 9.3 mmol), 10% Pd/C (300 mg) and MeOH (120 ml) was stirred at room temperature under a hydrogen atmosphere. After the theoretical amount of hydrogen had been absorbed, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to leave a residue, which was purified by silica gel column chromatography eluted with AcOEt–hexane (10:1) to provide 2.45 g (90%) of the amino derivative. Subsequent acylation was performed by treatment of a solution of the amino derivative (2.45 g, 8.4 mmol) in pyridine (60 ml) with Ac_2O (1.16 g, 11 mmol) for 1 h at room temperature. After usual work-up and purification by silica gel column chromatography eluted with AcOEt, 2.52 g (90%) of pure L-**14j** was obtained as a yellow powder: $[\alpha]_D^{20}$ −11.0° (c=1.0, MeOH); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (sh), 3430, 1710, 1670. ^{1}H-NMR ($CDCl_3$) δ 2.05, 2.10 (3H, d, $NHCOCH_3$), 3.15 (2H, d, J=6 Hz, CH_2), 3.60 (3H, s, $COOCH_3$), 3.65 (3H, s, $COOCH_3$), 4.3—4.9 (1H, m, CH), 5.30 (1H, br d, J=8 Hz, $NHCOOCH_3$), 6.90 (1H, br d, J=2 Hz, C(2)–H), 7.10 (2H, s, aromatic H), 7.65 (1H, br s, aromatic H), 7.70 (1H, br s, NH), 8.60 (1H, br s, NH); MS *m/z*: 333 (M^+), 301, 187 (100%), 145.

D-**14j**: 90% yield from D-**14i**; $[\alpha]_D^{20}$ +11.2° (c=1.0, MeOH).

5-Chloro-N_b-methoxycarbonyl-D-tryptophan Methyl Ester (D-14b)——According to the procedures reported for the preparation of racemic **14b** by Hino *et al.*,[4a] D-**14b** was prepared through two steps from the cyclic tautomer (D-

22a) in 88% yield: mp 106—108 °C (recrystallization from acetone–hexane); $[\alpha]_D^{20}$ +0.8° (c=1.0, MeOH).

5-Bromo-N_b-methoxycarbonyl-D-tryptophan Methyl Ester (D-14c)——This compound was prepared similarly from D-**22a** according to Hino's method.[4d] Reaction of D-**22a** with *N*-bromosuccinimide in AcOH gave the bromo derivative D-**22c**, mp 165—166 °C, $[\alpha]_D^{20}$ −144.0° (c=1.0, MeOH), in 90% yield, and this product was converted to D-**14c** in 85% yield on treatment with methanolic sulfuric acid: mp 116—117 °C (recrystallization from 2-PrOH–isoPr$_2$O); $[\alpha]_D^{20}$ +0.7° (c=1.0, MeOH).

5-Methyl-N_b-benzyloxycarbonyl-L-tryptophan Methyl Ester (15)——A solution of **7** (3.0 g, 10 mmol) in dioxane (10 ml) was added dropwise to a solution of *p*-methylphenylhydrazine HCl (1.6 g, 10 mmol) in H_2O (16 ml) containing 1 ml of 1 N HCl at 85—90 °C under an argon atmosphere. The solution was stirred for 80 min at the same temperature. Usual work-up gave 3.7 g of the crude product, which was purified by silica gel column chromatography eluted with hexane–AcOEt (3 : 2) to afford 2.0 g (55%) of **15** as a highly viscous oil: $[\alpha]_D^{20}$ −18.1° (c=1.65, MeOH); ^{1}H-NMR ($CDCl_3$) δ 2.41 (3H, s, CH_3), 3.25 (2H, d, J=6 Hz, CH_2), 3.65 (3H, s, $COOCH_3$), 4.5—4.9 (1H, m, CH), 5.07 (2H, s, $PhCH_2$), 5.30 (1H, br d, $NHCOOCH_3$), 6.85 (1H, d, J=2 Hz, C(2)–H), 7.0—7.4 (8H, m, aromatic H), 8.1 (1H, br s, NH); MS m/z: 366 (M^+), 258, 144 (100%), 91.

5-Benzyloxy-N_b-acetyl-L-tryptophan (16g)——A solution of **13g** (4.77 g, 13 mmol) in MeOH (40 ml) containing 15.4 ml of 1 N NaOH was stirred at room temperature for 2 h. After removal of the solvent, the residue was dissolved in a small amount of water and acidified with conc. HCl to pH 1, yielding the precipitate, which was collected by filtration and dried in a vacuum desiccator to afford 4.1 g of **16g** as a colorless solid. Recrystallization from MeOH gave 3.75 g (82%) of pure **16g**: mp 205—207 °C; $[\alpha]_D^{18}$ +7.1° (c=0.84, MeOH (lit.[1a] mp 198—199.5 °C, $[\alpha]_D^{26}$ +6.3° (c=0.8, MeOH)); IR ν_{max}^{Nujol} cm^{-1}: 3420, 3300, 1710, 1580. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ 1.90 (3H, s, $NHCOCH_3$), 3.0—3.7 (2H, m, CH_2), 4.6—5.1 (1H, m, CH), 5.05 (2H, s, $PhCH_2$), 6.6—7.7 (9H, m, aromatic H), 9.1 (1H, br s, NH), 9.5 (1H, br s, COOH); MS m/z: 352 (M^+), 334, 293, 236 (100%), 173, 91.

