

A Facile Total Synthesis of Hainanensine via an Unusual Rearrangement–Annulation Cascade

Zhi-Wei Zhang[†] and Wei-Dong Z. Li^{*,†,‡}

[†]State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China;

[‡]State Key Laboratory of Elemento-organic Chemistry, Nankai University, Tianjin 300071, China

wdli@nankai.edu.cn

General

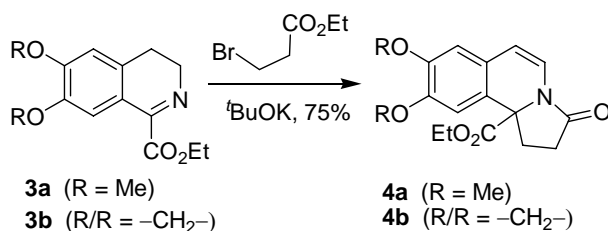
For product purification by flash column chromatography, silica gel (200~300 mesh) and light petroleum ether (bp. 60~90 °C) are used unless otherwise noted. All solvents were purified and dried by standard techniques, and distilled prior to use. All organic extracts were dried over anhydrous sodium sulfate, unless otherwise noted. IR spectra were recorded on a Nicolet NEXU 670 FT spectrometer as liquid film. ¹H and ¹³C NMR spectra were taken on a Varian mercury-300, Bruker AM-200 or AM-400 spectrometer with TMS as an internal standard and CDCl₃ as solvent. EI-MS was obtained on HP-5988A GC/MS instrument. HRMS were determined on a Bruker Daltonics APEXII 47e FT-ICR spectrometer. Melting points were measured on Kofler hot stage and are uncorrected. All moisture-sensitive reactions were performed in flame-dried glassware under stream of nitrogen. Other commercially available reagents and solvents were used as received without further purification unless indicated otherwise.

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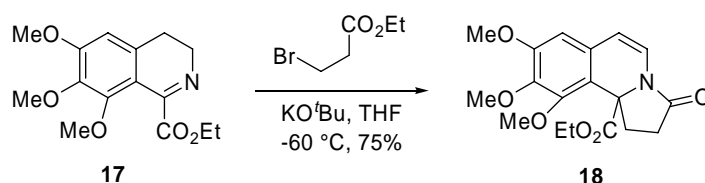
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Experimental

General procedures for the preparation of aldehyde **6a** and **6b**:



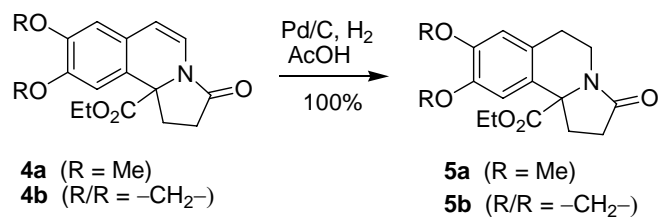
A mixture of $t\text{BuOK}$ (224 mg, 2.0 mmol) in 1 mL of anhydrous THF was added to a solution of compound **3a** or **3b** (1.0 mmol) in anhydrous THF (4 mL) at $-60\text{ }^\circ\text{C}$ under argon. After stirring for 10 min at this temperature, ethyl 3-bromopropionate (1.1 mmol) was added and stirring was continued for another 10 min. The mixture was treated with a saturated solution of NaHCO_3 (10 mL) and diluted with EtOAc (90 mL). The organic layer was washed with water ($3 \times 10\text{ mL}$), brine ($2 \times 10\text{ mL}$), dried over anhydrous Na_2SO_4 . After evaporation of the solvent, the crude product was purified by silica gel column chromatography eluting with petroleum ether- EtOAc (4 : 1) to give compound **4a** or **4b** (75%). Compound **4b**:¹ White crystals. mp. $109\text{--}110\text{ }^\circ\text{C}$; $R_f = 0.5$ (petroleum ether : $\text{EtOAc} = 1 : 1$); IR (film) ν_{max} : 2983, 1734, 1714, 1638 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 6.85 (1H, d, $J = 7.5\text{ Hz}$), 6.73 (1H, s), 6.47 (1H, s), 5.88 (2H, s), 5.79 (1H, d, $J = 7.8\text{ Hz}$), 4.04 (2H, m), 2.81-2.75 (1H, m), 2.53-2.35 (3H, m), 1.10 (3H, t, $J = 7.2\text{ Hz}$) ppm; $^{13}\text{C NMR}$ (DEPT) (75 MHz, CDCl_3): δ 172.4, 171.7, 147.6, 147.0, 125.3, 124.9, 67.2 (C); 120.1, 111.0, 106.3, 105.2 (CH); 101.2, 62.0, 31.7, 29.6 (CH_2); 13.9 (CH_3) ppm; HRMS (ESI) m/z : found for $[\text{M}+\text{H}]^+$ 302.1028, Calcd for $\text{C}_{16}\text{H}_{16}\text{O}_5\text{N}$ 302.1023.



