Synthetic Approaches to Fumitremorgins. III. Synthesis of Optically Active Pentacyclic Ring Systems, and Their Oxidation at Ring C[1)]

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Pictet–Spengler reaction of L-tryptophan methyl ester (9) and 6-methoxy-L-tryptophan methyl ester (40) with isovaleraldehyde (10) in methylene chloride in the presence of trifluoroacetic acid gave the *cis*-tetrahydro-β-carboline (11, 41) as the major isomer. The condensation of 11 and 41 with *N*-benzyloxycarbonyl-L-proline followed by deprotection gave the *cis–cis*-pentacycles (27, 44) which contain the parent ring system of fumitremorgins. The *trans–cis* (28), the *cis–trans* (29, 30) and the *trans–trans* (31) pentacycles were similarly prepared. Isopentylation of 27 and 44 gave the N_a-isopentyl derivatives (52, 53) accompanied with epimerization at the 12-position. Oxidation of 52 and 53 with dichlorodicyano-*p*-benzoquinone (DDQ) gave the 12,13-dehydro derivatives (54, 55) which provided demethoxy-13-*epi*-tetrahydrofumitremorgin B (57) and 17-bromo-13-*epi*-tetrahydro-fumitremorgin B (58) by *N*-bromosuccinimide (NBS)-oxidation in aqueous dimethoxyethane. Debromination of 58 gave 13-*epi*-tetrahydrofumitremorgin B (59).

Keywords fumitremorgin; fumitremorgin B; Pictet–Spengler reaction; tetrahydro-13-*epi*-fumitremorgin B; 6-methoxy-L-tryptophan methyl ester; tetrahydro-β-carboline; DDQ-oxidation; NBS-oxidation; synthesis; pentacyclic ring system

Fumitremorgins A (**1**) and B (**2**) are tremorgic mycotoxins isolated from *Aspergillus fumigatus*, and their structures were established by X-ray analysis.[2)] Verruculogen (**3**), acetoxyverruculogen (**4**), TR-2 (**5**), and fumitremorgin C (**6**) were also isolated from similar fungi.[3)] These mycotoxins have the same pentacyclic ring system, which is a cyclized form of cyclo-L-prolyl-2-prenyl-L-tryptophyl or *N*-prenyl-cyclo-L-prolyl-L-tryptophyl.

We have reported the synthesis of the β-carboline (**7**) by the acid-catalyzed rearrangement of the 3a-hydroxypyrroloindole derivative which was prepared by the dye-sensitized photooxygenation of N_b-methoxycarbonyl-1,2-diisopentyltryptamine.[4)] However, the similar oxidation-rearrangement of cyclo-L-prolyl-1,2-diisopentyl-L-tryptophyl failed to give the pentacycles (**8**). In this paper we describe the synthesis of the pentacyclic parent ring system (**8**) of fumitremorgins by the Pictet–Spengler (P–S) reaction of tryptophan methyl ester and isovaleraldehyde to form the A-B-C ring followed by the D-E ring formation. Furthermore, oxidations of the pentacycles in an approach to fumitremorgins are described.

Although the P–S reaction of tryptophans and tryptamines with aldehydes is well documented,[5)] the reaction with optically active tryptophan esters has scarcely been reported. Therefore, we examined the stereoselectivity and racemization in the P–S reaction of tryptophan methyl ester with isovaleraldehyde. When a benzene solution of L-tryptophan methyl ester (**9**) with isovaleraldehyde (**10**) was refluxed for 42 h without an acid catalyst,[6)] the *cis*-tetrahydro-β-carboline (**11**, 38%) and the *trans*-isomer (**12**, 32%) were obtained. Recrystallization of both isomers from benzene, however, gave the racemic *cis*-isomer (**11**), mp 143—145 °C, and the racemic *trans*-isomer (**12**), mp 120—121 °C. The specific rotations of crude **11** and **12** showed that considerable racemization occurred during the reaction (see Table I). The structures of the racemic **11** and **12** were confirmed by spectral data (see Experimental). Cook and coworkers have demonstrated that the signals of the C-1 and C-3 carbons in the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra of 1,3-disubstituted tetrahydro-β-carboline were observed at higher magnetic field in the *trans*-isomer than in the *cis*-isomer.[7)] The signals of the C-1 and C-3 carbons in the *trans*-isomer (**12**) appeared at 48.1 and 52.4 ppm, which were at higher field than those of the *cis*-isomer (50.6 and 56.5 ppm), and these values were very close to those of *cis*- and *trans*-1-ethyl-3-

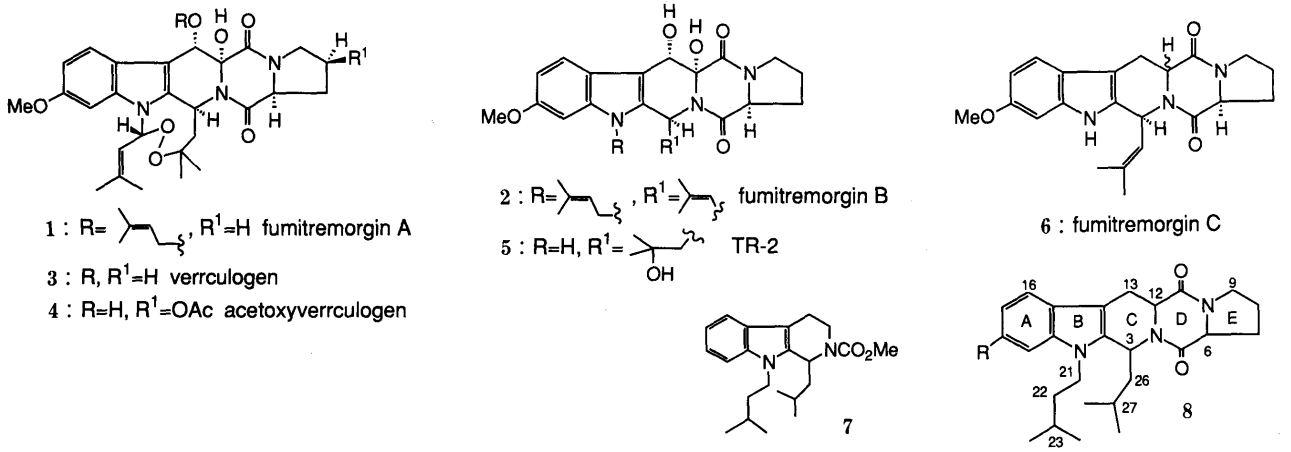

Chart 1

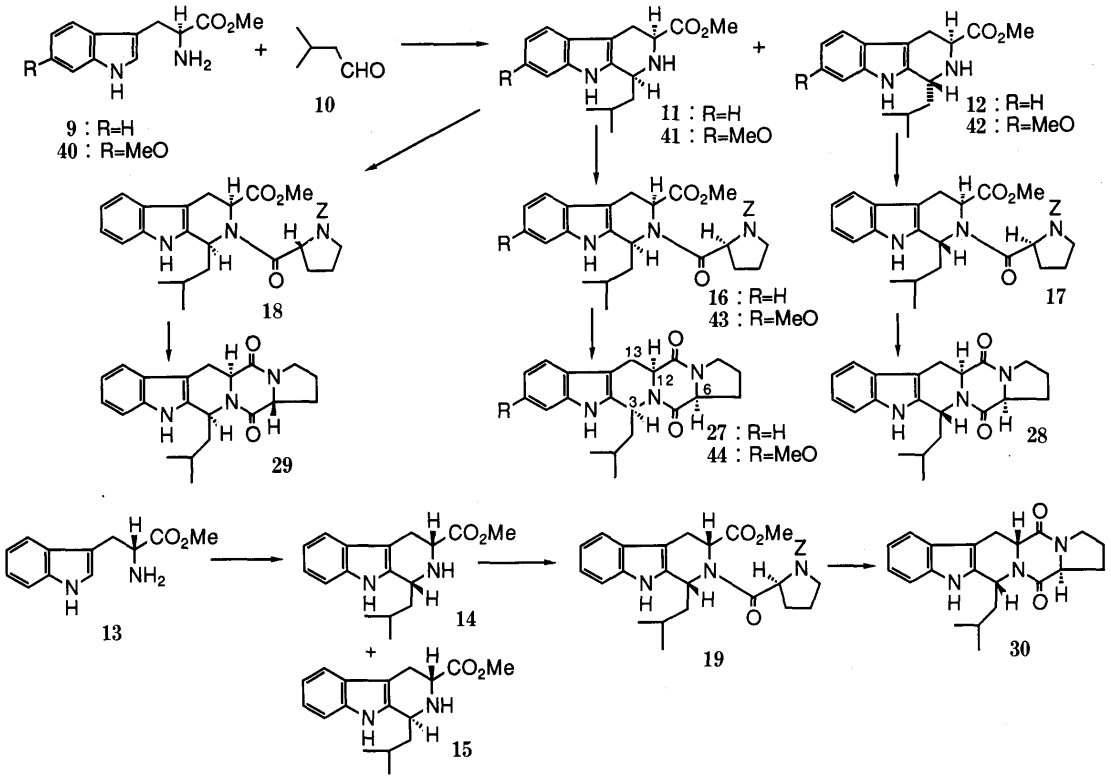

Chart 2

TABLE I. The Pictet–Spengler Reaction of L- or D-Tryptophan Methyl Ester (**9** or **13**) with Isovaleraldehyde (**10**)

Entry	TrpOMe	Solvent	Acid (mol eq)	Reaction temp. Reaction time	Yield % ($[\alpha]_D$)[b] 11 (14)	12 (15)
1	**9**	Benzene	—	Reflux 42 h	38 (−26.3°) (c=1.0)	32 (+16.9°) (c=1.0)
2	**9**	Benzene	TsOH (0.1)	Reflux 2 h	35 (−97.1°) (c=0.50)	43 (+51.0°) (c=0.50)
3	**9**	Benzene	TFA (5.7)	Reflux 1/3 h	32 (−110.0°) (c=0.52)	23 (+46.5°) (c=0.50)
4	**9**	MeOH	HCl	r.t. 21 h	28 (−108.1°) (c=0.50)	19 (+48.5°) (c=0.50)
5	**13**	CH_2Cl_2	TFA (9.4)	r.t.[a] 15 h	51 (+96.5°) (c=0.50)	19 (−52.4°) (c=0.50)
6	**9**	CH_2Cl_2	TFA (5.7)	r.t. 2 h	62 (−121.0°) (c=0.543)	33 (+43.1°) (c=0.536)

a) Before the addition of TFA, the Schiff's base was prepared by stirring **13** and **10** in benzene in the presence of Na_2SO_4. *b*) The specific rotation was measured in MeOH on a sample which showed a single spot on TLC after chromatographic separation.

methoxycarbonyl-1,2,3,4-tetrahydro-β-carbolines.[7] Thus, the stereochemistry of **11** and **12** was established.

As the stereoselectivity and optical purity of the product were not satisfactory, the P–S reaction was examined under various acidic conditions (Table I). Addition of *p*-toluenesulfonic acid or trifluoroacetic acid (TFA) (entries 2 and 3) accelerated the reaction and improved the optical purity of the products. However, the stereoselectivity of the reaction was not improved.

Recently the P–S reaction of tryptophan carboxyamide with aldehyde was reported to give the *cis*-isomer in 70% yield when the Schiff's base was treated with TFA in methylene chloride.[8] Therefore, D-tryptophan methyl ester (**13**) was treated with the aldehyde (**10**) in benzene at room temperature to form the Schiff's base, which was treated with TFA in methylene chloride at room temperature (entry 5). The *cis*-isomer (**14**) was obtained as the major product (51%). The best conditions so far found involve stirring a mixture of **9**, **10** and TFA (5.7 mol eq) in methylene chloride at room temperature (entry 6); the *cis*-isomer (**11**) was obtained in 62% yield together with the *trans*-isomer (**12**, 33%). These optically active β-carbolines (**11**, **12**) are amorphous, unlike the racemic compounds, and showed spectral data (NMR and infrared (IR) in chloroform) identical with those of racemic compounds. The optical purities of these β-carbolines (**11**, $[\alpha]_D$ −121°, **12**, $[\alpha]_D$ +43.1°) were examined by NMR spectroscopy using a chiral shift reagent, and the enantiomer was not detected (less than 5%) (see Experimental). The same β-carbolines (**11**, 67%, $[\alpha]_D$ −107.2° and **12**, 22%, $[\alpha]_D$ +52.8°) were obtained by a two step procedure, *i.e.*, the P–S reaction and the esterification of L-tryptophan following Brossi's procedure.[9] The result was comparable to that of entry 6 in Table I. The stereoselectivity of both methods is still not satisfactory, but we chose tryptophan ester as the starting materials for simplicity.

