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PAPER

Concise construction of the tetracyclic core of lycorine-type alkaloids and the formal synthesis of α-lycorane based on asymmetric bifunctional thiourea-catalyzed cascade reaction†

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A concise and stereoselective construction of the tetracyclic core of lycorine-type alkaloids and the formal synthesis of α-lycorane has been achieved. The feature of the current method is the employment of a bifunctional thiourea-catalyzed cascade reaction as a powerful tool to construct the skeleton of the natural product, which is a challenging yet very rarely explored strategy. As a result, the tetracyclic core is efficiently synthesized in just three simple operations involving two consecutive cascade reactions.

Introduction

Organocatalytic cascade reactions have emerged as a powerful tool for the rapid construction of complex molecules with multiple stereocenters in a biomimetic way.[1] These efficient transformations allow multiple bond-forming events to occur in a single vessel and as a consequence significantly increase resource efficiency for the overall process. Remarkably, despite great advances in the development of organocatalytic cascade reactions,[1] the application of these transformations remains a big challenge and only a few of them have been successfully applied in the total synthesis of natural products.[2] More specially, these applicable cascade reactions are predominantly secondary-amine-catalyzed transformations and the bifunctional thiourea-catalyzed cascade reactions are very rarely applied in natural product synthesis.[2a] To this end, it is highly desirable to implement this strategy into the synthesis of bioactive natural products to complement the current chemical synthesis. Thus, with our ongoing interest in the study of bifunctional thiourea-catalyzed cascade reactions[3] and extending our strategy for the construction of synthetically useful cyclohexanes,[3a] we describe herein an efficient strategy for the construction of lycorine-type alkaloids which is facilitated by a bifunctional thiourea-catalyzed cascade reaction in a sequence of reactions free of protection and deprotection steps.

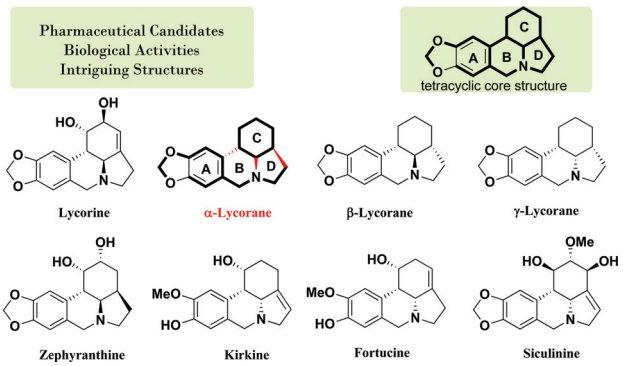

Fig. 1 Lycorine-type alkaloids.

The *Amaryllidaceae* alkaloids are a large family of natural products existing as potential drug candidates[4] which display biological properties including analgesic,[5a] antiviral,[5b] and anti-neoplastic activities,[5c–e] as well as insect antifeedant activities.[5f,g] The lycorine-type alkaloids, which are characterized by the presence of the ABCD tetracyclic core structure, represent an important subclass of this family (Fig. 1). Owing to the intriguing polycyclic structures and the special bioactive properties, lycorane alkaloids have attracted numerous synthetic interest and studies.[6]

Results and discussion

Retrosynthetic analysis

Our retrosynthetic analysis is depicted in Scheme 1. We envisaged that ring **C** is the crucial structure to construct these alkaloids. An organocatalytic enantioselective double Michael cascade reaction was designed for the modular synthesis of ring

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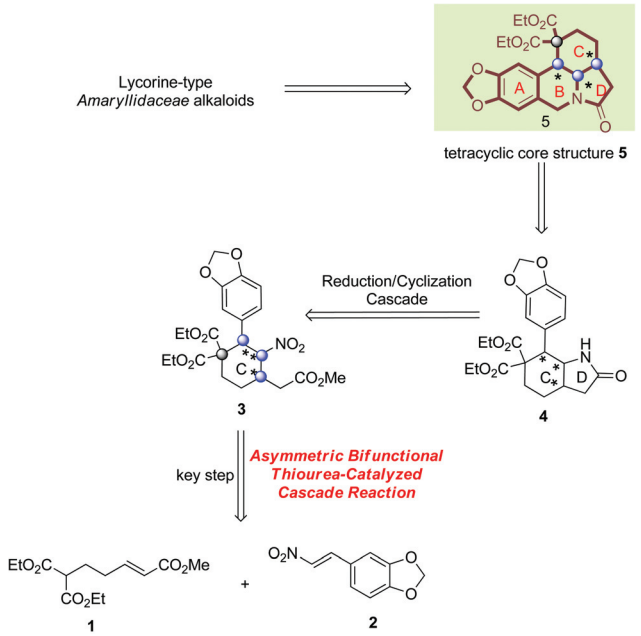
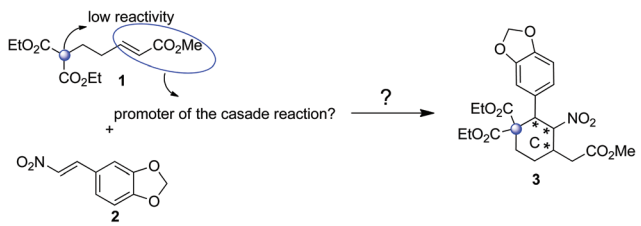
†Electronic supplementary information (ESI) available: ^{1}H, ^{13}C, HPLC spectra and cif file of compound **3a**. CCDC 724268. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob26422f