5-Methoxy-N_b-acetyl-L-tryptophan (16f)——This compound was obtained in 91% yield from **13f** by alkaline hydrolysis in the same manner as described for the preparation of **16g**: mp 175—176 °C (recrystallization from MeOH); $[\alpha]_D^{16}$ +16.0° (c=1.22, MeOH) (lit.[1a] mp 173—175 °C, $[\alpha]_D^{23}$ +14.3° (c=0.725, MeOH)); IR ν_{max}^{Nujol} cm^{-1}: 3400, 3350, 3330, 1720, 1610. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ 1.93 (3H, s, $NHCOCH_3$), 3.25 (2H, d, J=6 Hz, CH_2), 3.81 (3H, s, OCH_3), 4.6—5.0 (1H, m, CH), 6.72 (1H, dd, J=8, 2 Hz, C(6)–H), 7.4—7.6 (2H, m, C(2), (4)–H), 7.71 (1H, d, J=8 Hz, C(7)–H); MS m/z: 276 (M^+), 217, 174, 160 (100%), 145, 117.

5-Nitro-N_b-acetyl-L-tryptophan (16i)——This compound was obtained in 67% yield from **13i**: mp 194—196 °C (recrystallization from AcOEt); $[\alpha]_D^{20}$ +23.4° (c=1.0, MeOH); IR ν_{max}^{Nujol} cm^{-1}: 3350, 3270, 3100, 1740, 1660. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ 1.95 (3H, s, $NHCOCH_3$), 3.30 (2H, d, J=6 Hz, CH_2), 4.70 (1H, q, J=7 Hz, CH), 7.25 (1H, d, J=2 Hz, C(2)–H), 6.5—7.5 (1H, br, $NHCOCH_3$), 7.35 (1H, d, J=9 Hz, C(7)–H), 8.00 (1H, dd, J=9, 2 Hz, C(6)–H), 8.55 (1H, d, J=2 Hz, C(4)–H), 10.90 (1H, br, NH); MS m/z: 291 (M^+), 273, 232, 175 (100%), 145, 129. *Anal.* Calcd for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 16.86. Found: C, 52.68; H, 4.44; N, 16.91.

5-Methyl-N_b-benzyloxycarbonyl-L-tryptophan (21)——This compound was obtained in 85% yield from **15**: mp 147—149 °C (recrystallization from 2-PrOH–isoPr$_2$O), $[\alpha]_D^{20}$ −20.8° (c=1.0, MeOH); IR ν_{max}^{Nujol} cm^{-1}: 3400, 3360, 1740, 1670. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ 2.40 (3H, s, CH_3), 3.25 (2H, d, J=6 Hz, CH_2), 4.4—4.9 (1H, m, CH), 5.06 (2H, s, $PhCH_2$), 5.45 (1H, d, J=8 Hz, $NHCOOCH_2Ph$), 6.8—7.5 (9H, m, aromatic H), 8.75 (2H, br, COOH and NH); MS m/z: 352 (M^+), 244, 144 (100%), 115, 108, 107, 91, 79.

Debenzylation of 21——A mixture of **21** (1.3 g, 3.7 mmol), MeOH (200 ml), H_2O (50 ml) and 10% Pd/C (150 mg) was stirred under a hydrogen atmosphere at room temperature for 5 h. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* to leave 805 mg of a colorless solid, which was recrystallized from H_2O to furnish 487 mg (60%) of pure L-**18d**: mp 260 °C (dec.), $[\alpha]_D^{20}$ +10.6° (c=1.0, 1 N HCl); *Anal.* Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.98; H, 6.56; N, 12.76.

Acid Hydrolysis of L-16e——A mixture of **16g** (3.52 g, 10 mmol) in H_2O (20 ml) containing 440 mg of NaOH (11 mmol) and 10% Pd/C (1 g) was stirred under a hydrogen atmosphere at room temperature for 4 h. After addition of dilute HCl to adjust the solution to pH 4, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The concentrate was adjusted to pH 1 by addition of conc. HCl to generate a precipitate, which was collected by filtration, washed with water and dried in a vacuum desiccator to give 2.15 g (82%) of L-**16e** (mp 204—205 °C). A solution of L-**16e** (2.1 g, 8 mmol) in *ca.* 10% H_2SO_4 (20 ml) was heated at reflux for 10 h under an argon atmosphere. The solution was cooled to room temperature, adjusted to pH 4 with NH_4OH and concentrated *in vacuo* to leave a residue which was extracted with EtOH. The extract was evaporated *in vacuo* to give 616 mg of the crude product, which was recrystallized from H_2O, yielding 352 mg (20%) of pure L-**18e**: mp 250 °C (dec.), $[\alpha]_D^{20}$ −34.6° (c=1.0, H_2O).

Acid Hydrolysis of L-16f——A solution of L-**16f** (2.76 g, 10 mmol) in 10% H_2SO_4 (20 ml) was heated at reflux for 15 h under an argon atmosphere. Usual work-up provided 350 mg (15%) of pure L-**18f**: mp 250—252 °C (dec.), $[\alpha]_D^{20}$ −29.2° (c=0.9, H_2O).

Preparation of L-18f from L-16f by Treatment with Acylase——$CoCl_2 \cdot 6H_2O$ (1 mg) and acylase (obtained from Amano Seiyaku, 15000 u/g, 25 mg) were added to a solution of L-**16f** (497 mg, 1.8 mmol) in H_2O (10 ml) adjusted to pH 7.0 with 2 N NaOH. The solution was kept standing at 37±1 °C for 48 h. When deacetylation was complete, the

solution was adjusted to pH 5.90 by addition of 10% HCl and concentrated to 1/3 volume to give the precipitate, which was collected by filtration and dried. Recrystallization from H_2O gave 320 mg (76%) of pure L-**18f**: mp 250—251 °C (dec.), $[\alpha]_D^{20}$ −29.1° (c=0.87, H_2O).

Preparation of L-18i from L-16i by Treatment with Acylase——Similarly, 5-nitro-L-tryptophan (L-**18i**) was prepared from L-**16i** in 77% yield: mp 261—262 °C (dec.), $[\alpha]_D^{20}$ +48.6° (c=1.0, 1 N HCl).

