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Radical Cyclizations. A Convergent Total Synthesis of (±)-γ-Lycorane

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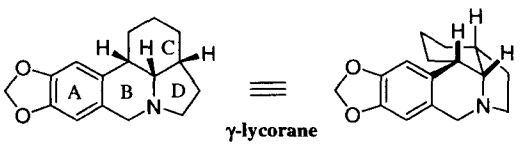
Abstract : (±)-γ-Lycorane has been synthesized in 10 steps from piperonylic alcohol. Two radical reactions were used successively to build the D and B rings. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords : radical reactions, alkaloids, halogenation, dehalogenation.

The lycorine-type natural products, which are characterized by the presence of the galanthane ring system, represent a significant sub-class within the *Amaryllidaceae* alkaloids family. Some of these compounds have useful biological properties such as antiviral, antineoplastic and insect antifeedant activity. Others are known to inhibit plant growth or to disrupt the formation of peptidic bonds during protein synthesis [1]-[2]. Because of the importance of the biological activity of these alkaloids, considerable efforts have been directed toward their total synthesis. Despite the apparent absence of useful pharmaceutical properties, γ-lycorane has become a popular target for illustrating potential new strategies for the synthesis of lycorine-type alkaloids [3]-[17].



γ-lycorane

We report here that the formation of the D and B rings of (±)-γ-lycorane can be achieved by using two consecutive radical cyclizations as the key steps. The synthesis was planned according to the following retrosynthetic scheme.

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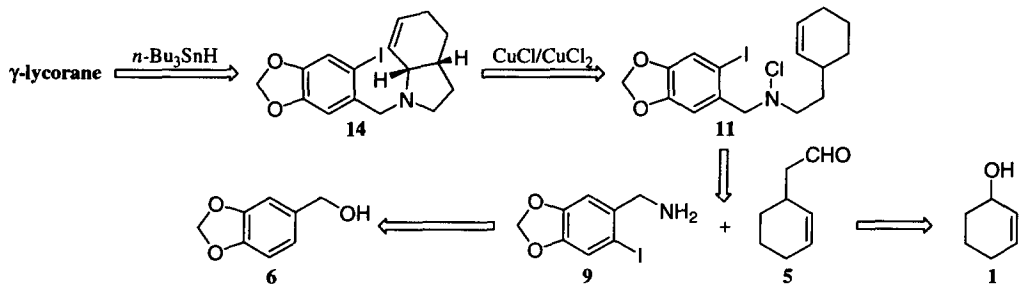
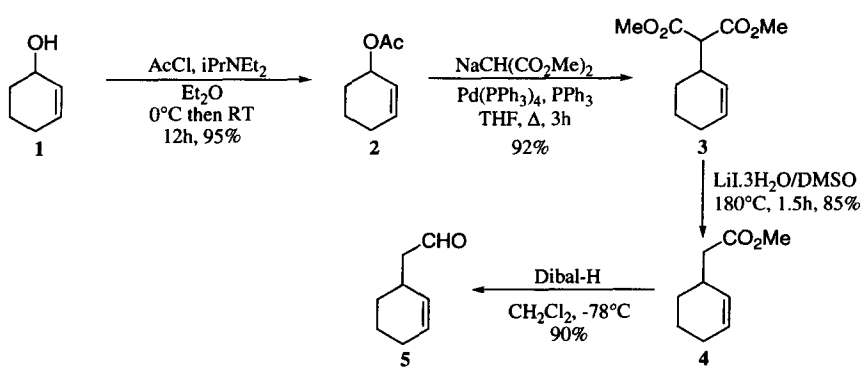
Scheme 1 : Retrosynthetic Scheme.

