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Synthesis of (+)-Lycoricidine by the Application of Oxidative and Regioselective Ring-Opening of Aziridines

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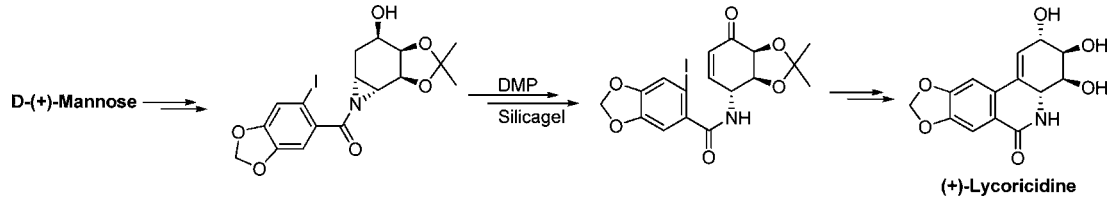
ABSTRACT



A highly stereoselective total synthesis of (+)-lycoricidine has been described. The salient features of this synthesis are the one-pot elimination followed by allylation reaction, ring-closing metathesis, stereoselective aziridine formation, Dess−Martin periodinane, and silica gel mediated oxidative ring-opening of aziridine to form α,β-unsaturated ketone (allyl amine) and intramolecular Heck cyclization.

Over the years, the plant extracts of the Amaryllidaceae family have attracted a lot of attention from the synthetic community because of their interesting structures and potent biological activities.[1] A unique subset of the phenanthridone alkaloids lycoricidine (**1**)[2] and narciclasine (**2**)[3] have been extracted from different daffodil bulbs (Figure 1). In the 1970s, structural determination of these protein synthesis inhibitors showed that they are highly oxygenated benzophenanthridone-type compounds. The antitumor activity of these compounds has also been investigated and seems to be related to the oxygenated cycle and to the tricyclic system. Compounds lacking this rigid arrangement failed to exhibit any biological properties.[4] Later, a related compound pancratistatin (**3**)[5] and its analogue 7-deoxypancratistatin (**4**)[6] were isolated and proved to be very strong antitumor agents.[7]

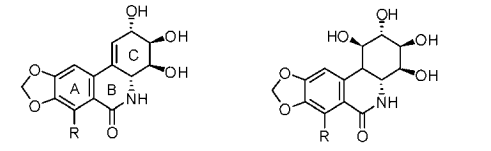


Figure 1. Structures of natural compounds.

The biological activities and stereochemical complexity made them synthetically challenging and attractive.

In continuation of our ongoing research program on the synthesis of bioactive complex natural products,[8] considering the biological activity and the exciting molecular architecture of these alkaloids, we report herein a concise approach for the total synthesis of (+)-lycoricidine.

Scheme 1 illustrates the retrosynthetic analysis of **1**. Disconnection at C8 and C7 afforded fragment **5**. Compound

(1) Reviews: (a) Ceriotti, G. *Nature* **1967**, *213*, 595. (b) Okamoto, T.; Torii, Y.; Isogai, Y. *Chem. Pharm. Bull.* **1968**, *16*, 1860. (c) Piozzi, C.; Fuganti, C.; Mondelli, R.; Ceriotti, G. *Tetrahedron* **1968**, *24*, 1119. (d) Piozzi, F.; Marino, M. L.; Fuganti, C.; Di Martino, A. *Phytochemistry* **1969**, *8*, 1745. (e) Rinner, U.; Hudlicky, T. *Synlett* **2005**, 365.

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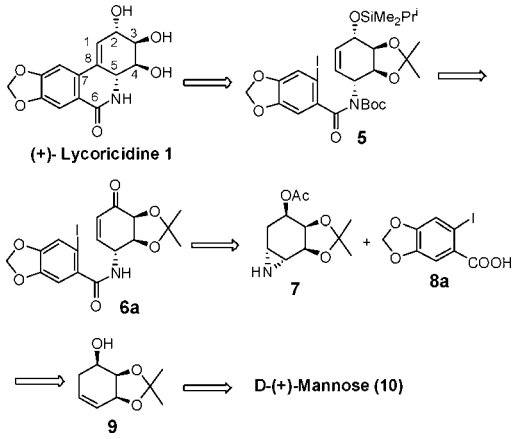
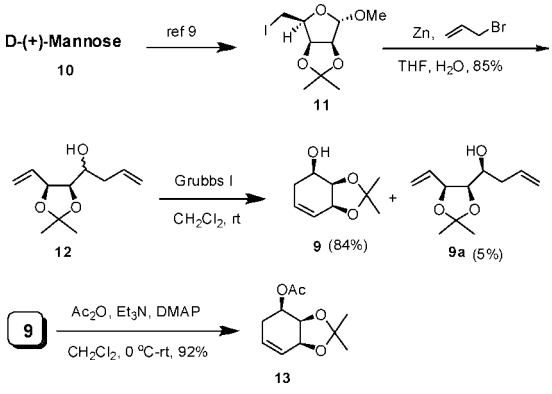
Scheme 1. Retrosynthetic Analysis of the (+)-Lycoricidine **1**



6 would be obtained by the DMP−silica-mediated oxidative ring-opening of aziridine. Aziridine **7** could be prepared from readily available D-(+)-mannose. The synthesis of compound **13** is summarized in Scheme 2.

