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

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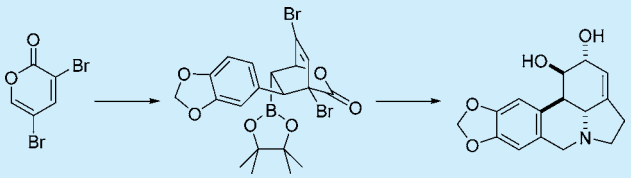
Supporting Information

ABSTRACT: A new synthetic route to (±)-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,

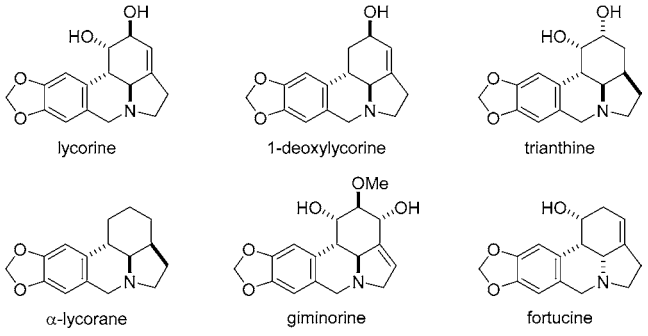
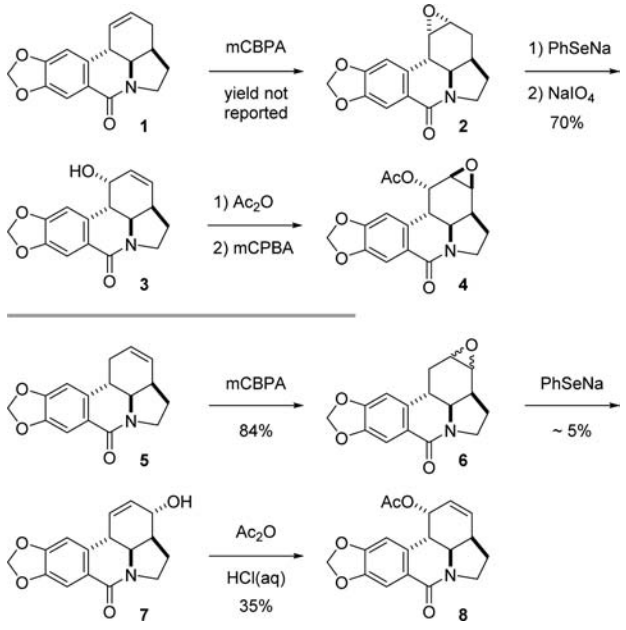


Figure 1. Selected pyrrolo[*de*]phenanthridine natural alkaloids.

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-yielding acid-catalyzed

Scheme 1. Oxidative Functionalization of Ring C



allylic transposition reaction delivered acetate **8** in 35% yield. With no further improvement availed, 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 bicyclolactone **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

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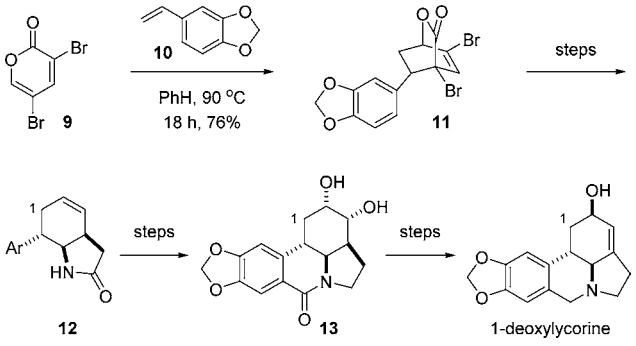
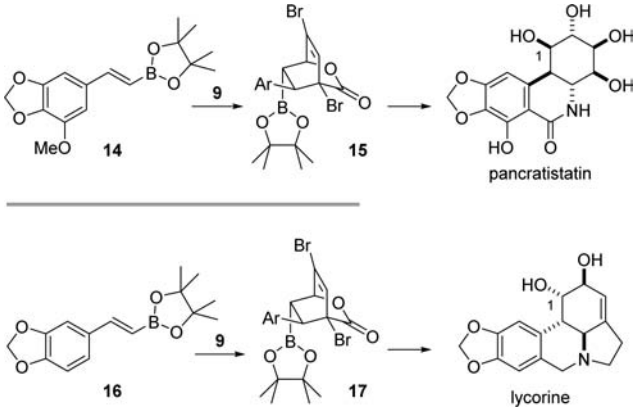
Scheme 2. Previous Synthesis of 1-Deoxylycorine



