Total Synthesis of γ-Lycorane

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The homophthalimide derivative was easily converted to the *cis*-octahydrophenanthridine derivative in good yield and this to γ-lycorane **1** [1].

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We have recently developed a method for the synthesis of *cis*-octahydrophenanthridine ring **4** stereoselectively from isocarbostyril derivative **3** prepared from homophthalimide **2** [2]. *cis*-Octahydrophenanthridine comprises part of the skeleton of γ-lycorane **1** derived from *Amaryllidaceae* alkaloid. The synthesis of γ-lycorane has been conducted by Sakan *et al.* [3].

Using the above method, the total synthesis of (±)-γ-lycorane from homophthalimide derivative **5** was carried out.

The starting material, 2-benzyl-6,7-methylenedioxy-homophthalimide **5** [4], was treated with methyl vinyl ketone in the presence of Triton-B to give 2-benzyl-6,7-methylenedioxy-4-(3-oxobutyl)homophthalimide **6**. Imide **6** thus obtained was ketalized in the usual manner, reduced with sodium borohydride and subsequently acidified with hydrochloric acid to give 2-benzyl-6,7-methylenedioxy-4-(3-oxobutyl)isocarbostyril **7**. The 4-substituted isocarbostyril derivative **7** was further ketalized, reduced with lithium aluminum hydride and then treated with hydrochloric acid to give the target *cis*-octahydrophenanthridine derivative **9** as the sole product.

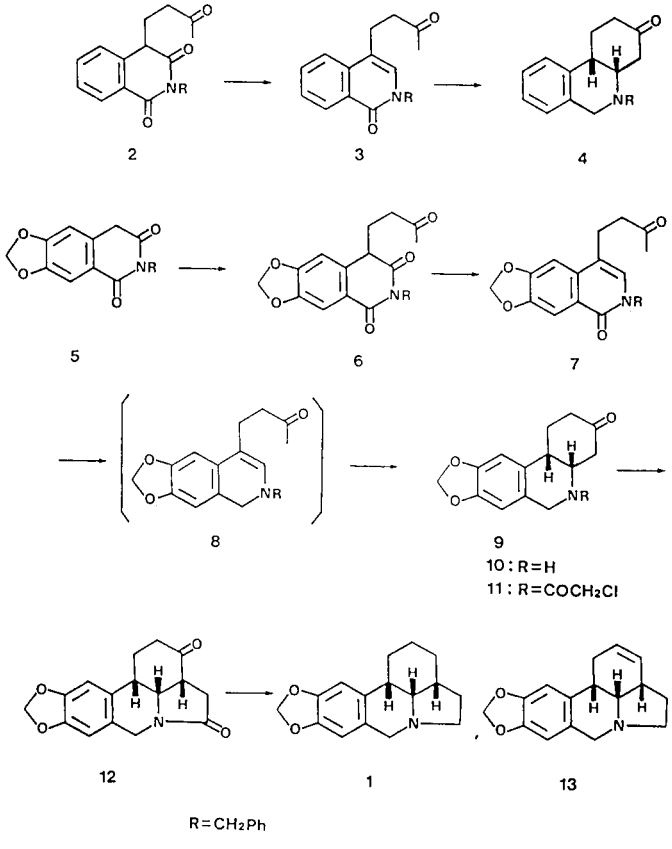
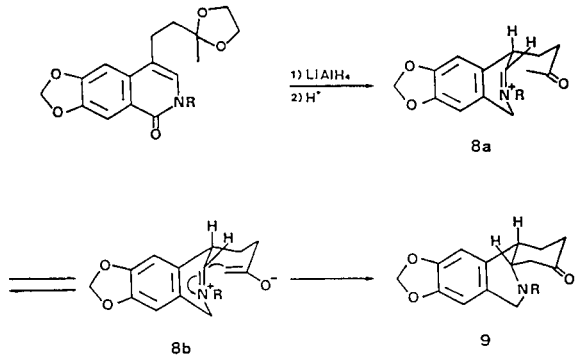


Chart 1

The stereoselective formation of the *cis*-octahydrophenanthridine skeleton was anticipated. To this end, 1,2-dihydroisoquinoline **8** was treated with hydrochloric acid to produce the C_4-protonated form **8a** which immediately underwent conversion to **8b** and then, by perpendicular attack at the C_3 position, to the stable compound **9**. These reactions are presented in Scheme 1 [5].



