# Supporting Information

## A Chemical Synthesis of 11-Methoxy Mitragynine Pseudoindoxyl Featuring the Interrupted Ugi Reaction

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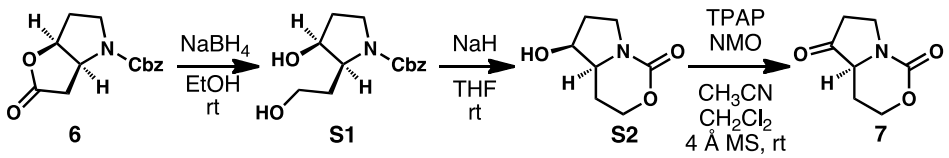
**General.** Bis(1,5-cyclooctadiene)nickel(0) was purchased from Strem Chemical. Unless otherwise stated, all other reagents were purchased from Aldrich and used without further purification. Methylene chloride, tetrahydrofuran, and acetonitrile were dried by passing through activated alumina columns. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plated (60 $F_{254}$) using UV light as a visualizing agent and aqueous potassium permanganate and heat as a developing agent. E. Merck silica gel 60 (230-400 mesh) was used for flash chromatographic separations.

**Instrumentation.** FT-IR spectra were obtained on a Perkin-Elmer Paragon 500. Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Inova-600, Inova-500, or Inova-400 instruments. Proton chemical shifts are reported in parts per million and are calibrated to the residual proton signal (7.26 ppm) in the $CDCl_3$ NMR solvent. Carbon chemical shifts are reported in parts per million and are calibrated to the residual solvent peaks (77.0 ppm). Coupling constant values were extracted assuming first-order coupling. The multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, qi = quintet, m = multiplet, and br = broad signal. High-resolution mass spectra were obtained on an Agilent ESI-TOF mass spectrometer.

**Geissman-Waiss lactone 6:** Lactone **6** was prepared according to the known procedures in literature.[1]

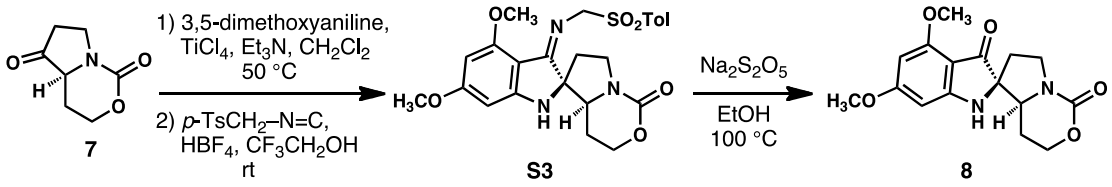



**Diol S1:** $NaBH_4$ (580mg, 15.3 mmol, 4.0 equiv) was added portionwise over 5 min to a stirred solution of Geissman-Waiss lactone **6** (1 g, 3.83 mmol, 1.0 equiv) in EtOH (35 mL) at 25 °C. The reaction was allowed to proceed for another 18 h at 25 °C. The resulting mixture was cooled to 0 °C and acetic acid was added slowly until the foaming stopped. The suspension was concentrated at reduced pressure and $CH_2Cl_2$ (50 mL) was added, followed by addition of $K_2CO_3$ and $Na_2SO_4$. The mixture was stirred

for 10-20 min at 25 °C, and filtered. The filtrate was concentrated, and purified by flash column chromatography (EtOAc) to afford 1 g (99%) of diol **S1** as a colorless oil. TLC: $R_f$ = 0.50 (EtOAc); IR (film) 3398, 2952, 2890, 1678, 1417, 1118, 698 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 5 H), 5.15 (s, 2 H), 4.52 (br s, 1 H), 4.36 (q, *J* = 6.4 Hz, 1 H), 3.97 (q, *J* = 6.4 Hz, 1 H), 3.72 (m, 1 H), 3.63 (t, *J* = 10.8 Hz, 1 H), 3.45 (m, 2 H), 2.00 (m, 2 H), 1.90 (m, 1 H), 1.83 (m, 1 H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 155.9, 136.4, 128.4, 127.9, 127.7, 70.6, 66.9, 59.1, 58.9, 43.5, 31.1, 30.4; HRMS (ESI-TOF) exact mass calculated for $[M+H]^+$ ($C_{14}H_{20}NO_4$) = 266.1387, found 266.1388.

**5-Hydroxy-hexahydropyrrolo[1,2-*c*][1,3]oxazin-1-one S2:** A flame-dried 500 mL round-bottomed flask containing diol **S1** (2.9 g, 10.9 mmol, 1.0 equiv) was charged with freshly distilled THF (126 mL). NaH (1.1 g, 27.3 mmol, 2.5 equiv) was then added portionwise to the stirred solution of the diol at 25 °C. [2] The reaction mixture was allowed to proceed overnight at 25 °C. The resulting mixture was then quenched with water, and concentrated at reduced pressure. Purification by flash column chromatography (gradient elution from 1:1 hexanes/EtOAc to 1:7 MeOH/EtOAc) afforded 1 g (58%) of 5-hydroxy-hexahydropyrrolo[1,2-*c*][1,3]oxazin-1-one **S2** as a white solid. TLC: $R_f$ = 0.30 (1:10 MeOH/EtOAc); IR (film) 3306, 2956, 2899, 1668, 1444, 1109 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 4.39 (ddd, *J* = 11.0, 4.4, 2.0 Hz, 1 H), 4.30 (m, 1 H), 4.19 (ddd, *J* = 13.1, 11.0, 2.1 Hz, 1 H), 3.78 (dt, *J* = 11.0, 8.0 Hz, 1 H), 3.56 (dt, *J* = 11.4, 3.5 Hz 1 H), 3.46 (ddd, *J* = 11.3, 9.0, 2.5 Hz, 1 H), 2.15 (ddt, *J* = 13.0, 11.5, 4.5 Hz, 1 H), 2.02 (m, 2 H), 1.95 (qi, *J* = 2.2 Hz, 1 H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 153.8, 71.8, 66.0, 61.1, 44.5, 32.0, 21.8; HRMS (ESI-TOF) exact mass calculated for $[M+H]^+$ ($C_7H_{12}NO_3$) = 158.0812, found 158.0811.

