Quinolizidines. XXXIII. A chiral synthesis of (-)-ophiorrhizine, a pentacyclic quaternary indole alkaloid from ophiorrhiza major RIDL

Quinolizidines. XXXIII.[1] A Chiral Synthesis of (−)-Ophiorrhizine, a Pentacyclic Quaternary Indole Alkaloid from *Ophiorrhiza major* RIDL.

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A detailed account is given of the first chiral synthesis of the *Ophiorrhiza* alkaloid ophiorrhizine [(−)-1]. The synthesis was started by coupling the lactim ether (+)-4, readily available from cincholoipon ethyl ester [(+)-3], with 6-benzyloxy-3-chloroacetylindole (6) to form the lactam ketone (+)-8 and proceeded through the intermediates (+)-9, (+)-10, 11, (−)-12, (−)-13, 14, (−)-15, and (−)-16. The identity of synthetic (−)-1·H_2O with natural ophiorrhizine unequivocally established the absolute stereochemistry of this alkaloid.

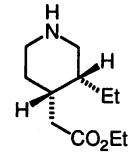
Keywords *Ophiorrhiza* alkaloid synthesis; ophiorrhizine configuration; cincholoipon; lactim ether *N*-alkylation; oxazolium hydrogenolysis; Bischler–Napieralski cyclization

According to Arbain *et al.*,[2] *Ophiorrhiza major* RIDL. (Rubiaceae) is a small shrub (*ca.* 20 cm high), which, although rare, is used by traditional healers in West Sumatra as a component of a poultice to treat skin disorders, especially eczema. In 1992, they reported the isolation of a new C_{19} pentacyclic quaternary indole alkaloid, named ophiorrhizine, from the fresh aerial parts of this medicinal plant.[2] The same Indonesian–Australian research group established the structure and relative stereochemistry of ophiorrhizine as **1** on the basis of its spectral properties and X-ray molecular structure.[2] However, its absolute stereochemistry has only been inferred to be (−)-**1**[3] from the negative sign and magnitude of the specific rotation of the alkaloid.[2] The correctness of this inference has now been verified by us as a result of the following chiral synthesis of the target compound with the candidate structure (−)-**1**. The synthesis features an adaptation of our favorite "cincholoipon-incorporating lactim ether route",[1,4] which has been developed in this laboratory as the best available vehicle for unified chiral syntheses of the benzo[*a*]quinolizidine-type *Alangium* alkaloids and *Corynanthe*-type indoloquinolizidine alkaloids. A brief account of the results reported here has been published in a preliminary form.[5]

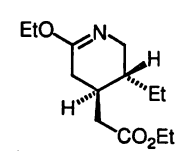
Our synthetic plan required two starting materials. One of them was the lactim ether (+)-**4**,[6,7] easily obtainable from cincholoipon ethyl ester [(+)-**3**] according to our previously reported procedure,[7] and the other, 6-benzyloxy-3-chloroacetylindole (**6**), was prepared in 36% yield from 6-benzyloxyindole (**5**)[8] and chloroacetyl chloride (pyridine/dioxane, 55—60 °C, 30 min)[9] according to a general 3-chloroacetylation procedure.[10] As anticipated,[4c,d,10] this 3-acylation was accompanied with the formation of a small amount (1% yield) of the 1-acylated derivative **7**.

The two starting materials, (+)-**4** and **6**, were then coupled in *N*,*N*-dimethylformamide (DMF) in the presence of KBr at 60 °C for 48 h to produce the lactam ketone (+)-**8** in 62% yield (Chart 1). Treatment of (+)-**8** with $POCl_3$ in boiling toluene for 1 h gave the oxazolium salt (+)-**9** (95% yield), which was then subjected to catalytic hydrogenation (Pt/H_2, EtOH, 1 atm, room temperature, 3 h), affording the lactam (+)-**10** in 58% yield. This two-step reduction of the ketonic group of (+)-**8** to the corresponding methylene group through the oxazolium salt (+)-**9** has precedents[4c-e] in structurally analogous compounds. Conversion of (+)-**10** into the tetracyclic ester (−)-**12** through the quaternary iminium salt **11** was achieved in 56% overall yield by means of Bischler–Napieralski cyclization ($POCl_3$, boiling toluene, 1.5 h) followed by catalytic hydrogenation (Pt/H_2, EtOH, 1 atm, room temperature, 1.5 h). The hydrogen at C(3) of (−)-**12** was assigned the α configuration by analogy with catalytic hydrogenation of similar heterocyclic ring systems.[4c-e,11] The appearance of absorption bands at 2810 and 2755 cm^{-1}, assignable to a *trans*-quinolizidine ring,[12] in the IR spectrum of (−)-**12** in $CHCl_3$ supported the correctness of this stereochemical assignment.