Scheme 1 Retrosynthetic analysis.

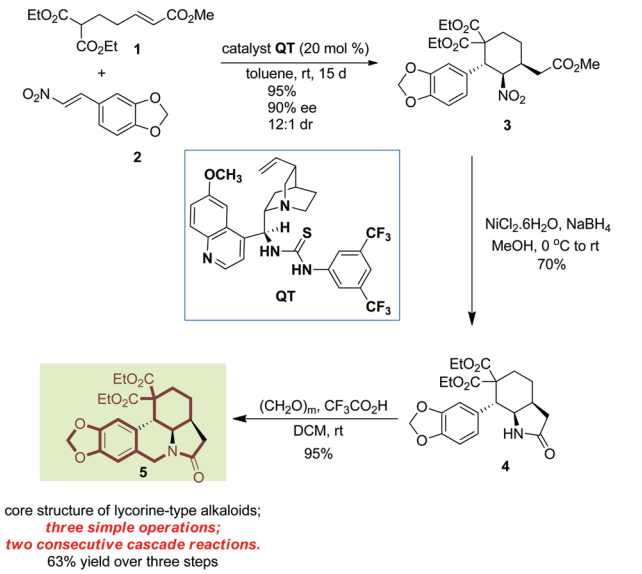


Scheme 2 Michael addition with difficult substrates.

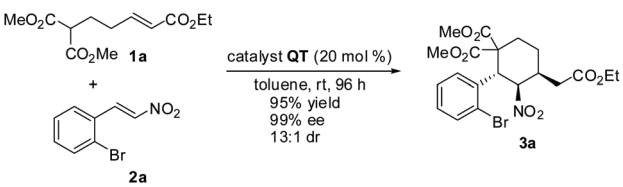
C. Followed by a reduction/cyclization cascade and Pictet–Spengler cyclization, the desired tetracyclic core structure of **5** would be efficiently constructed in this consecutive cascades and cyclization process. We anticipated that the key unit of **5** could be transformed to lycoranes and other related *Amaryllidaceae* alkaloids. Although the Michael addition between malonate and nitroolefins has been well established,[7] the challenge of this strategy is obvious: the alkyl substituted malonate **1** with very low reactivity meets strong electron-donating nitroolefin **2** to construct an all-carbon quaternary carbon center. However, we reasoned that an appropriate Michael addition reaction of second step would significantly promote the whole cascade process that is essential to the success of our strategy (Scheme 2).

The construction of the tetracyclic core

An extensive survey of reaction conditions and organocatalysts was carried out to establish the optimal reaction condition. To our delight, we found that this difficult cascade reaction indeed can work and the desired product **3** could be obtained with excellent yield (95%) and stereoselectivity (90% ee, 12 : 1 dr) using 20 mol % **QT** as the catalyst in toluene (Scheme 3). The



Scheme 3 Construction of the tetracyclic core of lycorine-type alkaloids.