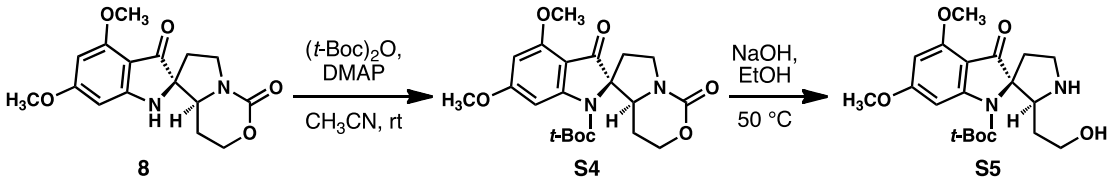
**Carbamate 7:** A flame-dried 100mL round-bottomed flask containing 5-hydroxy-hexahydropyrrolo[1,2-*c*][1,3]oxazin-1-one **S2** (226 mg, 1.44 mmol, 1.0 equiv) and powdered 4 Å molecular sieves (454 mg) was charged with freshly distilled $CH_2Cl_2$ (28 mL). To the suspension was added *N*-methylmorpholine-*N*-oxide (NMO) (253 mg, 2.16 mmol, 1.5 equiv) and freshly distilled $CH_3CN$ (14 mL) at 25 °C. Tetra-*N*-propylammonium perruthenate (TPAP) (25 mg, 0.07 mmol, 0.05 equiv) was then added to the mixture and the reaction was allowed to proceed for 1 h at 25 °C. The resulting black suspension was filtered through Celite and the filtrate was concentrated at reduced pressure. Purification by flash column chromatography (1:30 MeOH/EtOAc) afforded 169 mg (76%) of carbamate **7** as a white solid. TLC: $R_f$ = 0.46 (1:10 MeOH/EtOAc); IR (film) 2974, 2913, 1754, 1693, 1438 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 4.45 (m, 2 H), 4.28 (ddd, *J* = 12.7, 11.4, 2.5 Hz, 1 H), 3.74 (dd, *J* = 11.3, 4.9 Hz, 1 H), 3.57 (dt, *J* = 12.1, 9.0 Hz, 1 H), 2.56 (m, 2 H), 2.32 (dqi, *J* = 13.5, 2.2 Hz, 1 H), 1.81 (dddd, *J* = 13.8, 12.7, 11.4, 4.6 Hz, 1 H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 210.4, 151.8, 66.1, 59.1, 42.2, 35.2, 23.2; HRMS (ESI-TOF) exact mass calculated for $[M+H]^+$ ($C_7H_{10}NO_3$) = 156.0655, found 156.0657.




**Interrupted Ugi product S3:** A 1 M solution of $TiCl_4$ (380 μL, 0.38 mmol, 0.5 equiv) in $CH_2Cl_2$ was slowly added over 10 min to a mixture of ketone **7** (117 mg, 0.75 mmol, 1.0 equiv), 3,5-dimethoxyaniline (117 mg, 0.75 mmol, 1.0 equiv), and freshly distilled $Et_3N$ (631 μL, 4.52 mmol, 6.0 equiv) in dry $CH_2Cl_2$ (20 mL) at 25 °C. The resulting brown mixture was heated to reflux overnight, and then cooled back to 25 °C. The mixture was diluted with $Et_2O$ (40 mL) and filtered through Celite. The filtrate was concentrated to afford the crude imine as a yellow amorphous solid, which was used without further purification. A flame-dried 50 mL round-bottomed flask containing the crude imine was charged with freshly distilled $CF_3CH_2OH$ (15 mL). To the solution was added *p*-toluenesulfonylmethyl isocyanide (293 mg, 1.5 mmol, 2.0 equiv). $HBF_4 \cdot OEt_2$ (102 μL, 0.75 mmol, 1.0 equiv) was then added dropwise to the mixture at 25 °C. The reaction was allowed to proceed for 4 h at 25 °C, and then was quenched with aqueous $NaHCO_3$ solution and extracted with $CH_2Cl_2$ (3 X 15 mL). The combined organic extracts were dried over anhydrous $Na_2SO_4$, and concentrated at reduced pressure. Purification by flash column chromatography (gradient elution from 1:1 hexanes/EtOAc to 1:10 MeOH/EtOAc) afforded 273 mg (75%) of tetracyclic imine **S3** as a yellow solid. TLC: $R_f$ = 0.30 (1:10 MeOH/EtOAc); IR (film) 3347, 2941, 1681, 1611, 1513, 1208, 1138, 809 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.2 Hz, 2 H), 7.40 (d, *J* = 8.1 Hz, 2 H), 5.84 (d, *J* = 1.9 Hz, 1 H), 5.81 (d, *J* = 1.9 Hz, 1 H) 5.51 (d, *J* = 15.0 Hz, 1 H), 5.17 (d, *J* = 15.0 Hz, 1 H), 4.39 (br s, 1 H), 4.27 (ddd, *J* = 10.8, 4.4, 1.5 Hz, 1 H), 4.07 (ddd, *J* = 13.0, 10.8, 2.4 Hz, 1 H), 3.88 (s, 3 H), 3.79 (s, 3 H), 3.73 (dt, *J* = 10.5, 7.9 Hz, 1 H), 3.65 (dd, *J* = 11.4, 3.8 Hz, 1 H), 3.53 (t, *J* = 10.0 Hz, 1 H), 2.43 (s, 3 H), 2.15 (ddd, *J* = 12.6, 7.7, 1.5 Hz, 1 H), 1.95 (m, 2 H), 1.65 (dqi, *J* = 13.2, 1.7 Hz, 1 H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 171.2, 167.1, 159.8, 156.9, 152.5, 144.2, 135.6, 129.9, 128.6, 101.8, 90.2, 87.7, 76.4, 74.0, 66.6, 63.3, 55.6, 55.4, 45.1, 34.9, 22.3, 21.6; HRMS (ESI-TOF) exact mass calculated for $[M+H]^+$ ($C_{24}H_{28}N_3O_6S$) = 486.1693, found 486.1691.

