Isolation of Four 2,3,5,6,11,11b-Hexahydro-3-oxo-1*H*-indolizino[8,7-*b*]indole-5-carboxylic Acids from *Clerodendron Trichotomum* Thunb and Properties of Their Derivatives

Hajime IRIKAWA,* Yasuhiro TOYODA, Hiroaki KUMAGAI, and Yasuaki OKUMURA
Department of Chemistry, Faculty of Science, Shizuoka University, Ohya, Shizuoka 422
(Received October 12, 1988)

Four 2,3,5,6,11,11b-hexahydro-3-oxo-1*H*-indolizino[8,7-*b*]indole-5-carboxylic acids, plausible precursors of trichotomine, were isolated as the methyl esters from *Clerodendron trichotomum* Thunb, and the structures elucidated on the basis of their spectral and chemical evidences. The existence of two pairs of the C-11b epimers in the above plant were supported by the methoxide-catalyzed equilibrations of the compounds having the substituent on C-11b. Blue pigments were formed from the isolated compounds.

A blue pigment, trichotomine (**1**), was isolated from the fruits of *Clerodendron trichotomum* Thunb and the structure was elucidated by Iwadare et al.[1] The synthesis of **1** was reported by three groups.[2–4] Iwadare et al. prepared trichotomine dimethyl ester (**2**) by the autoxidation of **3**.[2] Kapadia and Rao synthesized **1** by one-pot reaction of L-tryptophan and 2-oxoglutaric acid, and suggested the intermediacy of **4**, formed from **5a** and/or **5b**, in the biosynthesis of **1**.[3] Since the skeleton of L-tryptophan with intact steric configuration is present in **1**, we attempted to search the extracts of the above plant for the substances supposed to be biosynthetic precursors of **1** in the lights of ultraviolet absorptions and color reactions with Ehrlich's reagent. Preliminary results of this study have been published in two communications.[5,6]

Isolation and Structure of 5a,b and 6a,b. The extracts were chromatographed on TSK gel G-3000s and then on Sephadex LH-20 to give four acidic compounds **5a,b** and **6a,b**, which showed characteristic blue sports on TLC with Ehrlich's reagent. On treatment with ethereal diazomethane, **5a,b** and **6a,b** afforded the dimethyl esters **7a,b** and the monomethyl esters **8a,b**, respectively.

The structures of **7a** and **7b** were deduced from the spectral data, and confirmed by the synthesis. Reaction of L-tryptophan methyl ester hydrochloride and dimethyl 2-oxoglutarate in methanol gave **7a** and **7b**, which were identical with the natural specimens of **7a** and **7b** by spectroscopic (IR, ^{1}H NMR, MS, and CD) and TLC comparisons, respectively. The diester **7b** was also prepared as follows. In a manner similar to that of Kapadia and Rao,[3] a mixture of L-tryptophan and 2-oxoglutaric acid in water was kept under nitrogen atmosphere at room temperature for two weeks to give **9a**, which was treated with ethereal diazomethane to afford the trimethyl ester **9b**. On treatment with 8 wt% hydrogen chloride–methanol, **9b** underwent cyclization to **7b**.

The stereochemical relationship of the two methoxycarbonyl groups in **7b** was determined in the following way. Reduction of **7b** with sodium borohydride in methanol–tetrahydrofuran gave the diol **10**, which afforded the ether **11** on treatment with *p*-toluenesulfonyl chloride in pyridine. Formation of **11** can be rationalized by tosylation of the hydroxymethyl group on C-5, followed by an intramolecular nucleophilic attack on the tosyloxymethyl carbon with the oxygen of the hydroxymethyl group on C-11b. Thus, formation of **11** indicates that the two methoxycarbonyl groups in **7b** bear 1,3-cis relationship to each other.

On treatment with sodium methoxide in methanol, the natural **7a** gave a mixture of **7a** and the antipode of **7b** in a ratio of 1:9, since the CD spectrum of the epimerization products was almost identical with that of the antipode of **7b** prepared from D-tryptophan methyl ester hydrochloride and dimethyl 2-oxoglutarate.

Accordingly, the structures of **7a** and **7b** were confirmed as shown in Fig. 1 including absolute configurations.

The structures of **8a** and **8b** were deduced from the spectral data, and confirmed by the synthesis.

Reaction of L-tryptophan methyl ester and 2-oxoglutaric acid in refluxing benzene afforded **8a** and **8b**[7] which were identical with the natural specimens of **8a** and **8b** in every respect of spectroscopic (IR, ^{1}H NMR, MS, and CD) and TLC comparisons, respectively. On treatment with sodium methoxide in methanol, **8a** underwent epimerization at C-5 to an epimer, which was identical with the antipode of **8b** prepared from D-tryptophan methyl ester and 2-oxoglutaric acid ($[\alpha]_D$, IR, ^{1}H NMR, and CD). The absolute configurations of the C-11b proton in **8a** and **8b** were supported by comparison of the CD spectra with those of yohimbane and pseudo-yohimbane, respectively.[8]

Accordingly, the structures of **8a** and **8b** were confirmed as shown in Fig. 1 including the absolute configurations.

Methoxide-Catalyzed Equilibrations. Tendency of epimerization at C-5 observed in **7a** and **8a** caused us to study on the methoxide-catalyzed equilibrations of the 11b-substituted derivatives of **8a** and **8b**.[6]

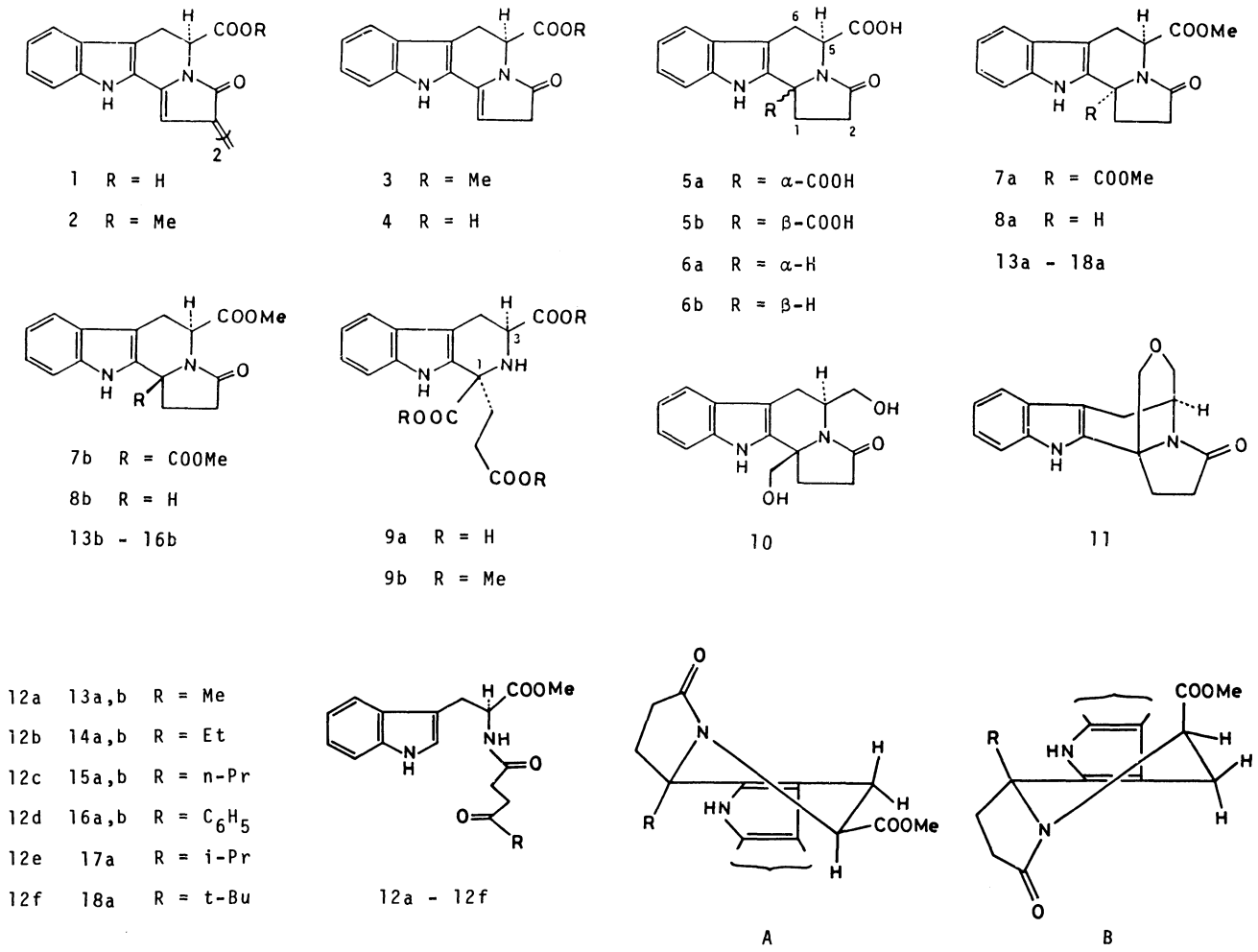


Fig. 1.

