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Total Synthesis of Lycorine-type Alkaloids by Cyclopropyl Ring-Opening Rearrangement

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Abstract: A practical method for the synthesis of lycorine-type alkaloids with *cis*-B/C ring structure has been developed. Based on the reactions of aminocyclization, palladium-mediated arylation and especially cyclopropyl ring-opening rearrangement, the synthesis of anhydrocaranine, (±)-γ-lycorane and putative (±)-amarbellisne was accomplished.

Key Words: lycorine-type alkaloids; cyclopropyl ring-opening rearrangement; anhydrocaranine; γ-lycorane; amarbellisne.

With the rich biological properties including antifungal, antibacterial and antieoplastic activities,[1] as well as tetracyclic pyrrolo [d, e] phenanthridine framework (galanthan ring system), lycorine-type alkaloids have attracted chemists' and pharmacologists' interests for decades.[2] This paper deals with synthesis of anhydrocaranine, γ-lycorane and amarbellisine. Anhydrocaranine (**1**) (Figure 1) was explored by Wildman and Heimer in 1967[3] but no NMR data have been reported up to now; γ-lycorane (**2**) wih *cis*-B/C, C/D rings is one of the most concerned molecular targets in the field;[4] and amarbellisine (**3**) also with both *cis*-B/C, C/D rings and interesting bio-activities was reported by Evidente's group.[5] We would like to present a new method with

cyclopropyl ring-opening rearrangement to compose the *cis*-B/C ring junction structures in galanthan as a key step to prepare above compounds.

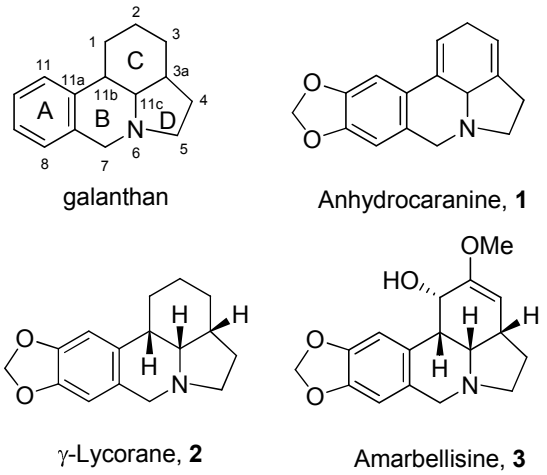
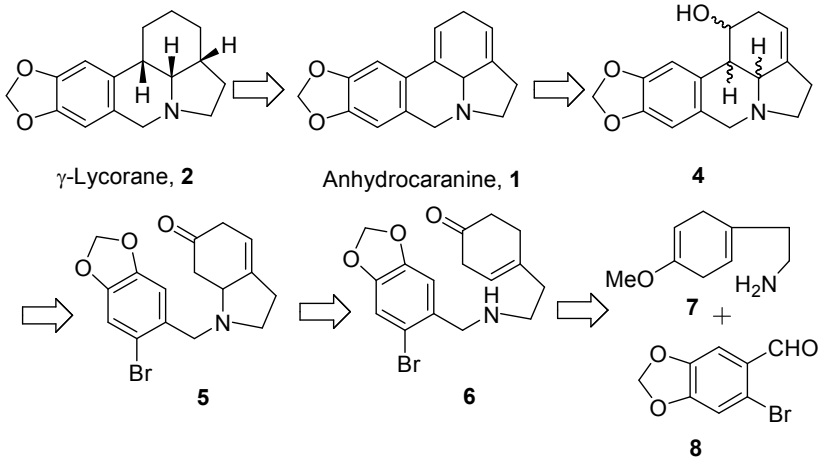


Figure 1. The structures of anhydrocaranine (**1**), γ-lycorane (**2**) and amarbellsine (**3**).

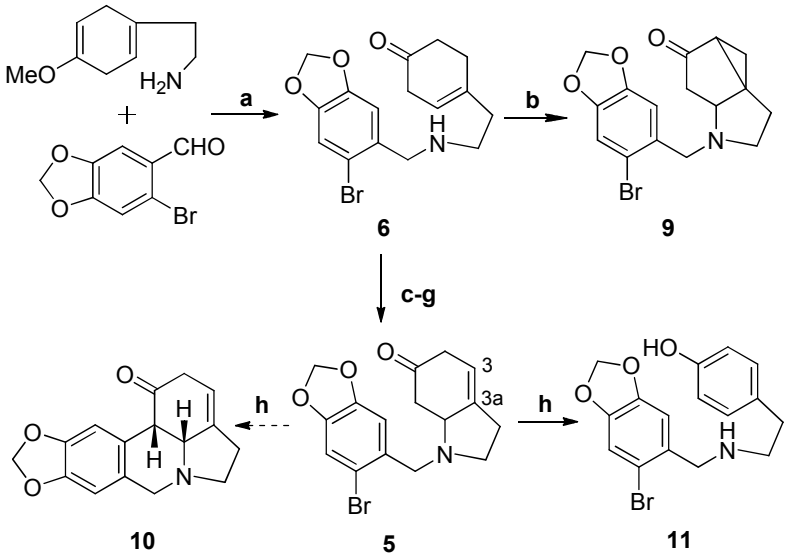
The initial retrosynthetic approach to anhydrocaranine and γ-lycorane was briefly outlined in Scheme 1, and the former could be afforded from alcohol **4**. Ketone **5**, the precursor of compound **4**, would be obtained from compounds **7** and **8** via compound **6** (Scheme 1).



Scheme 1. Retrosynthetic analysis of anhydrocaranine (**1**) and γ-lycorane (**2**)

Our synthesis began with secondary amine **6** (Scheme 2), which was prepared from 2-(4-methoxycyclohexa-1, 4-dienyl)ethylamine (**7**) and 6-bromopiperonal (**8**). The aminocyclization reaction[6] of compound **6** could not form ketone **5** directly but cyclopropyl ketone **9** was obtained. The compound **6** could be converted to ketone **5**

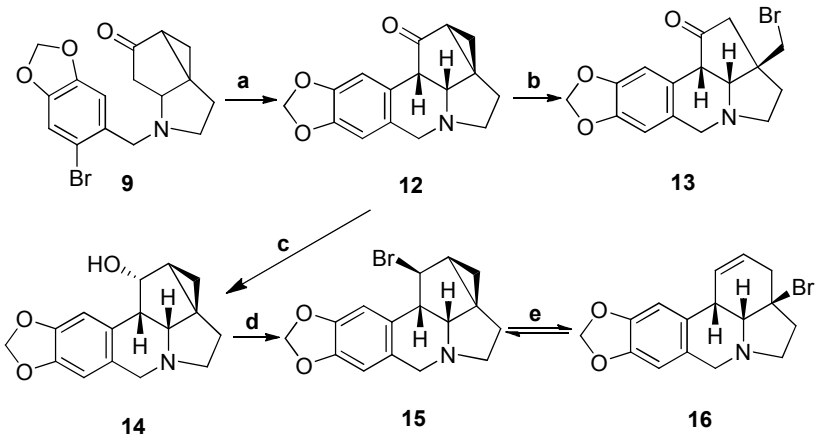
only via a series of reactions according to the previous research.[7] Unfortunately, compound **10** could not be prepared from ketone **5** by the reaction of palladium-mediated arylation,[8] but compound **11** was afforded. It seemed that the aromatization of C ring was initiated by C3-C3a double-bond in ketone **5**.



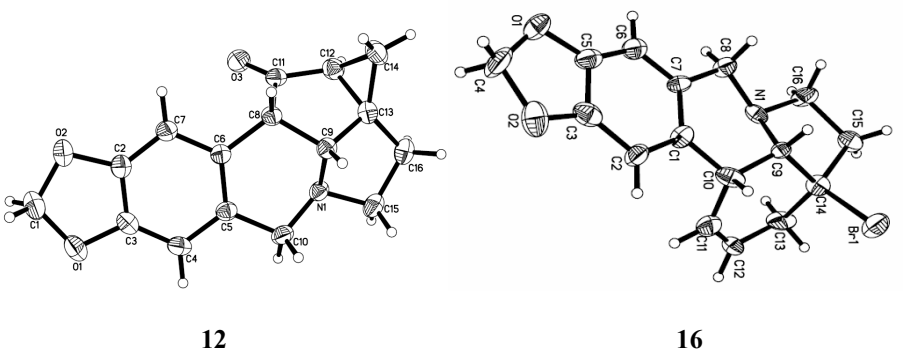
Scheme 2. Synthesis of the intermediate **9**. Reagents and conditions: a. 1). EtOH, 60 ºC, 3 h; 2). $NaBH_4$, EtOH, 0 ºC, 99%; 3). 2 M HCl aq., rt., 99%; b. 1). Br_2, AcOH, rt.; 2). K_2CO_3, MeOH, reflux, 82%; c. $NaBH_4$, EtOH, 0 ºC, 96%; d. TBDMSCl, imidazole, DMF, rt., 94%; e. 1). Br_2, DCM, -78 ºC; 2). K_2CO_3, MeOH, reflux, 80%; f. TBAF, THF, rt., 85%; g. DMSO, oxalyl chloride, DCM, -78 ºC, 1 h, then triethylamine, 91%; h. $Pd_2(dba)_3$, BINAP, ^{t}BuONa, toluene, 100 ºC, 85%.

