QUINOLIZIDINES. XXIX.[1] PREPARATION OF (–)-DIHYDROCORYNANTHEOL

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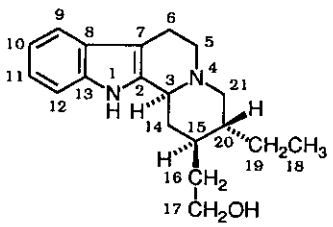
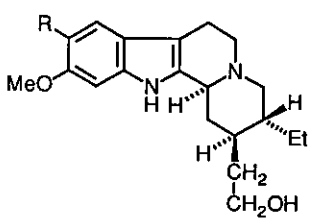
Abstract———An alternative, total synthesis of the indoloquinolizidine alkaloid (–)-dihydrocorynantheol [(–)-**1**], adaptable to that on a gram scale preparation, has been achieved *via* a "lactim ether route". The route started with an initial condensation between the lactim ether [(+)-**4**] and 3-(chloroacetyl)indole and proceeded through the lactam ketone [(+)-**5**], oxazolium salt (**6**), *N*-substituted lactam [(+)-**8**], quaternary iminium salt (**9**), and tetracyclic ester [(–)-**11**].

As part of a study on the chiral synthesis of indoloquinolizidine alkaloids in this laboratory, it was necessary to prepare (–)-dihydrocorynantheol (corynan-17-ol) [(–)-**1**][2] in gram quantity. This *Corynanthe*-type alkaloid has been isolated from the bark[3] and stem bark[4] of *Aspidosperma marcgravianum* Woodson (Apocynaceae); the bark of *A. auriculatum*;[5] the leaves of *Amsonia tabernaemontana* Walt. (Apocynaceae);[6] the leaves of *Mitragyna parvifolia* (Roxb.) Korth (Rubiaceae);[7] the bark of *Hunteria zeylanica*