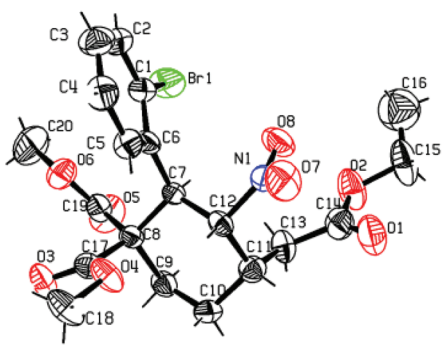
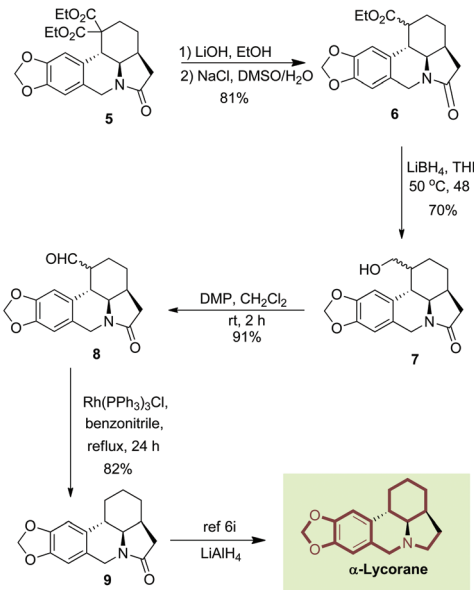


Fig. 2 X-ray crystal structure of **3a**.

enantiomeric excess was determined by HPLC analysis of pure product **3** and the diastereoisomer ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. As shown in Fig. 2, the stereochemistry was established by X-ray crystallographic determination of **3a** (99% ee) which was efficiently synthesized by using the similar method with excellent result (95% yield, 99% ee, 13 : 1 dr).† Reduction of **3** with nickel boride followed by cyclization cascade successfully afforded the product **4** in 70% yield. The tetracyclic structure **5** of lycorine-type alkaloids was obtained in 95% yield by treatment of **4** with paraformaldehyde and trifluoroacetic acid. As a result, the key skeleton **5** was efficiently synthesized with a total yield of 63% in only three simple operations involving two consecutive cascade reactions.



Scheme 4 Application in the formal synthesis of α-lycorane.

Application in the formal synthesis of α-lycorane

Then we applied this strategy to the formal synthesis of α-lycorane (Scheme 4). Compound **5** was subjected to deethoxycarbonylation, and the product **6** was obtained in 81% yield. Reduction of **6** to **7** with lithium borohydride followed by oxidation of **7** with Dess–Martin periodinane smoothly produced the target compound **8**. Then decarbonylation in the presence of $Rh(PPh_3)_3Cl$ in dry benzonitrile afforded the desired product **9** in 82% yield. The optical purities for the compounds **4**–**9** are not determined. Reduction of **9** by $LiAlH_4$ with well established reaction condition as reported in the literature gave the desired final product α-lycorane.

Conclusions

In conclusion, the tetracyclic core of lycorine-type alkaloids has been efficiently constructed in only three simple operations involving a bifunctional thiourea-catalyzed cascade reaction as the key step. The strategy described here was successfully applied to the formal synthesis of α-lycorane which demonstrates the synthetic potential of this method. Thus, this work is a nice complement to this research field. It is reasonable for us to suggest that further transformation should permit the efficient total synthesis of other members of the lycorine-type alkaloids. Further applications of this method are currently under active investigation, the results of which will be disclosed in due course.

Experimental section

General information

Chemicals and solvents were either purchased from commercial suppliers or purified by standard procedures as specified in *Purification of Laboratory Chemicals*, 4th Ed. (Armarego, W. L. F.; Perrin, D. D. Butterworth Heinemann: 1997). Analytical thin-layer chromatography (TLC) was performed on silica gel plates with F-254 indicator and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid in ethanol followed by heating. Flash column chromatography was carried out using silica gel (300–400 mesh) at increased pressure. ^{1}H NMR and ^{13}C NMR (400 MHz ^{1}H, 100 MHz ^{13}C) spectra were recorded in $CDCl_3$ as solvents at room temperature. ^{1}H and ^{13}C chemical shifts are reported in ppm relative to either the residual solvent peak (^{13}C) or TMS (^{1}H) as an internal standard. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet), coupling constant (Hz), and integration. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra are reported in wavenumbers (cm^{-1}). HRMS were measured with mass spectrometer (ESI). Enantiomeric excess values were determined by HPLC analysis. Optical rotation was measured on a polarimeter with $[\alpha]_D$ values reported in degrees with the concentration (c) in g per 100 mL.