In view of this disappointing result, we decided to use three-member ring compound **9** for the further palladium-mediated arylation. The palladium catalytic coupling reaction was running smoothly from cycloketone **9** to **12** in a yield of 82% (Scheme 3). This result suggested that cyclopropyl ring protected the C ring from aromatization and provided a potential double bond. The full C ring configuration of compound **12** was confirmed by ^{1}H, ^{13}C NMR and further X-ray crystallography (Figure 2).[9] With ketone **12** in hand, we explored a way to open the three-member ring. When treated with 40% hydrobromic acid in acetic acid at room temperature, ketone **12** was converted to compound **13**, but it was not our designed product. To avoid this undesired result, ketone **12** was reduced to cyclopropyl alcohol **14**, and the latter could be converted to corresponding cyclopropyl bromide **15** in the presence of phosphorus tribromide. Secondary bromide **15** could further undergo a cyclopropyl

ring opening rearrangement reaction to form homo-allylic bromide **16** with full lycorine-type skeleton. It was interestingly observed that the final ratio of compound **15** and **16** was constant at about 1 to 4, when either **15** or **16** was treated with aqueous hydrogen bromide. The structure and stereochemistry of compound **16** were confirmed by its NMR data and further by its X-ray crystallography (Figure 2).[9]



Scheme 3. Construction of lycorine-type skeleton and rearrangement between **15** and **16**. Reagents and conditions: a. $Pd_2(dba)_3$, BINAP, ^{t}BuONa, toluene, 100 ºC, 82%; b. 40% HBr/AcOH, rt., 97%; c. $NaBH_4$, EtOH, 0 ºC, 95%; d. PBr_3, DCM, 0 ºC, 95%; e. 47% HBr aq., rt. **15**:**16**≈1:4.

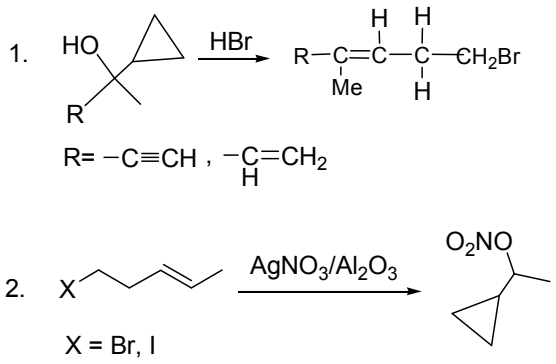


12 **16**

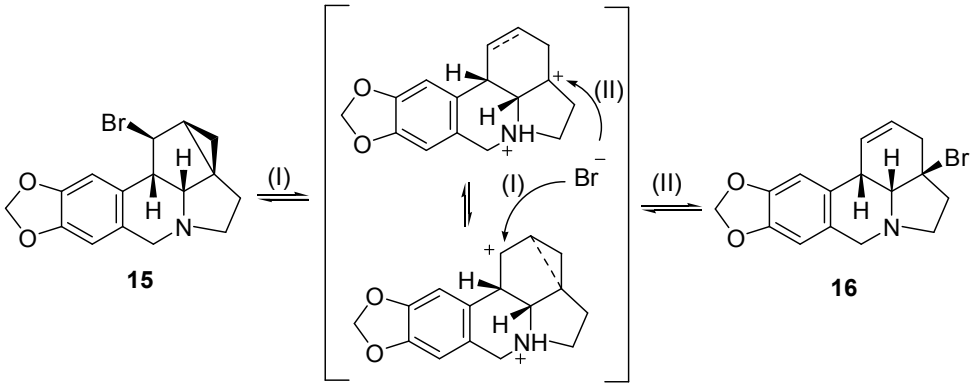
Figure 2. Crystal structures of compounds **12** and **16**

A similar reaction of cyclopropyl ring opening to form homo-allylic bromide was first reported by Julia over 50 years ago and followed with considerable development and synthetic applications (Scheme 4, 1.),[10] while the reverse reaction from homo-allylic bromide to cyclopropyl ring compound was reported before our reseach started mainly in anhydrous media such as silver nitrate-alumina and also got some attentions (Scheme 4, 2.).[11] But to the best of our knowledge, there was no such

equilibrium conversion between cyclopropyl ring and homo-allylic halides reported. Presumably, the suitable configuration of multi-ring fused structure made this nonclassical carbocation involved rearrangement as an equilibrium reactions possible (Scheme 5).

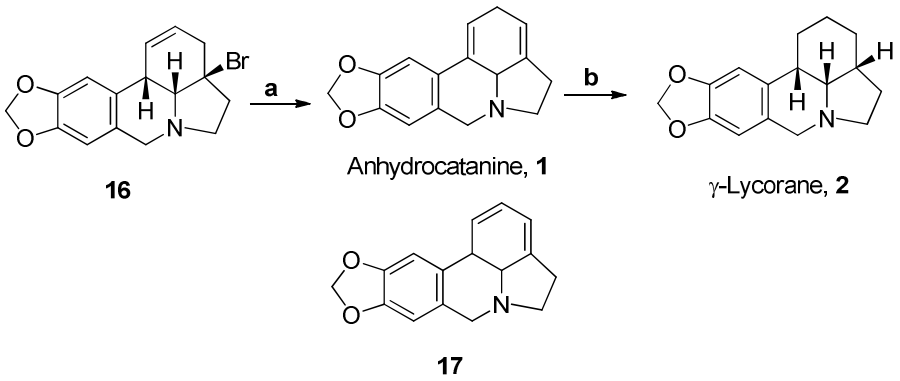


Scheme 4. The initial cyclopropyl ring opening (1) and corresponding formation (2) reactions



Scheme 5. Proposed equilibrium between 15 and 16 via nonclassical carbocation intermediate

Utilizing this rearrangement, the cyclopropyl compound **15** was converted to the homo-allylic bromide **16** in 77% yield. With the key intermediate **16** in hand, we could modify the functional groups to form different target products. Anhydrocaranine (**1**) was formed and no conjugated diene **17** observed, when bromide **16** was treated with bases such as NaOH or ^{t}BuONa. (±)-γ-Lycorane (**2**) was obtained as the only product conveniently from anhydrocaranine (**1**) by hydrogenation (Scheme 6).