(–)-**1**

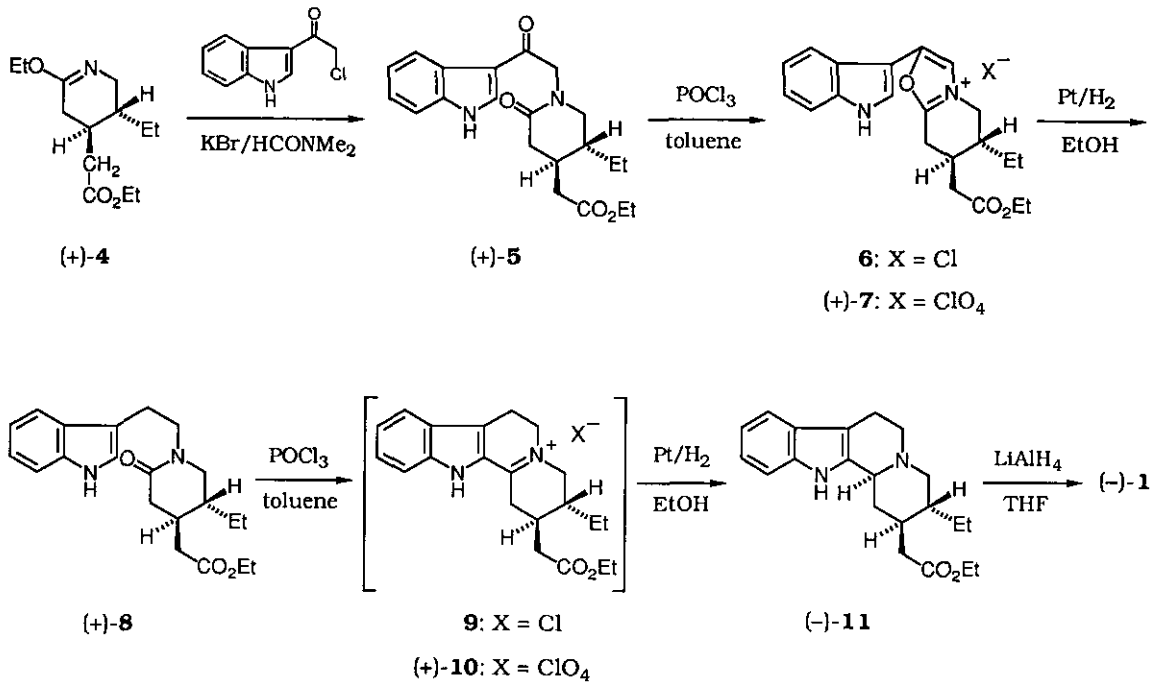


(–)-**2**: R = MeO

(–)-**3**: R = H

(Apocynaceae);[8] the trunk bark of *Ochrosia moorei* (Apocynaceae);[9] the root bark and trunk bark of *Aspidosperma marcgravianum*;[10] the roots of *Rhazya stricta* Decsne. (Apocynaceae);[11] the stem bark of *Strychnos johnsonii* Hutch *et* M. B. Mass (Loganiaceae);[12] the stem bark of *Ochrosia alyxioides* Guillaumin;[13] and the aerial part of *Aspidosperma oblongum*.[14] Semisynthetic (–)-**1** has been prepared from various alkaloids such as dihydrocorynantheine,[15] geissoschizol,[16] quinine,[17] ajmalicine,[18] and guettardine.[19] In 1985, Suzuki *et al.*[20] reported a milligram scale synthesis of (–)-**1** starting from (*R*)-1,2-isopropylideneglyceraldehyde. This has been the only total synthesis of (–)-**1** reported so far.[21] However, a repetition of any one of these preparative methods for attaining our purpose would encounter a difficulty in securing the plant materials (for extraction) or the starting alkaloids (for the partial synthesis) and/or the target alkaloid in sufficient amounts. On the other hand, our recent total syntheses of (±)-**1** (in a formal sense)[21i] and the *Neisosperma* alkaloids (–)-ochropposinine [(–)-**2**][22] and (–)-ochromianine [(–)-**3**][1,23] through the "lactim ether route"[24-26] would take the lead in designing a synthetic route to (–)-**1**. We therefore decided to follow a chiral, 10,11-unsubstituted version of these syntheses, as shown in Scheme 1, in the present study.

The initial step was coupling of the lactim ether [(+)-**4**][25b,27] with 3-(chloroacetyl)-indole, which proceeded in $HCONMe_2$ at 60°C in the presence of KBr for 72 h, giving the lactam ketone [(+)-**5**] in 68% yield. Treatment of (+)-**5** with $POCl_3$ in boiling toluene for 3 h afforded the oxazolium chloride (**6**), which was characterized as the crystalline perchlorate salt [(+)-**7**]. The crude chloride salt (**6**) was then reduced by catalytic hydrogenation (Pt/H_2, EtOH, 1 atm, room temperature, 3 h) to furnish the lactam [(+)-**8**] in 52% overall yield [from (+)-**5**]. Conversion of (+)-**8** into the tetracyclic ester [(–)-**11**] through the quaternary iminium salt (**9**) [characterized as the crystalline perchlorate salt [(+)-**10**]] was effected in 91% overall yield by means of Bischler–Napieralski cyclization ($POCl_3$, boiling toluene, 1 h) followed by catalytic hydrogenation (Pt/H_2, EtOH, 1 atm, room temperature, 1 h). The hydrogen at C(3) of (–)-**11** was assigned the α configuration by the analogy with catalytic hydrogenation of similar systems,[28] and the appearance of absorption bands, attributable to a *trans*-quinolizidine ring,[29] in the ir spectrum of (–)-**11** in $CHCl_3$ supported the correctness of this



Scheme1

assignment. On reduction with $LiAlH_4$ in tetrahydrofuran (THF) at room temperature for 30 min, (–)-**11** produced the desired alkaloid [(–)-**1**] in quantitative yield. The correctness of the structure of the synthetic (–)-**1** was confirmed by comparison of its melting point, specific rotation, and spectral data with those reported for authentic samples of natural and semisynthetic origin.

