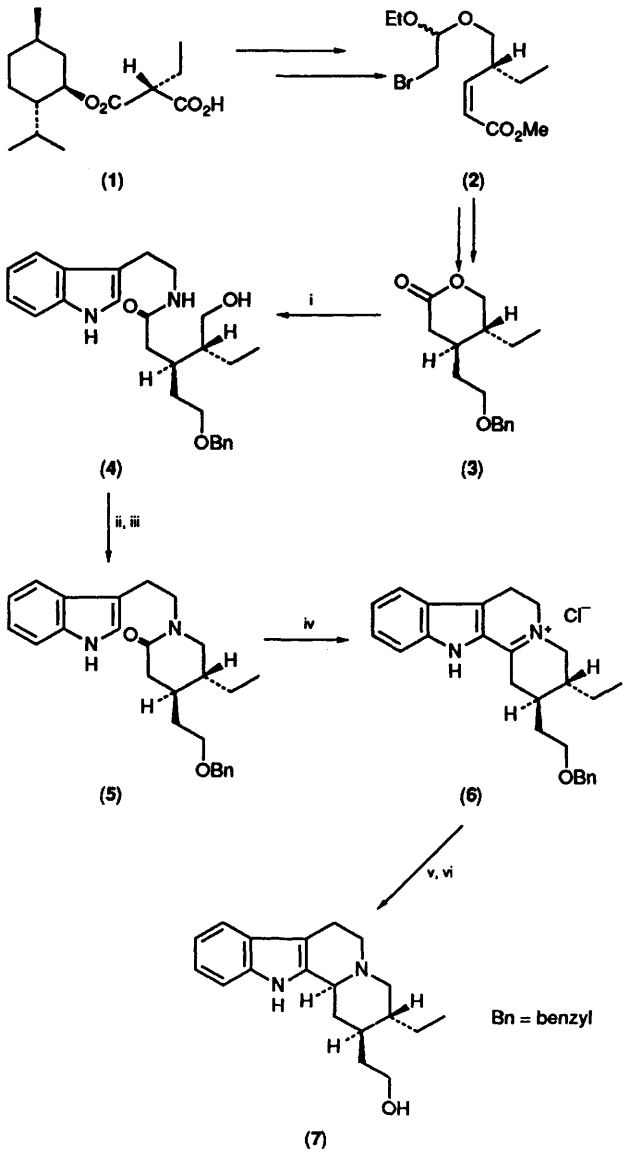
Homochiral Syntheses of (−)-Dihydrocorynantheol

Masataka Ihara, Nobuaki Taniguchi, Ken Yasui, and Keiichiro Fukumoto *
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

A Corynanthe-type indole alkaloid, (−)-dihydrocorynantheol (**7**), was enantioselectively synthesized from (+)-(4*S*,5*R*)-4-(2-benzyloxyethyl)-5-ethyl-3,4,5,6-tetrahydro-2-pyrone (**3**), derived from ethylmalonic acid. The synthetic compound (**7**) was identical in all respects with a sample prepared from yohimbine (**8**).

Recently, we developed asymmetric syntheses of chiral propane-1,3-diols by way of chiral half-esters of monoalkylmalonic acids, and discovered the diastereoselective formation of a single isomer of the menthyl half-ester (**1**) by crystallisation-induced asymmetric transformation.[1] The half-ester (**1**) was enantioselectively converted, through radical cyclisation of the (*Z*)-α,β-unsaturated ester (**2**), into the optically pure lactone (**3**), which was transformed into several ipecacuanha alkaloids.[2] As an extension of this work, the lactone (**3**) was further transformed into a Corynanthe-type indole alkaloid, (−)-dihydrocorynantheol (**7**).[3–5] Preparation of the same enantiomer (**7**) was also carried out starting from natural yohimbine (**8**). We report here homochiral syntheses of (−)-dihydrocorynantheol (**7**).



