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A New and Stereoselective Synthetic Route to an Amaryllidaceae Alkaloid, (±)-Lycorine

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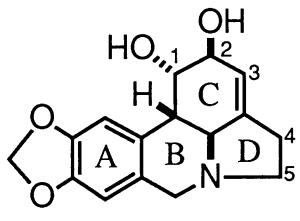
Formal and total syntheses of an Amaryllidaceae alkaloid, (±)-lycorine, were achieved by a new synthetic route via (±)-3-(phenylseleno)-seco-dihydro-B-norlycorin-5-one.

An amaryllidaceae alkaloid, lycorine (**1**), is an attractive target for exploring new synthetic methodology because of the stereostructure bearing four continuous asymmetric centers arranged in all-*anti* relationship and a double bond in ring C of **1**. Although many investigations[1)] on its synthesis have been reported so far, all of them except one elegant method[1f)] involve construction of an α-lycorane skeleton (e.g. **2**) followed by introduction of functional groups. In this paper, we wish to report a synthesis of (±)-3-(phenylseleno)-seco-dihydro-B-norlycorin-5-one (**3**) having functional groups similar to those of **1**, with proper stereochemistry, and formal and total syntheses of (±)-**1** from **3**.

The key compound (**3**) was prepared as follows. Intramolecular Diels-Alder reaction of **4**[2)] gave *cis*-δ-lactone (**5**)[2)] (mp 128-129 °C) (86%) and the *trans*-isomer (**6**)[2)] (mp 151.5-152.5 °C) (4.8%). Reduction of **5** followed by oxidation[3)] afforded the isomeric δ-lactone (**7**)[2)] (mp 139-140 °C) (98%), which was converted to iodo-γ-lactone (**8**)[2)] (oil) in



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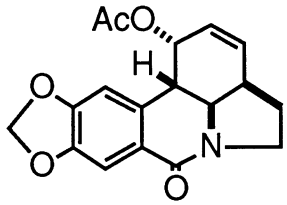

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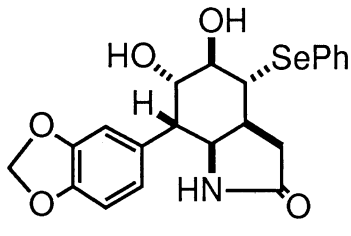

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the usual manner. Protection[4] of the hydroxymethyl group in **8**, successive dehydroiodation and deprotection gave the unsaturated γ-lactone (**9**)[2] (mp 139-140 °C) (50% from **7**).

In order to convert the hydroxymethyl group to an amino one, Jones oxidation of **9** followed by Curtius rearrangement[5] was carried out to give carbamoyl-γ-lactone (**10**)[2] (mp 213-215 °C) (42%). Acid treatment of **10** and cyclization with base afforded readily the desired γ-lactam (**11**)[2] (mp 147-148.5 °C) (98%).

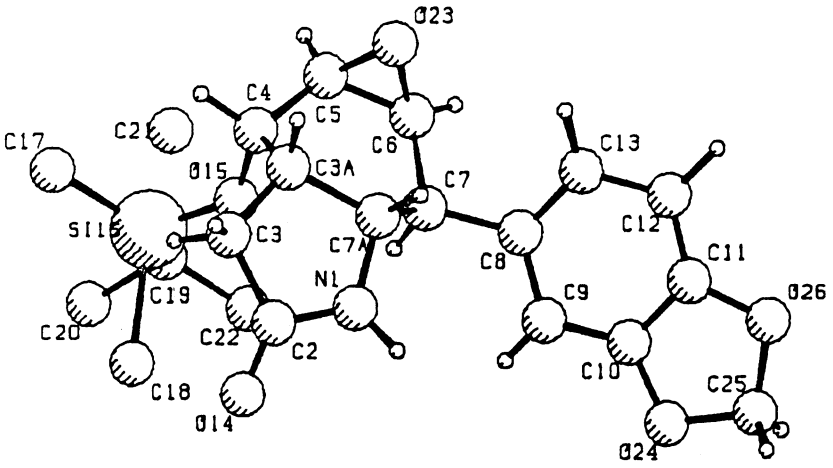

Fig. 1. The molecular structure of **14**.