The condensation of the *cis*-β-carboline (**11**) with *N*-benzyloxycarbonyl(Z)-L-proline chloride in triethylamine-methylene chloride gave the desired dipeptide (**16**), mp 192.5—193.5 °C, $[\alpha]_D$ −48.8°, in 92% yield. On the other hand, this condensation with *Z*-L-proline by diphenyl phos-

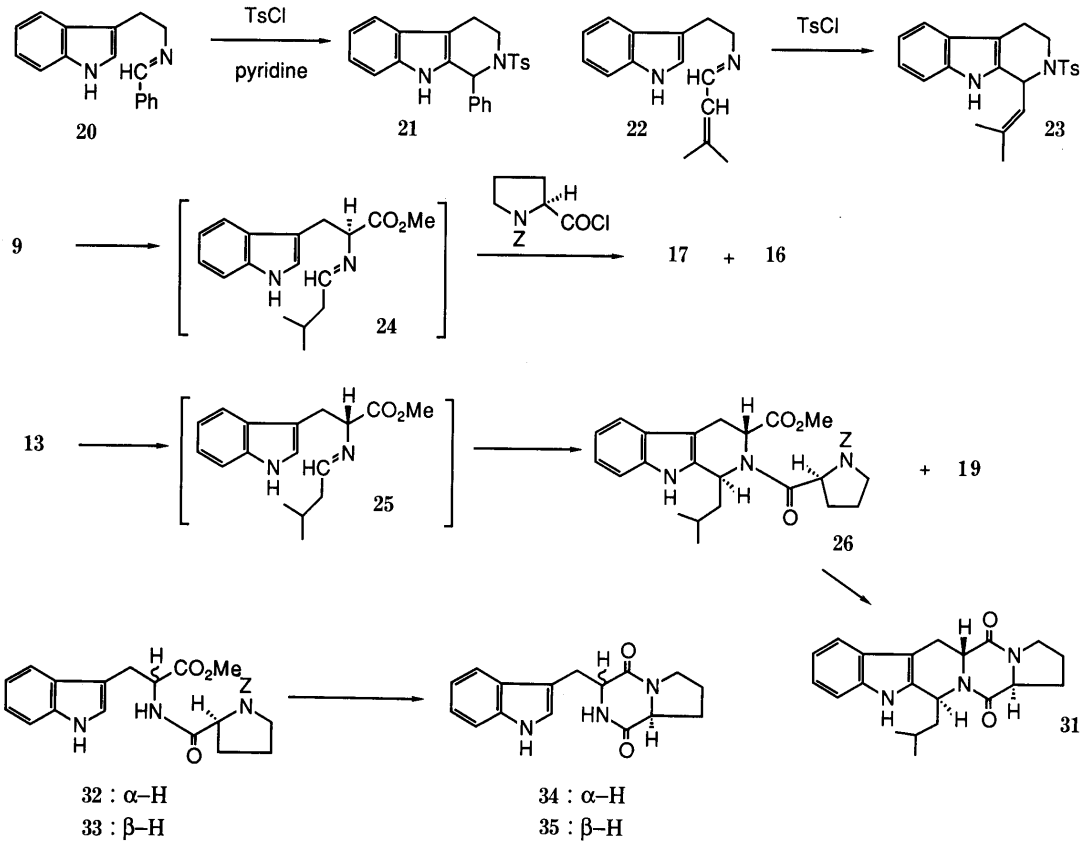

Chart 3

phorazidate (DPPA)[10] or by 2,2′-dipyridyl disulfide-triphenylphosphine[11] failed to give the dipeptide. The corresponding *trans*-dipeptide (**17**), mp 207—208 °C, was obtained from **12** and Z-L-proline with dicyclohexylcarbodiimide (DCC) in 56% yield. The dipeptides, **18** and **19**, were also prepared from **11** and **14** with Z-L-prolyl chloride in good yields.

We next examined the P–S reaction to obtain the dipeptide **16** and **17** directly. Jackson and Smith[12] have reported a modified P–S reaction in which the β-carboline (**21**) was obtained from pre-formed Schiff's base (**20**) with tosyl chloride in pyridine. Harrison[13] reported the similar reaction of **22** to give **23**, which was not obtained under the normal P–S reaction conditions using a proton acid. Furthermore, Yamanaka *et al.*[14] reported that tosyl chloride in this reaction could be replaced by methyl chloroformate, and the method was also applicable to tryptophan esters. Therefore, we carried out the P–S reaction with Z-L-prolyl chloride as the acylating agent. L-Tryptophan methyl ester (**9**) was treated with **10** in molecular sieves 4A-methylene chloride at room temperature to form the corresponding Schiff's base (**24**), to which Z-L-prolyl chloride and potassium carbonate were added. The *trans*-dipeptide (**17**, 41%) was obtained as the major product along with the *cis*-dipeptide (**16**, 4%). The similar reaction of the Schiff's base (**25**) prepared from D-tryptophan methyl ester (**13**) gave the *trans*-dipeptide (**26**, 46%) and the *cis*-dipeptide (**19**, 14%). In contrast to the simple P–S reaction, the *trans*-β-carbolines (**17** and **26**) were obtained as the major product by this acylation method, as expected from the results in the P–S reaction of the N_b-benzyltryptophan ester.[15] Therefore, both methods are complementary to each other for the preparation of the *cis* and *trans* dipeptides, although the yield of the acylation method was not satisfactory. The reaction of the Schiff's base (**24**) with L-proline carboxyanhydride instead of prolyl chloride as an acylating agent to obtain a pentacyclic compound such as **27** or **28** was unsuccessful.

For the formation of the desired pentacycles, the deprotection and the cyclization of the dipeptides were required. The hydrogenolysis of the dipeptides (**16**, **17**, **18**, **19**, and **26**) with Pd/C–H_2 at 60 °C or Pd/C–ammonium formate[16] at room temperature in methanol smoothly gave the corresponding pentacycles (**27**, **28**, **29**, **30**, and **31**). The cyclization did occur under the condition of the deprotection, contrary to the similar cyclization of the dipeptides (**32**, **33**), for which refluxing of the deprotected dipeptide in toluene–acetic acid was required.[17] These pentacycles (**27**—**31**) were obtained as crystals and their physical data are summarized in Table II. Four possible stereoisomers, *cis–cis* (**27**), *trans–cis* (**28**), *cis–trans* (**29**, **30**), and *trans–trsans* (**31**), were prepared, and two *cis–trans* isomers (**29**, **30**) prepared from L- and D-tryptophan methyl ester (**9**, **13**) were found to be enantiomeric. Therefore, no serious racemization or epimerization occurred during these syntheses. High-pressure liquid chromatographic analysis of four stereoisomers on a μ-Porasil column showed that the four stereoisomers could be separated from each other using two solvent systems as shown in Table III.

Base-catalyzed epimerization of the *cis–cis* isomer (**27**) with 0.1 N NaOH–MeOH gave the *trans–trans* isomer (**31**) by epimerization at the C-12 position. On the other hand, the *trans–cis* isomer (**28**) under similar conditions gave the (−)-*trans–trans* isomer, an enantiomer of **31**, by epimeri-

TABLE II. Physical Data for the Pentacycles **27**—**31** and **44**

Stereo	**27** *−cis,cis*	**28** *−trans,cis*	**29** *−cis,trans*	**30** *+cis,trans*	**31** *+trans,trans*	**44** *−cis,cis*
mp (°C)	289—290	197—200	264—266	263.5—266	164—166	267.5
$[\alpha]_D$	−76.3°	−171.4°	−95.1°	+95.3°	+105.2°	−80.6°
MS *m/z* M^+ (%)	351 (19)	351 (32)	351 (17)	351 (17)	351 (27)	381 (14)
Base peak	294	294	294	294	294	324
^{1}H-NMR						
13-H_2 (*J*, Hz)	3.12, dd (15.8, 11.9)	2.84, ddd (15.8, 11.2, 1.0)	3.04, ddd (15.5, 11.9, 2.0)	3.04, ddd (15.5, 11.9, 2.0)	2.93, ddd (15.4, 12.1, 1.0)	3.09, dd (15.9, 11.9)
	3.56, dd (15.8, 5.3)	3.59, dd (15.8, 5.0)	3.45, ddd (15.5, 4.0, 1.0)	3.45, ddd (15.5, 4.0, 1.0)	3.32, dd (15.3, 4.1)	3.50, dd (11.9, 5.2)
9-H_2	3.6—3.7, m	3.47, ddd (12.5, 9.1, 3.6)	3.5, m	3.5, m	3.6, m	3.55—3.75, m
		3.97, dt (12.5, 8.2)	3.8, m	3.8, m	3.8, m	
6-H	4.05—4.12, m	4.18, dd (10.5, 6.2)	4.11, dd (9.9, 6.3)	4.11, dd (9.9, 6.3)	4.11, dd (9.7, 6.1)	4.05—4.15, m
12-H	4.05—4.12, m	4.48, dd (11.4, 4.5)	4.22, dd (12.0, 3.6)	4.22, dd (12.0, 3.6)	4.41, dd (11.7, 4.1)	4.05—4.15, m
3-H	5.49, dd (9.4, 4.1)	5.99, t-like	4.9, t-like	4.9, t-like	5.87, dd (10.7, 3.8)	5.40—5.50, m
^{13}C-NMR						
C_{21}	46.13	44.26		40.92	43.10	
C_9	45.41	45.06		45.18	45.47	
C_3	50.88	47.74		55.86	48.20	
C_{12}	57.01	53.56		62.17	55.26	
C_6	59.32	59.26		59.95	58.86	

TABLE III. HPLC Retention Times (min) of the Pentacycles **27**—**29**, and **31**

Solvent	**27** *cis–cis*	**28** *trans–cis*	**29** *cis–trans*	**31** *trans–trans*
CH_2Cl_2 : iso-PrOH 100 : 1	16.3	15.2	16.1	14.2
50 : 1	8.6	8.3	8.4	8.1

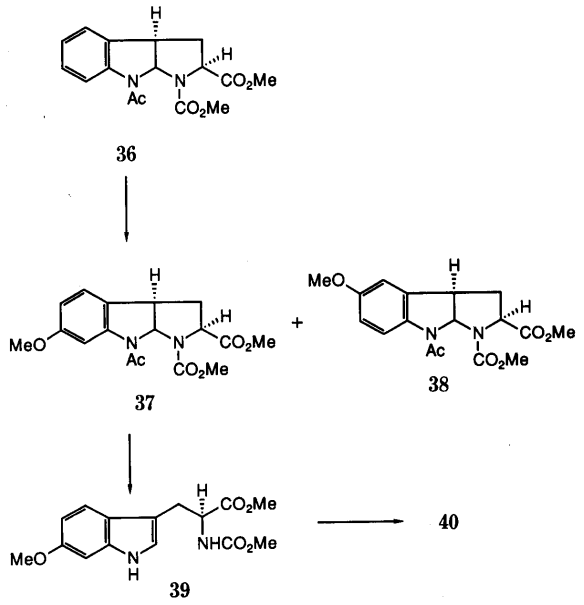

Chart 4

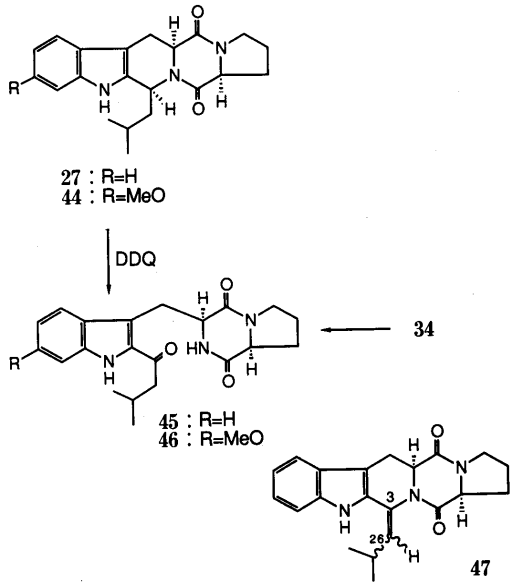

Chart 5

zation at the C-6 position (chiral center of proline). These results showed that epimerization occurred readily to form the stable *trans*-2,5-dioxopiperazine ring, and the *trans–trans* isomer is the most stable stereoisomer.

