Quinolizidines. XXVIII. Racemic and chiral syntheses of ochromianine, an indoloquinolizidine alkaloid from Neisosperma miana

Quinolizidines. XXVIII.[1] Racemic and Chiral Syntheses of Ochromianine, an Indoloquinolizidine Alkaloid from *Neisosperma miana*

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A full account is given of the first racemic and chiral syntheses of 11-methoxydihydrocorynantheol [(−)-1], a candidate structure for the *Neisosperma* alkaloid ochromianine. Coupling of (±)-*trans*-6-ethoxy-3-ethyl-2,3,4,5-tetrahydro-4-pyridineacetic acid ethyl ester [(±)-6] with 2-chloro-1-(6-methoxy-1*H*-indol-3-yl)ethanone (4) in the presence of KBr produced the lactam ketone (±)-7, which was then converted into the lactam (±)-9 through the oxazolium salt (±)-8. Bischler–Napieralski cyclization of (±)-9 followed by catalytic hydrogenation gave the tetracyclic ester (±)-11. On reduction with $LiAlH_4$, (±)-11 yielded the racemic target (±)-1. A parallel synthetic route starting from (+)-6 and 4 afforded the chiral target (−)-1 *via* (+)-7, 8, (+)-9, and (−)-11. Identity of synthetic (−)-1 with ochromianine unequivocally established the structure and absolute stereochemistry of this alkaloid.

Keywords *Neisosperma* alkaloid; ochromianine; 11-methoxydihydrocorynantheol; indoloquinolizidine alkaloid synthesis; chiral synthesis; lactim ether alkylation; keto amide cyclization; oxazolium salt reduction; Bischler–Napieralski cyclization; hydride reduction

In 1974, Koch and co-workers[2] reported the isolation of (−)-ochromianine, a new *Corynanthe*-type indoloquinolizidine alkaloid, from the bark of a New Caledonian plant named *Ochrosia miana* H. BN. ex GUILL. (family Apocynaceae) at that time. The name of the plant was later revised to *Neisosperma miana* (BAILLON ex-WHITE) BOITEAU.[3] The French group deduced the structure and absolute configuration of (−)-ochromianine to be (−)-**1**[4] on the basis of spectral analysis as well as chiroptical and biosynthetic rationales.[2] Now the correctness of this structure assignment has been confirmed by us as a result of the following racemic and chiral syntheses of the candidate structure **1**. A brief account of the results reported here has been published in a preliminary form.[3b]

In designing synthetic routes to (±)-**1** and (−)-**1**, our recent racemic and chiral syntheses of ochropposinine (**2**),[1,5] a structurally analogous alkaloid from *Neisosperma* and *Ochrosia* plants,[6] through the "lactim ether route"[7-9] were reliable guides, generating 10-demethoxy versions as shown in Chart 1. Thus, 3-chloroacetyl-6-methoxyindole (**4**), a precursor of rings A, B, and C in **1**, was first prepared from 6-methoxyindole (**3**)[10] in 50% yield according to a general 3-chloroacetylation procedure[11] using chloroacetyl chloride and pyridine in toluene (55—60 °C, 2 h). This

