

A Stereospecific Total Synthesis of *dl*-Hexahydroapoerysopine

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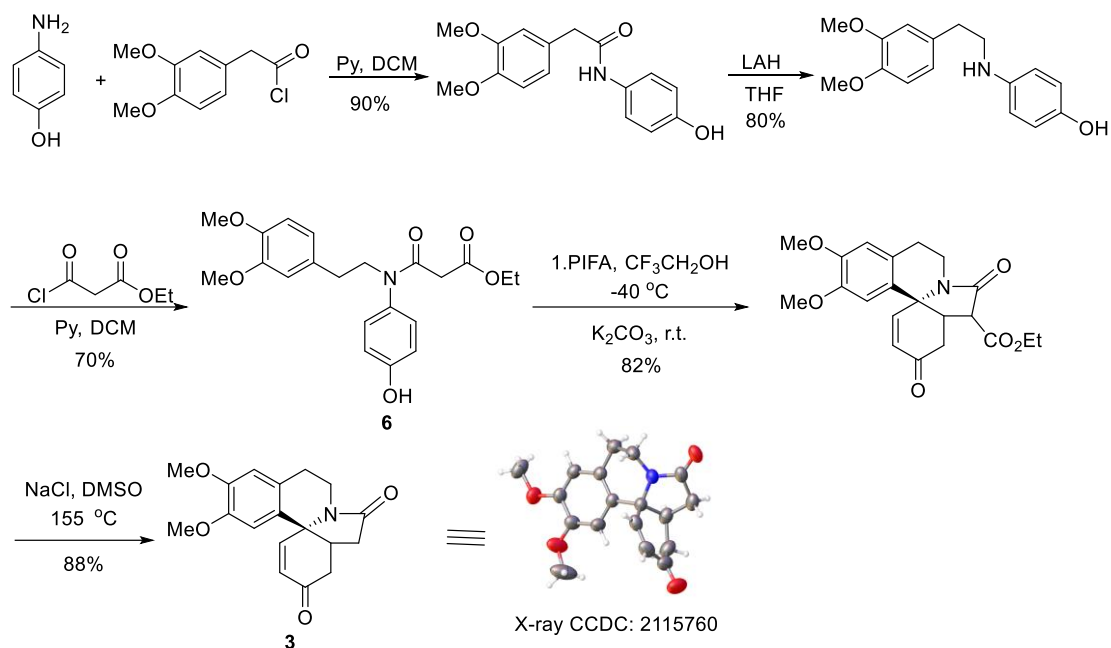
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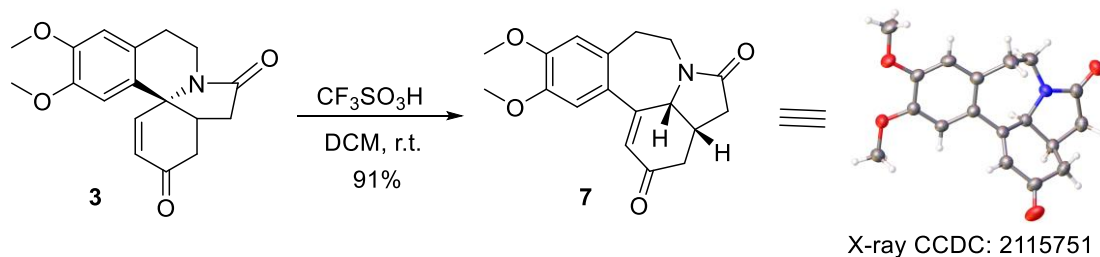
1. General Information

If not specifically mentioned, all commercially available reagents were used as received without further purification. Unless otherwise stated, all solvents employed in the reactions were distilled from appropriate drying agents prior to use. Analytical TLC was performed on silica gel GF254 plates. The TLC plates were visualized by ultraviolet light ($\lambda = 254$ nm). Melting points were measured using a SGWX-4A microscopy melting point meter and were uncorrected. ^1H and ^{13}C NMR spectra were recorded on 400 MHz (100 MHz for ^{13}C NMR) or 600 MHz (150 MHz for ^{13}C NMR) spectrometers using deuterated reagent with TMS or residual solvent as standard unless otherwise noted. Chemical shifts are reported as δ values in ppm relative to tetramethylsilane (TMS) for all recorded NMR spectra. IR spectra were recorded on a Bruker 100 FT-IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). ESI-HRMS was performed on a BioTOFQ mass spectrometer. X-ray crystallography analysis of the single crystal was performed on an Agilent SuperNova-CCD X-ray diffractometer.

2. Synthesis of *dl*-Hexhydroapoerysopine (4)

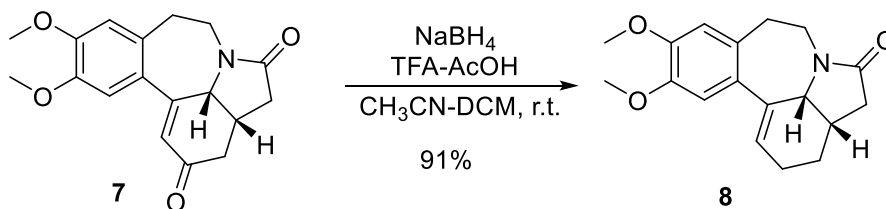


Compound **3** was synthesized according to the procedure reported by Zhang in the literature^[1], chromatographed on silica gel (200–300 mesh, Petroleum ether / EtOAc = 1: 1) to afford the enone **3**. mp. 162~163 °C [Lit. mp.: 161~162 °C^[1]]; ¹H NMR (400 MHz, CDCl₃): δ 6.67 (s, 2H), 6.65 (d, *J* = 10.2 Hz, 1H), 6.17 (d, *J* = 10.2 Hz, 1H), 4.43 (dd, *J* = 12.1, 4.4 Hz, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 3.07 (dd, *J* = 17.9, 5.7 Hz, 1H), 3.03–2.65 (m, 5H), 2.60 (dd, *J* = 16.4, 8.3 Hz, 1H), 2.37 (dd, *J* = 16.3, 12.1 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 195.7, 171.1, 148.8, 148.2, 145.4, 127.3, 127.1, 126.5, 112.6, 108.5, 60.8, 56.2, 55.9, 40.9, 37.6, 37.5, 35.0, 29.0 ppm. The NMR spectroscopic data was identical with the reported data^[1]. X-ray crystallographic data: CCDC number: 2115760.



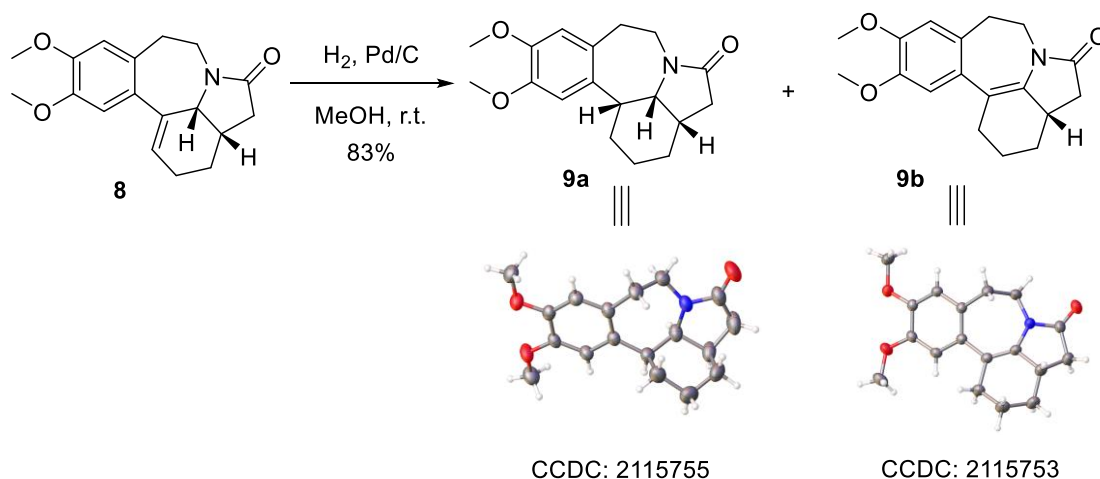
To a stirred solution of **3** (670 mg, 2.14 mmol) in DCM (20 mL) was added trifluoromethanesulfonic acid (3.21 g, 21.40 mmol) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature until the reaction was

complete, as demonstrated by TLC analysis, and was then diluted with water (50 mL). The reaction mixture was neutralized with saturated aqueous NaHCO₃, and the aqueous phase was extracted with EtOAc (30 mL × 3). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to dryness to give a brown residue. The residue was purified by flash column chromatography on silica gel (200–300 mesh, EtOAc / Petroleum ether = 2: 1) to afford unsaturated ketone **7** (610 mg, 91%) as light yellow solids, mp. 201~204 °C, R_f = 0.3 (EtOAc); IR (KBr): ν_{max} 3461, 2939, 2847, 1681, 1602, 1511, 1412, 1267 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 6.86 (s, 1H), 6.68 (s, 1H), 6.37 (s, 1H), 4.43 (d, J = 6.1 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.84 (d, J = 7.7 Hz, 1H), 3.64 (s, 1H), 3.13–3.01 (m, 1H), 2.99 (t, J = 5.3 Hz, 2H), 2.66 (dd, J = 16.5, 7.7 Hz, 1H), 2.62–2.49 (m, 2H), 2.29 (dd, J = 16.7, 5.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 197.2, 172.6, 155.2, 150.2, 147.8, 132.3, 129.1, 127.6, 113.6, 112.1, 58.0, 56.1, 56.0, 41.6, 38.6, 37.4, 35.0, 31.9 ppm; HRMS (ESI): calcd for C₁₈H₁₉NNaO₄[M+Na]⁺ 336.1212; found 336.1206. X-ray crystallographic data: CCDC number: 2115751.



NaBH₄ (380 mg, 9.99 mmol) was added in small portions to a stirred and cooled mixture of glacial acetic acid (5 mL), trifluoroacetic acid (5 mL), and acetonitrile (5 mL). A solution of **7** (626 mg, 1.99 mmol) in dry DCM (50 mL) was added to the mixture. Then the mixture was let to react at room temperature under nitrogen until consumption of all the starting material (6 h, TLC). The mixture was then neutralized with saturated aqueous NaHCO₃ and extracted with EtOAc (30 mL × 3). The combined organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The crude products were purified by flash column chromatography on silica gel (200–300 mesh, EtOAc / Petroleum ether = 1: 1) to give compound **8** (543 mg, 91%) as white solids, mp.: 181~183 °C, R_f = 0.2 (petroleum / EtOAc = 1:2); IR (KBr): ν_{max} 3345, 2990, 2939, 2849, 1678, 1512, 1460, 1275 cm⁻¹; ¹H NMR (600 MHz,

CDCl₃): δ 6.72 (s, 1H), 6.62 (s, 1H), 6.06 (t, $J = 4.0$ Hz, 1H), 4.26 (d, $J = 7.6$ Hz, 1H), 3.93 (d, $J = 6.2$ Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.97 (t, $J = 12.2$ Hz, 1H), 2.81 (dd, $J = 15.1, 10.9$ Hz, 1H), 2.72 (dd, $J = 15.1, 6.4$ Hz, 1H), 2.58–2.50 (m, 2H), 2.33–2.22 (m, 2H), 2.22–2.15 (m, 1H), 1.75–1.69 (m, 1H), 1.65–1.57 (m, 1H); ¹³C NMR (150 MHz, CDCl₃): δ 176.6, 145.0, 140.5, 136.9, 134.0, 133.5, 115.5, 115.3, 61.4, 58.7, 58.6, 44.6, 39.3, 37.9, 33.7, 27.3, 26.1 ppm; HRMS (ESI): calcd for C₁₈H₂₁NNaO₃[M+Na]⁺ 322.1419; found 322.1413.

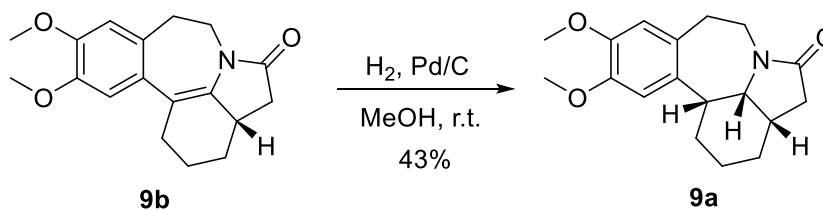


To a solution of unsaturated lactam **8** (325 mg, 1.08 mmol) in MeOH (35 mL) was added Pd/C (10 wt% Pd on carbon, 65 mg) at room temperature. The reaction flask was evacuated and recharged with H₂ three times by a H₂ balloon. After being stirred for 3 d under H₂ atmosphere, the suspension was filtered through Celite and washed with MeOH (50 mL). The resulting filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel (200–300 mesh, EtOAc / Petroleum ether = 1: 1) to afford **9a** (178 mg, 54%) and **9b** (94 mg, 29%) in overall yield 83%.

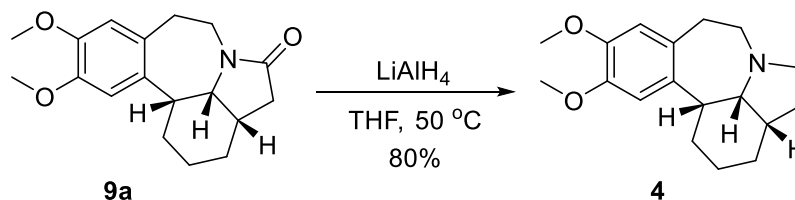
Compound **9a**: white solid, mp.: 160~162 °C [Lit. mp.: 157~158 °C ^[2]], $R_f = 0.2$ (Petroleum / EtOAc = 1:1); IR (KBr): ν_{\max} 3444, 2923, 2852, 2034, 1683, 1514, 1460, 1274 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 6.66 (s, 1H), 6.60 (s, 1H), 4.36 (dd, $J = 13.9, 6.2$ Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.72 (t, $J = 4$, 1H), 3.12–3.00 (m, 1H), 2.84–2.65 (m, 3H), 2.42 (dd, $J = 16.1, 7.0$ Hz, 1H), 2.30 (td, $J = 11.7, 5.7$ Hz, 1H), 2.06 (d, $J = 16.2$ Hz, 1H), 1.84–1.67 (m, 3H), 1.56 (d, $J = 11.8$ Hz, 1H), 1.49–1.37 (m, 1H), 1.36–1.24 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 177.2, 147.2, 147.1, 134.4, 132.7, 114.1, 113.7, 60.5, 56.0, 55.9, 49.2, 42.7, 39.3, 33.8, 33.1, 28.0, 26.9, 25.0;

HRMS (ESI): calcd for $C_{18}H_{22}NO_3[M+H]^+$ 302.1756; found 302.1750. X-ray crystallographic data: CCDC number: 2115755.

Compound **9b**: white solids, mp.: 225~228 °C [Lit. mp.: 230 °C ^[2]], $R_f = 0.3$ (Petroleum / EtOAc = 1:1); IR (KBr): ν_{max} 2924, 2848, 1709, 1642, 1519, 1450, 1348, 1248 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 6.88 (s, 1H), 6.61 (s, 1H), 4.22 (dd, $J = 13.2, 5.6$ Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.44 (dd, $J = 22.4, 10.6$ Hz, 1H), 3.05–2.92 (m, 2H), 2.90–2.76 (m, 2H), 2.57 (dd, $J = 16.2, 8.5$ Hz, 1H), 2.35 (dd, $J = 16.1, 5.8$ Hz, 1H), 2.23–2.02 (m, 3H), 1.74–1.64 (m, 2H), 1.50–1.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 147.5, 147.0, 138.4, 132.6, 130.4, 112.1, 109.2, 109.0, 56.0, 55.9, 48.1, 37.5, 37.3, 33.4, 29.4, 28.3, 22.7; HRMS (ESI): calcd for $C_{18}H_{21}NNaO_3[M+Na]^+$ 322.1419; found 322.1413. X-ray crystallographic data: CCDC number: 2115753.