(2*R*,3*R*,4*S*)-Diethyl 2-(benzo[*d*][1,3]dioxol-5-yl)-4-(2-methoxy-2-oxoethyl)-3-nitrocyclohexane-1,1-dicarboxylate (3). To a mixture of **1** (0.5 mmol, 136.1 mg) and **2** (0.2 mmol, 38.6 mg) in toluene (0.4 mL) was added catalyst **QT** (20 mol %, 0.04 mmol, 23.76 mg). The reaction mixture was then stirred at room temperature for 15 days and a clear solution appeared. The double Michael addition reaction was complete as judged by TLC analysis. Then the reaction mixture was concentrated and the residue was purified by column chromatography (eluent: petroleum ether–ethyl acetate = 6 : 1) to afford **3** (88.4 mg, 95% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, J = 1.2 Hz, 1H), 6.75 (dd, J = 8.0, 1.2 Hz, 1H), 6.65 (d, J = 8.0 Hz, 1H), 5.90 (d, J = 3.0 Hz, 2H), 5.79 (dd, J = 12.0, 5.2 Hz, 1H), 4.15–4.03 (m, 3H), 3.98–3.88 (m, 1H), 3.67 (s, 3H), 3.65 (d, J = 12.0 Hz, 1H), 3.18–3.10 (m, 1H), 2.65 (dd, J = 16.4, 8.8 Hz, 1H), 2.53 (dd, J = 16.4, 5.2 Hz, 1H), 2.29–2.15 (m, 2H), 1.92–1.84 (m, 2H), 1.14 (t, J = 6.8 Hz, 3H), 1.05 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 170.1, 169.7, 147.3, 147.0, 129.5, 123.0, 109.8, 107.7, 101.0, 87.2, 61.6, 61.3, 60.3, 51.9, 46.0, 33.8, 32.1, 28.1, 25.0, 13.8, 13.7; IR (KBr): 2983, 1727, 1552, 1492, 1445, 1371, 1260, 1037, 934, 864, 815, 756, 638 cm^{-1}; HRMS (ESI^+) exact mass calculated for $[M + NH_4]^+$ ($C_{22}H_{31}NO_{10}$) requires m/z 483.1973, found m/z 483.1981; $[\alpha]_D^{20} = -16$ (c 1.0, $CHCl_3$, 90% ee); HPLC (AD-H), n-hexane–i-PrOH = 90 : 10, 1.0 mL min^{-1}, λ = 206 nm, t_{major} = 16.31 min, t_{minor} = 15.02 min, 90% ee.

(2*S*,3*R*,4*S*)-Dimethyl 4-((ethoxycarbonyl)methyl)-2-(2-bromophenyl)-3-nitro-cyclohexane-1,1-dicarboxylate (3a). The title compound was prepared according to the similar procedure, as described above in 95% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.81 (m, 1H), 7.52–7.50 (m, 1H), 7.26–7.21 (m, 1H), 7.08–7.04 (m, 1H), 6.09 (dd, J = 5.2, 11.6 Hz, 1H), 4.32 (d, J = 11.6 Hz, 1H), 4.17–4.11 (m, 2H), 3.65 (s, 3H), 3.54 (s, 3H), 3.18–3.16 (m, 1H), 2.68 (dd, J = 9.6, 16.4 Hz, 1H), 2.52–2.45 (m, 2H), 2.13–2.08 (m, 1H), 1.94–1.90 (m, 1H), 1.84–1.81 (m, 1H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 170.0, 169.2, 135.9, 132.7, 129.2, 129.1, 127.8, 127.6,

87.4, 60.9, 59.3, 53.0, 52.6, 43.7, 33.9, 32.1, 27.9, 24.4, 14.1; IR (KBr): 2954, 1732, 1551, 1436, 1372, 1266, 1182, 1026, 755, 721 cm^{-1}; $[\alpha]_D^{20} = -61$ (*c* 1.0, $CHCl_3$, 99% ee); the enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane–i-PrOH = 90 : 10, flow rate 1.0 mL min^{-1}, λ = 210 nm), major enantiomer t_R = 11.21 min, minor enantiomer t_R = 15.73 min; HRMS (ESI): [M + NH_4] calcd for $[C_{20}H_{24}BrNO_8 + NH_4]^+$: 503.1024, found: 503.1016.