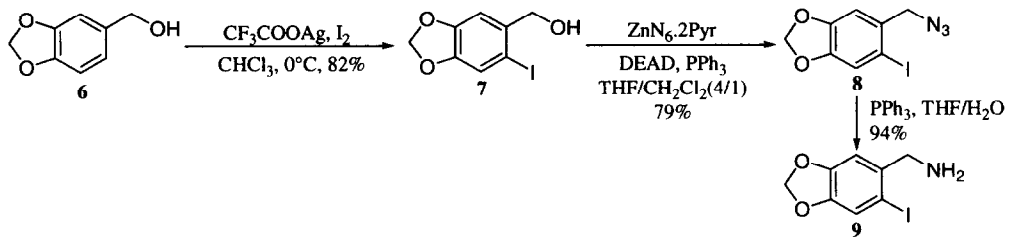


The precursor **11** of (±)-γ-lycorane was synthesized in a convergent manner from cyclohex-2-enol **1** and piperonylic alcohol **6**. Cyclohex-2-enol **1** was converted to the corresponding allylic acetate **2** (AcCl, Hünig's base) which was transformed to the diester **3** (92% yield) by treatment with $NaCH(CO_2Me)_2$ in the presence of a catalytic amount of $Pd(PPh_3)_4$ (0.04 equiv.) and triphenylphosphine (0.12 equiv.) [18]. After decarboxylation of **3** ($LiI.3H_2O$, DMSO, 180°C, 85% yield) [19] and reduction with Dibal-H in CH_2Cl_2 at -78°C, aldehyde **5** was obtained (90% yield). The iodoamine **9** was synthesized from piperonylic alcohol **6**. The iodination of piperonylic alcohol was achieved with I_2 (1.2 equiv.) in the presence of silver trifluoroacetate (1.2 equiv.) in chloroform at 0°C [20]. A Mitsunobu reaction [21] applied to the iodoalcohol **7** by using $ZnN_6.2Pyr$ (0.75 equiv.) in the presence of diethyl azodicarboxylate (1.5 equiv.) and PPh_3 (1.5 equiv) afforded the azide **8** (79% yield) which was reduced to amine **9** by using standard conditions (PPh_3, 1.5 equiv.; H_2O, 5 equiv.; THF; 72h) [22]. The coupling product **10** was produced by reductive amination of **5** by **9** using $NaBH_4$ in MeOH (4h, 75%) [23]. The chlorination of **10** was achieved with *t*-BuOCl in the presence of $NaHCO_3$ (Et_2O, 1h, 0°C) and produced **11** (95%) [24].

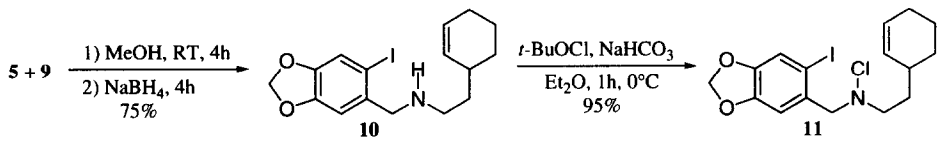
Scheme 2 : Synthesis of Aldehyde **5**.



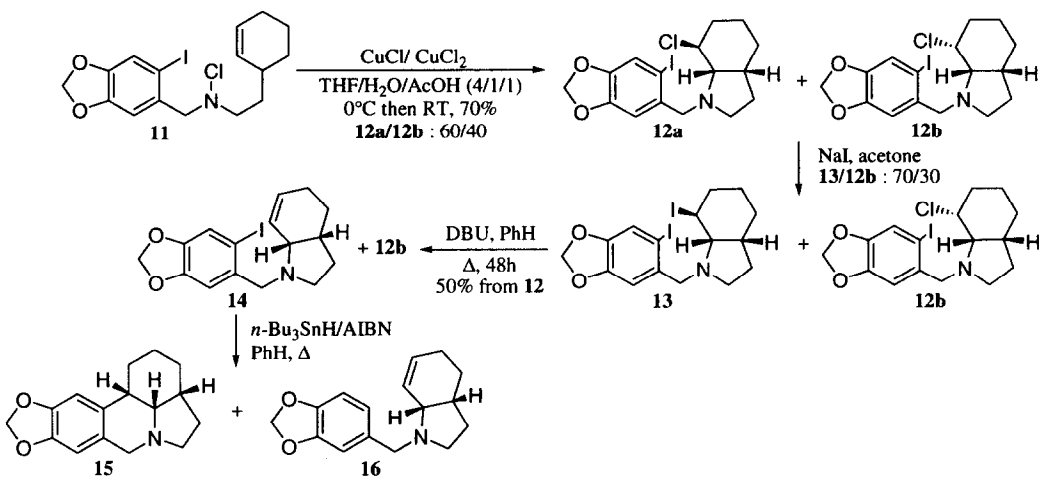
Scheme 3 : Synthesis of Amine **9**.