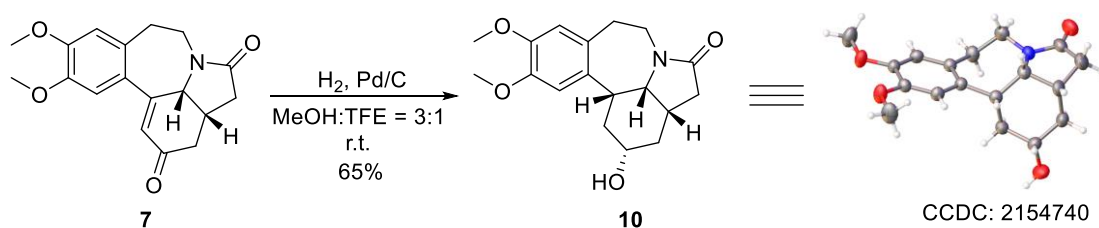


A suspension of unsaturated **9b** (150 mg, 0.50 mmol) and Pd/C (10 wt% Pd on carbon, 30 mg) in MeOH (35 mL) was stirred at r.t. for 3 d under hydrogen atmosphere (balloon). the suspension was filtered through Celite and washed with MeOH (30 mL). The resulting filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel (200–300 mesh, EtOAc / Petroleum ether = 1: 1) to afford **9a** (65 mg, 43%) as white solid.



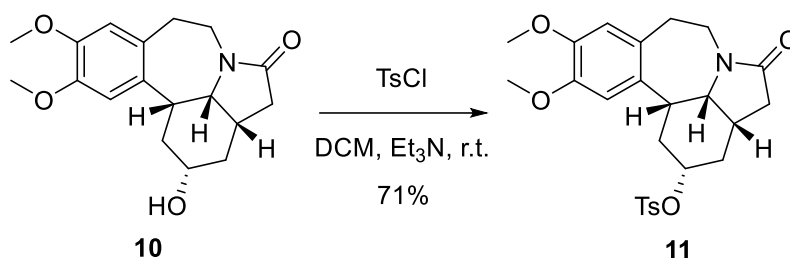
To a solution of **9a** (105 mg, 0.35 mmol) in anhydrous THF (25 mL), $LiAlH_4$ (39.8 mg, 1.05 mmol) was added cautiously in one portion under N_2 . The resulting mixture was gradually warmed up to room temperature then stirred at 50 °C until consumption of all the starting material (5 h, TLC). The reaction mixture was cooled

to 0 °C and was quenched with aqueous solution of saturated K₂CO₃ (5 mL). The mixture was diluted with water (30 mL) and extracted with EtOAc (20 mL × 3). The combined organic layer was then washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (200–300 mesh, EtOAc / Petroleum ether = 2: 1) to afford target product **4** (80 mg, 80%) as brown oil, R_f = 0.2 (petroleum / EtOAc = 1:2); IR (KBr): ν_{max} 3461, 2939, 2847, 1681, 1602, 1511 cm⁻¹; ¹H NMR (600 MHz, Acetone-*d*₆): δ 6.74 (s, 1H), 6.63 (s, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.22–3.16 (m, 1H), 3.11–3.04 (m, 2H), 2.90 (d, *J* = 13.1 Hz, 1H), 2.57 (dd, *J* = 15.0, 6.1 Hz, 1H), 2.29 (s, 1H), 2.25–2.18 (m, 1H), 2.06–2.01 (m, 2H), 1.81–1.74 (m, 2H), 1.64–1.50 (m, 1H), 1.49–1.41 (m, 2H), 1.38–1.22 (m, 3H); ¹³C NMR (150 MHz, Acetone-*d*₆): δ 148.4, 148.2, 137.7, 134.2, 116.2, 115.8, 67.3, 56.4, 56.3, 55.8, 55.7, 50.4, 42.0, 36.7, 30.7, 28.8, 28.0, 27.7; ¹H NMR (400 MHz, CDCl₃): δ 6.65 (s, 1H), 6.56 (s, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.29–3.11 (m, 3H), 2.85 (dt, *J* = 12.9, 3.0 Hz, 1H), 2.59 (dd, *J* = 15.3, 6.2 Hz, 1H), 2.34 (t, *J* = 3.5 Hz, 1H), 2.26 (td, *J* = 10.5, 6.4 Hz, 1H), 2.15–2.03 (m, 3H), 1.87–1.76 (m, 2H), 1.59–1.51 (m, 2H), 1.48–1.33 (m, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 146.8, 146.5, 136.6, 133.0, 114.3, 113.8, 66.6, 56.0, 55.9, 55.3, 54.9, 49.6, 40.8, 36.1, 29.9, 28.0, 27.0, 27.0; HRMS (ESI): calcd for C₁₈H₂₆NO₂[M+H]⁺ 288.1964; found 288.1952.

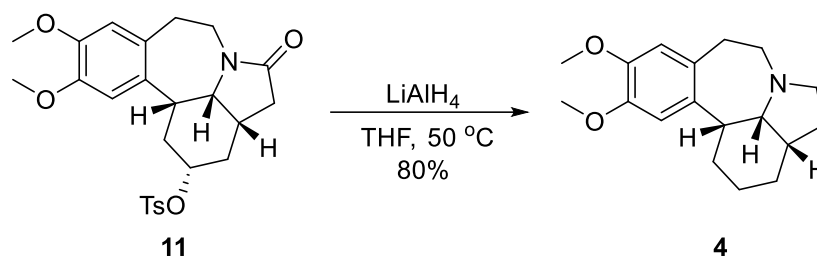


A suspension of unsaturated ketone **7** (626 mg, 1.99 mmol) and Pd /C (10 wt% Pd on carbon, 125 mg) in the mixed solution of MeOH (45 mL) and CF₃CH₂OH (15 mL) was exposed to H₂ atmosphere (balloon). The reaction mixture was then stirred at room temperature under a balloon of hydrogen until consumption of the starting material (3 d, TLC). The resultant mixture was filtered through Celite and washed with MeOH (50 mL). The filtrate was concentrated and the residue was chromatographed on silica gel (200–300 mesh, EtOAc) to afford **10** (410 mg, 65%) as

white solids. mp.: 289–291 °C; $R_f = 0.1$ (EtOAc); IR (KBr): ν_{\max} 3448, 3125, 2930, 1669, 1517, 1402, 1236 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 6.64 (s, 1H), 6.62 (s, 1H), 4.37 (dd, $J = 13.8, 6.1$ Hz, 1H), 3.86 (s, 6H), 3.84–3.74 (m, 1H), 3.64 (t, $J = 3.7$ Hz, 1H), 3.12–3.00 (m, 1H), 2.86 (dt, $J = 12.7, 3.6$ Hz, 1H), 2.80–2.67 (m, 2H), 2.54–2.37 (m, 2H), 2.12 (d, $J = 15.5$ Hz, 1H), 2.07–1.95 (m, 1H), 1.88–1.83 (m, 1H), 1.72 (d, $J = 4.4$ Hz, 1H), 1.66 (s, 1H), 1.32 (q, $J = 12.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 176.8, 147.3, 132.9, 132.7, 113.9, 113.9, 69.1, 59.4, 56.0, 55.9, 47.09, 42.7, 39.0, 37.4, 35.9, 33.6, 32.9; HRMS (ESI): calcd for $\text{C}_{18}\text{H}_{23}\text{NNaO}_4$ $[\text{M}+\text{Na}]^+$ 340.1525; found for: 340.1519. X-ray crystallographic data: CCDC number: 2154740.

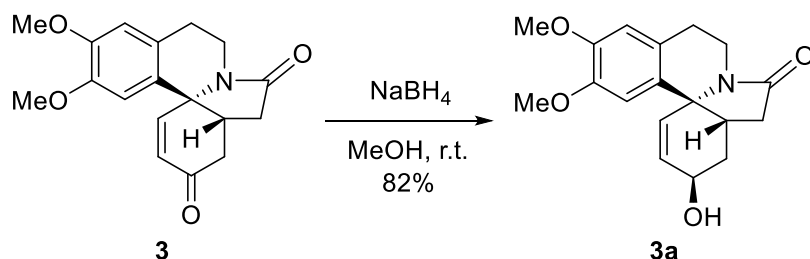


To a solution of **10** (250 mg, 0.79 mmol) and Et_3N (398 mg, 3.94 mmol) in dry DCM (50 mL) at 0 °C under N_2 , TsCl (225 mg, 1.18 mmol) was slowly added. The reaction mixture gradually warmed up to room temperature then stirred at this temperature until complete consumption of the starting material (2 h, TLC). The mixture was diluted with water (30 mL) and extracted with EtOAc (30 mL \times 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (200–300 mesh, EtOAc / Petroleum ether = 2: 1) to afford product **11** (263 mg, 71%) as white solids. mp.: 112~114 °C; $R_f = 0.4$ (EtOAc); IR (KBr): ν_{\max} 3525, 3439, 2936, 2855, 1695, 1518, 1174 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.65 (d, $J = 7.9$ Hz, 2H), 7.20 (d, $J = 7.9$ Hz, 2H), 6.48 (s, 2H), 4.54 (s, 2H), 4.22 (dd, $J = 13.4, 5.8$ Hz, 1H), 3.73 (d, 6H), 3.47 (s, 1H), 2.87 (t, $J = 13.6$ Hz, 1H), 2.73 (d, $J = 13.5$ Hz, 1H), 2.58 (dd, $J = 15.7, 5.4$ Hz, 2H), 2.31 (s, 4H), 2.07–1.88 (m, 2H), 1.89–1.76 (m, 2H), 1.38 (q, $J = 12.1$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 176.3, 147.5, 147.3, 144.8, 134.2, 132.8, 131.6, 129.9, 127.5, 113.9, 113.9, 78.8, 58.9, 56.02, 55.9, 46.7, 42.6, 38.7, 33.9, 33.6, 32.8, 21.7; HRMS (ESI): calcd for $\text{C}_{25}\text{H}_{30}\text{NO}_6\text{S}[\text{M}+\text{H}]^+$ 472.1794; found for 472.1773.

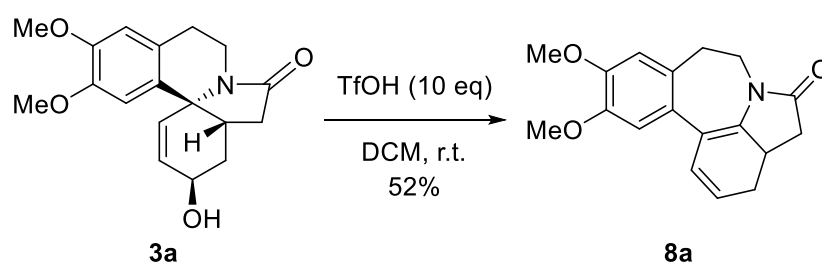


To a solution of **11** (165 mg, 0.35 mmol) in anhydrous THF (20 mL), LiAlH₄ (79 mg, 2.08 mmol) was added cautiously in one portion at 0 °C under N₂. The resulting mixture was gradually warmed up to room temperature then stirred at 50 °C until complete consumption of the starting material (4 h, TLC). The reaction mixture was cooled to 0 °C and was quenched with aqueous solution of saturated K₂CO₃ (10 mL). The mixture was diluted with water (30 mL) and extracted with EtOAc (25 mL × 3). The combined organic layer was then washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (200–300 mesh, EtOAc / Petroleum ether = 2: 1) to afford target product **4** (80 mg, 80%).

3. The rearrangement reaction of allylic alcohol **3a**

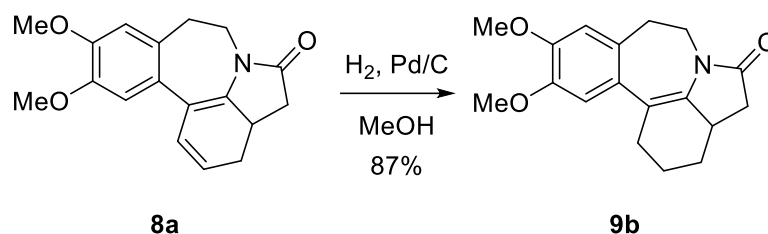


To a solution of cyclohexanone **3** (1.0 g, 3.2 mmol) in MeOH (30 mL) was added NaBH₄ (132 mg, 3.5 mmol) over 10 min. The reaction mixture was stirred for 5 h at r.t. and then quenched with H₂O (30 mL) and extracted with EtOAc (20 mL × 3). The combined organic extracts were washed with H₂O, dried over Na₂SO₄ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (200–300 mesh, EtOAc / Petroleum ether = 2: 1) to afford **3a** as yellowish solids (0.82 g, 82% yield); ¹H NMR (600 MHz, CDCl₃) δ 6.54 (d, *J* = 19.4 Hz, 2H), 5.97 (dd, *J* = 10.1, 3.5 Hz, 1H), 5.79 (d, *J* = 10.1 Hz, 1H), 4.48 (s, 1H), 4.27 (dd, *J* = 13.1, 6.1 Hz, 1H), 3.80 (d, *J* = 16.6 Hz, 6H), 3.04 (td, *J* = 12.6, 4.0 Hz, 1H), 2.93 (ddd, *J* = 17.9, 12.3, 6.1 Hz, 1H), 2.78 (dd, *J* = 16.3, 7.1 Hz, 2H), 2.56 (ddd, *J* = 20.8, 14.3, 5.0 Hz, 2H), 2.49 (dd, *J* = 16.4, 8.7 Hz, 1H), 2.29 (dt, *J* = 14.3, 5.1 Hz, 1H), 1.97 - 1.88 (m, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 173.6, 131.2, 129.5, 129.5, 126.4, 112.0, 109.1, 63.4, 61.4, 56.1, 55.9, 37.7, 37.4, 35.2, 32.9, 28.2.



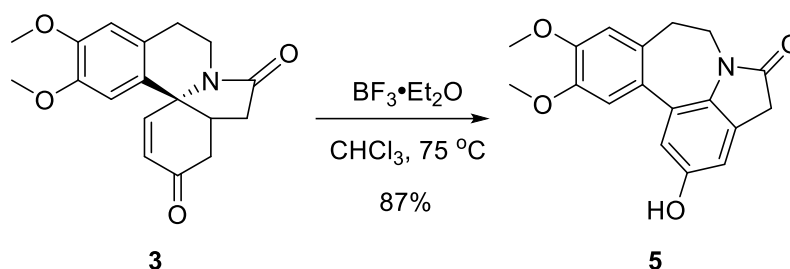
To a stirred solution of **3a** (31 mg, 0.09 mmol) in DCM (20 mL) was added dropwise trifluoromethanesulfonic acid (135 mg, 0.90 mmol) at 0 °C under nitrogen atmosphere, the reaction was stirred overnight at room temperature until complete transformation of the starting material (13 h, TLC). After dilution with water (50 mL), the reaction mixture was neutralized with saturated aqueous NaHCO₃, and the aqueous phase was extracted with EtOAc (20 mL × 3). The combined organic layer

was washed with brine (20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated to dryness to give brown residue. The residue was purified by flash column chromatography on silica gel (200–300 mesh, EtOAc / Petroleum ether = 2: 1) to afford **8a** (14 mg, 52%) as yellowish solids, mp. 146–148 °C, R_f = 0.6 (Petroleum / EtOAc = 1:1); ^1H NMR (400 MHz, CDCl_3) δ 6.80 (s, 1H), 6.63 (s, 1H), 6.41 (dd, J = 9.6, 3.1 Hz, 1H), 6.00 – 5.91 (m, 1H), 4.38 (s, 1H), 3.88 (s, 7H), 3.38 (s, 1H), 2.98 – 2.90 (m, 3H), 2.79 (dd, J = 16.9, 8.9 Hz, 1H), 2.50 (dt, J = 16.3, 7.0 Hz, 1H), 2.18 (dd, J = 16.9, 9.2 Hz, 1H), 2.07 – 1.95 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.6, 147.7, 147.2, 139.1, 132.1, 129.2, 128.4, 122.3, 112.4, 110.3, 107.8, 56.0, 56.0, 46.8, 36.7, 33.8, 33.5, 29.2.