**Indoxyl 8:** Sodium metabisulfite ($Na_2S_2O_5$) (489 mg, 2.57 mmol, 3.7 equiv) was added to a solution of imine **S3** (337 mg, 0.69 mmol, 1.0 equiv) in EtOH/$H_2O$ (1.7:1.0, 19 mL),[3] and then the reaction mixture was heated to reflux for 8 hours. The yellow mixture was quenched with aqueous $NH_4Cl$ solution, and extracted with $CH_2Cl_2$ (3 X 30 mL). The combined organic extracts were dried over anhydrous $Na_2SO_4$, and concentrated. Purification of the residue by flash column chromatography (gradient elution from 1:1 hexanes/EtOAc to 1:7 MeOH/EtOAc) afforded 136 mg (62%) of indoxyl **8** as a white solid. TLC: $R_f$ = 0.20 (1:10 MeOH/EtOAc); IR (film) 3293, 2968, 1678, 1617, 1590, 1514, 1207, 1114 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 5.95 (d, *J* = 1.6 Hz, 1 H), 5.77 (d, *J* = 1.6 Hz, 1 H), 5.72 (br s, 1 H), 4.31 (ddd, *J* = 10.8, 3.8, 1.8 Hz,

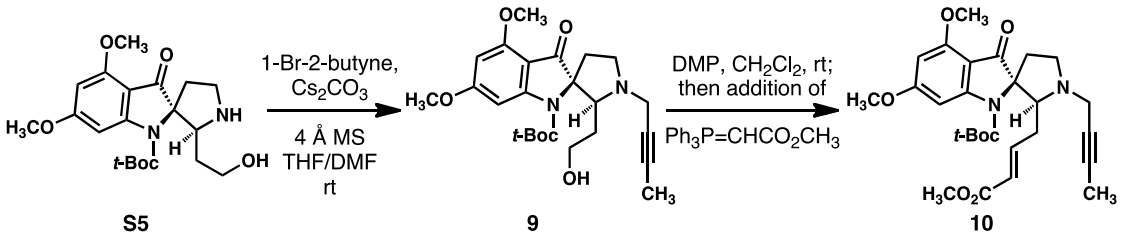
1 H), 4.16 (dt, *J* = 11.2, 3.5 Hz, 1 H), 4.03 (dt, *J* = 10.6, 8.1 Hz, 1 H), 3.88 (dd, *J* = 10.4, 5.3 Hz, 1 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 3.62 (ddd, *J* = 10.8, 8.6, 2.0 Hz, 1 H), 2.17 (m, 2 H), 1.84 (m, 2 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 196.4, 169.7, 163.6, 159.9, 153.2, 103.4, 90.3, 87.4, 72.4, 66.2, 60.7, 55.8, 55.7, 44.5, 31.8, 22.3; HRMS (ESI-TOF) exact mass calculated for $[M+H]^+$ ($C_{19}H_{19}N_2O_5$) = 319.1289, found 319.1289.




**Boc-protected indoxyl S4:** A solution of $(Boc)_2O$ (24 mg, 0.11 mmol, 3.6 equiv) in $CH_3CN$ (0.2 mL) was added to a stirred mixture of indoxyl **8** (10 mg, 0.03 mmol, 1.0 equiv) and 4-dimethylaminopyridine (DMAP) (16 mg, 0.13 mmol, 4.3 equiv) in $CH_3CN$ (0.7 mL) at 25 °C. After 18 h, the reaction mixture was quenched with aqueous $NH_4Cl$ solution, and extracted with EtOAc (3 X 5 mL). The combined organic extracts were washed with aqueous $NaHCO_3$ solution, and then dried over anhydrous $Na_2SO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (gradient elution from EtOAc to 1:30 MeOH/EtOAc) to afford 12 mg (96%) of Boc-protected indoxyl **S4** as a yellow solid. TLC: $R_f$ = 0.50 (1:10 MeOH/EtOAc); IR (film) 2975, 1702, 1606, 1211, 1160 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.27 (br s, 1 H), 6.13 (d, *J* = 1.8 Hz, 1 H), 4.48 (dd, *J* = 11.3, 3.9 Hz, 1 H), 4.29 (ddd, *J* = 11.0, 4.3, 2.0 Hz, 1 H), 4.12 (m, 2 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.70 (dt, *J* = 10.2, 3.6 Hz, 1 H), 2.78 (dt, *J* = 12.5, 9.5 Hz, 1 H), 2.13(ddd, *J* = 12.5, 8.8, 3.6 Hz, 1 H), 1.86 (dq, *J* = 12.6, 4.5 Hz, 1 H), 1.71 (m, 1 H), 1.63 (s, 9 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 193.9, 169.0, 159.5, 155.8, 152.5, 150.1, 105.2, 94.1, 93.5, 84.0, 75.3, 65.8, 57.9, 56.0, 55.9, 44.9, 29.3, 28.4, 22.6; HRMS (ESI-TOF) exact mass calculated for $[M+H]^+$ ($C_{21}H_{27}N_2O_7$) = 419.1813, found 419.1821.

