

Supporting Information for:

Cyclization Approaching to (–)-Lycojapodine A: Synthesis of Two Unnatural Alkaloids

Yu-Rong Yang,* Liang Shen, Kun Wei, Qin-Shi Zhao

State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming, 650204, China

yangyurong@mail.kib.ac.cn

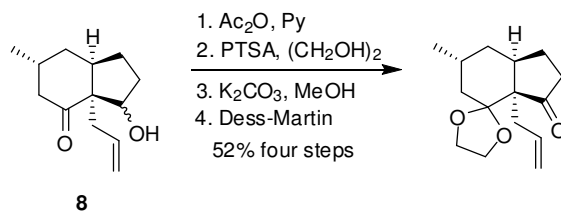
Table of Contents

General Information	Page1
Experimental Procedures	Page2-6
NMR Spectra	Page 6-22

General Information.

All reactions were performed under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF) and diethyl ether (Et₂O) were distilled over sodium-potassium alloy. Dichloromethane, toluene, dimethylformamide (DMF), acetonitrile, and benzene were distilled over calcium hydride. Yields refer to chromatographically and spectroscopically homogeneous materials, unless otherwise noted. Reagents were used as received without further purification, unless otherwise stated. Silica gel (200-300 mesh) was used for flash column chromatography. NMR spectra were recorded on 400 or 500 MHz spectrometers and calibrated using undeuterated solvent as an internal reference. IR spectra were recorded with KBr pellets. Optical rotations were determined on a polarimeter. HRMS data were recorded via positive ion electrospray or electron impact mass spectrometry using a time of flight analyzer.

Experimental Procedures

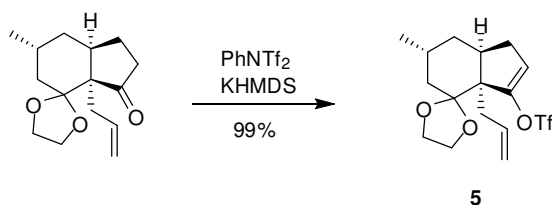


Acetylation. To a stirred solution of alcohol **8** (1.9 g, 9.18 mmol) in CH_2Cl_2 was added pyridine (4.5 mL), Ac_2O (3.5 mL) and catalytic amount of 4-DMAP (0.20 g). The reaction mixture was stirred for 2 h at rt, then poured into cold aqueous 1N HCl (80 mL), and extracted with ether. The combined extracts were washed with NaHCO_3 and brine, dried over Na_2SO_4 , concentrated. The crude product was used for the next step without purification.

Ketalization. To a solution of the above crude acetate (*ca.* 9.18 mmol), ethylene glycol (15 mL) in 50 mL of benzene was added *p*-TSA (0.35 g, 1.83 mmol). The mixture was refluxed with the Dean-Stark apparatus for 24 h. The reaction was cooled to rt and diluted with ether, washed with saturated NaHCO_3 and brine, dried over Na_2SO_4 , and concentrated. The crude oil was used for the next step without purification.

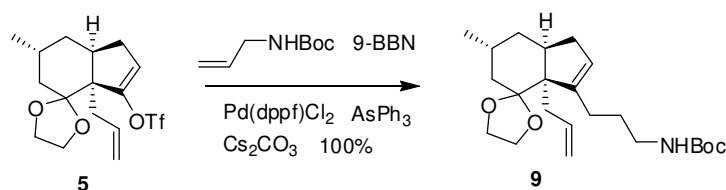
Deacetylation. To a stirred solution of above crude ketal (*ca.* 9.18 mmol) in MeOH (60 mL) was added solid K_2CO_3 (16.5 g, 0.119 mol) in several portions at rt. The reaction was stirred at rt for 1 day, and then diluted with ether and brine. The organic phase was separated and the aqueous phase was extracted with ether. The combined organic phases were washed with 1N HCl and brine to make it neutral, dried over Na_2SO_4 , and concentrated. The crude product was used for the next step without purification.