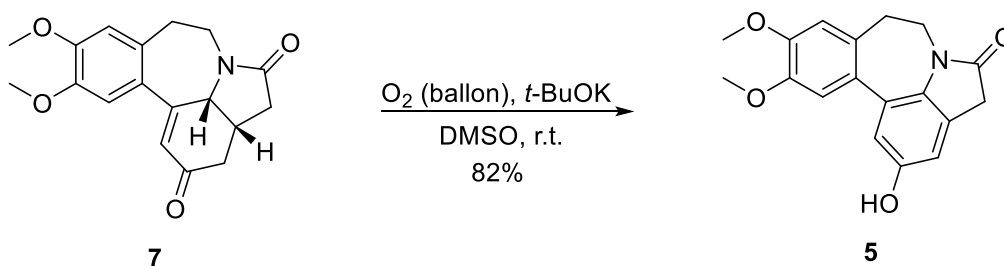


A suspension of cyclic diene **8a** (26 mg, 0.08 mmol) and Pd/C (10 wt% Pd/C, 5.2 mg) in MeOH (35 mL) was stirred at r.t. for 15 h under hydrogen atmosphere (1 atm). The resultant mixture was filtered through Celite and washed with MeOH (30 mL). After evaporation of the filtrate, the residue was chromatographed on silica gel (200–300 mesh, EtOAc / Petroleum ether = 1:1) to afford **9b** (21 mg, 87%) as white solids.

4. Synthesis of apoerysopine 5

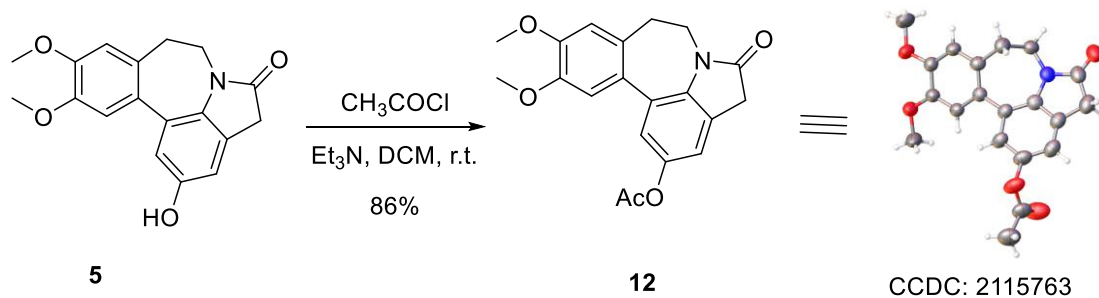


To a solution of enone **3** (314 mg, 1.0 mmol) in dry CHCl_3 (60 mL) was added $\text{BF}_3 \cdot \text{OEt}_2$ (1.42 g, 10.0 mmol), the reaction was stirred at 75 °C until complete consumption of the starting material (20 h, TLC). The reaction was then quenched with H_2O (50 mL) and was diluted in EtOAc (100 mL). The aqueous phase was extracted with EtOAc (30 mL \times 3), the combined organic layer was then washed with brine (30 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (200–300 mesh, EtOAc / Petroleum ether = 2: 1) to afford compound **5** (271 mg, 87%) as yellow solids, mp.: 308~310 °C, R_f = 0.2 (petroleum / EtOAc = 1:1); IR (KBr): ν_{max} 3552, 3475, 3414, 3232, 3008, 2030, 1672, 1638 cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.17 (s, 1H), 7.09 (s, 1H), 6.90 (s, 1H), 6.87 (s, 1H), 6.71 (s, 1H), 3.89–3.69 (m, 8H), 3.50 (s, 2H), 2.89 (s, 2H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 173.9, 153.3, 148.5, 148.2, 133.6, 133.5, 127.8, 123.0, 113.5, 112.7, 112.0, 56.1, 56.0, 45.40, 35.7, 33.5; HRMS (ESI): calcd for $\text{C}_{18}\text{H}_{18}\text{NO}_4[\text{M}+\text{H}]^+$ 312.1236; found 312.1224.



A solution of compound **7** (626 mg, 2.0 mmol) and *t*-BuOK (450 mg, 4.0 mmol) in DMSO (5 mL) was exposed to oxygen atmosphere (balloon). The reaction mixture was then vigorously stirred at room temperature under hydrogen until consumption of the starting material (24 h, TLC). The reaction mixture was then diluted in H_2O (30 mL), and the resultant mixture was extracted with EtOAc (30 mL \times 3). The combined

organic layer was then washed with brine (30 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (200–300 mesh, EtOAc / Petroleum ether = 2: 1) to give compound **5** (510 mg, 82%).



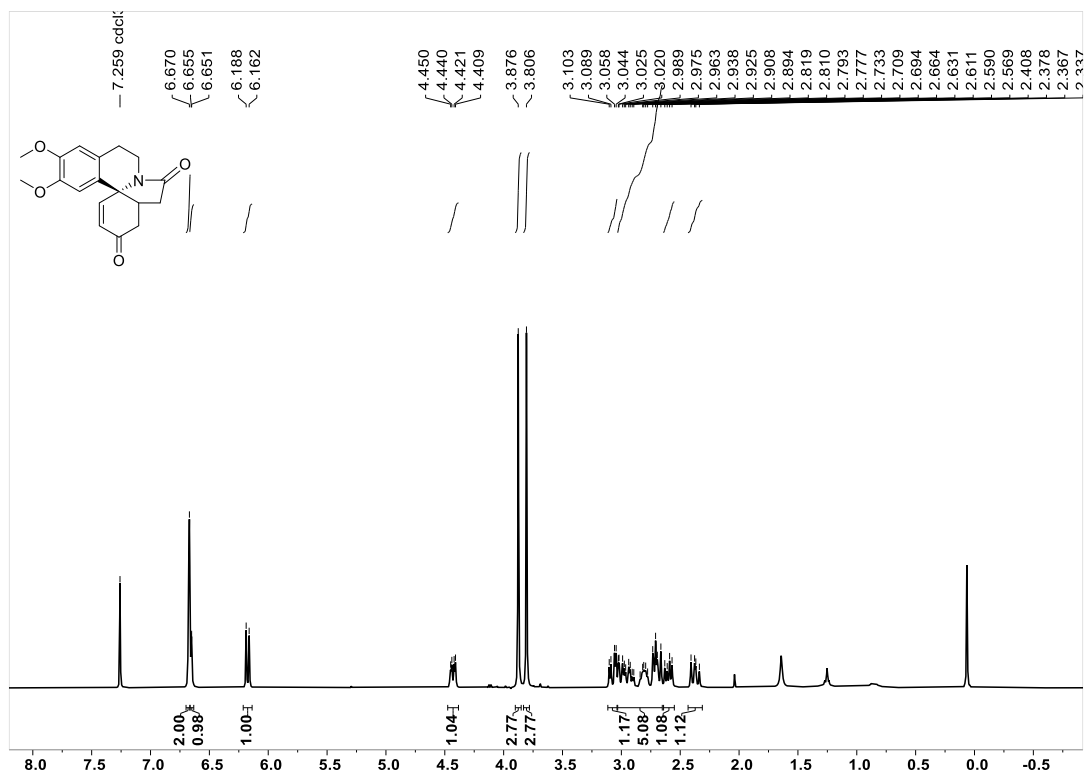
To a stirred solution of **5** (156 mg, 0.50 mmol) and Et_3N (152 mg, 1.50 mmol) in dry DCM (60 mL) was added dropwise acetyl chloride (47.1 mg, 0.60 mmol) at 0 °C under nitrogen, the resulting mixture was gradually warmed up to room temperature until complete consumption of the starting material (3 h, TLC). The reaction was quenched with water (30 mL) and the mixture was extracted with EtOAc (30 mL \times 3). The organic layer was washed with brine (30 mL), dried over anhydrous Na_2SO_4 , filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (200–300 mesh, EtOAc / Petroleum ether = 1: 1) to give compound **12** (152 mg, 86%) as light yellowish solids, mp.: 178~180 °C, R_f = 0.5 (petroleum / EtOAc = 1:2); IR (KBr): ν_{max} 3437, 2949, 2912, 2847, 1745, 1707, 1519, 1465 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.15 (s, 1H), 7.04 (s, 1H), 6.95 (s, 1H), 6.68 (s, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.55 (s, 2H), 2.96 (s, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 174.3, 167.0, 148.8, 148.2, 146.0, 138.8, 133.3, 127.0, 126.9, 123.6, 120.8, 116.8, 112.4, 112.4, 56.2, 56.0, 45.4, 35.7, 33.8, 21.1; HRMS (ESI): calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_5[\text{M}+\text{H}]^+$ 354.1341; found 354.1334. X-ray crystallographic data: CCDC number: 2115763.

5. References

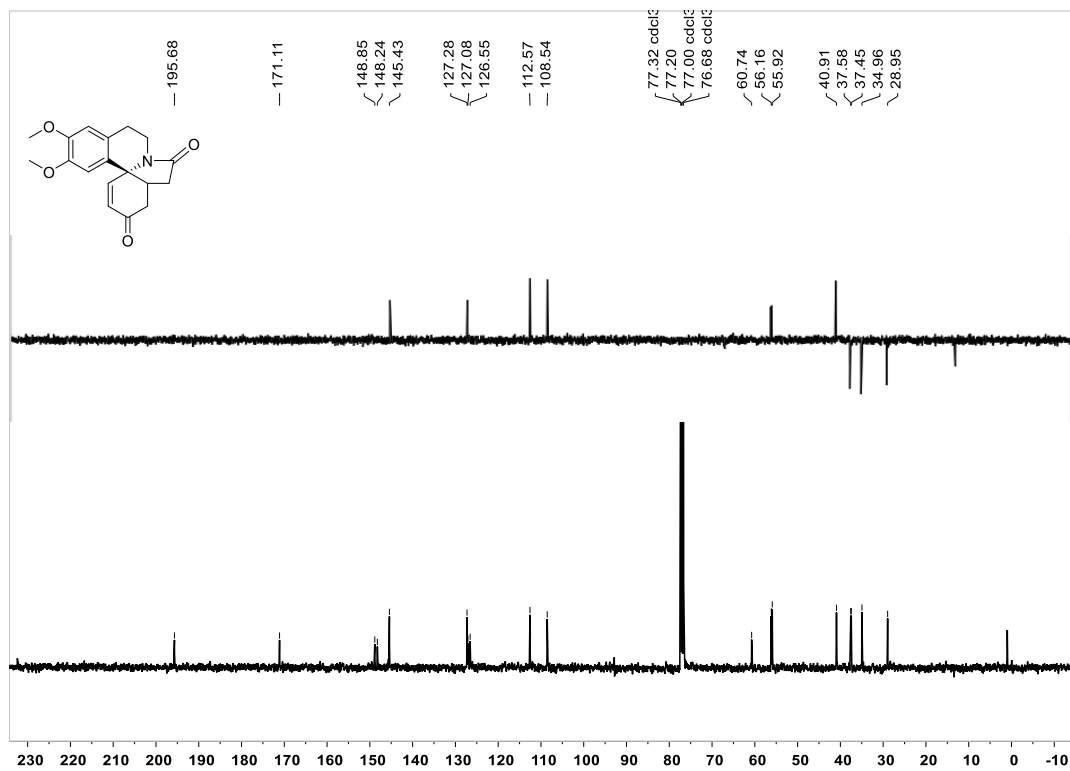
- [1]. Liang, J. X.; Chen, J. B.; Liu, J. P.; Li, L.; Zhang, H. B. *Chem. Commun.* **2010**, *46*, 3666–3668.
- [2]. Mondon, A.; Menz, H.-U. *Tetrahedron*, **1964**, *20*, 1729–1736.

6. Copies of NMR Spectra

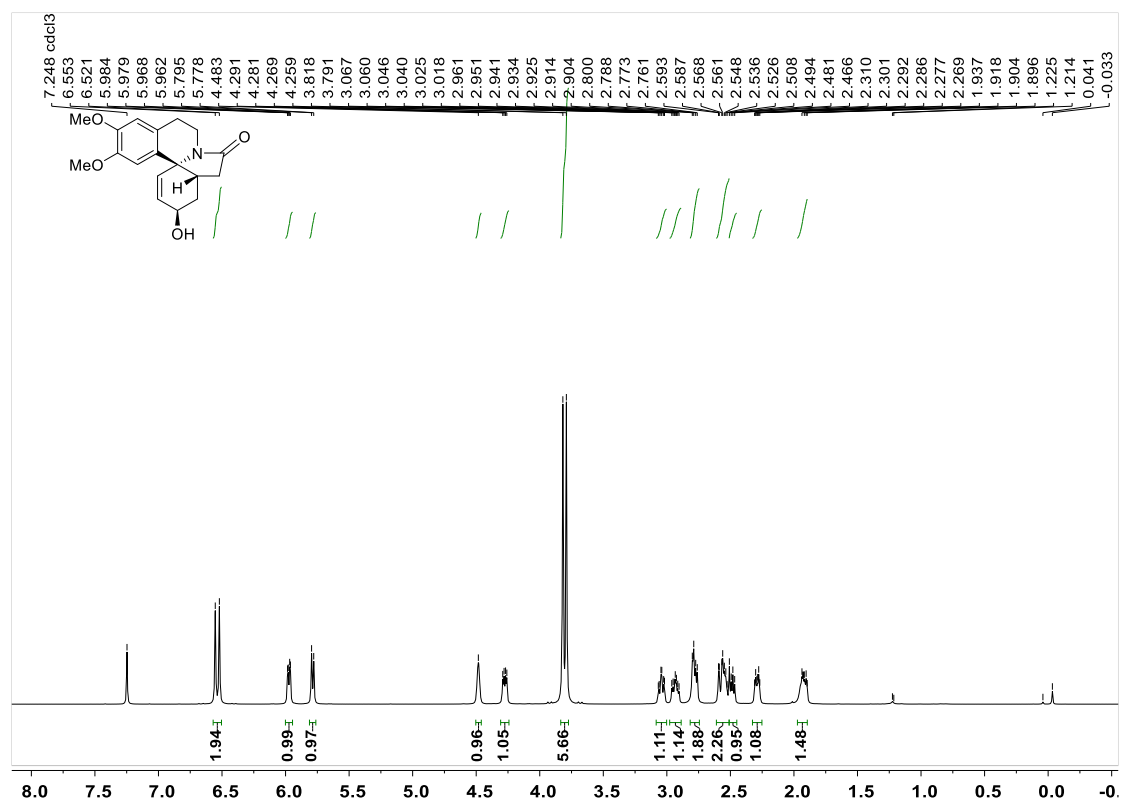
^1H NMR of **3** (400 MHz, CDCl_3)



