

Supporting Information-1 (experimental procedures and spectral data)

Novel Formal Synthesis of Cephalotaxine via a Facile Friedel–Crafts Cyclization

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Table of Contents

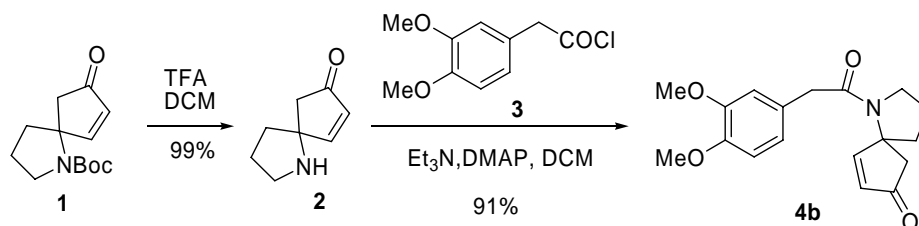
1. Preparation of compound 4b	S2
2. Cyclization of 4b and spectral data of compound 4a	S3
3. Preparation of compound 6	S4-S5
4. Preparation of compound 8b	S6
5. Cyclization of 8b and spectral data of 8a	S7
7. Spectral data of compound 10a and its cyclization product.....	S8
8. Spectral data of compound 10b and its cyclization product.....	S9
9. Spectral data of compound 11a and its cyclization product	S10
10. Spectral data of compound 12 and its cyclization product	S11
11. Spectral data of compound 13a and its cyclization product	S12
12. Spectral data of compound 11b and 13b	S13
10. Ring skeletal isomerization of 9b	S14

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.

Experimental

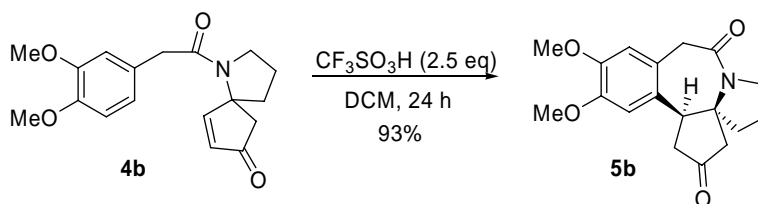
Preparation of spiro enone **4b**



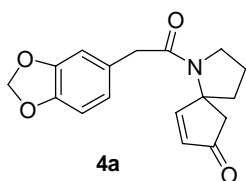
To a stirred mixture of compound **1** (238 mg, 1.0 mmol)¹ in dichloromethane (1 mL) was added TFA (1.0 mL) at 0 °C and the resulting mixture was stirred at the same temperature for 2 h. The solvent was evaporated under reduced pressure to give the crude **2** (140 mg). To a mixture of freshly prepared **3** [from the corresponding acid (294 mg, 1.50 mmol)] in dichloromethane (5 mL) was added dropwise a mixture of the above crude **2** in dichloromethane (2 mL). The resulting mixture was then treated with Et₃N (2 mL) and DMAP (20 mg) and stirred at room temperature for 10 h. The reaction mixture was diluted with dichloromethane (50 mL), and washed with water (3 × 10 mL), 1N HCl (10 mL), brine (2 × 10 mL), dried over anhydrous MgSO₄. After evaporation of the solvent, the resulting residue was purified by silica gel column chromatography eluting with petroleum ether-EtOAc (1 : 1) to give **4b** (287 mg, 91%) as a gum; *R_f* = 0.4 (petroleum ether : EtOAc = 1 : 3); IR (film) ν_{\max} 2959, 1714, 1643, 1590, 1515, 1402, 1263, 1144, 1027, 792, 759 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.72-1.73 (m, 1H), 1.91-1.98 (m, 3H), 2.18-2.25 (dd, *J* = 3 Hz, 1H), 2.90-2.96 (dd, *J* = 3 Hz, 1H), 3.50-3.51 (m, 2H), 3.57-3.61 (m, 1H), 3.64-3.65 (m, 1H), 3.78 (s, 6H), 6.03-6.07 (m, 1H), 6.68-6.77 (m, 3H), 7.32-7.35 (m, 1H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 23.7, 39.0, 42.1, 46.5, 48.0, 55.6, 68.8, 111.1, 111.7, 120.9, 126.5, 131.5, 147.7, 148.8, 166.2, 169.7, 205.6 ppm; HRMS (ESI) *m/z* obsd 316.1546 ([*M*+H]⁺ calcd 316.1543 for C₁₈H₂₂O₄N).