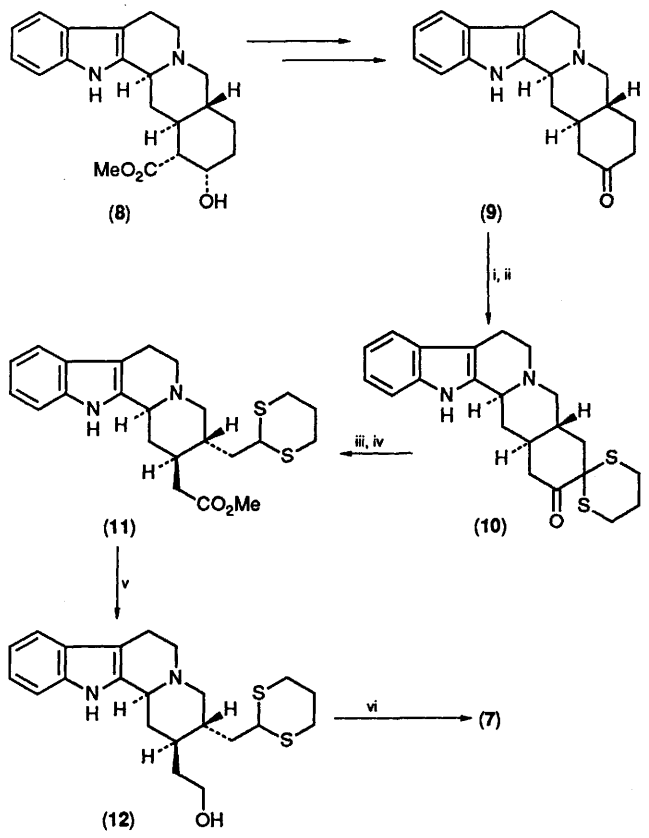
Scheme 1. *Reagents:* i, tryptamine; ii, MsCl, Et_3N; iii, KH, 18-crown-6; iv, $POCl_3$; v, $NaBH_4$; vi, H_2, $PdCl_2$.

Condensation of the lactone (**3**) with tryptamine gave the hydroxy amide (**4**), $[\alpha]_D^{25}$ +5.64° ($CHCl_3$), in 91% yield. Since reaction of compound (**4**) with phosphorus trichloride oxide did not produce the expected cyclised product (**6**), the amide (**4**) was transformed into the lactam (**5**), $[\alpha]_D^{24}$ +16.97° ($CHCl_3$) in 70% overall yield by successive methanesulphonylation followed by ring formation using potassium hydride in the presence of 18-crown-6. Treatment of the lactam (**5**) with phosphorus trichloride oxide in acetonitrile provided the iminium salt (**6**), which was reduced with sodium borohydride to the corresponding hexahydroquinolizidine, in 97% overall yield, as a mixture of two diastereoisomers. Catalytic hydrogenation of the mixture with palladium(II) dichloride under hydrogen atmosphere in a mixture of chloroform and methanol gave rise to debenzylation accompanied by isomerisation[4a] to furnish (−)-dihydrocoryanantheol (**7**), m.p. 178–181 °C; $[\alpha]_D^{23}$ −20.41° ($CHCl_3$) {lit.,[3a] m.p. 181–183 °C; $[\alpha]_D^{27}$ −19° ($CHCl_3$)}, as a single isomer in 77% yield (Scheme 1).

The same enantiomer (**7**) of the alkaloid was readily synthesized from yohimbine (**8**) as follows. The yohimbone (**9**),[6] derived from yohimbine (**8**), was first converted into the enamine, which was then treated with propane-1,3-dithiol di(toluene-*p*-sulphonate)[7] in the presence of triethylamine. Treatment of the dithioacetal (**10**), $[\alpha]_D^{25}$ −25.3° ($CHCl_3$), obtained in 97% overall yield from ketone (**9**), with potassium hydroxide in refluxing 2-methylpropan-2-ol[8] afforded the carboxylic acid, which was converted into the corresponding methyl ester (**11**), $[\alpha]_D^{26}$ +25.3° ($CHCl_3$), in 52% overall yield for two steps. Reduction of ester (**11**) with lithium aluminium hydride produced quantitatively the alcohol (**12**), $[\alpha]_D^{25}$ +4.65° ($CHCl_3$), which was further reduced with W-2 Raney nickel to afford (−)-dihydrocorynantheol (**7**) (Scheme 2). All physical properties of the product (**7**), obtained in 98% yield, were identical with those of the first specimen. Thus, homochiral syntheses of (−)-dihydrocorynantheol (**7**) were accomplished starting from both the key lactone (**3**) and yohimbine (**8**).