Table 1. ^{1}H and ^{13}C NMR Spectral Data (δ-values), and Equilibrations at C-5 (%)

Compound	5-H		OMe		C-5		C-11b		Ratio[a]	
	a[b]	b[c]	a	b	a	b	a	b	a	b
7 R=COOMe	4.39	5.48	3.83[d]	3.59	53.7	49.2	66.7	63.9	10	90
8 R=H	4.12	5.34	3.82	3.63	54.7	49.5	56.3	52.5	<1	>99
13 R=Me	4.09	5.40	3.79	3.66	52.2	48.7	61.9	59.8	19	81
14 R=Et	4.07	5.39	3.83	3.68	52.1	48.9	64.9	63.1	35	65
15 R=*n*-Pr	4.10	5.37	3.82	3.69	52.2	48.9	64.6	62.9	30	70
16 R=C_6H_5	3.88	5.23	3.74	2.89	52.1	48.3	68.1	64.4	46	54
17 R=*i*-Pr	4.15		3.81		51.8		67.7		100	0
18 R=*t*-Bu	4.51		3.78		53.9		70.5		100	0

a) Equilibration ratios determined by HPLC. b) Double doublet, J=10.0—11.1 and 5.1—5.8 Hz. c) Double doublet, J=6.6—8.1 and 1.5—2.1 Hz. d) Assignment may by interchangeable with the singlet at δ=3.87.

The amides **12a—12f** were prepared from L-tryptophan methyl ester and the corresponding 4-oxo carboxylic acids. On treatment with 13 wt% hydrogen chloride–methanol, **12a—12d** afforded **13a** and **13b** (in a ratio of 1:2), **14a** and **14b** (2:1), **15a** and **15b** (2:1), **16a** and **16b** (>20:1), respectively.[9] Cyclization of **12e** and **12f** under similar conditions yielded predominantly **17a** and **18a**, respectively. The stereoselective formation of **17a** and **18a** seems to be due to the interaction between the methoxycarbonyl group and the bulky R group (R=*i*-Pr or *t*-Bu) in the cyclization intermediates, respectively.[10]

The conformations of the compounds described above were analyzed as follows. As shown in Table 1, the ^{1}H NMR spectra of **7a**, **8a**, and **13a—18a** showed the signals at δ=3.88—4.51 (dd, $J_{5\alpha,6\beta}$=10.0—11.1 and $J_{5\alpha,6\alpha}$=5.1—5.8 Hz), which suggested the axial orientations of the C-5 proton in these compounds. On the

other hand, the double doublet signals in **7b**, **8b**, and **13b—16b** were observed at δ=5.23—5.48 ($J_{5\alpha,6\alpha}$=6.6—8.1 and $J_{5\alpha,6\beta}$=1.5—2.1 Hz), indicating the equatorial orientations of the C-5 proton in these compounds.[11] The proton signals of the methoxycarbonyl group in **7b**, **8b**, and **13b—15b** were observed at δ=3.59—3.69, while that in **16b** appeared at δ=2.89 because of the magnetic anisotropic effect of the phenyl group on C-11b, being in line with the 1,3-cis relationship of the two substituents on C-5 and -11b in **16b**.[12]

As shown in Table 1, the ^{13}C NMR signals for C-5 and -11b in **7a**, **8a**, and **13a—16a** appeared at lower field than those in the corresponding **7b**, **8b**, and **13b—16b**. This trend is also in agreement with the above-mentioned orientations of the methoxycarbonyl group in these compounds.[13,14] The ^{1}H and ^{13}C NMR characteristics are similar to those of the 1,3-disubstituted 1,2,3,4-tetrahydro-β-carbolines (^{1}H NMR signals of C-3 and -4 protons and ^{13}C NMR signals of C-1 and -3).[12,14,15]

Therefore, assuming that the indolizinone ring is cis-fused,[16] the conformer **A** was assigned to **7a**, **8a**, and **13a—18a**, and the conformer **B** to **7b**, **8b**, and **13b—16b**.

The methoxide-catalyzed equilibrations of the above-mentioned compounds were examined as follows. Each of the compounds **7a,b**, **8a,b**, **13a,b—16a,b**, **17a**, and **18a** was dissolved in 0.1 mol dm^{-3} methanolic sodium methoxide, and let stand at room temperature for a few days until the equilibrium was reached. The ratios of a pair of epimers were determined by HPLC, and the results were shown in Table 1.[9]

The unsubstituted **8a** is thermodynamically more unstable than **8b**, and exists to the extent of less than 1%. Compound **8a** seems to be destabilized by the interaction between the amide carbonyl group and the methoxycarbonyl group on C-5 as shown in the conformer **A** (R=H). Epimerization at C-5 in **7b**, and **13b—16b** seems to be affected by another interaction between the substituent on C-11b and the methoxycarbonyl group on C-5 as shown in the conformer **B**. No epimerization isomers of **17a** and **18a** were detected either by ^{1}H NMR or HPLC. Similar epimerization trend was reported in tetrahydro-β-carboline derivatives.[15]

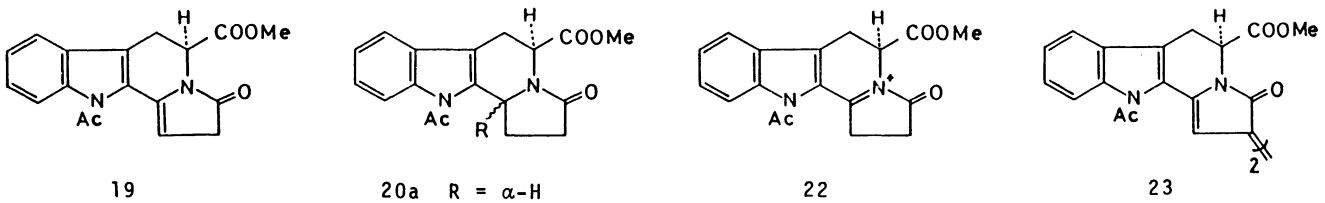
The equilibration experiments excluded the possibility of the epimerization at C-5 in **5a,b** and **6a,b** during the isolation procedure, and supported the existence of two pairs of **5a,b** and **6a,b** in the above plant.

Oxidative Dimerization. Autoxidation of indole compounds gave various products via 3*H*-indol-3-yl hydroperoxides.[17] The coloration of **8b** above its melting point resulted from the formation of **2**, which might proceed via the 3*H*-indol-3-yl hydroperoxide from **8b**.[18] Treatment of **8b** with *N*-bromosuccinimide in *t*-butyl alcohol gave **2** in one-pot reaction; **2** might be produced through **3** derived from **8b** via the corresponding 3-bromo-3*H*-indole. Trichotomine **1** was formed from **7b** by hydrolysis with potassium hydroxide in aqueous methanol, followed by autoxidation in aqueous acetic acid. These results suggested that **5a,b** and **6a,b** were plausible precursors of trichotomine **1**.