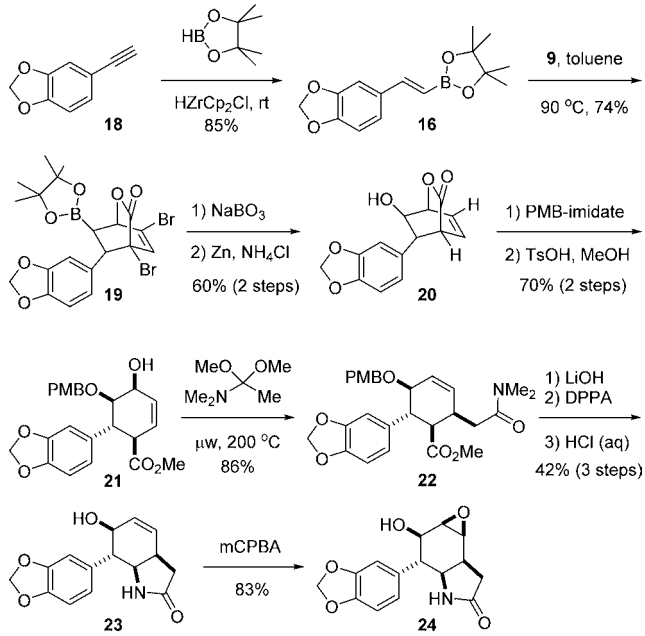
context, we envisaged the pivotal C1-OH of lycorine could be established in a similar way as in our previous synthesis of pancratistatin using (*E*)-*β*-borylstyrene **14** for the Diels–Alder reaction with 3,5-dibromo-2-pyrone **7**. The boryl group of *endo*-cycloadduct **15** was then oxidized to 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 (±)-lycorine (**16** → **17** → lycorine) (Scheme 3).

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



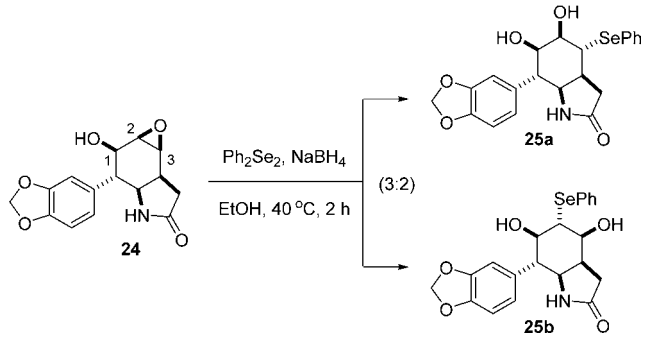
The synthesis commenced with the preparation of dienophile **16** from alkyne **18** by following the process reported previously (Scheme 4).[6a,7] The Diels–Alder cycloaddition with 3,5-dibromo-2-pyrone **9** proceeded in a highly endo-selective fashion to give bicyclolactone **19** in 74% yield. Oxidation 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-nitro-benzoic 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** → **27**, Scheme 6). During the reaction, the 4-nitro-benzoyl 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** → **29**, Scheme 7). Subsequent selenoxide elimination reaction

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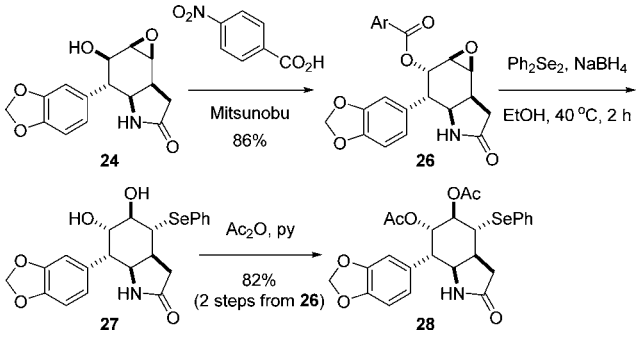
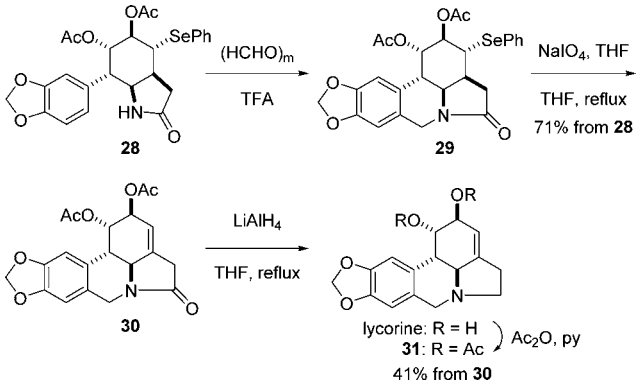
Scheme 6. Oxidative Functionalization of Ring C



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 (±)-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.

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(11) Actual yield was not measured due to the low solubility. The same reduction was reported in the literature, furnishing (±)-lycorine in 49% isolation yield (ref 3f).