Quinolizidines. XXVII.[1] Racemic and Chiral Syntheses of the *Neisosperma* and *Ochrosia* Alkaloid Ochropposinine

Tozo FUJII,* Masashi OHBA, Takeshi TACHINAMI, and Hisae MIYAJIMA

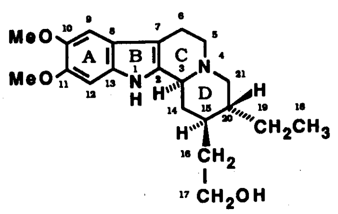
Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan. *Received October 17, 1989*

The first total synthesis of ochropposinine (1), a *Neisosperma* and *Ochrosia* alkaloid, has been accomplished in the form of a racemic modification by means of an initial coupling of the lactim ether (±)-3 with 5 and succeeding steps proceeding through the intermediates (±)-7, (±)-8, (±)-9, (±)-10, and (±)-11. A parallel synthetic route starting with (+)-3 produced the chiral target molecule (−)-1 *via* the intermediates (+)-7, (+)-8, (+)-9, 10, and (−)-11. As a result, the absolute configuration of ochropposinine has been unequivocally established to be that represented by formula (−)-1.

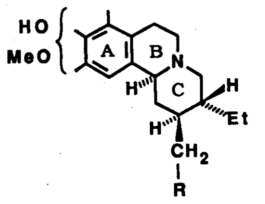
Keywords *Neisosperma* alkaloid; *Ochrosia* alkaloid; ochropposinine; indoloquinolizidine alkaloid synthesis; chiral synthesis; lactim ether alkylation; keto amide cyclization; oxazolium salt reduction; Bischler–Napieralski cyclization; hydride reduction

(−)-Ochropposinine, a member of the indoloquinolizidine alkaloids, was first isolated by Peube-Locou *et al.* in 1972 from the trunk bark of *Neisosperma oppositifolia* (LAMARCK) FOSBERG *et* SACHET (Apocynaceae).[2,3] Recently, two other research groups also reported isolations of this alkaloid from the same plant.[4] Furthermore, another species of the same genus, *Neisosperma glomerata*, and two species of a closely related genus, *Ochrosia vieillardii* and *Ochrosia moorei*, have so far been found to contain (−)-ochropposinine together with many other indole alkaloids.[5] The structure including the absolute configurations of three stereogenic centers of (−)-ochropposinine has been proposed to be (−)-1[6] on the basis of a combination of spectral analysis and a biosynthetic rationale.[3a,5d] In the present paper, we wish to record the details of the racemic and chiral syntheses of the candidate structure 1, which have confirmed the correctness of the above proposal.[7]

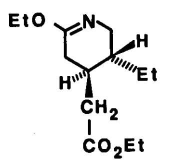
In connection with our synthetic study of the structurally related benzo[*a*]quinolizidine-type *Alangium* alkaloids (type 2) in racemic and chiral forms,[8] the lactim ether 3 seemed most attractive as a starting material to form ring D in 1 because 3 was readily available in any of the (±)-,[9] (+)-,[10,11] and (−)-forms[10] and had already been shown to be able to serve as a key intermediate for syntheses of the 2-type *Alangium* alkaloids by the "lactim ether route".[8,11−13] At the outset of the present synthesis, we needed 3-chloroacetyl-5,6-dimethoxyindole (5)[14] as another starting material for construction of rings A, B, and C in the target