(3a*S*,7*R*,7a*R*)-Diethyl-7-(benzo[*d*][1,3]dioxol-5-yl)-2-oxohexahydro-1*H*-indole-6,6-(2*H*)-dicarboxylate (4). Compound **3** (0.2 mmol, 93.3 mg) was dissolved in dry methol (5.0 mL) and cooled to 0 °C. Then $NiCl_2{\cdot}6H_2O$ (0.2 mmol, 47.6 mg) was added to the reaction mixture and the reaction mixture was stirred for 30 min. Then $NaBH_4$ (2.4 mmol, 90.7 mg) was added in portions and the reaction mixture was allowed to stir at room temperature. After 12 h, the reaction mixture was quenched with saturated NH_4Cl and the solvent was evaporated. The residue was extracted with ethyl acetate and the organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (eluent: petroleum ether–ethyl acetate = 1 : 1 then ethyl acetate) to afford **4** (56.4 mg, 70% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.07 (s, 1H), 6.73–6.67 (m, 2H), 5.93 (s, 2H), 5.43 (s, 1H), 4.43 (dd, *J* = 10.4, 7.2 Hz, 1H), 4.12 (q, *J* = 6.0 Hz, 2H), 4.02–3.91 (m, 1H), 3.89–3.82 (m, 1H), 2.82 (d, *J* = 10.4 Hz, 2H), 2.39 (dd, *J* = 16.8, 11.2 Hz, 1H), 2.28 (dd, *J* = 16.8, 8.8 Hz, 1H), 2.26–2.22 (m, 2H), 1.79–1.67 (m, 2H), 1.20 (t, *J* = 6.8 Hz, 3H), 0.95 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 170.7, 170.0, 147.6, 147.0, 131.0, 123.8, 110.0, 107.9, 101.0, 61.3, 61.1, 60.0, 55.3, 52.1, 33.7, 33.6, 29.2, 22.7, 13.9, 13.7; IR (KBr): 2979, 1720, 1491, 1445, 1367, 1261, 1185, 1036, 931, 815, 641 cm^{-1}; $[\alpha]_D^{25} = +74$ (*c* 1.0, $CHCl_3$); HRMS (ESI^+) exact mass calculated for $[M + H]^+$ ($C_{21}H_{26}NO_7$) requires *m*/*z* 404.1704, found *m*/*z* 404.1709.

(3a*S*,3a^1*R*,12b*R*)-Diethyl 5-oxo-3,3a,4,5,7,12b-hexahydro-1*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridine-1,1(2H,3a1H)-dicarboxylate (5). To a solution of **4** (0.2 mmol, 80.6 mg) in CH_2Cl_2 (5.0 mL) was added $(CH_2O)_m$ (1.0 mmol, 30.0 mg) and CF_3COOH (1.2 mmol, 89.1 μL). The reaction mixture was then stirred at room temperature for 12 h. The mixture was quenched by saturated $NaHCO_3$ and then diluted with CH_2Cl_2 (30 mL), followed by washing with H_2O and brine. The organic extract was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (eluent: petroleum ether–ethyl acetate = 1 : 1) to afford **5** (79.2 mg, 95%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 6.68 (s, 1H), 6.54 (s, 1H), 5.89 (dd, *J* = 6.0, 1.2 Hz, 2H), 4.97 (d, *J* = 16.8 Hz, 1H), 4.39–4.26 (m, 2H), 4.21–4.14 (m, 3H), 3.78 (dd, *J* = 10.8, 7.6 Hz, 1H), 3.25 (d, *J* = 10.8 Hz, 1H), 2.76–2.66 (m, 1H), 2.54 (dd, *J* = 16.8, 8.8 Hz, 1H), 2.37–2.22 (m, 3H), 1.95–1.87 (m, 1H), 1.70–1.63 (m, 1H), 1.32 (t, *J* = 6.8 Hz, 3H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 172.3, 169.6, 146.2, 145.9, 128.5, 125.7, 107.3, 106.2, 100.9, 62.3, 61.4, 56.4, 56.1, 43.0, 42.5, 35.1, 31.8, 30.5, 23.2, 14.0, 13.9; IR (KBr): 2979, 1724, 1692, 1448, 1369, 1242, 1210, 1037, 936, 862, 650 cm^{-1}; $[\alpha]_D^{25} = +46$ (*c* 1.0, $CHCl_3$); HRMS (ESI^+) exact mass calculated for $[M + H]^+$ ($C_{22}H_{26}NO_7$) requires *m*/*z* 416.1704, found *m*/*z* 416.1712.