Oxidation. To a stirred solution of above crude alcohol (*ca.* 9.18 mmol) in CH_2Cl_2 (70 mL) was added Dess-Martin reagent (5.06 g, 11.9 mmol) and NaHCO_3 (2.42 g, 28.8 mmol) at rt. The reaction was stirred at rt overnight, and then quenched with NaHSO_3 , extracted with CH_2Cl_2 , washed with saturated NaHCO_3 and brine, dried over Na_2SO_4 , and concentrated. The crude product was purified with flash column chromatography (petroleum ether/ethyl acetate 50:1) to provide 1.19 g of ketone (52% over four steps) as colorless oil. $[\alpha]_{\text{D}} = -71.7$ ($c = 0.21$, MeOH); IR (KBr) $\text{V}_{\text{max}} \text{ cm}^{-1}$: 2951, 1738, 1457, 1121, 1058. ^1H NMR (CDCl_3 , 500 MHz) δ ppm: 5.47 (1H, m), 5.01 (1H, t, $J = 2.5$ Hz), 4.61 (1H, t, $J = 13.4$ Hz), 3.95-3.70 (4H, m), 2.93 (1H, dd, $J = 14.0$, 5.4 Hz), 2.41 (1H, m), 2.32 (1H, dd, $J = 18.6$, 8.4 Hz), 2.17-2.09 (2H, m), 2.03-1.89 (2H, m), 1.71 (1H, m), 1.58 (1H, m), 1.48 (1H, m), 1.22 (1H, dt, $J = 12.9$, 5.5 Hz), 1.18 (1H, t, $J = 13.2$ Hz), 0.92 (3H, d, $J = 6.5$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ ppm: 220.9, 134.7, 118.1, 111.9, 64.9, 64.3, 56.1, 40.7, 39.8, 39.2, 34.8, 32.8, 24.9, 24.4, 22.0.

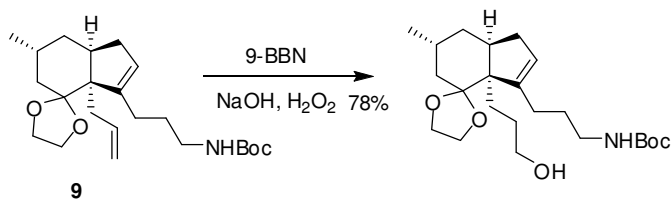


To a stirred solution of ketone (1.28 g, 5.12 mmol) in THF (16 mL) was added dropwise KHMDS (16.4 mL, 0.5N) at -78°C . The resulting solution was allowed to warm to -30°C over 1 h, and then a solution of PhNTf_2 (2.92 g, 8.18 mmol) in THF (18 mL) was added at same temperature. The reaction mixture was stirred for 20 min, then quenched with saturated NaHCO_3 (50 mL), extracted with ether (100 mL \times 3), washed with brine,

dried over Na₂SO₄, and concentrated. The crude product was purified with flash column chromatography (petroleum ether/ethyl acetate 150:1) to provide 1.94 g of triflate **5** (99%) as yellow oil. [α]_D = -46.1 (*c* = 1.16, CHCl₃) ; IR (film) V_{max} cm⁻¹: 2953, 2927, 1648, 1420, 1270, 1213, 1143, 1054, 962, 869; ¹H NMR (CDCl₃, 400 MHz) δ ppm: 5.73 (1H, s), 5.65 (1H, m), 5.09 (1H, t, *J* = 10.1 Hz), 3.89 (4H, m), 2.75 (1H, dd, *J* = 14.5, 5.5 Hz), 2.51 (1H, m), 2.32-2.09 (3H, m), 1.89 (1H, m), 1.59-1.50 (3H, m), 1.20-1.12 (2H, m), 0.93 (3H, d, *J* = 6.6 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ ppm: 149.3, 134.2, 118.4, 118.4 (q, *J*_{C-F} = 318), 116.2, 110.9, 64.9, 63.4, 54.6, 39.7, 39.0, 33.9, 32.7, 32.0, 25.2, 21.8. HR ESI *m/z*: calcd for C₁₆H₂₂O₅F₃S [M+H]⁺: 383.1140, found 383.1137.

