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Synthesis of the Putative Structure of (±)-Amarbellisine

Dandan Liu, Jingbo Chen, Long Ai, Hongbin Zhang, and Jianping Liu*

Key Laboratory of Medicinal Chemistry for Natural Resource (Yunnan University), Ministry of Education, School of Chemical Science and Technology, Yunnan University, Kunming, Yunnan 650091, P. R. China

jpliu@ynu.edu.cn

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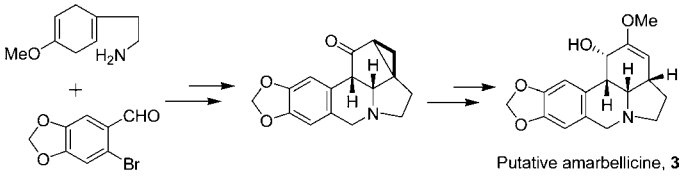
ABSTRACT



The title compound was synthesized mainly by palladium catalytic coupling, cyclopropyl ring-opening rearrangement, epoxidation, Swern oxidation, demethanol reactions, and selective reduction. This synthesis was achieved in 16 steps with 9.7% overall yield. Unfortunately, the published spectroscopic data do not match with those of our synthetic compound.

Due to their potential biological activities as antitumor,[1] antiviral, and antimicrobial activities,[2] as well as the pentacyclic structures, lycorine-type alkaloids have attracted both medicinal and synthetic chemists' interests for a long time.[3] More than 100 structurally diverse alkaloids, possessing a wide spectrum of biological activities, have been isolated from various *Amaryllidaceae* species.[4] Most of those isolated alkaloids have a *trans*-B/C ring system as lycorine (**1**),[5] and only a few showed *cis*-B/C ring configurations[6] as γ-lycorane (**2**). Evidente's group found a new lycorine-type alkaloid, which was named amarbellisine (**3**) (Figure 1). They reported this natural compound had both *cis*-B/C and C/D rings and showed interesting bioactivities.[7] In this context we report the synthesis of putative (±)-amarbellisine, and to the best of our knowledge, this is the first total synthesis of the compound reported.

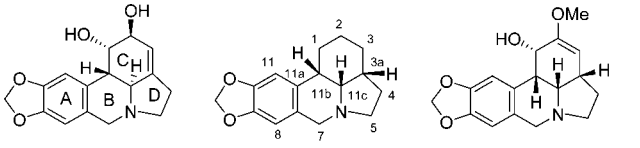


Figure 1. Lycorine-type alkaloids.

Retrosynthetic analysis is showed in Scheme 1. The target molecule ±(**3**) could be afforded from corresponding dihydroxyl compound **5**, which could be obtained from olefin **6**. The previous methodology developed in our group[8] would be employed for the construction of lycorine-type skeleton **6** from bromodiene **8**.

