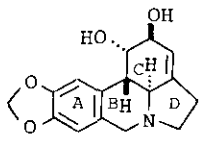
A MODIFIED TOTAL SYNTHESIS OF (±)-LYCORINE

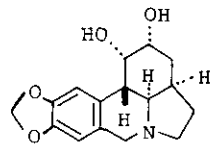
T. Sano*, N. Kashiwaba and J. Toda
Showa College of Pharmaceutical Sciences, Setagaya-Ku, Tokyo 154, Japan
Y. Tsuda
Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan
H. Irie
Faculty of Pharmaceutical Sciences, Kyoto University, Sakyo-Ku, Kyoto 606, Japan

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.

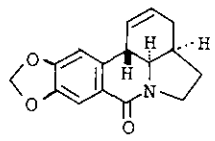
Recently, we have accomplished the first total synthesis of Amaryllidaceae alkaloids lycorine (1) and zephyranthine (2).[1] In that synthesis, the double bond on ring C of the tetracyclic six-membered lactam (3) was functionalized in a stereoselective manner elaborating these alkaloids. The tetracyclic 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.



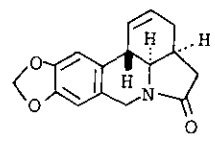
1



2

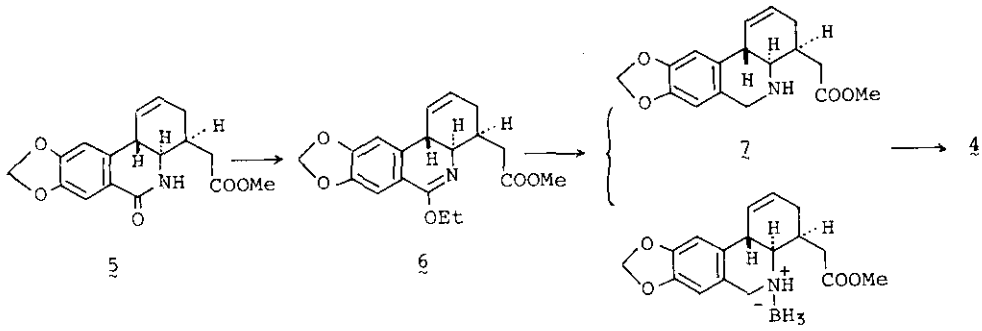


3



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 diethetate 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.

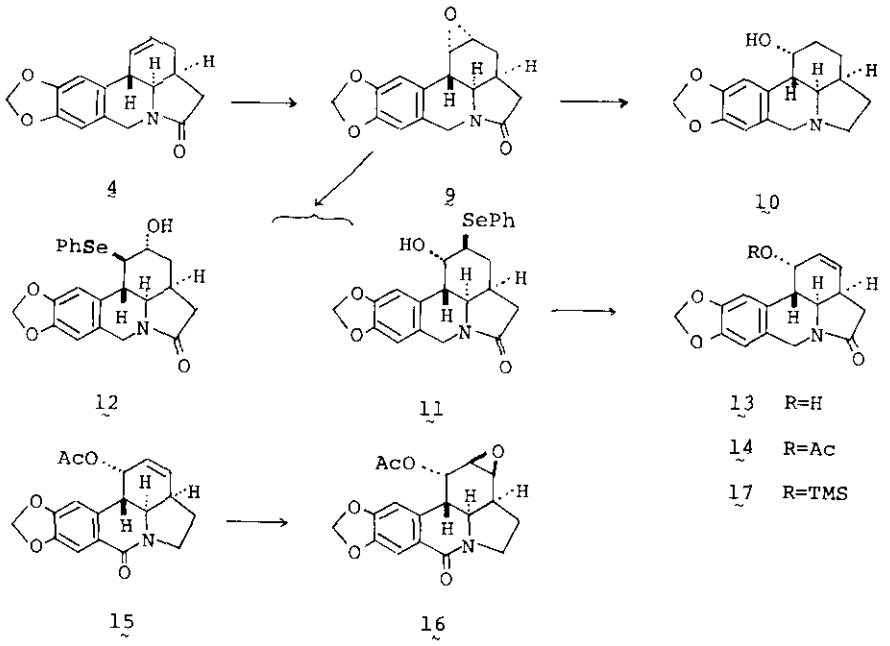


5 6 7 → 4 8

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

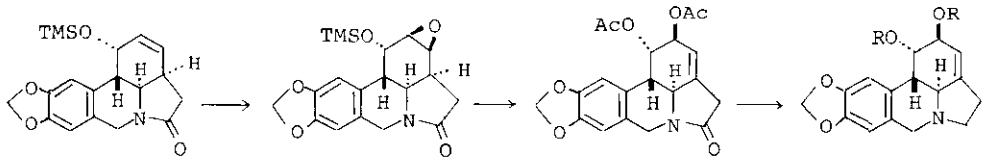
phenylseleno group of 11 was achieved by oxidation with sodium periodate as previously reported[1] to give the desired allylic alcohol (13), m.p. 241-242°, ν 3300 (OH), 1685 cm^{-1} (lactam), δ 6.00 (2H, m, olefinic protons), in 43% yield calculated from 9. Acetylation of the alcohol gave the acetate (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)]

ACKNOWLEDGEMENT. This work was supported in part by a Naito Research Grant (1978), for which we express our appreciation.

REFERENCE AND NOTE

1. a) Y. Tsuda, T. Sano, J. Taga, K. Isobe, J. Toda, H. Irie, H. Tanaka, S. Takagi M. Yamaki and M. Murata, *J.C.S. Chem. Comm.*, 1975, 933.
   b) M. Yamaki, M. Murata, S. Takagi, Y. Tsuda, J. Taga, K. Isobe, H. Tanaka, H. Irie and S. Uyeo, *Heterocycles*, 1976, 5, 163.
   c) Y. Tsuda, T. Sano, J. Taga, K. Isobe, J. Toda, S. Takagi, M. Yamaki, M. Murata H. Irie and H. Tanaka, *J.C.S. Perkin I*, 1979, 1358.
2. Y. Tsuda, T. Sano and H. Watanabe, *Synthesis*, 1977, 652.
3. K. B. Sharpless and R. F. Lauer, *J. Amer. Chem. Soc.*, 1973, 95, 2697.
4. When the acetylation was omitted, products having strong fluoresence instead of 5-oxolycorine were formed.

Received, 6th May, 1980