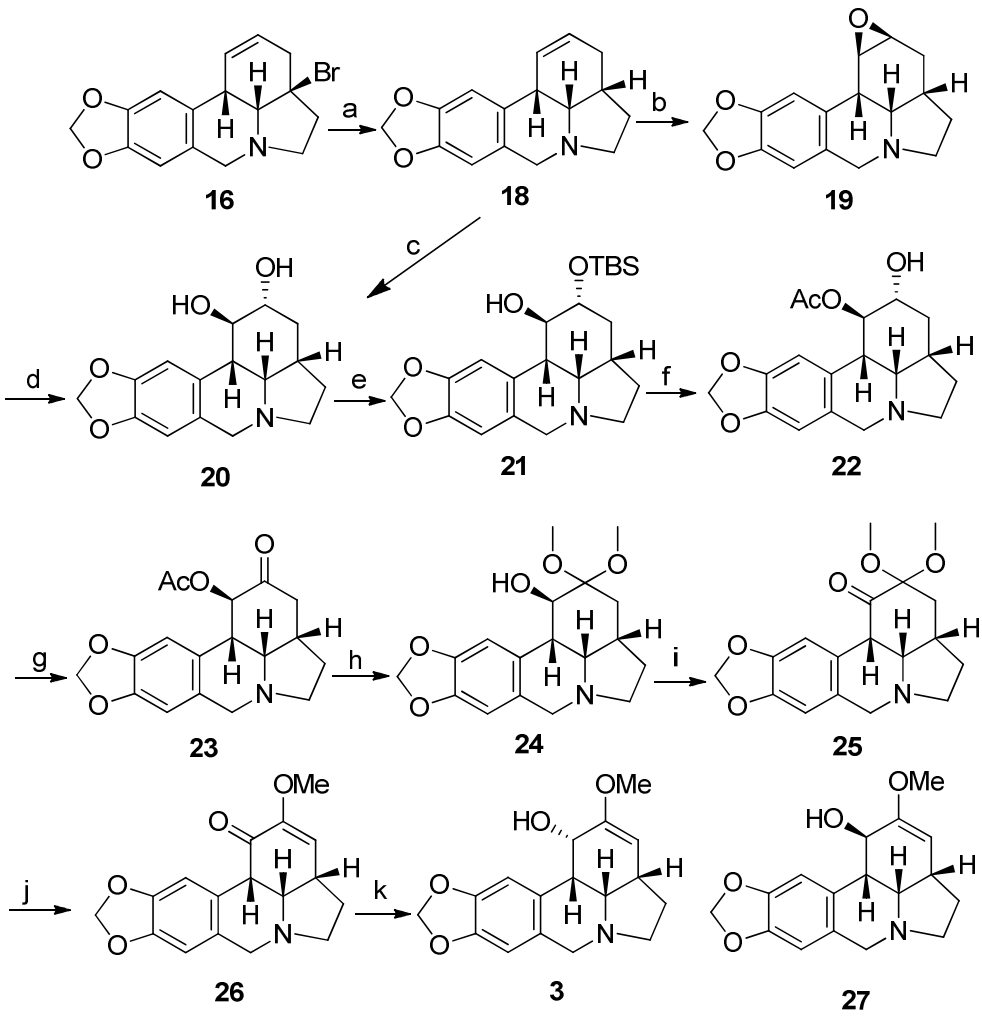


Scheme 6. Synthesis of anhydrocaranine (**1**) and (±)-γ-lycorane (**2**). a. ^{t}BuONa, EtOH, 60 ºC, 81%; b. Pd/C, H_2, AcOH, rt. 85%.

The structure of anhydrocaranine (**1**) was confirmed by its ^{1}H NMR, ^{13}C NMR data and COSY, HMQC, HMBC data. While the NMR data of (±)-γ-lycorane (**2**) were identical with the data reported before.[12]

At this stage, we hope to use the cycloproply ring-opening rearrangement reaction to synthesize more complex lycorine-type compound such as amarbellsine (**3**). The alkene compound **18** was obtained by reduction of bromide **16** with lithium aluminium hydride. Desired product **19** could be obtained, when compound **18** was treated with Cl_3CCN/H_2O_2 according to von Holleben's report,[13] but trifluoroacetic acid (TFA) should be employed to protect nitrogen in the molecule from oxidation. The diol **20** could be easily obtained by acid hydrolysis[14] of epoxide **19** and further investigation showed that it could be afforded from olefin **18** directly by treatment with $TFA/Cl_3CCN/H_2O_2$ system for a longer reaction time. 2-Hydroxyl in diol **20** could be selectivly protected by TBS group, while acetate ketone **23** could be afforded from silyl ether **21** by selective hydroxyl protect/deprotect performance followed with Swern oxidation. Dimethyl ketal **24** was formed from ketone **23** by treatment with trimethyl orthoformate and *p*-toluenesufonic acid,[15] and 1-acetyl was also removed at the same time. α,β–Unsaturated ketone **26** was afforded by carefully removal of one methanol molecule from dimethoxyl ketal **25**, which could be formed by Swern oxidation from 1-hydroxyl compound **24**. Compound ±(**3**) and its *epi*-isomer **27** were formed in a ratio of about 3 to 1 wether $NaBH_4/CeCl_3$ or Red-Al were employed to treat

with ketone **26**,[16] and finally, the target molecule (**3**) was obtained as the only isomer when DIBAL-H was used as the reagent (Scheme 7). The structure and configuration of compound **3** was confirmed by its NMR data and further by its X-ray crystallography (Figure 3).



Scheme 7. Synthesis of putative (±)-amarbellsine (**3**). Reagents and conditions: a. $LiAlH_4$, THF, 0 ºC, 80%; b. TFA, Cl_3CCN, H_2O_2, rt, 24 h, 54%; c. TFA, Cl_3CCN, H_2O_2, rt, 48 h, 55%; d. 10% H_2SO_4 aq., rt, 98%; e. TBSCl, imidazole, DMF, 99%; f. 1) Ac_2O, Et_3N, 2) 2 M HCl aq., 98% for 2 steps; g. DMSO, oxalyl chloride, DCM, -78 ºC, 1 h, then triethylamine, 75%; h. $CH(OMe)_3$, TsOH, MeOH, 98%; i. as step g above, 72%; j. AcOH, toluene, 80 ºC, 98%; k. DIBAL-H, toluene -78 ºC, 96%.

The NMR data of our synthesized compound ±(**3**) were compared with that of natural amarbellisine from Evidente's group[5a] and the results were summarized below (Tables 1 and 2).

Table 1. Comparison of the ^{13}C NMR spectra data

C	Synthetic product δ[a]	Natural product δ[a]	Δδ
1	71.2 *d*	79.8 *d*	-8.6[b]
2	157.2 *s*	154.3 *s*	2.9
3	96.9 *d*	112.9 *d*	-16
3a	35.3 *d*	58.6 *d*	-23.3
4	33.5 *t*	32.7 *t*	0.8
5	54.6 *t*	55.4 *t*	-0.8
7	56.2 t	60.9 t	-4.7
7a	128.9 s	132.5 s	-3.6
8	106.3 *d*	107.3 *d*	-1.0
9	146.6 *s*	146.0 *s*	0.6
10	146.6 *s*	146.7 *s*	-0.1
11	108.3 *d*	106.8 *d*	1.5
11a	128.*2*	124.6 *s*	3.6
11b	42.8 *d*	45.6 *d*	-2.8
11c	62.0 *d*	69.1 *d*	-7.1
12	100.9 *t*	100.7 *t*	0.2
OMe	54.4 *q*	57.6 *q*	-3.2

a. Multiplicites determined by DEPT spectrum.

b. Obvious differences were highlighted.

Table 2. Comparison of the ^{1}H NMR spectra data

C	Synthetic product δH	Natural product δH	Δδ
1	3.98	3.48	0.50
3	4.65	5.56	-0.91
3a	3.07	3.41	-0.34
4	2.30	2.14	0.16
	1.71	1.56	0.15
5	3.24	3.07	0.17
	2.16	3.02	-0.89
7	4.08	4.33	-0.25
	3.29	3.79	-0.50
8	6.56	6.45	0.11
11	6.72	6.54	0.18
11b	2.99	3.28	-0.29
11c	2.68	4.08	-1.40
12	5.93	5.88	0.05
	5.90	5.86	0.04
OMe	3.57	3.43	0.14

Since the obvious differences resonating positions for two compounds appeared at C3a, C3, C1 and C11c from ^{13}C NMR spectra, and H11c, H3, H3a, H1,

H5 and H7 from ^{1}H NMR spectra, these suggested that B/C or C/D ring configurations at two compounds might be different. At the same time, these ring configurations made the protons attached with C5 and C7 in two compounds surrounding with different environments. The X-ray crystallography data showed that the C ring of synthesized product adopted a half chair-like conformation (Figure 3), and six carbons on the ring were staying nearly in one plane except C11b, so the NMR values of axial-equatorial or axial-axial coupling in the system would not be typical as in a chair-like conformation system.

