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Efficient synthesis of (±)-γ-lycorane employing stereoselective conjugate addition to nitroolefin

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Abstract—(±)-γ-Lycorane **3** was synthesized in 52% overall yield via seven steps from **5** by employing the highly stereoselective nitro-Michael cyclization of **5** to **9** and diastereoselective conjugate addition of aryllithium to a nitroolefin **10** as two key steps.

We have been involved in the asymmetric synthesis of biologically active lycorine alkaloids **1**–**4** [1,2] through the conjugate addition to nitroolefin[3,4] and cyclization technology (Fig. 1). Deoxygenated skeletons of **4**, α- and β-lycoranes **1** and **2**,[5,6] were successfully synthesized by employing the chemoselective conjugate addition of 3,4-methylenedioxyphenyllithium to **6**, obtained from **5**, and subsequent stereoselective cyclization of **7** to **8** (Scheme 1).[7] Since all stereoisomers are necessary to fully evaluate biological activity of lycorine alkaloids, further study was focused on the stereoselective synthesis of γ-lycorane **3**.[8] We describe herein that the conjugate addition of the aryllithium to a nitroolefin **10** gave highly stereoselectively all *cis*-**11**, which was then converted to **3**.

Since the intramolecular nitro-Michael addition-type cyclization of **7** was sterically controlled by the chirality

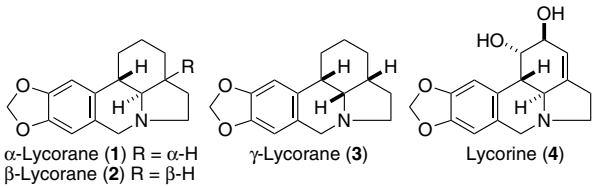
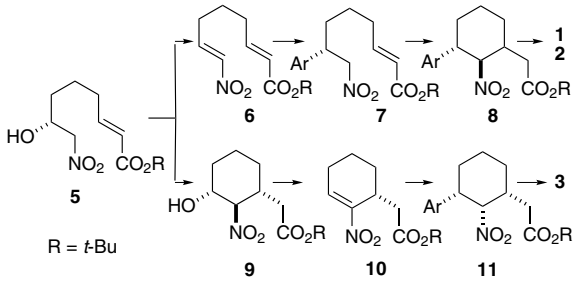


Figure 1. Lycoranes **1**–**3** and lycorine **4**.



Scheme 1. Cyclization and conjugate addition to nitroolefins giving **1**, **2**, and **3**.

at the β-position of a nitro group, cyclization of **5** was expected to give **9**, which is convertible to a nitroolefin **10** (Scheme 1). If the aryllithium addition to **10** takes place *cis* to an acetate moiety, subsequent protonation of a lithium nitronate intermediate takes place from the less hindered face to give all *cis*-**11** bearing the requisite stereochemistry for **3**.

A ψ-hydroxy-ω-nitro-α,β-enoate **5** was prepared by employing the reported nitro-aldol procedures[9,10] in four steps and 65% overall yield from tetrahydropyran-2-ol.[7] Intramolecular nitro-Michael cyclization of **5** with 2 equiv of cesium fluoride and 0.1 equiv of myristyltrimethylammonium bromide[11] in THF at room temperature for 24 h gave highly stereoselectively a separable diastereomeric mixture of **9** as colorless cubes of mp 89–90 °C in 84% yield and **9a** as a pale yellow oil in 4% yield (Scheme 2).

Keywords: Alkaloid; Synthesis; Nitroolefin; Addition.
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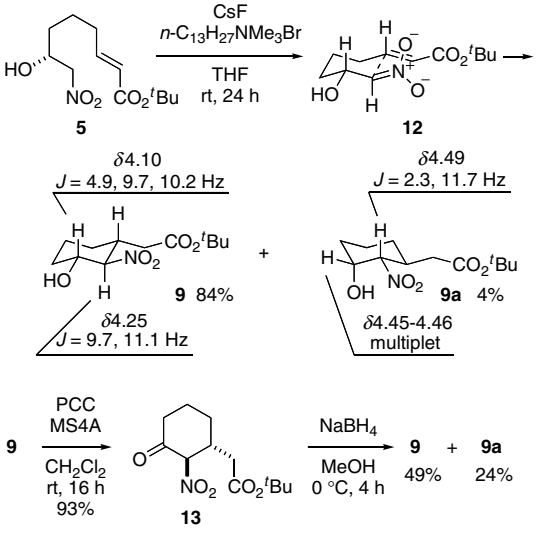
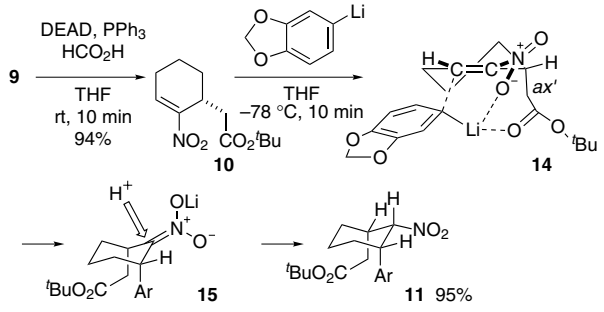