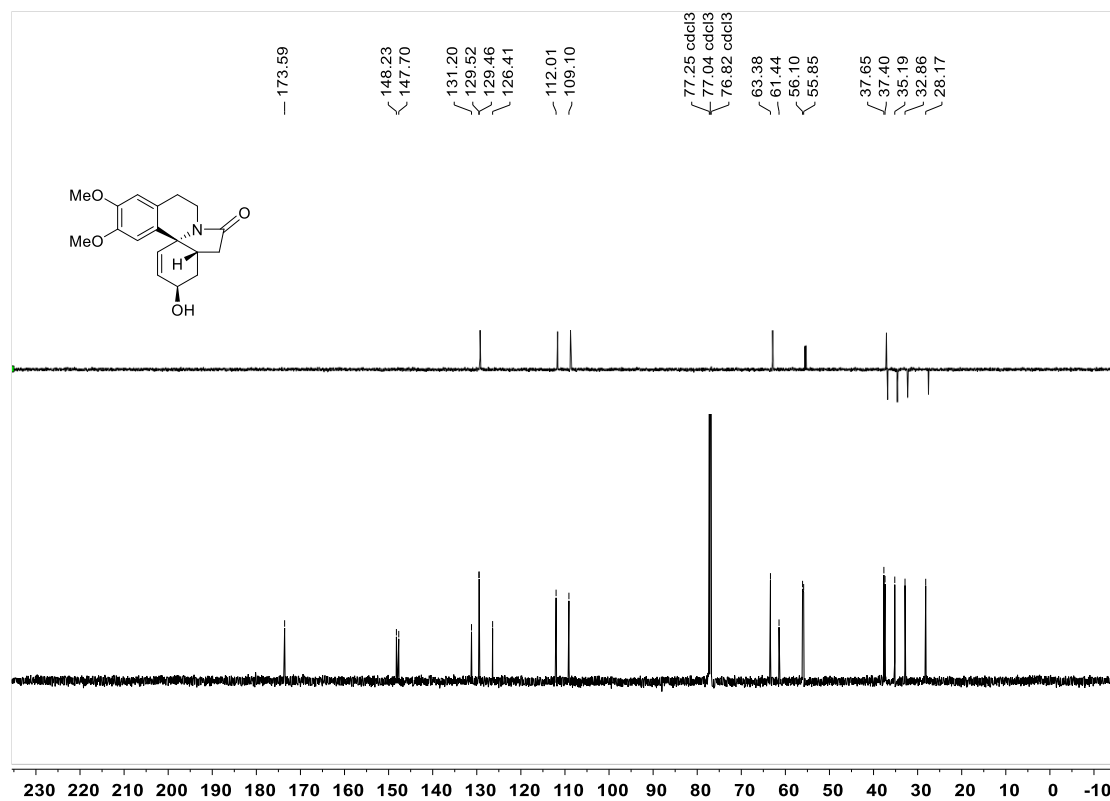
^{13}C and DEPT NMR of **3** (100 MHz, CDCl_3)



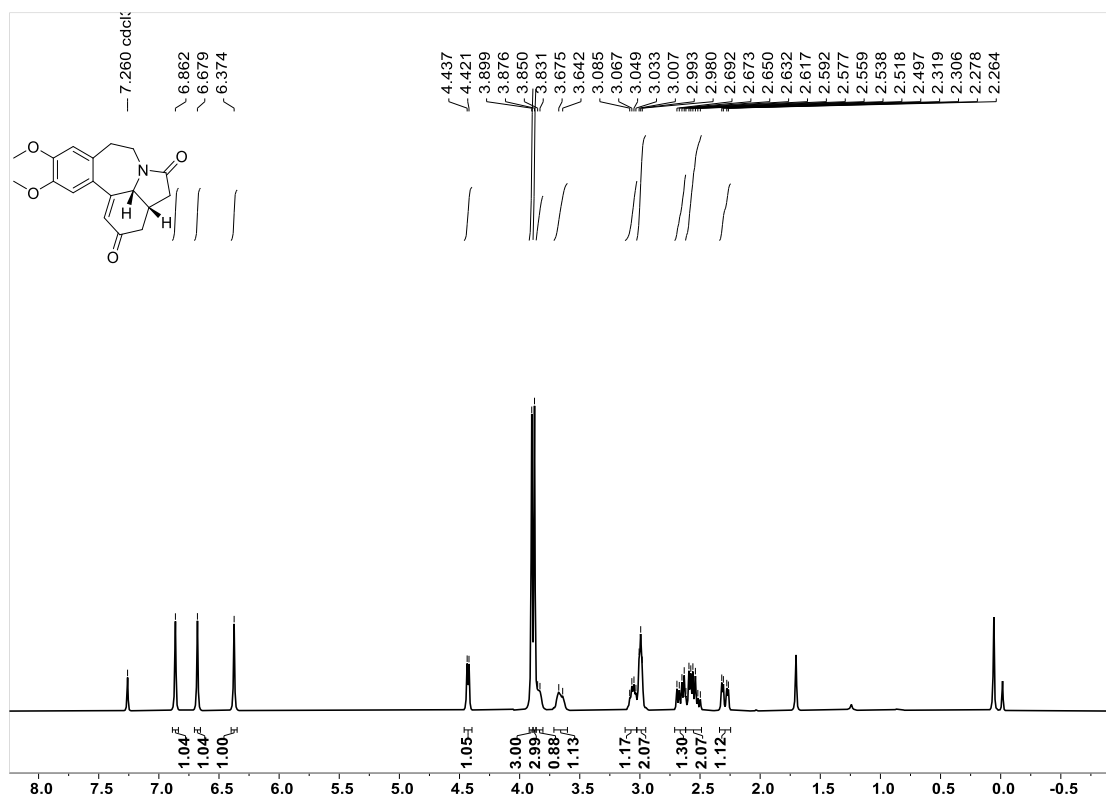
^1H NMR of **3a** (600 MHz, CDCl_3)



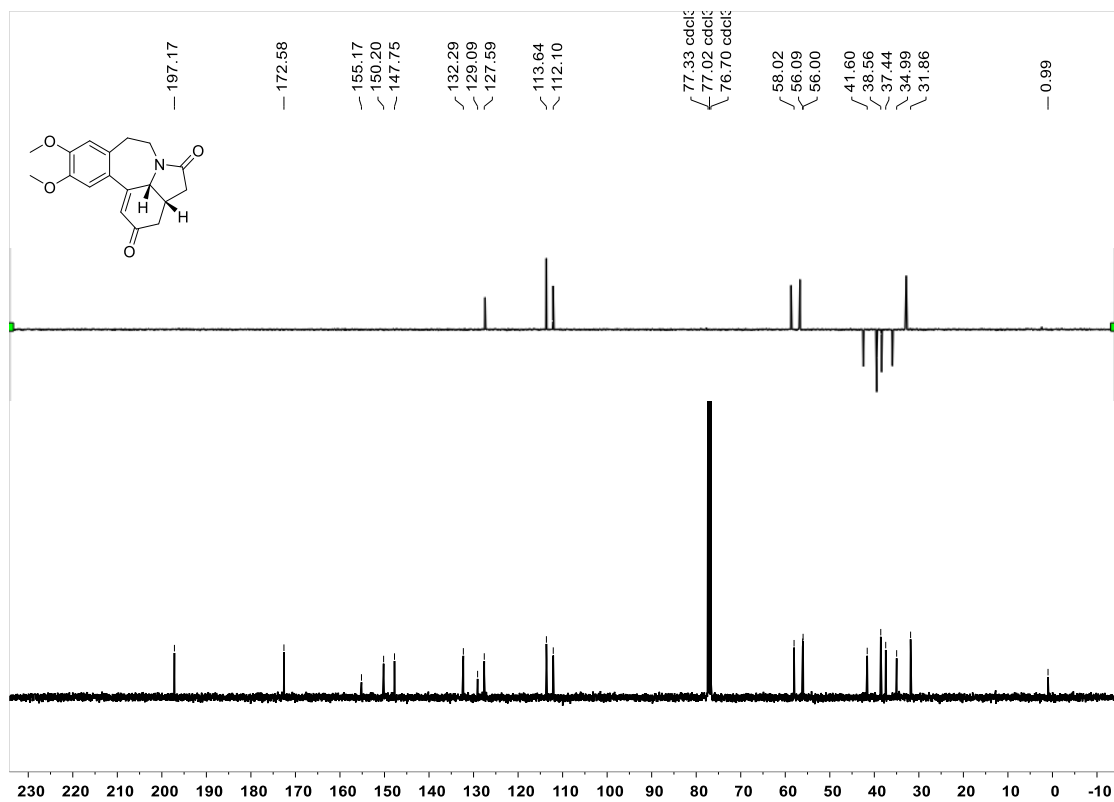
^{13}C and DEPT NMR of **3a** (150 MHz, CDCl_3)



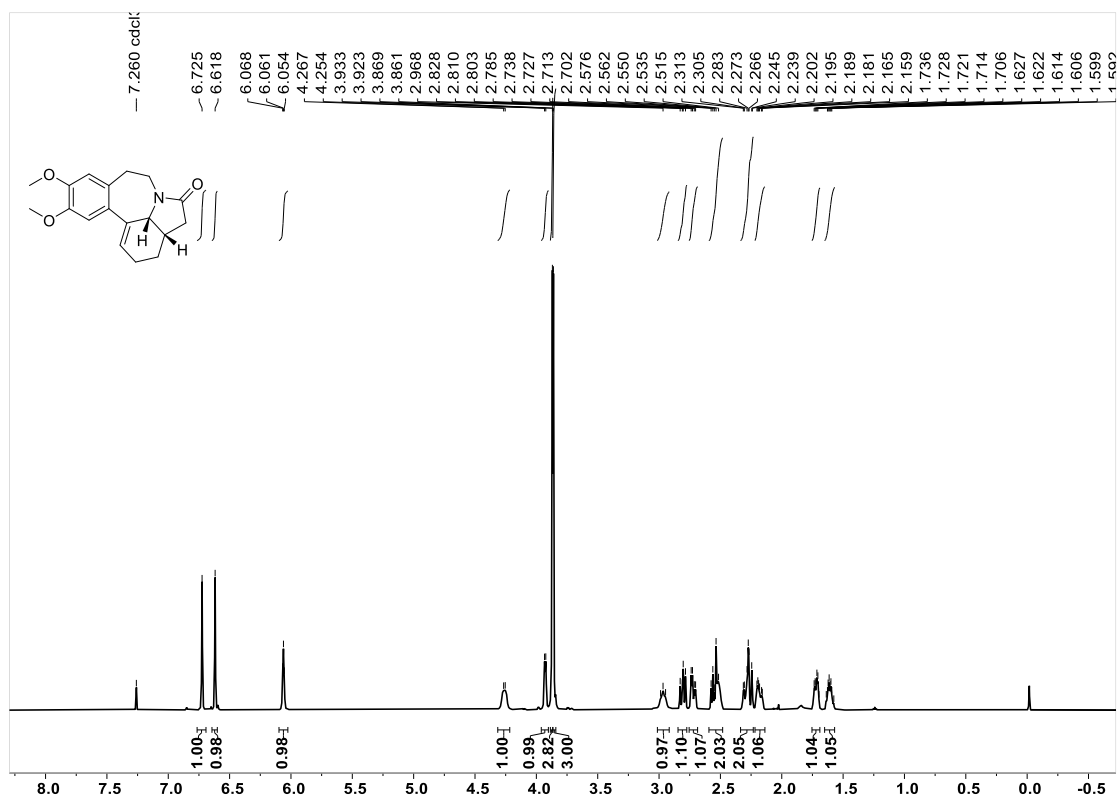
¹H NMR of **7** (400 MHz, CDCl₃)



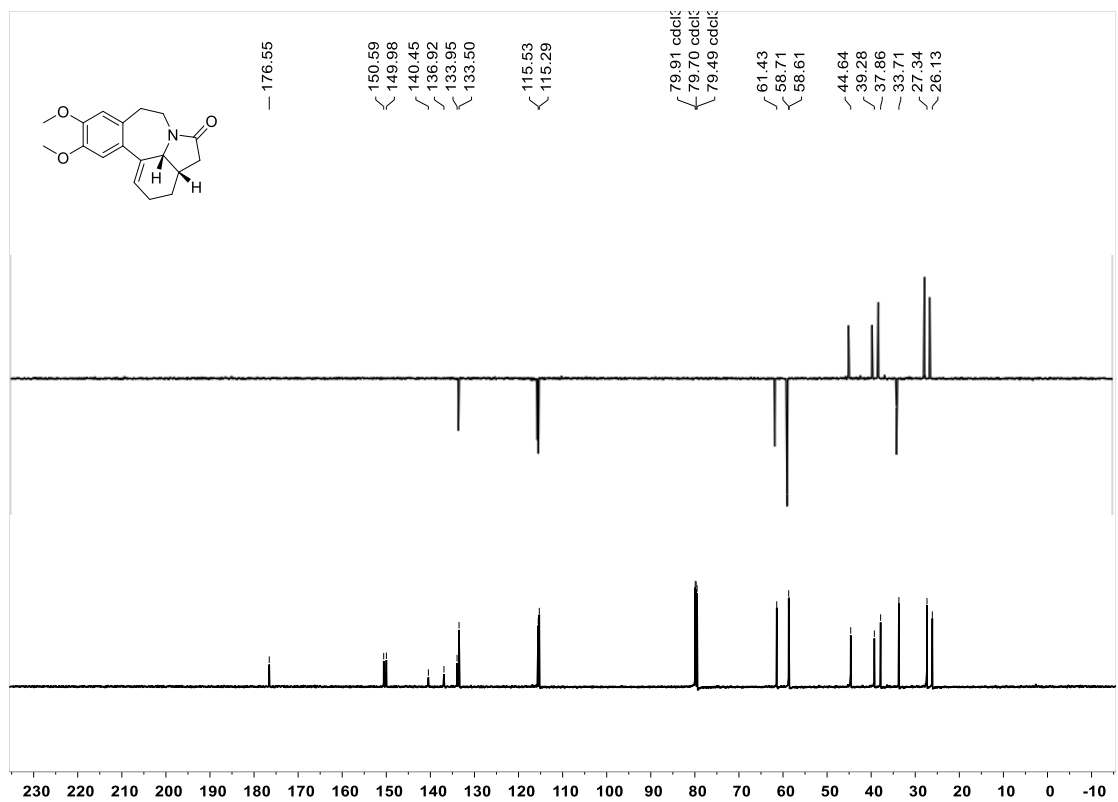
¹³C and DEPT NMR of **7** (100 MHz, CDCl₃)



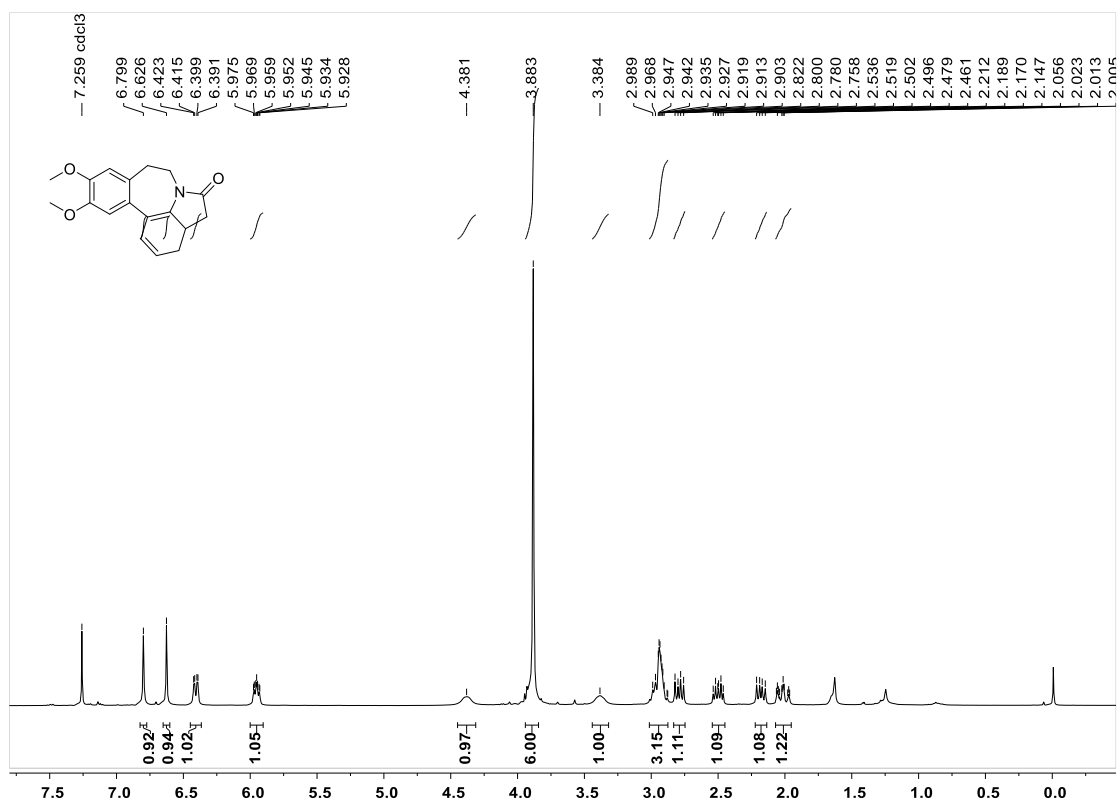
¹H NMR of **8** (600 MHz, CDCl₃)