To introduce *anti*-oriented vicinal hydroxyl groups and a double bond, epoxidation and isomerization of the epoxy group were performed. While epoxidation of acetoxy-γ-lactam (**12**)[2] failed,[6] silyloxy-γ-lactam (**13**)[2] (mp 158-159 °C) could be epoxidized to give 5α,6α-epoxy-γ-lactam (**14**)[2] (mp 145-145.5 °C) (98%), stereochemistry of which was confirmed by X-ray crystallographic analysis[7] (Fig. 1). Isomerization of the epoxy group in **15** was performed by base treatment to produce, after acetylation, the isomeric 4β,5β-epoxy-γ-lactam (**16**)[2] (mp 180-181 °C) (61%) accompanied by epoxide (**15**)[2] (mp 238-240 °C) (6%). Phenylselenenylation of **16** gave the key compound (**3**)[2] (mp 84-86 °C) (99%). Acetylation and successive oxidation of **3** proceeded smoothly to give the unsaturated γ-lactam (**17**)[2] (mp 206-208 °C) (84%) having functional groups similar to those of **1**. Furthermore, stereostructure of **3** was characterized by its transformation to (±)-1,2-diacetyllycorin-5-one (**18**) (mp 242-244 °C; lit.[1d] mp 244-245 °C), which is led to (±)-lycorine (**1**).

Although conversion of **17** to (±)-lycorine (**1**) was unsuccessful, reduction of **3** followed by cyclization[8] gave the cyclized product (**19**)[2] (mp 99-100 °C) (44%). Finally, **19** was oxidized to afford (±)-lycorine (**1**), diacetate (mp 216-217 °C; lit.[1d] mp 217-218 °C) (41% from **19**) of which was identical with that of natural **1** by comparison of their spectra (^{1}H-NMR, IR). Thus, stereoselective formal and total syntheses of (±)-lycorine (**1**) were accomplished by a new synthetic route via (±)-seco-dihydro-B-norlycorin-5-one (**3**).