General Procedures for 5-Substituted Tryptophans through Route A are Exemplified by the Preparation of L-18a *via* L-17a from L-14a——N_b-Methoxycarbonyl-L-tryptophan (L-**17a**): A mixture of L-**14a** (4.14 g, 15 mmol), MeOH (50 ml) and 1 N NaOH (18 ml) was stirred at room temperature for 3 h. After removal of the solvent, the residue was dissolved in water and washed with AcOEt. The aqueous layer was acidified with conc. HCl and the resultant precipitate was extracted with AcOEt. The extract was washed with water and then with saturated brine. Drying of the extract and evaporation gave 3.54 g (90%) of L-**17a** as colorless crystals: mp 153—155 °C, $[\alpha]_D^{20}$ +1.3° (c=1.7, MeOH); IR ν_{max}^{Nujol} cm^{-1}: 3380, 3340, 1720, 1670. ^{1}H-NMR ($CDCl_3$) δ 3.30 (2H, d, J=6 Hz, CH_2), 3.60 (3H, s, $COOCH_3$), 4.3—4.8 (1H, m, CH), 5.70 (1H, br d, J=9 Hz, $NHCOOCH_3$), 7.00 (1H, d, J=2 Hz, C(2)–H), 7.0—7.7 (4H, m, aromatic H), 8.15 (1H, br, NH), 9.65 (1H, br, COOH); MS m/z: 262 (M^+), 230, 130 (100%). *Anal.* Calcd for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68. Found: 59.64; H, 5.33; N, 10.55.

L-Tryptophan (L-**18a**): Me_3SiI (3.34 g, 16.7 mmol) was added to a solution of L-**17a** (2.0 g, 7.6 mmol) in $CHCl_3$ (20 ml) under an argon atmosphere and the solution was heated at reflux for 1.5 h. The reaction mixture was cooled to 5—10 °C in an ice-water bath and then 2 ml of MeOH was added. After being stirred for 10 min, the mixture was evaporated to give a residue, which was dissolved in water and washed with ether. The aqueous layer was adjusted to pH 5.94 with NH_4OH and was concentrated *in vacuo* to provide a precipitate, which was collected by filtration and recrystallized from 30% EtOH to yield 984 mg (63%) of pure L-**18a** as colorless crystals: mp 255—257 °C (dec.), $[\alpha]_D^{20}$ −32.6° (c=1.0, H_2O).

5-Benzyloxy-N_b-methoxycarbonyl-L- and -D-tryptophans (L-17g and D-17g)——These compounds were obtained by alkaline hydrolysis of L-**14g** and D-**14g**, respectively. L-**17g**: 92% yield, mp 145—147 °C (recrystallization from 2-PrOH), $[\alpha]_D^{20}$ −7.9° (c=1.2, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3380, 3320, 1720, 1660. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ 3.30 (2H, d, J=6 Hz, CH_2), 3.65 (3H, s, $COOCH_3$), 4.4—4.9 (1H, m, CH), 5.05 (2H, s, $PhCH_2$), 6.8—7.6 (10H, m, aromatic H, COOH), 8.55 (1H, br s, NH); MS m/z: 368 (M^+), 336, 236 (100%), 173, 145, 117, 91. UV λ_{max}^{MeOH} nm (ε): 223 (30000), 278 (6700), 296 (5500), 305 (3500). *Anal.* Calcd for $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60. Found: C, 65.17; H, 5.35; N, 7.65.

D-**17g**: 82% yield, mp 146—147 °C (recrystallization from 2-PrOH), $[\alpha]_D^{20}$ +7.0° (c=1.1, MeOH); *Anal.* Calcd for $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60. Found: C, 65.47; H, 5.52; N, 7.67.

5-Hydroxy-L- and -D-tryptophans (L-18e and D-18e)——A mixture of L-**17g** (2.0 g, 5.4 mmol), H_2O (20 ml) containing 260 mg (6.5 mmol) of NaOH and 10% Pd/C (500 mg) was stirred at room temperature under a hydrogen atmosphere for 2 h. After removal of the catalyst by filtration, the filtrate was acidified with dilute HCl to generate the precipitate. Extraction with AcOEt and evaporation gave 1.49 g (100%) of crude L-**17e**, $[\alpha]_D^{20}$ −18.2° (c=1.0, MeOH), which was dissolved in $CHCl_3$ (10 ml). To this solution was added Me_3SiI (3.2 g, 16 mmol), and the mixture was heated at reflux under an argon atmosphere for 1 h. When the reaction was complete, 2 ml of MeOH was added to the reaction mixture and the whole was stirred for 10 min. Work-up gave 536 mg (45%) of pure L-**18e**: mp 250—252 °C (dec.), $[\alpha]_D^{20}$ −32.5° (c=0.9, H_2O) [lit.[11] mp 273° (dec.), $[\alpha]_D^{22}$ −32.5° (c=1, H_2O)]; IR ν_{max}^{Nujol} cm^{-1}: 3390, 1620, 1580. ^{1}H-NMR (D_2O–DMSO-d_6) δ 2.9—3.7 (2H, m, CH_2), 3.9—4.2 (1H, m, CH), 6.90 (1H, dd, J=9, 2 Hz, C(6)–H), 7.20 (1H, d, J=2 Hz, C(4)–H), 7.35 (1H, s, C(2)–H), 7.45 (1H, d, J=9 Hz, C(7)–H); MS m/z: 220 (M^+), 146 (100%). *Anal.* Calcd for $C_{11}H_{12}N_2O_3 \cdot 1/3H_2O$: C, 58.40; H, 5.64; N, 12.38. Found: C, 58.25; H, 5.67; N, 12.34.