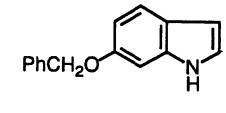
Next the tetracyclic ester (−)-**12** was reduced with $LiAlH_4$ in tetrahydrofuran (THF) at room temperature



(+)-3



(+)-4



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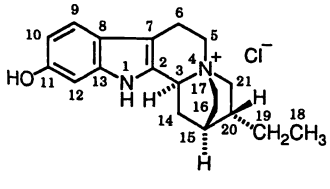
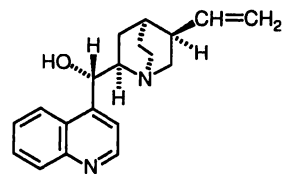
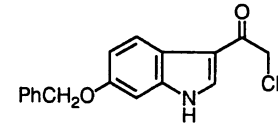


(−)-1



(+)-2



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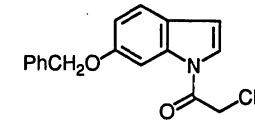

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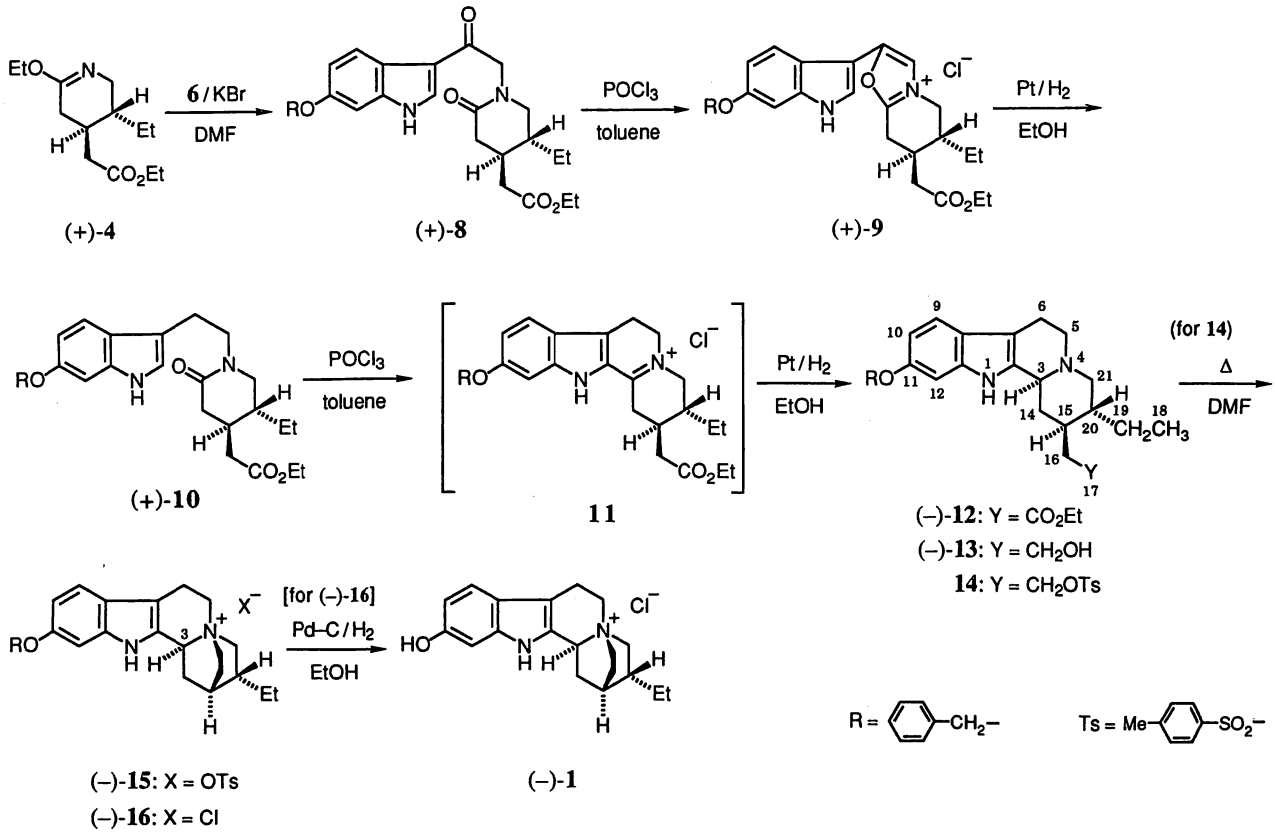

Chart 1

for 1.5 h to provide the alcohol (−)-**13** in 94% yield. Treatment of (−)-**13** with *p*-toluenesulfonyl chloride in pyridine at 4 °C for 24 h and heating of the resulting *O*-tosyl derivative **14** in boiling DMF for 30 min gave the 4,17-cyclocorynanium tosylate (−)-**15** in 73% overall yield [from (−)-**13**]. In the ^{1}H-NMR spectrum of (−)-**15** in Me_2SO-d_6, the C(3)-proton (at δ 5.04) resonated at lower field than did the corresponding proton (at δ 3.13 in $CDCl_3$) of (−)-**13**, reflecting the presence of the positively charged nitrogen in close proximity. Anion exchange of the tosylate salt (−)-**15** was effected with Amberlyst A-26 (Cl^-) in aqueous MeOH to furnish the chloride salt (−)-**16** in 96% yield.

