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# The effect of carbonyl on the isomerization of a galanthan ring system and total synthesis of (±)-β-lycorane†

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Lycorine-type alkaloids are privileged structures in drug development due to their attractive biological activities. In this paper, the carbonyl on the C ring was proved to have played a critical role in stereoselectivity during the synthesis process, and the galanthan skeleton with a *cis*-B/C ring is more thermodynamically stable in its presence. Furthermore, the total synthesis of (±)-β-lycorane was successfully completed by employing the Michael addition reaction to construct the galanthan skeleton with a *trans*-B/C ring. This system might be applied to other structural types with similar stereochemistry setting.



## Introduction

Amaryllidaceae plants have a rich history as herbal remedies since ancient Greece. To date, over 300 different alkaloids have been isolated from the amaryllidaceae plants. These amaryllidaceae alkaloids have attracted considerable attention due to their biological activities such as anti-Alzheimer, anticholinergic, antifungal, antibacterial, and antitumor activities.[1] Among them, lycorine-type alkaloids, especially lycorine, show antitumor activity against human cancer cell lines and inhibit cell growth and cell division.[2] These alkaloids are isoquinoline chemotypes characterized by a unique tetracyclic galanthan skeleton (Fig. 1). Amarbellisine and γ-lycorane share the galanthan skeleton with *cis*-B/C ring galanthan, whereas lycorine, α-lycorane and β-lycorane feature *trans*-B/C ring galanthan.

Owing to the preeminent biological activities of lycorine-type alkaloids and the infeasibility of isolation in larger quantity from plants, many research groups such as those of Tsuda,[3] Hudlicky,[4] Gong,[5] Ojima[6] and Booker-Milburn[7] have demonstrated their elegant studies on the total synthesis of such invaluable molecules. With the aim of developing efficient and flexible synthesis strategies for bioactive natural products and their analogues, our group has previously accomplished total synthesis of putative (±)-amarbellisine and (±)-γ-lycorane by a palladium-catalyzed carbonyl α-site arylation reaction.[8] Interestingly, the intramolecular arylation reactions have exhibited excellent stereoselectivities, and only the products with the galanthan skeleton of the *cis*-B/C ring were detected (Fig. 2A and B). Therefore, we recently have questioned whether the carbonyl on the C ring plays an important role in the determination of stereoselectivity. In this paper, our speculation was confirmed by the oxidation reaction of TBS-protected natural lycorine with a *trans*-B/C ring, which afforded the oxidation product with a *cis*-B/C ring by isomerization (Fig. 2C). In order to develop an efficient alternative synthesis method for amaryllidaceae alkaloids, the construction of the galanthan skeleton *via* the Michael addition was explored, resulting in total synthesis of β-lycorane (Fig. 2D), which differs from (±)-γ-lycorane in the stereochemistry of the central hydrogen adjacent to the ring nitrogen.

