

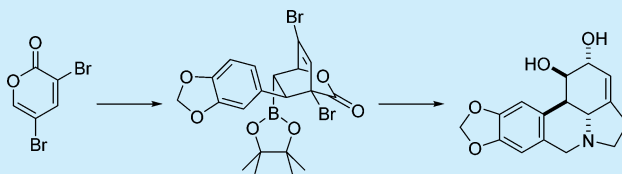
Total Synthesis of ($\pm$)-Lycorine from the *Endo*-Cycloadduct of 3,5-Dibromo-2-pyrone and (*E*)- β -Borylstyrene

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Supporting Information

ABSTRACT: A new synthetic route to ($\pm$)-lycorine, starting from the *endo*-cycloadduct of 3,5-dibromo-2-pyrone and (*E*)- β -borylstyrene, is reported. Boronate oxidation and a set of reactions including face-selective epoxidation provided the pivotal C1-OH group and C3/C3a double bond.



Lycorine is a naturally occurring alkaloid widespread in the Amaryllidaceae family of plants with a long history of use in traditional medicine.¹ In connection with the natural product based drug development, lycorine has received renowned attention for its potent antitumor, antiviral, and anticholinesterase activities.² Structurally, lycorine has a tetracyclic pyrrolo-[*de*]phenanthridine ring system with four contiguous stereogenic centers on ring C (Figure 1). Due to the C3/C3a double bond,

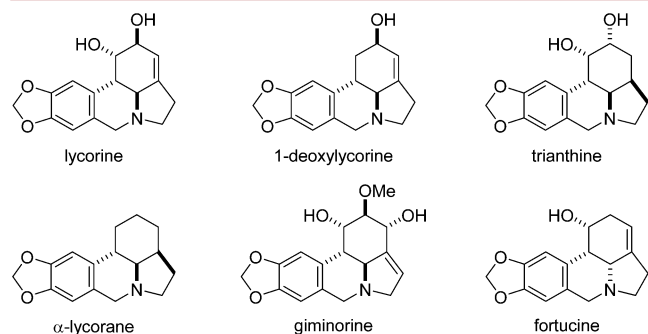
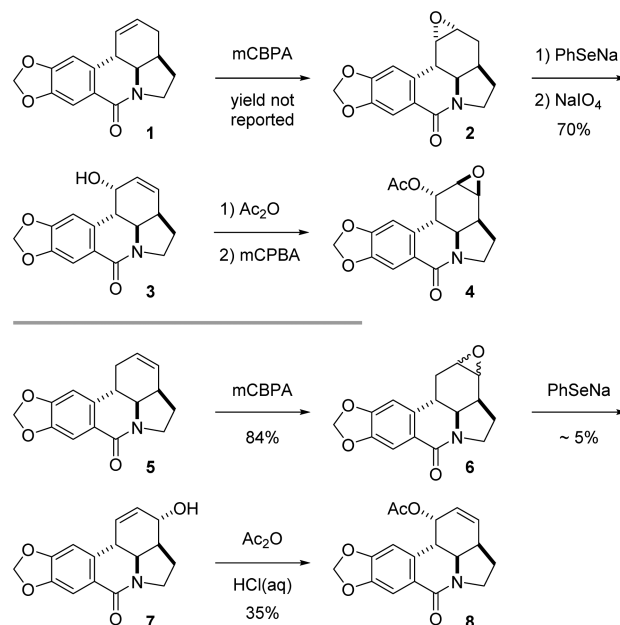


Figure 1. Selected pyrrolo[*de*]phenanthridine natural alkaloids.

ring C is in the same oxidation state as the aromatic A ring and thus susceptible to aromatization, imposing additional challenges in the synthesis. Not surprisingly, there are only a handful total syntheses reported in the literature,³ despite efforts since the structural determination.⁴

The problem in the synthesis arises from the installation of the anti-oriented vicinal hydroxyl groups, as exemplified in some early synthetic endeavors (Scheme 1). Tsuda and co-workers elaborated a synthetic route utilizing epoxide 2. Subsequent transformation to allylic alcohol 3 allowed the first total synthesis of lycorine. Nonetheless, their route became obsolete due to the inefficient low yielding synthesis of the cyclohexene 1. As an alternative, Torssell and co-workers proceeded along the path by way of more readily accessible cyclohexene intermediate 5. However, it fared worse, because of the poor yield in the synthesis of allylic alcohol 7. Another low-yielded acid-catalyzed

Scheme 1. Oxidative Functionalization of Ring C



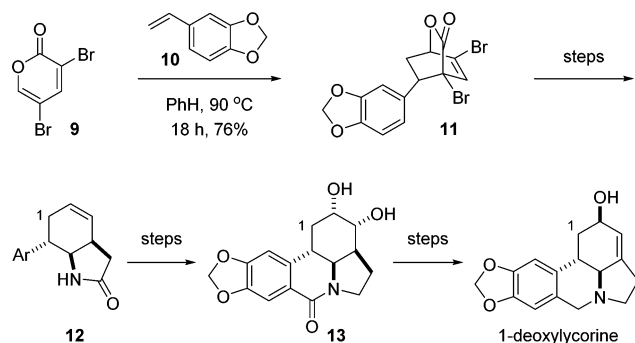
allylic transposition reaction delivered acetate 8 in 35% yield. With no further improvement available, many synthetic works reported thereafter often ended up at the stage of cyclohexene 5 (known as Torssell's intermediate).⁵