Experimental

General Methods.—M.p.s were measured on a Yanako micro melting-point apparatus and are uncorrected. IR spectra were recorded for $CHCl_3$ solutions on a Hitachi 260-10 spectrophotometer. NMR spectra were measured for $CDCl_3$ solutions



Scheme 2. *Reagents:* i, pyrrolidine; ii, $TsS[CH_2]_3STs$, Et_3N; iii, KOH; iv, MeOH, conc. H_2SO_4; v, $LiAlH_4$; vi, Raney Ni.

with JEOL JNM-PMX-60, JEOL-FX-90A, and JNM-GX-500 spectrometers. Chemical shifts are reported relative to internal $SiMe_4$. Mass spectra were taken on JEOL-JMS-O1SG-2 and JEOL-DX-300 spectrometers. Optical rotations were determined on a JASCO-DIP-340 polarimeter. All new compounds described in the Experimental section were homogeneous on TLC and HPLC.

(3S,4R)-(+)-3-(2-*Benzyloxyethyl*)-4-*hydroxymethyl*-N-[2-(*indol*-3-*yl*)*ethyl*]*hexanamide* (**4**).—A mixture of the lactone (**3**)[2] (270.9 mg, 1.03 mmol) and tryptamine (412 mg, 2.57 mmol) in dry toluene (5 ml) was heated under reflux for 6 h. After removal of the solvent, the residue was heated at 130 °C for an additional 3 h and then diluted with toluene. After evaporation, silica gel column chromatography of the residue with $CHCl_3$–AcOEt (1:4, v/v) as eluant gave the *amide* (**4**) (396.7 mg, 91%) as an oil (Found: M^+, 422.2549. $C_{26}H_{34}N_2O_3$ requires M, 422.2570); $[\alpha]_D^{25}$ +5.64° (*c* 4.56, $CHCl_3$); ν_{max} 3 550–3 150 (OH and NH) and 1 660 cm^{-1} (C=O); δ_H(90 MHz) 0.71–1.02 (3 H, m, CH_2Me), 1.97–2.28 (2 H, m, CH_2CONH), 2.63–3.00 (3 H, m, CH_2Ar and OH), 3.29–3.71 (6 H, m, 2 × CH_2O and CH_2N), 4.40 (2 H, s, OCH_2Ph), 5.81–6.10 (1 H, m, NHCO), 6.90–7.65 (10 H, m, 5 × ArH and Ph), and 8.14–8.33 (1 H, br s, NH).

(4S,5R)-(+)-4-(2-*Benzyloxyethyl*)-5-*ethyl*-N-[2-(*indol*-3-*yl*)*ethyl*]*piperidin*-2-*one* (**5**).—To a stirred solution of the above amide (**4**) (68.6 mg, 0.162 mmol) in dry benzene (5 ml) at 5 °C were added a solution of Et_3N (0.025 ml, 0.18 mmol) in dry benzene (0.25 ml) and a solution of methanesulphonyl chloride (0.013 ml, 0.17 mmol) in dry benzene (0.1 ml). After being stirred at the same temperature for 0.5 h, the reaction mixture was diluted with benzene, washed successively with saturated aq. $NaHCO_3$ (×2), 1% HCl, and water, and then dried (Na_2SO_4), and the solvent was evaporated off under protection from moisture. Water was completely removed by azeotropic distillation (×2) using benzene. The resulting mesyl ester was used for the next reaction without further purification.

To a stirred suspension of 18-crown-6 (8.0 mg, 0.03 mmol) and KH (65 mg, 1.6 mmol) in dry 1,2-dimethoxyethane (DME) (5 ml) at 0 °C was added slowly a solution of the above mesyl ester in dry DME (2 ml). The mixture was stirred at room temperature for 0.5 h, poured into saturated aq. NH_4Cl, and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated to give a residue. Silica gel column chromatography of the residue with benzene–acetone (85:15, v/v) as eluant afforded the *lactam* (**5**) (46.1 mg, 70% yield for two steps) as a viscous oil (Found: M^+, 404.2473. $C_{26}H_{32}N_2O_2$ requires M, 404.2464); $[\alpha]_D^{24}$ +16.97° (*c* 2.52, $CHCl_3$); ν_{max} 1 620 cm^{-1} (C=O); δ_H(500 MHz) 0.74 (3 H, t, *J* 7.6 Hz, CH_2Me), 2.07 (1 H, dd, *J* 8.7 and 16.3 Hz, $CHHCON$), 2.53 (1 H, dd, *J* 8.7 and 16.3 Hz, $>CHHCON$), 2.87 (1 H, dd, *J* 8.7 and 13.6 Hz, $>CHCHHNCO$), 3.03 (2 H, t, *J* 7.6 Hz, CH_2Ar), 3.16 (1 H, dd, *J* 5.4 and 13.6 Hz, $CHCHHNCO$), 3.40–3.75 (4 H, m, CH_2CH_2N and CH_2O), 4.49 (2 H, s, OCH_2Ph), 7.00–7.71 (10 H, m, 5 × ArH and Ph), and 8.10–8.22 (1 H, br s, NH).

