A MODIFIED TOTAL SYNTHESIS OF (±)-LYCORINE

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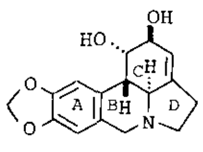
A modified total synthesis of lycorine was accomplished starting from the lactam-ester (5). Selective reduction of the lactam carbonyl of 5, followed by cyclization gave 5-oxolycorene (4). Epoxidation of 4 gave stereoselectively the α-epoxide (9). Repeated application of Sharpless method to convert epoxide into allylic alcohol and acetylation of the product gave diacetyl 5-oxolycorine (19). Lithium aluminium hydride reduction of 19 gave (±)-lycorine.

Recently, we have accomplished the first total synthesis of Amaryllidaceae alkaloids lycorine (1) and zephyranthine (2).[1] In that synthesis, the double bond on ring C of the tetracyclic six-membered lactam (3) was functionalized in a stereoselective manner elaborating these alkaloids. The tetracyclic five-membered lactam (4) with a carbonyl group on ring D is also an attractive synthetic intermediate for lycorine-type alkaloids, since it has a potency introducing functional groups not only on ring C but also on ring D. This communication presents the stereocontrolled transformation of the lactam (4) into (±)-lycorine.



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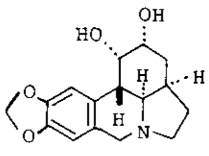

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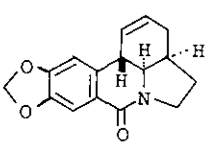

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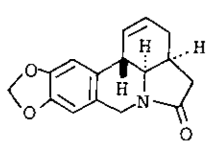
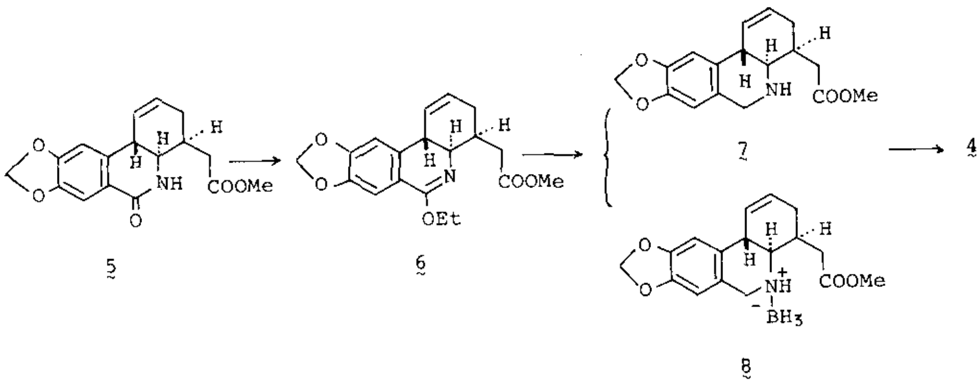