In conclusion, the above results represent an alternative, total synthesis of (–)-dihydrocorynantheol [(–)-**1**] since the starting lactim ether [(+)-**4**] is easily available not only by partially synthetic means [from the major *Cinchona* alkaloids (*e. g.*, cinchonine) through cincholoipon ethyl ester][25b] but also by totally synthetic means.[27] This new synthetic route to (–)-**1**, adaptable to its preparation on a gram-size scale, exemplifies the usefulness of our "lactim ether route"[22-26] for chiral syntheses of the *Corynanthe*-type indoloquinolizidine alkaloids. After completion of the present work, Fukumoto's group[30] has reported yet another total synthesis of (–)-**1**, together with a semisynthetic route from yohimbine.

EXPERIMENTAL

General Notes All melting points were taken on 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. See refs. 1 and 22b for details of chromatography, 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, m = multiplet, q = quartet, s = singlet, sh = shoulder, t = triplet.

(4*R*,5*R*)-5-Ethyl-1-[2-(1*H*-indol-3-yl)-2-oxoethyl]-2-oxo-4-piperidineacetic Acid Ethyl Ester [(+)-5]. A mixture of (+)-**4**[25b,27] (2.76 g, 11.4 mmol), 3-(chloroacetyl)indole[31] (2.30 g, 11.9 mmol), and KBr (3.37 g, 28.3 mmol) in $HCONMe_2$ (14 ml) was stirred at 60°C for 72 h. The reaction mixture was concentrated *in vacuo*, and the residue was partitioned by extraction with a mixture of H_2O (120 ml) and CH_2Cl_2 (120 ml). 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 (3.98 g). Purification of the oil by flash chromatography[32] (silica gel, AcOEt) afforded (+)-**5** (2.86 g, 68%) as a faintly orangy solid, mp 140–141.5°C. Recrystallization from AcOEt yielded an analytical sample as colorless needles, mp 146–147°C; $[\alpha]_D^{24}$ +38.0° (*c* 0.498, EtOH); ms *m/z*: 370 (M^+); uv λ_{max} (EtOH) 241 nm (ε 13800), 260.5 (sh) (9400), 298 (13600); ir ν_{max} (Nujol) cm^{-1}: 3180 (NH), 1727 (ester CO), 1660 (ArCO), 1620 (lactam CO); ^1H nmr ($CDCl_3$) δ: 0.93 (3H, t, *J* = 7 Hz, CCH_2Me), 1.27 (3H, t, *J* = 7 Hz, OCH_2Me), 1.3–3.6 [10H, m, CCH_2Me, C(3)-H's, C(4)-H, C(5)-H, C(6)-H's, and CH_2CO_2Et], 4.15 (2H, q, *J* = 7 Hz, OCH_2Me), 4.50 (2H, s, $COCH_2N$), 7.1–7.4 [3H, m, C(5')-H, C(6')-H, and C(7')-H], 7.77 [1H, d, *J* = 3 Hz, C(2')-H], 8.1–8.3 [1H, m, C(4')-H], 9.93 (1H, br, NH).[33] *Anal.* Calcd for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07; N, 7.56. Found: C, 68.23; H, 7.27; N, 7.32. The uv and ^1H nmr spectra of this sample were virtually identical with those of (±)-**5**.[21i]

(6*R*,7*R*)-7-(2-Ethoxy-2-oxoethyl)-6-ethyl-2-(1*H*-indol-3-yl)-5,6,7,8-tetrahydrooxazolo-[3,2-*a*]pyridinium Chloride (6). A mixture of (+)-**5** (1.48 g, 4.0 mmol) and $POCl_3$ (12.3 g, 80.2 mmol) in dry toluene (100 ml) was heated under reflux in an atmosphere of N_2

for 3 h. The reaction mixture was concentrated *in vacuo*, and the residue was washed with hexane (4 × 3 ml) to leave crude **6** (2.24 g) as a reddish purple solid. This sample was directly used in the next hydrogenation step without further purification.