Scheme 1

γ-Lycorane was then synthesized from product **9**. Cleavage of the benzyl group of *cis*-octahydrophenanthridine **9** by palladium chloride gave **10**. The latter was reacted with chloroacetyl chloride in the presence of triethylamine to obtain amide **11** which, on heating with potassium *t*-butoxide in *t*-butyl alcohol, gave the pyrrolophenanthridine derivative **12** as the sole product. This, when treated with tosylhydrazine, gave tosylhydrazone which was reduced with lithium aluminum hydride to produce (±)-γ-lycorane in 70% yield and (±)-γ-Δ^2-lycorane **13** in 15% yield as the by-product.

We succeeded in synthesizing the B/C *cis*-phenanthridine ring stereoselectively from the homophthalimide de-

rivative, thus demonstrating the present method applicable to the total synthesis of (±)-γ-lycorane **1**.

EXPERIMENTAL

Instrumentation.

The ^{1}H nmr spectra were recorded on a Varian EM 390 spectrometer using tetramethylsilane as the internal standard. Infrared spectra were recorded on a Hitachi 260 spectrophotometer. Melting points were measured on a Yanagimoto micro hot stage and reported uncorrected. Mass spectra were obtained on a Hitachi RMV-7L (70 eV).

2-Benzyl-6,7-methylenedioxy-4-(3-oxobutyl)homophthalimide **6**.

Methyl vinyl ketone (7.0 g, 100 mmoles) was added dropwise to a stirred solution of 2-benzylhomophthalimide **5** (29.5 g, 100 mmoles) in aqueous acetone (acetone-water 10:1, v/v) (300 ml) in the presence of Triton-B (55 ml) at room temperature. Stirring was continued for an additional 30 minutes, and the reaction mixture was acidified with hydrochloric acid. Following removal of the solvent, the residue was extracted with methylene chloride. The extract was washed with water, dried (magnesium sulfate) and evaporated to dryness to give **6** (24 g, 65%) as colorless needles, mp 110-112° (ethanol); ir (Nujol): 1695 (N-C=O), 1653 (N-C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.00 (3H, s, $COCH_3$), 3.79 (1H, m, C_4-H), 5.10 (2H, s, N-CH_2Ph), 6.01 (2H, s, -OCH_2O-), 6.73 (1H, s, C_5-H), 7.53 (1H, s, C_8-H); ms: m/z 365 (M^+).

Anal. Calcd. for $C_{21}H_{19}NO_5$: C, 69.04; H, 5.21; N, 3.84. Found: C, 69.00; H, 5.07; N, 3.63.

2-Benzyl-6,7-methylenedioxy-4-(3-oxobutyl)isocarbostyril **7**.

A mixture of **6** (18.25 g, 50 mmoles), ethylene glycol (31 g, 500 mmoles) and *p*-toluenesulfonic acid (2 g) was refluxed in benzene (200 ml) with azeotrope distillation of the liberated water. After 3 hours, the reaction mixture was washed with water, dried (magnesium sulfate) and evaporated. The residue was dissolved in methanol (300 ml) and reduced with sodium borohydride (37.8 g, 1000 mmoles) at room temperature for 1 hour. Following removal of the solvent, the residue was acidified with 10% hydrochloric acid and extracted with chloroform. The extract was washed with water, dried (potassium carbonate) and evaporated to give **7** (14 g, 80%) as colorless needles, mp 161-163° (ethanol); ir (Nujol): 1705 (C=O), 1650 (N-C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.08 (3H, s, $COCH_3$), 2.75 (4H, m), 5.12 (2H, s, N-CH_2Ph), 6.02 (2H, s, -OCH_2O-), 6.84 (1H, s, C_5-H), 6.88 (1H, s, C_3-H), 7.80 (1H, s, C_8-H); ms: m/z 349 (M^+).