As we had succeeded in the synthesis of four stereoisomers of pentacycles, we next turned to the synthesis of the methoxy pentacycle (**44**). For the synthesis of **44** by the above route, 6-methoxy-L-tryptophan methyl ester was required. We have already reported that the 6-methoxy-DL-tryptophan derivative could be obtained by the lead tetraacetate oxidation of the cyclic tautomer of N_b-methoxycarbonyl-DL-tryptophan methyl ester,[18] and optically active cyclic tautomers were readily obtained from L-tryptophan.[19] Following the procedure used for the DL-compound, lead tetraacetate oxidation of the *N*-acetyl cyclic tautomer (**36**), prepared from L-tryptophan, in TFA followed by methylation gave the 6-methoxy derivative (**37**, 56%), and the 5-methoxy derivative (**38**, 22%) (Chart 4). The ring opening of **37** with 10% H_2SO_4–MeOH gave the 6-methoxytryptophan derivative (**39**), mp 96.5—98.5 °C, $[\alpha]_D$ +3.5°, in 94% yield. The selective deprotection of **39** with trimethylsilyl iodide[20] gave 6-methoxy-L-tryptophan

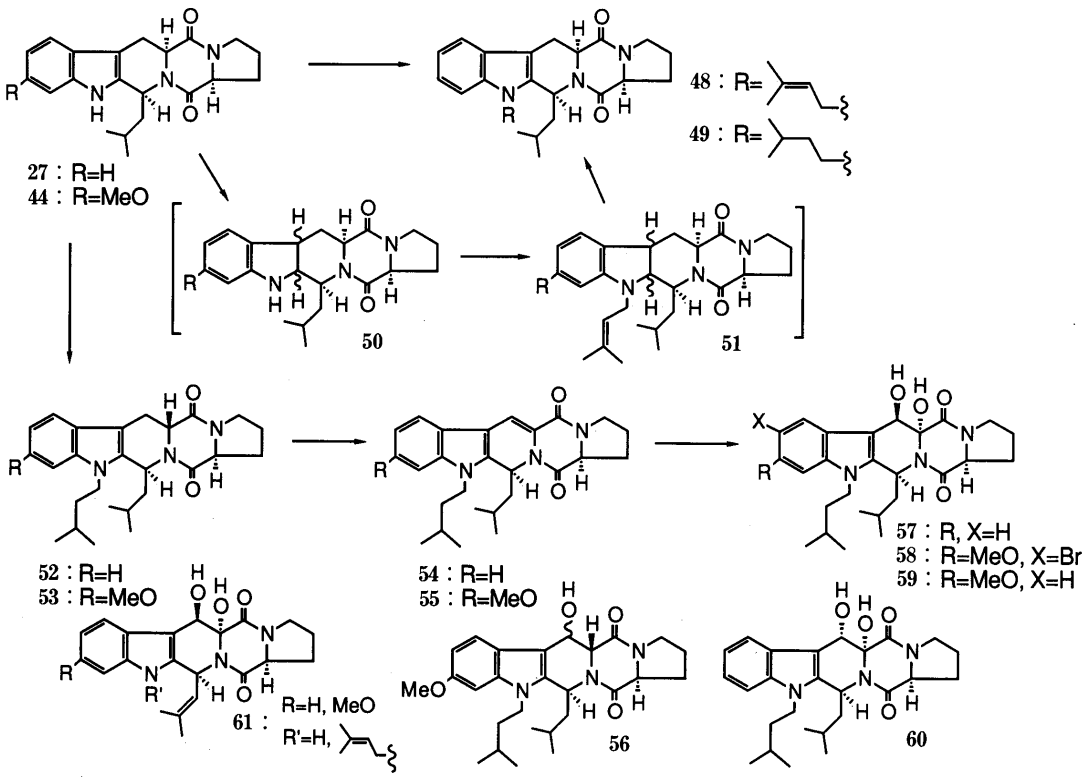

Chart 6

methyl ester (**40**), mp 99.5—101 °C, $[\alpha]_D$ +32°, quantitatively. The P–S reaction of **40** with the aldehyde (**10**) in TFA–methylene chloride as above gave the *cis*-β-carboline (**41**), mp 151—152 °C, $[\alpha]_D$ −122.3°, in 53% yield besides the *trans* isomer (**42**, 30%), mp 151.5—153.5 °C, $[\alpha]_D$ +58.4° (Chart 2). The condensation of **41** with Z-L-prolyl chloride gave the dipeptide (**43**), mp 242—242.5 °C, $[\alpha]_D$ −43.5°, which gave the methoxy pentacycle (**44**) in 95% yield on hydrogenolysis with Pd/C–ammonium formate in methanol. The physical data for **44** are also listed in Table II.

For the synthesis of tetrahydrofumitremorgins or their demethoxy derivatives from these pentacycles, hydroxylation at the C-ring was required. Oxidation of the *cis–cis* pentacycles (**27**) with dichlorodicyano-*p*-benzoquinone (DDQ)[21] in methylene chloride-acetic acid at room temperature gave the 2-acylindole derivative (**45**) in 26% yield but did not give the desired C-12,13 dehydro derivative (Chart 5). The structure **45** was confirmed by direct comparison with a sample prepared from **34** by acylation with isovaleroyl chloride. Lead tetraacetate oxidation of **27** in boiling benzene gave the C-3,26 dehydro derivative (**47**, 44%) as a mixture of geometrical isomers, while **45** was obtained as the major product (56%) in acetic acid. On the other hand, the methoxy derivative (**44**) gave **46** (33%) on DDQ oxidation in aqueous acetonitrile, under which condition **27** did not give **45**.

As satisfactory results were not obtained in the oxidation of **27** and **44**, we examined the oxidation of N_a-alkyl pentacycles. The prenylation of **27** with 3,3-dimethylallyl bromide–NaH–dimethylformamide (DMF) proceeded quickly to give the N_a-prenylated derivative (**48**), mp 138—140 °C, $[\alpha]_D$ −58.5°, which gave the isopentyl derivative (**49**) on catalytic hydrogenation (Chart 6). Compound **48** was also obtained by the reduction of **27** with pyridine–borane to the indoline (**50**) followed by prenylation with 3,3-dimethylallyl bromide in potassium carbonate–acetone, and dehydrogenation with DDQ. On the other hand, the direct alkylation of **27** with isopentyl bromide–NaH–DMF gave **52**, accompanied with epimerization at the C-12 position. DDQ oxidation of **49** in aqueous acetonitrile did not proceed and most of **49** was recovered. However, similar oxidation of **52** gave the desired **54** in 40% yield. The ultraviolet (UV) spectrum of **54** (λ_{max} 236, 261, and 367 nm) showed the presence of a conjugated olefin with the indole ring. The mass spectrum of **54** showed the molecular ion peak at *m/z* 419 and the base peak at *m/z* 362 (M^+ − isopentyl group). In the NMR spectrum of **54**, the methylene proton at C-13 and the methine proton at C-12 observed in **52** had disappeared and a new olefinic proton at C-13 was observed at 7.33 ppm as a singlet.

The similar isopentylation of the methoxy compound (**44**) gave **53** in excellent yield. The DDQ oxidation of **53** in aqueous acetonitrile gave a mixture of the dehydro derivative (**55**) and the 13-hydroxy derivative (**56**) which could be dehydrated to **55** on treatment with 10% H_2SO_4–MeOH. When the reaction mixture of DDQ oxidation was treated with acid, the dehydro derivative (**55**) was obtained in 60% yield, although the separation of **53** and **55** was difficult.

Transformation of **54** to the diol (**57**) met some difficulties. Woodward *cis*-hydroxylation,[22] epoxidation with *m*-chloroperbenzoic acid, oxidation with molybdenum complex–H_2O_2,[23] and osmium tetroxide oxidation of **54** failed to give the diol (**60**) or the corresponding epoxide. However, *N*-bromosuccinimide (NBS) oxidation of **54** in aqueous dimethoxyethane following Corey's procedure,[24] gave the *trans*-diol (**57**) in 85% yield. The stereochemistry of the diol (**57**) was determined as 12α,13β-diol by a com-

parison of its NMR spectrum with those of **61**, which were converted to fumitremorgin B or its demethoxy derivative by oxidation and reduction.[25] NBS oxidation of **55** under similar conditions gave the brominated *trans*-diol (**58**) which was readily convertedt to 13-*epi*-tetrahydrofumitremorgin B (**59**) on catalytic hydrogenation.

Experimental

All melting points are uncorrected. The UV spectra were taken with Hitachi 323 and 340 spectrophotometers, and the IR spectra with Hitachi 260-10 and 295 spectrophotometers. The mass spectra (MS) were recorded on Hitachi M-60 and 7M spectrometers, and NMR spectra in $CDCl_3$ solution on JEOL JNM-FX-270 and JNM-GX-270 apparatus using tetramethylsilane as an internal standard. The specific rotation was taken with a DIP-140 polarimeter using a 10 cm cell. High performance liquid chromatography (HPLC) was carried out on a Hitachi 655 apparatus with a UV-detector using a Waters μ-Porasil packed column. Kiesel gel 60 (70—230 mesh, Merck) or Silica gel BW-820 MH (Fuji-Davison) was used for silica gel column chromatography. Aluminiumoxyd 90 standardisiert (Aktivitätsstufe II—III, Merck) was used for alumina column chromatography. Kiesel gel GF_{254} type 60 (Merck) or DC-Fertigplatten SILG-50 UV_{254} was used for preparative thin layer chromatography.

Pictet–Spengler Reaction of Tryptophan Methyl Ester (9, 13) with Isovaleraldehyde (10). Formation of *cis*- and *trans*-1-Isobutyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carbolines (11 and 12) i) Benzene Reflux: Formation of Racemic **11** and **12**: A mixture of L-tryptophan methyl ester (**9**, 1.00 g, 4.59 mmol) and isovaleraldehyde (**10**, 500 mg, 5.82 mmol) in benzene (50 ml) was refluxed for 42 h with a Dean-Stark apparatus. Removal of the solvent gave a residue, which was chromatographed on silica gel (80 g). The first elution with CH_2Cl_2–acetone (20 : 1) gave the *cis* derivative (**11**, 504 mg, 38%), $[\alpha]_D^{28}$ −26.2° (c=1.0, MeOH), as a colorless caramel. The second elution gave the *trans* derivative (**12**, 421 mg, 32%), $[\alpha]_D^{28}$ +16.92° (c=1.0, MeOH), as a colorless caramel. From more polar fractions, **9** (66 mg) was recovered and found to be completely racemized. Repeated recrystallization of **11** from benzene gave racemic **11**, mp 143—145 °C, as colorless fine needles. UV λ_{max}^{MeOH} nm (ε): 224.5 (36700), 274 (7600), 281 (7600), 289.5 (6500). IR ν_{max}^{KBr} cm^{-1}: 3200 (NH), 1740 (CO). ^{1}H-NMR δ: 1.00 (3H, d, J=6.6 Hz, CH_3), 1.04 (3H, d, J=6.6 Hz, CH_3), 1.5—1.8 (3H, m, 1-CH_2, N_b-H, 2H multiplet on the addition of D_2O), 2.03 (1H, m, Me_2CH), 2.81 (1H, ddd, J=15.0, 11.2, 2.5 Hz, 4-H_a), 3.13 (1H, ddd, J=15.2, 4.3, 1.7 Hz, 4-H_b), 3.76 (1H, dd, J=11.7, 7.4 Hz, 3-H), 3.82 (3H, s, OCH_3), 4.2 (1H, m, 1-H), 7.1—7.5 (4H, arom. H), 7.77 (1H, s, N_a-H, exchangeable). ^{13}C-NMR δ: 21.77 (q, CH_3), 23.81 (q, CH_3), 24.36 (d, Me_2CH), 26.03 (t, C_4), 44.40 (t, C_1-CH_2), 50.62 (d, C_1), 52.15 (q, OCH_3), 56.52 (d, C_3), 107.81 (s, C_{4a}), 110.77 (d, C_8), 117.94 (d, C_5), 119.55 (d, C_6), 121.65 (d, C_7), 127.30 (s, C_{4b}), 135.91, 136.08 (s, C_{8a}, C_{9a}), 173.80 (s, CO). MS m/z (%): 286 (M^+, 13), 229 (100). *Anal.* Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.44; N, 9.78. Found: C, 71.46; H, 7.70; N, 9.79.

Repeated recrystallization of **12** from benzene gave racemic **12**, mp 120—121 °C. UV λ_{max}^{MeOH} nm (ε): 224.5 (34100), 274 (7500), 279 (7700), 289.5 (6100). IR ν_{max}^{KBr} cm^{-1}: 3140, 3040 (NH), 1750 (CO). ^{1}H-NMR δ: 1.00 (3H, d, J=6.6 Hz, CH_3), 1.03 (3H, d, J=6.6 Hz, CH_3), 1.51 (1H, ddd, J=13.9, 9.4, 4.3 Hz, 1-CH_a), 1.71 (1H, ddd, J=13.8, 9.9, 4.3 Hz, 1-CH_b), 1.8 (1H, br s, N_b-H, exchangeable), 1.9 (1H, m, Me_2CH), 2.97 (1H, ddd, J=15.3, 7.4, 1.5 Hz, 4-H_a), 3.11 (1H, ddd, J=15.1, 5.3, 1.0 Hz, 4-H_b), 3.75 (3H, s, OCH_3), 3.95 (1H, dd, J=7.3, 5.3 Hz, 3-H), 4.29 (1H, dd, J=9.4, 4.1 Hz, 1-H), 7.1—7.5 (4H, arom. H), 7.72 (1H, s, N_a-H, exchangeable). ^{13}C-NMR δ: 21.68 (q, CH_3), 23.64 (q, CH_3), 24.71 (d, Me_2CH), 25.08 (t, C_4), 44.52 (t, 1-CH_2), 48.14 (d, C_1), 52.06 (q, OCH_3), 52.41 (d, C_3), 106.79 (s, C_{4a}), 110.68 (d, C_8), 117.99 (d, C_5), 119.41 (d, C_6), 121.60 (d, C_7), 127.18 (s, C_{4b}), 135.85, 136.02 (s, C_{8a}, C_{9a}), 174.29 (s, CO). MS m/z (%): 286 (M^+, 34), 229 (100). *Anal.* Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.33; H, 7.70; N, 9.82.

ii) Pre-formation of Schiff's Base: A solution of **13** (300 mg, 1.38 mmol) and **10** (142 mg, 1.65 mmol) in benzene (10 ml) was stirred for 8 h at room temperature in the presence of Na_2SO_4 (5 g). After removal of the drying agent, the solvent was evaporated to leave a residue which was dissolved in CH_2Cl_2 (20 ml). TFA (1.0 ml) was added to the mixture and the whole was stirred for 13 h at room temperature. Work-up as above gave (+)-**14** (201 mg, 51%), $[\alpha]_D^{11}$ +96.5° (c=0.5, MeOH), and (−)-**15** (76 mg, 19%), $[\alpha]_D^{11}$ −52.4° (c=0.5, MeOH).

iii) CH_2Cl_2–CF_3COOH: Isovaleraldehyde (**10**, 296 mg, 3.44 mmol) and CF_3COOH (1 ml, 12.98 mmol) was added to a solution of **9** (500 mg, 2.29 mmol) in CH_2Cl_2 (20 ml) at room temperature. The mixture was stirred for 2 h at room temperature and diluted with CH_2Cl_2. The mixture was washed with saturated $NaHCO_3$ solution and saturated NaCl solution and dried. Evaporation of the solvent gave a residue which was separated by flash column chromatography (silica gel 230—400 mesh, 3 × 16 cm, AcOEt–hexane, 2 : 7) and preparative thin layer chromatography (TLC). (−)-**11** (405 mg, 62%), colorless caramel, $[\alpha]_D^{21}$ −121.0° (c=0.543, MeOH). (+)-**12** (213 mg, 33%), colorless caramel, $[\alpha]_D^{22}$ +43.1° (c=0.536, MeOH). These NMR spectra were identical with those of racemic **11** and **12**. The optical purities of **11** and **12** were checked by ^{1}H-NMR spectroscopy using tris 3-(heptafluoropropylhydroxymethylene)-*d*-camphorato europium(III) as a shift reagent. The racemic **11** showed two peaks at δ 7.66 (d) and 7.72 (d) ppm when 0.2 eq of the shift reagent was added, while optically active **11** showed the latter signal only. The integrated area at around 7.66 ppm was less than 5% of that at 7.72 ppm. Similar results were obtained for **12**.