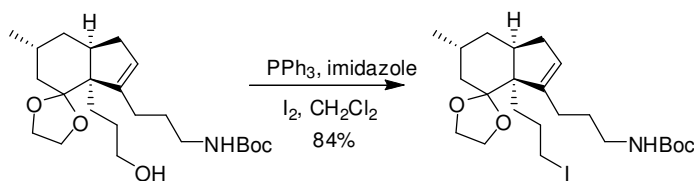


To a solution of allyl-carbamic acid *tert*-butyl ester (1.373 g, 8.74 mmol) in THF (42 mL) was added a solution of 9-BBN (23.3 mL, 0.5 N, 11.6 mmol) at rt. After stirring for 4 h at the same temperature, the resulting reaction was treated with degassed water (2.7 mL) and transferred via cannula to a mixture of vinyl triflate **5** (2.21 g, 5.82 mmol), Pd(dppf)Cl₂ (0.47 g, 0.58 mmol), AsPh₃ (0.178 g, 0.58 mmol) and Cs₂CO₃ (3.63 g, 11.1 mmol) in degassed DMF (30 mL). The mixture was stirred at 50 °C and began to turn dark brown. After 3.5 h, reaction solution was cooled to rt, poured into a saturated NH₄Cl (50 mL), and extracted with ether (80 mL × 3). The combined organic phases were washed with brine (30 mL × 3), dried over Na₂SO₄, concentrated. The crude product was purified with flash column chromatography (petroleum ether/ethyl acetate 20:1 → 5:1) to provide 2.78 g of cross-coupling product **9** (100%) as colorless oil. [α]_D = -47.3 (*c* = 0.71, CHCl₃); IR (KBr) V_{max} cm⁻¹: 3388, 2949, 2925, 1702, 1523, 1453, 1366, 1170, 1057, 583. ¹H NMR (CDCl₃, 500 MHz) δ ppm: 5.56 (2H, m), 5.03 (1H, d, *J* = 17.0 Hz), 4.99 (1H, d, *J* = 10.2 Hz), 4.59 (1H, br s), 3.91-3.81 (2H, m), 3.77 (1H, dd, *J* = 14.7, 7.5 Hz), 3.66 (1H, dd, *J* = 14.5, 7.3 Hz), 3.12 (2H, m), 2.70 (1H, dd, *J* = 14.7, 5.1 Hz), 2.31 (1H, m), 2.23 (1H, dd, *J* = 14.7, 9.0 Hz), 2.15-1.49 (9H, m), 1.42 (9H, s), 1.15 (2H, m), 0.87 (3H, d, *J* = 6.6 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ ppm: 155.9, 144.8, 136.1, 126.5, 116.7, 112.8, 78.9, 70.6, 64.7, 62.8, 56.3, 42.0, 40.7, 39.0, 35.6, 34.7, 33.0, 28.4, 27.8, 26.1, 25.1, 22.1.

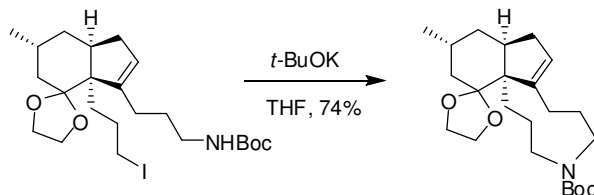


To a stirred solution of diene **9** (1.42 g, 3.63 mmol) was added 9-BBN (29 mL, 0.5 N, 14.5 mmol purchased from Acros) at rt. The reaction was placed in a 40 °C oil bath and stirred for 12 h. After cooling to rt, to the solution was added 3 N NaOH (9.0 mL) and H₂O₂ (30%, 9.0 mL) dropwise and the reaction was continue to stir for 3 h. The reaction was treated with saturated NH₄Cl (50 mL), extracted with ether (80 mL × 5), washed with brine (10 mL × 2), dried over Na₂SO₄, and concentrated. The crude product was purified with flash column chromatography (petroleum ether/ethyl acetate 5:1) to provide 1.16 g of alcohol (78%) as colorless oil. [α]_D = -4.8 (*c* = 1.0, CHCl₃); IR (KBr) V_{max} cm⁻¹: 3367, 2928, 2870, 1691, 1526, 1251, 1171, 1048. ¹H NMR (CDCl₃, 400 MHz) δ ppm: 5.57 (1H, s), 4.66 (1H, br s), 3.91-3.58 (6H, m), 3.12 (2H, dd, *J* = 12.4, 6.1 Hz), 2.33-2.27 (1H, m), 2.18-1.80 (6H, m), 1.77-1.47 (7H, m), 1.42 (9H, s), 1.26-1.16 (2H, m), 0.88 (3H, d, *J*

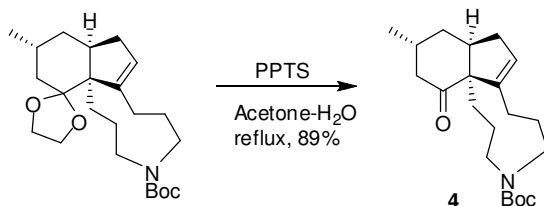
= 6.6 Hz); ^{13}C NMR (CDCl_3 , 100 MHz) δ ppm: 156.0, 144.9, 126.6, 113.0, 79.0, 64.6, 63.5, 62.7, 56.7, 41.5, 40.6, 38.9, 35.7, 33.9, 28.4, 28.2, 27.8, 25.9, 25.3, 25.0, 22.0.