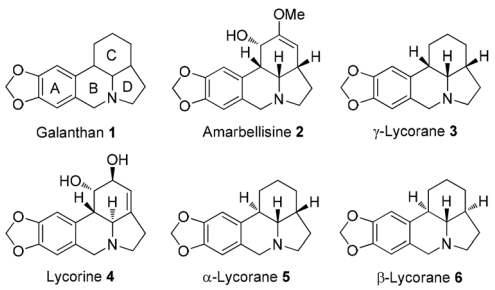


**Fig. 1** Lycorine-type alkaloids.

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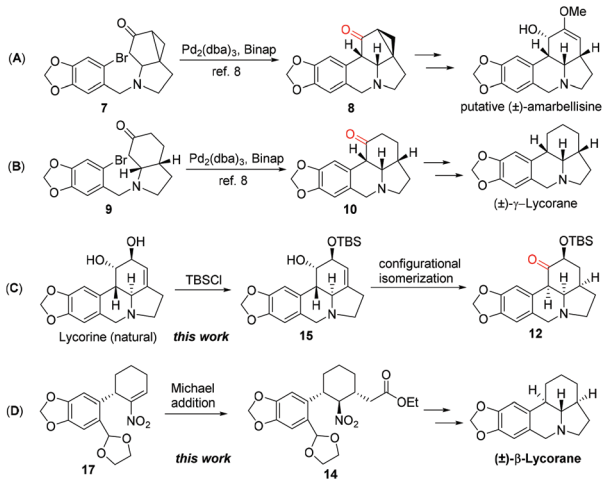
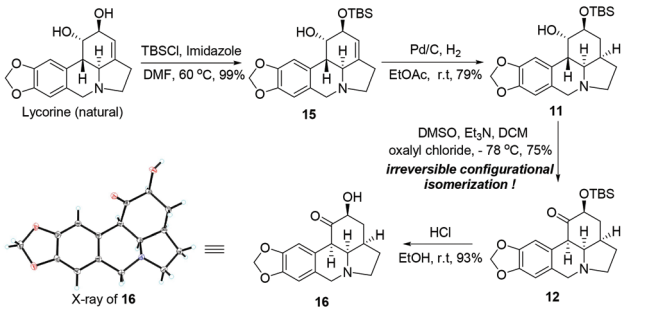



Fig. 2 Different stereoselectivities of arylation and Michael addition.

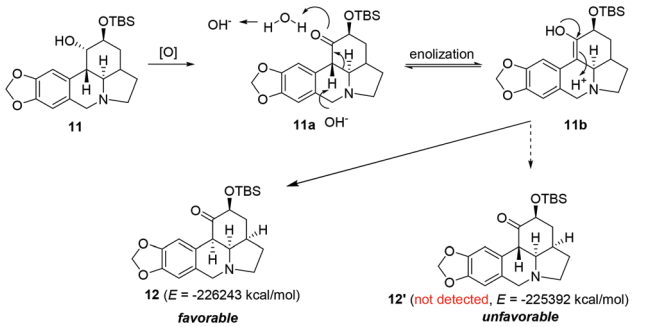
## Results and discussion

Initially, the speculation that the carbonyl on the C ring may determine the stereoselectivity was confirmed (Scheme 1). The hydroxyl group at the C2 position of natural lycorine (purchased) was selectively protected to give **15**, and subsequent hydrogenation and Swern oxidation afforded the product **12** as the only stereoisomer. To our delight, **12** was confirmed with the *cis*-B/C ring by two-dimensional $^1$H NMR analysis and X-ray analysis of its derivative **16**.[9]

The keto–enol tautomerization should be responsible for the isomerization process (Scheme 2). Firstly, **11** was transformed into its oxidation product **11a**. Subsequently, **11b** was formed by the keto–enol tautomerization. Then, **11b** attracted a proton from both faces but only gave **12** as a thermodynamically stable product. Finally, the quantum mechanics calculation showed that **12** has 2.15 kcal mol$^{-1}$ lower free energy than its thermodynamically unfavorable counterpart **12′**. DFT calculations were carried out with the Gaussian 09 program package using Becke's three-parameter hybrid functional (B3LYP) method and the 6-31G* basis set. The full geometry optimization computations were carried out. The stability of the optimized conformation of the compounds was confirmed by frequency analysis, which showed no imaginary frequency for each energy minimum.



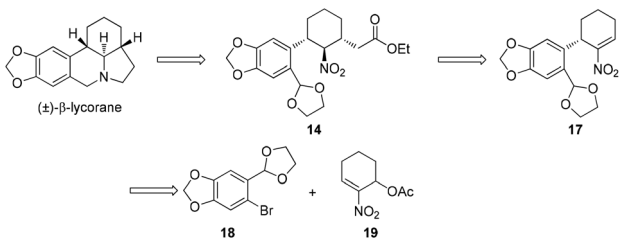

Scheme 1 Isomerization of the B/C ring.



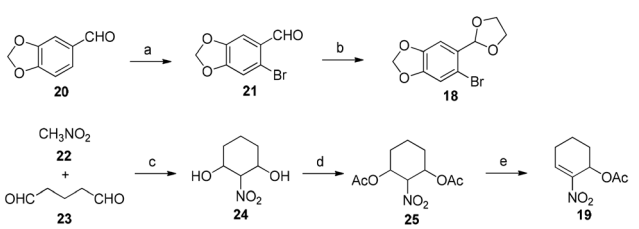

Scheme 2 Isomerization of **11**.