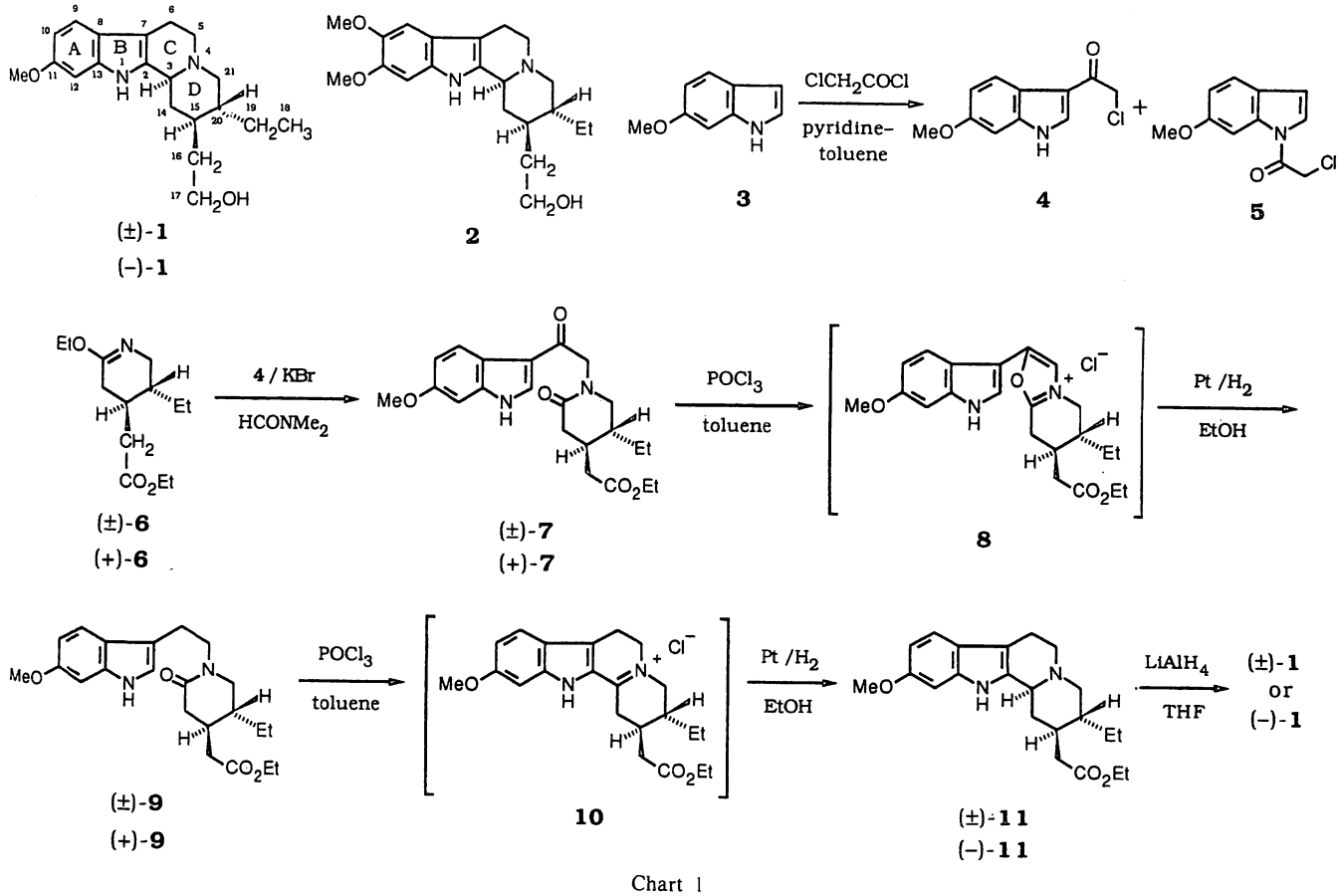

Chart 1

3-acylation was accompanied with the formation of a small amount (2% yield) of the 1-acylated derivative **5**, as anticipated.[1,5,11]