(3a*S*,3a^1*R*,12b*S*)-Ethyl-5-oxo-2,3,3a,3a1,4,5,7,12b-octahydro-1*H*-[1,3]dioxolo[4,5-*j*]-pyrrolo[3,2,1-*de*]phenanthridine-1-carboxylate (6). To a solution of **5** (0.2 mmol, 83.0 mg) in EtOH–H_2O (8.0 mL, 1 : 1, v/v) was added LiOH (25 mmol, 600 mg). The reaction mixture was then stirred at 40 °C for 48 h. After cooled, the solvent was removed and the residue was adjusted to neutral with 6*N* HCl. Then the mixture was extracted with ethyl acetate and the organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was dissolved in DMSO–H_2O (7.2 mL, 8 : 1, v/v) and NaCl (10 mmol, 585 mg) was added to this mixture. The reaction mixture was then heated at 140 °C for 24 h. After cooled, the reaction mixture was extracted with ethyl acetate (20 mL × 3) and the organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (eluent: petroleum ether–ethyl acetate = 1 : 1) to afford **6** (55.6 mg, 81%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 6.64 (s, 1H), 6.58 (s, 1H), 5.92 (s, 2H), 4.97 (d, *J* = 16.8 Hz, 1H), 4.20 (d, *J* = 17.2 Hz, 1H), 4.14–4.06 (m, 3H), 3.34 (dd, *J* = 10.0, 5.2 Hz, 1H), 2.75–2.67 (m, 2H), 2.54 (dd, *J* = 16.8, 8.8 Hz, 1H), 2.25 (dd, *J* = 16.8, 11.2 Hz, 1H), 2.02–1.92 (m, 2H), 1.73–1.67 (m, 2H), 1.21 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 173.5, 146.4, 129.5, 125.6, 106.7, 104.8, 101.0, 60.5, 55.4, 42.9, 42.7, 39.4, 38.9, 35.1, 30.0, 25.1, 23.0, 14.2; IR (KBr): 2929, 1727, 1684, 1485, 1419, 1247, 1178, 1036, 935, 853, 785 cm^{-1}; $[\alpha]_D^{25} = -41$ (*c* 1.0, $CHCl_3$); HRMS (ESI^+) exact mass calculated for $[M + H]^+$ ($C_{19}H_{22}NO_5$) requires *m*/*z* 344.1492, found *m*/*z* 344.1487.

(3a*S*,3a^1*R*,12b*S*)-1-(Hydroxymethyl)-2,3,3a,4,7,12b-hexahydro-1*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridin-5(3a1H)-one (7). To a solution of **6** (0.1 mmol, 34.3 mg) in dry THF (2.0 mL) was added $LiBH_4$ (2 mmol, 43.6 mg). The reaction mixture was then stirred at 50 °C for 48 h. After cooled, the reaction mixture was quenched with saturated NH_4Cl at 0 °C and extracted with ethyl acetate, the organic layer was then dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (eluent: petroleum ether–ethyl acetate = 1 : 2) to afford **7** (21.1 mg, 70%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 6.78 (s, 1H), 6.58 (s, 1H), 5.93 (d, *J* = 4.0 Hz, 2H), 4.94 (d, *J* = 16.8 Hz, 1H), 4.14 (d, *J* = 16.8 Hz, 1H), 3.77–3.61 (m, 3H), 3.42 (dd, *J* = 11.6, 7.6 Hz, 1H), 2.56–2.76 (m, 3H), 2.50 (dd, *J* = 16.8, 9.2 Hz, 1H), 2.27 (dd, *J* = 16.8, 11.2 Hz, 1H), 1.96–2.04 (m, 2H), 1.83–1.77 (m, 1H), 1.76–1.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 146.6, 146.4, 128.9, 126.1, 106.7, 105.5, 101.1, 59.5, 55.8, 42.8, 39.7, 35.1, 34.8, 30.4, 23.4, 21.5; IR (KBr): 3374, 2924, 1663, 1484, 1449, 1243, 1037, 934, 859 cm^{-1}; $[\alpha]_D^{25} = -68$ (*c* 1.0, $CHCl_3$); HRMS (ESI^+) exact mass calculated for $[M + H]^+$ ($C_{17}H_{20}NO_4$) requires *m*/*z* 302.1387, found *m*/*z* 302.1377.

(3a*S*,3a^1*R*,12b*S*)-5-Oxo-2,3,3a,3a1,4,5,7,12b-octahydro-1*H*-[1,3]-dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridine-1-carbaldehyde (8). To a solution of **7** (0.1 mmol, 30.2 mg) in CH_2Cl_2 (3.0 mL) was added DMP (1,1,1-triacetoxy-1,1-dihydro-1,2-benzoiodoxol-3-(1*H*)-one) (0.2 mmol, 84.8 mg). The reaction mixture was then