(2R,3R,12bS)-(−)-3-*Ethyl*-2-(2-*hydroxyethyl*)-1,2,3,4,6,7,12,12b-*octahydroindolo*[2,3-a]*quinolizine* (**7**) (*Dihydrocorynantheol*).—(*a*) A mixture of the lactam (**5**) (15.1 mg, 0.0373 mmol) and freshly distilled $POCl_3$ (0.2 ml, 2.15 mmol) in dry MeCN (2 ml) was heated under reflux for 2.5 h under protection from moisture; during the reaction hydrogen chloride gas was evolved. After removal of the solvent under reduced pressure, the reagents were removed by azeotropic distillation with toluene (×3) to give the iminium salt (**6**), which was used for the next reaction without further purification.

To a stirred solution of the above salt in distilled MeOH (2 ml) at 0 °C was added $NaBH_4$ (12 mg, 0.32 mmol). After being stirred at the same temperature for 1 h, the reaction mixture was poured into water, and the mixture was extracted with $CHCl_3$. The combined extracts were washed with brine, dried (K_2CO_3), and evaporated. Silica gel column chromatography of the residue with $CHCl_3$–MeOH (95:5, v/v) as eluant afforded quinolizidines (14 mg, 97%) as a yellowish oil.

A solution of the above product (14 mg, 0.036 mmol) in a mixture of distilled MeOH (2 ml) and distilled $CHCl_3$ (0.4 ml) was stirred with $PdCl_2$ (10 mg, 0.057 mmol) at room temperature under hydrogen (1 atm) for 40 min. The reaction mixture was poured into 10% aq. ammonium hydroxide. After extraction with $CHCl_3$, the combined extracts were washed with brine, dried (K_2CO_3), and evaporated to give a residue, which was subjected to silica gel column chromatography. Elution with $CHCl_3$–MeOH (96:4, v/v) afforded (−)-dihydrocorynantheol (**7**) (8.3 mg, 77%) as crystals, m.p. 178–181 °C (lit.,[3a] 181–183 °C) (Found: M^+, 298.2044. Calc. for $C_{19}H_{26}N_2O$: M, 298.2045); $[\alpha]_D^{23}$ −20.41° (*c* 0.25, $CHCl_3$) {lit.,[3a] $[\alpha]_D^{27}$ −19° (*c* 1.02, $CHCl_3$)}; ν_{max} 3 270 (OH) and 2 800–2 700 cm^{-1} (*trans*-quinolizidine bands); δ_H(500 MHz) 0.87–0.99 (3 H, m, CH_2Me), 2.56–2.78 (2 H, m, CH_2N), 2.98–3.25 (3 H, m, CH_2N and CHN), 3.70–3.84 (2 H, m, CH_2O), 7.04–7.49 (4 H, m, 4 × ArH), and 7.80–7.91 (1 H, br s, NH).

(*b*) To a solution of the dithioacetal (**12**) (see below) (12.3 mg, 0.0305 mmol) in acetone (5 ml) was added W-2 Raney nickel (1 g) under N_2. The mixture was heated under reflux for 18 h. The catalyst was removed by filtration, and the filtrate was evaporated under reduced pressure. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (19:1, v/v) as eluant to give (−)-dihydrocorynantheol (**7**) (8.9 mg, 98%) as an oil, whose physical properties were identical with those of the compound prepared by method (*a*).