¹ Prepared in an overall yield of ca. 30% from *L*-proline according to a published procedure by Ikeda et al. (Ikeda, M.; El Bialy, S. A. A.; Hirose, K.; Kotake, M.; Sato, T.; Bayomi, S. M. M.; Shehata, I. A.; Abdelal, A. M.; Gad, L. M.; Yakura, T. *Chem. Pharm. Bull.* **1999**, 47, 983). Compound **1**, mp. 62–64 °C; *R_f* = 0.3 (PET : EtOAc = 3 : 1); IR (film) ν_{\max} 2975, 1718, 1690, 1389, 1169, 1121 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.26-1.54 (m, 9H), 1.78-2.18 (m, 4H), 2.30-2.40 (m, 1H), 2.74-2.97 (m, 1H), 3.39-3.67 (m, 2H), 6.08-6.15 (m, 1H), 7.33-7.45 (m, 1H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 22.7, 23.2, 28.1, 28.3, 39.7, 40.7, 47.0, 47.6, 47.8, 67.3, 79.7, 80.4, 131.8, 153.4, 166.8, 206.8 ppm; HRMS (ESI) *m/z* obsd 260.1261 ([*M*+Na]⁺ calcd 260.1257 for C₁₃H₁₉O₃NNa)

Cyclization of spiro enone **4b** to **5b**



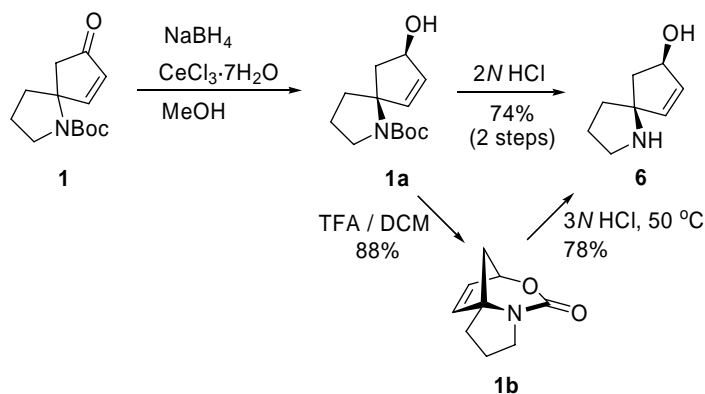
To a solution of compound **4b** (158 mg, 0.5 mmol) in dichloromethane (4 mL) was added $\text{CF}_3\text{SO}_3\text{H}$ (187 mg, 1.25 mmol) in one portion. The resulting slurry was stirred vigorously at room temperature for 10 h, neutralized carefully with saturated aqueous Na_2CO_3 solution at 0 °C, extracted with dichloromethane (5×10 mL), dried over anhydrous MgSO_4 . After evaporation of the solvent, the crude residue was purified by silica gel column chromatography eluting with petroleum ether-EtOAc (1 : 1) to give **10** (147 mg, 93%) as colorless crystals, mp. 222–224 °C;² R_f = 0.3 (petroleum ether : EtOAc = 1 : 3); IR (film) ν_{max} 2959, 1742, 1635, 1516, 1423, 1262, 1111, 731 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.77-1.90 (m, 2H) , 2.12-2.15 (m, 2H), 2.62-2.85 (m, 2H), 2.87-2.96 (m, 2H) , 3.35-3.45 (m, 2H), 3.60-3.68 (t, J = 10.5 Hz, 1H) , 3.72-3.80 (m, 2H) , 3.87 (s, 6H) , 6.68 (s, 1H), 6.82 (s, 1H) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 20.4, 41.8, 44.6, 46.2, 46.9, 48.2, 52.0, 55.8, 56.0, 67.4, 113.3, 114.1, 125.4, 129.2, 147.8, 148.1, 169.2, 213.5 ppm; HRMS (ESI) m/z obsd 316.1538 ($[\text{M}+\text{H}]^+$ calcd 316.1543 for $\text{C}_{18}\text{H}_{22}\text{O}_4\text{N}$).



Spectral data of 4a (prepared analogously as **4b**): R_f = 0.3 (petroleum ether : EtOAc = 1 : 2); IR (film) ν_{max} 2933, 1712, 1643, 1490, 1443, 1403, 1246, 1037, 927, 791 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.78-1.85 (m, 1H), 1.95-2.06 (m, 3H), 2.27 (d, J = 17.4 Hz, 1H), 2.98 (d, J = 17.4 Hz, 1H), 3.54-3.71 (m, 4H), 5.92 (s, 2H), 6.10-6.13 (m, 1H), 6.64-6.76 (m, 3H), 7.40 (m, 1H) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 23.7, 39.0, 42.0, 46.5, 48.1, 69.0, 100.8, 108.1, 109.2, 121.9, 127.6, 131.6, 146.4, 147.7 166.2, 169.8, 205.8 ppm; HRMS (ESI) m/z obsd 300.1232 ($[\text{M}+\text{H}]^+$ calcd 300.1230 for $\text{C}_{17}\text{H}_{18}\text{O}_4\text{N}$).

² Cf: Yasuda, S.; Yamada, T.; Hanaoka, M. *Tetrahedron Lett.* **1986**, 27, 2023.