**Amino alcohol S5:** A 2.0 M solution of aqueous NaOH (360 μL, 0.72 mmol, 10 equiv) was added to a stirred solution of indoxyl **S4** (30 mg, 0.07 mmol, 1 equiv) in EtOH (1.1 mL) at 25 °C. The reaction mixture was warmed to 50 °C, and then stirred for 2 h at 50 °C. The resulting blue solution was extracted with $CH_2Cl_2$ (4 X 5 mL), and the combined organic extracts were dried over anhydrous $Na_2SO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (gradient elution from 1:30 to 1:5 MeOH/EtOAc) to afford 17 mg (61%) of amino alcohol **S5** as a yellow amorphous solid. TLC: $R_f$ = 0.30 (1:5 MeOH/EtOAc); IR (film) 3394, 2973, 1712, 1686, 1604, 1210, 1159 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.36 (br s, 1 H), 6.08 (d, *J* = 1.7 Hz, 1 H), 3.89 (s, 6 H), 3.69 (d, *J* = 9.7 Hz, 1 H), 3.63 (m, 1 H), 3.58 (dt, *J* = 10.5, 3.8 Hz, 1 H), 3.24 (ddd, *J* = 11.5, 8.7, 2.5 Hz, 1 H), 3.15 (q, *J* = 9.0 Hz, 1 H), 2.39 (ddd, *J* = 12.1, 8.5, 1.6 Hz, 1 H), 2.09 (dt, *J* = 12.3, 8.5 Hz, 1 H), 1.59 (s, 9 H), 1.54 (m, 1 H), 1.38 (m, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 197.5, 168.8, 158.8, 156.7, 150.3, 105.4, 94.0, 92.9, 83.2, 77.4, 65.5, 61.8,

55.9, 55.9, 46.5, 34.5, 30.5, 28.4; HRMS (ESI-TOF) exact mass calculated for $[M+H]^+$ ($C_{20}H_{29}N_2O_6$) = 393.2020, found 393.2020.

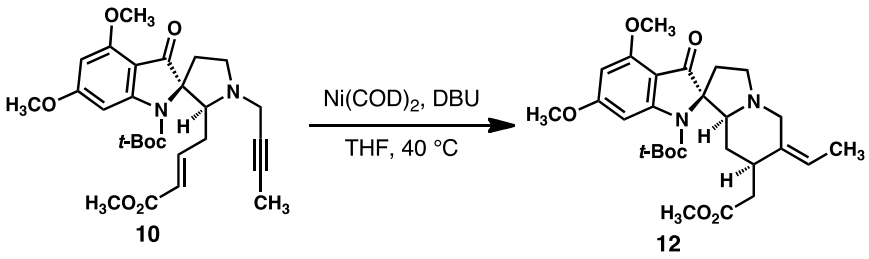



S5 9 10

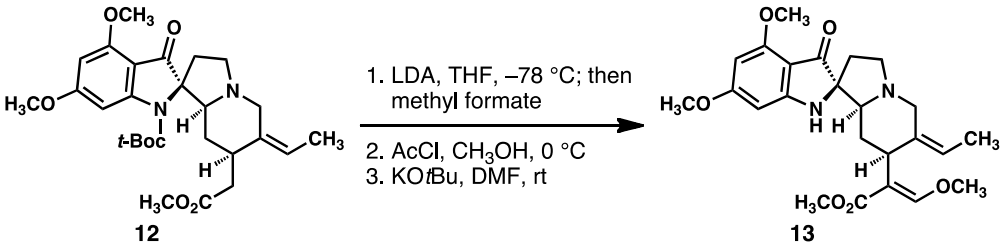
**Alkynyl alcohol 9:** Powdered 4 Å molecular sieves (11 mg) were added to a stirred solution of amino alcohol **S5** (19 mg, 0.05 mmol, 1.0 equiv) and $Cs_2CO_3$ (16 mg, 0.05 mmol, 1.01 equiv) in THF/DMF (1:1, 1 mL).[4] To the mixture was added 1-bromo-2-butyne (4.4 μL, 0.05 mmol, 1.05 equiv). The resulting mixture was stirred at 25 °C overnight, and quenched with water. The mixture was extracted with EtOAc (3 X 5 mL), and then the combined organic extracts were washed with water (3 X 5 mL). The organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography (gradient elution from EtOAc to 1:10 MeOH/EtOAc) afforded 14 mg (63%) of alkylation product **9** as a yellow solid. TLC: $R_f$ = 0.40 (1:10 MeOH/EtOAc); IR (film) 3470, 2969, 2930, 2849, 1698, 1604, 1210, 1159 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.45 (br s, 1 H), 6.10 (d, *J* = 1.7 Hz, 1 H), 3.92 (s, 3 H), 3.90 (s, 3 H), 3.62 (m, 3 H), 3.47 (m, 2H), 3.19 (q, *J* = 8.7 Hz, 1 H), 3.08 (ddd, *J* = 2.6, 9.5, 8.3 Hz, 1 H), 2.31 (m, 2 H), 1.86 (t, *J* = 2.0 Hz, 3 H), 1.75 (m, 1 H), 1.66 (s, 9 H), 1.59 (m, 2 H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 196.4, 168.7, 159.1, 156.4, 150.7, 105.9, 94.0, 93.1, 83.2, 81.3, 76.8, 73.6, 62.3, 60.5, 56.0, 55.9, 51.0, 40.1, 32.5, 30.9, 28.5, 3.8; HRMS (ESI-TOF) exact mass calculated for $[M+H]^+$ ($C_{24}H_{33}N_2O_6$) = 445.2333, found 445.2334.