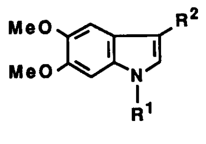
(±)-1
(−)-1



2



(±)-3
(+)-3



4 : $R^1 = R^2 = H$
5 : $R^1 = H$; $R^2 = COCH_2Cl$
6 : $R^1 = COCH_2Cl$; $R^2 = H$

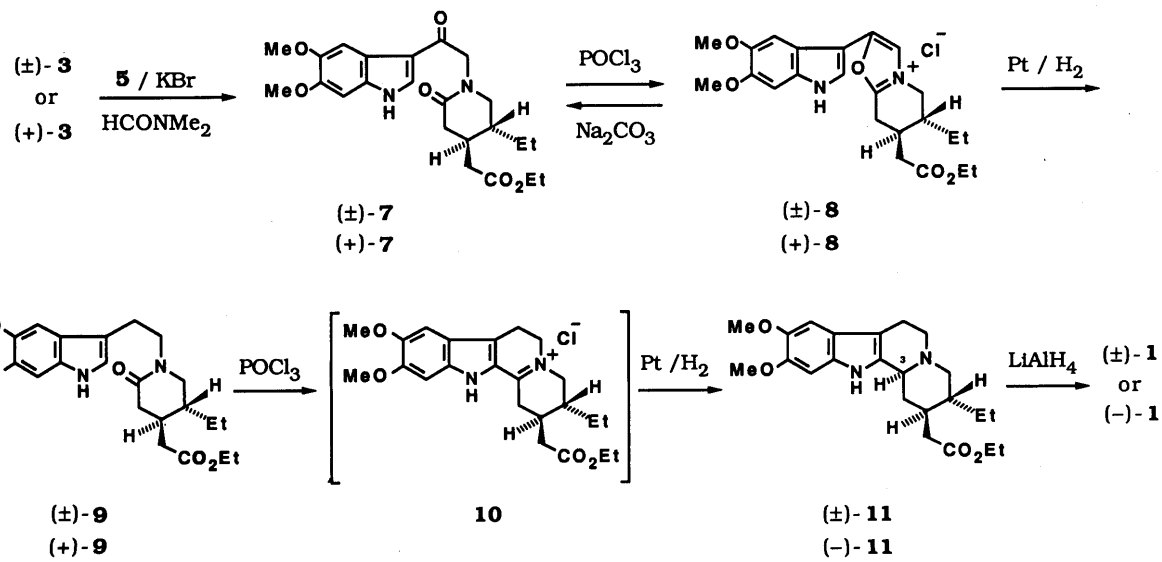


Chart 1

© 1990 Pharmaceutical Society of Japan

NII-Electronic Library Service

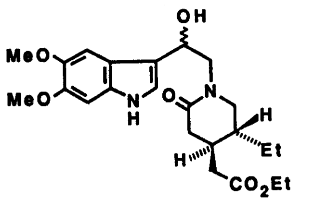
molecule **1**. According to a general 3-chloroacetylation procedure,[15] **5** was prepared in 51% yield from 5,6-dimethoxyindole (**4**)[16] by treatment with chloroacetyl chloride and pyridine in toluene at 55—60 °C for 40 min. In addition to the desired **5**, a small amount (7% yield) of the 1-acylated isomer **6** was also produced in this reaction.

For the racemic synthesis of the target molecule **1**, the lactim ether (±)-**3** was treated with **5** and KBr in $HCONMe_2$ at 60 °C for 48 h according to a precedent,[13a] providing the lactam ketone (±)-**7** in 71% yield. Reduction of (±)-**7** with a large excess of $NaBH_4$ in EtOH at room temperature for 3 h furnished a diastereomeric mixture of the lactam alcohol (±)-**12** (97% yield), which was then submitted to hydrogenolysis using hydrogen and 10% Pd–C catalyst under various conditions. However, the desired lactam ester (±)-**9** could not be obtained, most likely owing to the high reactivity at the indolylcarbinyl carbon atom. This failure led us to seek another method for reducing the carbonyl group to the methylene group.

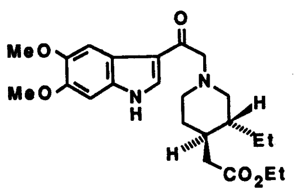
In 1930 Buck, in connection with the synthesis of papaverine, claimed that cyclization of the keto amide **14** with $POCl_3$, followed by catalytic hydrogenation of the resulting compound **15** in the presence of a very active platinum–palladium catalyst, afforded **16**.[17] Three years later, Young and Robinson, having doubts about these structures, proposed that the substance thitherto considered to be **15** by Buck was in reality the oxazole **17** as inferred from a general synthetic method of oxazole derivatives starting from keto amides, $R^1COCH_2NHCOR^2$, and the structure **16** should therefore be revised to the amide **18**.[18] It has also been shown that the oxazole **17** is reducible to the amide **18** by hydrogenolysis using hydrogen and Adams catalyst.[19] For reduction of the carbonyl group of (±)-**7** to the corresponding methylene group, we thus examined the applicability of the above oxazole method to our case. On treatment with $POCl_3$ in boiling toluene for 1 h, (±)-**7** produced the oxazolium salt (±)-**8** in 81% yield (Chart 1). As expected, the ^1H nuclear magnetic resonance (NMR) spectrum of (±)-**8** exhibited a one-proton singlet at δ 8.52, assignable to the oxazolium-ring proton. Conversely, treatment of (±)-**8** with Na_2CO_3 in aqueous EtOH at room temperature for 1.5 h reproduced the lactam ketone (±)-**7** in 86% yield. Hydrogenation of (±)-**8** was effected in EtOH over Adams catalyst at room temperature and atmospheric pressure for 10 h, giving the requisite lactam (±)-**9** in 51% yield. On the other hand, reduction of (±)-**8** with $NaBH_4$ (2 equivalent mol) in EtOH at 0 °C for 10 min and then at room temperature for 50 min led to the amino ketone (±)-**13** in 74% yield. It is of interest to note that the carbonyl group of (±)-**13** resisted the $NaBH_4$ reduction under these conditions.

Conversion of (±)-**9** into the tetracyclic ester (±)-**11** through the quaternary iminium salt (±)-**10** was carried out in 60% overall yield by Bischler–Napieralski cyclization ($POCl_3$, boiling toluene, 2 h) and subsequent catalytic hydrogenation (Pt/H_2, EtOH, 1 atm, room temperature, 4 h). Since catalytic hydrogenation of similar systems provides the more stable isomer,[20] the hydrogen at C-3 was assigned the α configuration, which was supported by the appearance of absorption bands due to a *trans*-quinolizidine ring[21] in the infrared (IR) spectrum of (±)-**11** in $CHCl_3$. Finally, reduction of (±)-**11** was achieved by using $LiAlH_4$ in tetrahydrofuran (THF) at room temperature for 3 h to afford the target alcohol (±)-**1** (89% yield), which was characterized as a crystalline hemihydrate (mp 199—200 °C). The ultraviolet (UV) (in EtOH), IR (in $CHCl_3$), ^1H-NMR (in $CDCl_3$), and mass spectra (MS) and thin-layer chromatographic (TLC) mobility of (±)-**1** were identical with those of natural (−)-ochropposinine.[2,3a,5c,d] Thus, the structure and relative stereochemistry of this alkaloid have been unequivocally established as **1** or its mirror image.