To a stirred solution of PPh_3 (0.351 g, 1.34 mmol) in CH_2Cl_2 (6 mL) was added I_2 (0.340 g, 1.34 mmol) and imidazole (0.114 g, 1.68 mmol) at rt. The resulting solution was stirred for 10 min before a solution of alcohol (0.274 g, 0.67 mmol) in CH_2Cl_2 (5 mL) was added. The reaction was stirred for 0.5 h at rt, and then was quenched with addition of solution of $\text{Na}_2\text{S}_2\text{O}_3$ (5 mL), extracted with ether (25 mL \times 3), washed with brine (5 mL \times 2), dried over Na_2SO_4 , and concentrated. The crude product was purified with flash column chromatography (petroleum ether/ethyl acetate 20:1) to provide 0.29 g of iodide (84%) as colorless oil. $[\alpha]_{\text{D}} = -2.4$ ($c = 2.0$, CHCl_3) IR (KBr) Vmax cm^{-1} : 3424, 2924, 1703, 1640, 1437, 1178, 1119, 721, 695, 542; ^1H NMR (CDCl_3 , 400 MHz) δ ppm: 5.57 (1H, s), 4.78 (1H, br s), 3.92-3.82 (2H, m), 3.78 (1H, dd, $J = 14.5$, 7.4 Hz), 3.67 (1H, dd, $J = 14.2$, 7.1 Hz), 3.16 (4H, m), 2.28-2.00 (3H, m), 1.96-1.50 (11H, m), 1.44 (9H, s), 1.20 (2H, m), 0.90 (3H, d, $J = 6.6$ Hz); ^{13}C NMR (CDCl_3 , 100 MHz) δ ppm: 155.8, 144.7, 126.7, 112.7, 78.9, 64.6, 62.7, 56.6, 41.7, 40.6, 38.9, 35.7, 33.3, 30.6, 29.3, 28.4, 27.7, 26.1, 25.0, 22.1.

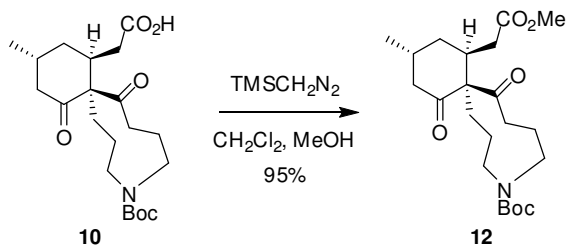


To a solution of iodide (0.177 g, 0.34 mmol) in THF (36 mL) was added $t\text{-BuOK}$ (77 mg, 0.688 mmol) at rt. The resulting solution was stirred for 20 min and then was quenched with addition of solution of NH_4Cl (10 mL), extracted with ether (25 mL \times 3), washed with brine (10 mL \times 2), dried over Na_2SO_4 , and concentrated. The crude product was purified with flash column chromatography (petroleum ether/ethyl acetate 25:1) to provide 98 mg of cyclized product (74%) as colorless oil. $[\alpha]_{\text{D}} = -29.4$ ($c = 0.5$, CHCl_3); IR (KBr) Vmax cm^{-1} : 2921, 1694, 1481, 1453, 1365, 1168; ^1H NMR (CDCl_3 , 400 MHz) δ ppm: 5.62 (1H, s), 3.86-3.69 (4H, m), 3.68-3.39 (1H, m), 3.28-3.10 (1H, m), 3.03-2.82 (2H, m), 2.30-1.48 (14H, m), 1.45 (9H, s), 1.25-1.12 (2H, m), 0.87 (3H, d, $J = 6.5$ Hz); ^{13}C NMR (CDCl_3 , 100 MHz) δ ppm: 156.8, 156.3, 145.7, 128.3, 113.3, 78.9, 78.8, 64.6, 64.5, 62.8, 57.6, 49.0, 48.6, 45.5, 44.6, 41.1, 40.9, 38.6, 36.5, 33.8, 33.6, 28.5, 27.9, 26.9, 25.2, 24.9, 24.7, 23.6, 22.6, 22.5, 22.3, 21.6.