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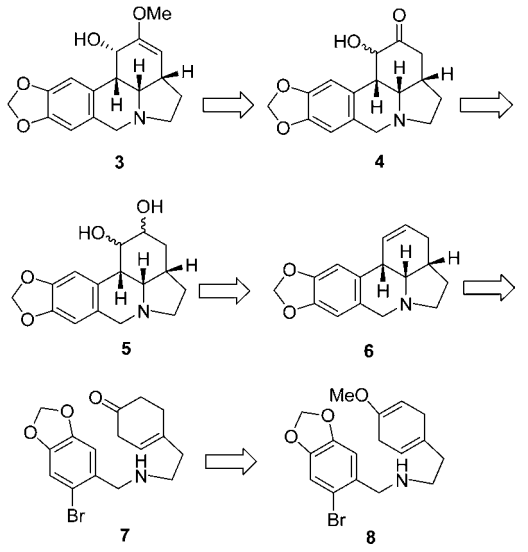
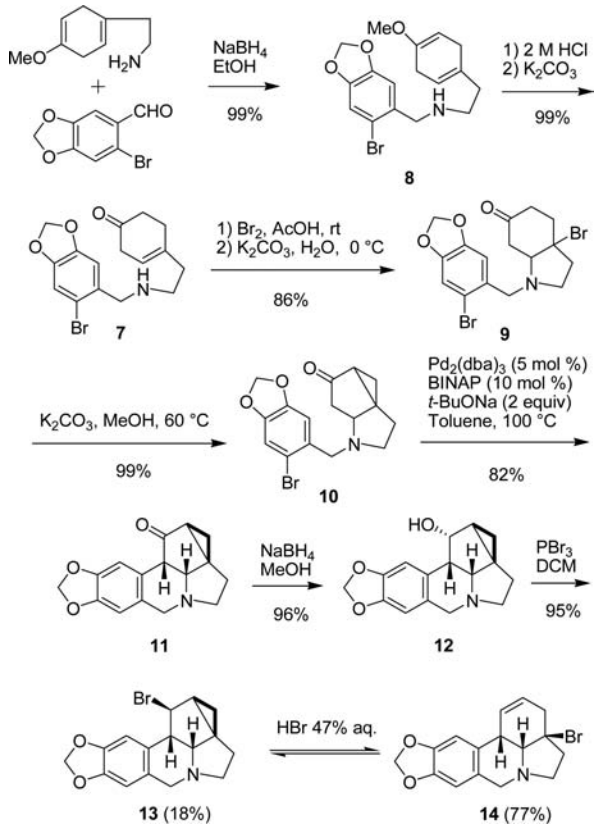
Scheme 1. Retrosynthetic Analysis of Putative Amarbellisine (**3**)



Scheme 2. Synthesis of the Intermediate **14**



Our journey started from diene bromide compound **8** (Scheme 2), which could be prepared from 2-(*p*-methoxyphenyl)ethylamine and piperonal according to our previous work.[9] Unsaturated ketone **7** was obtained by demethylation of **8** with 2 M HCl. Bromocyclization of **7** with bromine followed by base treatment at low temperature afforded bromoketone **9**. Cyclopropyl ring compound **10** was formed when **9** was further exposed to base. Compound **11**, with a full lycorine-type skeleton, was obtained from cycloketone **10** by a palladium catalytic coupling reaction.[10] The reduction of **11** with sodium borohydride afforded cyclopropyl alcohol **12**, which could be converted to corresponding cyclopropyl bromide **13** in the presence of PBr_3. Secondary bromide **13** could undergo a cyclopropyl ring-opening rearrangement reaction to form homoallylic bromide **14**. An interesting phenomena was observed with treatment of either **13** or **14** with aqueous hydrogen bromide: the final ratio of about 1:4 for compounds **13** and **14** was always observed. The cyclopropyl ring-opening rearrangement reaction was first reported by Julia over 50 years ago and was followed by considerable development and synthetic applications,[11] while the reverse reaction from homoallylic halides to cyclopropyl ring compounds was reported mainly in

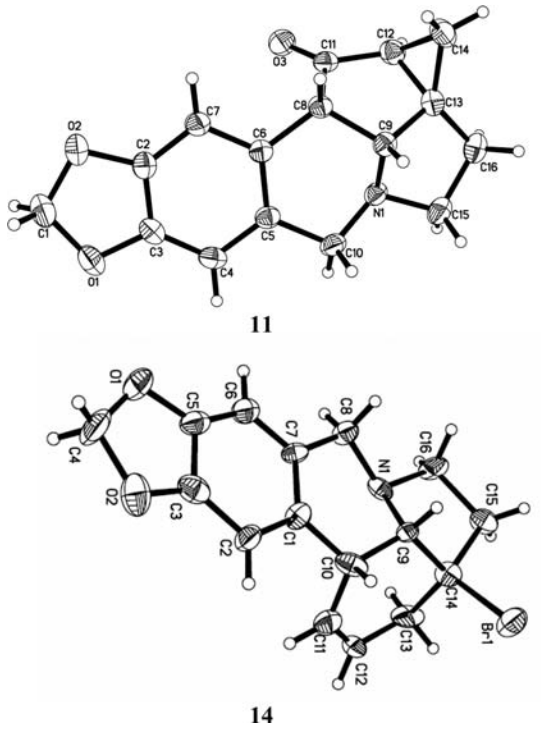


Figure 2. Crystal structures of compounds **11** and **14**.