Scheme 4 : Synthesis of Precursor **11**.



Scheme 5 : Radical Cyclizations. Synthesis of (±)-γ-Lycorane.



Treatment of compound **11** with $CuCl/CuCl_2$ [25] ($THF/H_2O/AcOH$: 4/1/1 ; 0°C→rt) produced the D ring of the (±)-γ-lycorane, due to the formation of an aminyl radical which attacked the olefinic system according to a 5-*exo*-trig process. Two inseparable isomeric products **12a** [26] and **12b** [27] were obtained in a 60/40 ratio with a yield of 70%. Formation of the B ring from intermediate **12** using different conditions (*n*-BuLi/CuI, SmI_2, Mg/CH_2Br_2) did not produce (±)-γ-lycorane. Because of these failures, a second radical cyclization was envisaged from compound **14**. As the treatment of **12** with different bases such as DBU, *t*-BuOK or iPr_2NEt did not lead to **14**, a halogen exchange (Cl→I) was carried out. Treatment of **12a/12b** with NaI in acetone allowed a stereoselective halogen exchange because **13** was the

only iodo compound formed [28]. After treatment of **13** with DBU (PhH, Δ, 48h) the unsaturated iodo compound **14** was isolated (50% yield from **12**) and compound **12b** was recovered in 25% yield. Treatment of **14** with *n*-Bu_3SnH (1.7 equiv.) in the presence of AIBN (0.1 equiv.) in refluxing benzene furnished (±)-γ-lycorane **15** (30%) and the dehalogenated compound **16** (25%) [29]. We have to point out that other radical initiator such as tris(trimethylsilyl)silane (TTMSH) [30] or tributylgermanium hydride (*n*-Bu_3GeH) [31] did not produce (±)-γ-lycorane.

The synthesis of (±)-γ-lycorane **15** has been achieved in 10 steps from piperonylic alcohol by using two consecutive radical cyclizations that allow the formation of the D and B rings of this alkaloid.

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[26] **12a** (always mixed with **12b**) ^1H NMR (C_6D_6) δ : 7.19 (s, 1H), 7.05 (s, 1H), 5.21 (s, 2H), 4.00-3.93 (m, 1H), 3.67 (d, J = 14.2 Hz, 1H), 3.40 (d, J = 14.2 Hz, 1H), 2.94-2.83 (m, 1H), 2.76-2.71 (m, 1H), 2.19-2.06 (m, 1H), 2.03 (td, J = 5.1 and 9.9 Hz, 1H), 1.90-1.80 (m, 1H), 1.79-0.80 (m, 7H).
[27] **12b** ^1H NMR (C_6D_6) δ : 7.40 (s, 1H), 7.21 (s, 1H), 5.23 (d, J = 1.5 Hz, 1H), 5.20 (d, J = 1.5 Hz, 1H), 4.57 (d, J = 15.2 Hz, 1H), 3.83 (td, J = 3.4 and 10.4 Hz, 1H), 3.69 (d, J = 15.2 Hz, 1H), 3.09-2.99 (m, 1H), 2.77 (dd, J = 3.8 and 5.2 Hz, 1H), 2.24 (td, J = 4.0 and 8.8 Hz, 1H), 1.99-1.86 (m, 1H), 1.79-0.80 (m, 8H).
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