Finally, debenzylation of the chloride salt (−)-**16** by means of catalytic hydrogenolysis (10% Pd–C/H_2, EtOH, 1 atm, room temperature, 6 h) gave the desired compound [(−)-**1**·H_2O] in 93% yield. The UV (MeOH), IR (KBr), ^{1}H-NMR (CD_3OD), and ^{13}C-NMR (CD_3OD) spectra and TLC mobility of the synthetic (−)-**1**·H_2O were virtually identical with those of natural (−)-ophiorrhizine. More importantly, the chiral identity of the synthetic (−)-**1**·H_2O with the alkaloid was established on the basis of the same sign of their specific rotations in MeOH as well as their virtually superimposable CD spectra in MeOH.

In conclusion, the absolute stereochemistry of the *Ophiorrhiza* alkaloid ophiorrhizine has now been defined to be as shown in formula (−)-**1** as a result of the above chiral synthesis. Interestingly, this synthesis is equivalent to a chemical correlation of ophiorrhizine with the *Cinchona* alkaloid cinchonine [(+)-**2**], because the lactim ether (+)-**4**[7] employed as one of the starting materials was prepared from (+)-**2** through its degradation product, cincholoipon ethyl ester [(+)-**3**].[13] The present work also enhances the usefulness of our "cincholoipon-incorporating lactim ether route"[4] for chiral syntheses of the *Corynanthe*-type indoloquinolizidine alkaloids.

Experimental

General Notes All melting points were determined by using a Yamato MP-1 or a Büchi model 530 capillary melting point apparatus and are corrected. TLC was run on Merck silica gel 60 F_{254} plates (0.25-mm thickness), and spots were detected by means of UV absorbance measurement (at 254 nm) and/or spraying with the standard $KMnO_4$ or I_2–KI reagent. Flash chromatography[14] was carried out by using Merck silica gel 60 (No. 9385). Spectra reported herein were recorded on a Hitachi 320 UV spectrophotometer, a JASCO A-202 or a Shimadzu FTIR-8100 IR spectrophotometer, a Hitachi M-80 mass spectrometer, a JEOL JNM-EX-270 (^{1}H 270 MHz and ^{13}C 67.8 MHz) or a JEOL JNM-GSX-500 (^{1}H 500 MHz) NMR instrument (chemical shifts are reported in ppm downfield from internal Me_4Si), or a JASCO J-500C spectropolarimeter. Optical rotations were measured with a JASCO DIP-181 polarimeter using a 1-dm sample tube. Elemental analyses and MS measurements 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, ddd = doublet-of-dd's, dq = doublet-of-quartets, m = multiplet, q = quartet, s = singlet, sh = shoulder, t = triplet.

1-(6-Benzyloxy-1*H*-indol-3-yl)-2-chloroethanone (6) and 6-Benzyloxy-1-(chloroacetyl)-1*H*-indole (7) A stirred mixture of 6-benzyloxyindole (**5**)[8] (4.00 g, 17.9 mmol) and pyridine (2.83 g, 35.8 mmol) in dioxane (25 ml) was kept at 55—60 °C in an atmosphere of N_2, and a solution of chloroacetyl chloride (4.04 g, 35.8 mmol) in dioxane (5 ml) was added dropwise over a period of 1.5 h. The resulting mixture was stirred at the same temperature for 30 min and then poured into an ice-cooled, stirred mixture of ether (16 ml) and H_2O (64 ml). Stirring was continued at 0 °C for 30 min, and the precipitate that resulted was filtered off to give **6** (1.92 g, 36%) as a pale brown solid, mp 217—224 °C (dec.). Recrystallization from DMF–EtOH–H_2O (1 : 1 : 1, v/v) afforded an analytical sample of **6** as a slightly brownish solid, mp 231—234 °C (dec.); MS *m/z*:

301, 299 (M^+); IR ν_{max}^{Nujol} cm^{-1}: 3180 (NH), 1646 (CO); ^{1}H-NMR (Me_2SO-d_6) δ: 4.84 (2H, s, $COCH_2Cl$), 5.15 (2H, s, OCH_2Ph), 6.95 [1H, dd, J=8.5 and 2.5 Hz, C(5')-H], 7.05 [1H, d, J=2.5 Hz, C(7')-H], 7.30—7.50 (5H, m, OCH_2Ph), 8.02 [1H, d, J=8.5 Hz, C(4')-H], 8.31 [1H, d, J=3 Hz, C(2')-H], 11.9 (1H, br, NH).[15] *Anal.* Calcd for $C_{17}H_{14}ClNO_2$: C, 68.12; H, 4.71; N, 4.67. Found: C, 67.96; H, 4.55; N, 4.69.