In general, indole compounds are stable against autoxidation when the indole nitrogen atom bears a protecting group. Therefore, we examined the oxidative dimerization of **19**, the acetate of **3**.

Acetylation of **8a** and **8b** with acetic anhydride and pyridine gave **20a** and **20b**, respectively. On electrolysis in methanol containing tetrabutylammonium tetrafluoroborate as a supporting electrolyte, both **20a** and **20b** afforded the methoxy lactam **21**, which was formed probably by addition of methanol to an intermediate **22**.[19] The ^{1}H NMR signals of the C-5 proton in **21** (δ=5.37, dd, J=7.2 and 0.9 Hz) indicated the β-orientation of the methoxyl group on C-11b. Treatment of **21** with formic acid yielded **19** after a loss of methanol. On aeration of a solution of **19** in butyl alcohol, **19** underwent oxidative dimerization to trichotomine dimethyl ester diacetate (**23**).[1]

Isolation of **5a** and **5b** shows the involvement of 2-oxo acid, 2-oxoglutaric acid, in the biosynthetic pathway of trichotomine **1** [L-tryptophan→**9a** and /or an epimer at C-1→**5a** and/or **5b**→(**6a** and/or **6b**)→**4**→**1**]; this indicates another example of G. Hahn's proposal.[3] The formation of **1** from **4** and of **23** from **19** might be another type of well-known oxidative dimerization of indoxyl to indigo.[20]



19 20a R = α-H 20b R = β-H 21 R = β-OMe 22 23

Fig. 2.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi EPI-G$_3$. ^{1}H NMR spectra were obtained on a Varian EM-390 (90 MHz) or a JNM-GSX-400 (400 MHz), and ^{13}C NMR spectra on a JNM-PFT-60 (15 MHz) or a JNM-GSX-400 (100 MHz), using $CDCl_3$ as solvent, unless otherwise stated. UV spectra were measured on a JASCO UVIDEC-510 and CD spectra on a JASCO J-500A, using MeOH as solvent. Mass spectra were obtained on a Hitachi M-52 or M-80 at an ionization energy of 70 eV. Optical rotations were measured on a Union PM-101. Analytical TLC was carried out on silica-gel plates (Kieselgel 60 F_{254}, E. Merk). HPLC were performed on a JASCO Trirotor apparatus using a 4.6×250 mm Fine SIL-5 column with $CHCl_3$–hexane (3:2) at 1.3 ml min^{-1} flow rate.

Isolation. The blue fruits of the plant *Clerodendron trichotomum* Thunb (30 kg) were collected in October and immersed in EtOH (75 l) at room temperature for 2 weeks and then filtered. The combined filtrates were concentrated under reduced pressure to ca. 12 l. The remaining aqueous solution (3 l) was washed with AcOEt (3 l×3), and then roughly separated by column chromatography on TSK-gel G-3000s (900 g) using a gradient solution of H_2O–EtOH to give 4 fractions: fraction 1, H_2O 1 l; fraction 2, H_2O–EtOH (4:1) 1 l; fraction 3, H_2O–EtOH (3:2) 1 l; fraction 4, H_2O–EtOH (2:3) 1 l. In the same way, the remaining aqueous solution was separated to 4 fractions. The eluates of fraction 2, 3, and 4 were concentrated under reduced pressure, respectively. Analytical TLC of the residues of fraction 2, 3, and 4 (*n*-BuOH–AcOH–H_2O, 4:1:1) showed the blue spots of **5a** (R_f 0.40), **5b** (R_f 0.52), and **6a,b** (R_f 0.63) with Ehrlich's reagent, respectively. The residue of fraction 2 was further separated by column chromatography on Sephadex LH-20 using MeOH as eluent to give an acidic compound **5a**. To a solution of **5a** in MeOH was added an ethereal solution of CH_2N_2. The mixture was allowed to stand at room temperature overnight, and evaporated to leave an oil, which was purified by column chromatography on SiO_2 using MeOH–$CHCl_3$ (3:100) to give the diester **7a** as a colorless oil (8 mg): IR($CHCl_3$) 3450, 1740, and 1705 cm^{-1}; ^{1}H NMR δ=2.1—3.0 (4H, m, C_1-2H, C_2-2H), 2.99 (1H, dd, J=15.9 and 5.4 Hz, C_6-H), 3.34 (1H, dd, J=15.9 and 10.5 Hz, C_6-H), 3.83 (3H, s, OMe), 3.87 (3H, s OMe), 4.39 (1H, dd, J=10.5 and 5.4 Hz, C_5-H), 7.0—7.6 (4H, m, aromatic protons), and 8.25 (1H, br s, NH); MS m/z (rel intensity) 342 (M$^+$; 3), 283 (100), and 223 (29); CD $[\theta]_{295}$ −1600, $[\theta]_{291}$ −800, $[\theta]_{286}$ −3200, $[\theta]_{259}$ 0, $[\theta]_{236}$ +38000, $[\theta]_{225}$ 0, and $[\theta]_{218}$ −48000. Found: m/z 342.1234. Calcd for $C_{18}H_{18}N_2O_5$: M, 342.1214.

According to essentially the same procedure as described above, fraction 3 afforded **7b** as crystals (76 mg): mp 189—190 °C; IR($CHCl_3$) 3450, 1741, and 1696 cm^{-1}; ^{1}H NMR δ=1.9—3.0 (4H, m, C_1-2H, C_2-2H), 3.06 (1H, dd, J=16.2 and 6.6 Hz, C_6-H), 3.31 (1H, dd, J=16.2 and 1.8 Hz, C_6-H), 3.59 (3H, s, OMe), 3.81 (3H, s, OMe), 5.48 (1H, dd, J=6.6 and 1.8 Hz, C_5-H), 7.0—7.6 (4H, m, aromatic protons), and 8.53 (1H, br s, NH); MS m/z (rel intensity) 342 (M$^+$; 14), 283 (100), and 223 (31); CD $[\theta]_{295}$ +900, $[\theta]_{290}$ 0, $[\theta]_{270}$ +4000, $[\theta]_{259}$ 0, $[\theta]_{238}$ −19000, $[\theta]_{231}$ 0, and $[\theta]_{221}$ +81000.

According to essentially the same procedure as described above, fraction 4 gave a mixture of **8a** and **8b**, which was separated by column chromatography on SiO_2 (MeOH–$CHCl_3$, 3:100). **8a** (as an oil, 9 mg): IR(film) 3300, 1740, and 1677 cm^{-1}; ^{1}H NMR δ=2.0—2.7 (4H, m, C_1-2H, C_2-2H), 2.98 (1H, ddd, J=15.9, 5.1, and 1.8 Hz, C_6-H), 3.35 (1H, ddd, J=15.9, 10.2, and 2.1 Hz, C_6-H), 3.82 (3H, s, OMe), 4.12 (1H, dd, J=10.2 and 5.1 Hz, C_5-H), 5.05 (1H, m, C_{11b}-H), 7.0—7.6 (4H, m, aromatic protons), and 8.02 (1H, br s, NH); MS m/z (rel intersity) 284 (M$^+$; 90), 225 (100), and 223 (60). **8b** (as an oil, 29 mg): IR(film) 3260, 1740, and 1671 cm^{-1}; ^{1}H NMR δ=1.7—2.9 (4H, m, C_1-2H, C_2-2H), 3.10 (1H, ddd, J=15.9, 7.2 and 2.1 Hz, C_6-H), 3.44 (1H, dt, J=15.9 and 1.5 Hz, C_6-H), 3.63 (3H, s, OMe), 5.16 (1H, m, C_{11b}-H), 5.34 (1H, dd, J=7.2 and 1.5 Hz, C_5-H), 7.0—7.6 (4H, m, aromatic protons), and 8.31 (1H, br s, NH); MS m/z (rel intensity) 284 (M$^+$; 100), 225 (60), and 223 (62).