Anal. Calcd. for $C_{21}H_{19}NO_4$: C, 72.21; H, 5.44; N, 4.01. Found: C, 72.14; H, 5.48; N, 3.92.

5-Benzyl-1,2,3,4,4a,5,6,10b-octahydro-8,9-methylenedioxy-*cis*-phenanthridin-3-one **9**.

The isocarbostyril derivative **7** was converted to the corresponding ketal in the usual manner in 90% yield. To a stirred solution of lithium aluminum hydride (9.25 g, 250 mmoles) in tetrahydrofuran (150 ml) was added a solution of this ketalized compound (3.39 g, 10 mmoles) in tetrahydrofuran (100 ml) under ice cooling. Stirring was continued for 1 hour and the reaction mixture was decomposed with 10% potassium hydroxide. After removal of the inorganic precipitate, the organic layer was evaporated to give an oil which was immediately treated with 12*N* hydrochloric acid (50 ml) at 100° for 1 hour. The reaction mixture was basified with concentrated ammonium hydroxide and extracted with chloroform. The extract was washed with water, dried (potassium carbonate) and evaporated to give an oil which was purified by column chromatography on a silica gel (50 g). Elution with chloroform gave **9** (2.68 g, 80%) as colorless needles, mp 146-147.5° (ethanol); ir (Nujol): 1697 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.67 (2H, s, N-CH_2Ph), 3.59, 3.92 (2H, AB-q, J = 13 Hz, N-CH_2), 5.87 (2H, s, -OCH_2O-), 6.43 (1H, s, aromatic-H), 6.74 (1H, s, aromatic-H); ms: m/z 335 (M^+).

Anal. Calcd. for $C_{21}H_{21}NO_3$: C, 75.22; H, 6.27; N, 4.18. Found: C, 75.14; H, 6.31; N, 4.13.

1,2,3,4,4a,5,6,10b-Octahydro-8,9-methylenedioxy-*cis*-phenanthridin-3-one **10**.

Phenanthridine derivative **9** (3.35 g, 10 mmoles) in methanol (50 ml) and 12*N* hydrochloric acid (4.5 ml) was hydrogenated over palladium chloride (0.5 g) under a hydrogen atmosphere at room temperature and 1 atmosphere for 4 hours. Filtration of the mixture, washing of the residue with methanol and concentration of the combined filtrates left an oil which was basified with concentrated ammonium hydroxide and extracted with chloroform. The extract was dried (potassium carbonate) and evaporated to give **10** (2.2 g, 90%) as colorless needles, mp 138-139° (ethanol); ir (Nujol): 3280 (NH), 1695 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.49 (1H, s, 4a-H), 3.90, 4.04 (2H, AB-q, J = 15 Hz, CH_2-N), 5.88 (2H, s), 6.45 (1H, s, aromatic-H), 6.58 (1H, s, aromatic-H); ms: m/z 245 (M^+).

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.57; H, 6.12; N, 5.71. Found: C, 68.31; H, 6.14; N, 5.71.

5-Chloroacetyl-1,2,3,4,4a,5,6,10b-octahydro-8,9-methylenedioxy-*cis*-phenanthridin-3-one **11**.