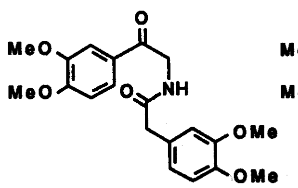
In order to confirm the absolute stereochemistry proposed on the basis of biogenetic considerations,[3a] the chiral synthesis of **1** was next undertaken by following the same reaction sequence as used for the above racemic synthesis (Chart 1). At first, the lactim ether (+)-**3**[10,11] was treated with **5** in $HCONMe_2$ in the presence of KBr to give the lactam ketone (+)-**7** in 66% yield. Cyclization of (+)-**7** with $POCl_3$ furnished the oxazolium salt (+)-**8** (58% yield), which was then reduced with hydrogen over Adams catalyst



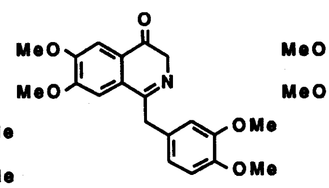
(±)-**12**



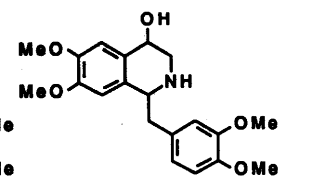
(±)-**13**



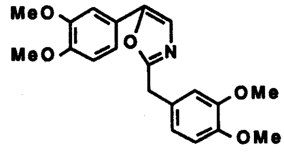
14



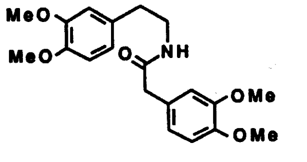
15



16



17



18

NII-Electronic Library Service

to afford the lactam (+)-**9** in 60% yield. On Bischler–Napieralski cyclization followed by catalytic hydogenation, (+)-**9** furnished the tetracyclic ester (−)-**11** *via* the iminium salt **10** in 86% overall yield. Finally, reduction of (−)-**11** with $LiAlH_4$ provided the desired alcohol (−)-**1** in 81% yield. The synthetic (−)-**1** proved to be identical with a natural sample of ochropposinine[2,3a,5c,d)] by a direct comparison of the UV, IR, ^{1}H-NMR, and ^{13}C-NMR spectra, MS, TLC behavior, and specific rotation.

In summary, the first total synthesis of the *Neisosperma* and *Ochrosia* alkaloid ochropposinine has been achieved in racemic and chiral forms through the reaction sequence shown in Chart 1. The synthesis has not only established unambiguously the structure of ochropposinine as 10,11-dimethoxydihydrocorynantheol [(−)-**1**] but also represents an example of the extension of the "lactim ether route",[8,11–13)] originally designed for unified racemic and chiral syntheses of the benzo[*a*]quinolizidine-type *Alangium* alkaloids (type **2**),[8)] to the synthesis of indoloquinolizidine alkaloids.[13)]

Experimental

General Notes All melting points were determined by using a Yamato MP-1 capillary melting point apparatus and are corrected. Unless otherwise noted, the organic solutions obtained after extraction were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Spectra reported herein were recorded on a Hitachi 320 UV spectrophotometer, a JASCO A-202 IR spectrophotometer, a JASCO J-500C spectropolarimeter, a Hitachi M-80 mass spectrometer, or a JEOL JNM-FX-100 NMR spectrometer at 25 °C with Me_4Si as an internal standard. Optical rotations were measured with a JASCO DIP-181 polarimeter using a 1-dm sample tube. Elemental analyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, d = doublet, dd = doublet-of-doublets, m = multiplet, q = quartet, s = singlet, sh = shoulder, t = triplet.

2-Chloro-1-(5,6-dimethoxy-1*H*-indol-3-yl)ethanone (5) A stirred mixture of 5,6-dimethoxyindole (**4**)[16)] (2.66 g, 15 mmol), pyridine (2.37 g, 30 mmol), and toluene (170 ml) was kept at 55—60 °C in an atmosphere of N_2, and a solution of chloroacetyl chloride (3.39 g, 30 mmol) in toluene (10 ml) was added dropwise over a period of 10 min. The reaction mixture was then stirred for 40 min and cooled to separate a dark reddish oil. The toluene layer was decanted and the residual oil was triturated with MeOH (15 ml) to afford a first crop (1.23 g) of **5** as a pinkish solid. The above toluene layer and MeOH solution were combined and concentrated *in vacuo*. The residue was dissolved in $CHCl_3$–EtOH (10 : 1, v/v) (180 ml) and the solution was washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, then dried, and concentrated to leave a dark brown oil. Purification of the oil by column chromatography [silica gel, benzene–AcOEt (5 : 1, v/v)] gave a second crop of **5** as a gray solid. The total yield of **5** was 1.94 g (51%). Recrystallization from MeOH produced an analytical sample as faintly pinkish minute scales, mp 229—230 °C (dec.); MS *m/z*: 253, 255 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 3190 (NH), 1640 (CO); UV λ_{max}^{EtOH} 248 nm (ε 13000), 285 (18800), 305 (14400); ^{1}H-NMR (Me_2SO-d_6) δ: 3.80 (6H, s, two MeO's), 4.81 (2H, s, CH_2), 7.00 (1H, s, $H_{(7)}$), 7.64 (1H, s, $H_{(4)}$), 8.24 (1H, d, J = 3 Hz, $H_{(2)}$), 11.83 (1H, br, NH). *Anal.* Calcd for $C_{12}H_{12}ClNO_3$: C, 56.82; H, 4.77; N, 5.52. Found: C, 56.90; H, 4.81; N, 5.46.