Synthesis of 7a and 7b. A mixture of L-tryptophan methyl ester hydrochloride (1.27 g, 5.0 mmol) and dimethyl 2-oxoglutarate (1.22 g, 7.0 mmol) in MeOH (15 ml) was refluxed for 24 h. The solution was concentrated under reduced pressure to ca. 4 ml,† and allowed to stand at 4 °C overnight to give the crystals of **7b** (0.52 g). The mother liquor was concentrated under reduced pressure to leave an oil, which was dissolved in $CHCl_3$. From the solution, the starting L-tryptophan methyl ester hydrochloride (0.12 g) was recovered by filtration. The filtrate was separated by column chromatography (SiO_2–$CHCl_3$) to give **7b** (0.45 g, total amount of **7b**, 0.97 g, 57%) and **7a** (as an oil, 0.15 g, 10%), which were identical with natural **7a** and **7b** by spectroscopic (IR, ^{1}H NMR, MS, and CD) and TLC comparisons, respectively. **7a**: $[\alpha]_D$ −37° (c 0.54, MeOH); UV 220 (ε 27400), 276 (7490), 282 (7810), and 291 nm (6380); ^{13}C NMR δ=22.6 (C-6), 29.4 (C-1*), 30.2 (C-2*), 52.5 (OMe), 53.3 (OMe), 53.7 (C-5), 66.7 (C-11b), 110.1 (C-6a), 111.5 (C-10), 118.7 (C-7), 120.1 (C-8), 123.1 (C-9), 126.1 (C-6b), 130.1 (C-11a), 136.8 (C-10a), 170.2 (-COO-), 171.3 (-COO-), and 175.2 (C-3). **7b**: $[\alpha]_D$ +110° (c 0.219, MeOH); UV 222 (ε 37600), 273 (8390), 280 (8350), and 290 nm (6550); ^{13}C NMR δ=24.0 (C-6), 30.8 (C-2), 34.0 (C-1), 49.2 (C-5), 52.3 (OMe), 52.8 (OMe), 63.9 (C-11b), 105.8 (C-6a), 111.4 (C-10), 118.5 (C-7), 119.7 (C-8), 122.6 (C-9), 126.0 (C-6b), 130.7 (C-11a), 137.0 (C-10a), 170.8 (-COO-), 172.2 (-COO-), and 174.9 (C-3). Anal. ($C_{18}H_{18}N_2O_5$) C, H, N.

Preparation of 9b. A mixture of L-tryptophan (4.0 g, 20 mmol) and 2-oxoglutaric acid (3.4 g, 23 mmol) in H_2O (250 ml) was allowed to stand at room temperature for 2 weeks under nitrogen atmosphere. The precipitate of the crude **9a** (1.4 g) was collected. To a solution of **9a** (0.80 g) in MeOH (30 ml) was added an ethereal solution of CH_2N_2. The solution was allowed to stand at room temperature for 4 h, and evaporated to leave an oil, which was crystallized from MeOH to give **9b** (0.49 g): mp 142.0—142.5 °C; $[\alpha]_D$ −41° (c 0.285, MeOH); UV 222 (ε 35300), 276 (sh, 8910), 283 (9580), and 291 nm (8090); IR(Nujol) 3420, 3330, 1753, and 1726 cm^{-1}; ^{1}H NMR δ=2.1—2.9 (4H, m), 2.74 (1H, dd, J=15.3 and 9.6 Hz), 3.11 (1H, dd, J=15.3 and 4.8 Hz), 3.60 (3H, s), 3.77 (3H, s,), 3.83 (3H, s), 3.6—3.8 (1H, m), 7.0—7.5 (4H, m), and 8.28 (1H, br s); ^{13}C NMR δ=25.8, 29.5, 34.3,

† HPLC analysis of this solution showed the presence of **7a** and **7b** in a ratio of 1:5. *Asterisks indicate that assignments are not unambiguous.

51.6, 52.3, 53.1, 61.4, 108.9, 111.2, 118.4, 119.6, 122.5, 126.5, 131,5, 136.1, 172.7, and 173.7; MS *m/z* 374 (M^+); CD $[\theta]_{298}$ +700, $[\theta]_{295}$ 0, $[\theta]_{291}$ −2600, $[\theta]_{288}$ −1200, $[\theta]_{283}$ −2600, $[\theta]_{267}$ −1300, $[\theta]_{235}$ −36600, $[\theta]_{227}$ 0, and $[\theta]_{219}$ +45200. Anal. ($C_{19}H_{22}N_2O_6$) C, H, N.

Cyclization of 9b to 7b. A solution of **9b** (43 mg) in 8 wt% HCl-MeOH (5 ml) was refluxed for 1 h. The solution was concentrated under reduced pressure to leave an oil, which was crystallized with $CHCl_3$–hexane to give **7b** (25 mg, 64%), which was identical with that obtained above by IR and TLC comparisons.

$NaBH_4$ Reduction of 7b. A mixture of **7b** (1.0 g, 2.9 mmol) and $NaBH_4$ (0.4 g, 11 mmol) in MeOH–THF (4—16 ml) was stirred at room temperature for 1 h, and then concentrated under reduced pressure. The residue was partitioned between H_2O and $CHCl_3$. The organic layer was dried over Na_2SO_4, and evaporated under reduced pressure to give **10** (0.58 g, 69%): mp 226—227 °C (from acetone–diisopropyl ether); $[\alpha]_D$ +138° (*c* 0.208, MeOH); UV 223 (ε 37400), 273 (7940), 278 (8090), 281 (8070), and 289 nm (6570); IR(Nujol) 3380, 3290, and 1664 cm^{-1}; ^1H NMR(CD_3OD) δ=1.9—3.1 (6H, m), 3.54 (1H, dd, *J*=10.8 and 8.4 Hz), 3.70 (1H, d, *J*=11.7 Hz), 3.72 (1H, dd, *J*=10.8 and 7.5 Hz), 3.92 (1H, d, *J*=11.7 Hz), 4.9 (1H, m), and 6.8—7.5 (4H, m); ^{13}C NMR (pyridine-d_5) δ=22.2, 31.5, 32.0, 49.7, 63.6, 64.1, 69.5, 104.9, 111.8, 118.8, 119.5, 121.9, 127.9, 135.9, 137.7, and 175.5; MS *m/z* 286 (M^+). Anal. ($C_{16}H_{18}N_2O_3$) C, H, N.

Formation of 11. A mixture of **10** (300 mg, 1.1 mmol) and *p*-toluenesulfonyl chloride (300 mg, 1.6 mmol) in pyridine (3 ml) was kept at 60 °C for 30 h. The solution was concentrated under reduced pressure to leave an oil, which was dissolved in $CHCl_3$. The solution was successively washed with dilute HCl, H_2O, and aqueous $NaHCO_3$, and then dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave an oil, which was crystallized from $CHCl_3$–hexane to yield **11** (96 mg, 34%): mp>300 °C (from EtOH); UV 224 (28800), 274 (sh 7210), 279 (sh 7430), 281 (7450), and 289 nm (6050); IR(Nujol) 3250, 1671, and 1649 cm^{-1}; ^1H NMR (pyridine-d_5) δ=1.7—2.8 (4H, m), 2.88 (1H, d, *J*=16.2 Hz), 3.39 (1H, ddd, *J*=16.2, 6.9, and 0.9 Hz), 3.48 (1H, d, *J*=10.5 Hz), 3.71 (1H, dd, *J*=11.4 and 2.7 Hz), 3.90 (1H, d, *J*=10.5 Hz), 3.99 (1H, dd, *J*=11.4 and 0.9 Hz), 4.60 (1H, dd, *J*=6.9 and 2.7 Hz), 7.2—7.7 (4H, m), and 8.70 (1H, br s); ^{13}C NMR (pyridine-d_5) δ=25.0, 25.6, 30.0, 46.1, 59.2, 72.2, 73.4, 110.5, 112.0, 118.5, 119.5, 121.7, 127.6, 135.1, 137.2, and 172.1; MS *m/z* 268 (M^+). Anal. ($C_{16}H_{16}N_2O_2$) C, H, N.