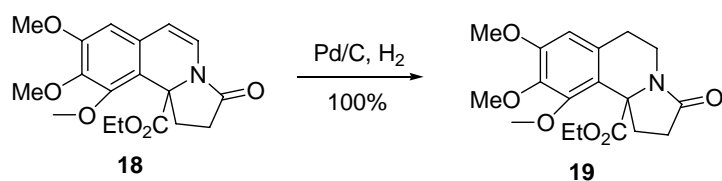
The reaction was carried out as above. Compound **18** (yield 75%).² $R_f = 0.5$ (petroleum ether : $\text{EtOAc} = 2 : 1$); IR (film) ν_{max} : 1730, 1708, 1633 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 6.98 (1H, d, $J = 7.5\text{ Hz}$), 6.43 (1H, s), 5.92 (1H, d, $J = 7.5\text{ Hz}$), 4.20-4.09 (2H, m), 3.98 (3H, s), 3.87 (3H, s), 3.86 (3H, s), 3.08-3.02 (1H, m), 2.73-2.60 (2H, m), 2.54-2.44 (1H, m), 1.20 (3H, t, $J = 7.2\text{ Hz}$) ppm; $^{13}\text{C NMR}$ (DEPT) (75 MHz, CDCl_3): δ 173.1, 172.1, 153.6, 151.9, 141.6, 126.9, 117.7, 66.7 (C); 121.2, 111.4, 104.2 (CH); 62.0, 32.6, 29.8 (CH_2); 60.7, 60.6, 55.8, 14.0 (CH_3) ppm; HRMS (ESI) m/z : found for $[\text{M}+\text{H}]^+$ 348.1444, calcd for $\text{C}_{18}\text{H}_{22}\text{O}_6\text{N}$ 348.1442.

(1) For the spectral data of compounds **4a**, **5a** and **6a**, see: Li, W.-D. Z.; Yang, H. *Tetrahedron* **2005**, *61*, 5037.

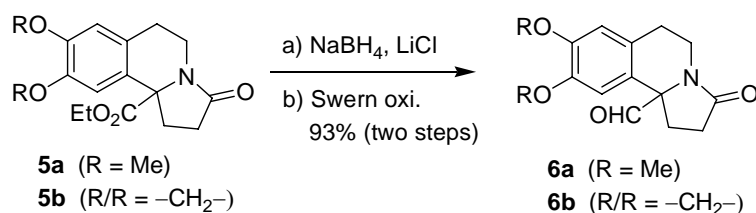
(2) Starting compound **17** was prepared by using 2-(3,4,5-trimethoxyphenyl)ethanamine as starting material, for the preparation, see: (a) Fang, F. G.; Maier, M. E.; Danishefsky, S. J.; Schulte, G. *J. Org. Chem.* **1990**, *55*, 831. (b) Li, W.-D. Z.; Yang, H. *Tetrahedron* **2005**, *61*, 5037.



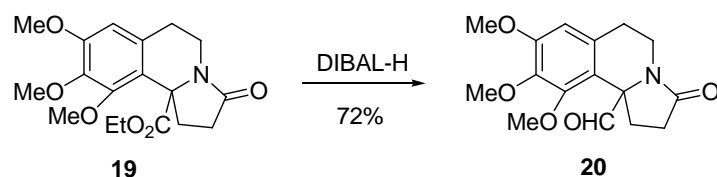
A mixture of compound **4a** or **4b** (1.0 mmol) and 10% Pd-C in 10 mL of AcOH was stirred under hydrogen atmosphere (1 atm). After 24 h at r.t., the reaction mixture was filtered and the filtrate was evaporated under reduced pressure to give a residue, which was purified by silica gel column chromatography eluting with petroleum ether-EtOAc (1 : 1) to give compound **5a** or **5b** as a colorless oil in quantitative yield. Compound **5b**: R_f = 0.3 (petroleum ether : EtOAc = 1 : 1); IR (film) ν_{\max} : 1731, 1697 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 6.87 (1H, s), 6.58 (1H, s), 5.95 (2H, s), 4.29-4.23 (1H, m), 4.22-4.14 (2H, m), 3.40-3.34 (1H, m), 3.01-2.95 (1H, m), 2.85-2.80 (1H, m), 2.75-2.69 (1H, m), 2.58-2.39 (2H, m), 2.13-2.02 (1H, m), 1.25 (3H, t, J = 6.9 Hz) ppm; ¹³C NMR (DEPT) (75 MHz, CDCl₃): δ 172.5, 171.8, 146.8, 146.1, 128.1, 126.6, 66.6 (C); 108.0, 105.6 (CH); 100.7, 61.6, 35.3, 32.6, 30.2, 27.4 (CH₂); 13.6 (CH₃) ppm; HRMS (ESI) m/z : found for [M+H]⁺ 304.1179 calcd for C₁₆H₁₈NO₅ 304.1179.



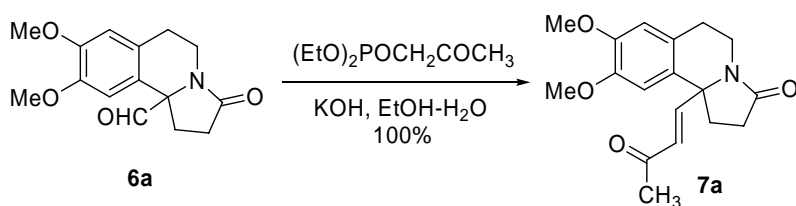
Compound **19** (yield 100%). R_f = 0.6 (petroleum ether : EtOAc = 1 : 2); IR (film) ν_{\max} : 1733, 1697 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 6.35 (1H, s), 4.27-4.17 (1H, m), 4.16-4.02 (2H, m), 3.80 (3H, s), 3.77 (3H, s), 3.74 (3H, s), 3.17 (1H, t, J = 9.3 Hz), 2.99 (2H, dt, J = 3.6 Hz, 12.3 Hz), 2.83-2.70 (2H, m), 2.62-2.56 (1H, m), 2.35-2.26 (1H, m), 1.87-1.75 (1H, m), 1.15 (3H, t, J = 7.2 Hz) ppm; ¹³C NMR (DEPT) (75 MHz, CDCl₃): δ 173.6, 171.3, 152.8, 150.2, 139.8, 129.0, 122.5, 65.7 (C); 106.8 (CH); 61.3, 35.1, 31.7, 31.0, 28.4 (CH₂); 60.4, 59.9, 55.6, 14.0 (CH₃) ppm; HRMS (ESI) m/z : found for [M+H]⁺ 350.1603, calcd for C₁₈H₂₄O₆N 350.1598.