The filtrate, obtained when the crude **6** was isolated, was extracted with ether (3 × 20 ml). The ethereal extracts were combined, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to leave a brown oil. Purification of the oil by repetition of flash chromatography[14] [silica gel, CH_2Cl_2; $CHCl_3$; $CHCl_3$–benzene (5 : 1, v/v)] furnished **7** (52 mg, 1%) as a colorless solid, mp 111—112.5 °C. Recrystallization from MeOH gave an analytical sample of **7** as colorless needles, mp 114—114.5 °C; UV $\lambda_{max}^{99\%aq.EtOH}$ 252 nm (ε 21100), 275 (sh) (9400); IR ν_{max}^{Nujol} 1717 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ: 4.56 (2H, s, $COCH_2Cl$), 5.14 (2H, s, OCH_2Ph), 6.63 [1H, d, J=3.5 Hz, C(3)-H], 7.02 [1H, dd, J=8.5 and 2.5 Hz, C(5)-H], 7.29 [1H, d, J=3.5 Hz, C(2)-H], 7.30—7.50 [5H, m, OCH_2Ph], 7.44 [1H, d, J=8.5 Hz, C(4)-H], 8.15 [1H, d, J=2.5 Hz, C(7)-H]. *Anal.* Calcd for $C_{17}H_{14}ClNO_2$: C, 68.12; H, 4.71; N, 4.67. Found: C, 68.04; H, 4.59; N, 4.65.

(4*R*,5*R*)-1-[2-(6-Benzyloxy-1*H*-indol-3-yl)-2-oxoethyl]-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(+)-8] A mixture of (+)-4[6,7] (1.84 g, 7.62 mmol), **6** (2.74 g, 9.14 mmol), and KBr (2.34 g, 19.7 mmol) in DMF (15 ml) was stirred at 60 °C in an atmosphere of N_2 for 48 h. The reaction mixture was concentrated *in vacuo*, and the residue was extracted with CH_2Cl_2 (3 × 100 ml) after addition of H_2O (50 ml). The CH_2Cl_2 extracts were combined, washed successively with saturated aqueous $NaHCO_3$ (50 ml) and H_2O (50 ml), dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to leave a dark brown oil. Purification of the oil by flash chromatography[14] (silica gel, AcOEt) gave (+)-**8** (2.25 g, 62%) as a slightly brown solid, mp 146—148 °C. Recrystallization of the solid from AcOEt–hexane (1 : 1, v/v) provided an analytical sample as colorless needles, mp 146—147 °C; $[\alpha]_D^{19}$ +25.2° (c=0.479, EtOH); MS m/z: 476 (M^+); UV $\lambda_{max}^{99\%aq.EtOH}$ 241 nm (ε 18400), 280 (14000), 300 (sh) (9900); IR ν_{max}^{Nujol} cm^{-1}: 3185 (NH), 1727 (ester CO), 1655 (ArCO), 1628 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, J=7.5 Hz, CCH_2Me), 1.26 (3H, t, J=7 Hz, OCH_2Me), 1.34 (1H), 1.62 (1H), 1.73 (1H), 2.25—2.33 (3H), 2.57 (1H), and 2.68 (1H) [m each, CCH_2Me, C(3)-H's, C(4)-H, C(5)-H, and CH_2CO_2Et], 3.20 [1H, dd, J=12 and 8.5 Hz, C(6)-H], 3.48 [1H, dd, J=12 and 5 Hz, C(6)-H], 4.14 (2H, q, J=7 Hz, OCH_2Me), 4.52 and 4.55 (2H, AB type d's, J=16 Hz, $ArCOCH_2N$), 5.07 (2H, s, OCH_2Ph), 6.90 [1H, d, J=2 Hz, C (7')-H], 6.95 [1H, dd, J=8.5 and 2 Hz, C(5')-H], 7.30—7.47 (5H, m, OCH_2Ph), 7.76 [1H, d, J=3 Hz, C(2')-H], 8.08 [1H, d, J=8.5 Hz, C(4')-H], 9.37 (1H, br, NH).[15] *Anal.* Calcd for $C_{28}H_{32}N_2O_5$: C, 70.57; H, 6.77; N, 5.88. Found: C, 70.53; H, 6.81; N, 5.60.

