ORGANIC LETTERS

2013
Vol. 15, No. 1
132–135

Total Syntheses of (±)-α-Lycorane and (±)-1-Deoxylycorine

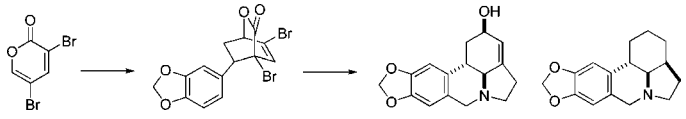
Yong-Geun Jung, Sang-Choul Lee, Hyun-Kyu Cho, Nitin B. Darvatkar, Ji-Young Song, and Cheon-Gyu Cho*

Department of Chemistry, Hanyang University, Seoul 133-791, Korea

ccho@hanyang.ac.kr

Received November 15, 2012

ABSTRACT



New synthetic routes to (±)-α-lycorane and (±)-1-deoxylycorine were exploited. The *endo*-cycloadduct of 3,5-dibromo-2-pyrone with styrene-type dienophile provided the pivotal intermediate for the syntheses of the titled natural products.

Lycorine (**1**) is a toxic crystalline alkaloid present in a number of Amaryllidaceae plant species that include *Lycoris*, *Pancratium*, *Narcissus*, *Galanthus*, *Zephyranthes*, and *Haemanthus*.[1] Bearing a pyrrolo[*de*]phenanthridine common framework (Figure 1),[2] lycorine and its congeneric natural compounds have many important biological activities ranging from the inhibition of ascorbic acid biosynthesis to the prevention of cyanide-insensitive respiration to the inhibition of growth and cell division in higher plants.[3] Because of their potentially useful bioactivities, lycorine alkaloids have been the targets of interest, along with other Amaryllidaceae small molecule constituents such as *trans*-dihydronarciclasin and pancratistatin.[4]

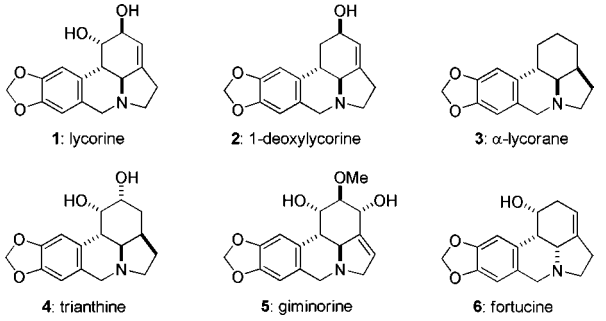


Figure 1. Selected pyrrolo[*de*]phenanthridine natural alkaloid.

Many synthetic studies were then followed,[5] leading to the development of various innovative synthetic strategies

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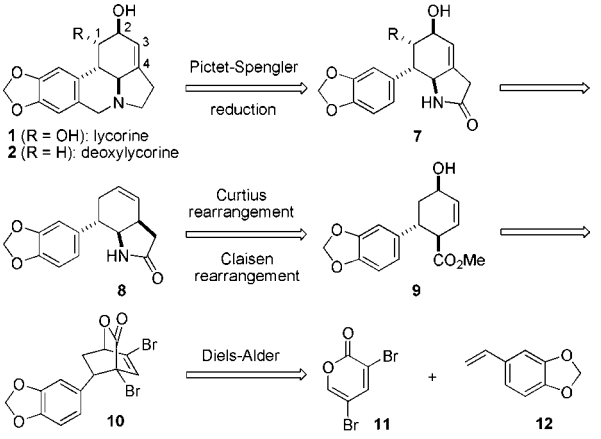
10.1021/ol303157b
Published on Web 12/19/2012

and structural analogues.[3a] As a part of our ongoing studies exploring the utility of 3,5-dibromo-2-pyrone in target-oriented synthesis,[6] we have envisioned that the pyrrolo[*de*]phenanthridine skeleton of lycorine and its congeners could be rapidly assembled from lactam **8** readily accessible from bicyclolactone **10**, the cycloadduct of 3,5-dibromo-2-pyrone **11**, and dienophile **12** (Scheme 1). Reported herein are our path-finding efforts that led to the total syntheses of (±)-α-lycorane (**3**) and (±)-1-deoxylycorine (**2**). The key features are the formation of the lactam **8** from allylic alcohol **9** and subsequent oxidative functionalization of the cyclohexene subuit (**8** → **7**).