Meanwhile, the R_f valve of compound **3** at silica gel TLC plate was great than 0.85 (while the R_f of HCl salt of compound **3** was less than 0.10) but that of natural compound was 0.48 under the reported conditions.[5a]

Based on the comparison, we suggested that the natural amarbellisine's struture should be reconfirmed, and our synthesized compound ±(**3**) could be only named as putative *rac*-amarbellisine. Part of the synthesis work for putative amarbellisine as well as structure discussion were published as a letter before.[9]

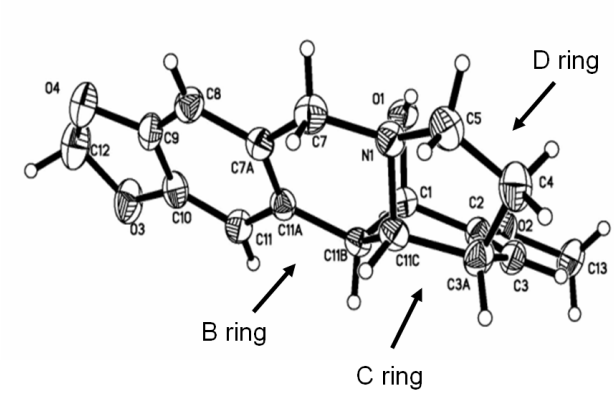


Figure 3. A half chair-like C ring conformation of the synthesized compound **3** from crystal structure

In summary, we developed a new practical method which mainly included cycloproply ring-opening rearrangement reaction for the synthesis of lycorin-type alkaloids. By this method, we successfully accomplished the synthesis of anhydrocaranine (**1**), (±)-γ-lycorane (**2**) and putative (±)-amarbellisine (**3**). The structure of anhydrocaranine (**1**) was confirmed by its one and two dimensional NMR

data, and the data were first reported to the best of our knowledge. While the structure of (±)-γ-lycorane (**2**) was confirmed by comparing its NMR data with literature reported one. The structures and relative stereochemistry from the target putative amarbellisine **3** were confirmed by its NMR data and X-ray crystallography, and it was different isomer of natural amarbellisine.

Experiment

Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Bruker Avance 300 or 400 spectrometer at 300 or 400 MHz. Carbon-13 nuclear magnetic resonance (^{13}C-NMR) was recorded on Bruker Avance 300 or 400 spectrometer at 75 or 100 MHz. Chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (TMS) for all recorded NMR spectra. High resolution mass spectra were taken on AB QSTAR Pulsar mass spectrometerm and Autospec Premier P776, by ESI or EI, which were indicated repectively. Melting points were determined on a capillary melting point apparatus and are uncorrected. Starting materials and reagents used in reactions were obtained commercially from Acros, Aldrich, Fluka and were used without further purification, unless otherwise indicated. All reactions were conducted in dried glassware under a positive pressure of dry nitrogen. Silica gel (Qingdao, 200-300 mesh) was used for column chromatography.

Compound 6: A solution of bromopiperonal **8** (4.6 g, 20 mmol) and 2-(4-methoxycyclohexa-1, 4-dienyl) ethylamine **7** (3.1 g, 20 mmol) in dry methanol (100 mL) was refluxed for 2.5 h. The solution was cooled to room temperature, then sodium borohydride (760 mg, 20 mmol) was added and the reaction mixture was stirred at room temperature for 30 min. The solvent was removed in *vacuo*. The residue was diluted with ethyl acetate, washed with brine, and dried over sodium sulfate, then the solvent was evaporated. To a solution of the above residue (183 mg, 0.5 mmol) in acetone (4 mL) was added at room temperature aqueous hydrochloric acid (2 M, 1 mL). After being stirred for 10 min, the reaction mixture was quenched with saturated aqueous potassium carbonate and extracted with ethyl acetate. The

combined organic layers were washed with brine, the organic solvent was dried (sodium sulfate), filtered, and evaporated. Compound **6** (174 mg, 99%) was obtained as yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.94 (1H, s), 6.83 (1H, s), 5.92 (2H, s), 5.47 (1H, s), 3.72 (2H, s), 2.81 (2H, brs), 2.67 (2H, t, *J* = 6.6 Hz), 2.45-2.41 (2H, m), 2.35-2.31 (2H, m) , 2.25 (2H, t, *J* = 6.6 Hz), 1.53 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 210.43, 147.38, 147.37, 136.38, 132.36, 119.66, 114.03, 112.71, 110.17, 101.69, 53.56, 46.37, 39.57, 38.54, 37.36, 28.35. HRMS (EI, m/z): calcd. for $C_{16}H_{18}NO_3Br$ (M^+): 351.0470, found: 351.0464.

Compound 9: To a solution of compound **6** (176 mg, 0.5 mmol) in acetic acid (4 mL) at room temperature was added bromine (80 mg, 0.5 mmol). The reaction mixture was stirred for 5 min, and then quenched with saturated aqueous sodium bisulfate and neutralized with saturated aqueous sodium bicarbonate. The reaction mixture was extracted with ethyl acetate, washed with brine, the organic solvent was dried (sodium sulfate), evaporated, and colorless oil was obtained. To a solution of colorless oil (258 mg, 0.6 mmol) in methanol (5 mL) was added potassium carbonate (166 mg, 1.2 mmol). After being stirred at 60°C for 12 h, the solvents were filtered and evaporated. The residue was purified by flash chromatography (elution with petroleum ether/ethyl acetate: 4/1) to give compound **9** (209 mg, >99%) as a white powder. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.95 (1H, s), 6.91 (1H, s), 5.94 (2H, s), 3.78 (1H, d, *J* = 13.8 Hz), 3.41 (1H, d, *J* = 13.8 Hz), 3.18 (1H, td, *J* = 9.0, 3.0 Hz), 2.97 (1H, d, *J* = 2.4 Hz), 2.43 (1H, dd, *J* = 8.6, 9.3 Hz), 2.20-2.16 (2H, m) , 2.14-2.09 (1H, m), 1.98-1.87 (1H, m), 1.66 (1H, dd, *J* = 9.0, 3.6 Hz), 1.46-1.41 (1H, m), 1.21-1.18 (1H, m) . ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 212.86, 147.39, 147.37, 130.85, 114.26, 112.52, 110.41, 101.66, 65.53, 57.53, 53.48, 40.46, 39.92, 35.00, 27.55, 16.72. HRMS (ESI, m/z): calcd. for $C_{16}H_{17}NO_3Br$ ($[M+H]^+$): 350.0391, found: 350.0394. m.p.: 118-119 °C.

Compound 12: A mixture of tris(dibenzylideneacetone)dipalladium (18 mg, 0.02 mmol), (±)-2, 2'-bis (diphenylphosphino)-1, 1'-binaphthalene (25 mg, 0.04 mmol) and sodium tertiary butoxide (38 mg, 0.4 mmol) in dry toluene (10 mL) was stirred at

room temperature for 1 h. Then the solution of **9** (70 mg, 0.2 mmol) in dry toluene (5 mL) were added. The reaction mixture was placed under nitrogen atmosphere. After being stirred at 95°C for 24 h, the reaction mixture was filtered and evaporated. The residue was purified by flash chromatography (elution with petroleum ether/ ethyl acetate: 3/1) to give **12** (44 mg, 82%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.78 (1H, s), 6.55 (1H, s), 5.90 (1H, d, *J* = 1.4 Hz), 5.87 (1H, d, *J* = 1.4 Hz), 3.79 (1H, d, *J* = 13.8 Hz), 3.44-3.38 (2H, m), 3.04 (1H, d, *J* = 4.2 Hz), 2.87 (1H, d, *J* = 4.5 Hz), 2.70 (1H, ddd, *J* = 9.0, 9.0, 9.0 Hz), 2.30 (1H, ddd, *J* = 12.3, 9.9, 2.0 Hz), 2.05-1.95 (1H, m), 1.59-1.55 (2H, m), 1.52-1.48 (1H, m). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 209.66, 146.25, 146.19, 129.02, 122.43, 110.95, 106.60, 100.90, 64.38, 52.55, 52.47, 47.33, 38.64, 33.09, 27.91, 16.58. HRMS (ESI, m/z): calcd. for $C_{16}H_{16}NO_3$ ($[M+H]^+$): 270.1130, found: 270.1135. m.p.: 175-176 °C.