Based on our findings described above, avoiding the ketone intermediate is crucial for the synthesis of lycorine-type alkaloids. Therefore, we anticipated that the (±)-β-lycorane with the *trans*-B/C ring could be synthesized from the intramolecular reductive aminocyclization of **14**, which was prepared though the Michael addition of **17** and AcOEt (Scheme 3). The intermediate **17** could be synthesized from **18** and nitroolefin **19** *via* another Michael addition reaction.

Our synthetic routes started from the preparation of **18** and **19** (Scheme 4). The reaction of piperonyl aldehyde **20** with bromine afforded the bromide **21**, which was then converted to glycol acetal **18** according to the related literature studies.[10] The nitroolefin **19** was prepared from 2-nitrocyclohexane-1,3-diol **24** studied through the double Henry reaction of nitromethane with glutaraldehyde.[11] Then, the hydroxyl groups in **24** were protected by careful treatment with acetic anhydride,




Scheme 3 Retrosynthetic analysis of (±)-β-lycorane.



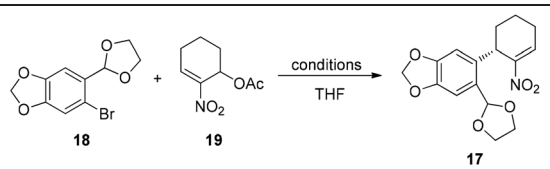

Scheme 4 Synthesis of intermediates **18** and **19**. Reagents and conditions: (a) $Br_2$, MeOH, r.t., 88%; (b) $HOCH_2CH_2OH$, *p*-TsOH, toluene, reflux, 96%; (c) $Na_2CO_3$, MeOH, r.t., 89%; (d) $Ac_2O$, DMAP, $Al_2O_3$, DCM, r.t., 87%; and (e) $NaHCO_3$, 1,4-dioxane, 110 °C, 93%.

and the product **25** was next converted to nitroolefin **19** under heating in the presence of $NaHCO_3$.

With **18** and nitroolefin **19** in hand, major efforts were made to the Michael addition–elimination reaction (Table 1).[12] The initially tested lithium hexamethyldisilazide (LiHMDS) at −78 °C failed to promote the reaction (Table 1, entry 1). By using *n*-butyllithium (*n*-BuLi), a trace amount of the Micheal addition product **17** was detected (Table 1, entry 2). It was found that the reaction accelerated remarkably at elevated temperature and the aimed product was obtained in 86% yield when the reaction mixture was allowed to warm slowly to room temperature and was stirred overnight (Table 1, entry 3). To our delight, the addition of CuI as an additive has further promoted the reaction to 91% yield within 6 hours (Table 1, entry 4).

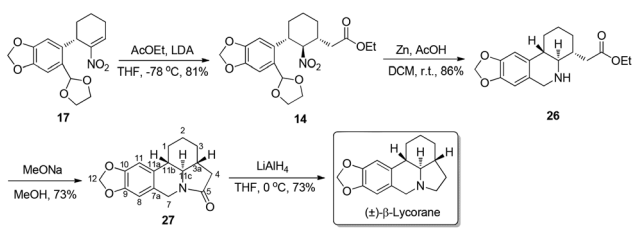
The Michael addition reaction of **17** with AcOEt furnished **14** in 81% yield. The reaction exhibited excellent stereoselectivity, and no diastereoisomer was observed. The following treatment of **14** with zinc in acetic acid successfully afforded the reductive aminocyclization product **26** in a single step. After the MeONa-mediated intramolecular amidation of **26**, the tetracyclic framework of β-lycorane was constructed successfully and it afforded **27**. The relative configuration of **27** was confirmed by two-dimensional NMR spectroscopy; H(11b) and H(11c) were *trans*, and H(11c) and H(3a) were also *trans*, in complete agreement with the reported spectra.[13] Finally, (±)-β-lycorane was synthesized by the reduction of **27** with $LiAlH_4$ (Scheme 5). The NMR spectra of our synthetic sample were in complete agreement with the reported data.[7,14]

**Table 1** Reaction condition screening for the synthesis of **17**[a]




| Entry | Base | Temperature (°C) | Time (h) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | LiHMDS | −78 | 12 | 0 |
| 2 | *n*-BuLi | −78 | 12 | 5 |
| 3 | *n*-BuLi | −15 to rt | 12 | 86 |
| 4[c] | *n*-BuLi | −15 to rt | 6 | 91 |

[a] Reaction conditions: reactions were conducted with **18** (2 mmol), **19** (2 mmol) and base (2.2 mmol) in THF (5.0 mL) under a $N_2$ atmosphere. [b] Isolated yield. [c] 0.2 mmol of CuI was added.