Scheme 1. Retrosynthesis of Lycorine and 1-Deoxylycorine



The synthesis began with the Diels–Alder reaction of 3,5-dibromo-2-pyrone (**11**) with styrene dienophile **12**. Heating in benzene afforded *endo*/*exo*-cycloadducts as a readily separable mixture (10:1) in 83% total yield (Scheme 2). The isolated *endo*-adduct **10** was subjected to the Zn-mediated reductive debromination process to give lactone **13** (82% yield). Acid-catalyzed methanolysis of the lactone delivered ester **9** in 83% yield. In order to effectuate the Eschenmoser–Claisen rearrangement reaction,[7] the resulting allylic alcohol **9** was heated with 1,1-dimethoxy-*N*,*N*-dimethylethanamine under microwave irradiation (300 W) in xylene. After 8 min, dimethylamide **14** was obtained in 91% yield. Hydrolysis of the methyl ester and subsequent Curtius rearrangement gave isocyanate **16** in 84% total yield over two steps. Successive treatment with LiOH and HCl (aq) gave rise to bicylic lactam **8**, which upon a reaction sequence involving a Pictet–Spengler reaction and reductions completed the synthesis of (±)-α-lycorane **3**.

After accompishing the synthesis of α-lycorane **3**, we have mulled over ways to manipulate the cyclohexene double bond toward the synthesis of more decorated 1-deoxylycorine. For this purpose, we examined the oxidative functionalizations of the intermediates **17** and **8** (Scheme 3).

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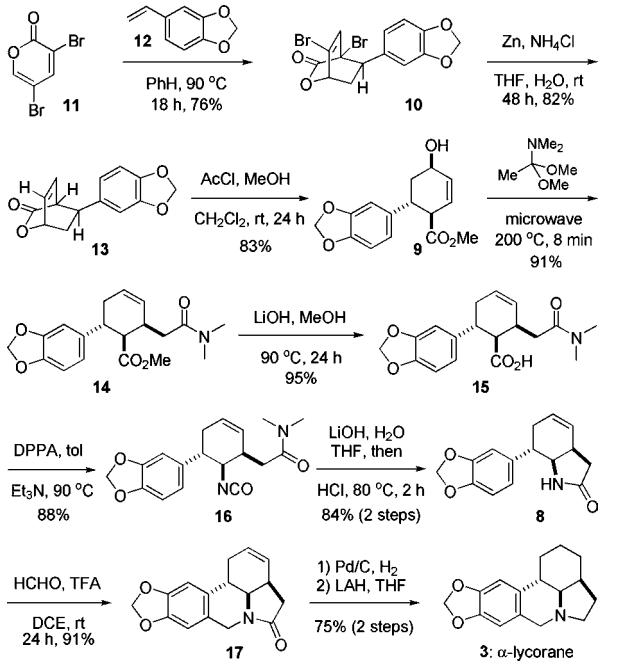
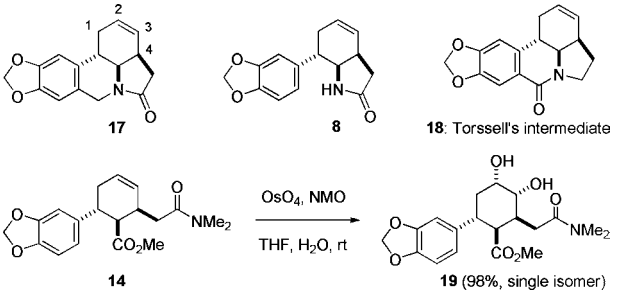
Scheme 2. Synthesis and Conversion of **8** to (±)-α-Lycorane