Compound 13: To a solution of compound **12** (50 mg, 0.19 mmol) in acetic acid (4 mL) at room temperature was added 40% HBr/AcOH (0.3 mL). The reaction mixture was stirred for 2 min, then neutralized with saturated aqueous sodium bicarbonate, and extracted with ethyl acetate, washed with brine. The organic layer was dried (sodium sulfate) and evaporated. The residue was purified by flash chromatography (elution with petroleum ether/ethyl acetate: 4/1) to give compound **13** (63 mg, 97%) as a white powder. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.82 (1H, s), 6.54 (1H, s), 5.92 (1H, d, *J* = 1.2 Hz), 5.90 (1H, d, *J* = 1.2 Hz), 3.82 (1H, d, *J* = 14.4 Hz), 3.61 (1H, s), 3.50-3.43 (2H, m), 3.26-3.20 (1H, m), 2.87 (1H, d, *J* = 3.9 Hz), 2.78 (1H, d, *J* = 18.9 Hz), 2.63 (1H, dd, *J* = 8.7, 17.4 Hz), 2.46 (1H, d, *J* = 19.2 Hz), 2.11-2.04 (2H, m). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 212.81, 146.52, 146.32, 127.48, 122.58, 110.47, 106.41, 100.96, 69.53, 52.73, 52.45, 49.33, 47.51, 41.26, 38.12. HRMS (ESI, m/z): calcd. for $C_{16}H_{17}NO_3Br$ ($[M+H]^+$): 350.0391, found: 350.0397. m.p.: 113-115°C.

Compound 14: To a solution of **12** (200 mg, 0.74 mmol) in methanol (20 mL) was

added sodium borohydride (56.3 mg, 1.5 mmol). After being stirred at room temperature for 1 h, the reaction mixture was extracted with ethyl acetate, washed with brine, dried (sodium sulfate), and evaporated. The residue was purified by flash chromatography (elution with ethyl acetate) to give **14** (191 mg, 95%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.66 (1H, s), 6.55 (1H, s), 5.90 (1H, d, *J* = 1.3 Hz), 5.89 (1H, d, *J* = 1.3 Hz), 4.16 (1H, d, *J* = 5.5 Hz), 3.83 (1H, d, *J* = 13.9 Hz), 3.37 (1H, ddd, *J* = 8.8, 8.7, 2.0 Hz), 3.27 (1H, d, *J* = 13.9 Hz), 2.66 (1H, t, *J* = 4.6 Hz), 2.51 (1H, ddd, *J* = 9.9, 9.0, 9.0 Hz), 2.44 (1H, d, *J* = 4.1 Hz), 2.28-2.21 (1H, m), 2.03-1.95 (1H, m), 1.27-1.23 (1H, m), 1.03-0.98 (1H, m), 0.68-0.64 (1H, m). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 146.47, 146.12, 130.02, 125.44, 109.39, 106.72, 100.85, 76.74, 69.19, 53.79, 53.10, 45.43, 34.07, 32.43, 28.10, 10.19. HRMS (EI, m/z): calcd. for $C_{16}H_{17}NO_3$ (M^+): 271.1208, found: 271.1203. m.p.: 114-116°C.

Compound 15: To a solution of **14** (100 mg, 0.37 mmol) in dichloromethane (20 mL) was added phosphorus tribromide (0.04 mL, 0.44 mmol). After being stirred at 0°C for 1 h, the reaction mixture was quenched with saturated aqueous potassium carbonate, extracted with ethyl acetate, washed with brine, dried (sodium sulfate), and evaporated. The residue was purified by flash chromatography (elution with petroleum ether/ ethyl acetate: 5/1) to give **15** (116 mg, 95%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.17 (1H, s), 6.55 (1H, s), 5.91 (2H, s), 4.57 (1H, dd, *J* = 7.5, 5.0 Hz), 3.81 (1H, d, *J* = 13.9 Hz), 3.38 (1H, dd, *J* = 8.8, 2.2 Hz), 3.32 (1H, d, *J* = 14.1 Hz), 3.04 (1H, t, *J* = 5.3 Hz), 2.58-2.52 (2H, m), 2.15 (1H, t, *J* = 9.0 Hz), 1.92-1.87 (1H, m), 1.54-1.51 (1H, m), 1.17 (1H, t, *J* = 6.2 Hz), 1.03 (1H, t, *J* = 4.4 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 146.50, 146.40, 128.96, 127.21, 108.97, 106.90, 101.03, 69.54, 62.44, 53.57, 53.08, 48.70, 39.73, 32.86, 28.50, 12.74. HRMS (EI, m/z): calcd. for $C_{16}H_{15}NO_2Br$ ($[M-H]^+$): 332.0286, found: 332.0288.

Compound 16: To a solution of **15** (120 mg, 0.36 mmol) in methanol (20 mL) was added 47% hydrobromic acid aqueous solution (2 mL, 0.44 mL). After being stirred at

room temperature for 144 h, the reaction mixture was quenched with saturated aqueous potassium carbonate, extracted with ethyl acetate, washed with brine, dried (sodium sulfate), and evaporated. The residue was purified by flash chromatography (elution with petroleum ether/ ethyl acetate: 5/1), to give **16** (92 mg, 77 %) as a yellow solid and recovered **15** (21 mg, 18%) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.80 (1H, s), 6.50 (1H, s), 5.92 (2H, s), 5.78 (1H, d, *J* = 10.1 Hz), 5.63-5.58 (1H, m), 3.98 (1H, d, *J* = 14.1 Hz), 3.64 (1H, brs), 3.39 (1H, d, *J* = 14.0 Hz), 3.40-3.33 (1H, m), 2.95 (1H, d, *J* = 4.6 Hz), 2.74-2.71 (2H, m), 2.60-2.53 (1H, m), 2.44-2.36 (2H, m). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 146.89, 146.25, 129.11x2, 127.23, 121.53, 108.79, 106.49, 101.03, 68.25, 60.88, 55.93, 51.53, 41.38, 37.85, 36.44. HRMS: (ESI, m/z) calcd. for $C_{16}H_{17}NO_2$ ($[M+H]^+$): 334.0442, found: 334.0447. m.p.: 187-190°C.

Treated compound **16** as starting material with above reaction conditions, the similar ratio of compound **15** and **16** was observed.

Anhydrocaranine (1): To a solution of **16** (50 mg, 0.15 mmol) in EtOH (10 mL) were added NaOH (12 mg, 0.3 mmol). After being stirred at 60°C for 12 h, the reaction mixture was cooled at room temperature and extracted with AcOEt, washed with brine, dried (sodium sulfate), and evaporated. The residue was purified by flash chromatography (elution with petroleum ether/AcOEt: 3/1) to give anhydrocaranine (1) (31 mg, 81%) as a yellow solid. The NMR data of compound **1** were listed below (Table 3).

Table 3. ^{13}C NMR and ^{1}H NMR data of anhydrocaranine (**1**).

H	^{1}H NMR δ	C	^{13}C NMR δ	HMBC
1	6.11 (1H, d, *J* = 2.8 Hz)	1	115.4 *d*	2.89
2+2’	2.89 (2H, brs)	2	28.7 *t*	6.11, 3.33, 2.97, 2.45
3	5.58 (1H, s)	3	115.1 *d*	5.91
3a		3a	132.0 *s*	7.11, 3.55
5’+4	2.57 (2H, overlap)	4	27.4 *t*	
4’	2.45 (1H, t, *J* = 9.1 Hz)			
5	3.33 (1H, m)	5	52.6 *t*	3.55, 2.57, 2.45

7+7'	4.01 (1H, d, *J* = 14.0 Hz) 3.55 (1H, d, *J* = 14.0 Hz)	7	56.1 *t*	6.54, 3.33, 2.97, 2.57
7a		7a	126.2 *s*	7.11, 6.54, 4.01,
8	6.54 (1H, s)	8	107.0 *d*	6.11, 4.01, 3.55, 3.33
9		9 (or 10)	146.9 *s*	7.11, 6.54, 5.91
10		10 (or 9)	147.0 *s*	
11	7.11 (1H, s)	11	102.8 *d*	6.54
11a		11a	128.8 *s*	7.11, 4.01, 3.55, 3.33, 2.89
11b		11b	137.7 s	2.97, 2.89, 2.57
11c	2.97 (1H, d, *J* = 8.1 Hz)	11c	61.3 *d*	6.11, 4.01, 3.55, 3.33
12	5.91 (2H, s)	12	101.1 *t*	6.11, 5.58

γ-Lycorane (2): To a solution of Anhydrocaranine (**1**) (50 mg, 0.2 mmol) in acetic acid (10 mL) were added 10% Pd/C (15 mg). The reaction mixtures were placed under an atmosphere of hydrogen and stirred for 6 h at room temperature. The reaction mixtures were then filtered and concentrated in *vacuo*. The mixtures were quenched with saturated aqueous potassium carbonate, extracted with ethyl acetate, washed with brine, dried (sodium sulfate), and organic solvent evaporated. The residue was purified by flash chromatography (elution with petroleum ether/ ethyl acetate: 3/1), to give γ-Lycorane (**2**) (43 mg, 85%) as a colorless oil. NMR data of our synthesized compound **2** as well as that of reported data[12a] were showed in Table 4 and 5.