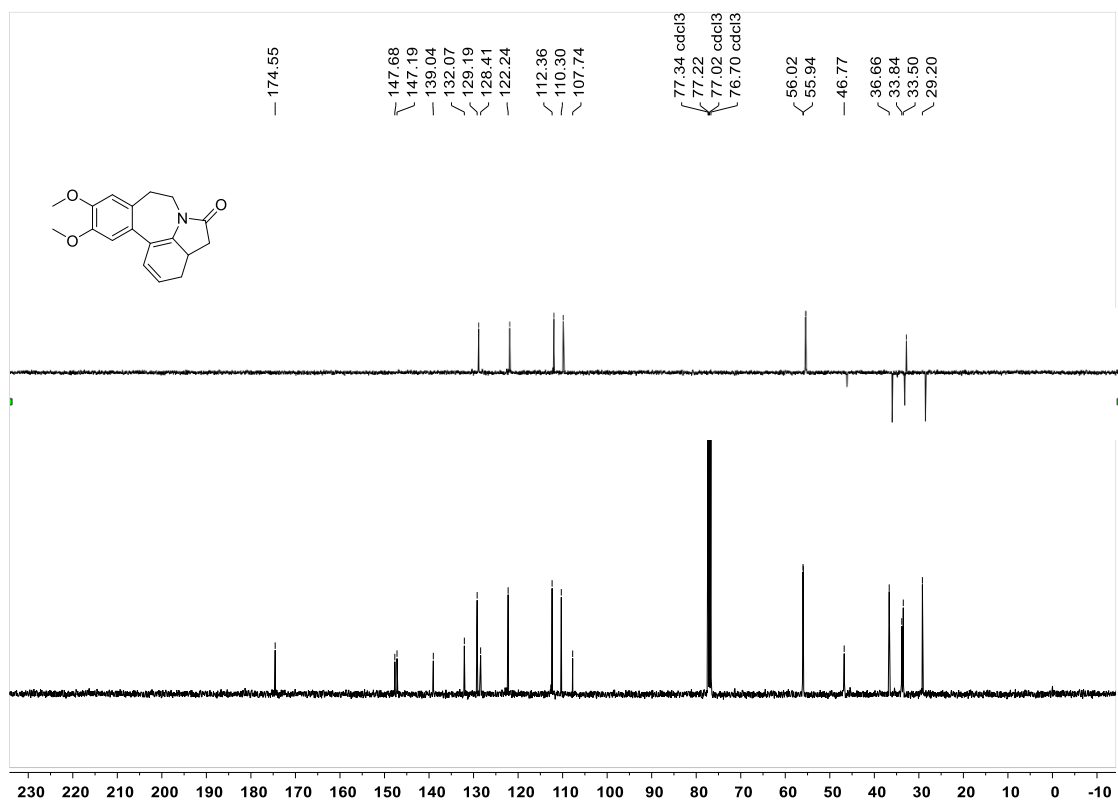
¹³C and DEPT NMR of **8** (150 MHz, CDCl₃)



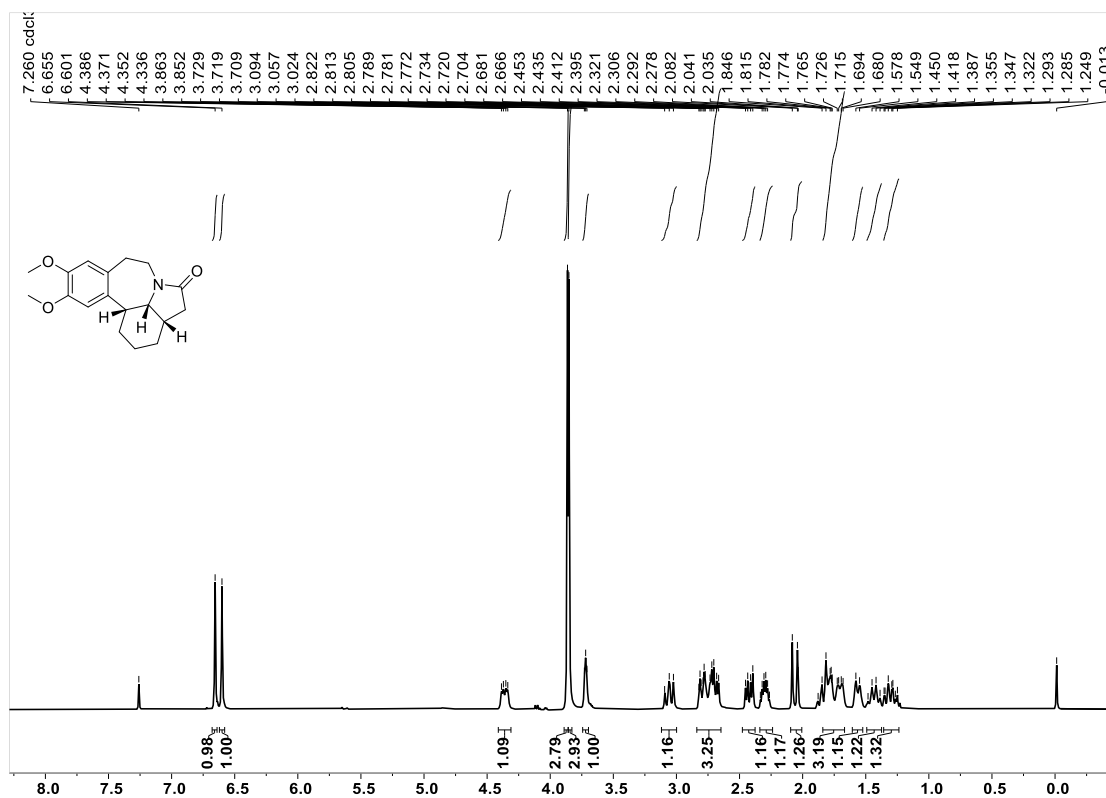
¹H NMR of **8a** (400 MHz, CDCl₃)



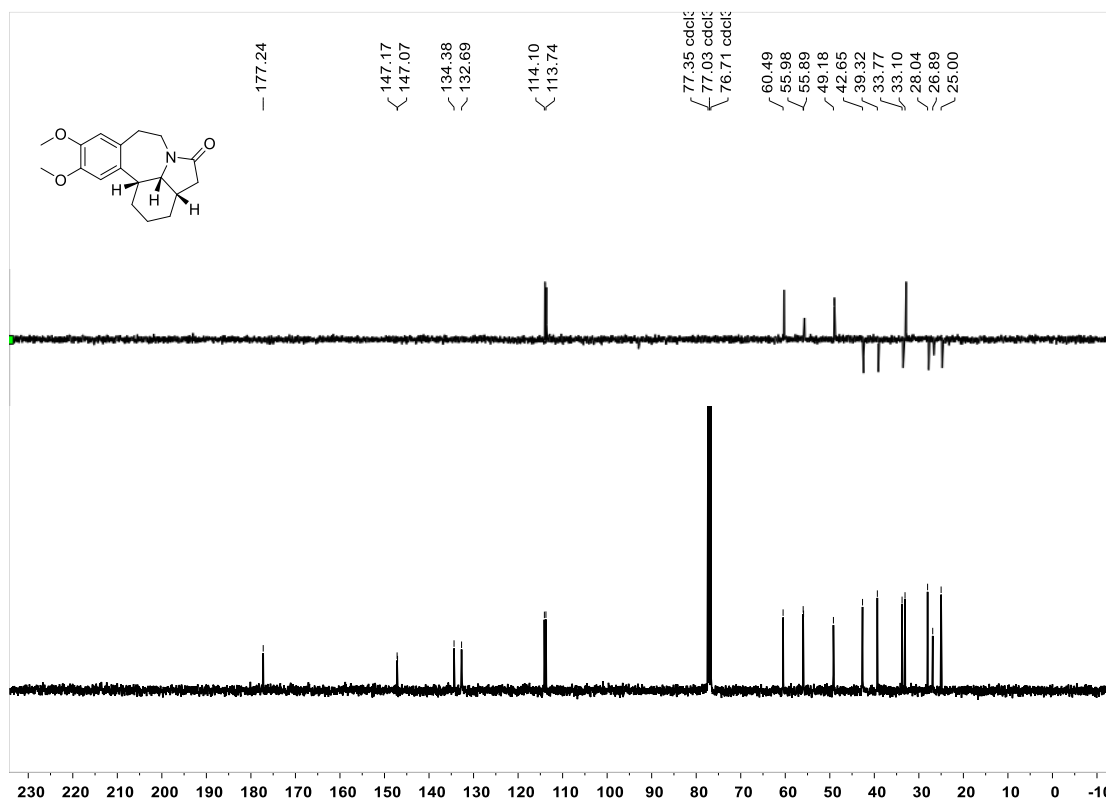
¹³C and DEPT NMR of **8a** (400 MHz, CDCl₃)



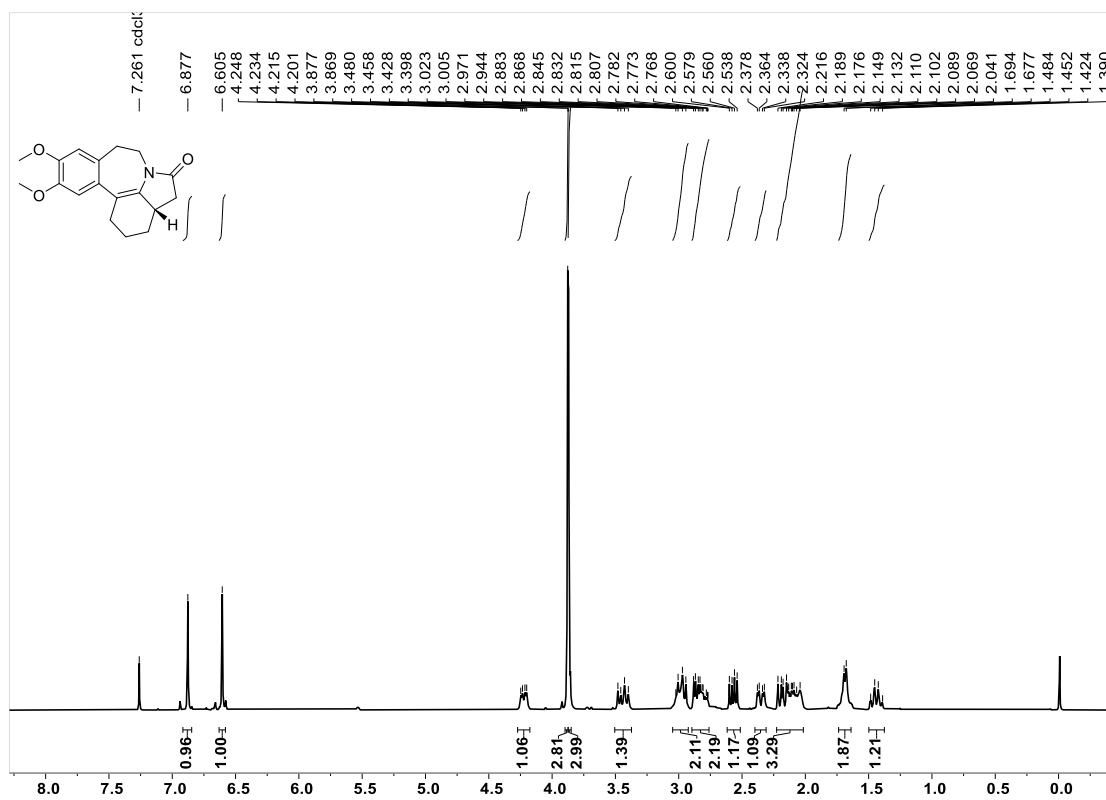
¹H NMR of **9a** (400 MHz, CDCl₃)



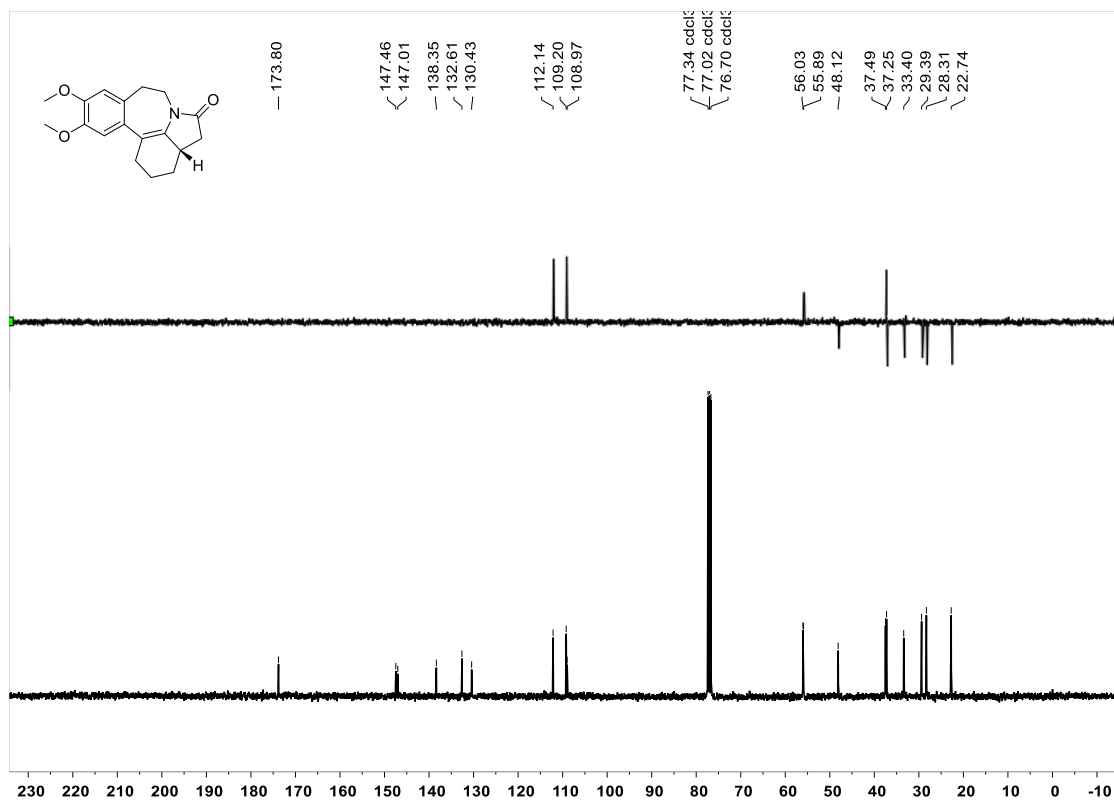
¹³C and DEPT NMR of **9a** (100 MHz, CDCl₃)