stirred at room temperature for 2 h. After the reaction was complete as judged by TLC analysis, the mixture was filtered and concentrated. The residue was purified by flash column chromatography (eluent: petroleum ether–ethyl acetate = 1 : 2) to afford **8** (27.2 mg, 91%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 6.63 (s, 1H), 6.60 (s, 1H), 5.93 (d, J = 0.8 Hz, 2H), 4.98 (d, J = 17.2 Hz, 1H), 4.21 (d, J = 17.2 Hz, 1H), 3.76 (dd, J = 11.2, 7.6 Hz, 1H), 3.39–3.37 (m, 1H), 2.85 (dd, J = 11.2, 4.8 Hz, 1H), 2.73–2.64 (m, 1H), 2.55 (dd, J = 16.8, 9.2 Hz, 1H), 2.25 (dd, J = 16.8, 10.8 Hz, 1H), 2.19–2.11 (m, 1H), 1.95–1.84 (m, 2H), 1.79–1.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.3, 174.2, 146.7, 146.6, 128.0, 125.7, 106.8, 105.2, 101.1, 55.9, 45.3, 42.9, 38.5, 35.0, 30.1, 23.0, 21.5; IR (KBr): 2927, 1682, 1485, 1422, 1371, 1244, 1036, 932, 860 cm^{-1}; $[\alpha]_D^{25}$ = −60 (c 1.0, $CHCl_3$); HRMS (ESI$^+$) exact mass calculated for $[M + H]^+$ ($C_{17}H_{18}NO_4$) requires m/z 300.1230, found m/z 300.1225.

(3a*S*,3a^1*R*,12b*S*)-2,3,3a,4,7,12b-Hexahydro-1*H*-[1,3]dioxolo-[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridin-5(3a1H)-one (9). To a solution of **8** (0.1 mmol, 29.9 mg) in dry benzonitrile (2.0 mL) was added $Rh(PPh_3)_3Cl$ (0.15 mmol, 138.8 mg) under argon atmosphere. The reaction mixture was then heated to reflux for 24 h. The solvent was evaporated under reduced pressure, and the reside was purified by a flash silica gel column (eluent: petroleum ether–ethyl acetate = 1 : 1) to afford **9** (22.2 mg, 82%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (s, 1H), 6.60 (s, 1H), 5.93 (d, J = 2.4 Hz, 2H), 4.98 (d, J = 17.2 Hz, 1H), 4.20 (d, J = 17.2 Hz, 1H), 3.22 (dd, J = 10.4, 7.6 Hz, 1H), 2.66–2.61 (m, 1H), 2.51 (dd, J = 16.8, 8.8 Hz, 1H), 2.42 (dt, J = 11.4, 3.4 Hz, 1H), 2.29–2.21 (m, 2H), 1.81–1.75 (m, 3H), 1.61–1.60 (m, 1H); 1.26–1.14 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 146.4, 146.2, 132.1, 125.4, 106.6, 104.9, 101.0, 59.7, 43.3, 38.1, 35.1, 30.7, 25.6, 24.2, 21.0; IR (KBr): 3386, 3192, 1647, 1576, 1404, 1243, 1119, 1035, 931, 852, 772, 696, 634 cm^{-1}; $[\alpha]_D^{25}$ = −20 (c 1.0, $CHCl_3$); HRMS (ESI$^+$) exact mass calculated for $[M + H]^+$ ($C_{16}H_{18}NO_3$) requires m/z 272.1281, found m/z 272.1284.

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Notes and references

1 For selected reviews, see: (*a*) A. M. Walji and D. W. C. MacMillan, *Synlett*, 2007, 1477; (*b*) D. Enders, C. Grondal and M. R. M. Hüttl, *Angew. Chem., Int. Ed.*, 2007, **46**, 1570; (*c*) A. Dondoni and A. Massi, *Angew. Chem., Int. Ed.*, 2008, **47**, 4638; (*d*) D. W. C. MacMillan, *Nature*, 2008, **455**, 304; (*e*) M. Nielsen, D. Worgull, T. Zweifel, B. Gschwend, S. Bertelsen and K. A. Jørgensen, *Chem. Commun.*, 2011, **47**, 632.

2 For selected reviews, see: (*a*) C. Grondal, M. Jeanty and D. Enders, *Nat. Chem.*, 2010, **2**, 167; (*b*) E. Marqués-López, R. P. Herrerabc and M. Christmann, *Nat. Prod. Rep.*, 2010, **27**, 1138.

3 (*a*) Y. Wang, R.-G. Han, Y.-L. Zhao, S. Yang, P.-F. Xu and D. J. Dixon, *Angew. Chem., Int. Ed.*, 2009, **48**, 9834; (*b*) Y. Wang, D.-F. Yu, Y.-Z. Liu, H. Wei, Y.-C. Luo, D. J. Dixon and P.-F. Xu, *Chem.–Eur. J.*, 2010, **16**, 3922; (*c*) Z.-X. Jia, Y.-C. Luo and P.-F. Xu, *Org. Lett.*, 2011, **13**, 832; (*d*) J.-B. Ling, Y. Su, H.-L. Zhu, G.-Y. Wang and P.-F. Xu, *Org. Lett.*, 2012, **14**, 1090.