Table 4. Comparison of the ^{13}C NMR spectra data of γ-Lycorane (**2**).

C	Synthetic product δ	Reported data δ	Δδ
1	29.3 *t*	29.3 *t*	0
2	25.2 *t*	25.2 *t*	0
3	30.4 *t*	30.4 *t*	0
3a	37.4 *d*	37.4 *d*	0
4	31.7 *t*	31.7 *t*	0
5	53.7 *t*	53.7 *t*	0
7	57.1 t	57.1 t	0
7a	127.3 *s*	127.3 *s*	0
8	106.3 *d*	106.3 *d*	0
9	145.7 *s*	145.6 *s*	0.1
10	146.1 *s*	146.0 *s*	0.1
11	108.3 *d*	108.3 *d*	0
11a	133.2 s	133.2 s	0
11b	39.5 *d*	39.5 *d*	0
11c	62.9 *d*	62.9 *d*	0

12	100.7 *t*	100.7 *t*	0

Table 5. Comparison of the ^{1}H NMR spectra data of γ-Lycorane (**2**).

C	Synthetic product δH	Natural product δH	Δδ
1,2,3,4	1.22- 1.60 (4H, m)	1.23-1.54(4H, m)	0.02
	1.62-1.93 (3H, m)	1.59-1.81(3H, m)	0.08
	1.98-2.07 (1H, m)	1.95-2.07 (1H, m)	0.02
3a+5	2.12-2.24 (2H, m)	2.09-2.24(2H, m)	0.02
11c	2.39 (1H, t, *J* = 4.8 Hz)	2.37(1H, t, *J* = 4.8 Hz)	0.02
11b	2.71-2.78 (1H, m)	2.70-2.78(1H, m)	0.01
7	3.21 (1H, d, *J* = 14.4 Hz)	3.21(1H, d, *J* = 14.4 Hz)	0.00
5’	3.38 (1H, ddd, *J* = 9.3, 9.2, 3.8 Hz)	3.38 (1H, ddd, *J* = 9.3, 9.2, 3.8 Hz)	0.00
7’	4.01 (1H, d, *J* = 14.4 Hz)	4.02 (1H, d, *J* = 14.4 Hz)	-0.01
12	5.87 (1H, d, *J* = 1.4 Hz)	5.88 (1H, d, *J* = 1.4 Hz)	-0.01
	5.89 (1H, d, *J* = 1.4 Hz)	5.89 (1H, d, *J* = 1.4Hz)	0.00
8	6.49 (1H, s)	6.49 (1H, s)	0.00
11	6.61 (1H, s)	6.61 (1H, s)	0.00

Compound 18: To a solution of **16** (50 mg, 0.15 mmol) in dry tetrahydrofuran (10 mL) was added lithium aluminium hydride (7 mg, 0.18 mmol). The reaction mixture was placed under a nitrogen atmosphere and stirred for 12 h at 0°C. The reaction mixture was quenched with saturated aqueous ammonium chloride, extracted with ethyl acetate, washed with brine, dried (sodium sulfate), and evaporated. The residue was purified by flash chromatography (elution with petroleum ether/ ethyl acetate: 1/1) to give **18** (30 mg, 80%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.75 (1H, s), 6.50 (1H, s), 5.90 (2H, s), 5.72 (2H, s), 4.98 (1H, d, *J* = 14.1 Hz), 3.42-3.28 (3H, m), 2.57 (1H, t, *J* = 5.1 Hz), 2.37-2.31 (2H, m), 2.29-2.12 (1H, m), 2.09-1.90 (2H, m), 1.61-1.57 (1H, m). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 146.41, 145.75, 130.76, 129.92, 128.11, 124.82, 108.60, 106.43, 100.72, 61.87, 56.09, 52.31, 38.04, 33.90, 30.59, 27.82.

HRMS (EI, m/z): calcd. for $C_{16}H_{17}NO_2$ (M^+): 255.1259, found: 255.1259.

Compound 19: A mixture of trichloroacetonitrile (0.1 mL) and 30% hydrogen peroxide (0.1 mL) in dichloromethane (5 mL) was stirred at room temperature for 1h. Then the solution of **18** (100 mg, 0.4 mmol) in a mixture of dichloromethane (3 mL)

and trifluoroacetic acid (1 mL) was added. After being stirred at room temperature for 24 h, the reaction mixture was quenched with 26% aqueous ammonia, extracted with ethyl acetate, washed with brine, dried (sodium sulfate), and evaporated. The residue was purified by flash chromatography (elution with petroleum ether/ethyl acetate: 1/1) to give **19** (57 mg, 54%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.85 (1H, s), 6.52 (1H, s), 5.92 (1H, d, *J* = 1.2 Hz), 5.91 (1H, d, *J* = 1.2 Hz), 3.93 (1H, d, *J* = 14.4 Hz), 3.37-3.23 (4H, m), 3.13 (1H, dd, *J* = 3.9, 1.2 Hz), 2.36-2.28 (2H, m), 2.25-2.18 (1H, m), 2.08 (1H, ddd, *J* = 15.0, 6.6, 2.1 Hz), 1.98-1.86 (1H, m) 1.77 (1H, ddd, *J* = 15.0, 10.2, 1.5 Hz), 1.56-1.50 (1H, m). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 146.70, 146.26, 129.13, 127.53, 108.94, 106.39, 100.92, 58.92, 55.83, 55.54, 54.29, 51.06, 37.36, 31.29, 28.64, 26.57. HRMS (EI, m/z): calcd. for $C_{16}H_{17}NO_3$ (M^+): 271.1208, found: 271.1214.

Compound 20: To a solution of **19** (50 mg, 0.18 mmol) in methanol (4 mL) was added 10% sulfuric acid (1 mL) at room temperature. After being stirred for 24 h, the reaction mixture was quenched with saturated aqueous potassium carbonate and extracted with ethyl acetate. The combined organic layers were washed with brine, the organic solvent was dried (sodium sulfate), filtered, and evaporated. Compound **20** (51 mg, 98%) was obtained as yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.91 (1H, s), 6.49 (1H,s), 5.87 (2H, s), 3.97 (1H, d, *J* = 14.4 Hz), 3.45-3.42 (2H, m), 3.32-3.24 (2H, m), 2.63-2.61 (1H, m), 2.46 (1H, t, *J* = 4.2 Hz), 2.33-2.25 (1H, m), 2.23-2.12 (1H, m), 2.03-1.91 (1H, m), 1.88-1.83 (1H, m), 1.54-1.48 (1H, m). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 146.24, 145.42, 128.76, 127.90, 111.00, 106.07, 100.70, 76.68, 73.35, 64.00, 56.77, 53.07, 44.42, 36.51, 36.03, 28.52. HRMS (EI, m/z): calcd. for $C_{16}H_{19}NO_4$ (M^+):289.1314, found: 289.1311. m.p.: 101-104°C.

Compound 21: A mixture of imidazole (48 mg, 0.70 mmol), *t*-butyl dimethyl chlorosilane (63 mg, 0.42 mmol) and **20** (100 mg, 0.35 mmol) in dry N, N-dimethylformamide (10 mL) was stirred at 60 °C for 24 h. Then the reaction mixture was quenched with saturated aqueous potassium carbonate and extracted with

ethyl acetate. The combined organic layers were washed with brine, the organic solvent was dried (sodium sulfate), filtered, and evaporated. Compound **21** (138 mg, 99%) was obtained as yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.99 (1H, s), 6.50 (1H, s), 5.90 (1H, d, *J* = 1.2 Hz), 5.87 (1H, d, *J* = 1.2 Hz), 4.06 (1H, d, *J* = 14.4 Hz), 3.55-3.51 (2H, m), 3.38-3.25 (2H, m), 2.73 (1H, dd, *J* = 9.0, 3.9 Hz), 2.61 (1H, s), 2.47 (1H, t, *J* = 4.3 Hz), 2.35-2.29 (1H, m), 2.26-2.15 (1H, m), 2.06-1.94 (1H, m), 1.81-1.75 (1H, m), 1.74-1.61 (1H, m) , 1.60-1.47 (1H, m) , 0.87 (9H, s) , 0.11-0.10 (6H, m). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 146.34, 145.46, 128.78, 127.93, 111.05, 105.94, 100.70, 76.62, 75.47, 63.47, 56.79, 53.06, 43.65, 37.51, 36.27, 28.57, 25.74, 17.96, -3.96, -4.72. HRMS (EI, m/z): calcd. for $C_{22}H_{33}NO_4Si$ (M^+): 403.2179, found: 403.2170.