Pictet–Spengler Reaction of L-Tryptophan with 10 L-Tryptophan (10 g, 49.0 mmol) was dissolved in hot water (400 ml). After cooling of the solution, 0.1 N H_2SO_4 (40 ml) and **10** (5.22 g, 60.7 mmol) were added under an argon atmosphere. The mixture was stirred for 24 h at room temperature and the separated crystals (*cis*-acid, 8.147 g) were collected. The mother liquor was left for one week at room temperature and the *cis* acid was again collected (877 mg, total 9.024 g, 67.7%). The aqueous solution was evaporated *in vacuo* to leave a residue. Crystals were suspended in anhydrous MeOH (250 ml). Dry HCl gas was introduced into the suspension for 4 h until saturation under ice cooling. The mixture was kept at room temperature overnight, and the solvent was evaporated off. The residue was dissolved in H_2O (500 ml) and made alkaline with Na_2CO_3, and then extracted with CH_2Cl_2. Usual work-up gave **11** (8.434 g). The residue was esterified similarly to give **11** (661 mg) and **12** (3.08 g) after silica gel column separation. **11**: 9.33 g, 66.6% from tryptophan, $[\alpha]_D^{18}$ −107.2° (c=0.5, MeOH). **12**: 3.08 g, 22%, $[\alpha]_D^{19}$ +52.8° (c=0.5, MeOH). ^{1}H-NMR and IR spectra in $CHCl_3$ of both esters were identical with those of the racemic esters.

***cis*-1-Isobutyl-3-methoxycarbonyl-2-Z-L-prolyl-1,2,3,4-tetrahydro-β-carboline (16)** Z-L-Prolyl chloride prepared from L-proline (2.043 g, 8.2 mmol) in CH_2Cl_2 (10 ml) was added to a chilled solution of the *cis*-ester (**11**, 1.723 g, 6.06 mmol) and Et_3N (1.204 g, 11.92 mmol) in CH_2Cl_2 (10 ml) during 15 min. The mixture was stirred for 1 h at room temperature. The mixture was diluted with CH_2Cl_2 (80 ml), washed with 10% Na_2CO_3, H_2O, 5% HCl, and saturated NaCl solution, and dried. Evaporation of the solvent gave **16**, which was recrystallized from benzene to give colorless prisms (2.869 g, 91.6%). Repeated recrystallization from the same solvent gave **16**, mp 192.5—193.5 °C, as colorless prisms. $[\alpha]_D^{12}$ −48.8° (c=0.5, MeOH). UV λ_{max}^{MeOH} nm (ε): 224 (39900), 272.5 (7200), 278.5 (7900), 289 (6000). IR ν_{max}^{KBr} cm^{-1}: 3230 (NH), 1750, 1680 (CO). MS m/z (%): 517 (M^+, 1.8), 285 (100). *Anal.* Calcd for $C_{30}H_{25}N_3O_5$: C, 69.61; H, 6.82; N, 8.12. Found: C, 69.71; H, 6.82; N, 8.09.

***trans*-1-Isobutyl-3-methoxycarbonyl-2-Z-L-prolyl-1,2,3,4-tetrahydro-β-carboline (17)** DCC (399 mg, 1.94 mmol) in CH_2Cl_2 (5 ml) was added to a solution of the *trans* ester (**12**, 500 mg, 1.75 mmol) and Z-L-proline (479 mg, 1.92 mmol) in CH_2Cl_2 (20 ml) at room temperature. The mixture was stirred for 94 h at room temperature. The separated urea derivative was removed and the solvent was evaporated off to leave a residue, which was dissolved in acetone. The insoluble urea derivative was removed. The solvent was evaporated *in vacuo* to leave a residue (1.261 g), which was chromatographed on a silica gel (30 g) column. Elution with CH_2Cl_2–acetone gave **12** (222 mg) and **17** (502 mg, 55.5%). Repeated recrystallization from benzene gave **17** as colorless prisms, mp 207—208 °C, $[\alpha]_D^{13}$ −104.7° (c=0.5, MeOH). UV λ_{max}^{MeOH} nm (ε): 223 (42700), 273 (7900), 279 (8300), 289.5 (6500). IR ν_{max}^{KBr} cm^{-1}: 3300 (NH), 1750, 1715 (CO). MS m/z (%): 517 (M^+, 2.9), 285 (100). *Anal.* Calcd for $C_{30}H_{35}N_3O_5$: C, 69.61; H, 6.82; N, 8.12. Found: C, 69.57; H, 6.85; N, 8.01.

Direct Synthesis of the Dipeptides (16 and 17) from 9 A mixture of **9** (218 mg, 1.0 mmol), **10** (95 mg, 1.1 mmol), and molecular sieves-4A (2.5 g) in CH_2Cl_2 (5 ml) was stirred for 18 h at room temperature. Z-L-Prolyl chloride (prepared from Z-L-proline (324 mg, 13 mmol)) and K_2CO_3 (1.0 g) in CH_2Cl_2 (5 ml) was added to the above mixture at room temperature. The mixture was stirred for 2.5 h. After removal of insoluble materials, the mixture was diluted with CH_2Cl_2 (30 ml), washed with 10% Na_2CO_3 and saturated NaCl solution and dried. Evaporation of the solvent *in vacuo* gave a residue (529 mg), which was separated on a silica gel column (30 g). Elution with AcOEt–hexane (1 : 1) gave **16** (21 mg, 4%) and **17** (192 mg, 41%), $[\alpha]_D^{13}$ −100° (c=0.5, MeOH). IR and UV spectra, and TLC behavior of both samples were identical with those of the authentic specimen obtained above.

Direct Synthesis of the Dipeptides (26 and 19) from 13 A mixture of D-tryptophan methyl ester (**13**, 872 mg, 4.0 mmol), isovaleraldehyde (**10**, 390 mg, 4.5 mmol), and molecular sieves-4A (10 g) in CH_2Cl_2 (15 ml) was stirred for 16 h at room temperature. Anhydrous K_2CO_3 (2.0 g) and Z-L-prolyl chloride (prepared from Z-L-proline (1.30 g, 5.2 mmol)) in CH_2Cl_2 (20 ml) was added to the mixture over 30 min under ice-cooling. The whole mixture was stirred for 4 h at room temperature. Work-up as described for the L-series gave the D-*trans* dipeptide (**26**, 921 mg, 44.5%) and D-*cis* dipeptide (**19**, 293 mg, 14.2%) each as a colorless powder. Recrystallization of **26** from benzene–hexane and benzene gave colorless prisms, mp 117—121 °C, $[\alpha]_D^{14}$ +42.1° (c=0.5, MeOH). UV λ_{max}^{MeOH} nm (ε): 223.5 (36500), 274 (7400), 279.5 (7500), 289.5 (5900). IR ν_{max}^{KBr} cm^{-1}: 3320 (NH), 1750, 1710, 1670 (CO). MS *m/z* (%): 517 (2.3, M^+), 285 (100). ^{1}H- and ^{13}C-NMR showed complex signals due to the presence of rotamers. *Anal.* Calcd for $C_{30}H_{35}N_3O_5$: C, 69.61; H, 6.82; N, 8.12. Found: C, 69.52; H, 6.80; N, 8.06. Recrystallization of **19** from benzene gave colorless prisms, mp 112—135.5 °C, which contained 1 mol of benzene. $[\alpha]_D^{13}$ +6.3° (c=0.5, MeOH). UV λ_{max}^{MeOH} nm (ε): 224 (36300), 274 (7600), 278.5 (7700), 289.5 (5900). IR ν_{max}^{KBr} cm^{-1}: 3260 (NH), 1760, 1690, 1670 (CO). MS *m/z* (%): 517 (M^+, 2.8), 285 (100). ^{1}H- and ^{13}C-NMR showed complex signals due to the presence of rotamers. *Anal.* Calcd for $C_{30}H_{35}N_3O_5+C_6H_6$: C, 72.58; H, 6.94; N, 7.05. Found: C, 72.70; H, 6.94; N, 6.98.

Compound **19** was also prepared from **14** and Z-L-proline chloride in 77% yield.

***cis–cis* Pentacycle (27)** A solution of the L-*cis*-dipeptide (**16**, 8.00 g, 15.46 mmol) in MeOH (800 ml) was hydrogenated in the presence of 5% Pd–C (800 mg) for 12 h at 60 °C. After removal of the catalyst, the solvent was evaporated off *in vacuo* to leave a residue, which was passed through a short silica gel column. The residue was recrystallized from MeOH to give the *cis–cis* pentacycle (**27**, 4.351 g). The mother liquor was chromatographed on a silica gel column (20 g, AcOEt–hexane, 1:1) to give **16** (207 mg, 2.6%) and **27** (257 mg, total 4.608 g, 84.8%). Repeated recrystallization from MeOH gave colorless prisms, mp 289—290 °C (dec.). $[\alpha]_D^{18}$ −76.3° (c=0.3, MeOH). UV λ_{max}^{MeOH} nm (ε): 222.5 (39800), 273.5 (7900), 278.5 (8000), 289 (6400). IR ν_{max}^{KBr} cm^{-1}: 3260 (NH), 1665 (CO), MS *m/z* (%): 351 (M^+, 19), 294 (100). NMR: See Table II. *Anal.* Calcd for $C_{21}H_{25}N_3O_2$: C, 71.77; H, 7.17; N, 11.96. Found: C, 71.79; H, 7.12; N, 11.97.

***trans–cis* Pentacycle (28)** The *trans* dipeptide (**17**, 650 mg, 1.26 mmol) was hydrogenated in MeOH (200 ml) in the presence of 5% Pd–C (100 mg) at room temperature. Work-up as above gave the *trans–cis* pentacycle (**28**, 338 mg, 76.4%). Recrystallization from benzene–iso-Pr_2O gave colorless prisms, mp 197—200 °C. $[\alpha]_D^{13}$ −171.4° (c=0.5, MeOH). UV λ_{max}^{MeOH} nm (ε): 223 (41200), 272.5 (7800), 278 (7800), 289.5 (6000). IR ν_{max}^{KBr} cm^{-1}: 3280 (NH), 1660 (CO). MS *m/z* (%): 351 (M^+, 32), 294 (100). NMR: See Table II. *Anal.* Calcd for $C_{21}H_{25}N_3O_2$: C, 71.77, H, 7.17; N, 11.96. Found: C, 71.82; H, 7.18; N, 11.92.

***cis–trans* Pentacycle (29)** Z-D-Proline chloride (prepared from Z-D-proline (1.33 g, 5.32 mmol)) in CH_2Cl_2 (8 ml) was added to a solution of L-*cis*-β-carboline (**11**, 1.47 g, 5.15 mmol) and Et_3N (1.00 g) in CH_2Cl_2 (10 ml) during 15 min under ice-cooling. The mixture was stirred for 1 h at room temperature. Usual work-up gave the dipeptide (**18**, 2.18 g, 74.7%), mp 126—136 °C, $[\alpha]_D^{27}$ −3.40° (c=0.47, MeOH). The dipeptide (**18**, 1.83 g, 3.07 mmol) was hydrogenated in MeOH (200 ml) in the presence of 5% Pd–C (600 mg) at 60 °C. Usual work-up gave the *cis–trans* pentacycle (**29**, 703 mg, 65%). Recrystallization from acetone gave colorless prisms, mp 264—266 °C (dec.) (drying at 80 °C *in vacuo* for 4 h). $[\alpha]_D^{27}$ −95.1° (c=0.37, MeOH). UV λ_{max}^{MeOH} nm (ε): 221 (40900), 274 (8200), 281 (8400), 289 (7000). IR ν_{max}^{KBr} cm^{-1}: 3240 (NH), 1675, 1660 (CO). MS *m/z* (%): 351 (M^+, 17), 294 (100). NMR: See Table II. *Anal.* Calcd for $C_{21}H_{25}N_3O_2$: C, 71.77; H, 7.17; N, 11.96. Found: C, 71.79; H, 7.16; N, 11.87.