Preparation of spiro amino alcohol **6**



To a stirred mixture of compound **1** (238 mg, 1.0 mmol) in anhydrous methanol (3 mL) was added $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (450 mg, 1.2 mmol), and stirring was continued for 20 min. at 0°C . To the above reaction mixture was added NaBH_4 (42 mg, 1.1 mmol) portionwise at 0°C . After stirring for 20 min., the reaction mixture was diluted with EtOAc (50 mL), washed with water ($3 \times 10\text{ mL}$), brine ($2 \times 10\text{ mL}$), dried over anhydrous MgSO_4 . After evaporation of the solvent, the crude residue was purified by silica gel column chromatography eluting with petroleum ether-EtOAc (5 : 1) to give the intermediate compound **1a** (222 mg, 92%) as a colorless oil, $R_f = 0.4$ (petroleum ether : EtOAc = 3 : 1); IR (film) ν_{max} 3432, 2973, 1679, 1392, 1172, 772 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.44 (s, 9H), 1.77-1.98 (m, 4H), 2.04-2.35 (m, 2H), 3.43 (t, $J = 6.3\text{ Hz}$, 2H), 4.90 (t, $J = 8.4\text{ Hz}$, 1H), 5.15 (d, $J = 10.8\text{ Hz}$, 1H), 5.63 (d, $J = 5.4\text{ Hz}$, 1H), 5.96-5.99 (m, 1H) ppm. ^{13}C NMR (75 MHz, CDCl_3) δ 23.4, 28.7, 41.15, 46.7, 48.4, 72.5, 75.7, 79.9, 135.2, 136.0, 154.2 ppm. HRMS (ESI) m/z obsd 262.1410 ($[\text{M}+\text{Na}]^+$ calcd 262.1414 for $\text{C}_{13}\text{H}_{21}\text{O}_3\text{NNa}$).

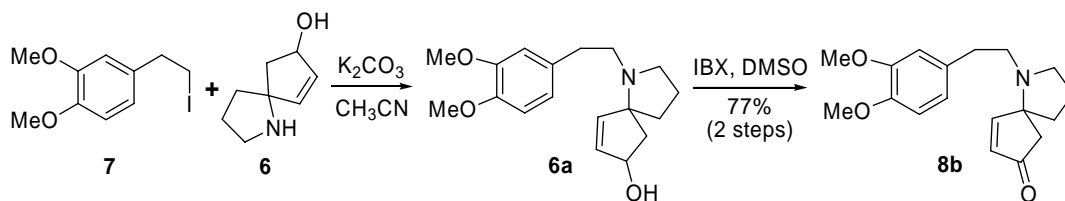
A mixture of the above compound **1a** (240 mg, 1.0 mmol) in 2N HCl (1 mL) was heated to 50°C for 30 min. and basicified with saturated aqueous Na_2CO_3 to pH 12. The resulting mixture was extracted with CHCl_3 ($8 \times 10\text{ mL}$), dried over anhydrous MgSO_4 , and evaporated under reduced pressure to give the residue, which was purified by silica gel column chromatography eluting with CHCl_3 -MeOH (1 : 1) to give the compound **6** (107 mg, 80%) as a single diastereomer (the *cis*-configuration was deduced from the following experimental evidence on the formation of an intermediate **1b**). $R_f = 0.2$ (CHCl_3 : CH_3OH = 1 : 3), IR(film) ν_{max} 3277, 2959, 1401, 1539, 1083, 1053, 778 cm^{-1} ; ^1H

NMR (300 MHz, CDCl₃) δ 1.64-1.77 (m, 2H), 1.80-1.89 (m, 3H), 2.19-2.30 (m, 1H), 2.94-3.02 (m, 2H), 3.48 (s, 2H), 4.68-4.71 (m, 0.5H), 4.91-4.94 (m, 0.5H), 5.78-5.84 (m, 1.5H), 5.86-5.88 (m, 0.5H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 25.4, 25.7, 37.6, 38.9, 45.5, 46.0, 48.0, 48.7, 72.8, 73.4, 75.4, 75.6, 135.0, 135.2, 138.6, 139.5 ppm.

Cyclic urethane **1b**³ was obtained cleanly (colorless gum, 88%) when the reduction product **1a** was treated with TFA in dichloromethane at 0 °C for 2 h, which was further hydrolyzed into the above spiro aminoalcohol **6** in a warming (50 °C) 3*N* hydrochloric acid solution. *Spectral data of 1b*: *R_f* = 0.2 (petroleum ether : EtOAc = 3 : 1); IR (film) ν_{max} 2922, 1742, 1360, 1048 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.85-2.21 (m, 4H), 2.38 (d, *J* = 17.7, 1H), 2.68 (m, 1H), 3.16-3.24 (m, 1H), 3.58-3.67 (m, 1H), 5.23 (s, 1H), 5.87-5.90 (m, 1H), 6.06-6.08 (m, 1H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ 25.6, 34.6, 44.2, 44.6, 73.8, 87.8, 128.7, 135.4, 160.4 ppm.

³ For a known cyclic urethane structure, see: Venit, J. J.; DiPierro, M.; Magnus, P. *J. Org. Chem.* **1989**, *54*, 4298.