The racemic synthesis of the candidate structure **1** started with coupling of the lactim ether (±)-**6**[12] (a precursor of ring D) with **4** in $HCONMe_2$ in the presence of KBr at 58 °C for 48 h, which produced the lactam ketone (±)-**7** in 61% yield. For reduction of the ketonic group of (±)-**7** to the corresponding methylene group, we followed the lead of the oxazole method that had been successfully applied to analogous structures.[1,5,13] Thus, (±)-**7** was treated with $POCl_3$ in boiling toluene for 2 h, and the crude product, presumed to be the oxazolium salt (±)-**8**, was reduced by catalytic hydrogenation (Pt/H_2, EtOH, 1 atm, room temperature, 2 h) to give the lactam (±)-**9** in 55% overall yield [from (±)-**7**]. Conversion of (±)-**9** into the tetracyclic ester (±)-**11** through the quaternary iminium salt (±)-**10** was effected in 87% overall yield by means of Bischler–Napieralski cyclization ($POCl_3$, boiling toluene, 2 h) followed by catalytic hydrogenation (Pt/H_2, EtOH, 1 atm, room temperature, 4 h). The hydrogen at C(3) was assigned the α configuration by analogy with catalytic hydrogenation of similar systems,[14] and the correctness of this assignment was supported by the appearance of absorption bands assignable to a *trans*-quinolizidine ring[15] in the infrared (IR) spectrum of (±)-**11** in $CHCl_3$. On reduction with $LiAlH_4$ in tetrahydrofuran (THF) at room temperature for 1 h, (±)-**11** afforded the target alcohol (±)-**1** in 90% yield. Although no sample of natural (−)-ochromianine was available for a direct comparison, the ultraviolet (UV) (in EtOH), IR (in $CHCl_3$), proton nuclear magnetic resonance (^{1}H-NMR) (in $CDCl_3$), and mass spectra (MS) of (±)-**1** were found to be virtually identical with those obtained previously with a natural sample. Accordingly, the structure and relative stereochemistry of this alkaloid have been unequivocally established as **1** or its mirror image.

For the chiral synthesis of (−)-**1**, a parallel sequence of conversions starting with the lactim ether (+)-**6**[8b,16] was followed (Chart 1). Treatment of (+)-**6** with **4** in $HCONMe_2$ in the presence of KBr at 60 °C for 72 h provided the lactam ketone (+)-**7** in 75% yield. Cyclization of (+)-**7** with $POCl_3$ and catalytic hydrogenation of the resulting crude oxazolium salt **8** gave the lactam (+)-**9** in 67% yield [from (+)-**7**]. On Bischler–Napieralski cyclization followed by catalytic hydrogenation, (+)-**9** afforded the tetracyclic ester (−)-**11** *via* the iminium salt **10** in 91% overall yield. Finally, $LiAlH_4$ reduction of (−)-**11** in THF produced the desired alcohol (−)-**1** in 87% yield. The UV, IR, and ^{1}H-NMR spectra and MS of the synthetic (−)-**1** were virtually identical with those of natural (−)-ochromianine, and the chiral identity of (−)-**1** with the alkaloid was shown by the same sign of their specific rotations and by their virtually identical circular dichroism (CD) spectra.

In conclusion, the structure of the *Neisosperma* alkaloid (−)-ochromianine has now been established as 11-methoxydihydrocorynantheol [(−)-**1**] as a result of the above racemic and chiral syntheses of **1**. These syntheses represent new additions to the range[9] of the synthesis of indoloquinolizidine alkaloids by the "lactim ether route",[7,8] which remains the best available vehicle for unified racemic and chiral syntheses of the benzo[*a*]quinolizidine-type *Alangium* alkaloids.[7]