D-**18e**: 54% yield from D-**17g**, mp 250 °C (dec.), $[\alpha]_D^{20}$ +32.7° (c=1.0, H_2O) [lit.[11] mp 274° (dec.), $[\alpha]_D^{22}$ +32.2° (c=1, H_2O]; *Anal.* Calcd for $C_{11}H_{12}N_2O_3 \cdot 1/4H_2O$: C, 58.79; H, 5.61; N, 12.47. Found: C, 58.98; H, 5.46; N, 12.48.

5-Methoxy-N_b-methoxycarbonyl-L-tryptophan (L-17f)——This compound was obtained in 79% yield from L-**14f**: mp 107—109 °C (recrystallization from 2-PrOH–isoPr$_2$O); $[\alpha]_D^{20}$ −4.5° (c=0.9, MeOH); IR ν_{max}^{Nujol} cm^{-1}: 3380, 3330, 1720, 1660. ^{1}H-NMR ($CDCl_3$) δ 2.8—3.5 (2H, m, CH_2), 3.60 (3H, s, $COOCH_3$), 3.80 (3H, s, OCH_3), 4.3—4.9 (1H, m, CH), 5.40 (1H, br d, J=9 Hz, $NHCOOCH_3$), 6.80 (1H, dd, J=9, 2 Hz, C(6)–H), 6.90 (1H, d, J=2 Hz, C(2)–H), 7.00 (1H, d, J=2 Hz, C(4)–H), 7.20 (1H, d, J=9 Hz, C(7)–H), 8.25 (1H, br, NH); MS m/z: 292 (M^+), 260, 160 (100%), 145. *Anal.* Calcd for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.59. Found: C, 57.37; H, 5.59; N, 9.75.

5-Methoxy-L-tryptophan (L-18f)——This compound was obtained by deprotection of L-**17f** in 48% yield: mp 250—251 °C (dec.), $[\alpha]_D^{20}$ −29.0° (c=0.9, H_2O). IR ν_{max}^{Nujol} cm^{-1}: 3560, 3460, 1620 (sh), 1600. ^{1}H-NMR (D_2O) δ 3.0—3.7 (2H, m, CH_2), 3.8—4.2 (1H, m, CH), 6.80 (1H, dd, J=9, 2 Hz, C(6)–H), 7.20 (1H, s, C(2)–H), 7.20 (1H, d, J=2 Hz, C(4)–H), 7.30 (1H, d, J=9 Hz, C(7)–H), 3.85 (3H, s, OCH_3). MS m/z: 234 (M^+), 160 (100%).

5-Nitro-N_b-methoxycarbonyl-L-tryptophan (L-17i)——This compound was obtained by alkaline hydrolysis of L-**14i** in 91% yield: mp 189—190 °C, $[\alpha]_D^{20}$ +1.5° (c=1.0, MeOH); IR ν_{max}^{Nujol} cm^{-1}: 3470, 3320, 1740, 1690. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ 3.30 (2H, d, J=6 Hz, CH_2), 4.3—4.8 (1H, m, CH), 3.60 (3H, s, $COOCH_3$), 6.00 (1H, br d, J=8 Hz, $NHCOOCH_3$), 7.20 (1H, d, J=2 Hz, C(2)–H), 7.35 (1H, d, J=9 Hz, C(7)–H), 8.00 (1H, dd, J=9, 2 Hz, C(6)–H), 8.55 (1H, d, J=2 Hz, C(4)–H), 10.85 (1H, br s, NH); MS m/z: 307 (M^+), 275, 245, 175 (100%), 145, 129. *Anal.*

Calcd for $C_{13}H_{13}N_3O_6$: C, 50.81; H, 4.26; N, 13.68. Found: C, 51.01; H, 4.30; N, 13.67.

5-Nitro-L-tryptophan (L-18i)——This compound was obtained by deprotection of L-**17i** in 52% yield: mp 266—268 °C (dec.), $[\alpha]_D^{20}$ +49.1° (c=1.0, 1 N HCl). IR ν_{max}^{Nujol} cm^{-1}: 3420, 1660, 1580. ^{1}H-NMR (CF_3COOH) δ 3.7—4.0 (2H, m, CH_2), 4.5—5.1 (1H, m, CH), 7.50 (1H, d, J=9 Hz, C(7)-H), 7.55 (1H, d, J=2 Hz, C(4)-H), 8.15 (1H, dd, J=9, 2 Hz, C(6)-H), 8.70 (1H, d, J=2 Hz, C(4)-H), 7.0—7.9 (1H, br, COOH), 9.50 (1H, br s, NH); MS m/z: 249 (M^+), 175 (100%), 159, 145, 129. *Anal.* Calcd for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 16.85. Found: C, 53.07; H, 4.49; N, 16.72.

5-Acetamido-N_b-methoxycarbonyl-L-tryptophan (L-17j)——This compound was obtained by alkaline hydrolysis of L-**14j** in 98% yield: $[\alpha]_D^{20}$ −24.6° (c=1.0, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3300, 1700, 1650 (sh), 1620. ^{1}H-NMR (DMSO-d_6) δ 1.95, 2.00 (3H, d, $NHCOCH_3$), 2.9—3.3 (2H, m, CH_2), 3.5 (3H, s, $COOCH_3$), 3.9—4.5 (1H, m, CH), 7.10 (1H, d, J=2 Hz, C(2)-H), 7.25 (2H, br s, aromatic H), 7.30 (1H, br d, J=8 Hz, $NHCOOCH_3$), 7.75 (1H, br s, C(4)-H), 9.65 (1H, br s, NH), 10.65 (1H, br s, NH); MS m/z: 319 (M^+), 287, 201, 187 (100%), 145.