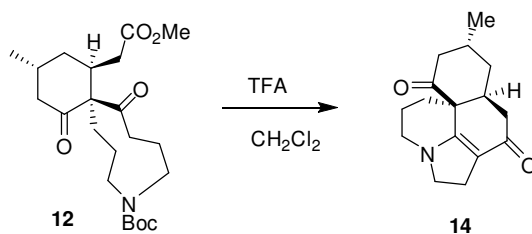


To a solution of acetal (0.286 g, 0.731 mmol) in acetone/ H_2O (10:1, 16 mL) was added pyridinium p -toluenesulfonate (31.2 mg, 0.124 mmol) at 25 $^\circ\text{C}$. The resulting solution was refluxed at 55 $^\circ\text{C}$ for 1 h and then was quenched by addition of saturated NaHCO_3 (10 mL), extracted with ether (30 mL \times 3), washed with brine (10 mL \times 2), dried over Na_2SO_4 , and concentrated. The crude product was purified with flash column

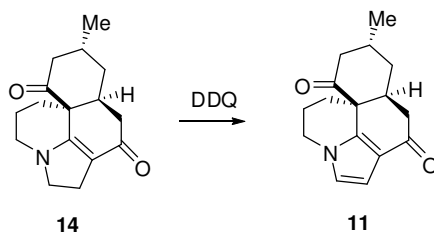
chromatography (petroleum ether/ethyl acetate 20:1) to provide 0.226 g of ketone **4** (89%) as clear oil. $[\alpha]_D = -143$ ($c = 0.2$, CHCl_3) IR (KBr) Vmax cm^{-1} : 3439, 3434, 3036, 2924, 1696, 1413, 1365, 1167, 770; $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ ppm: 5.70, 5.67 (1H, s), 3.53-3.33 (1H, m), 3.27-2.93 (3H, m), 2.71-2.32 (3H, m), 2.23-1.83 (7H, m), 1.71-1.52 (6H, m), 1.45, 1.44 (9H, s), 1.47-1.23 (1H, m), 0.94, 0.92 (3H, d, $J = 6.8$ Hz); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ ppm: 215.9, 215.7, 156.4, 155.9, 144.2, 143.7, 129.7, 129.1, 79.1, 79.0, 65.8, 65.7, 50.5, 49.7, 47.7, 46.7, 43.5, 42.6, 39.1, 37.9, 37.6, 36.4, 32.0, 29.8, 28.5, 27.2, 26.5, 26.2, 25.8, 25.6, 24.4, 22.4, 22.3, 21.8, 21.1.



To a stirred solution of keto acid **10** (20.8 mg, 0.053 mmol) in CH_2Cl_2 (1.0 mL) was added MeOH (0.10 mL) and $\text{TMSCH}_2\text{CN}_2$ (40 μL , 2.0M, 0.080 mmol) at rt. The resulting yellow solution was allowed to stir for 1 h, and then concentrated. The residue was purified with flash column chromatography ($\text{CHCl}_3/\text{MeOH}$ 40:1) to provide 20 mg of methyl ester **12** (95%) as colorless oil. $[\alpha]_D = -16.5$ ($c = 0.82$, CHCl_3); IR (KBr) Vmax cm^{-1} : 3440, 3432, 2960, 2928, 1738, 1699, 1367, 1260, 1170, 802; $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ ppm: 3.67 (3H, s), 3.52-3.19 (1H, m), 3.09-2.86 (3H, m), 2.69-2.57 (3H, m), 2.42-1.88 (9H, s), 1.73-1.67 (4H, m), 1.46 (9H, s), 1.01 (3H, d, $J = 6.7$ Hz); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ ppm: 211.1, 210.9, 173.4, 173.3, 157.1, 83.4, 83.0, 79.9, 70.1, 51.6, 47.5, 47.1, 47.0, 46.9, 44.2, 37.2, 37.0, 34.7, 33.6, 30.4, 30.2, 29.7, 28.4, 28.2, 28.0, 27.9, 23.3, 22.4, 21.8, 21.4, 20.9; HR ESI m/z : calcd for $\text{C}_{22}\text{H}_{34}\text{NO}_6$ $[\text{M}-\text{H}]^+$: 408.2386, found 408.2374.



To a stirred solution of methyl ester **12** (35 mg, 86 μmol) in CH_2Cl_2 was added TFA (0.5 mL) at 0°C , after 10 min, the cooling bath was removed and the reaction was allowed to stir for another 2 h at rt before being quenched by addition of saturated NaHCO_3 carefully. The neutralized reaction was extracted with CHCl_3 . The combined organic layers were washed with saturated NaHCO_3 (5 mL \times 3), brine and then dried and concentrated. The crude product was purified with flash column chromatography to provide 14.5 mg (65%) of alkaloid **14**.



To a stirred solution of alkaloid **14** (20 mg, 77 μ mol) in 4 mL of benzene was added DDQ (26 mg, 0.12 mmol), and the resulting reaction was stirred for 30 min before being quenched with saturated NaHCO_3 . The reaction was extracted with CHCl_3 . The combined organic layers were washed with brine, dried and concentrated. The crude product was purified with flash column chromatography to provide 15 mg (75%) of alkaloid **11**.