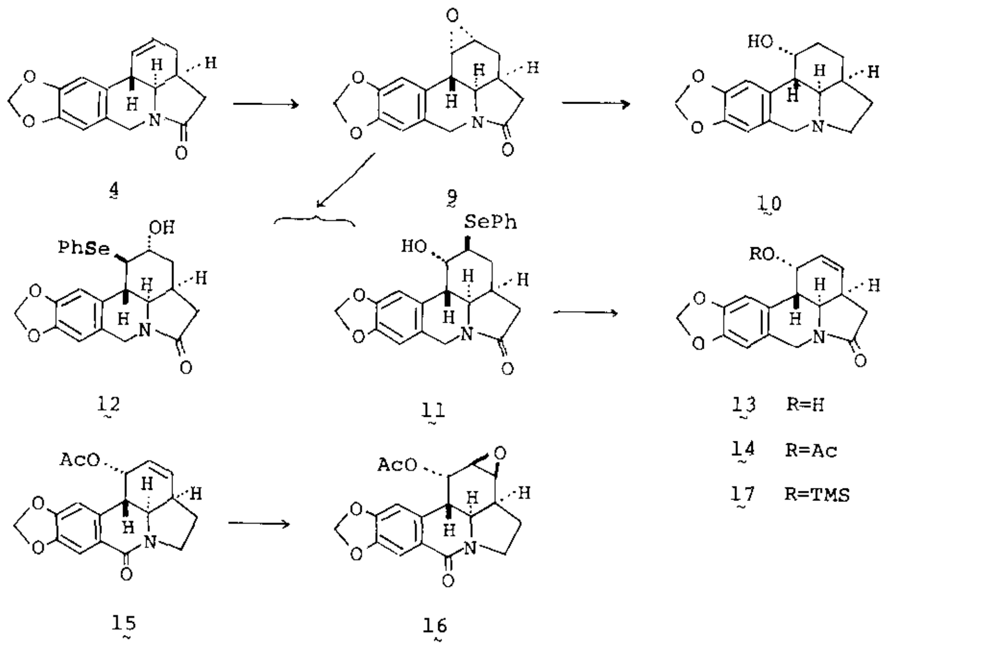
4

The conversion of the lactam-ester (5)[1] to 4 was already achieved by the selective reduction of the corresponding imidic ester (6) with the combined reagent of sodium borohydride-stannic chloride dietherate followed by cyclization of the resulting amine, though the yield was not satisfactory.[2] The yield was improved as follows. The treatment of 5 with excess Meerwein reagent in dry methylene chloride at room temperature for 18 hr. gave the imidic ester (6), m.p. 134-136°, ν 1740 (COOMe), 1640 cm^{-1} (N=C), in 67% yield. Reduction of 6 with sodium borohydride and anhydrous stannous chloride in dimethoxyethane at -60° gave a mixture of the amine (7) and borazane (8),[2] which, without separation, was heated in 5% methanolic potassium carbonate solution to give the desired lactam (4), m.p. 182-186°, ν 1685 cm^{-1} (lactam), δ 4.22, 4.98 (each 1H, d, J=18Hz, benzylic protons), in 74% yield. The *new reducing reagent* (*$NaBH_4$-$SnCl_2$*) *has some advantages to the previous reagent* ($NaBH_4$-$SnCl_4$.$2Et_2O$) in reducing an amount of sodium borohydride and in minimizing undesired side reactions. The optimum ratio of sodium borohydride to stannous chloride was 2:1.

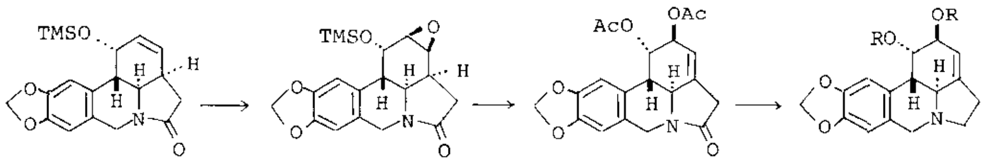


Oxidation of 4 with m-chloroperbenzoic acid in methylene chloride afforded an α-epoxide (9), m.p. 208-212°, ν 1690 cm^{-1} (lactam), in 72% yield. Lithium aluminium hydride reduction of 9 gave (±)-α-dihydrocaranine (10),[1] m.p. 179-182°, confirming α-configuration of the oxide ring in 9. In order to complete the alignment of the functional groups in ring C of lycorine, we applied the method introduced by Sharpless and his co-workers[3], which worked successfully in the previous synthesis of lycorine[1], to the epoxide (9). 9 was treated with diphenyl diselenide and sodium borohydride in ethanol to afford two regio-isomeric seleno-compounds (11), m.p. 214-218° and (12) m.p. 224-227°, in ratio of about 3:2. Oxidative removal of the phenylseleno group of 11 was achieved by oxidation with sodium periodate as previously reported[1)] to give the desired allylic alcohol (13), m.p. 241-242°, ν 3300 (OH), 1685 cm^{-1} (lactam), δ 6.00 (2H, m, olefinic protons), in 43% yield calculated from 9 Acetylation of the alcohol gave the acetate (14), m.p. 240-241°, ν 1740 (OAc), 1710 cm^{-1} (lactam).

The acetate (14) was unexpectedly resisted to the epoxidation by m-chloroperbenzoic acid in contrast to the oxidation of the isomeric allylic acetate (15) which gave the β-epoxide (16) smoothly.[1)] Various attempts (stirring in methylene chloride at room temperature for several days or refluxing in ethylene chloride in the presence of a radical inhibitor) were failed. The difficulty was overcome by the following procedure.



Treatment of 13 with trimethylsilylimidazole in dry acetonitrile gave the trimethylsilyloxy derivative (17) as an oil, δ 0.12 (9H, s, $OSi(CH_3)_3$), 5.97 (2H, m, olefinic protons), 5.71 (1H, m, >CH-OTMS), in quantitative yield. This was oxidized with m-chloroperbenzoic acid in methylene chloride at room temperature for 2 days to give the β-epoxide (18), which was, without purification, heated in ethanol with sodium borohydride and diphenyl diselenide for 1 hr. After the acetylation[4)] of the resulting product, the phenylseleno group was eliminated by oxidation with sodium periodate in ethanol. Acetylation of the crude product and purification through chromatography yielded diacetyl 5-oxolycorine (19), m.p. 244-245°, ν 1745 (OAc), 1710 cm^{-1} (lactam), δ 2.00 (OAc), 2.10 (OAc), 5.25 (1H, m, >CH-OAc), 5.60 (1H, m, >CH-OAc), 5.78 (1H, m, olefinic proton), as a sole product in yield of 36% calculated from the allylic alcohol (13).



17 18 19 1 R=H

20 R=Ac

Lithium aluminium hydride reduction of the diacetate (19) in tetrahydrofuran furnished (±)-lycorine (1) in 49% yield. Since (±)-lycorine was barely soluble in the usual organic solvents, the identity was confirmed by n.m.r. and i.r. spectral comparison of (±)-diacetyllycorine (20), m.p. 217-218°, with natural diacetyllycorine and also with the synthetic racemate.[1)]

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REFERENCE AND NOTE

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4. When the acetylation was omitted, products having strong fluoresence instead of 5-oxolycorine were formed.

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