Earlier fractions of the above chromatography furnished 1-(chloroacetyl)-5,6-dimethoxy-1*H*-indole (**6**) (248 mg, 7%) as a gray solid. Recrystallization of the solid from MeOH gave an analytical sample as slightly brownish needles, mp 149—150 °C; MS *m/z*: 253, 255 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 1720 (CO); UV λ_{max}^{EtOH} 261 nm (ε 24400), 297 (6430), 308 (sh) (5420); ^{1}H-NMR (Me_2SO-d_6) δ: 3.80 and 3.81 (3H each, s, two MeO's), 5.07 (2H, s, CH_2), 6.67 (1H, dd, J = 4, 0.5 Hz, $H_{(3)}$), 7.17 (1H, s, $H_{(4)}$), 7.69 (1H, d, J = 4 Hz, $H_{(2)}$), 7.93 (1H, br, $H_{(7)}$). *Anal.* Calcd for $C_{12}H_{12}ClNO_3$: C, 56.82; H, 4.77; N, 5.52. Found: C, 56.54; H, 4.78; N, 5.46.

(±)-*trans*-1-[2-(5,6-Dimethoxy-1*H*-indol-3-yl)-2-oxoethyl]-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(±)-7] A mixture of (±)-**3**[9)] (4.38 g, 18.1 mmol), **5** (4.19 g, 16.5 mmol), KBr (4.71 g, 39.6 mmol), and $HCONMe_2$ (20 ml) was stirred at 60 °C for 48 h. After addition of H_2O (120 ml), the reaction mixture was extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed successively with saturated aqueous $NaHCO_3$ and H_2O, then dried, and concentrated to leave a brown oil. The oil was purified by means of column chromatography [silica gel, AcOEt–EtOH (20 : 1, v/v)] to afford (±)-**7** (5.07 g, 71%) as a pale brown solid. Recrystallization of the solid from AcOEt gave an analytical sample as colorless needles, mp 156—157 °C; MS *m/z*: 430 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3230 (NH), 1728 (ester CO), 1657 (ArCO), 1620 (lactam CO); UV λ_{max}^{EtOH} 243 nm (sh) (ε 7130), 248 (7690), 282 (9200), 297 (sh) (7700); ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J = 6.5 Hz, $CCH_2\underline{Me}$), 1.27 (3H, t, J = 7 Hz, $OCH_2\underline{Me}$), 3.87 and 3.91 (3H each, s, two MeO's), 4.16 (2H, q, J = 7 Hz, $OC\underline{H}_2Me$), 4.43 (2H, s, $COCH_2N$), 6.84 (1H, s, $H_{(7')}$), 7.54 (1H, d, J = 3 Hz, $H_{(2')}$), 7.65 (1H, s, $H_{(4')}$), 9.96 (1H, br, NH).[22)] *Anal.* Calcd for $C_{23}H_{30}N_2O_6$: C, 64.17; H, 7.02; N, 6.51. Found: C, 63.98; H, 7.07; N, 6.29.

(4*R*,5*R*)-1-[2-(5,6-Dimethoxy-1*H*-indol-3-yl)-2-oxoethyl]-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(+)-7] The lactim ether (+)-**3**[10,11)] (1.15 g, 4.8 mmol) was allowed to react with **5** (1.33 g, 5.2 mmol) in $HCONMe_2$ (10 ml) at 60 °C for 48 h in the presence of KBr (1.49 g, 12.5 mmol). The reaction mixture was worked up as described above for the racemic modification, giving (+)-**7** (1.35 g, 66%) as a reddish orange oil, $[\alpha]_D^{16}$ +36.8° (c = 0.50, EtOH); MS *m/z*: 430 (M^+). The IR ($CHCl_3$) and ^{1}H-NMR ($CDCl_3$) spectra of this sample were identical with those of (±)-**7**.