***cis–trans* Pentacycle (30)** The D-*cis*-dipeptide (**19**, benzene solvate, 233 mg, 0.392 mmol) was hydrogenated in MeOH (70 ml) in the presence of 5% Pd–C (50 mg) for 6 h at 60 °C. Usual work-up gave the *cis–trans* pentacycle (**30**, 120 mg, 87%). Recrystallization from acetone gave colorless prisms, mp 263.5—266 °C (dec.) (after drying at 80 °C *in vacuo*). $[\alpha]_D^{25}$ +95.3° (c=0.3, MeOH). UV λ_{max}^{MeOH} nm (ε): 222 (41700), 272.5 (7900), 278 (7900), 289 (6200). IR ν_{max}^{KBr} cm^{-1}: 3240 (NH), 1675, 1660 (CO). The ^{1}H-NMR spectrum was identical with that of **29**. MS *m/z* (%): 351 (M^+, 17), 294 (100).

***trans–trans* Pentacycle (31)** The D-*trans*-dipeptide (**26**, 535 mg, 1.035 mmol) was hydrogenated in MeOH (50 ml) in the presence of 5% Pd–C (50 mg) at 60 °C. Work-up as above gave **31** (298 mg, 90%). Recrystallization from acetone–hexane gave colorless prisms, mp 149—157, 164—166 °C, which contained 1/3 mol of acetone. $[\alpha]_D^{25}$ +105.2° (c=0.3, MeOH). UV λ_{max}^{MeOH} nm (ε): 222 (40200), 273.5^{sh} (7900), 281 (8100), 289.5 (6700). IR ν_{max}^{KBr} cm^{-1}: 3290 (NH), 1720 (acetone), 1665 (CO). MS *m/z* (%): 351 (M^+, 27), 294 (100). NMR: See Table II. *Anal.* Calcd for $C_{21}H_{25}N_3O_2$ + 1/3C_3H_6O: C, 71.26; H, 7.34; N, 11.33. Found: C, 71.04; H, 7.32; N, 11.22.

Epimerization of 27 to 31 A solution of **27** (703 mg, 2.00 mmol) and 0.1 N NaOH–MeOH (18 ml) in MeOH (150 ml) was refluxed for 20 h. The mixture was neutralized with AcOH (1.5 ml) and evaporated *in vacuo* to leave a residue. Usual work-up gave **31**, mp 156—158 °C, in quantitative yield. The sample was identical with the above specimen (IR and $[\alpha]_D$).

Epimerization of 28 to the Enantiomer of 31 A solution of **28** (150 mg, 0.427 mmol) and 0.1 N NaOH–MeOH (4.3 ml) in MeOH (20 ml) was refluxed for 24 h. The mixture was neutralized with AcOH (0.1 ml) and evaporated *in vacuo* to leave a residue, which was purified by silica gel column chromatography and recrystallization from acetone–hexane to give the enantiomer of **31** (68.2 mg), mp 155—166 °C, $[\alpha]_D^{23}$ −95.9° (c=0.3, MeOH), as colorless prisms.

DDQ Oxidation of 27 DDQ (65 mg, 0.285 mmol) was added to a solution of **27** (100 mg, 0.285 mmol) in CH_2Cl_2 (2 ml) under an argon atmosphere. The mixture was stirred for 5 h at room temperature, then DDQ (65 mg) in CH_2Cl_2 (3 ml) and AcOH (1 ml) were added. The reaction mixture was further stirred for 5 h at room temperature and diluted with CH_2Cl_2 (50 ml). The mixture was washed with H_2O, saturated $NaHCO_3$ solution and saturated NaCl solution, and then dried. Evaporation of the solvent *in vacuo* gave a residue, which was separated by preparative TLC (silica gel, CH_2Cl_2–acetone, 2:1) to give **27** (16 mg) and the 2-acylindole (**45**, 28 mg, 26%). The acyl derivative (**45**) was identical with the sample prepared below (TLC, IR, UV).

Similar DDQ (11 mg) oxidation of the methoxy derivative (**44**, 10 mg) in acetonitrile–H_2O (7:3, 4 ml) gave the 2-acyl derivative (**46**, 3 mg) as a colorless caramel.

Acylation of Cyclo-L-prolyl-L-tryptophyl (34) with Isovaleroyl Chloride Isovaleroyl chloride (824 mg, 6.84 mmol) was added to a solution of **34** (1.00 g, 3.53 mmol) in CF_3COOH (15 ml). The mixture was stirred for 3 h at room temperature and poured into H_2O (100 ml). The mixture was extracted with CH_2Cl_2 and the extract was washed with saturated $NaHCO_3$ solution and saturated NaCl solution, and then dried. Evaporation of the solvent *in vacuo* gave a residue, which was chromatographed on a silica gel column (AcOEt–hexane, 4:1) to give **45** (225 mg, 17%) and the Na-trifluoroacetyl cyclic tautomer (246 mg, 18%). Recrystallization of **45** from AcOEt gave colorless prisms, mp 193.5—195 °C. $[\alpha]_D^{25}$ −70.9° (c=0.5, MeOH). UV λ_{max}^{MeOH} nm (ε): 208 (26800), 236 (15700), 312.5 (18100). IR ν_{max}^{KBr} cm^{-1}: 3250 (NH), 1670 (CO). ^{1}H-NMR δ: 0.96 (3H, d, J=6.8 Hz, CH_3), 0.97 (3H, d, J=6.8 Hz, CH_3), 1.8—2.1 (3H, m, proline 3-H_a + proline 4-H_2), 2.2—2.4 (2H, m, proline 3-H_b + $Me_2C\underline{H}$), 2.6—2.8 (2H, m, $COCH_2$), 3.47 (1H, dd, J=14.5, 9.0 Hz, ind-3-$C\underline{H}_aH_b$), 3.5—3.7 (2H, m, proline 5-H_2), 3.93 (1H, dd, J=14.3, 4.1 Hz, ind-3-$CH_a\underline{CH}_b$), 4.03 (1H, t, J=7.5 Hz, proline 2-H), 4.38 (1H, dd, J=9.5, 3.7 Hz, ind-3-CH_2–$C\underline{H}$), 7.01 (1H, s, N_b-H), 7.1—7.8 (4H, arom. H), 9.34 (1H, s, N_a-H). MS *m/z* (%): 367 (M^+, 18), 158 (100). *Anal.* Calcd for $C_{21}H_{25}N_3O_3$: C, 68.64; H, 6.86; N, 11.44. Found: C, 68.34; H, 6.89; N, 11.37.

Prenylation of 27 i) Direct Prenylation: The *cis–cis*-pentacyclic compound (**27**, 703 mg, 2.0 mmol) in DMF (12 ml) was added to a supension of NaH (50% oil dispersion, 115 mg, 2.4 mmol) in DMF (5 ml) under an argon atmosphere. The mixture was stirred for 30 min at room temperature. 3,3-Dimethylallyl bromide (358 mg, 2.4 mmol) in DMF (3 ml) was added to the mixture and the whole was stirred for 30 min at room temperature, then poured into H_2O (100 ml), and extracted with benzene–AcOEt (2:1). The extracts were washed with H_2O and saturated NaCl solution, and dried. Evaporation of the solvent gave a yellow oil (1.16 g), which was purified on a short silica gel column (CH_2Cl_2). The residue was recrystallized from AcOEt–hexane to give **48** (644 mg, 76.3%). Repeated recrystallization from the same solvent gave colorless needles, mp 138—140 °C. $[\alpha]_D^{11}$ −58.5° (c=0.3, MeOH). UV λ_{max}^{MeOH} nm (ε): 226 (39300), 276^{sh} (7700), 283.5 (8500), 292^{sh} (7200). IR ν_{max}^{KBr} cm^{-1}: 1675 (CO). ^{1}H-NMR δ: 0.90 (6H, d, J=6.3 Hz, 2×CH_3), 1.45—1.55 (3H, m, 3-CH_2, Me_2CH), 1.70 (3H, s, CH=C–$C\underline{H}_3$), 1.86 (3H, s, CH=C–$C\underline{H}_3$), 1.9—2.1 (2H, m, 8-H_2), 2.2—2.5 (2H, m, 7-H_2), 3.15 (1H, dd, J=15.8, 2.2 Hz, 13-H_a), 3.54 (1H, dd, J=16.0, 5.1 Hz, 13-H_b), 3.6—3.7 (2H, m, 9-H_2), 4.0—4.2 (2H, m, 6-H, 12-H), 4.6—4.8 (2H, m, $N_aC\underline{H}_2CH$=C), 5.17 (1H, t, J=1.3 Hz, C$\underline{H}$=C), 5.66 (1H, t, J=5.6 Hz, 3-H), 7.1—7.3 (3H, arom. H), 7.58 (1H, dd, J=7.1, 1.5 Hz, arom. H). MS *m/z* (%): 419 (M^+, 15), 362 (100). *Anal.* Calcd for $C_{26}H_{33}N_3O_2$: C, 74.43; H, 7.93; N, 10.02. Found: C, 74.34; H, 7.87; N, 10.03.

ii) Reduction–Prenylation–Dehydrogenation of **27**: Pyridine–borane (0.75 ml, 7.4 mmol) was added to **27** (500 mg, 1.43 mmol) in CF_3COOH (7.5 ml) during 2 min under ice-cooling. The mixture was stirred for a further 2 min under ice-cooling and poured into saturated $NaHCO_3$ solution (200 ml). The mixture was extracted with CH_2Cl_2. Usual work-up gave a mixture of indoline (**50**, 536 mg). A mixture of the indoline (**50**, 536 mg), anhydrous K_2CO_3 (2 g), and 3,3-dimethylallyl bromide (422 mg, 2.83 mmol) in acetone (20 ml) was stirred for 15 h at room temperature. Further K_2CO_3 (2 g) and the bromide (300 mg, 2.0 mmol) were added to the mixture and the whole was refluxed for 6 h. Evaporation of the solvent gave a residue, which was dissolved in CH_2Cl_2 and filtered to remove inorganic materials. The CH_2Cl_2 solution was washed with H_2O and saturated NaCl solution, and then dried. Evaporation of the solvent gave a residue which was purified on a silica gel column (CH_2Cl_2–acetone, 9 : 1) to give crude **51** (697 mg). A suspension of DDQ (355 mg, 1.53 mmol) in $CHCl_3$ (2 ml) was added to a solution of **51** (677 mg) in $CHCl_3$ (5 ml), and the mixture was stirred for 4.5 h at room temperature. Further DDQ (177 mg) was added, and the reaction mixture was stirred for a further 30 min, then filtered to remove insoluble materials and diluted with CH_2Cl_2. The $CHCl_3$–CH_2Cl_2 solution was washed with H_2O and saturated NaCl solution, and dried. Evaporation of the solvent gave a residue, which was separated by silica gel column chromatography (CH_2Cl_2–hexane) and preparative TLC (AcOEt–hexane, 2 : 1) to give **48** (360 mg, 61% from **27**), $[\alpha]_D^{10}$ −53.1° (c=0.7, MeOH). This sample was identical with the sample obtained by direct prenylation (TLC, IR and NMR).

Reduction of 48 A solution of **48** (321 mg, 0.766 mmol) in MeOH (20 ml) was hydrogenated in the presence of PtO_2 (10 mg) for 40 min at room temperature. Usual work-up gave the isopentyl derivative (**49**, 308 mg, 95.5%) as a white powder. $[\alpha]_D^{11}$ −68.3° (c=0.5, MeOH). UV λ_{max}^{EtOH} nm: 228, 277^{sh}, 285, 294^{sh}. IR ν_{max}^{KBr} cm^{-1}: 1660 (CO). ^{1}H-NMR δ: 0.92—1.02 (12H, 4 × CH_3), 1.5—1.8 (6H, m, 2 × $Me_2C\underline{H}C\underline{H}_2$), 1.9—2.1 (2H, m, CH_2), 2.2—2.5 (2H, m, $CHC\underline{H}_2$), 3.15 (1H, dd, J=15.8, 11.9 Hz, 13-H_a), 3.53 (1H, dd, J=15.8, 5.3 Hz, 13-H_b), 3.6 (2H, m, 9-H_2), 4.0—4.2 (4H, m, 6-H, 12-H, N_a-CH_2), 5.67 (1H, t-like, 3-H), 7.1—7.4 (3H, arom. H), 7.58 (1H, d, J=6.9 Hz, arom. H). MS m/z (%): 421 (M^+, 21), 364 (100).