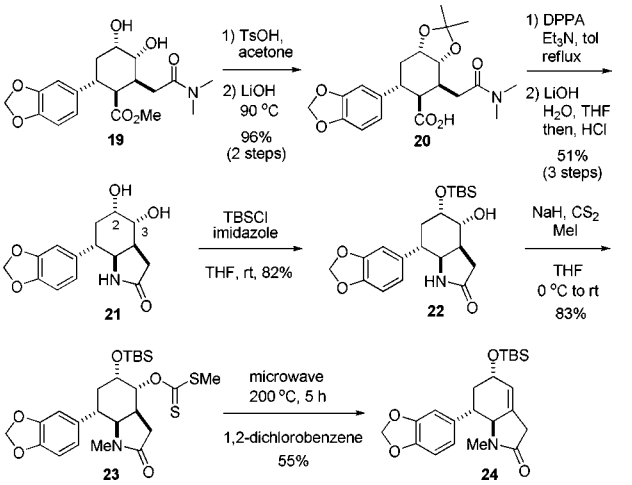
Scheme 3. Oxidative Functionalization of Various Intermediates



Similar to Tossell's intermediate **18**, lactam **17** did not give acceptable stereoselectivity or chemical yield when subjected into the typical epoxidation or dihydroxylation reaction. The nearby pyrrolidine ring provided little steric bias for the π-facial discrimination as it occupies a pseudoequatorial position with respect to the C4. Bicyclic lactam **8** gave a higher chemical yield but only marginal selectivity (55% total yield, 3:1 selectivity for epoxidation; 95% total yield, 2:1 selectivity for dihydroxylation). Further study revealed that monocyclic amide **14** is the system of choice as its dihydroxylation reaction produced diol **19** as single isomer in 98% yield. With diol **19** in hand, we explored the synthesis of 1-deoxylycorine (**2**). At this point, we realized the installation of the double bond between C3 and C4 could be problematic and must be settled before a full-fledged investigation. Using xanthate **23** as a model system, we opted to study the viability of the Chugaev elimination approach. Toward this end, ester **19**

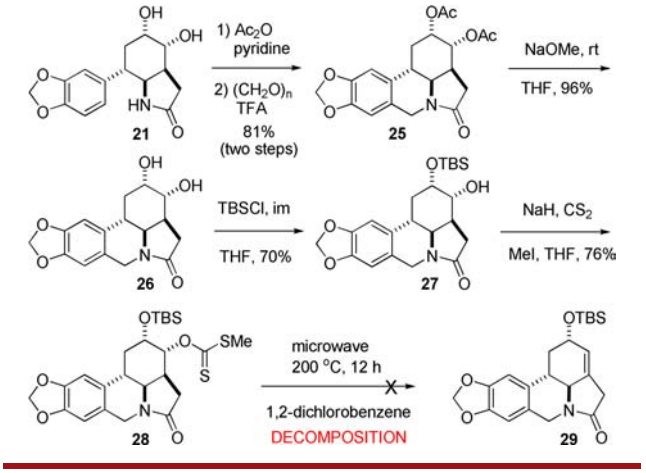
was hydrolyzed into acid **20** after protection of the *cis*-1, 2-diol function (Scheme 4). Subsequent Curtius rearrangement followed by sequential treatments with base and acid effected both lactam formation and acetonide deprotection to afford lactam diol **21** in 51% total yield over three steps.

