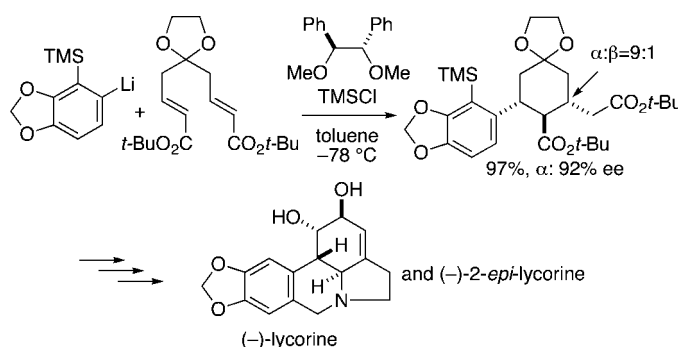# Total Synthesis of (−)-Lycorine and (−)-2-*epi*-Lycorine by Asymmetric Conjugate Addition Cascade

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ABSTRACT

Total syntheses of (−)-lycorine and (−)-2-*epi*-lycorine were accomplished using chiral ligand-controlled asymmetric cascade conjugate addition methodology, which enables the formation of two C−C bonds and three stereogenic centers in one pot to give synthetically useful chiral cyclohexane derivatives.

The Amaryllidaceae alkaloids are ideal candidates for clinically useful pharmaceuticals, such as galantamine for Alzheimer's disease.[1] (−)-Lycorine (**1**), a potent emetic first isolated in 1877, is the most abundant Amaryllidaceae alkaloid.[2] Recent studies revealed that lycorine has other interesting biologic activities, including antiviral activity and apoptosis induction.[3,4] Since its structure was determined by Uyeo in 1935,[5] it has attracted the attention of synthetic chemists, and many synthetic studies, including total syn-

theses, have been reported.[6] Only one asymmetric synthesis, however, has been reported to date.[7] Herein, we report the asymmetric synthesis of lycorine (**1**) and the first total synthesis of 2-*epi*-lycorine (**2**) using a chiral ligand-controlled[8] asymmetric cascade conjugate addition reaction.

In our strategy, chiral ligand **3** mediates an asymmetric conjugate addition reaction[9] of aryllithium **4** with a sym-

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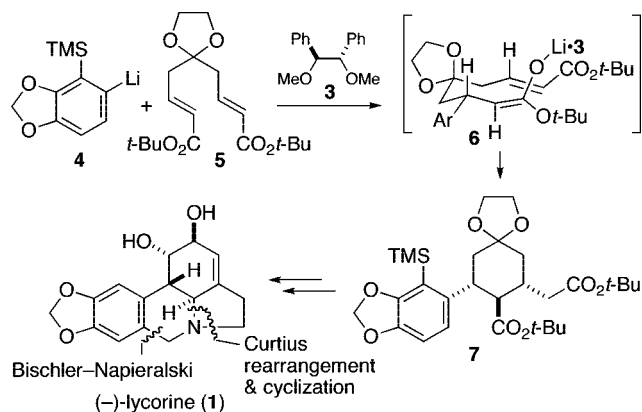
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metric Michael acceptor **5** that has two enoate moieties, which enantioselectively affords enolate **6** (Scheme 1). The
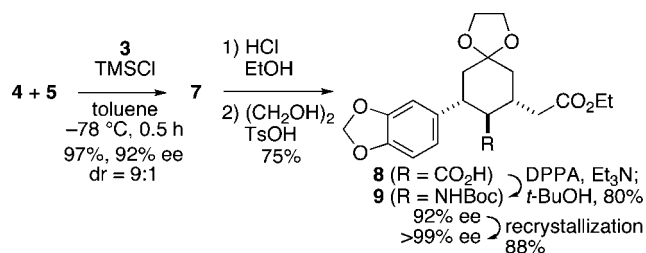
subsequent diastereoselective intramolecular Michael addition of **6** gives cyclohexane **7** bearing three adjacent stereogenic centers. The lycorine skeleton, therefore, derives from **7** via Curtius rearrangement and a Bischler−Napieralski reaction.

A toluene solution of enoate **5** was added to a solution of *ortho*-TMS-substituted aryllithium **4**,[10] prepared from the corresponding aryl bromide[11] and *tert*-butyllithium in the presence of chiral ligand **3** in toluene at −78 °C. In contrast to the related reaction of ω-nitroethenylalkenoate,[12] the desired cascade reaction proceeded within 0.5 h at −78 °C to give a 9:1 mixture of cyclization products *all-trans* **7** with 88% ee and its *trans−cis* isomer in 98% combined yield (Scheme 2). The relative and absolute configurations of **7**

and its isomer were confirmed by the conversion of **7** into (−)-lycorine (**1**) (vide infra).