(6*R*,7*R*)-2-(6-Benzyloxy-1*H*-indol-3-yl)-7-(2-ethoxy-2-oxoethyl)-6-ethyl-5,6,7,8-tetrahydrooxazolo[3,2-*a*]pyridinium Chloride [(+)-9] A stirred mixture of (+)-**8** (229 mg, 0.481 mmol) and $POCl_3$ (1.54 g, 10.0 mmol) in dry toluene (11 ml) was heated under reflux in an atmosphere of N_2 for 1 h. After cooling, the precipitate that resulted was filtered off and recrystallized from MeOH–ether (1 : 1, v/v) to give (+)-**9** (226 mg, 95%) as a colorless solid, mp 205—222 °C (dec.). Further recrystallizations of the solid from the same solvent system produced an analytical sample as colorless plates, mp 239—243 °C (dec.); $[\alpha]_D^{20}$ +54.2° (c=0.306, MeOH); UV $\lambda_{max}^{99\%aq.EtOH}$ 240 nm (sh) (ε 20500), 294 (16000), 310 (sh) (12800); IR ν_{max}^{Nujol} cm^{-1}: 3450 (NH), 1725 (ester CO), 1660 (C=N$^+$), 1620 (C=C); ^{1}H-NMR (Me_2SO-d_6) δ: 0.94 (3H, t, J=7.5 Hz, CCH_2Me), 1.22 (3H, t, J=7 Hz, OCH_2Me), 1.42 (1H), 1.65 (1H), 2.07 (1H), 2.47—2.57 (2H), and 2.70 (1H) [m each, CCH_2Me, C(6)-H, C(7)-H, and CH_2CO_2Et], 3.09 [1H, dd, J=19 and 7 Hz, C(8)-H], 3.42 [1H, dd, J=19 and 5 Hz, C(8)-H], 3.96 [1H, dd, J=14 and 8 Hz, C(5)-H], 4.12 (2H, q, J=7 Hz, OCH_2Me), 4.32 [1H, dd, J=14 and 5 Hz, C(5)-H], 5.16 (2H, s, OCH_2Ph), 6.97 [1H, dd, J=9 and 2.5 Hz, C (5')-H], 7.11 [1H, d, J=2.5 Hz, C(7')-H], 7.32—7.50 (5H, m, OCH_2Ph), 7.75 [1H, d, J=9 Hz, C(4')-H], 7.94 [1H, d, J=3 Hz, C(2')-H], 8.32 [1H, s, C(3)-H], 11.88 (1H, br, NH).[15] *Anal.* Calcd for $C_{28}H_{31}ClN_2O_4$: C, 67.94; H, 6.31; N, 5.66. Found: C, 67.95; H, 6.28; N, 5.62.

(4*R*,5*R*)-1-[2-(6-Benzyloxy-1*H*-indol-3-yl)ethyl]-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(+)-10] A solution of (+)-**9** (100 mg, 0.202 mmol) in EtOH (10 ml) was hydrogenated over Adams catalyst (16 mg) at atmospheric pressure and room temperature for 3 h. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* to leave a yellow oil, which was then partitioned between aqueous $NaHCO_3$ and CH_2Cl_2. The CH_2Cl_2 extracts were washed successively with H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to leave a brown oil. Purification of the oil by flash chromatography[14] [silica gel, AcOEt–hexane (5 : 1, v/v)] gave (+)-**10** (54 mg, 58%) as a yellowish solid, mp 110—116 °C. Recrystallization from AcOEt–hexane (1 : 2, v/v) afforded an analytical sample as colorless needles, mp 125.5—126 °C; $[\alpha]_D^{21}$ +64.3° (c=0.307, EtOH); MS m/z: 462 (M^+); UV $\lambda_{max}^{99\%aq.EtOH}$ 225 nm (ε 39300), 266 (sh) (4200), 276 (sh) (4500), 293 (5200); IR ν_{max}^{Nujol} cm^{-1}: 3285 (NH), 1740 (ester CO), 1622 (lactam CO); ^{1}H-NMR ($CDCl_3$) δ: 0.76 (3H, t, J=7.5 Hz, CCH_2Me), 1.26 (3H, t, J=7 Hz, OCH_2Me), 1.16 (1H), 1.37—1.52 (2H), 2.05—2.18 (3H), 2.41 (1H), and 2.56 (1H) [m each, CCH_2Me, C(3)-H's, C(4)-H, C(5)-H, and CH_2CO_2Et], 2.88 [1H, dd, J=12.5 and 8.5 Hz, C(6)-H], 3.00 (2H, m, $ArCH_2CH_2N$), 3.16 [1H, dd, J=12.5 and 5 Hz, C(6)-H], 3.56—3.72 (2H, m, $ArCH_2CH_2N$), 4.13 (2H, q, J=7 Hz, OCH_2Me), 5.11 (2H, s, OCH_2Ph), 6.88 [1H, dd, J=8.5 and 2 Hz, C(5')-H], 6.91 [1H, d, J=2 Hz, C(7')-H], 6.93 [1H, br d, J=2 Hz, C(2')-H], 7.29—7.48 (5H, m, OCH_2Ph), 7.53 [1H, d, J=8.5 Hz, C(4')-H], 7.85 (1H, br, NH).[15] *Anal.* Calcd for $C_{28}H_{34}N_2O_4$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.69; H, 7.45; N, 6.08.