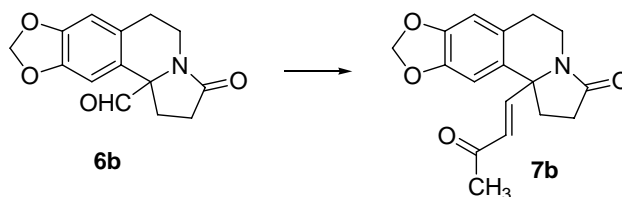
To a stirred mixture of NaBH₄ (95 mg, 2.5 mmol) and LiCl (106 mg, 2.5 mmol) in 10 mL of absolute EtOH was added a solution of compound **5a** or **5b** (1 mmol) in 5 mL of anhydrous THF at 0 °C. After stirring for 24 h at r.t., the reaction mixture was treated with saturated aqueous citric acid solution until the solution became clear. Evaporation of the solvent gave a residue, which was extracted with CH₂Cl₂ (5×10 mL). After evaporation of the solvent, the residue was used without purification on silica gel and subjected to a standard Swern Oxidation: To a cold solution of (COCl)₂ (140 mg, 1.1 mmol) in 5 mL of CH₂Cl₂ under argon atmosphere at -60 °C was added a solution of DMSO (172 mg, 2.2 mmol) in 5 mL of CH₂Cl₂ drop by drop. After the solution was stirred for 5 min, the crude alcohol (261 mg, 1 mmol) in 10 mL of CH₂Cl₂ was added and stirring was continued for 15 min at -60 °C. After 0.7 mL of Et₃N being added, the reaction mixture was warmed to room temperature, then 10 mL of saturated NaHCO₃ was added to terminate the reaction. The solution was washed with water, brine and dried over anhydrous Na₂SO₄. After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with petroleum ether-EtOAc (1 : 2) to give aldehyde **6a** or **6b** (93%) as a white foam. Compound **6b**: *R_f* = 0.4 (EtOAc); IR (film) ν_{max} : 1728, 1691 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 9.61 (1H, s), 6.69 (1H, s), 6.65 (1H, s), 5.97 (2H, s), 4.33-4.25 (1H, m), 3.24 -3.14 (1H, m), 2.93-2.77 (2H, m), 2.72-2.64 (1H, m), 2.49-2.44 (2H, m), 2.08-1.97 (1H, m) ppm; ¹³C NMR (DEPT) (75 MHz, CDCl₃): δ 173.2, 147.5, 147.0, 128.2, 124.9, 70.6 (C); 196.0, 109.2, 105.4 (CH); 101.3, 35.9, 30.0, 28.9, 27.8 (CH₂) ppm; HRMS (ESI) *m/z*: found for [M+H]⁺ 260.0920, calcd for C₁₄H₁₄NO₄ 260.0917.



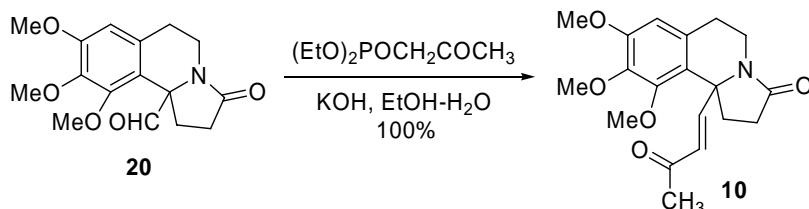
To a stirred solution of compound **19** (524 mg, 1.5 mmol) in dichloromethane (18 mL) was added DIBAL-H (3 mL, 1.0 M in toluene, 3 mmol) dropwise at -78 °C. After addition, the stirring was continued for 1 h at this temperature. 20 mL of brine was added to the solution. The reaction mixture was warmed to ambient temperature, extracted with EtOAc, dried over anhydrous Na₂SO₄. After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with petroleum ether-EtOAc (1 : 2) to give compound **20** (329 mg, 72%) as a colorless oil. *R_f* = 0.4 (pure EtOAc); IR (film) ν_{max} : 1727, 1694 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 9.69 (1H, s), 6.47 (1H, s), 4.39-4.34 (1H, m), 3.97 (3H, s), 3.76 (6H, s), 3.04 -2.82 (3H, m), 2.67-2.37 (3H, m), 2.19-2.00 (1H, m) ppm; ¹³C NMR (DEPT) (75 MHz, CDCl₃): δ 173.2, 153.5, 150.7, 140.3, 130.6, 118.7, 69.3 (C); 196.2, 107.6 (CH); 35.5, 29.9, 28.9, 28.3 (CH₂); 60.8, 60.6, 55.9 (CH₃) ppm; HRMS (ESI) *m/z*: found for [M+H]⁺ 306.1331, calcd for C₁₆H₂₀O₅N 306.1336.