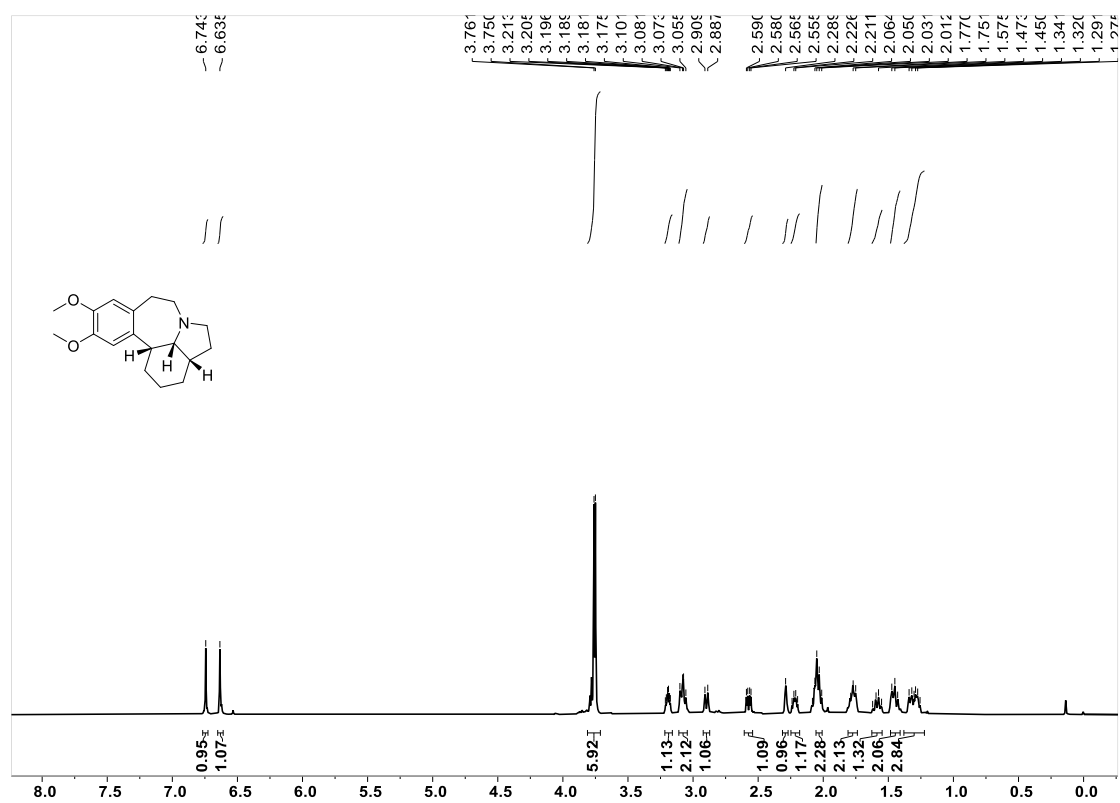
¹H NMR of **9b** (400 MHz, CDCl₃)



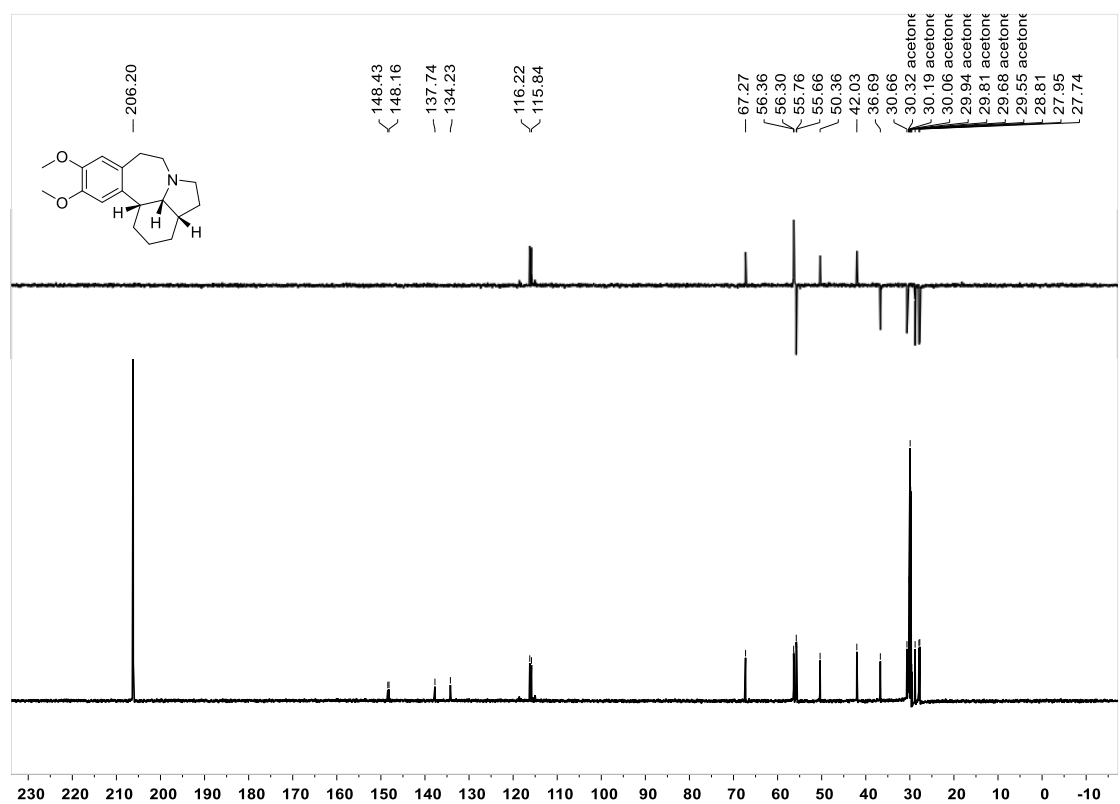
¹³C and DEPT NMR of **9b** (100 MHz, CDCl₃)



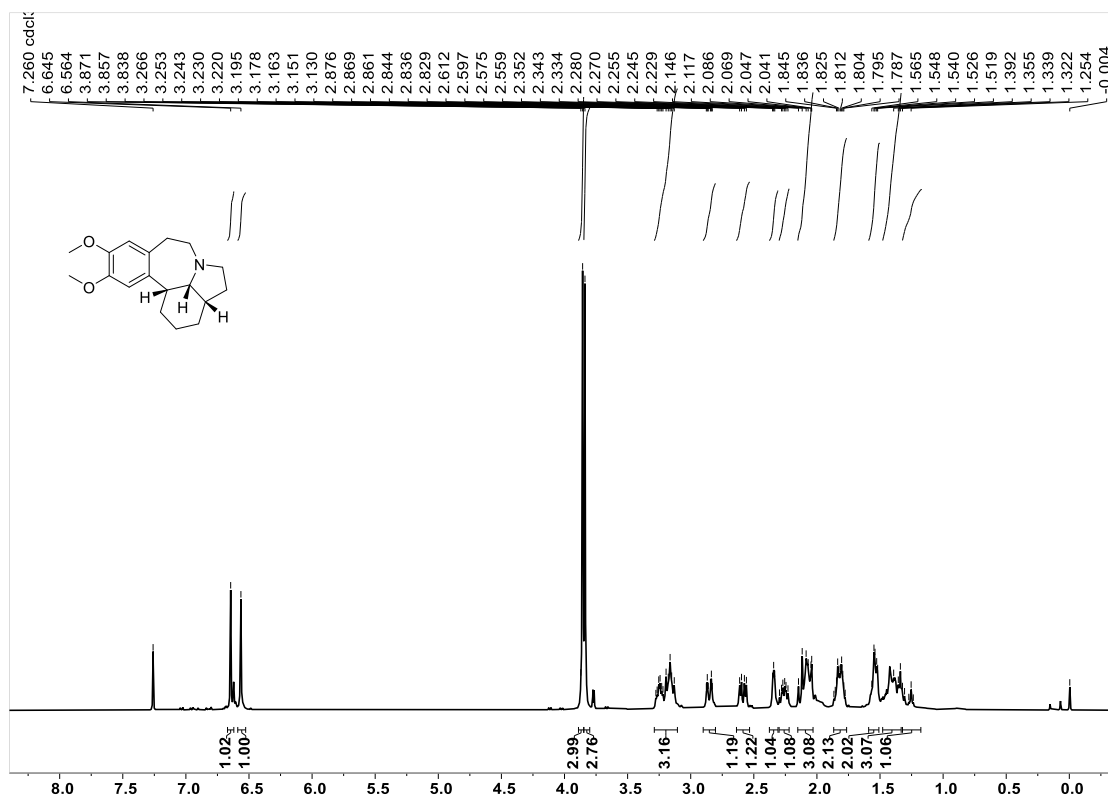
¹H NMR of **4** (600 MHz, Acetone-*d*₆)



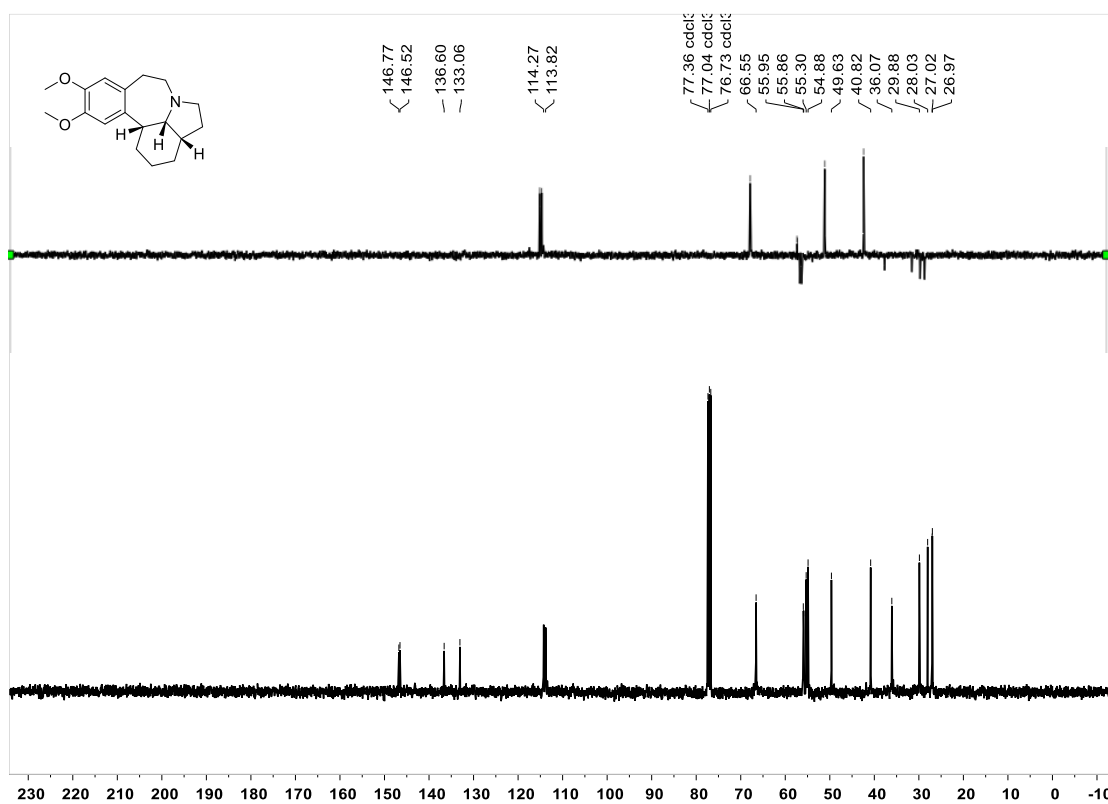
¹³C and DEPT NMR of **4** (150 MHz, Acetone-*d*₆)



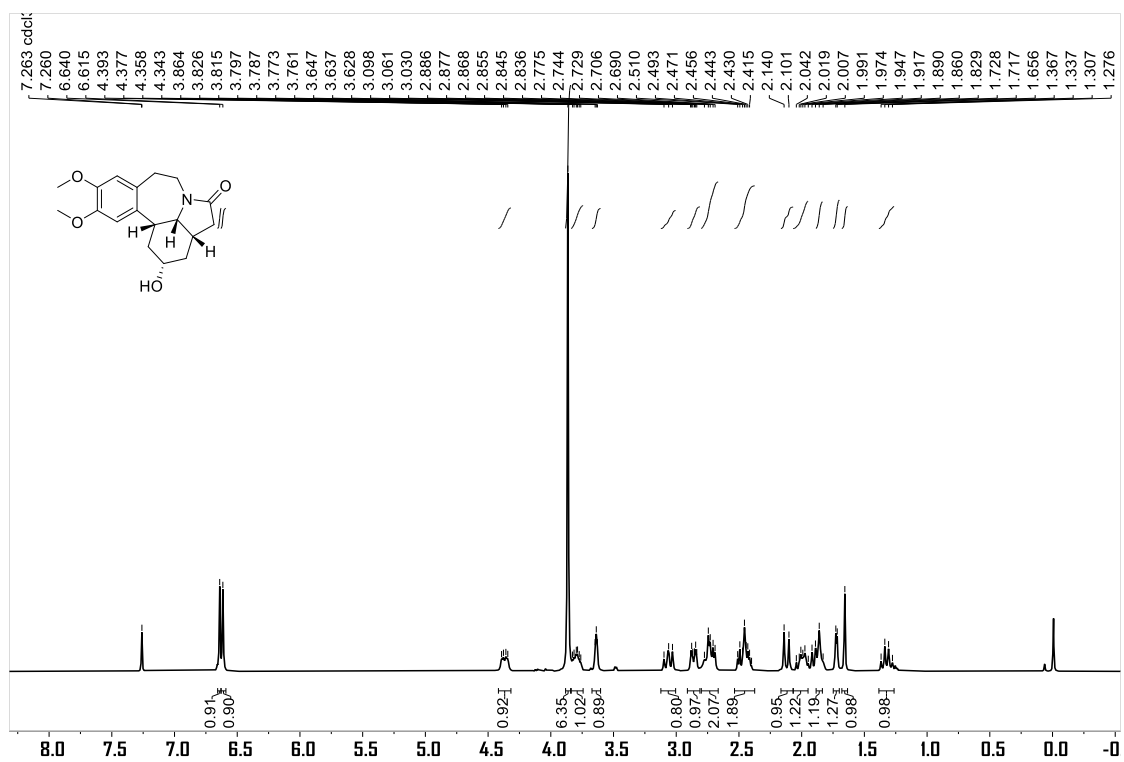
¹H NMR of **4** (400 MHz, CDCl₃)