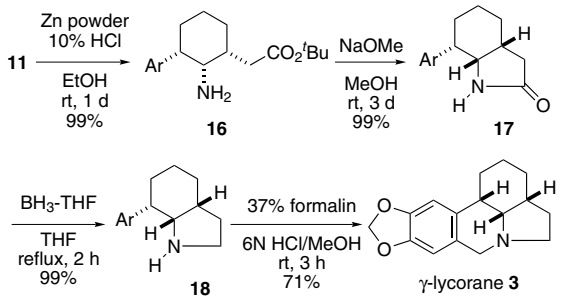
Scheme 2. Stereoselective nitro-Michael Cyclization of **5** to **9**.

The stereochemistry of **9** was determined by ^{1}H NMR (Scheme 2). Coupling constants of methine protons indicate that all substituents on a cyclohexane ring are equatorial in **9**. However, the stereochemistry of **9a** was hard to determine due to the complicated multiplicity of the methine proton attached by a hydroxyl group. PCC oxidation of **9** followed by sodium borohydride reduction of **13** afforded a mixture of **9** in 49% yield and **9a** in 24% yield, confirming **9a** as the epimer of **9** at the carbon attached by a hydroxy group. Preferred approach of an enoate moiety to a nitronate *anti* to a polarized HO–C bond in **12** is the controlling factor of the highly stereoselective cyclization.[12]

Dehydration of **9** to **10** with methanesulfonyl chloride-triethylamine[13] and trifluoroacetic anhydride-triethylamine,[9] which were effective methods for preparation of aliphatic nitroolefin **6** from **5**, was unsuccessful. Treatment with acetic anhydride-4-*N,N*-dimethylaminopyridine-Al_2O_3,[14] gave an acetylated product without formation of **10**. Fortunately, attempted conversion of an equatorial hydroxyl group to an axial one under the Mitsunobu conditions,[15] diethyl azodicarboxylate-triphenylphosphine-formic acid for 10 min at room temperature, smoothly afforded **10** in an excellently high yield of 94% (Scheme 3).



Scheme 3. Dehydration of **9** under the Mitsunobu conditions and diastereoselective conjugate addition giving **11**.



Scheme 4. Total synthesis of (±)-γ-lycorane **3**.

Reaction of **10** with 1.5 equiv of 3,4-methylenedioxyphenyllithium, generated by treating the corresponding bromide with butyllithium at −78 °C for 15 min in THF, and subsequent protonation with aq ammonium chloride gave an adduct **11**[16] as a sole product in 95% yield with perfect diastereoselectivity (Scheme 3). A pseudo-axially oriented acetate moiety in **14** due to the $A^{(1,2)}$ strain[17] directed the axial addition of aryllithium to an olefin in **10**. Coordination of a lithium cation to the carbonyl oxygen of the ester **14** may also direct the *cis*-addition of aryllithium reagent. Protonation of the resulting lithium nitronate takes place stereoselectively from the less hindered face of **15** bearing both axial aryl and acetate groups.[18]

Reduction of a nitro group of **11** with zinc powder in 10% aq HCl/ethanol[19] at room temperature for 1 d gave an amine **16** in 99% yield (Scheme 4). Treatment of **16** with sodium methoxide in methanol at room temperature for 3 d afforded a lactam **17** quantitatively, which is the established intermediate[8b] for the synthesis of **3**. Then, the total synthesis of **3** was accomplished in high overall yield according to the reported sequence[8b] through borane–THF reduction and the Pictet–Spengler-type cyclization. Spectroscopic data and the melting point[20] of synthetic (±)-γ-lycorane **3** were identical with those reported.[8]

In conclusion, we have succeeded in the stereoselective synthesis of γ-lycorane **3** through a stereoselective intramolecular nitro-Michael cyclization of ψ-hydroxy-ω-nitro-α,β-enoate **5**, and perfectly diastereoselective *cis*-conjugate addition of aryllithium to a cyclic nitroolefin **10** in high overall yield of 52% from **5** via seven steps. Syntheses of α-, β-, and γ-lycoranes from the same starting material **5** would be the basis for the further studies toward development of optically active lycorine-based pharmaceuticals.

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