(10) A TMS substituent often improves enantioselectivity in chiral ligand-controlled asymmetric addition reactions of lithiated nucleophiles: (a) Sakai, T.; Doi, H.; Kawamoto, Y.; Yamada, K.; Tomioka, K. *Tetrahedron Lett.* **2004**, *45*, 9261. (b) Yamashita, M.; Yamada, K.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, *126*, 1954. (c) Nishimura, K.; Ono, M.; Nagaoka, Y.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 12974.
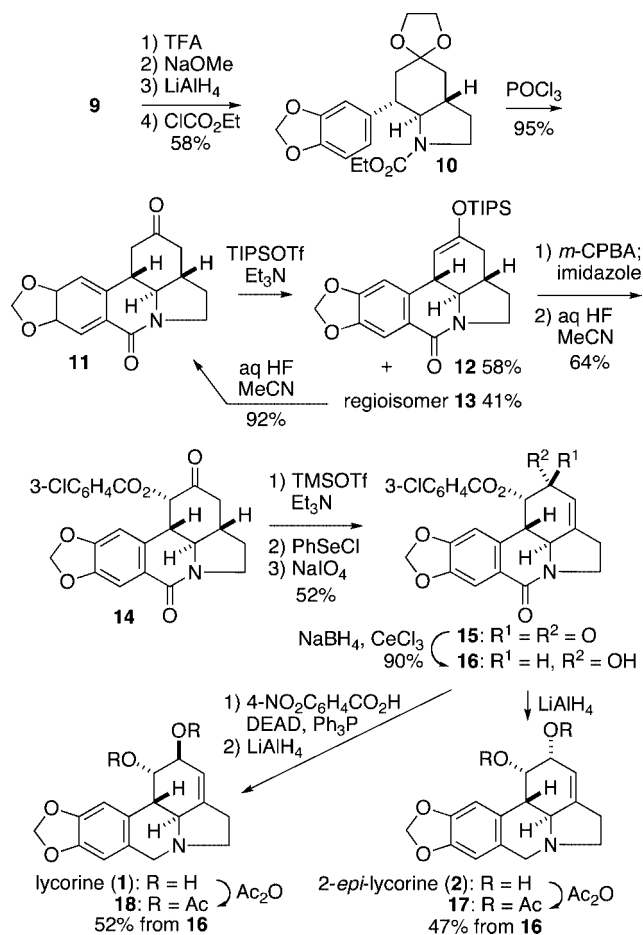
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The presence of chlorotrimethylsilane improved the enantioselectivity, and a 9:1 mixture of **7** with 92% ee and its isomer was obtained in 97% yield.[13] It is noteworthy that chiral ligand **3** was quantitatively recovered without loss of optical purity and was therefore reusable.

With the key intermediate **7** in hand, the total synthesis of lycorine was explored. Reaction of the 9:1 mixture of **7** and its isomer in refluxing ethanolic HCl removed the *tert*-butyl and the trimethylsilyl groups, accompanied by esterification of the less hindered carboxylic acid moiety, to give, after reketalization, monocarboxylic acid **8** as a single diastereomer, which was easily separated from the diethyl ester derived from the isomer of **7** (Scheme 2). Introduction of a nitrogen atom using diphenylphosphoryl azide (DPPA)[14] efficiently proceeded to form carbamate **9**. Recrystallization of **9** from hexane afforded enantiomerically pure (>99% ee) **9** in 88% yield. Ring construction by reductive alkylation of the nitrogen functionality, followed by treatment with ethyl chloroformate, gave carbamate **10**, which was subjected to a Bischler−Napieralski reaction, affording **11** in high yield (Scheme 3).

The first total synthesis of (−)-2-*epi*-lycorine (**2**) was achieved from **11**. Ketone **11** was converted into TIPS enol

ethers **12** and **13** in 58% and 41% yield, respectively. Although the regioselectivity of this enol formation was not high (3:2), the separated undesired regioisomer **13** was readily converted back into **11** for recycling by treatment with aqueous hydrogen fluoride in acetonitrile: thus, **11** was converted into **12** in 80% yield by repeating these transformations twice. This poor selectivity would be desirable if a 3-oxygenated derivative of lycorine were the target. In the same manner, **13** would be obtained from **11** in 63% yield by recycling **12** instead of **13**. The oxidation of **12** by Magnus' procedure[15] gave *m*-chlorobenzoate **14**. Dehydrogenation at the 3,12-position of **14** was regioselectively realized through phenylselenylation of the corresponding TMS enol ether to give enone **15** in 52% yield in three steps. Luche's reduction of **15** stereoselectively afforded allylic alcohol **16**. The subsequent LAH reduction furnished **2**, which was purified and characterized after conversion to known di-*O*-acetyl derivative **17** in 47% yield from **16**. The sign of the specific rotation of **17** was identical to that previously reported,[16] and the melting point and spectroscopic data were consistent with those of an authentic sample prepared by a previously reported procedure.[16]

Although an attempted *re* face-selective reduction[17] of **15** toward (−)-lycorine (**1**) failed, inversion of the stereochemistry of allylic alcohol **16** was accomplished by a modified Mitsunobu reaction[18] to give **1** after LAH reduction. The ^{1}H and ^{13}C NMR spectra, and the TLC behavior were identical to those of an authentic sample. Synthesized **1** was purified at the stage of di-*O*-acetyl derivative **18** (52% yield from **16**), whose TLC behavior, melting point, specific rotation, ^{1}H and ^{13}C NMR, MS, and IR data were consistent with those previously reported,[7] as well as those of an authentic sample prepared by a previously reported procedure.[16]

In summary, we achieved total syntheses of (−)-lycorine and (−)-2-*epi*-lycorine using our chiral ligand-controlled asymmetric cascade conjugate addition methodology. This methodology enables the formation of two C−C bonds and three stereogenic centers in one pot to give synthetically useful chiral cyclohexane derivatives. The synthetic strategy is flexible, and applicable for other natural and unnatural lycorine derivatives. Importantly, the chiral ligand could be recycled, and the one-pot reactions are economically and ecologically beneficial.

Supporting Information Available: Experimental details, characterization data of new compounds, and HPLC traces of **7** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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