Scheme 4. Installation of C3−C4 Double Bond: A Model Study



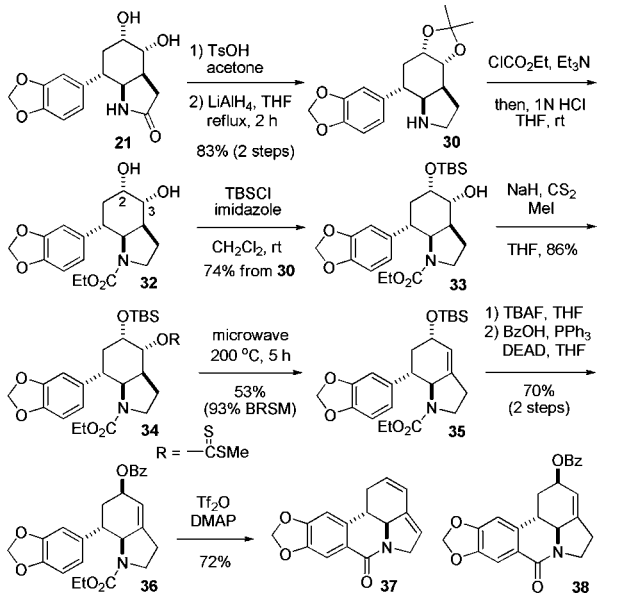
Despite our initial concern, simple treatment with TBSCl allowed selective protection of the lactam **21** C2-OH to afford mono-TBS ether **22** in 82% yield. Sequential treatments with NaH, CS_2, and MeI gave rise to xanthate **23**. During the reaction, the lactam nitrogen was inevitably methylated. After screening various reaction conditions in the literature, we learned that the elimination reaction is most effective when performed under microwave irradiation.[8] After 5 h at 200 °C, we obtained elimination product **24** in 55% isolation yield. We then decided to construct the B ring lactam before the installation of xanthate group in order to avoid the unnecessary protecting group manipulation (Scheme 5).

Scheme 5. Attempted Installation of C3−C4 Double Bond



Acetylations followed by a Pictet−Spengler cyclization and deprotection furnished diol **26** (78% total yield over three steps from **21**). Despite the possible change in the conformation of the cyclohexane, the silylation reaction occurred predominantly at C2-OH to provide TBS ether **27** in 70% yield. The xanthate group was then introduced for the ensuing Chugaev elimination reaction. Unfortunately, xanthate **28** did not give the anticipated pyrolysis product **29** but a complex mixture of decomposition products. This failure forced us to come back to our original plan and reshuffle the reaction sequence once again, accordingly, i.e., installing the double bond before the assembly of the B ring lactam as illustrated in Scheme 6.

Scheme 6. Attempted Synthesis of (±)-1-Deoxylycorine **2**



For easier workup and isolation, the diol function of lactam **21** was masked as an acetonide prior to the $LiAlH_4$ reduction. The resultant bicyclic pyrrolidine **30** was converted into ethyl carbamate. Treatment with 1 N HCl in THF, during the workup, afforded diol **32**. Similar to diol **21**, selective protection of the C2-OH required no special reagent or conditions; simple treatment with TBSCl afforded mono-TBS ether **33** in 85% yield. Installation of xanthate group and subsequent pyrolysis under the microwave irradiation gave the elimination product **35** (53% yield, 40% recovered starting xanthate, 93% yield based on recovered starting material) after 5 h at 200 °C. Removal of TBS group followed by the Mitsunobu reaction with benzoic acid afforded benzoate **36**. However, the B-ring lactam formation using the Bischler-Napieralski protocol did not give the expected lactam **38**, but diene **37** in 72% yield. Unable to resolve the above elimination problem during the lactam formation, we decided to