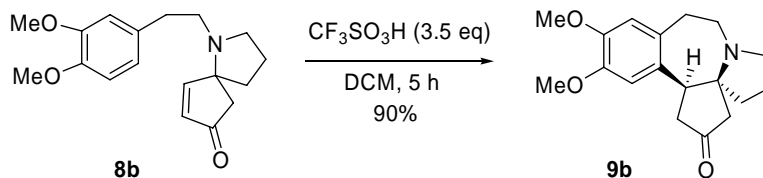
Preparation of spiro enone **8b**



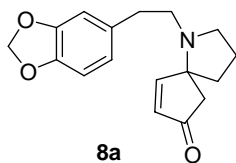
To a mixture of compound **6** (139 mg, 1.0 mmol) in CH₃CN (10 mL) was added compound **7** (588 mg, 1.5 mmol) and K₂CO₃ (276 mg, 2.0 mmol). The mixture was refluxed for 5 h, cooled down 0 °C, diluted with EtOAc (100 mL). The organic layer was washed with water (3 × 10 mL), brine (2 × 10 mL), and dried over anhydrous MgSO₄. After evaporation of the solvent under reduced pressure, the crude residue was purified by silica gel column chromatography eluting with CHCl₃-MeOH (30 : 1) to give the alcohol compound **6a** (257 mg, 85%). *Spectral data of 6a*: R_f = 0.4 (CHCl₃ : CH₃OH = 10 : 1), IR(film) ν_{max} 3383, 2938, 1714, 1515, 1262, 1144, 1029, 807, 766, 731 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.66-1.87 (m, 5H), 2.08-2.14 (m, 1H), 2.61-2.75 (m, 5H), 2.95-3.01 (m, 1H), 3.83-3.86 (m, 6H), 4.76 (d, J = 4.8 Hz, 3H), 5.74-5.82 (m, 2H), 6.71-6.79 (m, 3H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ 21.2, 35.4, 37.6, 40.1, 51.2, 51.7, 55.7, 74.7, 76.0, 111.0, 111.9, 120.4, 132.9, 134.8, 138.0, 147.1, 148.5 ppm.

To a mixture of allylic alcohol compound **6a** (303 mg, 1.0 mmol) in anhydrous DMSO (3 mL) was added IBX (700 mg, 2.5 mmol). The mixture was stirred for 1 h at 30 °C, diluted with EtOAc (100 mL). The organic layer was washed with water (2 × 10 mL), saturated aqueous NaHCO₃ (2 × 10 mL), and brine (10 mL), dried over anhydrous MgSO₄. After the evaporation of the solvent, the crude residue was purified by silica gel column chromatography eluting with petroleum ether-EtOAc (1 : 1) to give **8b** (271 mg, 90%); R_f = 0.2 (petroleum ether : EtOAc = 1 : 3); IR(film) ν_{ma} 2938, 1714, 1515, 1462, 1263, 1144, 1029, 804 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.76-2.11 (m, 5H), 2.36-2.48(m, 3H), 2.62-2.70 (m, 3H), 3.10-3.12(m, 1H), 3.81-3.83 (m, 6H), 6.07-6.09 (m, 1H), 6.64-6.75 (m, 3H), 7.28-7.31 (m, 1H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 21.6, 35.5, 37.7, 40.8, 51.1, 51.5, 55.63 71.4, 110.9, 111.7, 120.3, 132.5, 133.9, 147.1, 148.5, 167.7, 207.7 ppm; HRMS (ESI) m/z obsd 302.1756 ([M+H]⁺ calcd 302.1751 for C₁₈H₂₄O₃N).

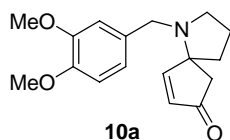
*Cyclization of spirocyclic enone **8b** to **9b***



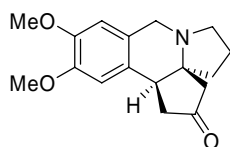
To a mixture of compound **8b** (300 mg, 1.0 mmol) in dichloromethane (5 mL) was added $\text{CF}_3\text{SO}_3\text{H}$ (525 mg, 3.5 mmol). The resulting slurry was stirred vigorously at room temperature for 5 h, basicified with saturated aqueous Na_2CO_3 , extracted with dichloromethane (5×10 mL), dried over anhydrous MgSO_4 . After evaporation of the solvent, the crude residue was purified by silica gel column chromatography eluting with petroleum ether-EtOAc (1 : 3) to give **9b** (271 mg, yield 90%) as a colourless gum; R_f = 0.2 (EtOAc); IR (film) ν_{max} 2940, 1737, 1516, 1461, 1259, 1223, 1118, 730 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.65-2.11 (m, 5H), 2.47-2.80 (m, 6H), 2.82-3.08 (m, 3H), 3.61 (t, J = 9.6 Hz, 1H), 3.86 (s, 6H), 6.66 (s, 1H), 6.70 (s, 1H), ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 20.0, 31.0, 41.8, 42.4, 44.9, 47.9, 50.1, 53.8, 55.8, 55.9, 66.8, 113.5, 113.7, 129.1, 131.8, 147.0, 147.6, 217.3 ppm; HRMS (ESI) m/z obsd 302.1745 ($[\text{M}+\text{H}]^+$) calcd 302.1751 for $\text{C}_{18}\text{H}_{24}\text{O}_3\text{N}$.