**Scheme 5** Completion of the total synthesis of (±)-β-lycorane.

## Conclusions

In conclusion, it has been verified that the carbonyl on the C ring plays an important role in the determination of stereoselectivity, and the galanthan skeleton with the *cis*-B/C ring is more thermodynamically stable in its presence. The mechanism of the isomerization was proposed with the keto–enol tautomerization process, which was confirmed by quantum chemistry calculations. The total synthesis of β-lycorane was successfully completed in 8 steps with 24% overall yield by employing the Michael addition reaction to construct the galanthan skeleton with the *trans*-B/C ring.

## Experimental section

### General

All reactions were conducted in dried glassware under positive pressure of dry nitrogen. THF was dried over Na-benzophenone ketyl. Proton nuclear magnetic resonance ($^1$H NMR) spectra were recorded on a Bruker Avance 300, 400 or 600 spectrometer at 300, 400 or 600 MHz. Carbon-13 nuclear magnetic resonance ($^{13}$C NMR) spectra were recorded on a Bruker Avance 300, 400 or 600 spectrometer at 75, 100 or 150 MHz. Chemical shifts are reported as $\delta$ values in parts per million (ppm) relative to tetramethylsilane (TMS) for all recorded NMR spectra. The starting materials and reagents used in the 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 positive pressure of dry nitrogen. Silica gel (Qingdao, 200–300 mesh) was used for column chromatography.

### (1*S*,2*S*,3*a*1*S*,12b*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-2,3a1,4,5,7,12b-hexahydro-1*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridin-1-ol (15)

A mixture of imidazole (48 mg, 0.7 mmol), *t*-butyl dimethyl chlorosilane (63 mg, 0.42 mmol) and lycorine (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 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. **15** (140 mg, 99%) was obtained as a yellow oil. $^1$H NMR ($CDCl_3$, 600 MHz) $\delta$ (ppm): 6.82 (1H, s), 6.58 (1H, s), 5.91 (2H, d, $J$ = 2.4 Hz), 5.41 (1H, s), 4.41 (1H, s), 4.27 (1H, s), 4.14–4.11 (1H, d, $J$ = 14.1 Hz), 3.49–3.47 (1H, d, $J$ = 13.9 Hz), 3.34–3.31 (1H, m), 2.94–2.86 (1H, d, $J$ = 43.7 Hz), 2.80–2.79 (1H, d, $J$ = 10.6 Hz), 2.71–2.69 (1H, d, $J$ = 10.5 Hz), 2.61–2.56 (2H, m), 2.36–2.31 (1H, m), 0.89 (9H, s), 0.14 (3H, s), 0.12 (3H, s). $^{13}$C NMR ($CDCl_3$, 150 MHz) $\delta$ (ppm): 146.7, 146.4, 142.0, 130.6, 128.1, 118.5, 107.9, 104.6, 101.1, 72.6, 72.4, 61.1, 57.3, 54.1, 41.2, 28.7, 26.0, 18.3, −4.3, −4.6. HRMS (ESI) calcd for $C_{22}H_{31}NO_4Si$ $(M + H)^+$ 402.2101, found 402.2095.