Epimerization of 7a. A solution of the natural **7a** (4 mg) in 0.1 mol dm^{-3} methanolic NaOMe (0.2 ml) was allowed to stand at room temperature overnight. After addition of AcOH (2 drops), the solution was concentrated under reduced pressure. The residue was partitioned between aqueous $NaHCO_3$ and $CHCl_3$. The organic layer was dried over Na_2SO_4, and concentrated under reduced pressure to give a mixture of **7a** and the antipode of **7b** in a ratio of 1:9 (by HPLC). CD of the reaction products $[\theta]_{238}$ +17000, $[\theta]_{231}$ 0, and $[\theta]_{221}$ −67000.

Antipode of 7b. According to essentially the same procedure as described above, the reaction of D-tryptophan methyl ester hydrochloride and dimethyl 2-oxoglutarate in MeOH yielded the antipode of **7b**: $[\alpha]_D$ −107° (*c* 0.205, MeOH); CD $[\theta]_{295}$ −1100, $[\theta]_{291}$ 0, $[\theta]_{286}$ −2200, $[\theta]_{284}$ −2000, $[\theta]_{270}$ −4300, $[\theta]_{259}$ 0, $[\theta]_{238}$ +18000, $[\theta]_{231}$ 0, and $[\theta]_{221}$ −78000.

Synthesis of 8a and 8b. According to the literature,[7] L-tryptophan methyl ester (4.36 g, 20 mmol) was dissolved in benzene (400 ml), and 2-oxoglutaric acid (3.5 g, 24 mmol) was added in small portions to the refluxing solution. After addition, reflux was continued for 19 h. The solution was washed with aqueous $NaHCO_3$, dried over Na_2SO_4, and then concentrated under reduced pressure to ca. 20 ml[††] to yield the crystals of **8b**[7] (2.94 g). The mother liquor was concentrated under reduced pressure to leave an oil, which was separated by column chromatography on SiO_2. Elution with $CHCl_3$ gave **8b** (0.62 g, total amount of **8b**, 3.56 g, 64%) and **8a** (0.94 g, 12%), which were identical with the natural **8b** and **8a** by spectroscopic (IR, ^1H NMR, MS, and CD), and TLC comparisons, respectively. **8a:** mp 109—111 °C (from $CHCl_3$); $[\alpha]_D$ −110° (*c* 0.218, MeOH); ^{13}C NMR δ=22.8 (C-6), 24.3 (C-1), 30.1 (C-2), 52.5 (OMe), 54.7 (C-5), 56.3 (C-11b), 108.0 (C-6a), 111.3, (C-10), 118.2 (C-7), 119.8 (C-8), 122.2 (C-9), 126.5 (C-6b), 133.3 (C-11a), 136.5 (C-10a), 170.2 (–COO–), and 175.9 (C-3); CD $[\theta]_{294}$ +2400, $[\theta]_{289}$ +100, $[\theta]_{285}$ +2700, $[\theta]_{282}$ +2400, $[\theta]_{269}$ +6100, $[\theta]_{246}$ +2700, $[\theta]_{231}$ +15700, $[\theta]_{226}$ 0, and $[\theta]_{218}$ −42300. Anal. ($C_{16}H_{16}N_2O_3 \cdot CHCl_3$) C, H, N. Found: *m/z* 284.1174. Calcd for $C_{16}H_{16}N_2O_3$: M, 284.1159. **8b:** mp 202—203 °C (from $CHCl_3$–hexane); $[\alpha]_D$ +187° (*c* 0.214, MeOH); ^{13}C NMR δ=23.7 (C-6), 26.3 (C-1), 31.6 (C-2), 49.5 (C-5), 52.5 (C-11b and OMe), 105.0 (C-6a), 111.1 (C-10), 118.3 (C-7), 119.7 (C-8), 122.1 (C-9), 126.6 (C-6b), 132.6 (C-11a), 136.5 (C-10a), 171.1 (–COO–), and 173.9 (C-3); CD $[\theta]_{295}$ −400, $[\theta]_{293}$ 0, $[\theta]_{289}$ +1600, $[\theta]_{286}$ 0, $[\theta]_{285}$ −200, $[\theta]_{284}$ 0, $[\theta]_{282}$ +400, $[\theta]_{280}$ 0, $[\theta]_{232}$ −22000, $[\theta]_{227}$ 0, and $[\theta]_{215}$ +61000.

Epimerization of 8a. A solution of **8a** (170 mg) in 0.1 mol dm^{-3} methanolic NaOMe (2 ml) was allowed to stand at room temperature for 2 h. After addition of AcOH (0.1 ml), the solution was worked up as described above to give an epimer almost quantitatively, which was identical with the antipode of **8b** prepared as described below ($[\alpha]_D$, IR, ^1H NMR, and CD).

Antipode of 8b. According to essentially the same procedure as described above, the reaction of D-tryptophan methyl ester and 2-oxoglutaric acid in benzene yielded the antipode of **8a** and the antipode of **8b**. Antipode of **8a:** $[\alpha]_D$ +112° (*c* 0.203, MeOH). Antipode of **8b:** $[\alpha]_D$ −186° (*c* 0.205, MeOH); CD $[\theta]_{295}$ +600, $[\theta]_{292}$ 0, $[\theta]_{289}$ −1700, $[\theta]_{285}$ −300, $[\theta]_{282}$ −800, $[\theta]_{278}$ 0, $[\theta]_{232}$ +23000, $[\theta]_{226}$ 0, and $[\theta]_{215}$ −61000.

Preparation of 12a. A solution of L-tryptophan methyl ester (2.18 g, 10 mmol) and 5-methyl-2(3*H*)-furanone (1.20 g, 12 mmol) in benzene (30 ml) was allowed to stand at room temperature for 22 h to give **12a** (2.86 g, 91%): mp 139—140 °C (from MeOH); IR(Nujol) 3360, 1753, 1701, and 1654 cm^{-1}; MS *m/z* 316 (M^+); Anal. ($C_{17}H_{20}N_2O_4$) C, H, N.

Preparation of the Amides 12b—12f. 1) A typical procedure is described for the preparation of **12b**. To a solution of L-tryptophan methyl ester (2.18 g, 10 mmol) and 4-oxohexanoic acid[21] (1.30 g, 10 mmol) in CH_2Cl_2 (60 ml) was added a solution of dicyclohexylcarbodiimide (2.06 g, 10 mmol) in CH_2Cl_2 (40 ml). The reaction mixture was stirred at room temperature for 7 h. AcOH (3 drops) was added to the reaction mixture, and the *N,N'*-dicyclohexylurea which precipitated was removed by filtration. The filtrate was concentrated under reduced pressure to leave an oil, which was crystallized from benzene to give the crude **12b**.

†† HPLC analysis of this solution showed the presence of **8a** and **8b** in a ratio of 1:3.

Recrystallization from MeOH afforded the colorless crystals of **12b** (2.70 g, 82%): mp 129—130 °C; IR(Nujol) 3280, 1753, 1708, and 1654 cm^{-1}; MS *m/z* 330 (M^+); Anal. ($C_{18}H_{22}N_2O_4$) C, H, N.

2) The amide **12c** was prepared using 4-oxoheptanoic acid.[22] **12c** (77%): mp 89—90 °C; IR(Nujol) 3390, 1739, 1720, and 1660 cm^{-1}; MS *m/z* 344 (M^+); Anal. ($C_{19}H_{24}N_2O_4$) C, H, N.

3) The amide **12d** was prepared using 3-benzoylpropanoic acid. **12d** (84%): mp 101—102 °C; IR(Nujol) 3310, 1739, and 1660 cm^{-1}; MS *m/z* 378 (M^+); Anal. ($C_{22}H_{22}N_2O_4$) C, H, N.

4) The amide **12e** was prepared using 5-methyl-4-oxohexanoic acid.[23] **12e** (88%): mp 128—129 °C; IR(Nujol) 3280, 1740, 1715, and 1660 cm^{-1}; MS *m/z* 344 (M^+); Anal. ($C_{19}H_{24}N_2O_4$) C, H, N.

5) The amide **12f** was prepared using 5,5-dimethyl-4-oxohexanoic acid.[23] **12f** (86%): mp 160—161 °C; IR(Nujol) 3270, 1740, 1709, and 1661 cm^{-1}; MS *m/z* 358 (M^+); Anal. ($C_{20}H_{26}N_2O_4$) C, H, N.