11-Benzyloxycorynan-17-oic Acid Ethyl Ester [(−)-12] A stirred mixture of (+)-**10** (591 mg, 1.28 mmol) and $POCl_3$ (1.18 g, 7.70 mmol) in dry toluene (10 ml) was heated under reflux in an atmosphere of N_2 for 1.5 h. After cooling, the reaction mixture was concentrated *in vacuo*, and the residue was partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ extracts were washed successively with H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to leave crude **11** (627 mg) as a yellow solid. The solid was dissolved in EtOH (60 ml), and the solution was hydrogenated over Adams catalyst (65 mg) at atmospheric pressure and room temperature for 1.5 h. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 and 10% aqueous Na_2CO_3. The CH_2Cl_2 extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to leave a pale yellow foam. Purification of the foam by flash chromatography[14] [silica gel, AcOEt–hexane (1 : 2, v/v)] yielded (−)-**12** [322 mg, 56% from (+)-**10**] as a yellow oil, $[\alpha]_D^{28}$ −22.0° (c=0.750, EtOH); MS m/z: 446 (M^+); UV $\lambda_{max}^{99\%aq.EtOH}$ 229 nm (ε 41700), 268 (5700), 297 (6200); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3470 (free NH), 3380 (associated NH), 2810 and 2755 (*trans*-quinolizidine ring[12]), 1725 (ester CO); ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.5 Hz, CCH_2Me), 1.17 (1H, m), 1.35 (1H, ddd, J=12 Hz each), 1.49 (1H, m), 1.62 (1H, m), and 1.81 (1H, m) [C(14)-H, C(15)-H, C(19)-H's, and C(20)-H], 1.29 (3H, t, J=7.5 Hz, OCH_2Me), 2.06—2.15 [2H, m, C(16)-H's], 2.21 [1H, ddd, J=12, 3.5, and 3 Hz, C(14)-H], 2.58 (1H, ddd, J=11, 11, and 4.5 Hz), 2.64—2.70 (2H, m), 2.97 (1H, m), and 3.04—3.12 (2H, m) [C(5)-H's, C(6)-H's, and C(21)-H's], 3.21 [1H, br d, J=12 Hz, C(3)-H], 4.17 (2H, br q, J=7.5 Hz, OCH_2Me), 5.09 (2H, s, OCH_2Ph), 6.83 [1H, dd, J=8.5 and 2 Hz, C(10)-H], 6.86 [1H, d, J=2 Hz, C(12)-H], 7.33 [1H, d, J=8.5 Hz, C(9)-H], 7.28—7.46 (5H, m, OCH_2Ph), 7.67 (1H, br, NH).

11-Benzyloxycorynan-17-ol [(−)-13] A solution of (−)-**12** (303 mg, 0.678 mmol) in dry THF (17 ml) was added dropwise to a stirred, ice-cooled suspension of $LiAlH_4$ (129 mg, 3.40 mmol) in dry THF (8 ml) over a period of 25 min. After the resulting mixture had been stirred at room temperature in an atmosphere of N_2 for 1.5 h, THF (5 ml), H_2O (0.13 ml), 10% aqueous NaOH (0.20 ml), and H_2O (0.39 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 (50 ml). The filtrate and washings were combined, dried over anhydrous K_2CO_3, and concentrated *in vacuo* to leave a pale yellow foam. Purification of the foam by flash chromatography[14] (silica gel, AcOEt) yielded (−)-**13** (257 mg, 94%) as a slightly yellow foam, $[\alpha]_D^{28}$ −30.0° (c=0.813, EtOH); MS m/z: 404 (M^+); UV $\lambda_{max}^{99\%aq.EtOH}$ 229 nm (ε 41800), 268 (5700), 298 (6200); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3620 (free OH), 3470 (free NH), 3330 (associated OH and NH), 2810 and 2755 (*trans*-quinolizidine ring[12]); ^{1}H-NMR ($CDCl_3$) δ: 0.92 [3H, t, J=7.5 Hz, C(18)-H's], 1.14 (1H, m), 1.25—1.52 (4H, m), 1.62—1.72 (2H, m), 1.94 (1H, m), 2.07 (1H, dd, J=11 Hz each), 2.17 (1H, ddd, J=12.5, 3, and 3 Hz), 2.56 (1H, ddd, J=11, 11, and 4.5 Hz), 2.67 (1H, br d, J=15.5 Hz), 2.97 (1H, m), and 3.04—3.10 (2H, m) [C(5)-H's, C(6)-H's, C(14)-H's, C(15)-H, C(16)-H's, C(19)-H's, C(20)-H, C(21)-H's, and OH], 3.13 [1H, br d, J=11.5 Hz, C(3)-H], 3.75 (2H, m, CH_2OH), 5.08 (2H, s, OCH_2Ph), 6.83 [1H, dd, J=8.5 and 2 Hz, C(10)-H], 6.87

[1H, d, J=2 Hz, C(12)-H], 7.33 [1H, d, J=8.5 Hz, C(9)-H], 7.28—7.47 (5H, m, $OCH_2\underline{Ph}$), 7.76 (1H, br, NH).