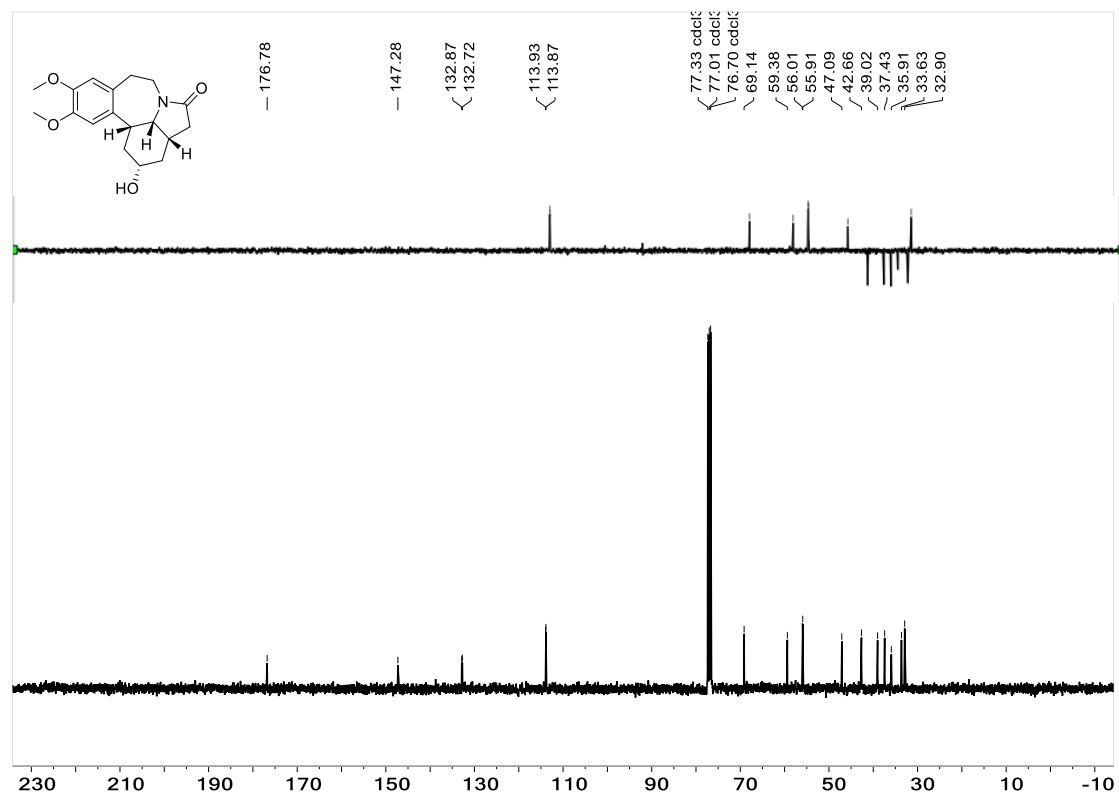
¹³C and DEPT NMR of **4** (100 MHz, CDCl₃)



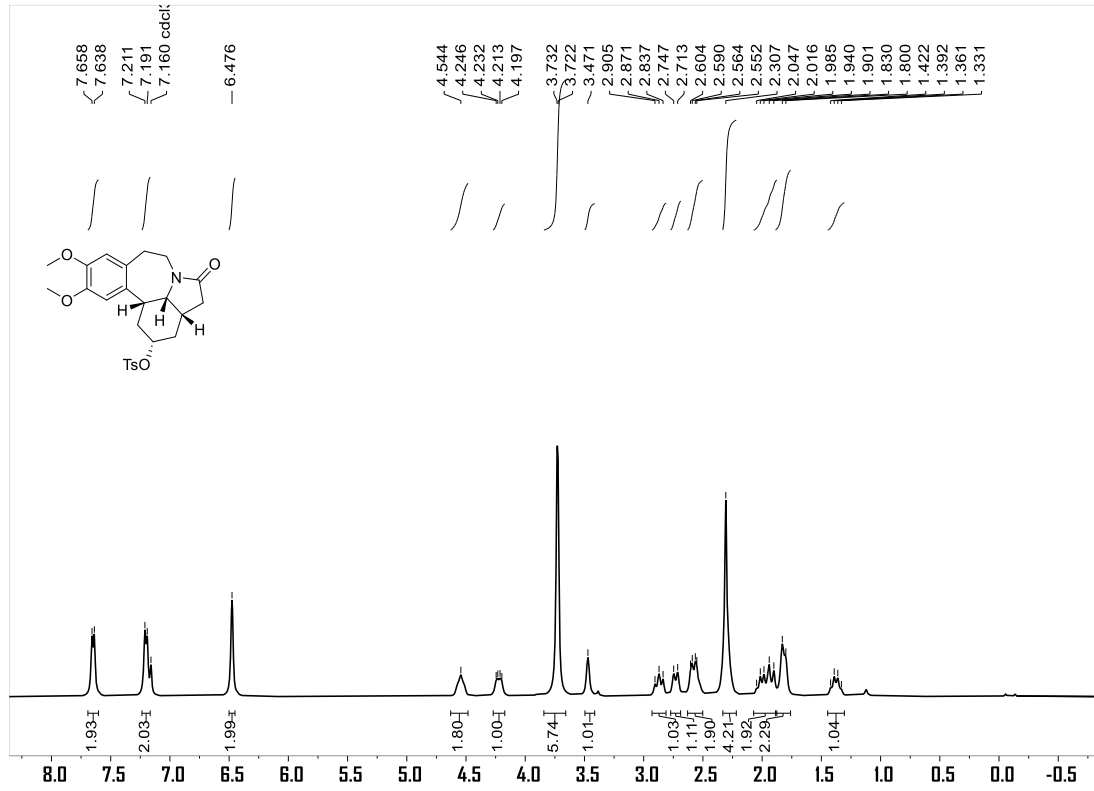
¹H NMR of **10** (400 MHz, CDCl₃)



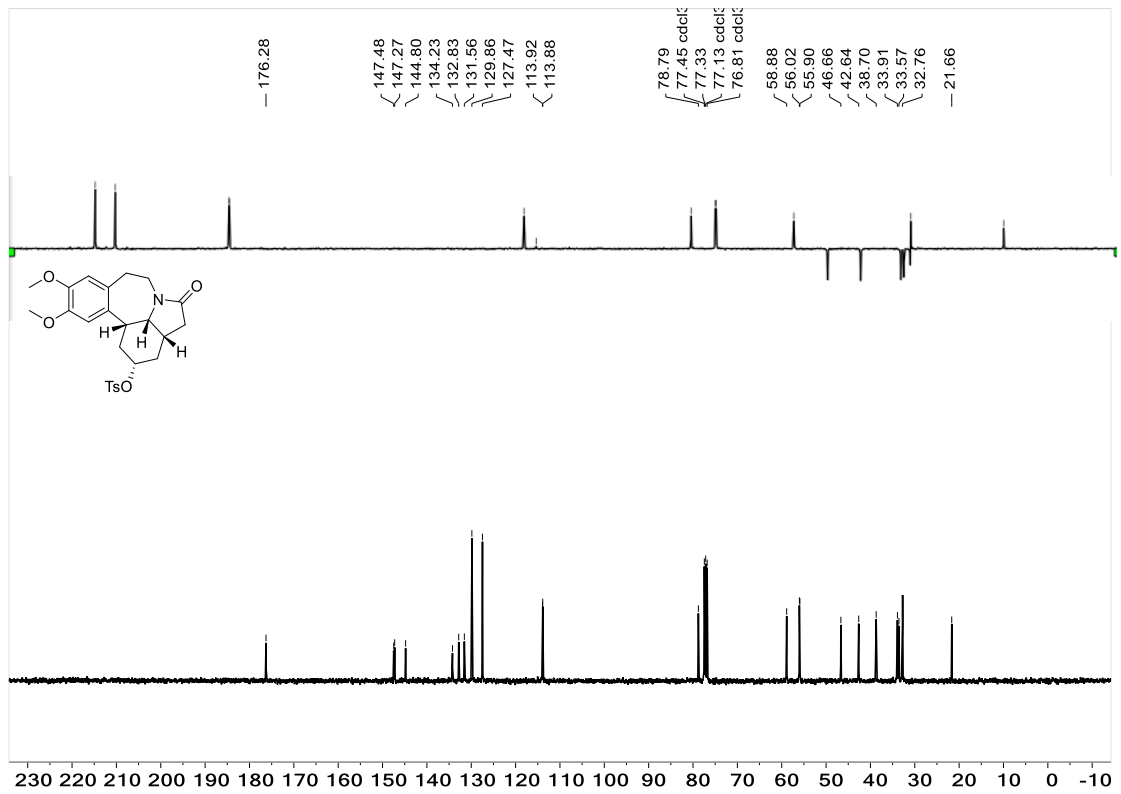
¹³C and DEPT NMR of **10** (100 MHz, CDCl₃)



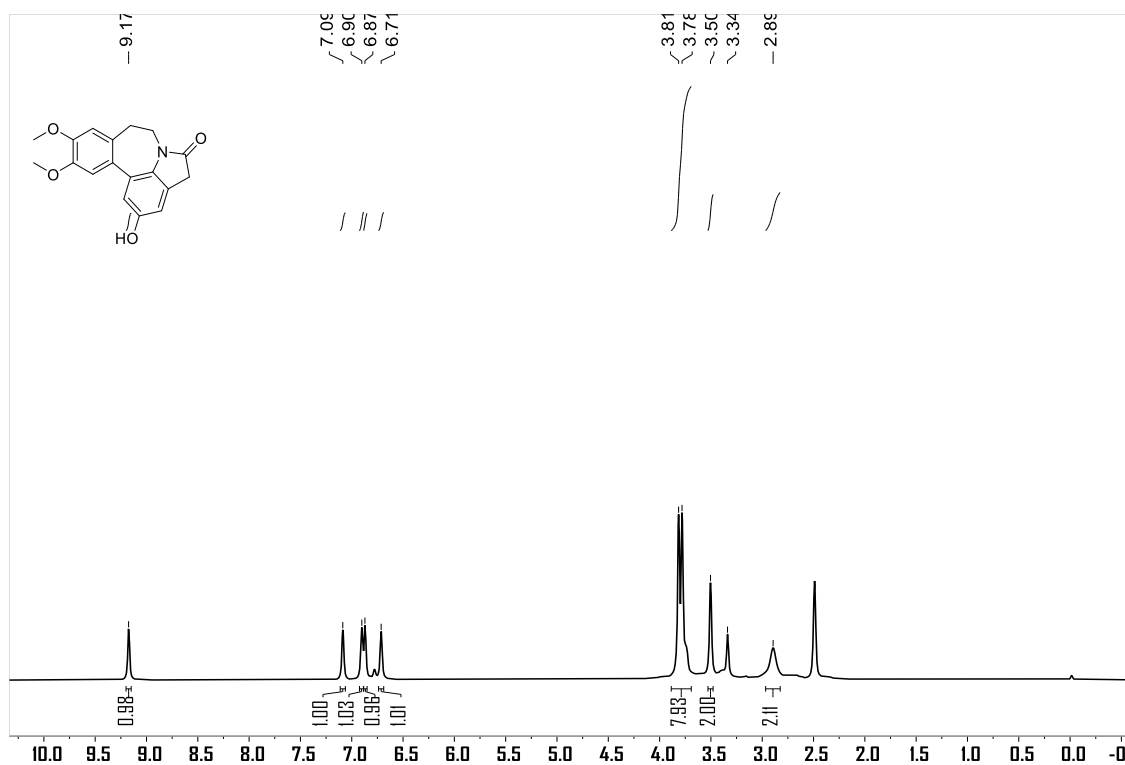
¹H NMR of **11** (400 MHz, CDCl₃)



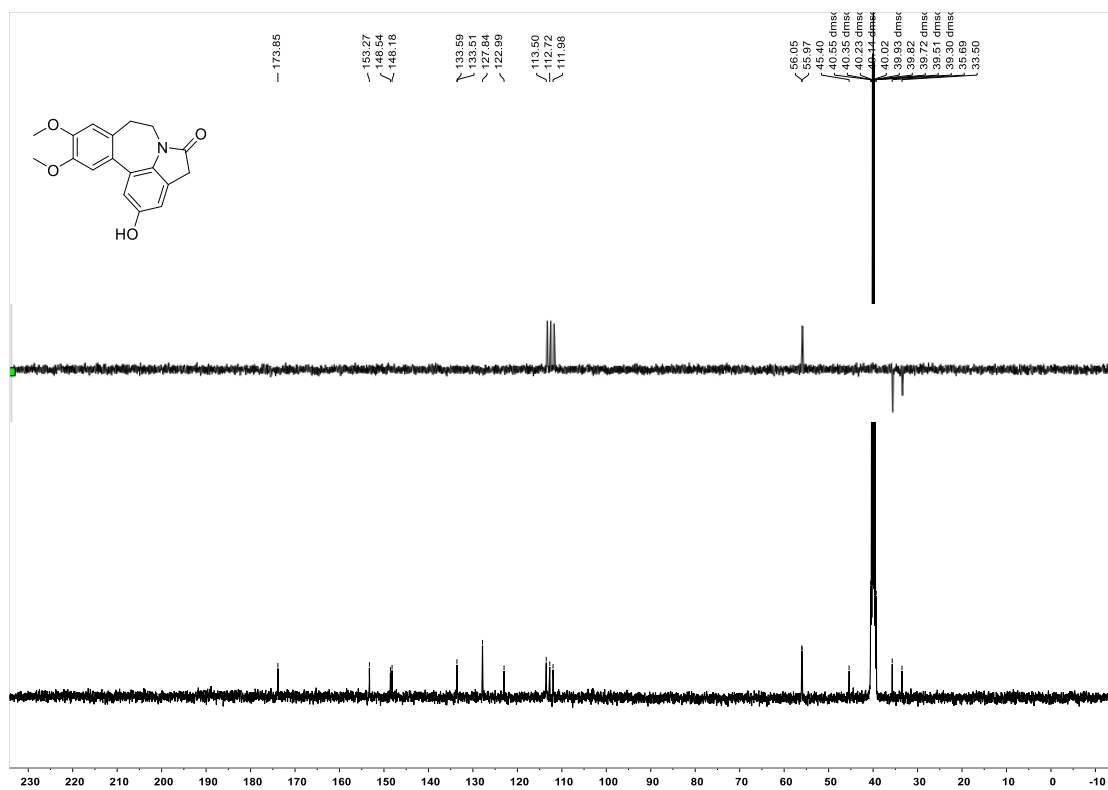
¹³C and DEPT NMR of **11** (100 MHz, CDCl₃)



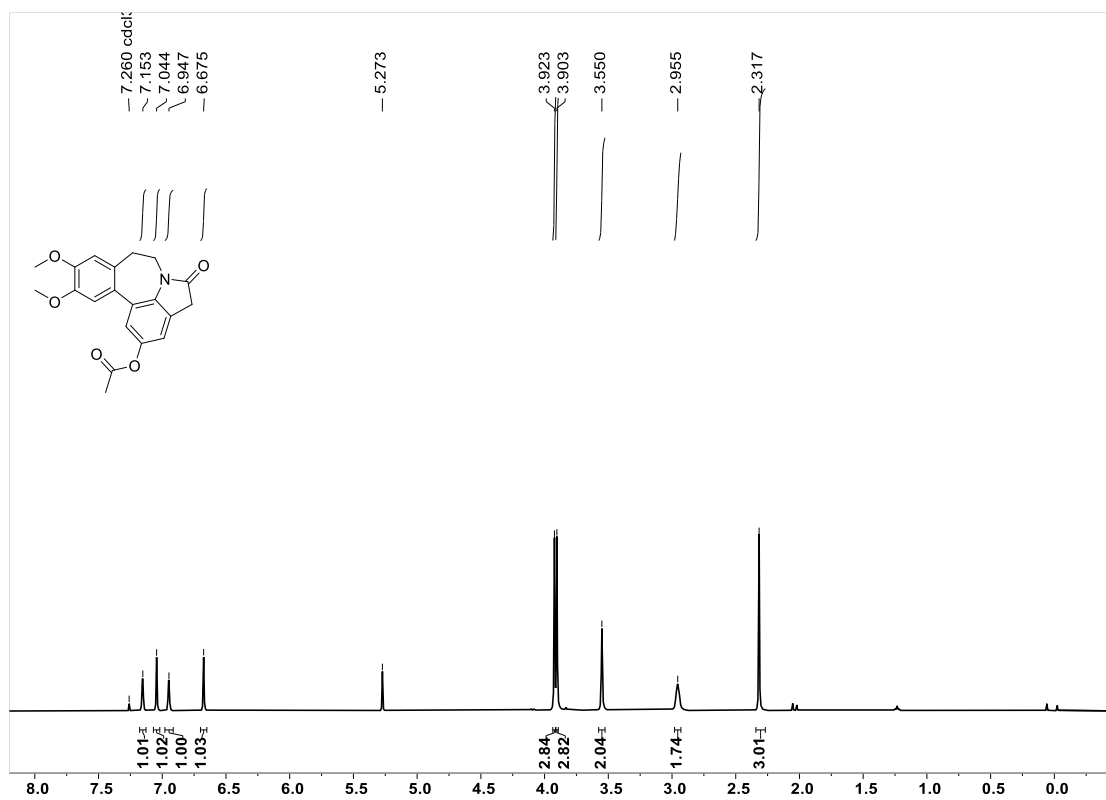
¹H NMR of **5** (400 MHz, CDCl₃)