5-Acetamido-L-tryptophan (L-18j)——This compound was obtained by deprotection of L-**17j** in 57% yield: mp 290—292 °C (dec.), $[\alpha]_D^{20}$ +18.6° (c=1.0, 1 N HCl); IR ν_{max}^{Nujol} cm^{-1}: 3400, 3250, 1620 (sh), 1600. ^{1}H-NMR (CF_3COOH) δ 3.5—3.9 (2H, m, CH_2), 2.65 (3H, s, $NHCOCH_3$), 4.5—5.0 (1H, m, CH), 7.0—7.9 (6H, m, aromatic H, NH_2), 9.60 (1H, br, NH), 10.15 (1H, br, NH); MS m/z: 261 (M^+), 187 (100%), 145. *Anal.* Calcd for $C_{13}H_{15}N_3O_3 \cdot 1/2H_2O$: C, 57.77; H, 5.97; N, 15.55. Found: C, 57.54; H, 5.85; N, 15.38.

General Procedures for 5-Substituted Tryptophan through Route B are Exemplified by the Preparation of L-18a *via* L-20a from L-14a——L-Tryptophan Methyl Ester (L-**20a**): Me_3SiI (2.74 g, 13.7 mmol) was added to a solution of L-**14a** (3.00 g, 10.8 mmol) in $CHCl_3$ (30 ml) under an argon atmosphere, and the mixture was heated at reflux for 1 h. The reaction mixture was cooled to 5—10 °C in ice-water bath and 2 ml of MeOH was added. Stirring was continued for 10 min and the solvent was removed *in vacuo* to leave a residue, which was dissolved in dilute HCl. The solution was washed with ether. The aqueous layer was treated with NH_4OH and the resultant precipitate was extracted with AcOEt. Drying and evaporation of the extract gave a crude product which was recrystallized from $isoPr_2O$–2-PrOH to afford 2.07 g (88%) of pure L-**20a**: mp 90—92 °C, $[\alpha]_D^{20}$ +37.0° (c=1.0, MeOH); IR ν_{max}^{Nujol} cm^{-1}: 3350, 3290, 1730. ^{1}H-NMR ($CDCl_3$) δ 1.55 (2H, s, NH_2), 2.8—3.5 (2H, m, CH_2), 3.65 (3H, s, $COOCH_3$), 3.6—4.0 (1H, m, CH), 6.95 (1H, d, J=2 Hz, C(2)-H), 6.9—7.8 (4H, m, aromatic H), 8.40 (1H, br, NH); MS m/z: 218 (M^+), 159, 130 (100%).

L-Tryptophan (L-**18a**): A mixture of L-**20a** (2.18 g, 10 mmol), MeOH (30 ml), and 1 N NaOH (12 ml, 12 mmol) was stirred at room temperature for 3 h. After removal of the solvent, the residue was dissolved in water and washed with AcOEt. The aqueous layer was acidified with 1 N HCl to pH 5.94 and concentrated *in vacuo* to yield a precipitate, which was collected by filtration. Recrystallization from 30% EtOH gave 1.69 g (83%) of pure L-**18a**: mp 253—255 °C (dec.), $[\alpha]_D^{20}$ −32.5° (c=1.1, H_2O), IR ν_{max}^{Nujol} cm^{-1}: 3400, 1660, 1580. ^{1}H-NMR (D_2O–DMSO-d_6) δ 3.2—3.5 (2H, m, CH_2), 3.9—4.2 (1H, m, CH), 7.1—7.9 (5H, m, aromatic H); MS m/z: 204 (M^+), 130 (100%).

D-Tryptophan Methyl Ester (D-20a)——The compound D-**20a** was obtained in 84% yield from D-**14a**: mp 90—91.5 °C; $[\alpha]_D^{20}$ −38.0° (c=1.0, MeOH); *Anal.* Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.03; H, 6.47; N, 12.81.

D-Tryptophan (D-18a)——This compound was obtained by alkaline hydrolysis of D-**20a** in 72% yield: mp 254—256 °C (dec.), $[\alpha]_D^{20}$ +32.0° (c=1.0, H_2O).

5-Methoxy-L- and -D-tryptophan Methyl Esters (L-20f and D-20f)——These compounds were obtained by deprotection of L-**14f** and D-**14f**, respectively. L-**20f**: 79% yield from L-**14f**, mp 126—127 °C (recrystallization from AcOEt); $[\alpha]_D^{20}$ +31.2° (c=1.0, MeOH); IR ν_{max}^{Nujol} cm^{-1}: 3360, 1725. ^{1}H-NMR ($CDCl_3$) δ 1.65 (2H, s, NH_2), 2.8—3.5 (2H, m, CH_2), 3.70 (3H, s, $COOCH_3$), 3.85 (3H, s, OCH_3), 3.7—4.1 (1H, m, CH), 6.80 (1H, dd, J=9, 2 Hz, C(6)-H), 6.95 (1H, d, J=2 Hz, C(2)-H), 7.05 (1H, d, J=2 Hz, C(4)-H), 7.20 (1H, d, J=9 Hz, C(7)-H), 8.35 (1H, br, NH); MS m/z: 248 (M^+), 189, 160 (100%), 145. UV λ_{max}^{MeOH} nm (ε): 220 (26000), 276 (6300), 297 (4900), 308 (3700). *Anal.* Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.72; H, 6.53; N, 11.31.

D-**20f**: 58% yield from D-**14f**, mp 125—127 °C (recrystallization from AcOEt); $[\alpha]_D^{20}$ −30.8° (c=1.1, MeOH); *Anal.* Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.83; H, 6.56; N, 11.06.