Cyclization of the Amides 12a—12f. 1) A typical procedure is described for the cyclization of the amide **12a**. A solution of **12a** (158 mg, 0.50 mmol) in 13 wt% hydrogen chloride–MeOH (10 ml) was allowed to stand at room temperature for 20 h. The solution was concentrated under reduced pressure. The residue was partitioned between aqueous $NaHCO_3$ and $CHCl_3$. The organic layer was dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave a mixture of **13a** and **13b** (ratio determined by HPLC, 1:2) almost quantitatively, which were separated after column chromatography (SiO_2–$CHCl_3$). **13a**: mp 247—248 °C (from MeOH); IR($CHCl_3$) 3460, 1740, and 1691 cm^{-1}; ^1H NMR δ=1.70 (3H, s), 2.1—2.8 (4H, m), 2.95 (1H, dd, *J*=15.9 and 5.1 Hz), 3.33 (1H, dd, *J*=15.9 and 10.8 Hz), 3.79 (3H, s), 4.09 (1H, dd, *J*=10.8 and 5.1 Hz), 7.0—7.6 (4H, m), and 8.33 (1H, br s); ^{13}C NMR δ=22.7, 27.0, 29.7, 32.1, 52.2, 52.4, 61.9, 107.1, 111.3, 118.3, 119.8, 122.2, 126.5, 136.4, 137.2, 170.7, and 176.6; MS *m/z* 298 (M^+) and 283; Anal. ($C_{17}H_{18}N_2O_3$) C, H, N. **13b**: mp 218—219 °C (from $CHCl_3$–hexane); IR($CHCl_3$) 3460, 1745, and 1683 cm^{-1}; ^1H NMR δ=1.58 (3H, s), 2.0—2.8 (4H, m), 2.98, (1H, dd, *J*=15.9 and 7.8 Hz), 3.57 (1H, dd, *J*=15.9 and 1.5 Hz), 3.66 (3H, s), 5.40 (1H, dd, *J*=7.8 and 1.5 Hz), 7.0—7.5 (4H, m), and 8.33 (1H, br s); ^{13}C NMR δ=21.8, 25.9, 30.6, 34.7, 48.7, 52.4, 59.8, 103.6, 111.1, 118.6, 119.6, 122.1, 126.5, 136.4, 136.7, 171.7, and 174.2; MS *m/z* 298 (M^+) and 283; Anal. ($C_{17}H_{18}N_2O_3$) C, H, N.

2) Cyclization of the amide **12b** gave a mixture of **14a** and **14b** (ratio, 2:1) almost quantitatively. **14a**: mp 246—247 °C (from MeOH); IR($CHCl_3$) 3460, 1748, and 1693 cm^{-1}; ^1H NMR δ=1.12 (3H, t, *J*=7.5 Hz), 1.98 (2H, q, *J*=7.5 Hz), 2.0—2.7 (4H, m), 2.96 (1H, dd, *J*=15.9 and 5.1 Hz), 3.34 (1H, dd, *J*=15.9 and 10.8 Hz), 3.83 (3H, s), 4.07 (1H, dd, *J*=10.8 and 5.1 Hz), 7.0—7.6 (4H, m), and 8.00 (1H, br s); ^{13}C NMR δ=8.1, 22.6, 28.2, 29.9, 31.9, 52.1, 52.4, 64.9, 106.9, 111.2, 118.2, 119.7, 122.1, 126.5, 136.4, 137.8, 170.6, and 176.6; MS *m/z* 312 (M^+) and 283; Anal. ($C_{18}H_{20}N_2O_3$) C, H, N. **14b**: mp 191—192 °C (from MeOH); IR($CHCl_3$) 3460, 1744, and 1681 cm^{-1}; ^1H NMR δ=1.08 (3H, t, *J*=7.2 Hz), 1.83, (2H, q, *J*=7.2 Hz), 2.0—2.9 (4H, m), 3.04 (1H, dd, *J*=16.2 and 8.1 Hz), 3.51 (1H, dd, *J*=16.2 and 2.1 Hz), 3.68 (3H, s), 5.39 (1H, dd *J*=8.1 and 2.1 Hz), 7.0—7.6 (4H, m), and 8.15 (1H, br s); ^{13}C NMR δ=8.5, 21.4, 30.3, 31.0, 33.7, 48.9, 52.3, 63.1, 104.1, 111.0, 118.6, 119.8, 122.2, 126.5, 136.2, 137.1, 171.8, and 174.7; MS *m/z* 312 (M^+) and 283; Anal. ($C_{18}H_{20}N_2O_3$) C, H, N.

3) Cyclization of the amide **12c** gave a mixture of **15a** and **15b** (ratio, 2:1). **15a** (54%): $[\alpha]_D$ −148° (*c* 0.119, MeOH); IR($CHCl_3$) 3450, 1742, and 1688 cm^{-1}; ^1H NMR δ=0.96 (3H, t, *J*=6.6 Hz), 1.3—2.0 (4H, m), 2.0—2.7 (4H, m), 2.96 (1H, dd, *J*=16.0 and 5.1 Hz), 3.34 (1H, dd, *J*=16.0 and 10.7 Hz), 3.82 (3H, s), 4.10 (1H, dd, *J*=10.7 and 5.1 Hz), 7.0—7.6 (4H, m), and 8.30 (1H, br s); ^{13}C NMR δ=14.3, 17.2, 22.6, 29.1, 29.9, 41.8, 52.2, 64.6, 107.0, 111.2, 118.2, 119.7, 122.1, 126.5, 136.3, 137.6, 170.6, and 176.5; MS *m/z* 326 and 283. Found: *m/z* 326.1612. Calcd for $C_{19}H_{22}N_2O_3$: M, 326.1628. **15b** (20%): mp 244—245°C (from $CHCl_3$–hexane); $[\alpha]_D$ +105° (*c* 0.124, MeOH); IR($CHCl_3$) 3450, 1740, and 1677 cm^{-1}; ^1H NMR δ=0.91 (3H, t, *J*=6.6 Hz), 1.2—2.0 (4H, m), 2.0—2.8 (4H, m), 3.03 (1H, dd, *J*=15.9 and 8.1 Hz), 3.51 (1H, dd, *J*=15.9 and 2.1 Hz), 3.69 (3H, s), 5.37 (1H, dd, *J*=8.1 and 2.1 Hz). 7.0—7.6 (4H, m), and 8.03 (1H, br s); ^{13}C NMR δ=14.3, 17.4, 21.4, 31.0, 43.3, 48.9, 52.4, 62.9, 103.8, 111.0, 118.5, 119.6, 122.1, 126.4, 136.2, 137.2, 171.7, and 174.7; MS *m/z* 326 (M^+) and 283; Anal. ($C_{19}H_{22}N_2O_3$) C, H, N.

4) Cyclization of the amide **12d** gave a mixture of **16a** and **16b** (ratio, >20:1). **16a** (82%): mp 236—237 °C (from MeOH); IR($CHCl_3$) 3450, 3270, 1735, and 1690 cm^{-1}; ^1H NMR δ=2.1—2.7 (4H, m), 2.87 (1H, dd, *J*=15.6 and 5.1 Hz), 3.42 (1H, dd, *J*=15.6 and 11.1 Hz), 3.74 (3H, s), 3.88 (1H, dd, *J*=11.1 and 5.1 Hz), 7.0—7.6 (9H, m), and 8.97 (1H, br s); ^{13}C NMR δ=22.2, 30.1, 34.1, 52.1, 52.4, 68.1, 109.6, 111.4, 118.5, 119.8, 122.6, 126.4, 126.5, 128.1, 128.7, 134.2, 136.5, 142.9, 170.4, and 177.0; MS *m/z* 360 (M^+) and 283; Anal. ($C_{22}H_{20}N_2O_3$) C, H, N. **16b** (3%): mp 265—266 °C (from $CHCl_3$–hexane); IR($CHCl_3$) 3450, 1745, and 1684 cm^{-1}; ^1H NMR δ=2.4—3.2 (4H, m), 2.89 (3H, s), 3.00 (1H, dd, *J*=15.6 and 7.8 Hz), 3.50 (1H, dd, *J*=15.6 and 1.8 Hz), 5.23 (1H, dd, *J*=7.8 and 1.8 Hz), 7.0—7.7 (9H, m), and 8.25 (1H, br s); ^{13}C NMR δ=20.7, 31.1, 34.3, 48.3, 51.7, 64.4, 107.5, 111.1, 118.9, 120.0, 122.6, 126.4, 127.1, 128.2, 128.7, 134.0, 136.4, 143.0, 170.4, and 173.8; MS *m/z* 360 (M^+) and 283; Anal. ($C_{22}H_{20}N_2O_3$) C, H, N.