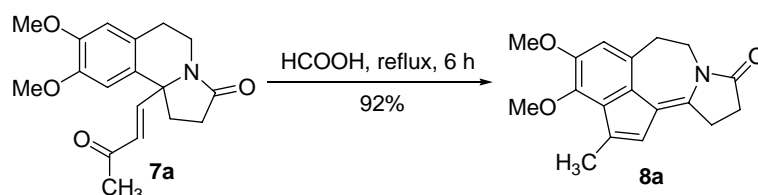
To a mixture of compound **6a** (275 mg, 1.0 mmol) in ethanol (8 mL) was added KOH (90 mg, in 2 mL of H₂O) and diethyl acetylmethylphosphate (1.5 mmol). The reaction mixture was stirred for 48 h under argon at ambient temperature. The resulting mixture was evaporated and the residue was taken in 50 mL of CHCl₃, washed with water and brine, dried over anhydrous Na₂SO₄. After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with petroleum ether-EtOAc (1 : 2) to give compound **7a** in quantitative yield as a colorless oil. *R_f* = 0.3 (pure EtOAc); IR (film) ν_{max} : 1689, 1619 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 6.85 (1H, d, *J* = 15.9 Hz), 6.61 (2H, s), 5.95 (1H, d, *J* = 15.9 Hz), 4.31-4.24 (1H, m), 3.90 (3H, s), 3.87 (3H, s), 3.07-2.85 (2H, m), 2.71-2.40 (4H, m), 2.28-2.20 (1H, m), 2.25 (3H, s) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 197.6, 172.8, 148.4, 148.2, 129.3, 125.6, 64.0 (C); 147.0, 127.6, 111.5, 107.9 (CH); 34.9, 33.6, 29.8, 27.6 (CH₂); 56.0, 55.7, 28.2 (CH₃) ppm; HRMS (ESI) *m/z*: found for [M]⁺ 315.1456, calcd for C₁₈H₂₁O₄N 315.1465.



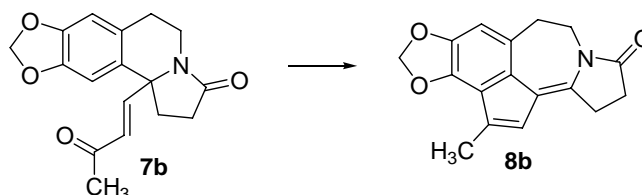
Compound **7b**, white solids (100%). mp. 149~151 °C; *R_f* = 0.4 (pure EtOAc); IR (film) ν_{max} : 1691, 1623 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 6.82 (1H, d, *J* = 15.6 Hz), 6.66 (1H, s), 6.59 (1H, s), 5.94 (1H, d, *J* = 15.9 Hz), 5.95 (2H, s), 4.24-4.17 (1H, m), 3.07-2.98 (1H, m), 2.92-2.81 (1H, m), 2.70-2.40 (4H, m), 2.26 (3H, s), 2.22-2.04 (1H, m) ppm; ¹³C NMR (DEPT) (100 MHz, CDCl₃): δ 197.1, 172.2, 146.7, 146.2, 130.1, 126.3, 63.7 (C); 146.3, 127.3, 108.1, 104.7 (CH); 100.6, 34.3, 33.2, 29.2, 27.5 (CH₂); 27.3 (CH₃) ppm; HRMS (ESI) *m/z*: found for [M+H]⁺ 300.1226, calcd for C₁₇H₁₈NO₄ 300.1230.



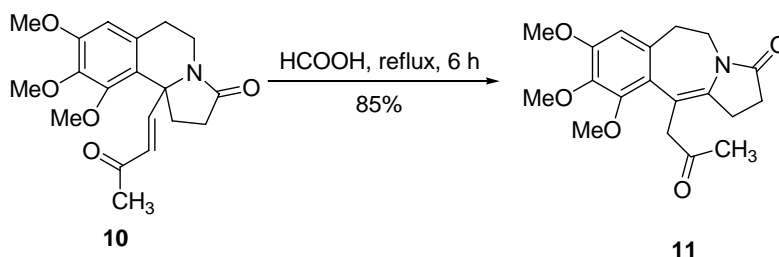
Compound **10**, colorless oil. *R_f* = 0.5 (EtOAc); IR (film) ν_{max} : 2939, 1694, 1494, 1415, 1257 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.03 (1H, d, *J* = 15.6 Hz), 6.41 (1H, s), 5.88 (1H, d, *J* = 16.2 Hz), 4.35-4.30 (1H, m), 3.98 (3H, s), 3.85 (6H, s), 2.91-2.76 (3H, m), 2.71-2.39 (3H, m), 2.27 (3H, s), 2.20-2.02 (1H, m) ppm; ¹³C NMR (DEPT) (75 MHz, CDCl₃): δ 198.3, 172.8, 153.1, 150.6, 140.6, 129.3, 123.1, 63.6 (C); 147.0, 127.5, 107.2 (CH); 34.3, 33.8, 29.7, 28.6 (CH₂); 60.7, 55.9, 27.8 (CH₃) ppm; HRMS (ESI) *m/z*: found for [M+H]⁺ 346.1649, calcd for C₁₉H₂₄NO₅ 346.1649.