Formation of 52 i) Isopentylation of **27**: A solution of **27** (1.054 g, 3.0 mmol) in DMF (15 ml) was added to a suspension of NaH (50% oil dispersion, 158 mg, 3.3 mmol) in DMF (5 ml) at room temperature under an argon atmosphere, and the mixture was stirred for 2 h. Isopentyl bromide (556 mg, 3.6 mmol) in DMF (1 ml) was added and the whole was stirred for 2 h at room temperature, poured into H_2O (100 ml) and extracted with benzene–AcOEt (2 : 1). The extracts were washed with H_2O and saturated NaCl solution, and then dried. Evaporation of the solvent *in vacuo* gave a residue, which was chromatographed on a silica gel column (20 g). Elution with CH_2Cl_2 gave **52** (1.198 g, 95%) as a white powder. $[\alpha]_D^{21}$ +103.2° (c=0.5, MeOH). UV λ_{max}^{EtOH} nm: 228, 276^{sh}, 285, 294^{sh}. IR ν_{max}^{KBr} cm^{-1}: 1665 (CO). ^{1}H-NMR δ: 0.95 (3H, d, J=6.6 Hz, CH_3), 1.01 (3H, d, J=6.3 Hz, CH_3), 1.02 (3H, d, J=5.9 Hz, CH_3), 1.15 (3H, d, J=6.3 Hz, CH_3), 1.5—2.2 (9H, m, 2 × $Me_2C\underline{H}C\underline{H}_2$, 7-$H_a$, 8-$H_2$), 2.5 (1H, m), 7-$H_b$), 2.94 (1H, dd, J=15.2, 12.2 Hz, 13-H_a), 3.34 (1H, dd, J=15.11, 4.6 Hz, 13-H_b), 3.6 (1H, m, 9-H_a), 3.8 (1H, m, 9-H_b), 3.9—4.2 (3H, m, N_a-CH_2, 6-H), 4.48 (1H, d, J=9.6 Hz, 12-H), 5.92 (1H, d, J=9.6 Hz, 3-H), 7.0—7.5 (4H, m, arom. H). MS m/z (%): 421 (M^+, 29), 364 (100).

ii) Epimerization of **49**: A solution of **49** (32 mg, 0.08 mmol) in DMF (2 ml) was added to a suspension of NaH (50%, 4.4 mg, 0.09 mmol) in DMF (1 ml). The mixture was stirred for 2 h at room temperature. Usual work-up gave **52** (20 mg, 62%) as a pale yellow amorphous powder, which was identical with the above sample (^{1}H-NMR, IR, and $[\alpha]_D$).

DDQ Oxidation of 52. Formation of the Dehydro Derivative (54) DDQ (2.327 g, 10 mmol) in CH_3CN–H_2O (7 : 3, 20 ml) was added to a solution of **52** (2.108 g, 5.0 mmol) in CH_3CN–H_2O (7 : 3, 40 ml) under an argon atmosphere. The mixture was stirred for 1.5 h at room temperature. The color of the mixture changed to reddish brown from black. The mixture was poured into H_2O (150 ml) and extracted with CH_2Cl_2. The extract was washed with saturated NaCl solution and dried. The solvent was evaporated off *in vacuo* to give a residue, which was chromatographed on an alumina column (CH_2Cl_2–acetone, 20 : 1) to give a mixture of **52** and the dehydro derivative (1.355 g). Repeated chromatography on a silica gel column (CH_2Cl_2) gave a mixture of **52** and **54** (1.10 g) which contained 79% of **54** as estimated by NMR spectroscopy or HPLC (μ-Porasil, CH_2Cl_2–iso-PrOH, 100 : 1) and the yield of **54** was 41%. A small sample of **54** was obtained by repeated silica gel column chromatography (CH_2Cl_2) and silica gel preparative TLC as a colorless powder, which showed a single peak in HPLC. $[\alpha]_D^{18}$ +145.8° (c=0.5, MeOH). UV λ_{max}^{EtOH} nm: 236, 261, 367. IR ν_{max}^{KBr} cm^{-1}: 1690, 1620 (CO). ^{1}H-NMR δ: 0.86 (3H, d, J=6.6 Hz, CH_3), 1.03 (3H, d, J=6.3 Hz, CH_3), 1.05 (3H, d, J=6.3 Hz, CH_3), 1.10 (3H, d, J=6.3 Hz, CH_3), 1.5—2.2 (9H, m, 2 × $Me_2C\underline{H}C\underline{H}_2$, 7-$H_a$, 8-$H_2$), 2.5 (1H, m, 7-$H_b$), 3.7 (2H, m, 9-$H_2$), 4.0—4.3 (3H, m, N_a-CH_2, 6-H), 6.19 (1H, dd, J=10.2, 3.0 Hz, 3-H), 7.16—7.35 (3H, arom H), 7.39 (1H, s, C=CH), 7.65 (1H, dd, J=6.6, 1.7 Hz, arom. H). ^{13}C-NMR δ: 22.14, 22.43, 22.55 (t, CH_2), 23.50, 24.19, 26.29, 29.17 (t, $CH\underline{C}H_2$), 38.84 (t), 42.38 (t), 43.51 (t), 44.83 (t), 47.28 (d, C_3), 59.06 (d, C_6), 106.37 (s, C_{14}), 110.05 (d, C_{19}), 112.47 (d, C_{13}), 118.57 (d, C_{16}), 121.08 (s, C_{17}), 121.57 (s, C_{12}), 122.35 (d, C_{18}), 124.16 (s, C_{15}), 136.97 (s, C_2 and C_{20}), 160.41 (s, CO), 167.18 (s, CO). MS m/z (%): 419 (M^+, 25), 362 (100).

NBS Oxidation of 54 NBS (80 mg, 0.45 mmol) was added to a solution of the dehydro derivative (**54**, 217 mg, 0.41 mmol, containing 21% **52**) in dimethoxyethane–H_2O (5 : 1, 30 ml) under ice-cooling. The mixture was stirred for 6 h at room temperature. Further NBS (10 mg, 0.06 mmol) was added and the reaction mixture was stirred for 8 h at room temperature, then poured into H_2O and extracted with CH_2Cl_2. The extract was washed with H_2O and saturated NaCl solution, and dried. The solvent was removed *in vacuo* to give a residue, which was purified by silica gel column chromatography (AcOEt–hexane, 1 : 1) and preparative TLC (silica gel, AcOEt–hexane, 2 : 1; CH_2Cl_2–acetone, 20 : 1). The *trans*-diol (**57**, 157 mg, 85%) was obtained as a colorless caramel. Recrystallization from CH_2Cl_2–hexane gave colorless fine needles, mp 231—232.5 °C. UV λ_{max}^{EtOH} nm: 224, 275^{sh}, 283, 291.5. IR ν_{max}^{KBr} cm^{-1}: 3500, 3200^{br}, 1650. ^{1}H-NMR δ: 0.94—1.05 (12H, m, CH_3 × 4), 1.6—2.1 (9H, m, 2 × $Me_2C\underline{H}C\underline{H}_2$, 8-$H_2$, 7-$H_a$), 2.51 (1H, dd, J=5.4, 11.5 Hz, 7-H_b), 2.67 (1H, br, 12-OH), 3.66 (2H, dd, J=2.8, 8.7 Hz, 9-H_2), 4.0—4.2 (2H, m, N_a-CH_2), 4.16 (1H, d, J=2.8 Hz, 13-OH), 4.46 (1H, dd, J=6.9, 9.5 Hz, 6-H), 5.61 (1H, dd, J=3.1, 7.7 Hz, 3-H), 5.65 (1H, d, J=2.8 Hz, 13-H), 7.15—7.75 (4H, m, arom. H). ^{13}C-NMR δ: 22.45 (q, CH_3), 22.78 (q, CH_3), 22.83 (t, CH_2), 23.29 (q, CH_3), 25.05 (d, $\underline{C}HMe_2$), 26.49 (d, $\underline{C}HMe_2$), 29.43 (t, CH_2), 38.70 (t, CH_2), 42.47 (t, CH_2), 45.44 (t, C_9), 47.63 (d, C_3), 49.76 (t, CH_2), 59.83 (d, C_6), 66.23 (d, C_{13}), 85.58 (s, C_{12}), 104.64 (s, C_{14}), 110.05 (d, C_{19}), 118.20 (d, C_{16}), 120.20 (d, C_{18}), 120.53 (d, C_{17}), 126.78 (s, C_{15}), 136.77 and 139.10 (s, C_2 and C_{20}), 164.62 (s, C=O), 171.96 (s, C=O). MS m/z (%): 453 (M^+, 20), 285 (100). *Anal.* Calcd for $C_{26}H_{35}N_3O_4 + 1/3H_2O$: C, 67.95; H, 7.82; N, 9.11. Found: C, 68.07; H, 7.65; N, 9.11.

8-Acetyl-6-methoxy-1,2-dimethoxycarbonylpyrrolo[2,3-*b*]indole Lead tetraacetate (6.68 g, 13.56 mmol) in CF_3COOH (20 ml) was added to a solution of **36**[18] (4.00 g, 12.57 mmol) in CF_3COOH (100 ml) during 35 min at −2—2 °C (inner temperature). The whole mixture was stirred for 4 h at −1—5 °C and poured into ice-water. The mixture was extracted with CH_2Cl_2, and the extract was washed with saturated $NaHCO_3$ and saturated NaCl solutions, and dried. Evaporation of the solvent gave a residue (4.50 g), which was dissolved in acetone (100 ml). Methyl iodide (8.92 g, 62.84 mmol) and anhydrous K_2CO_3 (8.68 g, 66.15 mmol) were added to the solution, and the reaction mixture was stirred for 26.5 h at room temperature. Further methyl iodide (8.92 g, total 26.52 g) was added after 5.5 and 24 h. After removal of inorganic materials, the solvent was evaporated off to give a residue, which was dissolved in CH_2Cl_2. Insoluble materials were removed. Evaporation of the solvent gave a residue (4.49 g), which was chromatographed on a silica gel column (AcOEt–hexane, 1 : 1). The 6-methoxy derivative (**37**, 2.43 g, 56%), and 5-methoxy derivative (**38**, 0.94 g, 22%) were obtained, each as a pale yellow amorphous powder. TLC behavior and UV spectra of the compounds were identical with those of the racemic compounds. **37**: $[\alpha]_D^{12}$ +79.8° (c=1.389, MeOH).

***N*$_b$-Methoxycarbonyl-6-methoxy-L-tryptophan Methyl Ester (39)** A 10% H_2SO_4–MeOH solution (100 ml) was added to a solution of **37** (4.89 g, 14.04 mmol) in MeOH (20 ml), and the mixture was stirred for 2.5 h at room temperature, poured into ice-water and extracted with CH_2Cl_2. Usual work-up gave **39** (4.02 g, 94%) as a colorless caramel. Repeated recrystallization from MeOH–iso-Pr_2O gave colorless fine prisms, mp 96.5—98.0 °C. $[\alpha]_D^{19}$ +3.5° (c=0.346, MeOH). The TLC behavior and UV spectrum of the sample were identical with those of the racemic compound. *Anal.* Calcd for $C_{15}H_{18}N_2O_5$: C, 58.82; H, 5.92; N, 9.15. Found: C, 58.72; H, 5.90; N, 9.06.

6-Methoxy-L-tryptophan Methyl Ester (40) A solution of **39** (2.52 g, 8.23 mmol) and trimethylsilyl iodide (2.00 ml, 14.05 mmol) in $CHCl_3$ (40 ml) was refluxed for 1.5 h. After cooling of the mixture, MeOH (3 ml) was added, and the whole was stirred for 40 min at room temperature. The solvent was evaporated off to give a residue, which was dissolved in Et_2O and 5% HCl. The ether layer was extracted with 5% HCl. The combined HCl solution was made alkaline with concentrated NH_4OH and extracted with AcOEt. The solvent was evaporated *in vacuo* after being dried to give **40** (2.03 g, 99%) as a colorless caramel. Repeated recrystallization from

AcOEt–hexane gave pale brown prisms, mp 99.5—101 °C. $[\alpha]_D^{15}$ +32.6° (c=0.537, MeOH). UV λ_{max}^{EtOH} nm (ε): 222.5 (33000), 273 (4200), 293 (5000). IR ν_{max}^{KBr} cm^{-1}: 3390, 1745, 1205. ^{1}H-NMR δ: 1.74 (2H, brs, NH_2, exchangeable), 3.01 (1H, dd, J=7.6, 14.2 Hz, ind-CH_a), 3.23 (1H, dd, J=4.8, 14.3 Hz, ind-CH_b), 3.71 (3H, s, OCH_3), 3.81 (1H, dd, J=4.8, 7.4 Hz, N-CHCO), 3.83 (3H, s, OCH_3), 6.79 (1H, dd, J=2.0, 8.6 Hz, 5-H), 6.83 (1H, d, J=2.3 Hz, 7-H), 6.93 (1H, d, J=2.0 Hz, 2-H, became a singlet on the addition of D_2O), 7.46 (1H, d, J=8.6 Hz, 4-H), 8.08 (1H, brs, ind-NH, exchangeable). MS m/z: (%): 248 (M^+, 22), 160 (100). *Anal.* Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.70; H, 6.49; N, 11.15.