Compound 22: To the solution **21**(740 mg, 1.8 mmol) in dry triethylamine (15mL) was added acetic anhydride (0.35 mL, 3.6mmol) and 4-dimethylamiopryidine (9 mg, 0.07 mmol). The reaction mixture was placed under nitrogen atmosphere. After being stirred at 60°C for 24 h, the reaction mixture was neutralized by aqueous potassium carbonate, extracted with ethyl acetate and evaporated. The crude product was suspended in 20 mL of methanol at 0°C. Hydrochloric acid (2 M, 2 mL) was added slowly and the mixture was stirred at room temperature. After being stirred for 4 h, the reaction mixture was quenched with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The combined organic layers were washed with brine, the organic solvent was dried (sodium sulfate), filtered, and evaporated. Compound **22** (595 mg, 98%) was obtained as yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.64 (1H, s), 6.49 (1H, s), 5.87 (2H, s), 4.97 (1H, t, *J* = 9.6 Hz), 4.06 (1H, d, *J* = 14.7 Hz), 3.67-3.59 (1H, m), 3.38-3.26 (2H, m), 2.84 (1H, dd, *J* = 10.2, 3.9 Hz), 2.54 (1H, t, *J* = 4.2 Hz), 2.35-2.19 (3H, m), 2.09 (3H, s), 2.03-1.94 (2H, m), 1.73-1.65 (1H, m), 1.61-1.50 (1H, m). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 171.9, 146.6, 145.6, 128.4, 127.4, 109.5, 106.4, 100.8, 79.4, 72.5, 63.2, 56.4, 52.7, 42.7, 37.6, 36.1, 28.5,

21.3. HRMS (EI, m/z): calcd. for $C_{18}H_{21}NO_5$ (M^+): 331.1420, found: 331.1410. m.p.: 169-170°C.

Compound 23: To a solution of oxalyl chloride (0.24 mL, 2.8 mmol) in dry dichloromethane (3 mL) under a nitrogen atmosphere was added dropwise dimethyl sulfoxide (0.35 mL, 4.9 mmol) in dry dichloromethane (3 mL) at -78°C for 40 min. Then a solution of **22** (230 mg, 0.7 mmol) in dry dichloromethane (10 mL) was added dropwise. After being stirred for 1 h, triethylamine (1 mL, 7 mmol) was added slowly. After being stirred for 10 min, the reaction mixture was warmed to temperature, quenched with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The combined organic layers were washed with brine, the organic solvent was dried (sodium sulfate), filtered, and evaporated. The residue was purified by flash chromatography (elution with petroleum ether/ ethyl acetate: 4/1) to give **23** (174 mg, 76%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.68 (1H, s), 6.53 (1H, s), 5.90 (2H, s), 5.39 (1H, d, J = 11.1 Hz), 4.15 (1H, d, J = 14.7 Hz), 3.48-3.40 (2H, m), 3.17 (1H, dd, J = 11.1, 3.3 Hz), 2.75-2.68 (2H, m), 2.64-2.59 (1H, m), 2.48-2.35 (2H, m), 2.14-2.11 (4H, m), 1.69-1.60 (1H, m). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 204.61, 169.94, 146.97, 145.76, 128.19, 126.85, 109.84, 106.37, 100.93, 78.51, 62.59, 56.24, 52.52, 45.07, 43.30, 39.55, 29.58, 20.76. HRMS (EI, m/z): calcd. for $C_{18}H_{19}NO_5$ (M^+): 329.1263, found: 329.1269. m.p.: 199-202°C.

Compound 24: A mixture of **23** (300 mg, 0.9 mmol), trimethyl orthoformate (1.2 mL, 7.8 mmol) and *p*-toluenesulfonic acid (300 mg, 1.74 mmol) in methanol (20 mL) was refluxed for 30 h under nitrogen atmosphere. Then the reaction mixture was quenched with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The combined organic layers were washed with brine, the organic solvent was dried (sodium sulfate), filtered, and evaporated. The residue was purified by flash chromatography (elution with ethyl acetate) to give **24** (298mg, 98%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.94 (1H, s), 6.50 (1H, s), 5.89 (1H, s), 5.87 (1H,

s), 4.05 (1H, d, *J* = 14.7 Hz), 3.78 (1H, d, *J* = 10.2 Hz), 3.43 (3H, s), 3.35-3.25 (5H, m), 2.90 (1H, dd, *J* = 10.2, 3.6 Hz), 2.47 (1H, t, *J* = 4.2 Hz), 2.36-2.28 (2H, m), 2.24-2.16 (1H, m) , 2.05-1.92 (2H, m) , 1.59-1.43 (2H, m). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 146.4, 145.4, 128.6, 128.2, 111.3, 105.9, 100.7, 99.8, 75.9, 63.2, 56.7, 53.2, 49.9, 49.8, 43.4, 35.0, 34.8, 28.3. HRMS (EI, m/z): calcd. for $C_{18}H_{23}NO_5$ (M^+): 333.1576, found: 333.1584.

Compound 25: The procedure was similar as preparing compound **23** above. The residue was purified by flash chromatography (elution with petroleum ether/ sodium sulfate: 2/1) to give **25** (275 mg, 72%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.52 (1H, s), 6.45 (1H, s), 5.92 (2H, s), 4.07 (1H, d, *J* = 4.8 Hz), 4.02 (1H, d, *J* = 14.7 Hz), 3.42-3.25 (8H, m), 2.92 (1H, t, *J* = 4.2 Hz), 2.70-2.64 (1H, m), 2.34-2.27 (2H, m), 2.11-2.02 (1H, m) , 1.86-1.78 (1H, m) , 1.57-1.50 (1H, m). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 204.50, 146.86, 145.96, 128.71, 123.56, 110.54, 106.15, 100.91, 99.93, 66.45, 55.85, 52.80, 50.60, 49.89, 49.15, 37.64, 34.34, 27.81. HRMS (EI, m/z): calcd. for $C_{18}H_{21}NO_5$ (M^+): 331.1420, found: 331.1418.

Compound 26: The solution of **25** (120 mg, 0.36 mmol) and glacial acetic acid (0.01 mL, 0.18 mmol) in 5 mL of dry toluene was stirred at 80°C for 3 h, then the reaction mixture was cooled to room temperature and quenched with saturated aqueous sodium bicarbonate, extracted with ethyl acetate. The combined organic layers were washed with brine, the organic solvent was dried (sodium sulfate), filtered, and evaporated. The residue was purified by flash chromatography (elution with petroleum ether/ ethyl acetate: 4/1) to give **26** (106 mg, 98%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.73 (1H, s), 6.50 (1H, s), 5.93 (2H, s), 5.52 (1H, d, *J* = 3.3 Hz), 4.02 (1H, d, *J* = 14.7 Hz), 3.65 (1H, d, *J* = 3.9 Hz) , 3.58 (3H, s), 3.38-3.25 (3H, m), 2.90 (1H, t, *J* = 5.1 Hz), 2.40-2.24 (2H, m), 1.82-1.77 (1H, m). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 191.26, 148.28, 147.97, 145.83, 127.86, 123.52, 117.22, 112.01, 105.93, 100.92, 62.02, 55.99, 54.96, 54.20, 49.62, 35.33, 31.58. HRMS (EI, m/z): calcd. for $C_{17}H_{17}NO_4$ (M^+): 299.1158, found: 299.1157. m.p.: 147-149°C