A solution of chloroacetyl chloride (1.34 g, 12 mmoles) in methylene chloride (10 ml) was added to a stirred solution of amine **10** (2.45 g, 10 mmoles) and triethylamine (1.5 g, 15 mmoles) in methylene chloride (30 ml) at room temperature over a period of 1 hour. The reaction mixture was washed with water, dried (potassium carbonate) and evaporated. The remaining residue was purified by column chromatography on a silica gel (50 g). Elution was carried out with chloroform to give **11** (3.05 g, 95%) as an oil: ir (chloroform): 1710 (C=O), 1645 (N-C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.33 (1H, s, 4a-H), 4.13 (2H, s, $COCH_2Cl$), 5.96 (2H, s, -OCH_2O-), 6.64 (1H, s, aromatic-H), 6.85 (1H, s, aromatic-H); ms: m/z 321 (M^+), 323 (M^++2).

Anal. Calcd. for $C_{16}H_{16}ClNO_4$: C, 59.71; H, 5.01; N, 4.35. Found: C, 59.61; H, 4.98; N, 4.36.

(±)-γ-Lycorane-3,5-dione **12**.

A mixture of **11** (1.6 g, 5 mmoles) and potassium *t*-butoxide (0.67 g, 7 mmoles) in *t*-butyl alcohol (10 ml) was refluxed for 30 minutes. The solvent was evaporated and the residue poured into water and extracted with chloroform. The extract was washed with water, and dried (potassium carbonate) and evaporated *in vacuo* to give **12** (1.12 g, 85%) as colorless prisms, mp 255-257° (ethanol-benzene); ir (Nujol): 1700 (C=O), 1680 (N-C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 4.22, 4.65 (2H, AB-q, J = 17 Hz, CH_2-N), 5.92 (2H, s, -OCH_2O-), 6.57 (1H, s, aromatic-H), 6.65 (1H, s, aromatic-H); ms: m/z 285 (M^+).

Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.37; H, 5.30; N, 4.91. Found: C, 67.13; H, 5.37; N, 4.78.

(±)-γ-Lycorane **1** and (±)-γ-Δ^2-Lycorane **13**.

A mixture of **12** (0.713 g, 2.5 mmoles) and *p*-toluenesulfonyl hydrazide (0.558 g, 3 mmoles) in methanol (5 ml) was refluxed for 2 hours. The solvent was then evaporated to give hydrazone (0.963 g, 85%) as colorless prisms: mp 280-285° (ethanol); ir (Nujol): 3200, 1678 cm^{-1}. This product was subsequently added to a stirred solution of lithium aluminum hydride (1.0 g, 2 mmoles) in tetrahydrofuran (50 ml) under ice cooling. After 24 hours of additional stirring under refluxing, the reaction mixture was decomposed with 10% potassium hydroxide. Following removal of the inorganic precipitate, the organic layer was evaporated to give an oil which was subsequently purified by column chromatography on alumina (10 g). Elution with benzene-hexane (1:1, v/v) gave (±)-γ-lycorane **1** (0.36 g, 70%) as colorless prisms, mp 101-103° (petroleum ether) (lit [3] mp 105-106°); ir (carbon disufide): 2900, 2850, 2800, 2720 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.22, 4.02 (2H, AB-q, J = 14.5 Hz, C_7-H), 5.85 (2H, s, -OCH_2O-), 6.46 (1H, s, C_8-H), 6.58 (1H, s, C_{11}-H); ms: m/z 257 (M^+), 256 (M^+-1, base peak). These spectral data were identical with those of an authentic specimen [1].

Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.51: H, 7.31; N, 5.41

Futher elution with benzene gave (±)-γ-Δ^2-lycorane **13** (0.038 g, 15%) as colorless prisms, mp 120-123° (petroleum ether); ir (carbon disulfide): 3000, 2940, 2900, 2870, 2850, 2750 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.26, 4.03 (2H, AB-q, J = 14 Hz, C_7-H), 5.60 (1H, s, olefinic-H), 5.62 (1H, s, olefinic-H), 5.84 (2H, s, $-OCH_2O-$), 6.46 (1H, s, C_8-H), 6.53 (1H, s, C_{11}-H); ms: m/z 255 (M^+), 254 (M^+-1, base peak).

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.43; H, 6.59; N, 5.58.

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