***cis*- and *trans*-1-Isobutyl-7-methoxy-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline (41 and 42)** Isovaleraldehyde (**10**, 1.26 g, 14.58 mmol) and CF_3COOH (1.20 ml, 15.58 mmol) were added to a solution of **40** (1.82 g, 7.33 mmol) in CH_2Cl_2 (50 ml). The mixture was stirred for 70 min at room temperature and diluted with CH_2Cl_2. The solution was washed with saturated $NaHCO_3$ and saturated NaCl solutions, and dried. Evaporation of the solvent gave a residue, which was separated by repeated silica gel column chromatography (AcOEt–hexane) to give the less polar *cis*-isomer (**41**, 1.23 g, 53%), $[\alpha]_D^9$ −122.3° (c=0.593, MeOH), and the more polar *trans*-isomer (**42**, 0.69 g, 30%), $[\alpha]_D^{16}$ +58.4° (c=0.551, MeOH), each as a white solid. **41**: mp 151.0—152 °C (from Et_2O) as colorless plates. UV λ_{max}^{EtOH} nm: 228, 272.5, 297, 308^{sh}. IR ν_{max}^{KBr} cm^{-1}: 1750, 1735 (CO). ^{1}H-NMR δ: 1.00 (3H, d, J=6.6 Hz, CH_3), 1.03 (3H, d, J=6.6 Hz, CH_3), 1.56—1.72 (2H, m, 1-CH_2), 1.95—2.09 (2H, m, Me_2CH and N_b-H (exchangeable)), 2.78 (1H, ddd, J=2.6, 11.2, 15.2 Hz, 4-H_a), 3.08 (1H, ddd, J=1.6, 4.3, 15.3 Hz, 4-H_b), 3.77 (1H, dd, J=4.3, 11.2 Hz, 3-H), 3.81 and 3.82 (each 3H, s, OMe), 4.19 (1H, dt, J=2.6, 5.4 Hz, 1-H), 6.77 (1H, dd, J=2.3, 8.6 Hz, 6-H), 6.83 (1H, d, J=2.3 Hz, 8-H), 7.33 (1H, d, J=8.6 Hz, 5-H), 7.66 (1H, br, N_a-H, exchangeable). ^{13}C-NMR δ: 21.71 (q, CH_3), 23.84 (q, CH_3), 24.30 (d, Me_2C), 26.03 (t, C_4), 44.40 (t, CH_2), 50.59 (d, C_1), 52.12 (q, OCH_3), 55.69 (q, OCH_3), 56.52 (d, C_3), 95.11 (d, C_8), 107.49 (s, C_{4a}), 108.87 (d, C_6), 118.40 (d, C_5), 121.77 (s, C_{4b}), 134.90 (s, C_{9a}), 136.71 (s, C_{8a}), 156.15 (s, C_7), 173.83 (s, C=O). MS m/z (%): 316 (M^+, 18), 259 (100). *Anal.* Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.42; H, 7.69; N, 8.83.

42: mp 151—153.5 °C (from Et_2O), colorless prisms. UV λ_{max}^{EtOH} nm: 228, 268, 298, 307^{sh}. IR ν_{max}^{KBr} cm^{-1}: 1745 (CO). ^{1}H-NMR δ: 1.00 (3H, d, J=6.6 Hz, CH_3), 1.02 (3H, d, J=6.6 Hz, CH_3), 1.49 (1H, ddd, J=4.3, 9.6, 13.8 Hz, 1-CH_a), 1.68 (1H, ddd, J=4.9, 9.9, 13.8 Hz, 1-CH_b), 1.94 (1H, m, Me_2CH), 2.13 (1H, br, N_b-H, exchangeable), 2.93 (1H, ddd, J=1.3, 7.6, 15.5 Hz, 4-H_a), 3.07 (1H, ddd, J=1.0, 5.3, 15.9 Hz, 4-H_b), 3.75 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.95 (1H, dd, J=5.3, 7.6 Hz, 3-H), 4.25 (1H, dd, J=4.3, 9.9 Hz, 1-H), 6.76 (1H, dd, J=2.3, 8.6 Hz, 6-H), 6.81 (1H, d, J=2.0 Hz, 8-H), 7.34 (1H, d, J=8.2 Hz, 5-H), 7.60 (1H, br, N_a-H, exchangeable). ^{13}C-NMR δ: 21.68 (q, CH_3), 23.64 (q, CH_3), 24.71 (d, Me_2CH), 25.08 (t, C_4), 44.49 (t, C_{10}), 48.17 (d, C_1), 52.06 (q, OCH_3), 52.38 (d, C_3), 55.75 (q, OCH_3), 95.08 (d, C_8), 106.57 (s, C_{4a}), 108.70 (d, C_6), 118.43 (d, C_5), 121.68 (s, C_{4b}), 134.81 (s, C_{9a}), 136.66 (s, C_{8a}), 156.15 (s, C_7), 174.32 (s, C=O). MS m/z (%): 316 (M^+, 31), 259 (100). *Anal.* Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.40; H, 7.64; N, 8.87.

Condensation of 41 with L-Proline. Formation of the Dipeptide (43) Z-L-Prolyl chloride (prepared from Z-L-proline 800 mg, 3.21 mmol) in CH_2Cl_2 (3 ml) was added to the *cis*-β-carboline (**41**, 566 mg, 1.79 mmol) and Et_3N (0.45 ml, 3.23 mmol) in CH_2Cl_2 (10 ml) during 5 min under ice-cooling. The mixture was stirred for 1.5 h under ice-cooling, and diluted with CH_2Cl_2. Usual work-up gave the crude dipeptide (**43**), which was recrystallized from AcOEt–hexane to give a colorless powder (803 mg), mp 243—245 °C. A further crop of **43** (73 mg, total 875 mg, 89%) was obtained by preparative TLC (silica gel, AcOEt–hexane) of the mother liquor. Recrystallization from MeOH gave colorless needles, mp 242—242.5 °C. $[\alpha]_D^{20}$ −43.5° (c=0.131, MeOH). UV λ_{max}^{EtOH} nm: 227.5, 266, 297, 305^{sh}. IR ν_{max}^{KBr} cm^{-1}: 1740, 1670 (CO). MS m/z (%): 547 (M^+, 5), 315 (100). The ^{1}H-NMR spectrum of **43** showed complex signals due to the presence of rotamers. *Anal.* Calcd for $C_{31}H_{37}N_3O_6$: C, 67.99; H, 6.81; N, 7.67. Found: C, 67.70; H, 6.81; N, 7.60.

***cis,cis*-Methoxy-pentacyclic Compound (44)** A mixture of the dipeptide **43** (824 mg, 1.51 mmol), $HCOONH_4$ (1.897 g, 30.09 mmol), and 10% Pd–C (200 mg) in MeOH (100 ml) was stirred for 13.5 h at room temperature. The mixture was filtered to remove the catalyst and the solvent was evaporated off *in vacuo* to leave a residue, which was dissolved in CH_2Cl_2. The CH_2Cl_2 solution was washed with saturated NaCl solution and dried. Evaporation of the solvent gave the residue, which was recrystallized from MeOH to give the pentacyclic compound (**44**, 519 mg), mp 272—275 °C. A further crop of **44** (29 mg, total 548 mg, 95%) was obtained by preparative TLC (silica gel, AcOEt–hexane, 2:1) of the mother liquor. Recrystallization from MeOH gave colorless prisms, mp 267.5 °C. $[\alpha]_D^{32}$ −80.6° (c=0.124, MeOH). UV λ_{max}^{EtOH} nm: 225, 262^{sh}, 270, 297, 306. IR ν_{max}^{KBr} cm^{-1}: 3300, 1675, 1660, ^{1}H-NMR: See Table II. *Anal.* Calcd for $C_{22}H_{27}N_3O_3$: C, 69.27; H, 7.13; N, 11.02. Found: C, 69.11; H, 7.15; N, 10.99.

Isopentylation of 44. Formation of 53 A solution of **44** (1.24 g, 3.25 mmol) in DMF (25 ml) was added to a suspension of NaH (52.9% oil dispersion, 251 mg, 5.54 mmol) in DMF (8 ml) under a N_2 atmosphere. After 1 h of stirring, isoamyl bromide (835 mg, 5.53 mmol) in DMF (5 ml) was added to the mixture. The reaction mixture was stirred for 1 h at room temperature. Saturated NH_4Cl (10 ml) and H_2O (40 ml) were added, and the whole was extracted with AcOEt–benzene (1:2). The extract was washed with H_2O and saturated NaCl solution, and dried. The solvent was evaporated off *in vacuo* to leave a residue, which was chromatographed on a silica gel column (50 g, AcOEt–hexane, 3:2) to give **53** (1.447 g, 99%) as an amorphous powder. $[\alpha]_D^{10}$ +125.9° (c=0.390, MeOH). UV λ_{max}^{EtOH} nm: 230, 277, 296, 307^{sh}. IR ν_{max}^{KBr} cm^{-1}: 1660 (CO). ^{1}H-NMR δ: 0.94 (3H, d, J=6.3 Hz, CH_3), 1.01 and 1.02 (total 6H, each d, J=6.3 Hz, CH_3 × 2), 1.15 (3H, d, J=6.3 Hz, CH_3), 1.5—2.15 (9H, m, 7-H_a, 8-H_2, 2 × Me_2CHCH_2), 2.50 (1H, m, 7-H_b), 2.91 (1H, dd, J=12.4, 15.0 Hz, 13-H_a), 3.29 (1H, dd, J=4.6, 15.5 Hz, 13-H_b), 3.60 (1H, m, 9-H_a), 3.80 (1H, m, 9-H_b), 3.88 (3H, s, OCH_3), 3.90—4.15 (3H, m, ind-N-CH_2, 6-H), 4.46 (1H, dd, J=4.5, 12.0 Hz, 12-H), 5.88 (1H, d, J=10.2 Hz, 3-H), 6.75—6.80 (2H, m, 17-H, 19-H), 7.30 (1H, d, J=8.9 Hz, 16-H). ^{13}C-NMR δ: 21.74 (q, CH_3), 22.06 (t, C_{13}), 22.49 (q, CH_3), 22.57 (q, CH_3), 23.64 (q, CH_3), 25.34 (d, Me_2CH), 25.80 (t, CH_2), 26.38 (d, Me_2CH), 30.03 (t, CH_2), 38.32 (t, CH_2), 42.24 (t, CH_2), 42.59 (t, C_{26}), 45.38 (t, C_9), 46.88 (d, C_3), 54.51 (d, C_{12}), 55.86 (q, OCH_3), 58.83 (d, C_6), 94.04 (d, C_{19}), 105.39 (s, C_{14}), 108.47 (d, C_{17}), 118.66 (d, C_{16}), 120.96 (s, C_{15}), 133.66 (s, C_2), 137.15 (s, C_{20}), 156.35 (s, C_{18}), 165.25 (s, C=O), 166.60 (s, C=O). Exact Mass Calcd for $C_{27}H_{37}N_3O_3$: 451.2837. Found 451.2828. MS m/z (%): 451 (M^+, 31), 394 (100).

DDQ Oxidation of 53 i) Formation of the 13-Hydroxy Derivative (**56**) and the Dehydro Derivative (**55**): DDQ (46 mg, 0.20 mmol) was added to a solution of **53** (45 mg, 0.10 mmol) in CH_3CN–H_2O (7:3, 5 ml). The mixture was stirred for 15 min, poured into H_2O, and extracted with CH_2Cl_2. The extract was washed successively with saturated $NaHCO_3$ and saturated NaCl solutions, and dried. The solvent was evaporated off *in vacuo* to give a residue, which was purified by preparative TLC (silica gel, AcOEt–hexane, 2:1) to give a mixture of the dehydro derivative (**55**) and the starting material (**53**) (1:1, 20 mg), and the 13-hydroxy derivative (**56**, 12 mg, 27%). **56**: White caramel. UV λ_{max}^{EtOH} nm: 225, 273, 295, 303^{sh}. ^{1}H-NMR δ: 0.94 (3H, d, J=6.6 Hz, CH_3), 1.02 (3H, d, J=6.3 Hz, CH_3), 2.34 (1H, br, OH, exchangeable), 4.39 (1H, d, J=2.0 Hz, 12-H), 5.39 (1H, br, 13-H, became a doublet (J=2.3 Hz) on the addition of D_2O), 5.99 (1H, dd, J=2.6, 11.5 Hz, 3-H), 6.77 (1H, d, J=2.0 Hz, 19-H), 6.80 (1H, dd, J=2.3, 8.6 Hz, 17-H), 7.48 (1H, d, J=8.6 Hz, 16-H). MS m/z (%): 467 (M^+, 29), 410 (100).