(6*R*,7*R*)-7-(2-Ethoxy-2-oxoethyl)-6-ethyl-2-(1*H*-indol-3-yl)-5,6,7,8-tetrahydrooxazolo-[3,2-*a*]pyridinium Perchlorate [(+)-7]. A small sample (*ca.* 0.5 mmol) of crude **6** was triturated with a solution of $NaClO_4 \cdot H_2O$ (140 mg, 1 mmol) in H_2O (7 ml). The dark brown gum that resulted was filtered off, washed with H_2O, then dried, and triturated with hexane to give crude (+)-**7** as a brown solid. Recrystallization of the solid from $CHCl_3$ furnished an analytical sample as colorless needles, mp 131–132°C; $[\alpha]_D^{26}$ +66.4° (*c* 0.503, EtOH); uv λ_{max} (EtOH) 241.5 nm (sh) (ε 12500), 249 (sh) (10900), 308 (15500); ir ν_{max} (Nujol) cm^{-1}: 3315 (NH), 1722 (ester CO), 1657 (C=N$^+$), 1625 (C=C); ^1H nmr (Me_2SO-d_6) δ: 0.95 (3H, t, *J* = 7 Hz, CCH_2Me), 1.23 (3H, t, *J* = 7 Hz, OCH_2Me), 1.35–4.45 [10H, m, CCH_2Me, C(5)-H's, C(6)-H, C(7)-H, C(8)-H's, and CH_2CO_2Et], 4.13 (2H, q, *J* = 7 Hz, OCH_2Me), 7.15–7.9 [4H, m, C(4')-H, C(5')-H, C(6')-H, and C(7')-H], 8.07 [1H, d, *J* = 2.5 Hz, C(2')-H], 8.30 [1H, s, C(3)-H], 11.98 (1H, br, NH).[33] *Anal.* Calcd for $C_{21}H_{25}N_2O_7Cl$: C, 55.69; H, 5.56; N, 6.19. Found: C, 55.43; H, 5.60; N, 6.08.

(4*R*,5*R*)-5-Ethyl-1-[2-(1*H*-indol-3-yl)ethyl]-2-oxo-4-piperidineacetic Acid Ethyl Ester [(+)-8]. A solution of crude **6** (*vide supra*) (2.24 g) in EtOH (165 ml) was hydrogenated over Adams catalyst (315 mg) at atmospheric pressure and room temperature for 3 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 (80 ml) and CH_2Cl_2 (80 ml). The CH_2Cl_2 extracts were washed successively with H_2O and saturated aqueous NaCl, dried, and concentrated to leave a brown oil (1.25 g). Purification of the oil by flash chromatography[32] [silica gel, AcOEt–hexane (5 : 1, v/v)] gave (+)-**8** [737 mg, 52% overall yield from (+)-**5**] as a faintly brownish solid, mp 121–123.5°C. Recrystallization of the solid from AcOEt–hexane (1 : 1, v/v) yielded an analytical sample of (+)-**8** as almost colorless prisms, mp 124.5–125.5°C; $[\alpha]_D^{17}$ +86.2° (*c* 0.499, EtOH); ms *m/z*: 356 (M$^+$); uv λ_{max} (EtOH) 274.5 nm (sh) (ε 5400), 282.5 (6000), 291 (5180); ir ν_{max} (Nujol) cm^{-1}: 3155 (NH), 1725 (ester CO), 1620 (lactam CO); ^1H nmr ($CDCl_3$) δ: 0.75