**(1*S*,2*S*,3a1*R*,12b*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-2,3,3a,3a1,4,5,7,12b-octahydro-1*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridin-1-ol (11)**

To a solution of **15** (0.1 g, 0.25 mmol) in glacial acetic acid (10 mL) was added 10% palladium on carbon (10 mg). The device was vacuumized, hydrogen was introduced 3 times, and then the reaction mixture was stirred at room temperature for 24 h. The solid was collected by suction filtration and then washed with ethyl acetate. The filtrate was evaporated, and the pH was adjusted to neutral with saturated aqueous sodium bicarbonate. The solution was 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: 1/1) to give **11** (80 mg, 79%) as a white solid. $^1$H NMR ($CD_3OD$, 400 MHz) $\delta$ (ppm): 6.92 (1H, s), 6.73 (1H, s), 5.86–5.85 (2H, d, $J$ = 3.8 Hz), 4.45–4.41 (1H, d, $J$ = 13.8 Hz), 4.27 (1H, s), 3.96 (1H, s), 3.91–3.88 (1H, d, $J$ = 13.9 Hz), 3.46–3.41 (2H, m), 3.30–3.25 (1H, m), 3.19–3.18 (2H, d, $J$ = 1.4 Hz), 3.07–3.04 (1H, d, $J$ = 11.8 Hz), 2.52–2.41 (2H, m), 2.17–2.12 (1H, m), 2.01–1.98 (1H, m), 0.80 (9H, s), 0.04 (3H, s), 0.02 (3H, s). $^{13}$C NMR ($CD_3OD$, 100 MHz) $\delta$ (ppm): 149.8, 147.9, 133.0, 124.7, 108.6, 106.8, 102.7, 71.7, 69.8, 64.4, 56.5, 54.0, 37.1, 33.0, 30.5, 28.2, 26.3, 18.9, −4.8, −4.9. HRMS (ESI) calcd for $C_{22}H_{33}NO_4Si$ $(M + H)^+$ 404.2257, found 404.2252.

**(2*S*,3a$^1$*R*,12b*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-2,3,3a,3a 1,4,5,7,12b-octahydro-1*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*] phenanthridin-1-one (12)**

To a solution of oxalyl chloride (0.17 mL, 2 mmol) in dry dichloromethane (10 mL) under a $N_2$ atmosphere was added dropwise dimethyl sulfoxide (0.18 mL, 2.5 mmol) in dry dichloromethane (5 mL) at −78 °C for 40 min. Then, a solution of **11** (200 mg, 0.5 mmol) in dry dichloromethane (10 mL) was added dropwise. After being stirred at −78 °C for 1.5 h, triethylamine (0.7 mL, 5 mmol) was added slowly, and the solution was kept at the same temperature for another 30 min. The reaction mixture was then warmed to room temperature, quenched with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The combined organic layers were washed with brine, and the organic solvent was dried (sodium sulfate), filtered, and evaporated. The residue was purified by flash chromatography (elution with petroleum ether–ethyl acetate: 5/1) to give **12** (150 mg, 75%) as a yellow oil. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm): 6.50 (1H, s), 6.49 (1H, s), 5.92–5.89 (2H, dd, $J$ = 9.6, 1.4 Hz), 4.43–4.38 (1H, m), 4.01–3.98 (1H, d, $J$ = 14.5 Hz), 3.63–3.62 (1H, d, $J$ = 4.4 Hz), 3.36–3.25 (2H, m), 2.93–2.90 (1H, t, $J$ = 4.4 Hz), 2.70–2.66 (1H, m), 2.32–2.26 (1H, m), 2.14–1.98 (3H, m), 1.61–1.54 (1H, m), 0.89 (9H, s), 0.10 (3H, s), 0.03 (3H, s). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ (ppm): 207.2, 146.9, 145.9, 128.6, 123.4, 110.8, 106.1, 100.9, 75.0, 66.4, 55.8, 52.5, 51.2, 40.4, 36.1, 28.1, 25.8, 18.6, −4.4, −5.3. HRMS (ESI) calcd for $C_{22}H_{31}NO_4Si$ $(M + H)^+$ 402.2101, found 402.2095.