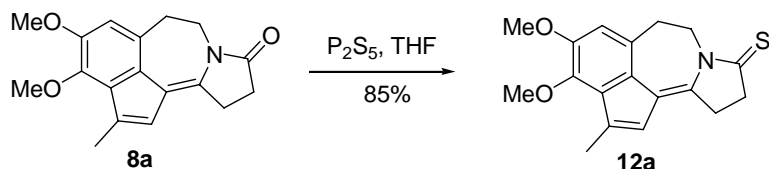
A solution of enone **7a** (3.15 g, 10.0 mmol) in 50 mL of formic acid was heated under reflux for 6 h. TLC then showed complete consumption of the enone. The mixture was concentrated under reduced pressure to give a residue, which was neutralized carefully with saturated aqueous NaHCO_3 solution, extracted with CH_2Cl_2 (5×10 mL), dried over anhydrous Na_2SO_4 . After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with petroleum ether-EtOAc (2 : 1) to give **8a** (2.73 g, 92%) as yellow solids. mp. 152~154 °C; R_f = 0.5 (petroleum ether : EtOAc = 1 : 1); IR (film) ν_{max} : 1725, 1642 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 6.52 (1H, s), 6.37 (1H, s), 4.18-3.90 (2H, br), 3.87 (6H, s), 3.12 (2H, t, J = 7.2 Hz), 3.02 (2H, t, J = 4.5 Hz), 2.71-2.66 (2H, m), 2.43 (3H, s) ppm; ^{13}C NMR (DEPT) (75 MHz, CDCl_3): δ 176.0, 150.9, 142.8, 142.6, 136.3, 134.9, 130.2, 127.2, 116.0 (C); 123.7, 109.8 (CH); 41.2, 34.2, 29.0, 23.4 (CH_2); 61.5, 56.4, 15.7 (CH_3) ppm; HRMS (ESI) m/z : found for $[\text{M}+\text{H}]^+$ 298.1434, calcd for $\text{C}_{18}\text{H}_{20}\text{O}_3\text{N}$ 298.1438.



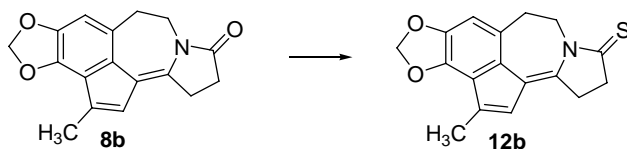
Compound **8b** (yield 34%), colorless solids. mp. 228~230 °C; R_f = 0.6 (petroleum ether : EtOAc = 1 : 1); IR (film) ν_{max} : 1724, 1707, 1636 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 6.48 (1H, s), 6.39 (1H, s), 5.97 (2H, s), 3.96 (2H, br), 3.13 (2H, t, J = 7.8 Hz), 2.99 (2H, m), 2.72-2.67 (2H, m), 2.35 (3H, s) ppm; ^{13}C NMR (DEPT) (75 MHz, CDCl_3): δ 175.9, 145.8, 143.0, 139.0, 133.7, 128.0, 127.7, 124.6, 116.6 (C); 123.5, 105.1 (CH); 100.9, 41.2, 34.2, 29.0, 23.5 (CH_2); 14.7 (CH_3) ppm; HRMS (ESI) m/z : found for $[\text{M}+\text{H}]^+$ 282.1131, calcd for $\text{C}_{17}\text{H}_{16}\text{O}_3\text{N}$ 282.1125.



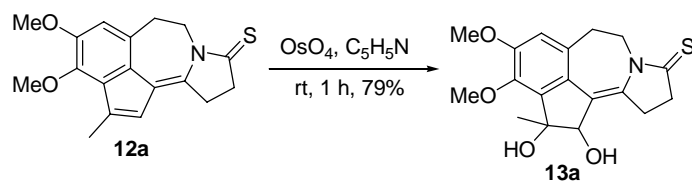
Compound **11** (yield 85%), colorless oil. R_f = 0.6 (EtOAc); IR (film) ν_{max} : 1715, 1636, 1597 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 6.41 (1H, s), 3.86 (6H, s), 3.68 (3H, s), 3.48 (2H, s), 2.89-2.86 (2H, m), 2.75 (2H, m), 2.56 (2H, m), 2.17 (3H, s) ppm; ^{13}C NMR (DEPT) (75 MHz, CDCl_3): δ 205.2, 175.8, 151.7, 151.6, 141.2, 140.7, 136.8, 123.8, 103.2 (C); 107.4 (CH); 48.9, 47.6, 34.6, 28.9, 24.7 (CH_2); 60.9, 60.8, 55.9, 29.5 (CH_3) ppm; HRMS (ESI) m/z : found for $[\text{M}+\text{H}]^+$ 346.1646, calcd for $\text{C}_{19}\text{H}_{24}\text{NO}_5$ 346.1649.