5-Methoxy-L- and -D-tryptophans (L-18f and D-18f)——These compounds were obtained by alkaline hydrolysis of L-**20f** and D-**20f**, respectively. L-**18f**: 83% yield, mp 249—250 °C (dec.), $[\alpha]_D^{20}$ −28.9° (c=1.0, H_2O); *Anal.* Calcd for $C_{12}H_{14}N_2O_3$: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.45; H, 6.07; N, 12.03.

D-**18f**: 96% yield, mp 248—250° (dec.); $[\alpha]_D^{20}$ +28.8° (c=1.0, H_2O); *Anal.* Calcd for $C_{12}H_{14}N_2O_3$: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.49; H, 6.09; N, 11.99.

5-Chloro-L- and -D-tryptophan Methyl Esters (L-20b and D-20b)——These compounds were obtained by deprotection of L-**14b** and D-**14b**, respectively. L-**20b**: 87% yield from L-**14b**: mp 71—72 °C (recrystallization from 2-PrOH–$isoPr_2O$), $[\alpha]_D^{20}$ +51.2° (c=1.0, MeOH); IR ν_{max}^{Nujol} cm^{-1}: 3350, 3130, 3080, 1730, 1720. ^{1}H-NMR ($CDCl_3$) δ 2.45 (2H, s, NH_2), 2.7—3.4 (2H, m, CH_2), 3.70 (3H, s, $COOCH_3$), 3.7—4.0 (1H, m, CH), 6.95 (1H, d, J=2 Hz, C(2)-H), 7.1—7.3 (2H, m, C(6), C(7)-H), 7.55 (1H, br s, C(4)-H), 8.55 (1H, br s, NH); MS m/z: 254, 252 (M^+), 193, 166, 164 (100%), 128. UV λ_{max}^{MeOH} nm (ε): 227 (34500), 282 (5200), 290 (5500), 300 (4200). *Anal.* Calcd for $C_{12}H_{13}ClN_2O_2$: C, 57.04; H, 5.19; Cl, 14.03; N, 11.09. Found: C, 56.93; H, 5.20; Cl, 13.93; N, 11.09.

D-**20b**: 90% yield from D-**14b**, mp 70—72 °C (recrystallization from 2-PrOH–$isoPr_2O$); $[\alpha]_D^{20}$ −51.6° (c=1.0,

MeOH).

5-Chloro-L- and -D-tryptophans (L-18b and D-18b)——These compounds were obtained by alkaline hydrolysis of L-**20b** and D-**20b**, respectively. L-**18b**: 56% yield, mp 268—270 °C (dec.); $[\alpha]_D^{20}$ +21.8° (c=1.0, 1 N HCl); IR ν_{max}^{Nujol} cm^{-1}: 3460, 3420, 1670, 1590. ^{1}H-NMR (D_2O–CF_3COOH) δ 3.40 (2H, d, J=6 Hz, CH_2), 4.45 (1H, t, J=6 Hz, CH), 7.15 (1H, dd, J=9, 2 Hz, C(6)–H), 7.30 (1H, s, C(2)–H), 7.40 (1H, d, J=9 Hz, C(7)–H, 7.55 (1H, d, J=2 Hz, C(4)–H); MS m/z: 240, 238 (M^+), 166, 164 (100%). *Anal.* Calcd for $C_{11}H_{11}ClN_2O_2$: C, 55.36; H, 4.64; Cl, 14.85; N, 11.74. Found: C, 55.03; H, 4.59; Cl, 15.14; N, 11.50.

D-**18b**: 50% yield, mp 261—263 °C (dec.), $[\alpha]_D^{20}$ −21.0° (c=1.0, 1 N HCl). *Anal.* Calcd for $C_{11}H_{11}ClN_2O_2$: C, 55.36; H, 4.64; Cl, 14.85; N, 11.74. Found: C, 55.54; H, 4.86; Cl, 14.87; N, 11.68.

5-Bromo-L- and -D-tryptophan Methyl Esters (L-20c and D-20c)——These compounds were obtained by deprotection of L-**14c** and D-**14c**, respectively. L-**20c**: 78% yield from L-**14c**, mp 100—102 °C (recrystallization from 2-PrOH–isoPr$_2$O), $[\alpha]_D^{20}$ +48.6° (c=1.0, MeOH); IR ν_{max}^{Nujol} cm^{-1}: 3380, 3300, 3140, 1740. ^{1}H-NMR ($CDCl_3$) δ 1.95 (2H, s, NH_2), 2.9—3.2 (2H, m, CH_2), 3.70 (3H, s, $COOCH_3$), 3.6—3.9 (1H, m, CH), 7.10 (1H, d, J=2 Hz, C(2)–H), 7.7 (1H, br s, C(4)–H), 7.2—7.4 (2H, m, C(6), C(7)–H), 10.44 (1H, br s, NH); MS m/z: 298, 296 (M^+), 239, 237, 210, 208 (100%), 129. UV λ_{max}^{MeOH} nm (ε): 226 (35000), 282 (5000), 290 (5400), 299 (4000). *Anal.* Calcd for $C_{12}H_{13}BrN_2O_2$: C, 48.50; H, 4.41; Br, 26.89; N, 9.43. Found: C, 48.53; H, 4.40; Br, 26.73; N, 9.29.

D-**20c**: 80% yield from D-**14c**, mp 98—100 °C (recrystallization from 2-PrOH–isoPr$_2$O), $[\alpha]_D^{20}$ −49.2° (c=1.0, MeOH).