11-Benzyloxy-4,17-cyclocorynanium *p*-Toluenesulfonate [(−)-15] A mixture of (−)-**13** (252 mg, 0.623 mmol) and *p*-toluenesulfonyl chloride (355 mg, 1.86 mmol) in pyridine (5 ml) was kept in a refrigerator (4 °C) for 24 h. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in $CHCl_3$ (100 ml). The resulting solution was washed successively with H_2O (20 ml), 3% aqueous NaOH (30 ml), and saturated aqueous NaCl (30 ml), dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to leave a brown solid (327 mg). The solid was dissolved in DMF (5 ml), and the solution was heated under reflux in an atmosphere of N_2 for 30 min and then cooled in an ice bath. The colorless precipitate that deposited was filtered off, washed successively with DMF (2 ml) and EtOH, and dried to yield a first crop (123 mg) of (−)-**15**, mp 275—282 °C (dec.). The filtrate and washings were combined and concentrated *in vacuo* to leave a brown solid. Trituration of the solid with EtOH and collection of the insoluble material by filtration yielded a second crop (130 mg) of (−)-**15**, mp 270—280 °C (dec.). The total yield of (−)-**15** was 253 mg [73% from (−)-**13**]. Recrystallization of the crude (−)-**15** from DMF gave an analytical sample as colorless needles, mp 275—285 °C (dec.); $[\alpha]_D^{32}$ −67.4° (c=0.514, MeOH); UV $\lambda_{max}^{99\%aq.EtOH}$ 222 nm (ε 53700), 263 (6700), 268 (sh) (6500), 294 (7900), 301 (sh) (6400); IR ν_{max}^{Nujol} 3470 cm^{-1} (NH); ^{1}H-NMR (Me_2SO-d_6) δ: 0.95 [3H, t, J=7.5 Hz, C(18)-H's], 1.59 [2H, dq, J=7.5 Hz each, C(19)-H's], 1.77—1.92 [2H, m, C(16)-H's], 1.80 [1H, dd, J=13 and 9 Hz, C(14)-H], 2.04 [1H, m, C(20)-H], 2.16 [1H, m, C(15)-H], 2.29 (3H, s, p-$\underline{Me}C_6H_4SO_3^-$), 2.57 [1H, m, C(14)-H], 2.90—3.05 [2H, m, C(6)-H's], 3.23—3.35 [2H, m, C(17)-H and C(21)-H], 3.48—3.62 [3H, m, C(5)-H's and C(17)-H], 3.79 [1H, dd, J=12.5 and 10.5 Hz, C(21)-H], 5.04 [1H, br dd, J=9 Hz each, C(3)-H], 5.12 and 5.14 (2H, AB type d's, J=12.5 Hz, $OC\underline{H}_2Ph$), 6.79 [1H, dd, J=8.5 and 2 Hz, C(10)-H], 6.94 [1H, d, J=2 Hz, C(12)-H], 7.10 and 7.47 (2H each, d, J=8 Hz, p-$MeC_6\underline{H}_4SO_3^-$), 7.28—7.48 (5H, m, $OCH_2\underline{Ph}$), 7.37 [1H, d, J=8.5 Hz, C(9)-H], 10.97 (1H, s, NH). *Anal.* Calcd for $C_{33}H_{38}N_2O_4S$: C, 70.94; H, 6.86; N, 5.01. Found: C, 70.82; H, 6.93; N, 5.13.

11-Benzyloxy-4,17-cyclocorynanium Chloride [(−)-16] A solution of (−)-**15** (237 mg, 0.424 mmol) in MeOH–H_2O (3:1, v/v) (50 ml) was passed through a column of Amberlyst A-26 (Cl^-) (9 ml), which had been washed successively with H_2O (100 ml) and MeOH–H_2O (3:1, v/v) (100 ml), and the column was then eluted with MeOH–H_2O (3:1, v/v) (100 ml). The eluates were combined and concentrated *in vacuo* to leave a colorless solid. The solid was recrystallized from EtOH–ether (10:1, v/v) to give (−)-**16** (172 mg, 96%), mp 285—295 °C (dec.). Further recrystallization from EtOH–ether (20:1, v/v) yielded an analytical sample as colorless prisms, mp 285—300 °C (dec.); $[\alpha]_D^{29}$ −88.1° (c=0.199, EtOH); UV $\lambda_{max}^{99\%aq.EtOH}$ 222 nm (ε 42700), 264 (6300), 269 (6300), 294 (7800), 301 (sh) (6300); IR ν_{max}^{Nujol} 3400 cm^{-1} (NH); ^{1}H-NMR (CD_3OD) δ: 1.05 [3H, t, J=7.5 Hz, C(18)-H's], 1.71 [2H, m, C(19)-H's], 1.93—2.01 [3H, m, C(14)-H and C(16)-H's], 2.17 [1H, m, C(20)-H], 2.27 [1H, m, C(15)-H], 2.73 [1H, ddd, J=14, 9, and 4.5 Hz, C(14)-H], 3.02 [1H, br d, J=16.5 Hz, C(6)-H], 3.15 [1H, m, C(6)-H], 3.23—3.35 [2H, m, C(17)-H and C(21)-H], 3.59—3.68 [2H, m, C(5)-H's], 3.72 [1H, m, C(17)-H], 3.84 [1H, dd, J=12.5 and 10.5 Hz, C(21)-H], 5.01 [1H, br dd, J=9 Hz each, C(3)-H], 5.11 (2H, s, $OC\underline{H}_2Ph$), 6.83 [1H, dd, J=9 and 2.5 Hz, C(10)-H], 6.96 [1H, d, J=2.5 Hz, C(12)-H], 7.27—7.46 (5H, m, $OCH_2\underline{Ph}$), 7.37 [1H, d, J=9 Hz, C(9)-H]. *Anal.* Calcd for $C_{26}H_{31}ClN_2O$: C, 73.83; H, 7.39; N, 6.62. Found: C, 73.58; H, 7.34; N, 6.38.