(±)-*trans*-1-[2-(5,6-Dimethoxy-1*H*-indol-3-yl)-2-hydroxyethyl]-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(±)-12] A solution of (±)-**7** (431 mg, 1 mmol) in EtOH (35 ml) was stirred under ice-cooling, and $NaBH_4$ (1.13 g, 30 mmol) was added portionwise. After the mixture had been stirred at room temperature for 3 h, acetone (25 ml) was added under ice-cooling. The resulting mixture was stirred for 20 min and then concentrated *in vacuo*. The residue was partitioned by extraction with a mixture of CH_2Cl_2 and H_2O. The CH_2Cl_2 extracts were washed with H_2O, dried, and concentrated to leave a diastereomeric mixture of (±)-**12** (417 mg, 97%) as a colorless oil, MS *m/z*: 414 ($M^+ - 18$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (NH), 3370 (OH), 1727 (ester CO), 1620 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.73 and 0.77 (3H, t each, J = 6.5 Hz, diastereomeric $CCH_2\underline{Me}$'s), 1.26 (3H, t, J = 7 Hz, $OCH_2\underline{Me}$), 1.73 (1H, br, OH), 3.89 and 3.93 (3H each, s, two MeO's), 4.13 (2H, q, J = 7 Hz, $OC\underline{H}_2Me$), 5.30 [1H, br, $ArC\underline{H}(OH)$], 6.86 (1H, s, $H_{(7')}$), 7.06 (1H, d, J = 2 Hz, $H_{(2')}$), 7.18 and 7.20 (1H, s each, diastereomeric $H_{(4')}$'s), 8.15 (1H, br, NH).[22)]

(±)-*trans*-2-(5,6-Dimethoxy-1*H*-indol-3-yl)-7-(2-ethoxy-2-oxoethyl)-6-ethyl-5,6,7,8-tetrahydrooxazolo[3,2-*a*]pyridinium Chloride [(±)-8] A mixture of (±)-**7** (1.72 g, 4 mmol) and $POCl_3$ (5 ml) in dry toluene (45 ml) was heated under reflux for 1 h. After cooling, the precipitate that resulted was filtered off and recrystallized from EtOH to give (±)-**8** (1.45 g, 81%), mp 259.5—261.5 °C (dec.). Further recrystallizations from EtOH furnished an analytical sample as colorless needles, mp 261—263 °C (dec.); IR ν_{max}^{Nujol} cm^{-1}: 3410 (NH), 1731 (ester CO), 1661 ($C=N^+$), 1625 ($C=C$); UV λ_{max}^{EtOH} 248 nm (ε 12000), 304 (18000); ^{1}H-NMR (Me_2SO-d_6) δ: 0.94 (3H, t, J = 7 Hz, $CCH_2\underline{Me}$), 1.23 (3H, t, J = 7 Hz, $OCH_2\underline{Me}$), 3.81 and 3.87 (3H each, s, two MeO's), 4.13 (2H, q, J = 7 Hz, $OC\underline{H}_2Me$), 7.08 (1H, s, $H_{(7')}$), 7.26 (1H, s, $H_{(4')}$), 7.85 (1H, d, J = 2.5 Hz, $H_{(2')}$), 8.52 (1H, s, $H_{(3)}$), 11.98 (1H, br, NH).[22)] *Anal.* Calcd for $C_{23}H_{29}ClN_2O_5$: C, 61.53; H, 6.51; N, 6.24. Found: C, 61.26; H, 6.66; N, 6.07.

Hydrolysis of (±)-8 A mixture of (±)-**8** (90 mg, 0.2 mmol) and 10% aqueous Na_2CO_3 (1 ml) in EtOH (5 ml) was stirred at room temperature for 1.5 h. The reaction mixture was concentrated *in vacuo*, and the residue was partitioned by extraction with a mixture of CH_2Cl_2 and H_2O. The CH_2Cl_2 extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated to leave (±)-**7** (74 mg, 86%) as a colorless solid, mp 153—154.5 °C. This sample was identical [by comparison of the IR spectrum (Nujol) and TLC behavior] with authentic (±)-**7**.

(6*R*,7*R*)-2-(5,6-Dimethoxy-1*H*-indol-3-yl)-7-(2-ethoxy-2-oxoethyl)-6-ethyl-5,6,7,8-tetrahydrooxazolo[3,2-*a*]pyridinium Chloride [(+)-8] A mixture of (+)-**7** (1.07 g, 2.5 mmol), $POCl_3$ (5.35 g, 35 mmol), and dry toluene (30 ml) was heated under reflux for 1 h. The reaction mixture was worked up as described above for the racemic series, and (+)-**8** (649 mg, 58%) was obtained as a pale yellow solid, mp 258—261.5 °C (dec.). Two more recrystallizations from EtOH afforded an analytical sample as colorless minute needles, mp 261.5—263.5 °C (dec.); $[\alpha]_D^{23}$ +70.8° (c = 0.52, EtOH); IR (Nujol) and ^{1}H-NMR (Me_2SO-d_6), identical with those of (±)-**8**. *Anal.* Calcd for $C_{23}H_{29}ClN_2O_5$: C, 61.53; H, 6.51; N, 6.24. Found: C, 61.23; H, 6.56; N, 5.94.