5-Bromo-L- and -D-tryptophans (L-18c and D-18c)——These compounds were obtained by alkaline hydrolysis of L-**20c** and D-**20c**, respectively. L-**18c**: 70% yield, mp 274—277 °C (dec.), $[\alpha]_D^{20}$ +23.4° (c=1.0, 1 N HCl); IR ν_{max}^{Nujol} cm^{-1}: 3450, 3410, 1660, 1590. ^{1}H-NMR (D_2O–CF_3COOH) δ 3.40 (2H, d, J=6 Hz, CH_2), 4.40 (1H, t, J=6 Hz, CH), 7.30 (3H, br s, aromatic H), 7.65 (1H, br s, C(4)–H); m/z: 284, 282 (M^+), 210, 208 (100%), 186, 129. *Anal.* Calcd for $C_{11}H_{11}BrN_2O_2$: C, 46.67; H, 3.92; Br, 28.22; N, 9.89. Found: C, 46.55; H, 3.83; Br, 28.11; N, 9.86.

D-**18c**: 53% yield from D-**20c**, mp 266—269 °C (dec.), $[\alpha]_D^{20}$ −22.5° (c=1.0, 1 N HCl). *Anal.* Calcd for $C_{11}H_{11}BrN_2O_2$: C, 46.67; H, 3.92; Br, 28.22; N, 9.89. Found: C, 46.32; H, 3.84; Br, 28.41; N, 9.76.

5-Methyl-L-tryptophan Methyl Ester (L-20d)——This compound was obtained in 93% yield from L-**14d**: highly viscous oil, $[\alpha]_D^{20}$ +33.6° (c=1.2, MeOH), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 3340, 1750. ^{1}H-NMR ($CDCl_3$) δ 1.55 (2H, s, NH_2), 2.45 (3H, s, CH_3), 2.8—3.5 (2H, m, CH_2), 3.7—4.0 (1H, m, CH), 3.70 (3H, s, $COOCH_3$), 6.90 (1H, d, J=2 Hz, C(2)–H), 7.0—7.4 (3H, m, aromatic H), 8.30 (1H, br s, NH); MS m/z: 232 (M^+), 173, 144 (100%), 115. UV λ_{max}^{MeOH} nm (ε): 222 (32000), 275 (5900), 286 (5900), 296 (4300).

L-**20d** HCl: mp 209—211 °C (recrystallization from 2-PrOH–isoPr$_2$O); $[\alpha]_D^{20}$ +17.2° (c=1.0, MeOH).

5-Methyl-L-tryptophan (L-18d)——This compound was obtained by alkaline hydrolysis of L-**20d** in 84% yield: mp 275—277 °C (dec.), $[\alpha]_D^{20}$ +11.2° (c=1.0, 1 N HCl) (lit.[12] mp 249—259 °C (dec.), $[\alpha]_D^{20}$ +10.1° (c=1.19, 1 N HCl); IR ν_{max}^{Nujol} cm^{-1}: 3400, 1670, 1590. ^{1}H-NMR (D_2O–CF_3COOH) δ 2.50 (3H, s, CH_3), 3.45 (2H, d, J=6 Hz, CH_2), 4.40 (1H, t, J=6 Hz, CH), 7.1—7.6 (4H, m, aromatic H); MS m/z: 218 (M^+), 144 (100%). *Anal.* Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.80; H, 6.44; N, 12.84.

5-Methylthio-L-tryptophan Methyl Ester (L-20h)——This compound was obtained in 71% yield from L-**14h**: mp 79—81 °C (recrystallization from 2-PrOH–isoPr$_2$O), $[\alpha]_D^{20}$ +46.6° (c=1.0, MeOH); IR ν_{max}^{Nujol} cm^{-1}: 3300, 3160, 1740 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.60 (2H, s, NH_2), 2.50 (3H, s, SCH_3), 2.7—3.5 (2H, m, CH_2), 3.70 (3H, s, $COOCH_3$), 3.7—4.0 (1H, m, CH), 7.00 (1H, d, J=2 Hz, C(2)–H), 7.22 (2H, br s, C(6), C(7)–H), 7.60 (1H, s, C(5)–H), 8.40 (1H, br s, NH); MS m/z: 264 (M^+), 176 (100%), 161. UV λ_{max}^{MeOH} nm (ε): 229 (27000), 251 (13000), 286 (4500). *Anal.* Calcd for $C_{13}H_{16}N_2O_2S$: C, 59.07; H, 6.10; N, 10.60; S, 12.13. Found: C, 58.96; H, 6.07; N, 10.52; S, 11.95.

5-Methylthio-L-tryptophan (L-18h)——This compound was obtained by alkaline hydrolysis of L-**20h** in 42% yield: mp 240—242 °C (dec.), $[\alpha]_D^{20}$ −23.8° (c=1.0, H_2O), $[\alpha]_D^{20}$ +30.0° (c=1.0, 1 N HCl); IR ν_{max}^{Nujol} cm^{-1}: 3280, 1630. ^{1}H-NMR (D_2O–CF_3COOH) δ 2.55 (3H, s, SCH_3), 3.40 (2H, d, J=6 Hz, CH_2), 4.40 (1H, t, CH), 7.20 (1H, dd, J=8, 2 Hz, C(6)–H), 7.30 (1H, s, C(2)–H), 7.45 (1H, d, J=8 Hz, C(7)–H), 7.55 (1H, d, J=2 Hz, C(4)–H); MS m/z: 250 (M^+), 176 (100%), 161. *Anal.* Calcd for $C_{12}H_{14}N_2O_2S \cdot 1/2H_2O$: C, 55.58; H, 5.83; N, 10.80; S, 12.36. Found: C, 55.60; H, 5.63; N, 10.74; S, 12.19.