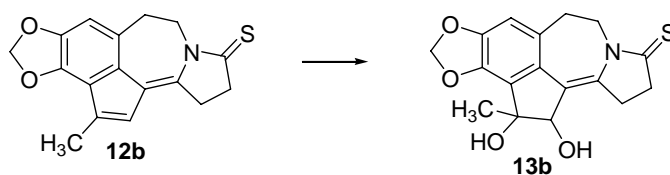
To a stirred solution of compound **8a** (297 mg, 1.0 mmol) in 10 mL of anhydrous THF was added P_2S_5 (333 mg, 1.5 mmol) at room temperature. After 1 h at r.t., the resulting mixture was filtered and the filtrate was evaporated. The residue was purified by silica gel column chromatography eluting with petroleum ether-EtOAc (8 : 1) to give compound **12a** (266 mg, yield 85%) as reddish solids. mp. 172~174 °C; R_f = 0.8 (petroleum ether: EtOAc = 2 : 1); IR (film) ν_{max} : 2922, 1650, 1385, 1257 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 6.54 (1H, s), 6.31 (1H, s), 3.89 (3H, s), 3.87 (3H, s), 3.90-3.80 (2H, m), 3.25-3.20 (2H, m), 3.15-3.11 (2H, m), 3.05 (2H, t, J = 4.8 Hz), 2.41 (3H, s) ppm; ^{13}C NMR (75 MHz, CDCl_3): δ 205.6, 151.5, 144.2, 142.3, 138.8, 135.1, 130.9, 126.2, 124.5, 117.8, 109.4, 61.5, 55.1, 45.8, 42.0, 33.1, 25.7, 15.8 ppm; HRMS (ESI) m/z : found for $[\text{M}+\text{H}]^+$ 314.1204, calcd for $\text{C}_{18}\text{H}_{20}\text{NO}_2\text{S}$ 314.1209.



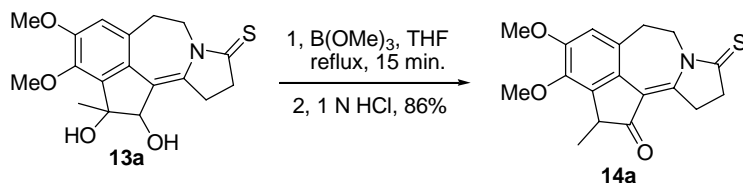
Compound **12b** (yield 85%), yellowish solids. mp. 214~216 °C; R_f = 0.6 (petroleum ether : EtOAc = 4 : 1); IR (film) ν_{max} : 1730, 1643, 1383, 1033 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 6.49 (1H, s), 6.32 (1H, s), 5.98 (2H, s), 4.49 (2H, br), 3.30-3.14 (2H, m), 3.12-3.03 (2H, m), 2.99-2.93 (2H, m), 2.25 (3H, s) ppm; ^{13}C NMR (DEPT) (75 MHz, CDCl_3): δ 205.6, 146.8, 144.5, 139.3, 136.4, 129.0, 127.1, 124.3, 118.6 (C); 124.7, 105.2 (CH); 101.1, 45.9, 42.0, 33.3, 25.9 (CH_2); 14.9 (CH_3) ppm; HRMS (ESI) m/z : found for $[\text{M}+\text{H}]^+$ 298.0892, calcd for $\text{C}_{17}\text{H}_{16}\text{O}_2\text{NS}$ 298.0896.



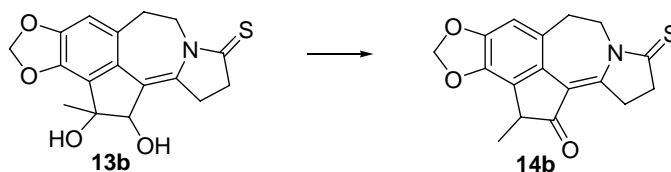
A solution of osmium tetroxide (254 mg, 1.0 mmol) dissolved in pyridine (1 mL) was added to a solution of compound **12a** (313 mg, 1.0 mmol) in pyridine (4 mL) at room temperature. After the solution being stirred under nitrogen for 1 h, sodium bisulfite (400 mg, in 6 mL of H₂O) and methanol (12 mL) was added and stirring was continued for another 10 min. The resulting mixture was evaporated under reduce pressure to give a residue, which was taken up in 50 mL of CHCl₃, washed with water and brine, dried over Na₂SO₄. After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with petroleum ether-EtOAc (1 : 2) to give compound **13a** (79%) as a foam. *R_f* = 0.3 (pure EtOAc). IR (film) ν_{max} : 3404, 1675, 1497, 1402, 1273 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 6.62 (1H, s), 4.36 (1H, d, *J* = 3.3 Hz), 3.92 (3H, s), 3.83 (3H, s), 3.66 (1H, br), 3.46 (1H, d, *J* = 4.2 Hz), 3.15-3.00 (3H, m), 2.98-2.80 (3H, m), 1.62 (3H, s) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 203.6, 151.6, 144.3, 141.5, 138.6, 132.6, 127.7, 117.0, 113.5, 80.3, 78.6, 61.0, 56.0, 45.5, 42.0, 33.3, 26.9, 24.2 ppm; HRMS (ESI) *m/z*: found for [M+H]⁺ 348.1271, calcd for C₁₈H₂₂NO₄S 348.1264.