**1,7-Enyne 10:** Dess-Martin periodinane (DMP) (72 mg, 0.17 mmol, 1.5 equiv) was added to a solution of alcohol **9** (50 mg, 0.11 mmol, 1.0 equiv) in $CH_2Cl_2$ (3 mL) at 25 °C. Via TLC analysis, the oxidation to the corresponding aldehyde was judged to be complete after 15 min. At this point, methyl(triphenylphosphoranylidene)acetate (115 mg, 0.35 mmol, 3.0 equiv) was directly added to the $CH_2Cl_2$ solution containing the aldehyde. After stirring for 8 hours at room temperature, the reaction was quenched by the addition of water. The mixture was then extracted with $Et_2O$ (3 X 10 mL), and the combined organic extracts were dried over anhydrous $Na_2SO_4$. After filtration, the solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (gradient elution from 1:1 to 1:10 hexanes/EtOAc) to afford 37 mg (68%) of α,β-unsaturated ester **10**. TLC: $R_f$ = 0.60 (1:10 MeOH/EtOAc); IR (film) 2955, 2927, 2852, 1737, 1704, 1605, 1313, 1210, 1056, 901, 832 $cm^{-1}$; $^1H$ NMR (500 MHz, $C_6D_6$) δ 7.79 (br s, 1 H), 6.85 (dt, *J* = 15.1, 7.5 Hz, 1 H), 5.98 (d, *J* = 1.7 Hz, 1 H), 5.58 (d, *J* = 15.8 Hz, 1 H), 3.69 (t, *J* = 6.5 Hz, 1 H), 3.42 (m, 5H), 3.31 (s, 6 H), 3.14 (m, 1 H), 2.92 (t, *J* = 8.0 Hz, 1 H), 2.40 (dt, *J* = 13.0, 8.9 Hz, 1 H), 2.27 (t, *J* = 6.8 Hz, 2 H), 2.07 (dd, *J* = 12.0, 8.2 Hz, 1 H), 1.53 (s, 3 H), 1.45(s, 9 H); $^{13}C$ NMR (125

MHz, $C_6D_6$) δ 193.7, 168.2, 165.7, 159.1, 156.4, 150.8, 145.0, 122.5, 107.2, 94.2, 93.6, 82.3, 80.8, 76.6, 73.7, 64.9, 55.2, 55.0, 51.1, 50.4, 39.9, 32.2, 31.6, 28.2, 3.31; HRMS (ESI-TOF) exact mass calculated for $[M+H]^+$ ($C_{27}H_{35}N_2O_7$) = 499.2439, found 499.2440.