**(2*S*,3a$^1$*R*,12b*R*)-2-Hydroxy-2,3,3a,3a$^1$,4,5,7,12b-octahydro-1*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridin-1-one (16)**

To a solution of **12** (100 mg, 0.25 mmol) in EtOH (10 mL) was added 2 M hydrochloric acid (2 mL) slowly. After being stirred at room temperature for 3 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. The residue was purified by flash chromatography (elution with petroleum ether/ethyl acetate: 1/1) to give **16** (67 mg, 93%) as a white solid. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm): 6.53 (1H, s), 6.50 (1H, s), 5.93–5.92 (2H, dd, $J$ = 2.1, 1.4 Hz), 4.37–4.32 (1H, qd, $J$ = 6.0, 1.2 Hz), 4.03–4.00 (1H, d, $J$ = 14.6 Hz), 3.75–3.73 (1H, d, $J$ = 4.7 Hz), 3.38–3.32 (1H, td, $J$ = 9.3, 5.1 Hz), 3.31–3.27 (1H, d, $J$ = 14.6 Hz), 2.99–2.96 (1H, t, $J$ = 4.7 Hz), 2.72–2.69 (1H, m), 2.33–2.27 (2H, m), 2.10–2.07 (1H, m), 1.89–1.80 (1H, q, $J$ = 12.6 Hz), 1.62–1.56 (1H, m). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ (ppm): 208.7, 146.1, 145.1, 127.6, 121.3, 109.7, 105.2, 100.0, 72.0, 65.6, 54.7, 51.5, 49.4, 38.6, 34.3, 26.9. HRMS (ESI) calcd for $C_{16}H_{17}NO_4$ $(M + H)^+$ 288.1236, found 288.1228.

**2-Nitrocyclohexane-1,3-diol (24)**

To a solution of 50% aqueous glutaraldehyde (0.4 mL, 2 mmol) in dry methanol (5 mL) was added nitromethane (120 mg, 2 mmol) and 5% aqueous sodium carbonate (1 mL). The reaction mixture was stirred at room temperature for 24 h. The solvents were evaporated to remove methanol, then extracted with ethyl acetate and 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: 2/1) to give **24** (290 mg, 89%) as a white powder. $^1$H NMR ($CD_3OD$, 300 MHz) $\delta$ (ppm): 4.31–4.24 (1H, t, $J$ = 9.8 Hz), 4.05–3.97 (2H, m), 2.10–2.05 (2H, m), 1.87–1.82 (1H, m), 1.51–1.35 (3H, m). $^{13}$C NMR ($CD_3OD$, 75 MHz) $\delta$ (ppm): 99.7, 71.9, 33.9, 20.8.

**2-Nitrocyclohexane-1,3-diyl diacetate (25)**

To a solution of **24** (3.3 g, 20 mmol) in dry dichloromethane (20 mL) was added acetic anhydride (1.9 mL, 20 mmol). After adding DMAP (12 mg, 0.1 mmol) and basic aluminum oxide (4.1 g, 40 mmol), the reaction mixture was stirred at room temperature for 36 h. The solvents were filtered and evaporated. The residue was purified by flash chromatography (elution with petroleum ether–ethyl acetate: 5/1) to give **25** (4.2 g, 87%) as a white solid. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm): 5.21–5.14 (2H, td, $J$ = 10.8, 4.8 Hz), 4.60–4.55 (1H, t, $J$ = 10.4 Hz), 2.26–2.21 (2H, dd, $J$ = 13.0, 3.7 Hz), 2.01 (6H, s), 1.85–1.81 (1H, m), 1.53–1.45 (1H, m), 1.39–1.29 (2H, m). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ (ppm): 169.5, 91.0, 71.9, 29.5, 20.8, 19.4.

**2-Nitrocyclohex-2-en-1-yl acetate (19)**

A solution of **25** (2.58 g, 10 mmol) and sodium bicarbonate (6.72 g, 80 mmol) in 1,4-dioxane (20 mL) was refluxed for 3 h.

The reaction mixture was filtered, extracted with ethyl acetate and washed with brine. The organic solvent was dried (sodium sulfate) and evaporated, and a yellow oil was obtained. The residue was purified by flash chromatography (elution with petroleum ether–ethyl acetate: 10/1) to give compound **19** (1.73 g, 93%) as a light yellow oil. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm): 7.59–7.57 (1H, m), 6.01 (1H, s), 2.56–2.49 (1H, m), 2.34–2.27 (1H, m), 2.10–2.07 (1H, d, $J$ = 11.2 Hz), 2.03 (3H, s), 1.76–1.68 (3H, m). $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ (ppm): 169.8, 147.4, 140.4, 63.2, 28.4, 25.1, 21.0, 16.1.