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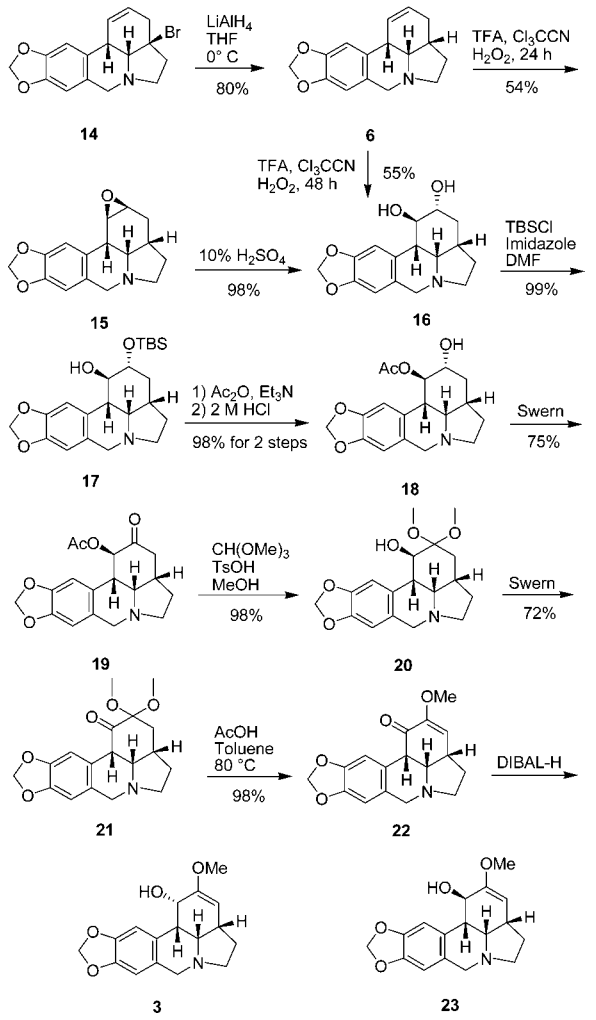
Scheme 3. Synthesis of Putative Amarbellisine (**3**)



anhydrous media,[12,13] but there was no such equilibrium reported.

The structures as well as the relative configurations of cyclopropyl ketone **11** and rearrangement product **14** were confirmed by crystal X-ray crystallography (Figure 2).

The epoxidation of alkene compound **6**, which was obtained by reduction of bromide **14**, encountered some problems. Desired product **15** could not be obtained when compound **6** was reacted directly with mCPBA, or Cl_3CCN/H_2O_2 according to von Holleben's report,[14] until trifluoroacetic acid (TFA) was employed. We thought that TFA shielded nitrogen by formation of a corresponding salt in **6** and kept it nonoxidizable, so selective epoxidation with olefin became possible. The diol **16** could be easily