5) Cyclization of the amide **12e** gave **17a** (80%): $[\alpha]_D$ −80° (*c* 0.201, MeOH); IR($CHCl_3$) 3460, 1742, and 1689 cm^{-1}; ^1H NMR δ=1.09 (3H, d, *J*=7.1 Hz), 1.17 (3H, d, *J*=7.1 Hz), 2.0—2.6 (5H, m), 2.96 (1H, dd, *J*=15.9 and 5.4 Hz), 3.37 (1H, dd, *J*=15.9 and 10.8 Hz), 3.81 (3H, s), 4.15 (1H, dd, *J*=10.8 and 5.4 Hz), 7.0—7.6 (4H, m), and 8.27 (1H, br s); ^{13}C NMR δ=17.2, 22.4, 24.5, 29.8, 35.5, 51.8, 52.4, 67.7, 108.0, 111.2, 118.3, 119.8, 122.3, 126.5, 136.2, 137.2, 170.6, and 176.8; MS *m/z* 326 and 283. Found: *m/z* 326.1642. Calcd for $C_{19}H_{22}N_2O_3$: M, 326.1629.

6) Cyclization of the amide **12f** gave **18a** (79%): mp 231—232 °C (from benzene); $[\alpha]_D$ −90° (*c* 0.201, MeOH); IR ($CHCl_3$) 3460, 1740, and 1685 cm^{-1}; ^1H NMR δ=1.16 (9H, s), 2.0—2.7 (4H, m), 2.98 (1H, dd, *J*=16.0 and 5.8 Hz), 3.31 (1H, dd, *J*=16.0 and 10.0 Hz), 3.78 (3H, s), 4.51 (1H, dd, *J*=10.0 and 5.8 Hz), 7.0—7.6 (4H, m), and 8.20 (1H, br s); ^{13}C NMR δ=22.2, 27.1, 28.0, 30.0, 39.6, 52.3, 53.9, 70.5, 109.0, 111.2, 118.2, 119.6, 122.2, 126.3, 135.5, 136.4, 171.1, and 177.9; MS *m/z* 283 (M^+ −57). Anal. ($C_{20}H_{24}N_2O_3$) C, H, N.

Methoxide-Catalyzed Equilibration. Each compound **7a,b**, **8a,b**, **13a,b**—**16a,b**, **17a**, and **18a** (0.1 mmol) was dissolved in 0.1 mol dm^{-3} methanolic NaOMe (3 ml). Each solution was kept at room temperature for a few days until the equilibrium was reached. After addition of AcOH (2 drops), each solution was worked up as described above to give a

residue, which was analyzed by HPLC. The results were summarized in Table 1.

***N*-Bromosuccinimide (NBS) Oxidation of 8b.** A mixture of **8b** (57 mg, 0.20 mmol) and NBS (53 mg, 0.30 mmol) in *t*-BuOH (30 ml) was stirred at 26—32 °C for 2 days. The resulting blue solution was concentrated under reduced pressure to give a residue, which was dissolved in AcOEt. The solution was washed with water, dried over Na_2SO_4, and evaporated under reduced pressure. Separation of the residue by column chromatography (SiO_2–$CHCl_3$) afforded **2** (6 mg, 11%), which was identical with that synthesized following the procedure of Iwadare et al.[2] (IR, ^1H NMR, CD, and TLC).

Conversion of 7b into 1. A solution of **7b** (103 mg, 0.30 mmol) and KOH (45 mg, 0.80 mmol) in H_2O–MeOH (0.8—8 ml) was allowed to stand at 26—30 °C for 22 h to give crystals of the potassium salt of **5b** (90 mg, 77%): IR(Nujol) 1676, 1640, and 1609 cm^{-1}; ^1H NMR (D_2O) δ=1.98 (1H, m), 2.44 (1H, m), 2.63 (1H, m), 2.84 (1H, dd, J=15.8 and 7.3 Hz), 2.98 (1H, m), 3.19 (1H, dd, J=15.8 and 1.5 Hz), 4.96 (1H, dd, J=7.3 and 1.5 Hz), 7.14 (1H, t, J=8.0 Hz), 7.22 (1H, t, J=8.0 Hz), 7.46 (1H, d, J=8.0 Hz), and 7.54 (1H, d, J=8.0 Hz); ^{13}C NMR (D_2O) δ=26.4, 34.4, 36.3, 55.5, 70.1, 107.5, 114.2, 121.1, 121.9, 124.4, 128.7, 137.6, 139.1, 179.3, 180.1, and 181.1.

A solution of the potassium salt of **5b** (30 mg) in H_2O–AcOH (3—0.2 ml) was stirred at 24—29 °C for 4 days to give a dark blue precipitate (13 mg). Analytical TLC of the precipitate (*n*-BuOH–AcOH–H_2O, 4:1:1) showed the presence of a blue spot (R_f 0.88) corresponding to trichotomine **1**. To a solution of the precipitate (13 mg) in MeOH (10 ml) was added an ethereal solution of CH_2N_2. The mixture was allowed to stand at 24 °C for 2 h, and evaporated. Separation of the blue residue by column chromatography (SiO_2–$CHCl_3$) gave **2** (0.3 mg), which was identical with the authentic sample[2] (^1H NMR and TLC).

Acetylation of 8a. A solution of **8a** (202 mg, 0.50 mmol) in acetic anhydride–pyridine (5—8 ml) was heated at 88—93 °C for 15 h. The solution was concentrated under reduced pressure to give an oil, which was purified by column chromatography (SiO_2–$CHCl_3$), and crystallized from MeOH to give **20a** (102 mg, 63%): mp 261—263 °C; $[\alpha]_D$ −314° (*c* 0.042, MeOH); UV 204 (ε 27900), 241 (18100), 264 (11700), 291 (6160), and 299 nm (6160); IR(Nujol) 1742, 1703, and 1682 cm^{-1}; ^1H NMR δ=1.8—2.9 (4H, m), 2.80, (3H, s), 2.91 (1H, ddd, J=16.8, 4.8 and 2.4 Hz), 3.28 (1H, ddd, J=16.8, 10.8, and 2.7 Hz), 3.88 (3H, s), 3.99 (1H, dd, J=10.8 and 4.8 Hz), 5.48 (1H, m), and 7,2—7.8 (4H, m); ^{13}C NMR δ=23.3, 25.3, 26.9, 29.8, 52.5, 53.9, 58.8, 114.0, 117.1, 119.2, 123.5, 124.9, 129.6, 135.3, 137.0, 168.7, 169.7, and 175.4; MS *m/z* 326 (M^+), 283, 225, and 223; CD $[\theta]_{288}$ −11300, $[\theta]_{282}$ −10800, $[\theta]_{252}$ −42700, $[\theta]_{242}$ 0, $[\theta]_{226}$ +55600, $[\theta]_{210}$ 0; Anal. ($C_{18}H_{18}N_2O_4$) C, H, N.