Experimental

General Notes All melting points were taken on a Yamato MP-1 capillary melting point apparatus and are corrected. Unless otherwise stated, the organic solutions obtained after extraction were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Thin-layer chromatography (TLC) was developed on Merck silica gel 60 F_{254} plates (0.25-mm thickness) or Merck aluminum oxide F_{254} (type E) plates (0.25 mm), and spots were detected by means of UV absorbance measurement (at 254 nm) and/or by spraying with the standard $KMnO_4$ or I_2–KI reagent. Flash chromatography[17] was carried out by using Merck silica gel 60 (No. 9385). See ref. 1 for details of instrumentation and measurements. 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-(6-methoxy-1*H*-indol-3-yl)ethanone (4) and 1-(Chloroacetyl)-6-methoxy-1*H*-indole (5) A stirred mixture of 6-methoxyindole (**3**)[16] (3.97 g, 27 mmol) and pyridine (4.27 g, 54 mmol) in dry toluene (60 ml) was kept at 55—60 °C in an atmosphere of N_2, and a solution of chloroacetyl chloride (6.10 g, 54 mmol) in dry toluene (12 ml) was added dropwise over a period of 40 min. The resulting mixture was stirred at the same temperature for 2 h and then cooled to deposit a dark oil. The oil was separated from the toluene layer, washed with three 5-ml portions of toluene, and triturated with MeOH. The precipitate that resulted was filtered off to give **4** (3.02 g, 50%) as a brown solid, mp 224.5—225.5 °C (dec.). Recrystallization from $CHCl_3$–EtOH (1 : 1, v/v) yielded an analytical sample of **4** as colorless prisms, mp 250—252 °C (dec.); MS *m/z*: 225, 223 (M^+); UV λ_{max}^{EtOH} 242 nm (ε 12500), 281 (12600), 309 (9170); IR ν_{max}^{Nujol} cm^{-1}: 3180 (NH), 1628 (CO); ^{1}H-NMR (Me_2SO-d_6) δ: 3.79 (3H, s, OMe), 4.82 (2H, s, $COCH_2Cl$), 6.85 [1H, dd, *J* = 8.5, 2 Hz, C(5′)-H], 6.97 [1H, d, *J* = 2 Hz, C(7′)-H], 8.00 [1H, d, *J* = 8.5 Hz, C(4′)-H], 8.30 [1H, d, *J* = 3 Hz, C(2′)-H], 11.91 (1H, br, NH).[18] *Anal.* Calcd for $C_{11}H_{10}ClNO_2$: C, 59.07; H, 4.51; N, 6.26. Found: C, 59.00; H, 4.47; N, 6.26.

The above toluene layer, obtained from the reaction mixture by decantation, was concentrated *in vacuo*, and the residue was dissolved in $CHCl_3$–EtOH (10 : 1, v/v) (120 ml). The resulting solution was washed successively with H_2O, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried, and concentrated to leave a brown oil. Purification of the oil by flash chromatography[17] using CH_2Cl_2 as the eluent gave **5** (105 mg, 2%) as a yellowish solid, mp 98—100.5 °C. Recrystallization from MeOH produced an analytical sample of **5** as a colorless fluff, mp 111—111.5 °C; MS *m/z*: 225, 223 (M^+); UV λ_{max}^{EtOH} 252 nm (ε 21800), 275 (sh) (8720); IR ν_{max}^{Nujol} 1722 cm^{-1} (CO); ^{1}H-NMR (Me_2SO-d_6) δ: 3.81 (3H, s, OMe), 5.08 (2H, s, $COCH_2Cl$), 6.71 [1H, d, *J* = 4 Hz, C(3)-H], 6.93 [1H, dd, *J* = 8.5, 2 Hz, C(5)-H], 7.52 [1H, d, *J* = 8.5 Hz, C(4)-H], 7.71 [1H, d, *J* = 4 Hz, C(2)-H], 7.91 [1H, d, *J* = 2 Hz, C(7)-H]. *Anal.* Calcd for $C_{11}H_{10}ClNO_2$: C, 59.07; H, 4.51; N, 6.26. Found: C, 58.92; H, 4.51; N, 6.38.