*Spectral data of **8a***: R_f = 0.2 (petroleum ether : EtOAc = 2 : 1); IR (film) ν_{max} 2926, 1712, 1682, 1573, 1490, 1442, 1248, 1189, 1038, 930, 809 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.78-2.15 (m, 5H), 2.40-2.69 (m, 3H), 2.67-2.72 (m, 3H), 3.11-3.19 (m, 1H), 5.92 (s, 2H), 6.13 (d, J = 5.4 Hz, 1H), 6.61 (t, J = 10.5 Hz, 2H), 6.72 (d, J = 8.1 Hz, 1H), 7.34 (d, J = 5.7 Hz, 1H) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 21.7, 35.6, 37.8, 40.9, 51.4, 51.6, 71.7, 100.8, 108.1, 109.1, 121.4, 133.8, 134.1, 145.8, 147.4, 167.7, 207.8 ppm; HRMS (ESI) m/z obsd 286.1434 ($[\text{M}+\text{H}]^+$) calcd 286.1438 for $\text{C}_{17}\text{H}_{20}\text{O}_3\text{N}$.

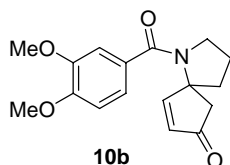


Spectral data of 10a (prepared analogously as **8b**): R_f = 0.4 (petroleum ether : EtOAc = 2 : 1); IR (film) ν_{max} 2957, 1714, 1590, 1513, 1462, 1263, 1234, 1138, 1028, 802 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.84-1.94 (m, 3H), 2.01-2.16 (m, 1H), 2.20 (d, J = 18.3 Hz, 3H), 2.51-2.56 (m, 1H), 2.60 (d, J = 18.3 Hz, 3H), 2.92-3.01 (m, 1H), 3.45 (dd, J = 12.9 Hz, 2H), 3.86 (s, 3H), 3.88 (s, 3H), 6.15 (d, J = 5.4 Hz, 1H), 6.80-6.82 (m, 3H), 7.45 (d, J = 5.4 Hz, 1H) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 21.5, 38.0, 40.8, 51.6, 53.1, 55.8, 71.3, 110.7, 111.3, 120.3, 131.8, 133.8, 147.9, 148.7, 168.0, 207.9 ppm; HRMS (ESI) m/z obsd 288.1591 ($[\text{M}+\text{H}]^+$ calcd 288.1594 for $\text{C}_{17}\text{H}_{22}\text{O}_3\text{N}$).

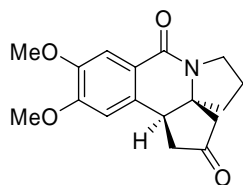


Spectral data of cyclization product (similar conditions as for 8b, 92%)⁴ of 10a: R_f = 0.2 (petroleum ether : EtOAc = 1 : 3); IR (film) ν_{max} 2937, 1740, 1516, 1461, 1256, 1100, 755 cm^{-1} ; ^1H NMR (300MHz, CDCl_3) δ 1.86-2.05 (m, 5H), 2.30 (d, J = 17.4 Hz, 1H), 2.59-2.65 (m, 2H), 2.76 (dd, J = 18.9 Hz, 1H), 3.12-3.18 (m, 1H), 3.35 (d, J = 7.5 Hz, 1H), 3.68 (d, J = 15.9 Hz, 1H), 3.85 (s, 6H), 3.95 (d, J = 15.9 Hz, 1H), 6.56 (s, 1H), 6.61 (s, 1H) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 20.0, 37.5, 38.6, 42.7, 44.7, 48.6, 51.5, 55.9, 55.8, 66.25, 109.0, 110.7, 125.4, 128.1, 147.6, 148.2, 216.4 ppm; HRMS (ESI) m/z obsd 288.1593 ($[\text{M}+\text{H}]^+$ calcd 288.1594 for $\text{C}_{17}\text{H}_{22}\text{O}_3\text{N}$).

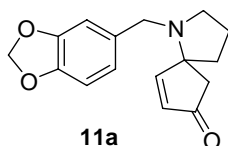
⁴ A single diastereomer of the cyclization product was obtained.



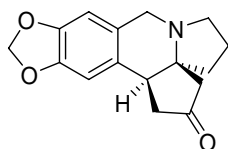
Spectral data of 10b: R_f = 0.3 (petroleum ether : EtOAc = 1 : 1); IR (film) ν_{max} 2968, 1714, 1626, 1582, 1516, 1456, 1420, 1391, 1338, 1263, 1184, 1139, 1024, 751 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.91-2.02 (m, 2H), 2.04-2.19 (m, 1H), 2.33 (d, J = 17.4 Hz, 1H), 3.29 (d, J = 17.4 Hz, 1H), 3.64-3.72 (m, 2H), 3.89 (s, 6H), 6.18 (d, J = 5.7 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 7.10-7.13 (m, H), 7.49 (d, J = 5.7 Hz, 1H) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 24.2, 39.5, 46.6, 51.1, 55.71, 69.4, 109.9, 110.6, 119.9, 129.0, 132.2, 148.5, 150.4, 165.7, 169.0, 206.0 ppm; HRMS (ESI) m/z obsd 302.1391 ($[\text{M}+\text{H}]^+$ calcd 302.1387 for $\text{C}_{17}\text{H}_{20}\text{O}_4\text{N}$).