Scheme 2. Synthesis of Compound **13**



Thus, ω-iodo glycoside **11** was obtained from readily available D-(+)-mannose **10** following the previously established protocol in five steps.[9] On treatment of compound **11** with zinc/allyl bromide in THF/H_2O[10] afforded diene **12** (87%, dr 85:15). Cyclization of diene **12** following the ring-closing metathesis reaction furnished cyclohexenol derivative **9** (84%), and the unreacted isomer **9a** was recovered in 5% yield. The acetylation of the hydroxy group present in **9** yielded compound **13** in a high yield (92%).

The strategy toward the synthesis of **7** began with the acetylated compound **13**. The compound **13** was transformed to aziridine **7** in two different routes. In the first method (Scheme 3), the acetate **13** was treated with PhINTs[11] in the presence of $Cu(acac)_2$, which yielded the *N*-tosylaziridine **17f** (52%) as a single isomer. Treatment of the compound **17f** with sodium naphthalenide[12] afforded the aziridine **7** (67%).

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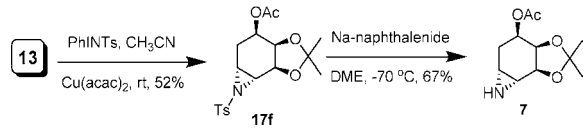
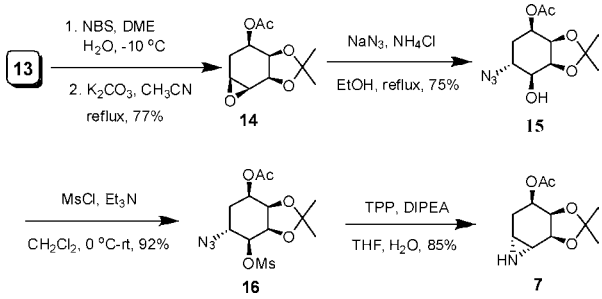
Scheme 3. Synthesis of Aziridine **7**



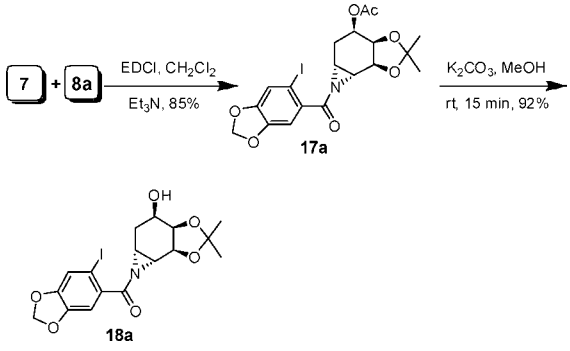
In the second method (Scheme 4), **13** was converted to aziridine **7** by a four-step process which began by treatment with NBS to form a mixture of bromohydrins, which was subsequently treated with K_2CO_3 in dry acetonitrile to form epoxide **14** (77%, two steps). The regioselective ring-opening of epoxide with NaN_3[13] and NH_4Cl in ethanol afforded the azido alcohol **15** (75%). Mesylation followed by TPP and DIPEA treatment gave the desired aziridine **7** (85%).

Scheme 4. Synthesis of Aziridine **7**



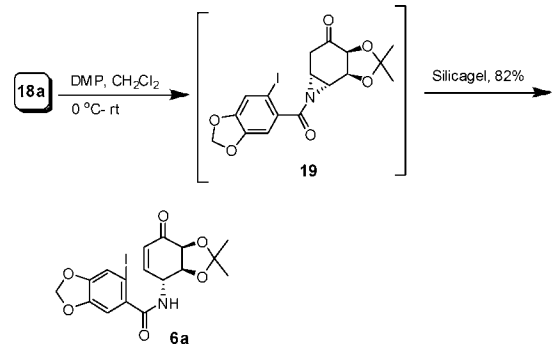
Having compound **7** in hand, we turned our attention toward the synthesis of the key intermediate **6a**. Thus, compound **7** was condensed with 6-iodopiperonylic acid[14] (**8a**) using EDCI[15] as the coupling reagent to obtain the desired amide **17a** in a high yield (85%) (Scheme 5).