(±)-*trans*-1-[2-(6-Methoxy-1*H*-indol-3-yl)-2-oxoethyl]-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(±)-7] A mixture of (±)-**6**[12] (1.25 g, 5.2 mmol), **4** (1.23 g, 5.5 mmol), and KBr (1.62 g, 13.6 mmol) in $HCONMe_2$ (8 ml) was stirred at 58 °C for 48 h. After cooling, the reaction mixture was diluted with H_2O (40 ml) and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were combined and washed successively with saturated aqueous $NaHCO_3$ and H_2O, then dried, and concentrated to leave an orange oil. The oil was dissolved in AcOEt (15 ml), and the resulting solution was kept at 4 °C for 2 h. The precipitate that resulted was filtered off to give a first crop (1.06 g) of (±)-**7** as a pale yellowish solid, mp 141—143 °C. The filtrate was concentrated *in vacuo*, and the residual oil was purified by column chromatography (silica gel, AcOEt) to yield a second crop (0.21 g) of (±)-**7**, mp 145—147 °C. The total yield of (±)-**7** was 1.27 g (61%). Recrystallization of the crude (±)-**7** from AcOEt furnished an analytical sample as a colorless solid, mp 147.5—149 °C; MS *m/z*: 400 (M^+); UV λ_{max}^{EtOH} 241 nm (ε 15600), 280 (13300), 370 (sh) (9260); IR ν_{max}^{Nujol} cm^{-1}: 3170 (NH), 1722 (ester CO), 1656 (ArCO), 1610 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, *J* = 7.5 Hz, $CCH_2\underline{Me}$), 1.27 (3H, t, *J* = 7 Hz, $OCH_2\underline{Me}$), 3.80 (3H, s, OMe), 4.15 (2H, q, *J* = 7 Hz, $O\underline{CH_2}Me$), 4.43 (2H, s, $ArCO\underline{CH_2}N$), 6.83 [1H, d, *J* = 2.5 Hz, C(7′)-H], 6.86 [1H, dd, *J* = 9, 2.5 Hz, C(5′)-H], 7.62 [1H, d, *J* = 3 Hz, C(2′)-H], 8.08 [1H, d, *J* = 9 Hz, C(4′)-H], 9.80 (1H, br, NH).[18] *Anal.* Calcd for $C_{22}H_{28}N_2O_5$: C, 65.98; H, 7.05; N, 7.00. Found: C, 65.82; H, 7.11; N, 6.85.

(4*R*,5*R*)-1-[2-(6-Methoxy-1*H*-indol-3-yl)-2-oxoethyl]-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(+)-7] A mixture of (+)-**6**[8b,16]

1.13 g, 4.7 mmol), **4** (1.10 g, 4.9 mmol), and KBr (1.44 g, 12.1 mmol) in $DCONMe_2$ (9 ml) was stirred at 60 °C in an atmosphere of N_2 for 72 h. Work-up of the reaction mixture was similar to the first half of that described above for (±)-**7**, giving a reddish brown oil (1.98 g). Purification of the oil by flash chromatography[17] (AcOEt) gave (+)-**7** (1.41 g, 75%) as a reddish brown glass, which crystallized from AcOEt–hexane (1 : 1, v/v). Recrystallization from the same solvent system yielded an analytical sample as colorless prisms, mp 98.5—100.5 °C; $[\alpha]_D^{21}$ +34.5° (*c* = 0.50, EtOH); MS *m/z*: 400 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460 (free NH), 3215 (associated NH), 1728 (ester CO), 1660 (ArCO), 1628 (lactam CO). *Anal.* Calcd for $C_{22}H_{28}N_2O_5$: C, 65.98; H, 7.05; N, 7.00. Found: C, 66.13; H, 7.14; N, 6.80. The IR ($CHCl_3$), UV (EtOH), and ^{1}H-NMR ($CDCl_3$) spectra and TLC mobility of this sample were identical with those of (±)-**7**.