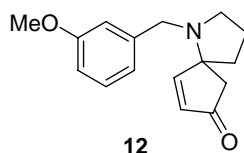
Spectral data of cyclization product (85%) of 10b: mp. 210–212 $^{\circ}\text{C}$; R_f = 0.2 (petroleum ether : EtOAc = 1 : 2); IR (film) ν_{max} 2963, 1745, 1643, 1601, 1514, 1459, 1435, 1385, 1278, 1217, 1103, 778, 731 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.92-2.15 (m, 5H), 2.31 (d, J = 6.3 Hz, 2H), 2.75 (dd, J = 7.5 Hz, 1H), 3.01 (d, J = 18.9 Hz, 1H), 3.61 (d, J = 6.8 Hz, 1H), 3.70-3.79 (m, 2H), 3.90 (s, 6H), 6.62 (s, 1H), 7.61 (s, 1H) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 20.8, 39.3, 43.7, 43.9, 45.3, 47.3, 56.1, 66.4, 108.5, 110.5, 122.2, 130.8, 148.4, 152.3, 161.6, 212.5 ppm; HRMS (EI) m/z obsd 301.1313 ($[\text{M}]^+$ calcd 301.1309 for $\text{C}_{17}\text{H}_{19}\text{O}_4\text{N}$).



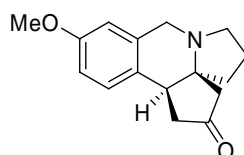
Spectral data of 11a: R_f = 0.5 (petroleum ether : EtOAc = 2 : 1), IR (film) ν_{max} 2911, 1715, 1489, 1443, 1242, 1038, 929, 804 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.80-1.96 (m, 3H), 2.04-2.11 (m, 1H), 2.15 (d, J = 18 Hz, 1H), 2.48-2.52 (m, 1H), 2.59 (d, J = 18 Hz, 1H), 2.89-2.97 (m, 1H), 3.25 (d, J = 13.2 Hz, 1H), 3.42 (d, J = 13.2 Hz, 1H), 5.93 (s, 2H), 6.16 (d, J = 5.7 Hz, 1H), 6.72-6.81 (m, 3H), 7.44 (d, J = 5.7 Hz, 1H) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 21.6, 38.0, 41.0, 51.5, 53.1, 71.4, 100.8, 107.9, 108.6, 121.2, 133.3, 134.0, 146.5, 147.6, 167.9, 207.9 ppm; HRMS (ESI) m/z obsd 272.1277 ($[\text{M}+\text{H}]^+$ calcd 272.1281 for $\text{C}_{16}\text{H}_{18}\text{O}_3\text{N}$).



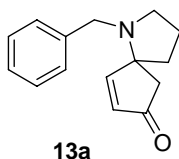
Spectral data of cyclization product (90%) of 11a: R_f = 0.25 (petroleum ether : EtOAc = 2 : 1); IR (film) ν_{max} 2899, 1740, 1484, 1234, 1038, 934, 730 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.84-2.05 (m, 5H), 2.30 (d, J = 17.4 Hz, 1H), 2.53-2.67 (m, 2H), 2.75 (dd, J = 18.6 Hz, 1H), 3.10-3.17 (m, 1H), 3.33 (d, J = 8.4 Hz, 1H), 3.67 (d, J = 15.9 Hz, 1H), 3.90 (d, J = 15.9 Hz, 1H), 5.91 (s, 1H), 5.93 (s, 1H), 6.54 (s, 1H), 6.61 (s, 1H) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 20.2, 37.6, 38.8, 43.3, 44.8, 49.0, 51.5, 66.3, 100.9, 106.3, 108.0, 126.6, 129.5, 146.2, 147.0, 216.2 ppm; HRMS (ESI) m/z obsd 272.1285 ($[\text{M}+\text{H}]^+$ calcd 272.1281 for $\text{C}_{16}\text{H}_{18}\text{O}_3\text{N}$).



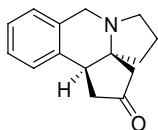
Spectral data of 12: $R_f = 0.4$ (petroleum ether : EtOAc = 3 : 1); IR (film) ν_{max} 2961, 1715, 1660, 1601, 1488, 1458, 1266, 1156, 1047, 785 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.83-1.94 (m, 3H), 2.02-2.09 (m, 1H), 2.20 (d, $J = 18.6$ Hz, 1H), 2.54-2.61 (m, 1H), 2.58 (d, $J = 18.6$ Hz, 1H), 2.92-2.98 (m, 1H), 3.31 (d, $J = 13.2$ Hz, 1H), 3.50 (d, $J = 13.2$ Hz, 1H), 3.80 (s, 3H), 6.16 (d, $J = 5.7$ Hz, 1H), 6.76 -6.96 (m, 3H), 7.19-7.24 (m, 1H), 7.47 (d, $J = 5.7$ Hz, 1H) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 21.6, 37.9, 41.0, 51.6, 53.2, 55.1, 71.4, 112.0, 113.9, 120.5, 129.2, 134.0, 141.1, 159.6, 167.9, 207.9 ppm; HRMS (ESI) m/z obsd 258.1487 ($[\text{M}+\text{H}]^+$ calcd 258.1489 for $\text{C}_{16}\text{H}_{20}\text{O}_2\text{N}$).