### 5-Bromo-6-(1,3-dioxolan-2-yl)benzo[*d*][1,3]dioxole (18)

A solution of piperonal (2 g, 13 mmol) in dry methanol (20 mL) was stirred at 0 °C, and liquid bromine (1 mL, 20 mol) was dripped slowly through a constant pressure funnel. After being stirred at room temperature for 10 h, the excess bromine was removed from the reaction mixture with saturated sodium bisulfite. The solid was collected by suction filtration and then washed with cold water. The residue was recrystallized from ethyl acetate to afford compound **21** (2.7 g, 88%) as white crystals. To a solution of **21** (2.5 g, 11 mmol) and ethylene glycol (1.3 g, 22 mmol) in dry toluene (20 mL) was added *p*-toluenesulfonic acid (95 mg, 0.55 mmol), and then the solution was refluxed and water was segregated over 24 h. The reaction mixture was cooled to room temperature, potassium carbonate was added, and then the solution was stirred for 0.5 h, filtered, and evaporated. The residue was purified by flash chromatography (elution with petroleum ether–ethyl acetate: 10/1) to give **18** (2.9 g, 96%) as a white solid. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ (ppm): 7.09 (1H, s), 7.01 (1H, s), 6.07–5.98 (3H, m), 4.18–4.01 (4H, m). $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ (ppm): 149.0, 147.5, 130.0, 114.0, 112.8, 107.7, 102.6, 101.9, 65.4.

### 5-(1,3-Dioxolan-2-yl)-6-(2-nitrocyclohex-2-en-1-yl)benzo[*d*] [1,3] dioxole (17)

To a solution of **18** (550 mg, 2 mmol) in dry tetrahydrofuran (5.0 mL) under a $N_2$ atmosphere was added 2.5 M *n*-BuLi (0.88 mL, 2.2 mmol) at −78 °C for 0.5 h, and then cuprous iodide (38 mg, 0.2 mmol) was added. After being stirred at −78 °C for 1 h, the reaction mixture was warmed in an ice bath. **19** (370 mg, 2 mmol) was added, and the reaction mixture was stirred at room temperature for 6 h. The solution 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: 5/1) to give **17** (580 mg, 91%) as a light yellow oil. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ (ppm): 7.14 (1H, s), 6.50 (1H, s), 6.13 (1H, s), 5.91 (2H, d, $J$ = 1.8 Hz), 4.53 (1H, s), 4.20–4.01 (4H, m), 2.55–2.35 (2H, m), 2.12–2.01 (1H, m), 1.90–1.81 (1H, m), 1.70–1.60 (3H, m). $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ (ppm): 151.7, 147.9, 146.4, 136.2, 134.6, 128.8, 107.1, 106.7, 101.2, 100.8, 65.3, 65.2, 35.1, 31.3, 25.0, 17.4. HRMS (ESI) calcd for $C_{16}H_{17}NO_6$ $(M + Na)^+$ 342.0954, found 342.0948.