(±)-*trans*-1-[2-(6-Methoxy-1*H*-indol-3-yl)ethyl]-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(±)-9] A mixture of (±)-**7** (443 mg, 1.1 mmol) and $POCl_3$ (3.40 g, 22.2 mmol) in dry toluene (30 ml) was heated under reflux in an atmosphere of N_2 for 2 h. After cooling, the precipitate that resulted was filtered off, washed successively with hexane (10 ml) and ether (10 ml), and dried to afford a grayish solid (486 mg), presumed to be (±)-**8**. The solid was dissolved in EtOH (40 ml), and the ethanolic solution was hydrogenated over Adams catalyst (90 mg) at atmospheric pressure and room temperature for 2 h. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was then partitioned by extraction with a mixture of aqueous $NaHCO_3$ and CH_2Cl_2. The CH_2Cl_2 extracts were washed successively with H_2O and saturated aqueous NaCl, dried, and concentrated to leave a brown oil (323 mg). Purification of the oil by flash chromatography[17] [AcOEt–hexane (5 : 1, v/v)] furnished (±)-**9** [235 mg, 55% overall yield from (±)-**7**] as a brown solid. Recrystallization from AcOEt–hexane (1 : 1, v/v) gave an analytical sample as faintly brownish pillars, mp 98—99.5 °C; MS *m/z*: 386 (M^+); UV λ_{max}^{EtOH} 225 nm (ε 34900), 266 (sh) (3550), 275 (4180), 294 (4920); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3490 (free NH), 3295 (associated NH), 1728 (ester CO), 1628 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.77 (3H, t, *J* = 7 Hz, $CCH_2\underline{Me}$), 1.26 (3H, t, *J* = 7 Hz, $OCH_2\underline{Me}$), 3.84 (3H, s, OMe), 4.13 (2H, q, *J* = 7 Hz, $OC\underline{H}_2Me$), 6.79 [1H, dd, *J* = 8.5, 2 Hz, C(5′)-H], 6.85 [1H, d, *J* = 2 Hz, C(7′)-H], 6.93 [1H, d, *J* = 2 Hz, C(2′)-H], 7.52 [1H, d, *J* = 8.5 Hz, C(4′)-H], 7.89 (1H, br, NH).[18] *Anal.* Calcd for $C_{22}H_{30}N_2O_4$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.38; H, 7.96; N, 7.37.

(4*R*,5*R*)-1-[2-(6-Methoxy-1*H*-indol-3-yl)ethyl]-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(+)-9] A mixture of (+)-**7** (1.69 g, 4.2 mmol) and $POCl_3$ (12.9 g, 84.1 mmol) in dry toluene (105 ml) was heated under reflux in an atmosphere of N_2 for 2 h. Work-up of the reaction mixture, catalytic hydrogenation [Adams catalyst (330 mg), 1 atm, room temperature, 3 h] of the resulting crude **10** (2.28 g) in EtOH (170 ml), and flash chromatography[17] [AcOEt–hexane (5 : 1, v/v)] of the hydrogenated product were carried out in a manner similar to that described above for (±)-**9**, giving (+)-**9** [1.09 g, 67% overall yield from (+)-**7**] as a reddish brown solid. Recrystallization from AcOEt–hexane (1 : 2, v/v) provided an analytical sample as faintly brownish pillars, mp 81.5—82.5 °C; $[\alpha]_D^{19}$ +77.6° (*c* = 0.50, EtOH); MS *m/z*: 386 (M^+). *Anal.* Calcd for $C_{22}H_{30}N_2O_4$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.41; H, 8.03; N, 7.48. The IR ($CHCl_3$), UV (EtOH), and ^{1}H-NMR ($CDCl_3$) spectra and TLC behavior of this sample were identical with those of (±)-**9**.