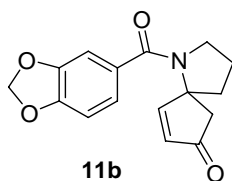
Spectral data of major cyclization product (82%) of 12: $R_f = 0.3$ (petroleum ether : EtOAc = 1 : 1), IR(film) ν_{max} 2958, 1740, 1612, 1501, 1246, 1164, 1038 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.89 -2.05 (m, 5H), 2.30 (d, $J = 17.4$ Hz, 1H), 2.58-2.81 (m, 3H), 3.10-3.16 (m, 1H), 3.35 (d, $J = 8.1$ Hz, 1H), 3.79 (d, $J = 15.9$ Hz, 1H), 3.78 (s, 3H), 3.98 (d, $J = 15.9$ Hz, 1H), 6.61 (d, $J = 1.8$ Hz, 1H), 6.71-6.81 (m, 1H), 7.07 (d, $J = 9$ Hz, 1H) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 20.2, 37.6, 39.0, 42.5, 44.8, 49.2, 51.7, 55.2, 68.5, 111.2, 113.6, 128.4, 129.6, 134.6, 157.9, 216.5 ppm; HRMS (ESI) m/z obsd 258.1486 ($[\text{M}+\text{H}]^+$ calcd 258.1489 $\text{C}_{16}\text{H}_{20}\text{O}_2\text{N}$).



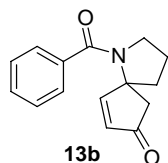
Spectral data of 13a: R_f = 0.4 (petroleum ether : EtOAc = 3 : 1); IR (film) ν_{max} 2965, 2800, 1716, 1664, 1586, 1494, 1453, 1406, 1343, 1262, 1183, 1070, 800, 742, 702 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.81-1.99 (m, 3H), 2.03-2.15 (m, 1H), 2.20 (d, J = 18.6 Hz, 1H), 2.50-2.57 (m, 1H), 2.59 (d, J = 18.6 Hz, 1H), 2.89-2.97 (m, 1H), 3.34 (d, J = 13.5 Hz, 1H), 3.53 (d, J = 13.5 Hz, 1H) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 21.6, 38.0, 41.0, 51.6, 53.3, 71.5, 126.9, 128.3, 134.0, 139.4, 138.0, 208.0 ppm; HRMS (ESI) m/z obsd 228.1378 ($[\text{M}+\text{H}]^+$ calcd 228.1383 for $\text{C}_{15}\text{H}_{18}\text{ON}$).



Spectral data of cyclization product (under refluxing conditions, 75%) of 13a: R_f = 0.2 (petroleum ether : EtOAc = 2 : 1); IR (film) ν_{max} 2922, 1741, 1650, 1455, 1402, 1267, 1167, 752 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.84-2.02 (m, 5H), 2.30 (d, J = 18 Hz, 1H), 2.63-2.69 (m, 2H), 2.80 (dd, J = 5.1 Hz, 1H), 3.13-3.20 (m, 1H), 3.43 (d, J = 5.4 Hz, 1H), 3.76 (d, J = 15.9 Hz, 1H), 4.03 (d, J = 15.9 Hz, 1H) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 20.2, 37.6, 39.2, 43.3, 44.7, 49.1, 51.7, 66.4, 126.3, 126.8, 127.2, 128.6, 133.4, 136.5, 216.3 ppm. HRMS (ESI) m/z obsd 228.1376 ($[\text{M}+\text{H}]^+$ calcd 228.1382 for $\text{C}_{15}\text{H}_{18}\text{ON}$).