(−)-18,18-*Trimethylenedithioyohimban*-17-*one* (**10**).—A solution of yohimbone (**9**)[6] (662 mg, 2.25 mmol) and pyrrolidine (0.26 ml, 3.15 mmol) in dry benzene (30 ml) was heated under N_2 for 3 h in a flask equipped with a Dean–Stark trap for azeotropic removal of water. Removal of the solvent gave the enamine. A solution of the above enamine, propane-1,3-dithiol di(toluene-*p*-sulphonate)[7] (1.03 g, 2.48 mmol), and Et_3N (1 ml) in dry MeCN (30 ml) was heated under reflux for 14 h under N_2. After removal of the solvent, a mixture of 1.2M-HCl (5 ml) and $CHCl_3$ (5 ml) was added to the residue and then the mixture was stirred for 10 min at room temperature. The reaction mixture was basified with 10% aq. ammonia and extracted thoroughly with $CHCl_3$. The combined extracts were washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with $CHCl_3$ as eluant to afford the *dithioacetal* (**10**) (868 mg, 97%) as an oil (Found: M^+, 398.1479. $C_{22}H_{26}N_2OS_2$ requires M, 398.1486); $[\alpha]_D^{25}$ −25.3° (*c* 0.64, $CHCl_3$); ν_{max} 3 470 (NH) and 1 705 cm^{-1} (C=O); δ_H(90 MHz) 1.22–3.91 (21 H, m, 9 × CH_2 and 3 × CH), 6.91–7.56 (4 H, m, 4 × ArH), and 7.66–7.90 (1 H, br s, NH); *m*/*z* 398 (M^+).

(2R,3S,12bS)-(+)-*Methyl* {3-[(1,3-*Dithian*-2-*yl*)*methyl*]-1,2,3,4,6,7,12,12b-*octahydroindolo*[2,3-a]*quinolizin*-2-*yl*}*acetate* (**11**).—To a solution of the dithioacetal (**10**) (554.5 mg, 1.39 mmol) in dry 2-methylpropan-2-ol (20 ml) was added KOH (782 mg, 13.9 mmol) and the mixture was heated under reflux for 2.5 h. After evaporation of the solvent, the residue was dissolved in MeOH (30 ml) and acidified with conc. H_2SO_4 (0.6 ml). The resulting mixture was stirred for 7 h at room temperature and for 3.5 h at 50 °C. After concentration, the residue was basified with 10% aq. ammonia and extracted thoroughly with $CHCl_3$. The extracts were washed with water, dried (Na_2SO_4), and evaporated. The residue was subjected to silica gel column chromatography with $CHCl_3$–AcOEt (19:1, v/v) as eluant to afford the *ester* (**11**) (312.6 mg, 52%) as a yellowish oil (Found: M^+, 430.1728. $C_{23}H_{30}N_2O_2S_2$ requires M, 430.1749); $[\alpha]_D^{26}$ +25.3° (*c* 0.64, $CHCl_3$); ν_{max} 3 470 (NH) and 1 730 cm^{-1} (C=O); δ_H(90 MHz) 1.05–3.34 (21 H, m, 9 × CH_2 and 3 × CH), 3.73 (3 H, s, OMe), 4.03 (1 H, dd, *J* 4.5 and 9.8 Hz, CHS_2), 6.93–7.54 (4 H, m, 4 × ArH), and 7.70–7.93 (1 H, br s, NH); *m*/*z* 430 (M^+).

(2R,3S,12bS)-(+)-3-[(1,3-*Dithian*-2-*yl*)*methyl*]-2-(2-*hydroxyethyl*)-1,2,3,4,6,7,12,12b-*octahydroindolo*[2,3-a]*quinolizine* (**12**).—To a suspension of lithium aluminium hydride (1.8 mg, 0.047 mmol) in dry tetrahydrofuran (THF) at 0 °C (2 ml) was added under N_2 a solution of the methyl ester (**11**) (27 mg, 0.062 mmol) in dry THF (3 ml). After being stirred for 30 min, the reaction mixture was treated by successive addition of 10% aq. ammonium chloride (0.1 ml) and $CHCl_3$. After being stirred for 1 h, the mixture was filtered through Celite, dried (Na_2SO_4), and evaporated. Purification of the residue by silica gel column chromatography with $CHCl_3$–MeOH (99:1, v/v) as eluant afforded the *alcohol* (**12**) (25 mg, 100%) as a yellowish oil (Found: M^+, 402.1794. $C_{22}H_{30}N_2OS_2$ requires M, 402.1799); $[\alpha]_D^{25}$ +4.65° (*c* 0.43, $CHCl_3$); ν_{max} 3 480 (NH) and 3 300 cm^{-1} (OH); δ_H(90 MHz) 1.10–3.27 (22 H, m, 9 × CH_2, 3 × CH, and OH), 3.51–3.88 (2 H, m, CH_2OH), 3.91–4.19 (1 H, m, CHS_2), 6.95–7.75 (4 H, m, 4 × ArH), and 8.22–8.42 (1 H, br s, NH); *m*/*z* 402 (M^+).

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