As a part of our ongoing studies exploring the utility of 3,5-dibromo-2-pyrone in target-oriented synthesis,⁶ we have demonstrated that lactam 12, accessed from bicyclic lactone 11, the cycloadduct of 3,5-dibromo-2-pyrone 9, and dienophile 10, could be readily converted into 1-deoxylycorine (Scheme 2).^{6b}

However, the direct application to the synthesis of lycorine would be unattractive as the C1-OH installation may require the conversion of lactam 12 to Torssell's intermediate 5. In this

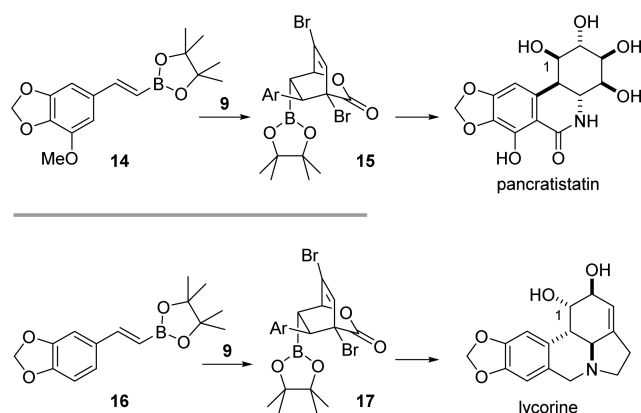
Received: September 22, 2014

Scheme 2. Previous Synthesis of 1-Deoxylycorine

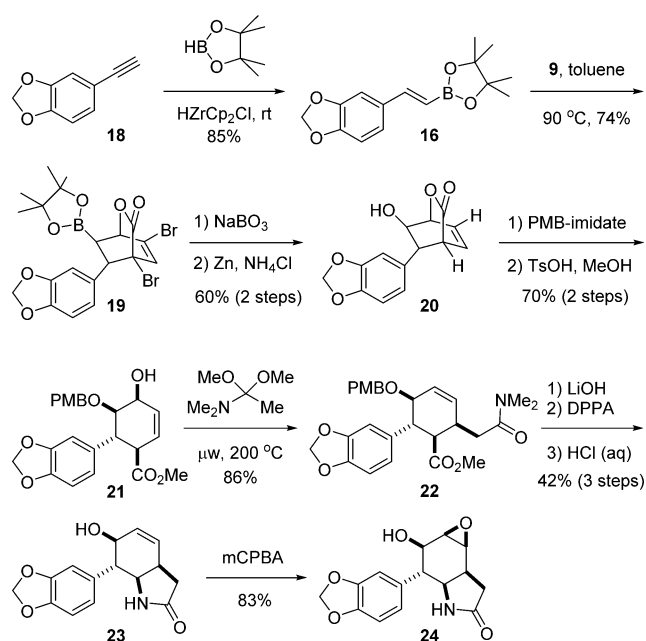


context, we envisaged the pivotal C1-OH of lycorine could be established in a similar way as in our previous synthesis of pancratistatin using (*E*)- β -borylstyrene **14** for the Diels–Alder reaction with 3,5-dibromo-2-pyrone **7**. The boryl group of *endo*-cycloadduct **15** was then oxidized to install the C1-OH group of pancratistatin.^{6a} Herein we wish to report our successful integration of two synthetic strategies that allows an efficient total synthesis of ($\pm$)-lycorine (**16** $\rightarrow$ **17** $\rightarrow$ lycorine) (Scheme 3).

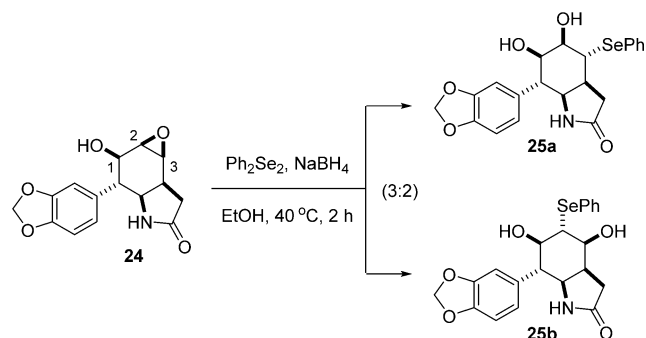
Scheme 3. Boronate as a Synthetic Equivalent of C1-OH Group of Pancratistatin and Lycorine