### Ethyl 2-(1,2,3,4,4a,5,6,11b-octahydro-[1,3]dioxolo[4,5-*j*] phenanthridin-4-yl)acetate (26)

To a solution of diisopropylamine (0.17 mL, 1.2 mmol) in dry tetrahydrofuran (5 mL) under a $N_2$ atmosphere was added 2.5 M n-BuLi (0.48 mL, 1.2 mmol) at −78 °C for 0.5 h and then dry ethyl acetate (0.1 mL, 1 mmol) was added. After being stirred for 0.5 h, **17** (160 mg, 0.5 mmol) was added. The reaction mixture was stirred for 3 h, quenched with pure water, 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: 10/1) to give **14** (170 mg, 81%) as a white solid. To a solution of **14** (110 mg, 0.28 mmol) and acetic acid (6 mL) was added activated zinc powder (1 g), and then stirred at room temperature for 16 h. The reaction mixture was diluted with dichloromethane and neutralized with potassium carbonate solid until alkaline. After being filtered and evaporated, the residue was purified by flash chromatography (elution with petroleum ether/ethyl acetate: 3/1) to give **26** (76 mg, 86%) as a white solid. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ (ppm): 6.78 (1H, s), 6.45 (1H, s), 5.88 (2H, d, $J$ = 0.9 Hz), 4.17–4.10 (2H, m), 3.94–3.92 (2H, d, $J$ = 7.5 Hz), 2.86–2.79 (1H, dd, $J$ = 15.3, 5.1 Hz), 2.35–2.29 (2H, m), 2.16–2.09 (2H, m), 2.06–2.04 (1H, d, $J$ = 6.6 Hz), 1.91–1.84 (4H, m), 1.53–1.48 (1H, m), 1.31–1.26 (3H, t, $J$ = 7.2 Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ (ppm): 173.8, 146.1, 145.5, 131.8, 129.4, 105.9, 105.6, 100.6, 63.1, 60.1, 49.1, 43.4, 40.2, 38.6, 32.3, 30.4, 25.6, 14.3. HRMS (ESI) calcd for $C_{18}H_{23}NO_4$ $(M + H)^+$ 318.1705, found 318.1696.

### 2,3,3a,4,7,12b-Hexahydro-1*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridin-5(3a1*H*)-one (27)

A solution of sodium methylate (54 mg, 1 mmol) in dry methanol (5 mL) was stirred until being cooled. **26** (50 mg, 0.16 mmol) was added and then stirred at room temperature for 3 h. The reaction mixture was evaporated and dissolved with ethyl acetate. After being filtered and evaporated, the residue was purified by flash chromatography (elution with petroleum ether/ethyl acetate: 1/1) to give **27** (31 mg, 73%) as a white solid. $^1$H NMR ($CDCl_3$, 600 MHz) $\delta$ (ppm): 6.69 (1H, s), 6.60 (1H, s), 5.93–5.92 (2H, dd, $J$ = 5.2, 1.3 Hz), 4.46–4.38 (2H, q, $J$ = 17.0 Hz), 2.72–2.69 (1H, t, $J$ = 10.2 Hz), 2.53–2.49 (1H, td, $J$ = 10.9, 3.3 Hz), 2.48–2.44 (1H, dd, $J$ = 15.4, 6.5 Hz), 2.41–2.38 (1H, m), 2.18–2.13 (1H, dd, $J$ = 14.8, 12.9 Hz), 2.04–2.01 (1H, m), 1.98–1.92 (2H, m), 1.63–1.58 (1H, ddd, $J$ = 17.2, 13.1, 9.1 Hz), 1.41–1.29 (2H, m). $^{13}$C NMR ($CDCl_3$, 150 MHz) $\delta$ (ppm): 175.0, 146.7, 146.2, 130.6, 125.0, 107.2, 104.7, 101.0, 64.7, 42.9, 42.8, 40.5, 38.2, 27.8, 27.8, 25.8. HRMS (ESI) calcd for $C_{16}H_{17}NO_3$ $(M + H)^+$ 272.1287, found 272.1281.

### (±)-β-Lycorine

To a solution of **27** (20 mg, 0.074 mmol) in dry THF (5 mL) was added $LiAlH_4$ (4.2 mg, 0.11 mmol) at 0 °C for 1 h. 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 β-lycorine (15 mg, 73%) as a white solid. $^{1}$H NMR ($CDCl_3$, 300 MHz) $\delta$ (ppm): 6.72 (1H, s), 6.51 (1H, s), 5.90–5.89 (2H, d, $J$ = 3.3 Hz), 4.10–4.05 (1H, d, $J$ = 14.1 Hz), 3.42–3.33 (2H, m), 2.54–2.47 (1H, t, $J$ = 10.2 Hz), 2.36–2.25 (2H, m), 2.06–1.91 (3H, m), 1.67–1.57 (4H, t, $J$ = 14.5 Hz), 1.28–1.10 (2H, m). $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ (ppm): 146.4, 145.9, 131.5, 128.6, 107.1, 105.6, 100.9, 72.1, 57.5, 54.0, 43.2, 41.9, 30.3, 29.1, 28.5, 26.6.

## Conflicts of interest

There are no conflicts to declare.

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