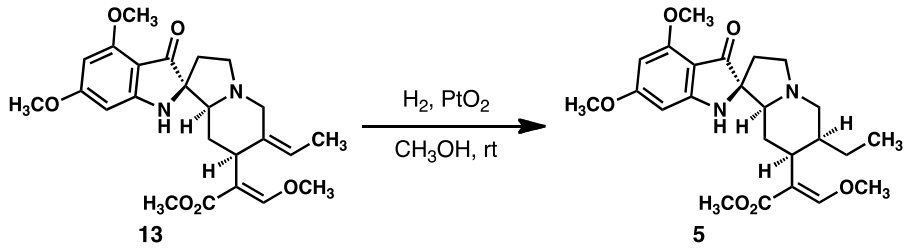



**Tetracyclic piperidine 12:** A solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (45 μL, 0.30 mmol, 3.0 equiv) in degassed THF (2 mL) was added to $Ni(COD)_2$ (42 mg, 0.15 mmol, 1.5 equiv) at 25 °C and stirred for 3–5 min. A solution of 1,7-enyne **10** (50 mg, 0.10 mmol, 1.0 equiv) in THF was slowly added to the nickel solution at 25 °C. The reaction mixture was stirred at 40 °C overnight and then quenched by the addition of water. The resulting mixture was stirred at 25 °C for 15 min and then extracted with EtOAc (3 X 10 mL). The combined organic extracts were dried over anhydrous $Na_2SO_4$, filtered and concentrated. Purification of the residue by flash column chromatography (EtOAc) afforded 32 mg (63%) of reductive cyclization product **12** as an amorphous yellow solid. TLC: $R_f$ = 0.60 (1:10 MeOH/EtOAc); IR (film) 2951, 2850, 1737, 1703, 1605, 1310, 1160, 1056, 834 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.33 (br s, 1 H), 6.08 (d, *J* = 1.6 Hz, 1 H), 5.05 (q, *J* = 6.3 Hz, 1 H), 4.05 (d, *J* = 11.8 Hz, 1 H), 3.90 (s, 3 H), 3.88 (s, 3 H), 3.61 (s, 3 H), 3.24 (t, *J* = 7.8 Hz, 1 H), 3.01 (d, *J* = 10.5 Hz, 1 H), 2.80 (m, 1 H), 2.61 (dd, *J* = 15.7, 7.54 Hz, 1 H), 2.39 (m, 3 H), 2.27 (dd, *J* = 13.1, 7.4 Hz, 1 H), 2.16 (dd, *J* = 16.0, 6.3 Hz, 1 H), 1.66 (s, 9 H), 1.61 (d, *J* = 6.5 Hz, 3 H), 1.38 (dt, *J* = 11.3, 3.1 Hz, 1 H), 1.16 (q, *J* = 11.7 Hz, 1 H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 195.7, 173.5, 168.4, 159.0, 156.2, 150.6, 135.4, 116.0, 105.7, 93.9, 93.1, 83.3, 76.3, 69.0, 56.0, 55.8, 53.5, 53.3, 51.5, 37.7, 36.9, 33.1, 32.2, 28.8, 13.4; HRMS (ESI-TOF) exact mass calculated for $[M+H]^+$ ($C_{27}H_{37}N_2O_7$) = 501.2595, found 501.2596.




**Methyl enol ether 13:** To a solution of diisopropyl amine (49 μL, 0.35 mmol, 3.74 equiv) in THF (1 mL) was slowly added a 2.5 M solution of *n*-BuLi (138 μL, 0.35 mmol, 3.68 equiv) at 0 °C. After 30 min, the solution containing newly formed lithium diisopropylamide (LDA) was cooled to –78 °C and a solution of methyl ester **12** (47 mg, 0.09 mmol, 1.0 equiv) in THF (3.5 mL) was added. After 1 hour, methylformate

(488 μL, 7.91 mmol, 84.0 equiv) was added to the reaction mixture at –78 °C. The resulting solution was then stirred and warmed to 0 °C over a period of 4 hours. The reaction mixture was then poured into water (5 mL), the pH was adjusted to 12 by the addition of 10% NaOH solution, and the mixture was washed with $Et_2O$. The aqueous solution was then acidified with citric acid and extracted with $CH_2Cl_2$. The extract was dried and evaporated, yielding 33 mg (66%) of the desired formylation product (as a mixture aldehyde and enol forms). The formylation product was dissolved in dry MeOH (2 mL) and acetyl chloride (1 mL) was slowly added at 0 °C. The reaction mixture was allowed to warm to 25 °C and stirred overnight, afterwhich it was quenched with solid $NaHCO_3$. The resulting suspension was extracted with $CH_2Cl_2$ (3 X 5 mL). The extracts were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure to yield 22 mg (75%) of the desired, crude dimethylacetal. This substance was dissolved in DMF (6 mL) and treated with potassium *tert*-butoxide (KO*t*Bu)[5](11 mg, 0.09 mmol, 2.0 equiv) at 25 °C. After 18 hours, the reaction mixture was quenched by the addition of water, and extracted with EtOAc (3 X 10 mL). The combined organic extracts were washed with water several times, and dried over anhydrous $Na_2SO_4$. The dried solution was then filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (1:5 MeOH/EtOAc) to afford 19 mg (87%) of methyl enol ether (vinylogous carbonate) **13**. TLC: $R_f$ = 0.30 (1:6 MeOH/EtOAc); IR (film) 3316, 2938, 2849, 1682, 1614, 1455, 1241, 811, 733 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.34 (s, 1 H), 5.80 (d, *J* = 1.7 Hz, 1 H), 5.72 (d, *J* = 1.7 Hz, 1 H), 5.10 (q, *J* = 6.6 Hz, 1 H), 3.97 (d, *J* = 13.1 Hz, 1 H), 3.82 (s, 3 H), 3.78 (s, 3 H), 3.74 (s, 3 H), 3.63 (s, 3 H), 3.26 (d, *J* = 12.6 Hz, 1 H), 3.23 (dt, *J* = 9.0, 3.0 Hz, 1 H), 2.73 (br s, 1 H), 2.57 (br s, 2 H), 2.49 (dt, *J* = 17.0, 8.5 Hz, 1 H), 2.29 (q, *J* = 12.4 Hz, 1 H), 1.88 (m, 1 H), 1.56 (d, *J* = 6.8 Hz, 3 H), 1.34 (t, *J* = 12.7, 3.0 Hz, 1 H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 197.7, 169.1, 168.6, 162.9, 160.5, 159.7, 135.4, 111.0, 118.2, 103.8, 90.1, 86.7, 72.4, 74.2, 61.7, 55.7, 55.6, 51.3, 51.1 (2 C), 38.7, 35.1, 28.0, 13.1; HRMS (ESI-TOF) exact mass calculated for $[M+H]^+$ ($C_{24}H_{31}N_2O_6$) = 443.2177, found 443.2184.