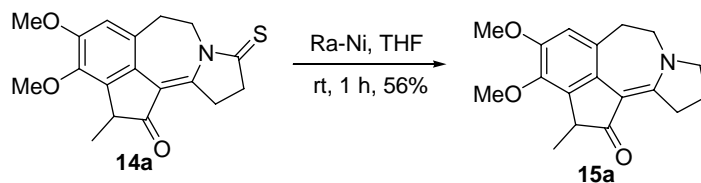
Compound **13b** (yield 27%), yellowish solids. mp. 160~162 °C; *R_f* = 0.4 (pure EtOAc); IR (film) ν_{max} : 3365, 1675, 1478, 1389, 1257 cm⁻¹; ¹H NMR (600 MHz, CDCl₃): δ 6.61 (1H, s), 6.02 (2H, s), 4.47 (1H, s), 3.21-3.14 (3H, m), 2.94-2.70 (4H, m), 2.65 (1H, m), 1.65 (3H, s) ppm; ¹³C NMR (DEPT) (75 MHz, CDCl₃): δ 203.8, 147.9, 142.2, 141.9, 130.7, 128.8, 117.1, 100.0, 77.2 (C); 109.7, 80.7, (CH); 101.9, 45.8, 42.1, 33.6, 24.6(CH₂); 25.4 (CH₃) ppm. HRMS (ESI) *m/z*: found for [M+H]⁺ 332.0947, calcd for C₁₇H₁₈O₄NS 332.0951.



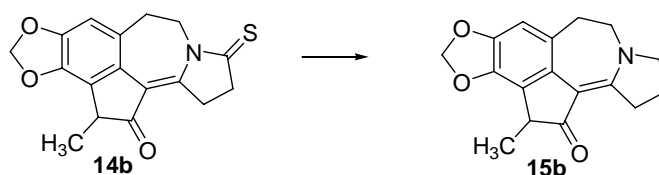
To a solution of compound **13a** (347 mg, 1.0 mmol) in anhydrous THF (5 mL) was added B(OMe)₃ (3 mmol) under argon. After the solution being stirred for 15 min at reflux, HCl (1 N, 10 mL) was added and stirring was continued for another 15 min at reflux. The reaction mixture was taken up in 50 mL of EtOAc, washed with brine, dried over Na₂SO₄. After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with petroleum ether-EtOAc (6 : 1) to give compound **14a** (283 mg, yield 86%) as yellow solids. mp. 152~153 °C; *R*_f = 0.6 (petroleum ether: EtOAc = 2 : 1); IR (film) ν_{max} : 1709, 1617, 1374, 1254, 1181 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 6.64 (1H, s), 3.87 (3H, s), 3.86 (3H, s), 3.90-3.81 (2H, m), 3.47 (1H, q, *J* = 6.9 Hz), 3.33 (2H, t, *J* = 4.2 Hz), 3.21-3.17 (2H, m), 3.02 (2H, m), 1.46 (3H, d, *J* = 7.8 Hz) ppm; ¹³C NMR (DEPT) (75 MHz, CDCl₃): δ 208.2, 207.8, 152.2, 151.5, 144.4, 134.4, 131.1, 129.0, 112.5 (C); 111.9, 45.6 (CH); 45.6, 42.2, 33.4, 26.4 (CH₂); 60.5, 55.8, 15.8 (CH₃) ppm; HRMS (ESI) *m/z*: found for [M+H]⁺ 330.1157, calcd for C₁₈H₂₀NO₃S 330.1158.



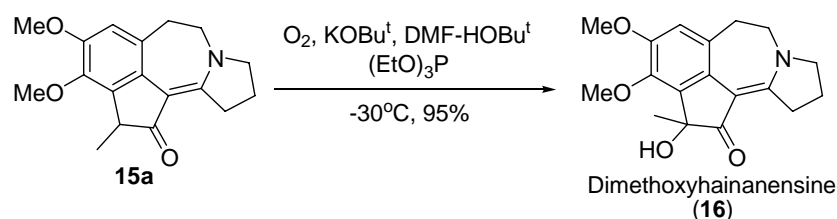
Compound **14b** (yield 86%), yellowish solids. mp. 187~188 °C; *R*_f = 0.6 (petroleum ether : EtOAc = 3 : 1); IR (film) ν_{max} : 1734, 1709, 1601, 1378, 1252 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 6.61 (1H, s), 6.00 (2H, s), 4.49 (2H, br), 3.47 (1H, q, *J* = 7.5 Hz), 3.37 (2H, t, *J* = 6.0 Hz), 3.22 (2H, t, *J* = 7.2 Hz), 3.01 (2H, t, *J* = 3.0 Hz), 1.46 (3H, d, *J* = 7.5 Hz) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 208.4, 207.2, 152.8, 147.1, 142.2, 130.0, 129.2, 121.7, 112.4, 108.1, 101.5, 45.8, 44.3, 42.2, 33.6, 26.6, 14.6 ppm; HRMS (ESI) *m/z*: found for [M+H]⁺ 314.0851, calcd for C₁₇H₁₆O₃NS 314.0845.