(3H, t, J = 7 Hz, CCH_2Me), 1.26 (3H, t, J = 7 Hz, OCH_2Me), 1.05–3.3 [12H, m, CCH_2Me, CH_2Ar, C(3)-H's, C(4)-H, C(5)-H, C(6)-H's, and CH_2CO_2Et], 3.55–3.8 (2H, m, CH_2CH_2Ar), 4.13 (2H, q, J = 7 Hz, OCH_2Me), 7.0–7.7 (5H, m, aromatic protons), 8.11 (1H, br, NH). *Anal.* Calcd for $C_{21}H_{28}N_2O_3$: C, 70.76; H, 7.92; N, 7.86. Found: C, 70.80; H, 7.96; N, 7.64. The uv and ^1H nmr spectra of this sample were virtually identical with those of (±)-**8**.[21i]

3,4-Didehydro-17-ethoxy-17-oxocorynanium Chloride (9). A mixture of (+)-**8** (535 mg, 1.5 mmol) and $POCl_3$ (1.38 g, 9.0 mmol) in dry toluene (9 ml) was heated under reflux in an atmosphere of N_2 for 1 h. After cooling, the reaction mixture was concentrated *in vacuo*, and the residue was partitioned by extraction with a mixture of $CHCl_3$ (40 ml) and H_2O (15 ml). The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave crude **9** (622 mg) as a brown glass. This sample was directly used in the next hydrogenation step without further purification.

3,4-Didehydro-17-ethoxy-17-oxocorynanium Perchlorate [(+)-10]. A small sample (127 mg) of crude **9** was dissolved in MeOH (1 ml), and a solution of $NaClO_4 \cdot H_2O$ (126 mg, 0.897 mmol) in MeOH (0.5 ml) was added. The yellowish crystals that deposited were filtered off, washed successively with MeOH (0.5 ml) and H_2O (2 ml), and dried to give (+)-**10** [121 mg, 92% overall yield from (+)-**8**], mp 183.5–185°C (decomp). Recrystallization from MeOH–ether (2 : 1, v/v) provided an analytical sample as almost colorless needles, mp 193.5–194.5°C (decomp); $[\alpha]_D^{23}$ +84.0° (*c* 0.499, MeOH); uv λ_{max} (EtOH) 246 nm (ε 10600), 354 (19200); ir ν_{max} (Nujol) cm^{-1}: 3270 (NH), 1728 (ester CO), 1643 (C=N$^+$); ^1H nmr (Me_2SO-d_6) δ: 0.92 (3H, t, J = 7 Hz, CCH_2Me), 1.23 (3H, t, J = 7 Hz, OCH_2Me), 1.3–4.1 [14H, m, CCH_2Me, C(5)-H's, C(6)-H's, C(14)-H's, C(15)-H, C(20)-H, C(21)-H's, and C(16)-H's], 4.14 (2H, q, J = 7 Hz, OCH_2Me), 7.05–7.8 (4H, m, aromatic protons), 12.25 (1H, br, NH). *Anal.* Calcd for $C_{21}H_{27}N_2O_6Cl$: C, 57.47; H, 6.20; N, 6.38. Found: C, 57.24; H, 6.20; N, 6.38.

Corynan-17-oic Acid Ethyl Ester [(–)-11]. A solution of crude **9** (*vide supra*) (622 mg) in EtOH (60 ml) was hydrogenated over Adams catalyst (60 mg) at atmospheric pressure