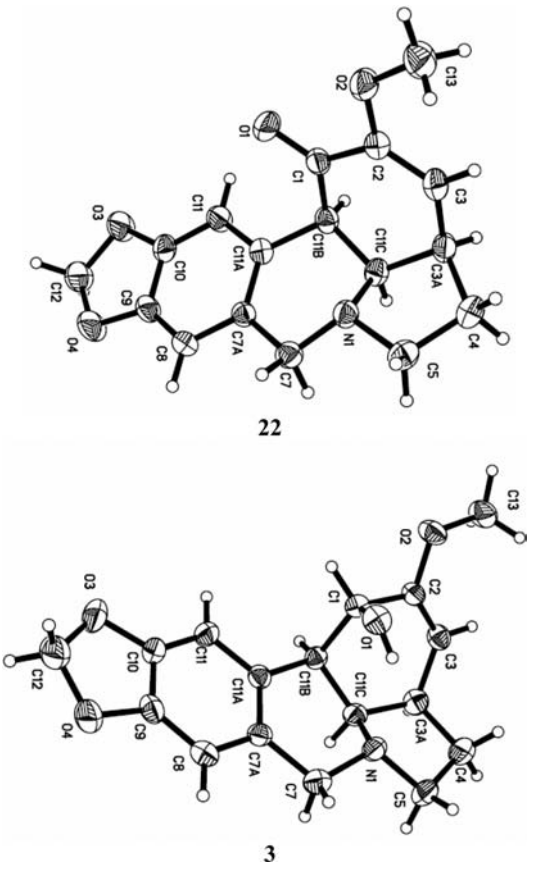


Figure 3. Crystal structures of **22** and **3**.

obtained by acid hydrolysis[15] of epoxide **15**, and further investigation showed that it could be afforded from olefin **6** directly by treatment with the $TFA/Cl_3CCN/H_2O_2$ system for a longer reaction time. Acetate **18** could be afforded from diol **16** by selective hydroxyl protection/deprotection. Corresponding ketone **19** was obtained from acetate **18** by Swern oxidation.[16] Dimethyl ketal **20** was formed from compound **19** by treatment with trimethyl orthoformate and *p*-toluenesulfonic acid;[17] the acetyl was also removed in this manipulation. Methoxyl ethylene compound **22** was afforded by careful removal of methanol from dimethoxyl ketal **21**, which could be formed by oxidation from ketal **20**. Putative *rac*-amarbellisine (**3**) was obtained as the only isomer by reduction of ketone **22** with DIBAL-H, while the target compound ±(**3**) and its *epi*-isomer **23** could be formed in a ratio of about 3:1 if $NaBH_4/CeCl_3$ or Red-Al were employed as a reduction system (Scheme 3).[18]

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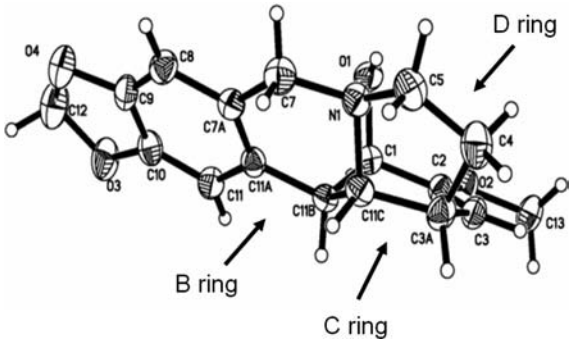

Figure 4. A half-chairlike C ring conformation of the synthesized compound **3** from another angle of crystal.

Finally, the synthesis of putative amarbeillisine was achieved in 16 steps with 9.7% overall yield; the structures and relative stereochemistry of the target compound ± (**3**) and its precursor **22** were confirmed by X-ray crystallography (Figure 3).

The NMR data of our synthesized compound ±(**3**) were compared with those of natural amarbellisine from Evidente's group, and the results suggested they were different isomers.[19] Since the obvious differences in resonating positions for the two compounds appeared at C3a, C3, C1, and C11c from ^{13}C NMR spectra, and H11c, H3, H1, H5, and H7 from ^{1}H NMR spectra, it seemed that the B/C or C/D ring configuration of the two compounds might be different. The X-ray crystallography data showed that the C ring of the synthesized product adopted a half-chairlike conformation (Figure 4), and six carbons on the ring remained nearly in one plane except for C11b, so the values of the axial−equatorial or axial−axial coupling in the system would not be so typical. It suggested that the configuration of the natural amarbellisine reported should be reconfirmed.

(19) ^{13}C NMR signals for C3, C3a of ±(**3**) appeared at 96.9 and 35.3 ppm, while Evidente's compound signals appeared at 112.9 and 58.6 ppm respectively; ^{1}H NMR signals for H1, H5, H7 and H11c of ± (**3**) appeared at 3.98, 3.24, 3.29, and 2.68 ppm, while those for Evidente's compound were at 3.48, 3.02, 3.79, and 4.08 ppm. Whole comparison tables were shown in the Supporting Information, pp S11−S12.

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

The authors declare no competing financial interest.