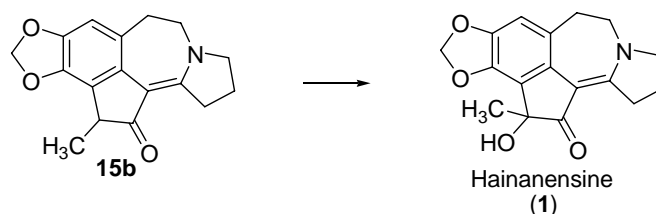
To a solution of compound **14a** (89 mg, 0.27 mmol) in 20 mL of anhydrous THF was added 1 mL of water, methanol, and anhydrous THF-washed Raney-Ni. The suspension was stirred for 1h and filtered. The Raney-Ni was washed with 10 mL of anhydrous THF and the combined filtrate was evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with petroleum ether-EtOAc (2 : 1) to give compound **15a** (45 mg, yield 56%) as a yellow gum. R_f = 0.2 (petroleum ether : EtOAc = 1 : 1); IR (film) ν_{max} : 1666, 1571 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 6.52 (1H, s), 3.85 (3H, s), 3.83 (3H, s), 3.62-3.52 (4H, m), 3.39-3.31 (3H, m), 3.04 (2H, t, J = 4.8 Hz), 2.08-2.00 (2H, m), 1.45 (3H, d, J = 7.5 Hz) ppm; ^{13}C NMR (DEPT) (75 MHz, CDCl_3): δ 204.6, 160.0, 148.6, 144.5, 133.3, 132.2, 126.5, 102.3 (C); 111.8, 45.6 (CH); 56.0, 48.3, 35.0, 33.5, 21.4 (CH_2); 60.3, 56.0, 15.7 (CH_3) ppm; HRMS (ESI) m/z : found for $[\text{M}+\text{H}]^+$ 300.1599, calcd for $\text{C}_{18}\text{H}_{22}\text{NO}_3$ 300.1594.



Compound **15b** (yield 56%), colorless solids. mp. 167~169 $^{\circ}\text{C}$; R_f = 0.5 (petroleum ether : EtOAc = 1 : 2); IR (film) ν_{max} : 1663, 1567 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 6.46 (1H, s), 5.90 (2H, s), 3.60-3.52 (4H, m), 3.38 (2H, t, J = 7.8 Hz), 3.28 (1H, q, J = 7.5 Hz), 3.00 (2H, t, J = 4.5 Hz), 2.10-2.00 (2H, m), 1.41 (3H, d, J = 7.5 Hz) ppm; ^{13}C NMR (DEPT) (75 MHz, CDCl_3): δ 204.0, 160.2, 144.1, 141.7, 134.0, 123.9, 120.0, 102.4 (C); 107.2, 44.2 (CH); 100.7, 56.2, 48.6, 35.1, 33.7, 21.4 (CH_2); 14.7 (CH_3) ppm; HRMS (ESI) m/z : found for $[\text{M}+\text{H}]^+$ 284.1280, calcd for $\text{C}_{17}\text{H}_{18}\text{O}_3\text{N}$ 284.1281.



To a stirring solution of compound **15a** (43 mg, 0.14 mmol) in anhydrous ^tBuOH (1 mL) and DMF (2 mL) was added (EtO)₃P (0.42 mmol) and KO^tBu at –30 °C under oxygen atmosphere. After stirring for 15 min at this temperature, the solution was diluted with EtOAc, washed with water and brine, dried over Na₂SO₄. After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with petroleum ether-EtOAc (1 : 1) to give dimethoxyhainanensine **16**, (45 mg, yield 95%) as colorless crystals. mp. 221~223 °C; *R*_f = 0.3 (petroleum ether : EtOAc = 1 : 2); IR (film) ν_{max} : 3386, 1661, 1569 cm^{–1}; ¹H NMR (300 MHz, CDCl₃): δ 6.56 (1H, s), 3.95 (3H, s), 3.83 (3H, s), 3.63–3.54 (4H, m), 3.45–3.29 (2H, m), 3.03 (2H, t, *J* = 4.2 Hz), 2.62 (1H, br), 2.11–2.01 (2H, m), 1.59 (3H, s) ppm; ¹³C NMR (DEPT) (75 MHz, CDCl₃): δ 202.8, 160.8, 149.2, 145.5, 132.3, 132.2, 126.9, 99.1, 77.4 (C); 113.6 (CH); 56.3, 48.4, 34.9, 33.7, 21.4 (CH₂); 61.4, 56.2, 23.9 (CH₃) ppm; HRMS (ESI) *m/z*: found for [M+H]⁺ 316.1539, calcd for C₁₈H₂₂O₄N 316.1543; X-ray crystallographic data of **16**: C₁₈H₂₁NO₄, FW 315.36, monoclinic, space group *P*2₁/*c*, *a* = 8.465(3) Å, *b* = 9.532(3) Å, *c* = 19.588(7) Å, α = 90.00°, β = 101.510(6)°, γ = 90.00°, *Z* = 4, *d*_{calcd} = 1.352 g/cm³, *R*₁(*I* > 2σ(*I*)) = 0.0502, *wR*₂ = 0.1459.



Hainanensine **1** (yield 95%), colorless crystals. mp. 240~244 °C; *R*_f = 0.4 (petroleum ether : EtOAc = 1 : 4); IR (film) ν_{max} : 3284, 1646, 1564 cm^{–1}; ¹H NMR (300 MHz, CDCl₃): δ 6.49 (1H, s), 5.97 (2H, s), 3.62–3.57 (4H, m), 3.56–3.30 (2H, m), 3.01–3.00 (2H, m), 2.66 (1H, br), 2.14–2.03 (2H, m), 1.57 (3H, s) ppm; ¹³C NMR (DEPT) (75 MHz, CDCl₃): δ 202.4, 161.1, 144.9, 142.3, 132.8, 124.2, 119.9, 99.3, 75.9 (C); 108.7 (CH); 101.3, 56.4, 48.7, 35.0, 33.8, 21.4 (CH₂); 23.6 (CH₃) ppm; HRMS (ESI) *m/z*: found for [M+Na]⁺ 322.1045 calcd for C₁₇H₁₇NO₄Na 322.1050.