The synthesis commenced with the preparation of dienophile **16** from alkyne **18** by following the process reported previously (Scheme 4).^{6a,7} The Diels–Alder cycloaddition with 3,5-dibromo-2-pyrone **9** proceeded in a highly *endo*-selective fashion to give bicyclic lactone **19** in 74% yield. Oxidation of the boronate group and Zn-mediated reductive removal of both Br groups gave rise to alcohol **20** in 60% overall yield. The hydroxyl group was then protected as PMB ether before the acidic methanolysis of the lactone bridge to afford ester **21** (70% yield over two steps). Subsequent Eschenmoser–Claisen rearrangement was carried out under microwave irradiation conditions to provide amide **22** in 86% yield.^{6b,8} Ester hydrolysis followed by Curtius rearrangement and acidic hydrolysis gave lactam **23** in 42% total yield over three steps from amide **22**. Epoxidation of the allylic double bond with mCPBA proceeded in a highly selective manner, efficiently directed by the pseudo-equatorial allylic hydroxyl group, to afford epoxide **24** as a single product in 83% yield.⁹ Notably, no reaction was observed, when subjected to vanadium-catalyzed epoxidation [*t*-BuOOH, VO(acac)₂ (cat.)].¹⁰

Scheme 4. Synthesis of Bicyclic Lactam Epoxide **24**

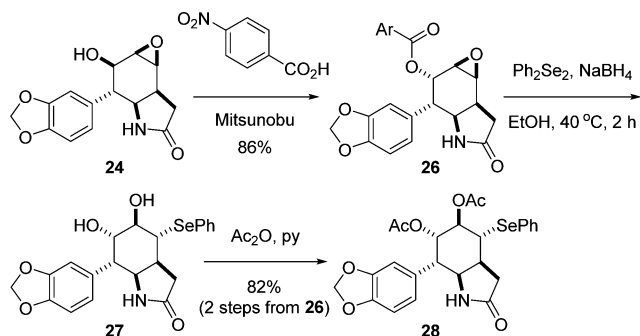
However, further manipulation of epoxide **24** encountered a deadlock, as the epoxide ring opening with phenyl selenide anion afforded an inseparable mixture of two regioisomeric diols **25a** and **25b** (3:2, Scheme 5). Evidently, there is little selectivity on the nucleophilic attack at C2 vs C3.

Scheme 5. Epoxide Opening Reaction of **24**

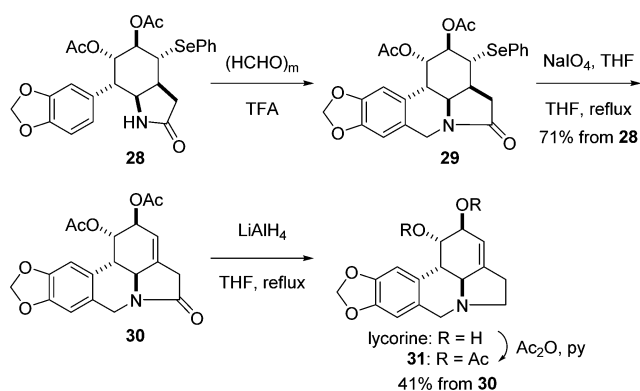
We envisaged the undesired α -face attack at C2 that gives epoxide opening product **25b** could be suppressed if the equatorial hydroxyl group was replaced by a large axially oriented substituent. Toward this end, epoxide **24** was employed in a Mitsunobu reaction with 4-nitrobenzoic acid to give rise to benzoate **26**. As expected, the axial 4-nitrobenzoate group effectively blocked the nucleophilic reaction at the C2 carbon and resulted in the exclusive formation of a C3-opening product (**26** $\rightarrow$ **27**, Scheme 6). During the reaction, the 4-nitrobenzoyl group was concomitantly cleaved off. The unstable diol **27** was immediately converted into diacetate **28** (82% overall yield from epoxide **27**).

For the end-game synthesis, we adapted the route developed by Sano and co-workers to build ring B prior to the installation of the C3–C3a double bond.^{3f} In fact, the synthesis in reverse order proved to be ineffective.^{3d} Subjection to Pictet–Spengler reaction conditions allowed a rapid construction of ring B (**28** $\rightarrow$ **29**, Scheme 7). Subsequent selenoxide elimination reaction

Scheme 6. Oxidative Functionalization of Ring C



Scheme 7. End Game Synthesis of Lycorine



generated the C3/C3a double bond, which provided tetracyclic lactam **30** in 71% over two steps. LiAlH_4 reduction of lactam **31** in THF gave rise to lycorine.¹¹ Because of poor solubility in standard organic solvents, the lycorine product was converted into diacetate **31** for the structural confirmation.

In summary, we have developed a new synthetic route to ($\pm$)-lycorine starting from the *endo*-cycloadduct of 3,5-dibromo-2-pyrone and (*E*)- β -borylstyrene. Boronate oxidation and a set of reactions including face-selective epoxidation provided the pivotal C1-OH group and C3/C3a double bond. We are currently pursuing enantioselective syntheses of the Amaryllidaceae type alkaloids including (–)-lycorine with the development of catalytic asymmetric Diels–Alder reactions of 3,5-dibromo-2-pyrone.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the grants from the National Research Foundation of Korea (2012R1A2A4A01005064 and 2012M3A7B4049661).

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