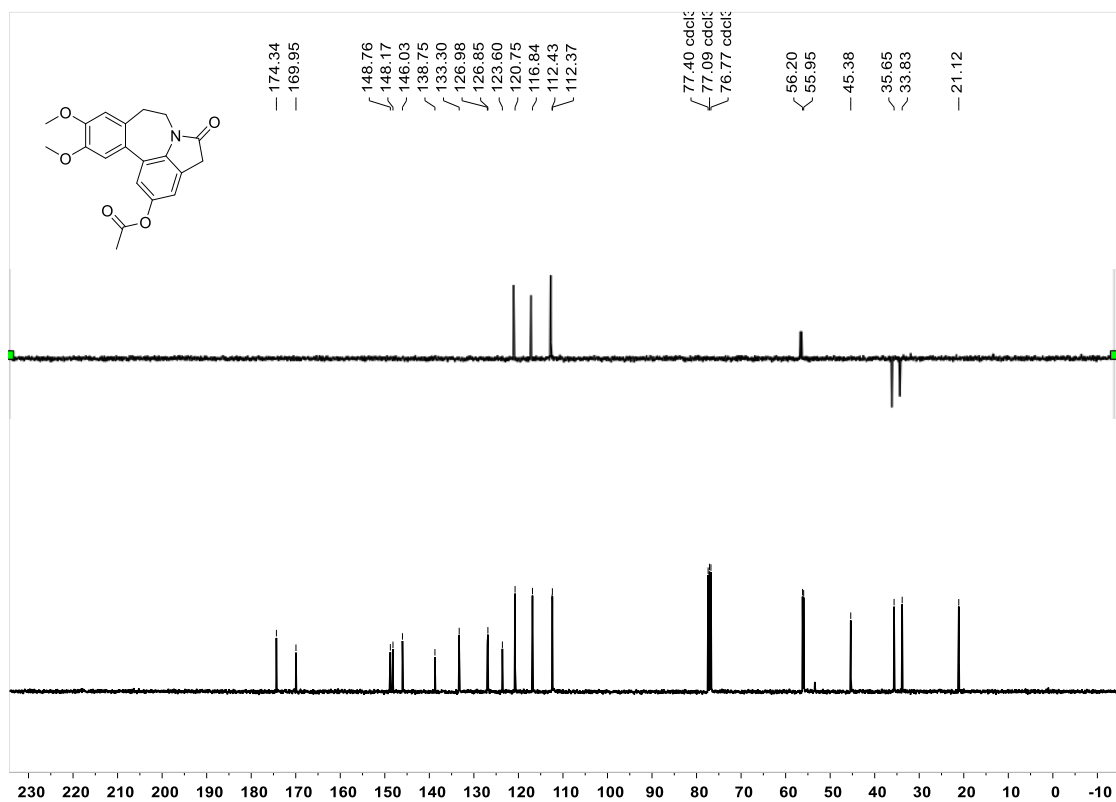
¹³C and DEPT NMR of **5** (100 MHz, CDCl₃)



¹H NMR of **12** (400 MHz, CDCl₃)



¹³C and DEPT NMR of **12** (100 MHz, CDCl₃)



7. Crystallographic Data of Compounds **3**, **7**, **9a**, **9b**, **10** and **12**

The single crystals (CCDC Number: 2115760, 2115751, 2115755, 2115753 and 2115763) of compounds **3**, **7**, **9a**, **9b** and **12** were obtained by slow diffusion of the solution of hexanes / EtOAc, and The single crystals (CCDC Number: 2154740) of compounds **10** was obtained by slow diffusion of the solution of MeOH. Data were collected on an Agilent SuperNova-CCD X-Ray diffractometer. Using Olex 2, the structure was solved with the XT structure solution program using Intrinsic Phasing and refined with the XL refinement package using Least Squares minimisation. See below for other details.

Crystallographic data of **3**:

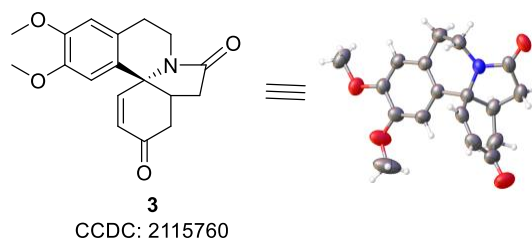


Table 1 Crystal data and structure refinement for **3**

Identification code	C ₁₈ H ₁₉ NO ₄
Empirical formula	C ₁₈ H ₁₉ NO ₄
Formula weight	313.34
Temperature/K	293(2)
Crystal system	monoclinic
Space group	P21/n
a/Å	11.2707(4)
b/Å	18.5868(5)
c/Å	16.0997(5)
α/°	90
β/°	110.192(4)
γ/°	90
Volume/Å ³	3165.39(19)
Z	8
ρ _{calc} /cm ³	1.315
μ/mm ⁻¹	0.093

F(000)	1328.0
Crystal size/mm ³	0.43 × 0.42 × 0.39
Radiation	MoK α (λ = 0.71073)
2 θ range for data collection/ $^{\circ}$	6.964 to 52.74
Index ranges	$-11 \leq h \leq 14, -23 \leq k \leq 20, -20 \leq l \leq 19$
Reflections collected	15911
Independent reflections	6460 [$R_{\text{int}} = 0.0213, R_{\text{sigma}} = 0.0315$]
Data/restraints/parameters	6460/0/419
Goodness-of-fit on F^2	1.044
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0543, wR_2 = 0.1298$
Final R indexes [all data]	$R_1 = 0.0801, wR_2 = 0.1464$
Largest diff. peak/hole / e \AA^{-3}	0.27/−0.30

Crystallographic data of **7**:

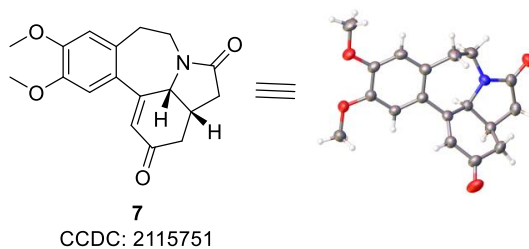


Table 2 Crystal data and structure refinement for **7**

Identification code	C ₁₈ H ₁₉ NO ₄
Empirical formula	C ₁₈ H ₁₉ NO ₄
Formula weight	313.34
Temperature/K	293(2)
Crystal system	monoclinic
Space group	P21/c
a/ \AA	9.7090(5)
b/ \AA	15.8571(6)
c/ \AA	10.2126(5)
$\alpha/^\circ$	90
$\beta/^\circ$	106.923(5)
$\gamma/^\circ$	90

Volume/Å ³	1504.21(12)
Z	4
ρ _{calc} /cm ³	1.384
μ/mm ⁻¹	0.098
F(000)	664.0
Crystal size/mm ³	0.18 × 0.16 × 0.15
Radiation	MoKα (λ = 0.71073)
2θ range for data collection/°	6.618 to 52.736
Index ranges	-12 ≤ h ≤ 12, -19 ≤ k ≤ 19, -12 ≤ l ≤ 9
Reflections collected	7641
Independent reflections	3071 [R _{int} = 0.0224, R _{sigma} = 0.0316]
Data/restraints/parameters	3071/0/210
Goodness-of-fit on F ²	1.041
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0478, wR ₂ = 0.1090
Final R indexes [all data]	R ₁ = 0.0657, wR ₂ = 0.1205
Largest diff. peak/hole / e Å ⁻³	0.21/-0.23

Crystallographic data of **9b**:

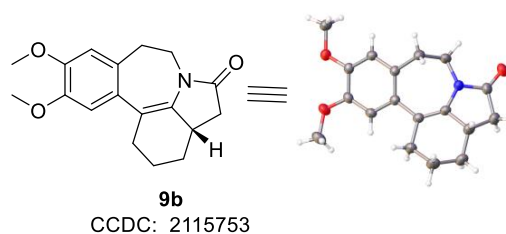


Table 3 Crystal data and structure refinement for **9b**

Identification code	C ₁₈ H ₂₁ NO ₃
Empirical formula	C ₁₈ H ₂₁ NO ₃
Formula weight	299.36
Temperature/K	293(2)
Crystal system	monoclinic
Space group	P21/n
a/Å	11.9211(6)
b/Å	7.5981(3)
c/Å	17.1600(10)

$\alpha/^\circ$	90
$\beta/^\circ$	109.380(6)
$\gamma/^\circ$	90
Volume/ \AA^3	1466.24(14)
Z	4
$\rho_{\text{calc}}/\text{cm}^3$	1.356
μ/mm^{-1}	0.092
F(000)	640.0
Crystal size/ mm^3	$0.27 \times 0.26 \times 0.25$
Radiation	MoK α ($\lambda = 0.71073$)
2Θ range for data collection/ $^\circ$	7.212 to 58.144
Index ranges	$-16 \leq h \leq 14, -9 \leq k \leq 9, -16 \leq l \leq 23$
Reflections collected	6366
Independent reflections	3374 [$R_{\text{int}} = 0.0211, R_{\text{sigma}} = 0.0422$]
Data/restraints/parameters	3374/0/201
Goodness-of-fit on F^2	1.049
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0545, wR_2 = 0.1316$
Final R indexes [all data]	$R_1 = 0.0799, wR_2 = 0.1509$
Largest diff. peak/hole / $e \text{\AA}^{-3}$	0.21/−0.21

Crystallographic data of **9a**:

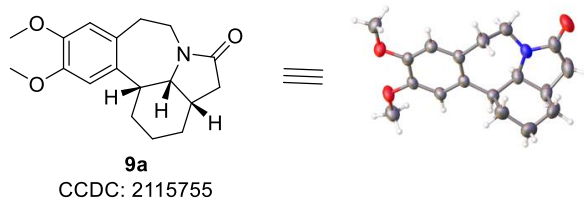


Table 4 Crystal data and structure refinement for **9a**

Identification code	C ₁₈ H ₂₃ NO ₃
Empirical formula	C ₁₈ H ₂₃ NO ₃
Formula weight	301.37
Temperature/K	293(2)
Crystal system	monoclinic
Space group	P21/c

a/Å	12.8274(5)
b/Å	9.7027(4)
c/Å	12.2527(5)
α /°	90
β /°	92.669(4)
γ /°	90
Volume/Å ³	1523.32(11)
Z	4
ρ calcg/cm ³	1.314
μ /mm ⁻¹	0.089
F(000)	648.0
Crystal size/mm ³	0.32 × 0.31 × 0.3
Radiation	Mo K α (λ = 0.71073)
2 Θ range for data collection/°	7.244 to 57.784
Index ranges	-16 ≤ h ≤ 16, -13 ≤ k ≤ 10, -16 ≤ l ≤ 16
Reflections collected	6642
Independent reflections	3436 [R _{int} = 0.0288, R _{sigma} = 0.0472]
Data/restraints/parameters	3436/0/201
Goodness-of-fit on F ²	1.042
Final R indexes [I >= 2 σ (I)]	R ₁ = 0.0551, wR ₂ = 0.1188
Final R indexes [all data]	R ₁ = 0.0815, wR ₂ = 0.1365
Largest diff. peak/hole / e Å ⁻³	0.20/-0.18

Crystallographic data of **10**:

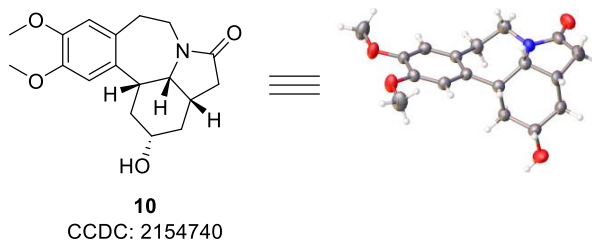
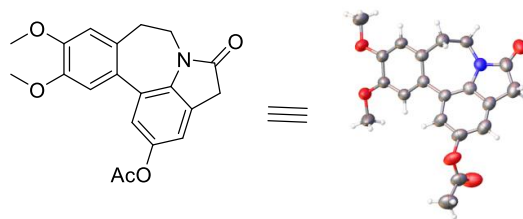


Table 5 Crystal data and structure refinement for **10**

Identification code	C ₁₈ H ₂₃ NO ₄
Empirical formula	C ₁₈ H ₂₃ NO ₄

Formula weight	317.37
Temperature/K	293(2)
Crystal system	orthorhombic
Space group	P2 ₁ 2 ₁ 2 ₁
a/Å	9.0338(4)
b/Å	12.5800(6)
c/Å	13.9834(6)
α/°	90
β/°	90
γ/°	90
Volume/Å ³	1589.15(12)
Z	4
ρ _{calc} /cm ³	1.327
μ/mm ⁻¹	0.093
F(000)	680.0
Crystal size/mm ³	0.31 × 0.3 × 0.28
Radiation	Mo Kα (λ = 0.71073)
2θ range for data collection/°	6.668 to 58.356
Index ranges	-7 ≤ h ≤ 12, -15 ≤ k ≤ 16, -10 ≤ l ≤ 18
Reflections collected	7183
Independent reflections	3650 [R _{int} = 0.0280, R _{sigma} = 0.0478]
Data/restraints/parameters	3650/0/211
Goodness-of-fit on F ²	1.106
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0499, wR ₂ = 0.1052
Final R indexes [all data]	R ₁ = 0.0642, wR ₂ = 0.1149
Largest diff. peak/hole / e Å ⁻³	0.18/-0.23
Flack parameter	-1.9(9)

Crystallographic data of **12**:



12
CCDC: 2115763

Table 6 Crystal data and structure refinement for **12**

Identification code	C ₂₀ H ₁₉ NO ₅
Empirical formula	C ₂₀ H ₁₉ NO ₅
Formula weight	353.36
Temperature/K	295(2)
Crystal system	monoclinic
Space group	Pn
a/Å	19.2614(16)
b/Å	5.0789(4)
c/Å	19.9253(17)
α/°	90
β/°	115.610(10)
γ/°	90
Volume/Å ³	1757.7(3)
Z	4
ρ _{calc} /cm ³	1.335
μ/mm ⁻¹	0.096
F(000)	744.0
Crystal size/mm ³	0.33 × 0.31 × 0.29
Radiation	MoKα (λ = 0.71073)
2θ range for data collection/°	7.378 to 58.352
Index ranges	-25 ≤ h ≤ 25, -5 ≤ k ≤ 6, -27 ≤ l ≤ 26
Reflections collected	7168
Independent reflections	5660 [R _{int} = 0.0229, R _{sigma} = 0.0548]
Data/restraints/parameters	5660/2/475
Goodness-of-fit on F ²	1.082
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0548, wR ₂ = 0.1242

Final R indexes [all data]	$R_1 = 0.0850, wR_2 = 0.1507$
Largest diff. peak/hole / e Å ⁻³	0.28/-0.19
Flack parameter	-0.2(9)