(±)-*trans*-1-[2-(5,6-Dimethoxy-1*H*-indol-3-yl)ethyl]-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(±)-9] A solution of (±)-**8** (2.00 g, 4.45 mmol) in EtOH (100 ml) was hydrogenated over Adams catalyst

NII-Electronic Library Service

(200 mg) at room temperature and atmospheric pressure for 10 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was partitioned by extraction with a mixture of H_2O (40 ml), saturated aqueous $NaHCO_3$ (40 ml), and CH_2Cl_2. The CH_2Cl_2 extracts were washed with H_2O, dried, and concentrated to leave a pale brown oil. Purification of the oil by column chromatography [silica gel, AcOEt–EtOH (10:1, v/v)] afforded (±)-**9** (954 mg, 51%) as a slightly yellow oil, MS *m/z*: 416 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (NH), 1728 (ester CO), 1627 (lactam CO); UV λ_{max}^{EtOH} 222 nm (ε 21500), 280 (sh) (4170), 297 (6220), 302 (sh) (6070), 308 (sh) (5210); ^{1}H-NMR ($CDCl_3$) δ: 0.78 (3H, t, J=7 Hz, CCH$_2$<u>Me</u>), 1.25 (3H, t, J=7 Hz, OCH$_2$<u>Me</u>), 2.98 (2H, dull t, J= 6.5 Hz, ArC<u>H</u>$_2$CH$_2$), 3.55—3.75 (2H, m, ArCH$_2$C<u>H</u>$_2$), 3.88 and 3.94 (3H each, s, two MeO's), 4.13 (2H, q, J=7 Hz, OC<u>H</u>$_2$Me), 6.86 (1H, s, $H_{(7')}$), 6.89 (1H, d, J=2.5 Hz, $H_{(2')}$), 7.11 (1H, s, $H_{(4')}$), 8.13 (1H, br, NH).[22]

(4*R*,5*R*)-1-[2-(5,6-Dimethoxy-1*H*-indol-3-yl)ethyl]-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(+)-9] A solution of (+)-**8** (793 mg, 1.77 mmol) in EtOH (40 ml) was reduced by catalytic hydrogenation [Adams catalyst (84 mg), 1 atm, room temperature, 8 h] as described above for (±)-**9**. Work-up of the reaction mixture also followed that described above for (±)-**9**, furnishing (+)-**9** (441 mg, 60%) as a yellow oil, $[\alpha]_D^{25}$ +62.2° (c=0.61, EtOH); MS *m/z*: 416 (M^+). The IR ($CHCl_3$) and ^{1}H-NMR ($CDCl_3$) spectra of this sample were identical with those of (±)-**9**.

(±)-*trans*-1-[2-(5,6-Dimethoxy-1*H*-indol-3-yl)-2-oxoethyl]-3-ethyl-4-piperidineacetic Acid Ethyl Ester [(±)-13] A solution of (±)-**8** (45 mg, 0.1 mmol) in EtOH (3 ml) was stirred under ice-cooling, and $NaBH_4$ (7.6 mg, 0.2 mmol) was added portionwise. Stirring was continued at 0 °C for 10 min and at room temperature for 50 min, then acetone (0.5 ml) was added and the mixture was concentrated *in vacuo*. The residue was partitioned by extraction with a mixture of CH_2Cl_2 and H_2O. The CH_2Cl_2 extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated to leave (±)-**13** (31 mg, 74%) as a colorless glass, MS *m/z*: 416 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3475 (NH), 1724 (ester CO), 1636 (ArCO); UV λ_{max}^{EtOH} 244 nm (sh), 249, 282, 299 (sh); ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, t, J= 7 Hz, CCH$_2$<u>Me</u>), 1.26 (3H, t, J=7 Hz, OCH$_2$<u>Me</u>), 3.62 (2H, s, COCH$_2$N), 3.90 and 3.96 (3H each, s, two MeO's), 4.13 (2H, q, J=7 Hz, OC<u>H</u>$_2$Me), 6.90 (1H, s, $H_{(7')}$), 7.90 (1H, s, $H_{(4')}$), 8.12 (1H, d, J=3 Hz, $H_{(2')}$), 8.74 (1H, br, NH).[22]

(±)-10,11-Dimethoxycorynan-17-oic Acid Ethyl Ester [(±)-11] A solution of (±)-**9** (1.21 g, 2.9 mmol) and $POCl_3$ (4.10 g, 26.7 mmol) in dry toluene (25 ml) was heated under reflux for 2 h in an atmosphere of N_2. After cooling, the solvent and excess $POCl_3$ were distilled off *in vacuo*, and the residue was partitioned by extraction with a mixture of $CHCl_3$ and H_2O. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave crude (±)-**10** (1.33 g) as a yellow glass. The glass was dissolved in EtOH (80 ml), and the solution was hydrogenated over Adams catalyst (120 mg) at atmospheric pressure and room temperature for 4 h. The catalyst was filtered off, and the filtrate was concentrated *in vacuo* to leave a greenish solid (1.23 g), which was dissolved in H_2O. The aqueous solution was made basic with 10% aqueous Na_2CO_3 and then extracted with benzene. The benzene extracts were washed with H_2O, dried, and concentrated to leave a brown glass (1.10 g). Purification of the glass by column chromatography (alumina, AcOEt) and recrystallization of the resulting solid from AcOEt furnished (±)-**11** [698 mg, 60% overall yield from (±)-**9**] as colorless needles. Further recrystallizations from AcOEt produced an analytical sample as colorless needles, mp 161—162 °C; MS *m/z*: 400 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3490 (NH), 2835, 2805, 2755 (*trans*-quinolizidine ring[21]), 1726 (ester CO); UV λ_{max}^{EtOH} 227 nm (ε 26100), 280 (sh) (5230), 299 (8820), 303 (8900), 309 (sh) (7550); ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, J=6.5 Hz, CCH$_2$<u>Me</u>), 1.29 (3H, t, J= 7 Hz, OCH$_2$<u>Me</u>), 3.89 and 3.91 (3H each, s, two MeO's), 4.17 (2H, q, J= 7 Hz, OC<u>H</u>$_2$Me), 6.84 (1H, s, $H_{(9)}$ or $H_{(12)}$), 6.90 (1H, s, $H_{(12)}$ or $H_{(9)}$), 7.65 (1H, br, NH). *Anal*. Calcd for $C_{23}H_{32}N_2O_4$: C, 68.97; H, 8.05; N, 6.99. Found: C, 68.68; H, 8.17; N, 6.85.