11-Hydroxy-4,17-cyclocorynanium Chloride [(−)-Ophiorrhizine][(−)-1] A solution of (−)-**16** (110 mg, 0.260 mmol) in EtOH (60 ml) was hydrogenated over 10% Pd–C catalyst (120 mg) at atmospheric pressure and room temperature for 6 h. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* to leave (−)-**1**·H_2O (85 mg, 93%) as a yellowish solid, mp 195—280 °C (dec.). Recrystallization from AcOEt–MeOH (1:1, v/v) and drying over P_2O_5 at 2 mmHg and 75 °C for 2 h then at room temperature for 12 h gave an analytical sample of (−)-**1**·H_2O as colorless needles, mp 282—285 °C (dec.); $[\alpha]_D^{30}$ −102° (c=0.209, MeOH); CD (c=2.56×10^{-4} M, MeOH) $[\theta]^{20}$ (nm): +1100 (302) (pos. max.), −230 (285) (neg. max.), +980 (270) (pos. max.), +570 (264) (neg. max.), +1020 (257) (pos. max.), −760 (245) (neg. max.); UV λ_{max}^{MeOH} 220 nm (ε 37700), 264 (sh) (5400), 270 (5500), 295 (7400); ^{1}H-NMR (CD_3OD) δ: 1.05 [3H, t, J=7.5 Hz, C(18)-H's], 1.71 [2H, m, C(19)-H's], 1.92—2.01 [3H, m, C(14)-H and C(16)-H's], 2.17 [1H, m, C(20)-H], 2.26 [1H, m, C(15)-H], 2.73 [1H, ddd, J=14, 9, and 5 Hz, C(14)-H], 2.99 [1H, br d, J=16.5 Hz, C(6)-H], 3.12 [1H, m, C(6)-H], 3.25—3.35 [2H, m, C(17)-H and C(21)-H], 3.61 [2H, m, C(5)-H's], 3.71 [1H, m, C(17)-H], 3.84 [1H, dd, J=12.5 and 10.5 Hz, C(21)-H], 4.96 [1H, br dd, J=9 Hz each, C(3)-H], 6.64 [1H, dd, J=8.5 and 2 Hz, C(10)-H], 6.79 [1H, d, J=2 Hz, C(12)-H], 7.28 [1H, d, J=8.5 Hz, C(9)-H]; ^{1}H-NMR (Me_2SO-d_6) δ: 0.95 [3H, t, J=7.5 Hz, C(18)-H's], 1.59 [2H, dq, J=7.5 Hz each, C(19)-H's], 1.77—1.93 [2H, m, C(16)-H's], 1.80 [1H, dd, J=13 and 9 Hz, C(14)-H], 2.05 [1H, m, C(20)-H], 2.16 [1H, m, C(15)-H], 2.55 [1H, m, C(14)-H], 2.88—3.02 [2H, m, C(6)-H's], 3.25—3.37 [2H, m, C(17)-H and C(21)-H], 3.49—3.63 [3H, m, C(5)-H's and C(17)-H], 3.79 [1H, dd, J=12.5 and 10.5 Hz, C(21)-H], 5.02 [1H, br dd, J=9 Hz each, C(3)-H], 6.57 [1H, dd, J=8.5 and 2 Hz, C(10)-H], 6.76 [1H, d, J=2 Hz, C(12)-H], 7.25 [1H, d, J=8.5 Hz, C(9)-H], 9.05 (1H, s, OH), 10.81 (1H, s, NH); ^{13}C-NMR (CD_3OD) δ: 12.1 [C(18)], 18.3 [C(6)], 25.2 [C(15)], 26.3 [C(16)], 26.9 [C(14)], 28.0 [C(19)], 38.1 [C(20)], 49.2 [C(17)], 61.3 [C(5)], 62.2 [C(3)], 65.3 [C(21)], 98.1 [C(12)], 105.4 [C(7)], 111.1 [C(10)], 119.8 [C(9)], 120.8 [C(8)], 127.8 [C(2)], 140.0 [C(13)], 155.3 [C(11)]. *Anal.* Calcd for $C_{19}H_{25}ClN_2O \cdot H_2O$: C, 65.04; H, 7.76; N, 7.98. Found: C, 64.97; H, 7.76; N, 7.94.

The UV (MeOH), IR (KBr), ^{1}H-NMR (CD_3OD), ^{13}C-NMR (CD_3OD), and CD (MeOH) spectra and TLC behavior [silica gel, 1-butanol–H_2O–conc. aqueous NH_3 (4:1:1, v/v) or MeOH–AcOH (50:1, v/v)] of this sample were virtually identical with those of natural (−)-ophiorrhizine [CD (c=2.77×10^{-4} M, MeOH) $[\theta]^{19}$ (nm): +1080 (302) (pos. max.), −180 (286) (neg. max.), +940 (270) (pos. max.), +540 (264) (neg. max.), +810 (257) (pos. max.), −1080 (245) (neg. max.)].

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