5-Nitro-L- and -D-tryptophan Methyl Esters (L-20i and D-20i)——These compounds were obtained by deprotection of L-**14i** and D-**14i**, respectively. L-**20i**: 72% yield from L-**14i**, mp 142—143.5 °C (recrystallization from 2-PrOH), $[\alpha]_D^{20}$ +78.8° (c=1.0, MeOH); IR ν_{max}^{Nujol} cm^{-1}: 3380, 3290, 3100, 1740. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ 1.90 (2H, s, NH_2), 3.1—3.3 (2H, m, CH_2), 3.70 (3H, s, $COOCH_3$), 3.7—4.0 (1H, m, CH), 7.20 (1H, d, J=1 Hz, C(2)–H), 7.35 (1H, d, J=9 Hz, C(7)–H), 8.00 (1H, dd, J=9, 2 Hz, C(6)–H), 8.50 (1H, d, J=2 Hz, C(4)–H), 10.65 (1H, br s, NH); MS m/z: 263 (M^+), 204, 175 (100%), 159, 129. *Anal.* Calcd for $C_{12}H_{13}N_3O_4$: C, 54.75; H, 4.98; N, 15.96. Found: C, 54.80; H, 5.05; N, 15.90.

D-**20i**: 79% yield from D-**14i**, mp 142.5—143.5 °C (recrystallization from 2-PrOH), $[\alpha]_D^{20}$ −78.8° (c=1.0, MeOH); *Anal.* Calcd for $C_{12}H_{13}N_3O_4$: C, 54.75; H, 4.98; N, 15.96. Found: C, 54.64; H, 5.03; N, 16.10.

5-Nitro-L- and -D-tryptophans (L-18i and D-18i)——These compounds were obtained by alkaline hydrolysis of L-**20i** and D-**20i**, respectively. L-**18i**: 80% yield, mp 266—268 °C (dec.), $[\alpha]_D^{20}$ +48.4° (c=1.0, 1 N, HCl). *Anal.* Calcd for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 16.85. Found: C, 52.85; H, 4.42; N, 17.11.

D-**18i**: 86% yield, mp 268—270 °C (dec.), $[\alpha]_D^{20}$ +49.0° (c=1.0, 1 N HCl). *Anal.* Calcd for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 16.85. Found: C, 52.93; H, 4.45; N, 17.08.

5-Acetamido-L- and -D-tryptophan Methyl Esters (L-20j and D-20j)——These compounds were obtained by deprotection of L-**14j** and D-**14j**, respectively. L-**20j**: 82% yield from L-**14j**, mp 146—147 °C (recrystallization from 2-PrOH–isoPr$_2$O), $[\alpha]_D^{20}$ +47.2° (c=1.0, MeOH); IR ν_{max}^{Nujol} cm^{-1}: 3360, 3280, 1710, 1650. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ 2.10 (3H, s, $NHCOCH_3$), 2.7—3.5 (2H, m, CH_2), 1.95 (2H, s, NH_2), 3.6—3.9 (1H, m, CH), 3.65 (3H, s, $COOCH_3$), 7.00 (1H, d, J=2 Hz, C(2)–H), 7.20 (2H, s, aromatic H), 7.75 (1H, s, aromatic H), 9.00 (1H, br s, NH), 9.95 (1H, br s, aromatic H); MS m/z: 275 (M^+), 216, 187 (100%), 145. UV λ_{max}^{MeOH} nm (ε): 238 (27000), 311 (2000) (sh). *Anal.* Calcd for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.26. Found: C, 60.79; H, 6.36; N, 15.04.

D-**20j**: 72% yield from D-**14j**, mp 147—148 °C (recrystallization from 2-PrOH–isoPr$_2$O), $[\alpha]_D^{20}$ −47.7° (c=0.6, MeOH); *Anal.* Calcd for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.26. Found: C, 60.78; H, 6.28; N, 15.07.

5-Acetamido-L- and -D-tryptophans (L-18j and D-18j)——These compounds were obtained by alkaline hydrolysis of L-**20j** and D-**20j**, respectively. L-**18j**: 80% yield, mp 289—290 °C (dec.), $[\alpha]_D^{20}$ +18.6° (c=1.0, 1 N HCl); IR ν_{max}^{Nujol} cm^{-1}: 3400, 3250, 1620 (sh), 1600. ^{1}H-NMR (CF_3COOH) δ 2.65 (3H, s, $NHCOCH_3$), 3.5—3.9 (2H, m, CH_2), 4.5—5.0 (1H, m, CH), 7.0—7.9 (7H, m), 9.60 (1H, br, NH), 10.15 (1H, br, NH); MS m/z: 261 (M^+), 187 (100%), 145. *Anal.* Calcd for $C_{13}H_{13}N_3O_3 \cdot 1/2H_2O$: C, 57.77; H, 5.97; N, 15.55. Found: C, 57.74; H, 5.85; N, 15.38.

D-**18j**: 82% yield, mp 300—303 °C (dec.), $[\alpha]_D^{20}$ −19.0° (c=1.0, 1 N HCl); *Anal.* Calcd for $C_{13}H_{13}N_3O_3 \cdot 1/4H_2O$: C, 58.75; H, 5.88; N, 15.81. Found: C, 58.87; H, 5.88; N, 15.74.

Deprotection of L-17a with Me_3SiCl–NaI——Me_3SiCl (1.08 g, 10 mmol) was added to a mixture of **17a** (1.05 g, 4 mmol), dry MeCN (10 ml), and NaI (1.5 g, 10 mmol) under an argon atmosphere and the mixture was stirred and heated at reflux for 7 h. The reaction mixture was cooled to room temperature, treated with MeOH (2 ml) and stirred for a further 15 min. Work-up gave 703 mg of the crude product, which was recrystallized from H_2O to furnish 340 mg (42%) of L-tryptophan: $[\alpha]_D^{20}$ −31.5 (c=0.9, H_2O).

Acknowledgement The authors are grateful to Profs. S. Yamada of Josai University and T. Hino of Chiba University for their valuable suggestions. The authors are also grateful to the staff of the Analytical Center of this company for spectral measurements and elemental analyses.

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