(±)-11-Methoxycorynan-17-oic Acid Ethyl Ester [(±)-11] A mixture of (±)-**9** (485 mg, 1.25 mmol) and $POCl_3$ (1.15 g, 7.5 mmol) in dry toluene (7 ml) was heated under reflux in an atmosphere of N_2 for 2 h. After cooling, the reaction mixture was concentrated *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** (516 mg) as a yellow glass. The glass was dissolved in EtOH (60 ml), and the solution was hydrogenated over Adams catalyst (60 mg) at atmospheric pressure and room temperature for 4 h. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* to leave a solid, which was dissolved in H_2O (120 ml). The resulting aqueous solution was made alkaline with 10% aqueous Na_2CO_3 and then extracted with benzene. The benzene extracts were combined, washed with H_2O, dried, and concentrated to leave a brown oil (444 mg). Purification of the oil by flash chromatography[17] [AcOEt–hexane (1 : 1, v/v)] gave (±)-**11** [403 mg, 87% overall yield from (±)-**9**] as a yellow solid. Recrystallization from AcOEt–hexane (1 : 4, v/v) furnished an analytical sample as colorless needles, mp 120—124 °C; MS *m/z*: 370 (M^+); UV λ_{max}^{EtOH} 228 nm (ε 35300), 270 (4790), 298 (6170); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3490 (free NH), 3390 (associated NH), 2840, 2810, 2760 (*trans*-quinolizidine ring[15]), 1725 (ester CO); ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, *J* = 6.5 Hz, $CCH_2\underline{Me}$), 1.29 (3H, t, *J* = 7 Hz, $OCH_2\underline{Me}$), 3.83 (3H, s, OMe), 4.18 (2H, q, *J* = 7 Hz, $OC\underline{H}_2Me$), 6.74 [1H, dd, *J* = 8.5, 2 Hz, C(10)-H], 6.81 [1H, d, *J* = 2 Hz, C(12)-H], 7.33 [1H, d, *J* = 8.5 Hz, C(9)-H], 7.65 (1H, br, NH). *Anal.* Calcd for $C_{22}H_{30}N_2O_3$: C, 71.32; H, 8.16; N, 7.56. Found: C, 71.07; H, 8.24; N, 7.78.

11-Methoxycorynan-17-oic Acid Ethyl Ester [(−)-11] Cyclization of (+)-**9** (1.07 g, 2.8 mmol) was carried out [$POCl_3$ (2.55 g, 16.6 mmol), dry toluene (15 ml), 1 h] as described above for (±)-**11**, affording **10** (1.20 g) as a yellowish brown solid. Catalytic hydrogenation of the total amount of **10** in EtOH (130 ml) [Adams catalyst (130 mg), 1 atm, room temperature, 1 h] and work-up of the reaction mixture were also effected as described above for (±)-**11**, giving (−)-**11** [930 mg, 91% overall yield from (+)-**9**] as a yellowish solid, mp 106.5—107.5 °C. Recrystallization of the solid from AcOEt–hexane (1 : 4, v/v) produced an analytical sample as colorless needles, mp 106.5—108.5 °C; $[\alpha]_D^{22}$ −22.1° (*c* = 0.50, EtOH); MS *m/z*: 370 (M^+). *Anal.* Calcd for $C_{22}H_{30}N_2O_3$: C, 71.32; H, 8.16; N, 7.56. Found: C, 71.22; H, 8.31; N, 7.61. The IR ($CHCl_3$), UV (EtOH), and ^{1}H-NMR ($CDCl_3$) spectra and TLC mobility of this sample were identical with those of (±)-**11**.