4 For reviews on *Amaryllidaceae* alkaloids, see: (*a*) S. F. Martin, in *The Alkaloids*, ed. A. Brossi, Academic Press, New York, 1987, vol. 30, pp. 251–376; (*b*) O. Hoshino, in *The Alkaloids*, ed. G. A. Cordell, Academic Press, San Diego, 1998, vol. 51, pp. 323–424; (*c*) Z. Jin, *Nat. Prod. Rep.*, 2005, **22**, 111; (*d*) Z. Jin, *Nat. Prod. Rep.*, 2007, **24**, 886.

5 (*a*) M. Tanker, G. Citoglu, B. Gumusel and B. Sener, *Int. J. Pharmacogn.*, 1996, **34**, 194; (*b*) B. Gabrielsen, T. P. Monath, J. W. Huggins, D. F. Kefauver, G. R. Pettit and G. Groszek, *J. Nat. Prod.*, 1992, **55**, 1569; (*c*) G. Ceriotti, *Nature*, 1967, **213**, 595; (*d*) A. Jimenez, A. Santos, G. Alonso and D. Vazquez, *Biochim. Biophys. Acta*, 1976, **425**, 342; (*e*) A. Baez and D. Vazquez, *Biochim. Biophys. Acta*, 1978, **518**, 95; (*f*) A. Numata, T. Takemura, H. Ohbayashi, T. Katsuno, K. Yamamoto, K. Sato and S. Kobayashi, *Chem. Pharm. Bull.*, 1983, **31**, 2146; (*g*) R. P. Singh and N. C. Pant, *Experientia*, 1980, **36**, 552.

6 For selected examples on the total syntheses of optically active lycoranes, see: (*a*) H. Yoshizaki, H. Satoh, Y. Sato, S. Nukui, M. Shibasaki and M. Mori, *J. Org. Chem.*, 1995, **60**, 2016; (*b*) J. Cossy, L. Tresnard and D. G. Pard, *Eur. J. Org. Chem.*, 1999, 1925; (*c*) M. G. Banwell, J. E. Harvey and D. C. Hockless, *J. Org. Chem.*, 2000, **65**, 4241; (*d*) L. Dong, Y.-J. Xu, L.-F. Cun, X. Cui, A.-Q. Mi, Y.-Z. Jiang and L.-Z. Gong, *Org. Lett.*, 2005, **7**, 4285; (*e*) B. D. Chapsal and I. Ojima, *Org. Lett.*, 2006, **8**, 1395; (*f*) H. Fujioka, K. Murai, Y. Ohba, H. Hirose and Y. Kita, *Chem. Commun.*, 2006, 832; For selected recent examples on the total syntheses of racemic lycoranes, see: (*g*) A. Padwa, M. A. Brodney and S. M. Lynch, *J. Org. Chem.*, 2001, **66**, 1716; (*h*) O. Tamura, H. Matsukida, A. Toyao, Y. Takeda and H. Ishibashi, *J. Org. Chem.*, 2002, **67**, 5537; (*i*) L. D. Miranda and S. Z. Zard, *Org. Lett.*, 2002, **4**, 1135; (*j*) T. Yasuhara, K. Nishimura, M. Yamashita, N. Fukuyama, K.-i. Yamada, O. Muraoka and K. Tomioka, *Org. Lett.*, 2003, **5**, 1123; (*k*) S. Gao, Y. Q. Tu, Z. Song, A. Wang, X. Fan and Y. Jiang, *J. Org. Chem.*, 2005, **70**, 6523; (*l*) R. J. Huntley and R. L. Funk, *Tetrahedron Lett.*, 2011, **52**, 6671. See also ref. 4.

7 For selected examples of organocatalytic enantioselective addition of malonates on nitroolefins, see: (*a*) H. Li, Y. Wang, L. Tang and L. Deng, *J. Am. Chem. Soc.*, 2004, **126**, 9906; (*b*) J. Ye, D. J. Dixon and P. S. Hynes, *Chem. Commun.*, 2005, 4481; (*c*) T. Okino, Y. Hoashi, T. Furukawa, X. Xu and Y. Takemoto, *J. Am. Chem. Soc.*, 2005, **127**, 119; (*d*) J. M. Andrés, R. Manzano and R. Pedrosa, *Chem.–Eur. J.*, 2008, **14**, 5116.