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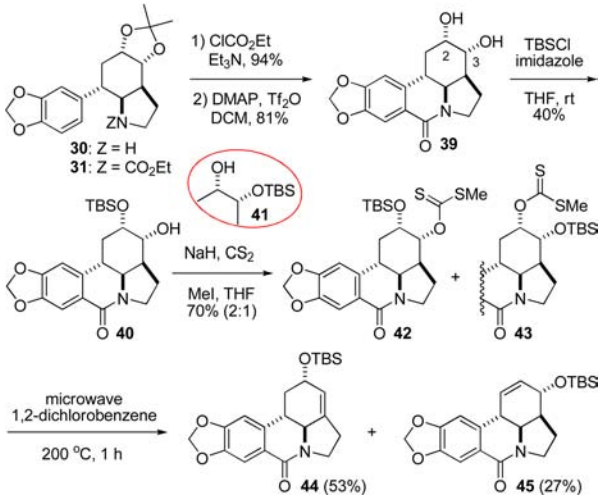
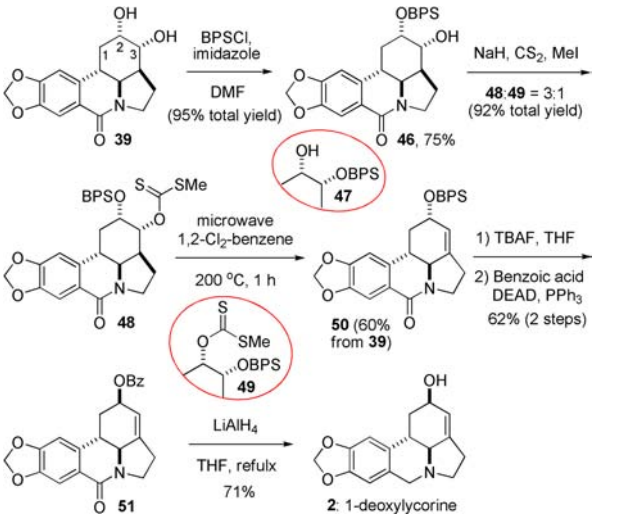
reinvestigate the Chugaev elimination approach at the fully functionalized tetracyclic lactam stage as a last venture. At this point, we came to believe that the location of lactam carbonyl function may affect the elimination process. For this, we prepared tetracyclic lactam **39** with the lactam carbonyl group on the left six-membered ring side (Scheme 7).

Scheme 7. Attempted Synthesis of (±)-1-Deoxylycorine



Thus, carbamate **31** obtained from **30** in 94% yield was treated with Tf_2O and DMAP to construct the lactam B ring. After concomitant removal of the acetonide group under the conditions, diol **39** was obtained in 81% total yield. Although not unexpected, silylation of diol **39** was much less selective than that of diol **26**, affording both C2-OTBS **40** and C3-OTBS **41** in the ratio of 2:1. Since the undesired **41** can be recycled, the low selectivity of the monosilylation would not be a serious issue at the moment. What mattered was that the xanthate forming process with the isolated **40** gave not only **42** but also the regioisomeric **43** as an inseparable 2:1 mixture. Evidently, the TBS group in **40** was migrated onto the C3-OH during the installation of xanthate group. The use of bulkier silicon-based protecting group may suppress the silyl group migration. Also expected would be a higher selectivity in the C2-OH protection of diol **39**. When employed for the selective protection, BPSCl (*tert*-butyldiphenylsilyl chloride) indeed gave much better results, providing the corresponding BPS ethers **46** and **47** in 75% and 20% isolation yield, respectively (Scheme 8). Moreover, the xanthate forming reaction of the BPS protected **46** gave desired xanthate **48** in

Scheme 8. End-Game Synthesis of (±)-1-Deoxylycorine



higher selectivity and total yield (**48**:**49** = 3:1, inseparable, 92% total yield). Interestingly, the same reaction with the isolated regioisomeric BPS ether **47** also produced a mixture of **48** and **49** in the same ratio (3:1), indicating the reversible nature of the silyl group migration. Thus, the mixture of BPS ethers **46** and **47** were directly subjected into the xanthate installation process without separation to afford the same product mixture (**48** and **49**, 3:1) in 92% total yield. The resultant mixture was heated under the microwave irradiation conditions to afford elimination product **50** in 60% overall yield from diol **39** (three steps). After the removal of the BPS group, the configuration of the allylic OH group was inverted under the Mitsunobu protocol. The reduction of amide **51** finally deconvoluted our synthesis of (±)−1-deoxylycorine **2**.

In summary, new synthetic routes to (±)-α-lycorane and (±)-1-deoxylycorine were developed. The cycloadduct of 3,5-dibromo-2-pyrone with styrene type dienophile provided the pivotal intermediates for the syntheses of the titled natural alkaloids.

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

Supporting Information Available. Details of experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.