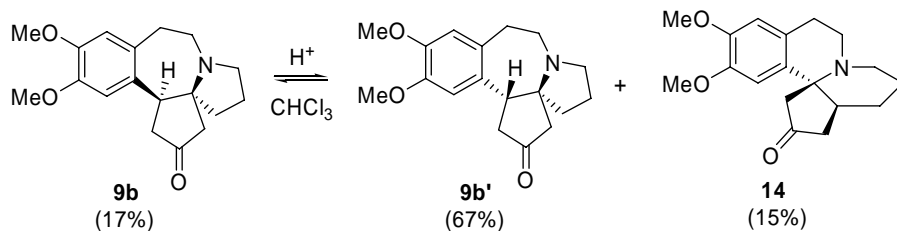


Spectral data of 11b: R_f = 0.3 (petroleum ether : EtOAc = 2 : 1); IR (film) ν_{max} 2963, 1710, 1625, 1599, 1501, 1442, 1394, 1246, 1035, 927, 804, 757 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.90-2.01 (m, 3H), 2.02-2.15 (m, 1H), 2.35 (d, J = 17.4 Hz, 1H), 3.23 (d, J = 17.4 Hz, 1H), 3.62-3.64 (m, 2H), 5.98 (s, 2H), 6.18 (d, J = 4.8 Hz, 1H), 6.79 (d, J = 10.8 Hz, 1H), 6.98-7.03 (m, 2H), 7.47 (d, J = 4.8 Hz, 1H) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 24.1, 39.6, 46.5, 51.06, 69.3, 101.2, 107.6, 107.7, 121.3, 130.4, 132.2, 147.2, 148.8, 165.7, 168.8, 206.0 ppm; HRMS (ESI) m/z obsd 286.1069 ($[\text{M}+\text{H}]^+$ calcd 286.1074 for $\text{C}_{16}\text{H}_{16}\text{O}_4\text{N}$).



Spectral data of 13b: mp. 115–117 °C; R_f = 0.4 (petroleum ether : EtOAc = 2 : 1); IR (film) ν_{max} 2971, 1714, 1628, 1578, 1401. 1341, 1261, 1191, 1071, 792, 727, 703, 659 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.93-2.01 (m, 3H), 2.10-2.19 (m, 1H), 2.38 (d, J = 17.4 Hz, 1H), 3.30 (d, J = 17.4 Hz, 1H), 3.59-3.61 (m, 2H), 6.24 (d, J = 4.5 Hz, 1H), 7.41-7.53 (m, 6H) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 24.2, 39.6, 46.6, 51.1, 69.3, 126.6, 128.2, 129.9, 132.4, 136.8, 165.8, 169.6, 206.1 ppm; HRMS (ESI) m/z obsd 242.1175 ($[\text{M}+\text{H}]^+$ calcd 242.1176 for $\text{C}_{15}\text{H}_{16}\text{O}_2\text{N}$).

*Skeletal isomerization of **9b** and formation of cyclopentanone products **9b'** and **14***



Compound **9b** (300 mg, 1.0 mmol) in CHCl_3 (10 mL) was kept at room temperature for a period of 45 days. After evaporation of the solvent under reduced pressure, the resulting residue was purified by silica gel column chromatography eluting with pure EtOAc to give the known ketone **14** (45 mg, 15%) as a colorless crystals (mp. 171–172 °C)⁵, followed by starting ketone **9b** (50 mg, 17%) as a colorless gum; a more polar fraction was eluted with 5–10 % MeOH in CHCl_3 to give trans ketone **9b'** (200 mg, 67%) as colorless crystals (mp. 223–225 °C). *Spectral data of **9b'***: $R_f = 0.4$ (CHCl_3 : $\text{CH}_3\text{OH} = 10 : 1$); IR (film) ν_{max} 2958, 1744, 1516, 1463, 1298, 1278, 1219, 1116, 730 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.40–1.46 (m, 2H), 1.70–1.74 (m, 1H), 1.84–1.90 (m, 1H), 2.45–2.53 (m, 2H), 2.55–2.91 (m, 5H), 2.96–3.04 (m, 1H), 3.10–3.16 (m, 1H), 3.22–3.28 (m, 1H), 3.88 (s, 6H), 4.12 (dd, $J = 7.6$ Hz, 1H), 6.61 (s, 1H), 6.68 (s, 1H) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 20.7, 26.6, 34.0, 42.4, 44.4, 50.1, 53.8, 54.6, 55.8, 56.1, 70.7, 110.1, 112.7, 128.8, 133.4, 146.9, 147.4, 213.7 ppm; HRMS (ESI) m/z obsd 302.1753 ($[\text{M}+\text{H}]^+$ calcd 302.1751 for $\text{C}_{18}\text{H}_{24}\text{O}_3\text{N}$).

*Spectral data of **14***:⁵ $R_f = 0.4$ (EtOAc); IR (film) ν_{max} 2933, 1741, 1607, 1513, 1462, 1257, 1219 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.40–1.54 (m, 2H), 1.56–1.60 (m, 1H), 1.82–1.88 (m, 1H), 2.26 (d, $J = 17.7$ Hz, 1H), 2.30–2.38 (m, 2H), 2.62–2.66 (m, 2H), 2.86 (d, $J = 17.7$ Hz, 1H), 2.83–2.90 (m, 2H), 3.02–3.11 (m, 2H), 3.32–3.41 (m, 1H), 3.83 (s, 3H), 3.84 (s, 3H), 6.56 (s, 1H), 6.77 (s, 1H) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 19.5, 21.8, 22.0, 38.3, 39.0, 45.2, 47.4, 55.6, 56.0, 56.8, 63.1, 107.6, 111.9, 127.1, 128.4, 147.6, 147.8, 215.9 ppm; HRMS (ESI) m/z obsd $[\text{M}+\text{NH}_4]^+$ 318.1690 ($[\text{M}+\text{H}]^+$ calcd 302.1751 for $\text{C}_{18}\text{H}_{24}\text{O}_3\text{N}$).

⁵ For an alternative preparation and X-ray structure, see: Li, W.-D. Z.; Ma, B.-C. *J. Org. Chem.* **2005**, 70, 3277.