(±)-11-Methoxycorynan-17-ol [(±)-11-Methoxydihydrocorynantheol] [(±)-1] A solution of (±)-**11** (111 mg, 0.3 mmol) in dry tetrahydrofuran (THF) (2 ml) was added dropwise to a stirred, ice-cooled suspension of $LiAlH_4$ (34.4 mg, 0.91 mmol) in THF (3 ml) over a period of 15 min. After the resulting mixture had been stirred at room temperature for 1 h, THF (2 ml), H_2O (0.08 ml), 10% aqueous NaOH (0.08 ml), and H_2O (0.16 ml) were added in that order under ice-cooling. Stirring was continued at room temperature for 30 min, and the insoluble material that resulted was filtered off and washed with THF (20 ml). The filtrate and washings were combined, dried over anhydrous K_2CO_3, and concentrated to leave a yellow glass. Purification of the glass by flash chromatography[17] [AcOEt–EtOH (20 : 1, v/v)] yielded (±)-**1** (88.8 mg, 90%) as a yellowish solid. Recrystallization from AcOEt gave an analytical sample as colorless needles, mp 174—176 °C (dec.); MS *m/z* (relative intensity): 329 ($M^+ + 1$) (39), 328 (M^+) (100), 327 (100), 326 (8), 299 (9), 283 (17), 281 (7), 255 (31), 214 (11), 201 (9), 200 (44), 199 (23), 186 (16), 174 (8); UV λ_{max}^{EtOH} 228 nm (ε 37100), 270 (4840), 298 (6180); IR ν_{max}^{KBr} cm^{-1}: 3430 (NH), 3245 (NH, OH), 2860, 2810, 2760 (*trans*-quinolizidine ring[15]); $\nu_{max}^{CHCl_3}$ cm^{-1}: 3635 (free OH), 3490 (free NH), 3285 (associated NH and OH), 2810, 2760 (*trans*-quinolizidine ring[15]); ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, *J* = 6.5 Hz, $CCH_2\underline{Me}$), 1.95 (1H, br, $CH_2O\underline{H}$), 3.65—3.85 (2H, m, $C\underline{H}_2OH$), 3.82 (3H, s, OMe), 6.74 [1H, dd, *J* = 8.5, 2 Hz, C(10)-H], 6.82 [1H, d, *J* = 2 Hz, C(12)-H], 7.32 [1H, d, *J* = 8.5 Hz, C(9)-H], 7.92 (1H, br, NH). *Anal.* Calcd for $C_{20}H_{28}N_2O_2$: C, 73.14; H, 8.59; N, 8.53. Found: C, 73.02; H, 8.81; N, 8.53. The IR ($CHCl_3$), UV (EtOH), and ^{1}H-NMR ($CDCl_3$) spectra and MS of this sample were virtually identical with those[19] of natural (−)-ochromianine.[2]

11-Methoxycorynan-17-ol (11-Methoxydihydrocorynantheol) [(−)-1] Reduction of the tetracyclic ester (−)-**11** (371 mg, 1 mmol) with $LiAlH_4$ (113 mg, 3 mmol) [THF (16 ml), room temperature, 1 h], work-up of the reaction mixture, and purification of the crude product were effected as described above for the racemic series, yielding (−)-**1** (287 mg, 87%) as a yellow solid. Recrystallization of the solid from AcOEt gave an analytical sample as yellowish needles, mp 162—169 °C (dec.); MS *m/z*: 328 (M^+); $[\alpha]_D^{25}$ −28.0° (*c* = 1.00, EtOH); $[\alpha]_{577}^{25}$ −29.8° (*c* = 1.00, EtOH); CD (*c* = 1.22 × 10^{-4} M, EtOH) $[\theta]^{23}$ (nm): +2620 (304) (pos. max.), +660 (285) (neg. max.), +3770 (273) (pos. max.), +1640 (254) (neg. max.), +16500 (238) (pos. max.). *Anal.* Calcd for $C_{20}H_{28}N_2O_2$: C, 73.14; H, 8.59; N, 8.53. Found: C, 72.94; H, 8.80; N, 8.45. The MS, IR ($CHCl_3$), UV (EtOH), and ^{1}H-NMR ($CDCl_3$) spectra and TLC mobility of this sample were identical with those of (±)-**1**. The synthetic (−)-**1** was virtually identical (by comparison of the above spectra, CD spectrum, and specific rotation) with natural (−)-ochromianine [$[\alpha]_{578}^{20}$ −15° (*c* = 1, EtOH)].[2,19,20]

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20) The previously published values[2)] for $\Delta\varepsilon$ in the CD spectrum of natural (−)-ochromianine are apparently about 5 times as large as those of the synthetic (−)-**1**. According to a personal communication from Professor M. Koch (Université René Descartes) in February 1989, their published values were incorrect, most probably due to a transcription or calculation error.