Putative amarbellisine (3): Compound **26** (32 mg, 0.1 mmol) was suspended in dry toluene (5 mL) and cooled to -78°C under nitrogen atmosphere. Diisobutylaluminum hydride (1.1 M in cyclohexane, 0.12 mL, 0.13 mmol) was added slowly by Syringe and the mixture was stirred at -78°C for 30 min. The mixture was quenched with 5 mL saturated ammonium chloride solution and extracted with additional portions ethyl acetate. The combined organic layers were washed with brine, the organic solvent was dried (sodium sulfate), filtered, and evaporated. The residue was purified by flash chromatography (elution with petroleum ether/ ethyl acetate: 1/1) to give **3** (31 mg, 96%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.72 (1H, s), 6.56 (1H, s), 5.93 (1H, d, *J* = 1.6 Hz), 5.90 (1H, d, *J* = 1.6 Hz), 4.65 (1H, d, *J* = 4.8 Hz), 4.08 (1H, d, *J* = 14.4 Hz), 3.98 (1H, d, *J* = 1.6 Hz) , 3.57 (3H, s), 3.29 (1H, d, *J* = 14.8 Hz), 3.24 (1H, d, *J* = 8.4 Hz), 3.10-3.04 (1H, m), 2.99 (1H, t, *J* = 6.8 Hz) , 2.68 (1H, dd, *J* = 8.4, 1.6 Hz) , 2.34-2.26 (1H, m) , 2.19-2.12 (1H, m), 1.74-1.67 (1H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 157.2, 146.6, 128.9, 128.2, 108.3, 106.3, 100.9, 96.9, 71.2, 62.0, 56.2, 54.6, 54.4, 42.8, 35.3, 33.5. HRMS (EI, m/z): calcd. for $C_{17}H_{19}NO_4$ (M^+): 301.1314, found: 301.1325. m.p.: 185-187°C

***epi*- Putative amarbellisine (27):** To the solution of **26** (40 mg, 0.12 mmol) in dry tetrahydrofuran (4mL) was added dropwise sodium bis(2-methoxyethoxy)aluminum dihydride (65% in toluene, 0.04 mL, 0.13 mmol) at 0°C. Then the reaction mixture was stirred under nitrogen atmosphere for 12 h at room temperature. Aqueous solution of sodium hydroxide (40%, 3mL) was added slowly at 0°C. The mixture was extracted with ethyl acetate, dried (sodium sulfate), filtered, and evaporated. The residue was purified by flash chromatography (elution with petroleum ether/ ethyl acetate: 1/1) to give **3** (29 mg, 72%) as a white solid, and **27** (9 mg, 22%) was also a white powder with following data: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.99 (1H, s), 6.53 (1H, s), 5.91 (1H, d, *J* = 1.5 Hz), 5.89 (1H, d, *J* = 1.5 Hz), 4.61 (1H, d, *J* = 3.9 Hz), 4.13-4.08 (2H, m), 3.55 (3H, s) , 3.31-3.22 (2H, m), 3.01-2.97 (1H, m), 2.79 (1H, dd, *J* = 8.7, 3.6 Hz), 2.50 (1H, dd, *J* = 7.2, 3.9 Hz), 2.28-2.20 (1H, m), 2.18-2.05 (1H, m),

1.62-1.53 (1H, m) . ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 151.9, 146.5, 145.6, 129.9, 127.6, 110.7, 106.2, 100.8, 98.6, 69.6, 61.9, 56.8, 54.6, 54.5, 44.6, 35.1, 32.2. HRMS (EI, m/z): calcd. for $C_{17}H_{19}NO_4$ (M^+): 301.1314, found: 301.1309. m.p.: 122-125°C

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References

(1) (*a*) Martin, S. F. In the Alkaloids, Vol. 30 (Ed.: Brossi, A.), Academic Press, New York, 1987, pp. 251-376; (*b*) Ghosal, S., Saini, K. S., Razdan, S. *Phytochemistry*, **1985**, *24*, 2141; (*c*) Wang, Y.; Luo, Y.; Zhang, H.; Xu, P. *Org. Biomol. Chem*., **2012**, *10*, 8211; (*d*) Jin, Z. *Nar. Prod. Rep.* **2009**, *26*, 363. (*e*) Tang, W.; Hemm, I.; Bertram, B. *Planta Med.* **2003,** *69*, 97 and references cited therein; (*f*) Lewis, J. R. Nat. *Prod. Rep*. **1998**, *15*, 107; **1994**, *11*, 329.

(2) (*a*) Padaw, A.; Zhang, H. *J. Org. Chem.* **2007**, *72*, 2570. (*b*) Martin, S. F. The Amaryllidaceae Alkaloids. In The Alkaloids; Brossi, A., Ed.; Academic Press: New York, **1987**; Vol. *30*, Chapter 3, p 251. (*c*) Biechy, A., Hachisu, S., Quiclet-Sire, B., Zard, S. Z. *Angew. Chem. Int. Ed.* **2008**, *47*, 1436. (*d*) Dong, L.; Xu, Y.; Cun, L.; Cui, X.; Mi, A.; Jiang, Y.; Gong, L. *Org. Lett*. **2005**, *7*, 4285.

(3) Wildman, W. C.; Heimer, N. E. *J. Am. Chem. Soc.* **1967**, *89*, 20, 5265.

(4) Fujioka, H.; Murai, K.; Ohba, Y.; Hirose, H.; Kita, Y. *Chem.Commun.* **2006**, 832.

(5) (*a*) Evidente, A.; Andolfi, A.; Abou-Donia, A. H.; Touema, S. M.; Hammoda, H. M.; Shawky, E.; Motta, A. *Phytochemistry,* **2004**, *65*, 2113; (*b*) Van Goietsenoven, G.; Andolfi, A.; Lallemand, B.; Cimmino, A.; Lamoral-Theys, D.; Gras, T.; Abou-Donia, A.; Dubois, J.; Lefranc, F.; Mathieu, V.; Kornienko, A.; Kiss, R.; Evidente, A. *J. Nat. Prod.* **2010**, *73*, 1223.

(6) Shao, Z.; Chen, J.; Tu, Y.; Li, L. Zhang, H. *Chem. Comm*. **2003**, 1918.

(7) Shao, Z. Synthetic studies towards the Amaryllidaceae alkaloids (in Chinese), Lanzhou: Lanzhou University, 2004.

(8) (*a*) Shao, Z.; Chen, J.; Huang, R.; Wang, C.; Li, L.; Zhang, H. *Synlett,* **2003**, 2228; (*b*) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 676; (*c*) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082.

(9) Liu, D.; Chen, J.; Ai, L.; Zhang, H.; Liu, J. *Org. Lett*. **2013**, *15*, 2, 410.

(10) (*a*) Julia, M.; Julia, S.; Guegan, R. *Bull. Soc. Chim. Fr.* **1960**, 1072; (*b*) Hoffsommer, R. D.; Taub, D.; Wendler, N. L. *J. Org. Chem.* **1962**, *27*, 4143; (*c*) Ferreri, C.; Ambrosone, M.; *Synth. Commun*. **1995**, *25*, 3351; (*d*) Michelliza, S.; Al-Mourabit, A.; Gateau-Olesker, A.; Marazano, C. *J. Org. Chem.* **2002**, *67*, 6474; (*e*) McCormick, J. P.; Barton, D. L. *J. Org. Chem.* **1980**, *45*, 2566.

(11) (*a*) Hrubiec, R. T.; Smith, M. B. *J. Chem. Soc. Perkin Trans. 1*, **1984**, 107; (*b*) Previtera, L.; Monaco, P.; Mangoni, L. *Tetrahedron Lett*. **1984**, *25*, 1293; (*c*) Taylor, R. E.; Engelhardt, F. C.; Schimitt, M. J. *Tetrahedron*, **2003**, *59*, 5623.

(12) (*a*) Ikeda, M., Ohtani, S., Sato, T., Ishibashi, H. *Synthesis*, **1998**, 1803; (*b*) Fujioka, H., Murai, K., Ohba, Y. Hirose, H., Kita, Y. *Chem. Comm.* **2006**, 832.

(13) Von Holleben, M. L. A.; Livotto, P. R.; Schuch, C. M. *J. Braz. Chem. Soc*. **2001**, *12*, 1, 42.

(14) Takeda, K.; Kotera, K. *Chem. Pharm. Bull.* **1957**, *5*, 234.

(15) Rapoport, H.; Lovell, C. H.; Reist, H. R.; Warren, M. E. Jr. *J. Am. Chem. Soc*. **1967**, *89*, 8, 1942.

(16) (*a*) Antoine, J.; Emilie, L.; Jean-luc, V. *Org. Lett*. **2010**, *12*, 22, 5128; (*b*) Joseph, E.; Jeremy, W.; David, G. *J. Am. Chem. Soc*. **2006**, *128*, 10370; (*c*) Thomas, E.; Michael, L.; Rajesh, I. *J. Org. Chem*. **1999**, *64*, 2391. (*d*) Luche, J. L. *J. Am. Chem. Soc*. **1978**, *100*, 2226.