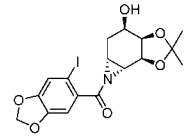
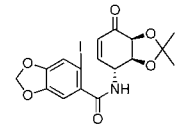
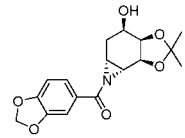
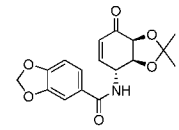
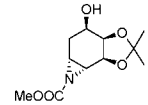
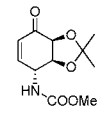
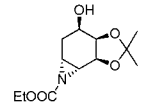
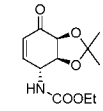
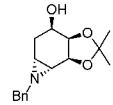
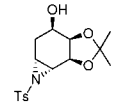
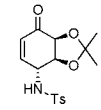
Scheme 5. Synthesis of Amide **18**



Hydrolysis of the acetyl group followed by Dess−Martin periodinane (DMP) oxidation followed by purification of the expected compound **19** through silica gel column chromatography surprisingly afforded a new unexpeced product which was confirmed by spectral data to be α,β-unsaturated ketone (allyl amine) **6a** (82%).[16] Such an unprecedented oxidative ring-opening of aziridine was observed for the first time by our group. This result provided the incentive for further study of the reaction with various substrates. Interestingly, methyl and ethyl carbamate derivatives (**18c**,**d**) and *N*-tosylaziridine (**18f**) participated well in this reaction. In all cases except for compound **18e**, the reaction proceeded well to afford the desired α,β-unsaturated ketones (allyl amines) in good yields. The scope and generality of the reaction are presented in Table 1.

Table 1. DMP−Silica-Mediated Oxidative and Regioselective Ring-Opening of Aziridine

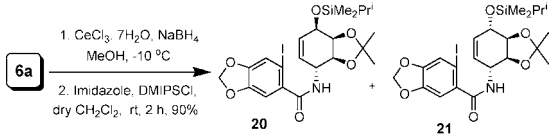


entry	alcohol (18)	ketone (6)[a]	time (h)	yield (%)[b]
a			6.0	82
b			5.5	80
c			4.5	77
d			4.5	76
e		Complex mixture	5.5	--
f			5.0	75

[a] Products were characterized by ^{1}H NMR, ^{13}C NMR, IR, and mass spectroscopy. [b] Isolated yield after column chromatography.

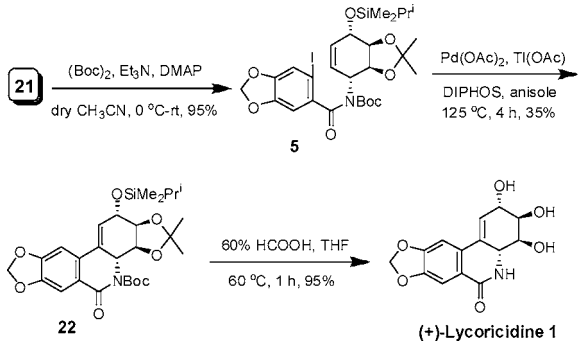
The Luche reduction of **6a** gave an inseparable mixture of alcohol which upon silylation allowed us to separate the mixture by simple chromatography to get the diastereoisomers **20** and **21** (90%, two steps, dr 60:40) (Scheme 6). The undesired isomer **20** was converted to the required isomer **21** by following a repetative oxidation and reduction process.

Scheme 6. Synthesis of Compound **21**



Protection of the carbamate nitrogen of **21** with a Boc group gave the compound **5** (95%). Having compound **5** in hand, the next step was the ring closure to afford the phenanthridone skeleton. Following Hudlicky[2h] and Ogawa's[2g] strategy of intramolecular Heck reaction, compound **5** was exposed to $Pd(OAc)_2$, Tl(OAc), and DIPHOS (1,2-bis-diphenylphosphinoethane) in anisole at 125 °C for 4 h gave the phenanthridone skeleton **22** in 35% yield. Removal of the protecting groups of compound **22** using 60% formic acid in THF at 60 °C for 1 h completed the synthesis of (+)-lycoricidine (**1**) (95%) (Scheme 7).

Scheme 7. Synthesis of (+)-Lycoricidine (**1**)



In summary, we have achieved an efficient and convergent synthesis of a highly oxygenated phenanthridone (+)-lycoricidine starting from commercially available D-(+)-mannose. Highlights of the synthesis include one-pot elimination followed by allylation reaction, ring-closing metathesis, and oxidative ring-opening of aziridine to form α,β-unsaturated ketone (allyl amine). Following the above strategy, other related natural product syntheses are in progress and will be reported in due course.

Acknowledgment. G.S. thanks the Council of Scientific and Industrial Research (CSIR), New Delhi, India, for financial assistance.

Supporting Information Available: Experimental details, selected spectral data, and copies of ^1H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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