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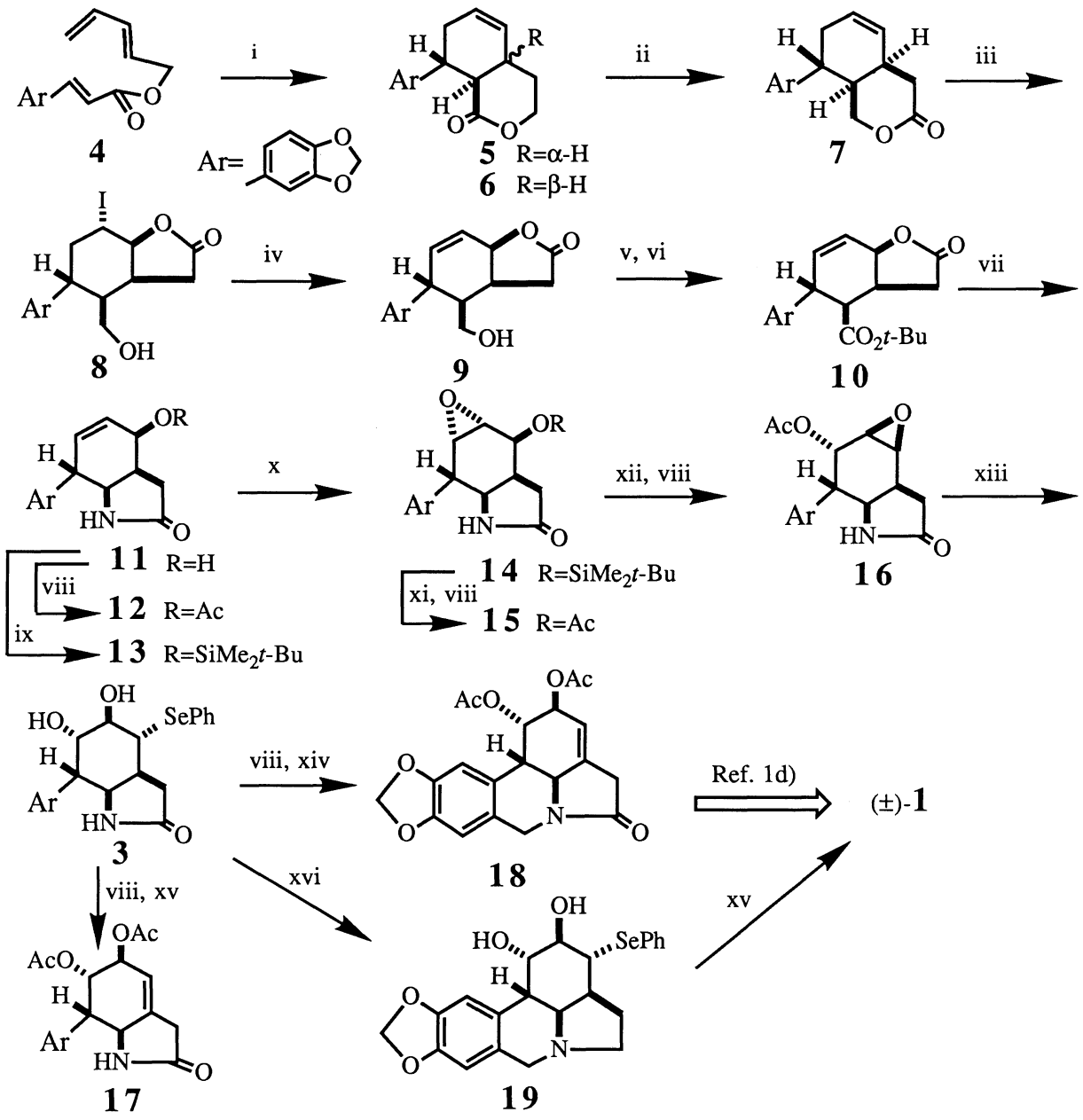

Reaction conditions: i) *o*-$Cl_2C_6H_4$, 235 °C, sealed tube: ii) $LiAlH_4$, THF, reflux; Ag_2CO_3-Celite,[3] C_6H_6, reflux: iii) K_2CO_3, MeOH, H_2O, reflux; I_2, KI, aq. K_2CO_3, MeOH, rt: iv) DHP, CH_2Cl_2, H^+, rt; DBU, C_6H_6, reflux; MeOH, CH_2Cl_2, H^+, rt: v) CrO_3, H_3O^+, acetone, 0 °C: vi) DPPA,[5] Et_3N, *t*-BuOH, reflux: vii) TFA, CH_2Cl_2, rt; 5% NaOMe, MeOH, rt: viii) Ac_2O, pyridine, rt: ix) *t*-$BuMe_2SiCl$, imidazole, DMF, rt: x) MCPBA, CH_2Cl_2, rt: xi) Bu_4NF, THF, rt: xii) 5% aq. K_2CO_3, MeOH, rt: xiii) Ph_2Se_2, $NaBH_4$, EtOH, reflux: xiv) 35% formalin, THF, K_2CO_3 (cat.), rt; TFA, CH_2Cl_2, rt: xv) $NaIO_4$, THF, MeOH, H_2O, 40 °C: xvi) $Na(MeOCH_2CH_2O)_2AlH_2$, toluene, reflux; $Me_2N^+{=}CH_2I^-$,[8] THF, reflux.

their skillful technical assistance, to Miss Noriko Sawabe and Mrs. Fumiko Hasegawa, this faculty, for their ^{1}H-NMR and mass spectral measurements, and to Sankyo Co., Ltd. for elementary analyses.

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