10,11-Dimethoxycorynan-17-oic Acid Ethyl Ester [(−)-11] Cyclization of (+)-**9** (426 mg, 1.02 mmol) was carried out [$POCl_3$ (1 ml), boiling toluene (14 ml), 2 h] as described above for (±)-**11**, giving **10** (453 mg) as a yellow glass. Catalytic hydrogenation of **10** over Adams catalyst (40 mg) in a manner similar to that described above for (±)-**11** and purification of the crude, yellow glassy product (381 mg) by column chromatography (alumina, AcOEt) gave (−)-**11** [352 mg, 86% overall yield from (+)-**9**] as a yellow glass, $[\alpha]_D^{17}$ −6.3° (c=0.50, EtOH); MS *m/z*: 400 (M^+); IR ($CHCl_3$) and ^{1}H-NMR ($CDCl_3$), identical with those of (±)-**11**.

(±)-10,11-Dimethoxycorynan-17-ol [(±)-10,11-Dimethoxydihydrocorynantheol] [(±)-1] A solution of (±)-**11** (230 mg, 0.57 mmol) in dry THF (5 ml) was added dropwise to a stirred, ice-cooled suspension of $LiAlH_4$ (44 mg, 1.16 mmol) in dry THF (5 ml) over a period of 15 min. After the mixture had been stirred at room temperature for 3 h, H_2O (0.1 ml), 10% aqueous NaOH (0.1 ml), and H_2O (0.2 ml) were successively added under ice-cooling. The insoluble material that resulted was filtered off, and the filtrate was then dried (K_2CO_3) and concentrated to leave (±)-**1** (188 mg, 89%) as a pale yellow solid. Recrystallization of the solid from MeCN and drying over P_2O_5 at 2 mmHg and 55 °C for 12 h afforded a hemihydrate as colorless needles, mp 199—200 °C; MS *m/z* (relative intensity): 359 (M^++1) (22), 358 (M^+) (100), 357 (99), 356 (12), 355 (6), 343 (8), 341 (6), 313 (9), 311 (12), 285 (14), 244 (5), 231 (5), 230 (20), 229 (7), 216 (6); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3630, 3360 (OH), 3485 (NH), 2835, 2805, 2755 (*trans*-quinolizidine ring[21]); UV λ_{max}^{EtOH} 227 nm (ε 28400), 282 (sh) (5630), 299 (9420), 303 (9490), 309 (sh) (8120); ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J= 6.5 Hz, CH$_2$<u>Me</u>), 3.87 and 3.90 (3H each, s, two MeO's), 6.84 (1H, s, $H_{(9)}$ or $H_{(12)}$), 6.89 (1H, s, $H_{(12)}$ or $H_{(9)}$), 7.95 (1H, br, NH). *Anal*. Calcd for $C_{21}H_{30}N_2O_3 \cdot 1/2H_2O$: C, 68.64; H, 8.50; N, 7.62. Found: C, 68.79; H, 8.27; N, 7.78. The UV, IR, ^{1}H-NMR, and MS and TLC behavior of this sample were identical with those of natural ochropposinine.[2,3a,5c,d]

10,11-Dimethoxycorynan-17-ol (10,11-Dimethoxydihydrocorynantheol) [(−)-1] Reduction of the tetracyclic ester (−)-**11** (320 mg, 0.8 mmol) with $LiAlH_4$ (60 mg, 1.58 mmol) was effected [THF (14 ml), room temperature, 3 h] as described above for the racemic series, and the crude yellowish glass was purified by means of column chromatography [alumina, AcOEt–EtOH (30:1, v/v)] to furnish (−)-**1** (233 mg, 81%) as a yellowish glass, $[\alpha]_D^{17}$ −15.9° (c=1.00, $CHCl_3$); $[\alpha]_{577}^{17}$ −15.7° (c=1.00, $CHCl_3$); MS *m/z*: 359 (M^++1), 358 (M^+); ^{13}C-NMR ($CDCl_3$) δ: 11.0 (C-18), 21.8 (C-6), 23.5 (C-19), 35.5 (C-14, C-16), 37.2 (C-15), 41.8 (C-20), 53.2 (C-5), 56.4 (two MeO's), 60.0 (C-3), 60.3 (C-17 or C-21), 60.4 (C-21 or C-17), 95.3 (C-12), 100.5 (C-9), 107.6 (C-7), 120.3 (C-8), 130.3 (C-13), 133.7 (C-2), 144.7 (C-10), 146.2 (C-11); CD (c=8.95×10^{-5} M, EtOH) $[\theta]^{22}$ (nm): 0 (318), +500 (313) (pos. max.), 0 (306), −450 (299) (neg. max.), 0 (296), +5140 (271) (pos. max.), +2460 (251) (neg. max.), +12060 (237) (pos. max.). The synthetic (−)-**1** was identical [by comparison of the UV (in EtOH), IR (in $CHCl_3$), ^{1}H-NMR (in $CDCl_3$), ^{13}C-NMR (in $CDCl_3$), and MS, TLC behavior, and specific rotation] with natural (−)-ochropposinine [$[\alpha]_{578}^{20}$ −18° (c=1, $CHCl_3$)].[2,3a,5c,d]

Acknowledgment We are grateful to Professor Michel Koch (Université René Descartes) for his invaluable help in making a comparison between the natural and synthetic alkaloids. This work was supported by a Grant-in-Aid for Scientific Research (No. 58570869) from the Ministry of Education, Science and Culture, Japan.