Acetylation of 8b. A solution of **8b** (284 mg) in acetic anhydride–pyridine (5—7 ml) was heated at 90 °C for 8 h, and work up as described above to give **20b** (257 mg, 79%): mp 183—184 °C (from MeOH); $[\alpha]_D$ +277° (*c* 0.205, MeOH); UV 204 (ε 24000), 241 (16100), 263 (10100), 290 (5090), and 299 nm (5020); IR(Nujol) 1745, 1716, and 1697 cm^{-1}; ^1H NMR δ=1.6—3.2 (5H, m), 2.79 (3H, s), 3.41 (1H, dt, J=16.5 and 1.5 Hz), 3.67 (3H, s), 5.39 (1H, dd, J=7.2 and 1.2 Hz), 5.50 (1H, m), and 7.2—7.8 (4H, m), ^{13}C NMR δ=23.7, 27.1, 31.0, 48.4, 52.6, 55.0, 114.0, 119.1, 123.2, 124.7, 129.5, 135.1, 135.5, 168.6, 170.6, and 173.9; MS *m/z* 326 (M^+), 283, 225, and 223; CD $[\theta]_{256}$ +28700, $[\theta]_{242}$ 0, and $[\theta]_{227}$ −36400; Anal. ($C_{18}H_{18}N_2O_4$) C, H, N.

Electrolysis of 20a and 20b. A mixture of **20a** (65 mg, 0.20 mmol), tetrabutylammonium tetrafluoroborate (330 mg) and MeOH (80 ml) was placed in a beaker-type undivided cell, and glassy carbon rods were used as an anode and a cathode, respectively.[24] After electrolysis at constant potential of 1.3 V vs. SCE (electricity: ca. 5.5 F mol^{-1} (1F=96480 C)), the electrolytic solution was concentrated under reduced pressure to give a residue, which was dissolved in benzene. The solution was washed with H_2O and with brine, and then dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave an oil, which was purified by column chromatography (SiO_2–$CHCl_3$) to afford **21** (as an oil, 47 mg, 66%): IR($CHCl_3$) 1744 and 1708 cm^{-1}; ^1H NMR δ=2.2—3.5 (4H, m), 2.80 (3H, s), 2.89 (1H, dd, J=16.2 and 7.2 Hz), 3.32 (3H, s), 3.53 (1H, dd, J=16.2 and 0.9 Hz), 3.70 (3H, s), 5.37 (1H, dd, J=7.2 and 0.9 Hz), and 7.2—7.8 (4H, m); MS *m/z* 356 (M^+), 325, 283, 282, and 223. Found: *m/z* 356.1387. Calcd for $C_{19}H_{20}N_2O_5$: M, 356.1371.

Under similar conditions to those described above, **20b** (65 mg, 0.20 mmol) was electrolyzed to give **21** (43 mg, 61%), which was identical with that obtained from **20a** by ^1H NMR and TLC comparisons.

Formation of 19. A solution of **21** (49 mg, 0.14 mmol) in 99% HCOOH–$CHCl_3$ (0.3—2.7 ml) was kept at 15 °C for 1 h. The solution was washed with aqueous $NaHCO_3$, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave an oil, which was purified by column chromatography (SiO_2–$CHCl_3$) to yield **19** (as an oil, 37 mg, 82%): IR($CHCl_3$) 1748, 1710, and 1641 cm^{-1}; ^1H NMR δ=2.77 (3H, s), 3.12 (1H, dd, J=16.8 and 6.9 Hz), 3.35 (2H, m), 3.66 (3H, s), 3.67 (1H, dd, J=16.8 and 1.2 Hz), 5.22 (1H, dd, J=6.9 and 1.2 Hz), 5.71 (1H, t, J=3.0 Hz), 7.2—7.8 (3H, m), and 7.90 (1H, m); MS *m/z* 324 (M^+), 282, and 223. Found: *m/z* 324.1105. Calcd for $C_{18}H_{16}N_2O_4$: M, 324.1109.

Air Oxidation of 19. According to Iwadare's method,[2] air was bubbled with capillary tubing through a solution of **19** (37 mg) in *n*-BuOH (50 ml) kept at 66—76 °C for 19 h. The blue solution was concentrated under reduced pressure. The residue was separated by column chromatography (SiO_2–$CHCl_3$) to give **23** (8 mg, 22%), which was identical with that synthesized following the procedure of Iwadare et al.[1,2] (IR, ^1H NMR, and TLC). **23**: ^{13}C NMR δ=24.8, 27.0, 48.5, 53.0, 102.7, 115.1, 120.2, 123.2, 124.0, 126.8, 127.5, 128.0, 128.9, 136.2, 139.3, 168.1, 169.8, and 170.4; CD $[\theta]_{427}$ −12000, $[\theta]_{407}$ 0, $[\theta]_{364}$ +55000, $[\theta]_{345}$ 0, and $[\theta]_{326}$ −38400.

We would like to thank Dr. Hiroshi Sakurai of Meijo University for obtaining the mass spectra.

References

1) S. Iwadare, Y. Shizuri, K. Sasaki, and Y. Hirata, *Tetrahedron*, **30**, 4105 (1974).

2) S. Iwadare, Y. Shizuri, K. Yamada, and Y. Hirata, *Tetrahedron*, **34**, 1457 (1978).

3) G. J. Kapadia and R. E. Rao, *Tetrahedron Lett.*, **1977**, 975, and references cited therein.

4) G. Palmisano, B. Danieli, G. Lesma, and R. Riva, *J. Org. Chem.*, **50**, 3322, (1985).

5) Y. Toyoda, H. Kumagai, H. Irikawa, and Y.

Okumura, *Chem. Lett.*, **1982**, 903.
6) H. Irikawa and Y. Okumura, *Chem Lett.*, **1983**, 1055.
7) D. Soerens, J. Sandrin, F. Ungemach, P. Mokry, G. S. Wu, E. Yamanaka, L. Hutchins, M. DiPierro, and J. M. Cook, *J. Org. Chem.*, **44**, 535 (1979).
8) L. Bartlett, N. J. Dastoor, J. Hrbek jr., W. Klyne, H. Schmid, and G. Snatzke, *Helv. Chim. Acta*, **54**, 1238 (1971).
9) The figures of the products show the relative configurations of the methoxycarbonyl group on C-5 and the substituent on C-11b because of the epimerization at C-5.
10) F. Ungemach, M. DiPierro, R. Weber, and J. M. Cook, *J. Org. Chem.*, **46**, 164 (1981).
11) B. E. Maryanoff, D. F. McComsey, and B. A. Duhl-Emswiler, *J. Org. Chem.*, **48**, 5062 (1983).
12) F. Hamaguchi, T. Nagasaka, and S. Ohki, *Yakugaku Zasshi*, **94**, 351 (1974).
13) N. K. Wilson and J. B. Stothers, "Topics in Stereochemistry," ed by E. L. Eliel and N. L. Allinger, J. Wiley & Sons, New York (1974), Vol. 8, p. 26.
14) F. Ungemach, D. Soerens, R. Weber, M. DiPierro, O. Campos, P. Mokry, J. M. Cook, and J. V. Silverton, *J. Am. Chem. Soc.*, **102**, 6976 (1980).
15) K. T. D. DeSilva, D. King, and G. N. Smith, *J. Chem. Soc., Chem. Commun.*, **1971**, 908.
16) E. Wenkert, S. Garratt, and K. G. Dave, *Can. J. Chem.*, **42**, 489 (1964).
17) S. McLean and G. I. Dmitrienko, *Can. J. Chem.*, **49**, 3642 (1971), and references cited therein.
18) H. Irikawa and Y. Okumura, *Bull. Chem. Soc. Jpn.*, **60**, 3797 (1987).
19) T. Shono, H. Hamaguchi, and Y. Matsumura, *J. Am. Chem. Soc.*, **97**, 4264 (1975).
20) G. A. Russell and G. Kaupp, *J. Am. Chem. Soc.*, **91**, 3851 (1969).
21) M. C. Kloetzel, *J. Am. Chem. Soc.*, **70**, 3571 (1948).
22) A. S. Perlin and C. B. Purves, *Can. J. Chem.*, **31**, 227 (1953).
23) P. W. Ford, *Aust. J. Chem.*, **27**, 2525 (1974).
24) T. Shono, Y. Matsumura, and K. Tsubata, *Org. Synth.*, Vol. 63, 206 (1984).