The 13-hydroxy derivative (**56**, 13 mg) was dissolved in 10% H_2SO_4–MeOH (2 ml) and the solution was stirred for 15 min. The mixture was poured into H_2O and extracted with CH_2Cl_2. The extract was washed successively with saturated $NaHCO_3$ and saturated NaCl solutions, and dried. The solvent was evaporated off *in vacuo* to leave a residue, which was purified by preparative TLC (silica gel, AcOEt–hexane, 2:1) to give the dehydro derivative (**55**, 8 mg, 66%) as a pale yellow caramel. UV λ_{max}^{EtOH} nm: 219, 236^{sh}, 268, 298, 376. ^{1}H-NMR δ: 0.86 (3H, d, J=6.6 Hz, CH_3), 1.00 (3H, d, J=6.6 Hz, CH_3), 1.05 (3H, d, J=6.3 Hz, CH_3), 1.09 (3H, d, J=6.3 Hz, CH_3), 1.5—2.2 (9H, m, Me_2CHCH_2 × 2, 7-H_a, 8-H_2), 2.45 (1H, m, 7-H_b), 3.5—3.8 (2H, m, 9-H_2), 3.88 (3H, s, OCH_3), 3.9—4.2 (3H, m, N_a-CH_2, 6-H), 6.15 (1H, dd, J=3.0, 10.2 Hz, 3-H), 6.79 (1H, d, J=2.0 Hz, 19-H), 6.86 (1H, dd, J=2.3, 8.6 Hz, 17-H), 7.33 (1H, s, 13-H), 7.52 (1H, d, J=8.6 Hz, 16-H). MS m/z (%): 449 (M^+, 14), 392 (100).

ii) Formation of **55**: Acid Treatment of the Reaction Mixture: A mixture of **53** (452 mg, 1.00 mmol) and DDQ (463 mg, 2.00 mmol) in CH_3CN–H_2O (7:3, 55 ml) was stirred for 1 h at room temperature. Then 5% HCl (1 ml) was added, and the reaction mixture was stirred for 3 h at room temperature, and passed through an alumina column (50 g, CH_2Cl_2). The eluent was washed with saturated $NaHCO_3$ and saturated NaCl solution, and dried. The solvent was evaporated off *in vacuo* to leave a residue (492 mg), which was chromatographed on a silica gel column (30 g, AcOEt–hexane, 3:2). A mixture of **53** and **55** (292 mg) was obtained as a yellow caramel. HPLC analysis (μ-Porasil, CH_2Cl_2–iso-PrOH, 100:1) showed that the ratio of **53**:**55** was 8:92.

NBS Oxidation of 55 NBS (100 mg, 0.56 mmol) was added to a solution of the dehydro derivative (**55**, 209 mg, 0.46 mmol from the purity)

in dimethoxyethane–H_2O (5 : 1, 30 ml) under ice-cooling. After 1 h of stirring under ice-cooling, further NBS (40 mg, 0.22 mmol) was added. The reaction mixture was stirred for 30 min under ice-cooling and for 4 h at room temperature, then diluted with CH_2Cl_2, washed with H_2O and saturated NaCl solution, and dried. The solvent was evaporated off *in vacuo* to leave a residue, which was purified by silica gel column chromatography (CH_2Cl_2–acetone, 2 : 1) and preparative TLC (silica gel, CH_2Cl_2–acetone, 20 : 1). The bromodiol (**58**, 137 mg, 52%) was obtained as a colorless caramel. Recrystallization from CH_2Cl_2–hexane gave colorless fine needles, mp 236—237 °C. UV λ_{max}^{EtOH} nm: 229, 282^{sh}, 304, 313^{sh}. ^{1}H-NMR δ: 0.9—1.1 (12H, m, $CH_3 \times 4$), 1.5—2.2 (9H, m, $Me_2CHCH_2 \times 2$, 7-H_a, 8-H_2), 2.50 (1H, m, 7-H_b), 2.64 (1H, br, 12-OH, exchangeable), 3.67 (2H, m, 9-H_2), 4.08 (2H, m, ind-N-CH_2), 4.18 (1H, d, J=2.6 Hz, 13-OH, exchangeable), 4.45 (1H, m, 6-H), 5.55 (1H, d, J=2.3 Hz, 13-H, became a singlet on addition of D_2O), 5.59 (1H, m, 3-H), 6.81 (1H, s, 19-H), 7.85 (1H, s, 16-H). MS *m/z* (%): 563 (M^++2, 25), 561 (M^+, 26), 506 (96), 504 (100). *Anal.* Calcd for $C_{27}H_{36}BrN_3O_5 + 1/3H_2O$: C, 57.04; H, 6.50; N, 7.39. Found: C, 57.16; H, 6.42; N, 7.40.

The bromodiol (**58**, 36 mg, 0.07 mmol) in THF–H_2O (95 : 5, 8 ml) was hydrogenated for 23 h in the presence of 10% Pd–C (66 mg) and H_2. The mixture was diluted with CH_2Cl_2 and dried with K_2CO_3. The solvent was evaporated off *in vacuo* to leave a residue, which was purifed by preparative TLC (silica gel, CH_2Cl_2–acetone, 20 : 1) to give the *trans*-diol (**59**, 16 mg, 53%) and **58** (13 mg, 36%). **59**: colorless caramel. $[\alpha]_D^{30}$ −85.0° (c = 0.16, $CHCl_3$). UV λ_{max}^{EtOH} nm: 226, 275, 297, 305^{sh}. ^{1}H-NMR δ: 0.9—1.1 (12H, m, $CH_3 \times 4$), 1.5—2.2 (9H, m, $Me_2CHCH_2 \times 2$, 8-H_2, 7-H_a), 2.52 (1H, m, 7-H_b), 2.72 (1H, br, 12-OH), 3.68 (2H, m, 9-H_2), 3.88 (3H, s, OCH_3), 4.09 (2H, m, N_a-CH_2), 4.15 (1H, br, 13-OH), 4.45 (1H, m, 6-H), 5.58 (1H, m, 3-H), 5.60 (1H, br, 13-H), 6.82 (1H, d, J=2.0 Hz, 19-H), 6.86 (1H, dd, J=2.0, 8.6 Hz, 17-H), 7.57 (1H, d, J=8.6 Hz, 16-H). ^{13}C-NMR δ: 22.49 (q, CH_3), 22.83 (q, CH_3), 23.29 (q, CH_3), 23.76 (t, C_8), 25.05 (d, Me_2CH), 26.46 (d, Me_2CH), 29.43 (t, C_7), 38.44 (t, C_{26}), 42.38 (t, C_{22}), 45.41 (t, C_9), 47.68 (d, C_3), 49.81 (t, C_{21}), 55.89 (q, OCH_3), 59.86 (d, C_6), 66.28 (d, C_{13}), 85.55 (s, C_{12}), 94.50 (d, C_{19}), 104.61 (s, C_{14}), 109.59 (d, C_{17}), 118.80 (d, C_{16}), 121.17 (s, C_{15}), 130.87 (s, C_2), 137.95 (s, C_{20}), 156.58 (s, C_{18}), 164.64 (s, C=O), 171.93 (s, C=O). MS *m/z* (%): 483 (M^+, 21), 426 (100).

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References and Notes

1) A part of this paper has been published as a communication Part II: M. Nakagawa, H. Fukushima, T. Kawate, M. Hongu, S. Kodato, T. Une, M. Taniguchi, and T. Hino, *Tetrahedron Lett.*, **27**, 3235 (1986).
2) M. Yamazaki, K. Sasago, and K. Miyaki, *J. Chem. Soc., Chem. Commun.*, **1974**, 408; M. Yamazaki and H. Fujimoto, *Tetrahedron Lett.*, **1975**, 27; M. Yamazaki, K. Suzuki, H. Fujimoto, T. Akiyama, U. Sankawa, and Y. Iitaka, *Chem. Pharm. Bull.*, **28**, 861 (1980); H. W. Schroeder, R. J. Cole, J. Hein, Jr., and J. W. Kirksey, *Appl. Microbiol.*, **29**, 857 (1975); P. Steyn, R. Vleggaar, and C. R. Rabie, *Phytochemistry*, **20**, 583 (1981); D. T. Dix, J. Mortin, and C. E. Moppett, *J. Chem. Soc., Chem. Commun.*, **1972**, 1168; R. T. Gallagher and G. C. M. Latch, *Appl. Environ. Microbiol.*, **33**, 730 (1977); M. Yamazaki, H. Fujimoto, and T. Kawasaki, *Tetrahedron Lett.*, **1975**, 1241; *idem, Chem. Pharm. Bull.*, **28**, 245 (1980); N. Eickman, J. Clardy, R. J. Cole, and J. W. Kirksey, *Tetrahedron Lett.*, **1975**, 1051; G. W. Lanigan, A. L. Payne, and P. A. Cockrum, *Aust. J. Exp. Biol. Med. Sci.*, **57**, 31 (1979); P. R. Giesecke, G. W. Lanigan, and A. L. Payne, *Aust. Vet. J.*, **55**, 444 (1979).
3) J. Fayos, D. Lokensgard, J. Clardy, R. J. Cole, and J. W. Kirksey, *J. Am. Chem. Soc.*, **96**, 6785 (1974); M. Uramoto, M. Tanabe, K. Hirotsu, and J. Clardy, *Heterocycles*, **17**, 349 (1982); R. J. Cole, J. W. Kirksey, J. W. Dorner, D. M. Wilson, J. C. Johnson Jr., A. N. Johnson, D. M. Bedell, J. P. Springer, K. K. Chexal, J. C. Clardy, and R. H. Cox, *J. Agric. Food. Chem.*, **25**, 826 (1977); R. J. Cole, *J. Food Prod.*, **44**, 715 (1981); For the synthesis of TR-2 and FTC: P. H. H. Hermkens, R. Plate, and H. C. J. Ottenheijm, *Tetrahedron Lett.*, **29**, 1323 (1988); *idem, Tetrahedron*, **44**, 1991 (1988); G. J. O'Malley and M. P. Cava, *Tetrahedron Lett.*, **28**, 1131 (1987).
4) M. Nakagawa, K. Matsuki, and T. Hino, *Tetrahedron Lett.*, **24**, 2171 (1983).
5) Recent review: F. Ungemach and J. M. Cook, *Heterocycles*, **9**, 1089 (1978).
6) D. Soerens, J. Sandrin, F. Ungemach, P. Mokey, C. S. Wu, E. Yamanaka, L. Hutchdins, M. DiPierro, and J. M. Cook, *J. Org. Chem.*, **44**, 535 (1979); D. M. Harrison and R. B. Sharma, *Tetrahedron Lett.*, **27**, 521 (1986).
7) J. Sandrin, D. Soerens, and J. M. Cook, *Heterocycles*, **4**, 1249 (1976); F. Ungemach, D. Soerens, R. Webu, M. DiPierro, O. Campos, P. Mokry, J. M. Cook and J. V. Silverton, *J. Am. Chem. Soc.*, **102**, 6976 (1980).
8) G. Massiot and T. Mulamba, *J. Chem. Soc., Chem. Commun.*, **1983**, 1149.
9) A. Brossi, A. Focella, and S. Teitel, *J. Med. Chem.*, **16**, 418 (1973).
10) T. Shioiri, K. Ninomiya, and S. Yamada, *J. Am. Chem. Soc.*, **94**, 6203 (1972); T. Shioiri and S. Yamada, *Chem. Pharm. Bull.*, **22**, 849, 855, 859 (1974).
11) T. Mukaiyama, R. Matsueda, and M. Suzuki, *Tetrahedron Lett.*, **1970**, 1901.
12) A. H. Jackson and A. E. Smith, *Tetrahedron*, **21**, 989 (1965).
13) D. M. Harrison, *Tetrahedron Lett.*, **1981**, 2501.
14) E. Yamanaka, N. Shibata, and S. Sakai, *Heterocycles*, **22**, 371 (1984).
15) F. Ungemach, M. DiPierro, R. Weber, and J. M. Cook, *J. Org. Chem.*, **46**, 164 (1981).
16) M. K. Anwer and A. F. Spatola, *Synthesis*, **1980**, 929.
17) P. S. Steyn, *Tetrahedron*, **29**, 107 (1973); T. Hino, J. Saegusa, K. Nakayama, and M. Nakagawa, unpublished observation.
18) T. Hino, M. Taniguchi, A. Gonsho, and M. Nakagawa, *Heterocycles*, **12**, 1027 (1979); M. Taniguchi, T. Anjiki, M. Nakagawa, and T. Hino, *Chem. Pharm. Bull.*, **32**, 2544 (1984).
19) M. Taniguchi and T. Hino, *Tetrahedron*, **37**, 1487 (1981).
20) K. Irie, A. Ishida, T. Nakamura, and T. Oh-ishi, *Chem. Pharm. Bull.*, **32**, 2126 (1984).
21) Y. Oikawa and O. Yonemitsu, *J. Org. Chem.*, **42**, 1213 (1977).
22) F. D. Gunstone and L. J. Morris, *J. Chem. Soc.*, **1957**, 487.
23) B. M. Trost and Y. Masuyama, *Tetrahedron Lett.*, **25**, 173 (1984).
24) E. J. Corey and J. Das, *Tetrahedron Lett.*, **23**, 4217 (1982).
25) M. Nakagawa, S. Kodato, M. Hongu, T. Kawate, and T. Hino, *Tetrahedron Lett.*, **27**, 6217 (1986); S. Kodato, M. Nakagawa, M. Hongu, T. Kawate, and T. Hino, *Tetrahedron*, **44**, 359 (1988); S.-I. Nakatsuka, K. Teranishi, and T. Goto, *Tetrahedron Lett.*, **27**, 6361 (1986).