References and Notes

1) Paper XXVI in this series, T. Fujii, M. Ohba, and N. Sasaki, *Chem. Pharm. Bull.*, **37**, 2822 (1989).
2) N. Peube-Locou, M. Koch, M. Plat, and P. Potier, *Ann. Pharm. Fr.*, **30**, 821 (1972).
3) *a*) N. Peube-Locou, M. Koch, M. Plat, and P. Potier, *Phytochemistry*, **11**, 2109 (1972); *b*) This plant was formerly named *Ochrosia oppositifolia* (LMK) K. SCHUM. For the change of name, see F. R. Fosberg, P. Boiteau, and M.-H. Sachet, *Adansonia Ser. 2*, **17**, 23 (1977).
4) *a*) A. S. Amarasekera and L. S. R. Arambewela, *Fitoterapia*, **57**, 55 (1986); *b*) A. A. L. Gunatilaka, H. C. Fernando, Atta-ur-Rahman, M. M. Qureshi, and S. Balasubramaniam, *Heterocycles*, **28**, 999 (1989).
5) *a*) E. Seguin, M. Koch, and T. Sevenet, *J. Nat. Prod.*, **45**, 738 (1982); *b*) E. Seguin, F. Hotellier, M. Koch, and T. Sevenet, *ibid.*, **47**, 687 (1984); *c*) J. Bruneton, T. Sevenet, and A. Cavé, *Phytochemistry*, **11**, 3073 (1972); *d*) A. Ahond, H. Fernandez, M. Julia-Moore, C. Poupat, V. Sánchez, P. Potier, S. K. Kan, and T. Sévenet, *J. Nat. Prod.*, **44**, 193 (1981).
6) Unless otherwise noted, the structural formulas of optically active compounds in this paper represent their absolute configurations.
7) A preliminary account of this work has been published: T. Fujii, M. Ohba, T. Tachinami, H. Miyajima, M. Koch, and E. Seguin, *Heterocycles*, **24**, 1215 (1986).
8) For reviews, see *a*) T. Fujii and M. Ohba, "The Alkaloids," Vol. XXII, ed. by A. Brossi, Academic Press, New York, 1983, Chapter 1; *b*) T. Fujii, *Yakugaku Zasshi*, **103**, 257 (1983); *c*) T. Fujii, M. Ohba, and S. Yoshifuji, *Heterocycles*, **27**, 1009 (1988).
9) *a*) T. Fujii and S. Yoshifuji, *Chem. Pharm. Bull.*, **27**, 1486 (1979); *b*) J. Gutzwiller, G. Pizzolato, and M. R. Uskoković, *Helv. Chim. Acta*, **64**, 1663 (1981).

NII-Electronic Library Service

10) T. Fujii, M. Ohba, K. Yoneyama, and H. Kizu, *Chem. Pharm. Bull.*, **33**, 358 (1985).
11) T. Fujii, M. Ohba, K. Shimohata, and S. Yoshifuji, *Heterocycles*, **26**, 2949 (1987).
12) T. Fujii, M. Ohba, K. Yoneyama, H. Kizu, and S. Yoshifuji, *Chem. Pharm. Bull.*, **34**, 669 (1986).
13) For the "lactim ether route" leading to the indolo[2,3-*a*]quinolizidine systems, see *a*) T. Fujii, S. Yoshifuji, and H. Ito, *Chem. Pharm. Bull.*, **36**, 3348 (1988); *b*) T. R. Govindachari and S. Rajeswari, *Indian J. Chem.*, **22B**, 531 (1983).
14) S. Sakai, N. Saito, N. Hirose, and E. Yamanaka, *Heterocycles*, **17**, 99 (1982).
15) J. Bergman, J.-E. Bäckvall, and J.-O. Lindström, *Tetrahedron*, **29**, 971 (1973).
16) A. K. Sinhababu and R. T. Borchardt, *J. Org. Chem.*, **48**, 3347 (1983).
17) J. S. Buck, *J. Chem. Soc.*, **52**, 3610 (1930).
18) P. C. Young and R. Robinson, *J. Chem. Soc.*, **1933**, 275.
19) A. P. Kozikowski and A. Ames, *J. Org. Chem.*, **45**, 2548 (1980).
20) E. E. van Tamelen and J. B. Hester, Jr., *J. Am. Chem. Soc.*, **91**, 7342 (1969).
21) *a*) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958); *b*) E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **78**, 6417 (1956).
22) For convenience, each position of the indole ring is indicated by a primed number.

NII-Electronic Library Service