and room temperature for 1 h. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* to leave an oil, which was dissolved in H_2O (100 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 saturated aqueous NaCl, dried, and concentrated to leave a dark greenish glass (492 mg). Purification of the glass by flash chromatography[32] [silica gel, AcOEt–hexane (1 : 3, v/v)] furnished (–)-**11** [464 mg, 91% overall yield from (+)-**8**] as a faintly yellowish glass (lit.,[34] mp 54–55°C); $[\alpha]_D^{24}$ –4.6° (*c* 0.521, EtOH) [lit.,[34] $[\alpha]_D^{25}$ –12° (*c* and solvent unspecified)]; ms *m/z*: 340 (M^+); uv λ_{max} (EtOH) 225.5 nm (ε 36200), 274.5 (sh) (7000), 282 (7440), 290 (6250); ir ν_{max} ($CHCl_3$) cm^{-1}: 3475 (free NH), 3375 (associated NH), 2805, 2755 (*trans*-quinolizidine ring[29]), 1724 (ester CO); ^1H nmr ($CDCl_3$) δ: 0.92 (3H, t, *J* = 7 Hz, CCH_2Me), 1.29 (3H, t, *J* = 7 Hz, OCH_2Me), 1.1–3.35 [15H, m, CCH_2Me, C(3)-H, C(5)-H's, C(6)-H's, C(14)-H's, C(15)-H, C(20)-H, C(21)-H's, and C(16)-H's], 4.18 (2H, q, *J* = 7 Hz, OCH_2Me), 6.95–7.55 (4H, m, aromatic protons), 7.80 (1H, br, NH). The ^1H nmr and mass spectral data were in agreement with those[34] reported for authentic (–)-**11**. In an attempt to crystallize the above sample, however, it turned dark.

Corynan-17-ol (Dihydrocorynantheol) [(–)-1]. A solution of (–)-**11** (447 mg, 1.31 mmol) in dry tetrahydrofuran (THF) (9 ml) was added dropwise to a stirred, ice-cooled suspension of $LiAlH_4$ (149 mg, 3.93 mmol) in dry THF (9 ml) over a period of 15 min. After the resulting mixture had been stirred at room temperature for 30 min, THF (1 ml), H_2O (0.1 ml), 10% aqueous NaOH (0.1 ml), and H_2O (0.2 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 (30 ml). The filtrate and washings were combined, dried over anhydrous K_2CO_3, and concentrated to leave (–)-**1** (390 mg, 100%) as a yellowish solid, mp 178.5–182°C. Recrystallization of the solid from AcOEt–hexane (1 : 1, v/v) yielded an analytical sample as colorless needles, mp 184.5–186°C (lit., mp 181–183°C;[3] 185–187°C;[16] 184–185°C[17]); $[\alpha]_D^{21}$ –35.4° (*c* 0.486, pyridine) [lit., $[\alpha]_D^{27}$ –34° (*c* 0.47, pyridine);[3] $[\alpha]_D^{23}$ –37±2° (*c* 0.938, pyridine)[16]]; $[\alpha]_D^{22}$ –14.2° (*c* 0.921, $CHCl_3$);[35] $[\alpha]_D^{23}$ –13.0° [*c* 0.508, $CHCl_3$–EtOH

(100 : 1, v/v)]; ms *m/z*: 298 (M^+); uv λ_{max} (EtOH) 225.5 nm (ε 38100), 273.5 (sh) (7340), 282 (7820), 289.5 (6530); ir ν_{max} ($CHCl_3$) cm^{-1}: 3625 (OH), 3480 (NH), 3295 (associated OH and NH), 2810, 2755 (*trans*-quinolizidine ring[29]); ^1H nmr ($CDCl_3$) δ: 0.92 [3H, t, J = 6.5 Hz, C(18)-H's], 1.61 (1H, br, OH), 1.05–3.3 [15H, m, C(14)-H's, C(15)-H, C(16)-H's, C(19)-H's, C(20)-H, C(3)-H, C(5)-H's, C(6)-H's, and C(21)-H's], 3.65–3.85 [2H, m, C(17)-H's], 7.0–7.55 (4H, m, aromatic protons), 8.80 (1H, br, NH). *Anal.* Calcd for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.32; H, 8.82; N, 9.35. The uv, ir, ^1H nmr, and mass spectral data were virtually identical with those[16,17,20] reported for authentic (–)-**1**.

ACKNOWLEDGMENT

We are pleased to acknowledge the support of this work by a grant from the Japan Research Foundation for Optically Active Compounds.

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Received, 20th December, 1990