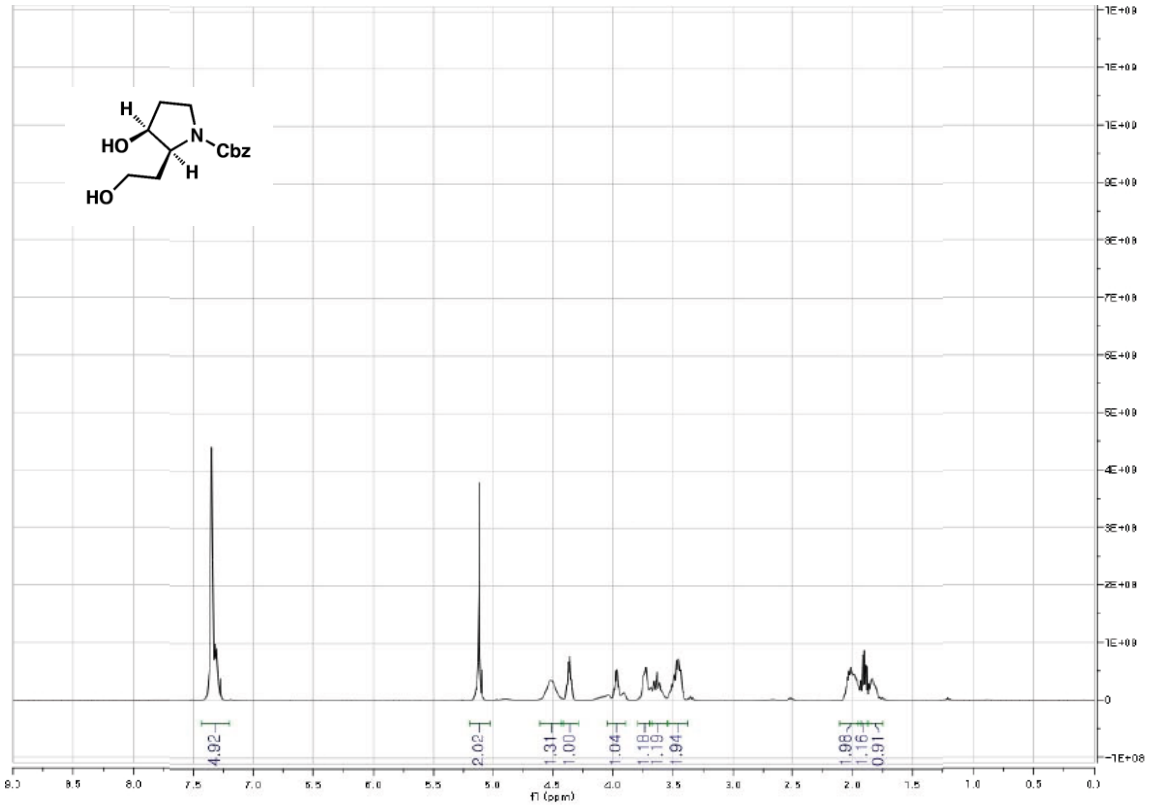


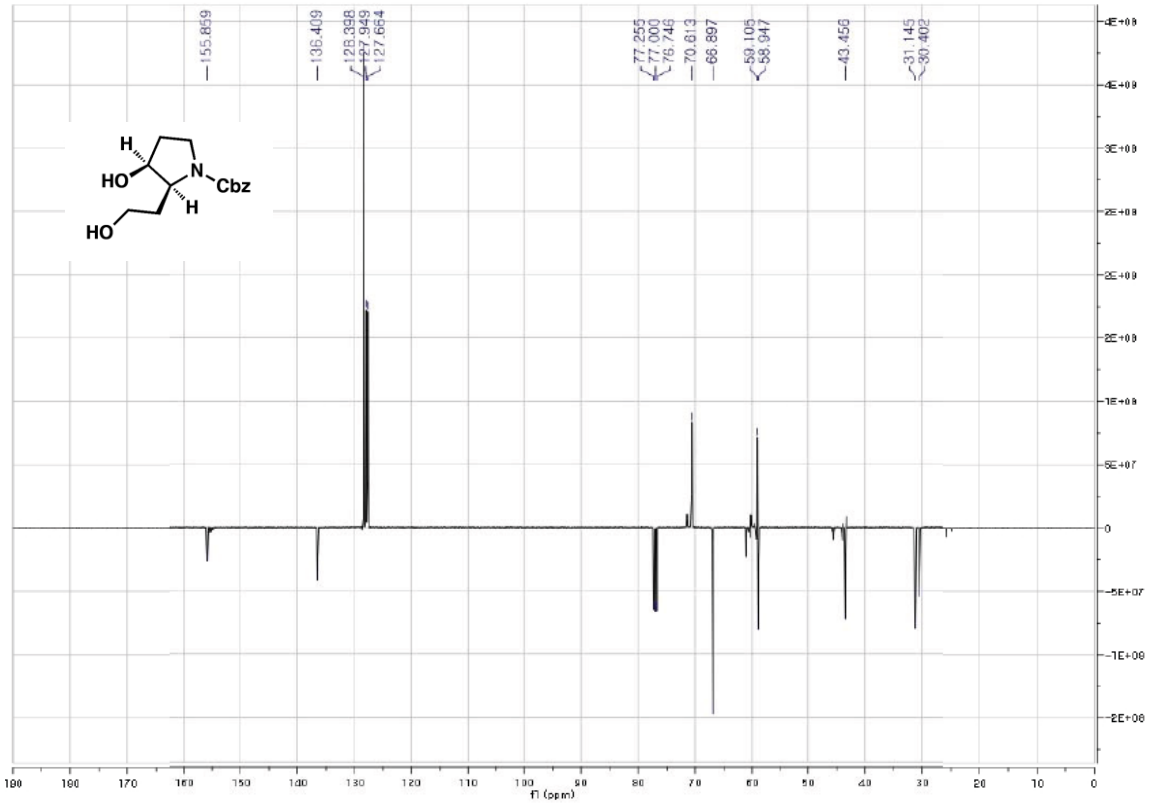
**13** **5**

**11-Methoxy mitragynine pseudoindoxyl** (**5**)**:** Adam's catalyst ($PtO_2$) (6 mg, 0.02 mmol, 0.5 equiv) was added to a solution of vinylogous carbonate **13** (18 mg, 0.04 mmol, 1.0 equiv) in methanol (MeOH) (1 mL) and the resulting mixture was filled with 1 atm $H_2$. After 5 hours, the suspension was filtered through Celite; the filtrate was concentrated and the resulting residue purified by flash column chromatography (1:8 MeOH/EtOAc) to afford 14 mg (72%) of 11-methoxy mitragynine pseudoindoxyl (**5**). TLC: $R_f$ = 0.40 (1:8 MeOH/EtOAc); IR (film) 3321, 2937, 1679, 1616, 1460, 1245,

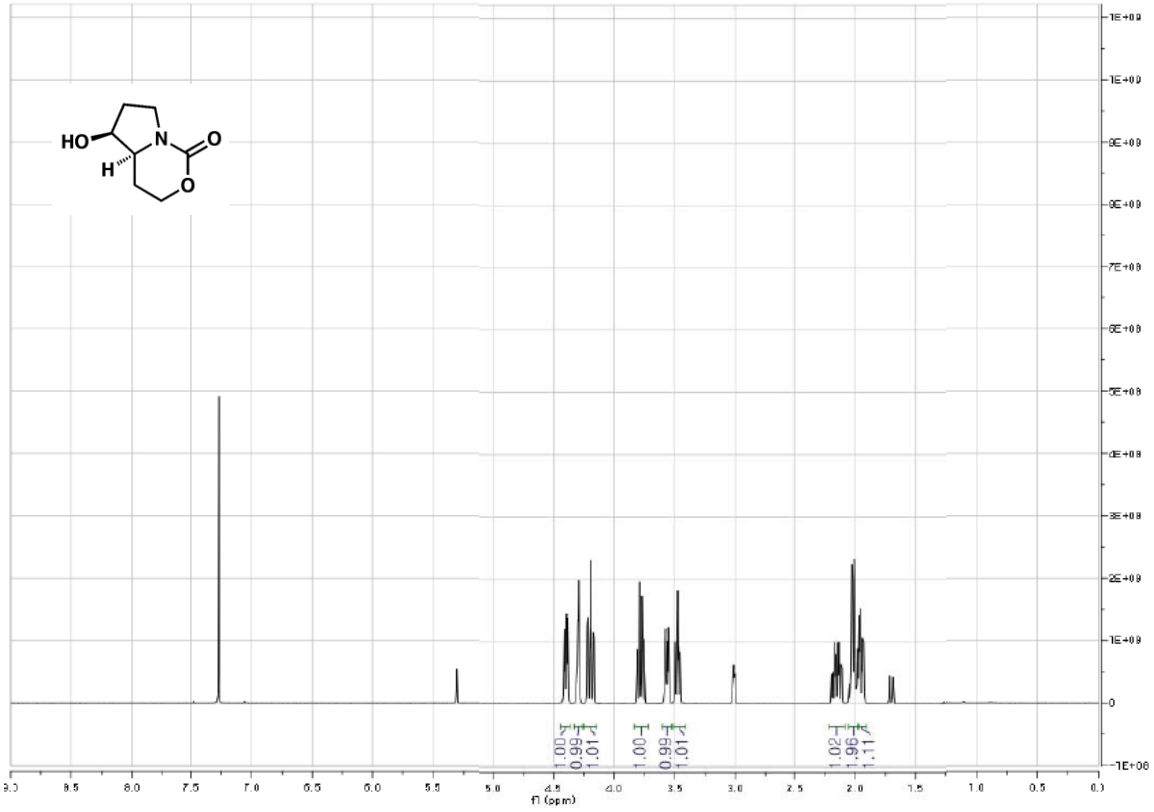
1156 $cm^{-1}$; $^{1}H$ NMR (500 MHz, $CDCl_3$) δ 7.30 (s, 1 H), 5.79 (d, *J* = 1.7 Hz, 1 H), 5.74 (s, *J* = 1.7 Hz, 1 H), 4.52 (br s, 1 H), 3.84 (s, 3 H), 3.78 (s, 3 H), 3.66 (s, 3 H), 3.62 (s, 3 H), 3.14 (m, 2 H), 2.63 (dt, *J* = 10.2, 2.7 Hz, 1 H), 2.40 (m, 1 H), 2.26 (q, *J* = 12.6 Hz, 1 H), 2.18 (q, *J* = 9.4 Hz, 1 H), 1.96 (br s, 2 H), 1.73 (m, 2 H), 1.43 (m, 1 H), 1.14 (m, 2 H), 0.80 (t, *J* = 7.4 Hz, 3 H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 197.7, 169.3, 168.7, 163.1, 160.6, 159.7, 111.0, 104.0, 90.0, 86.6, 75.7, 73.9, 61.8, 55.7, 55.6, 55.1, 54.0, 51.3, 40.5, 40.2, 35.0, 24.6, 19.0, 13.0; HRMS (ESI-TOF) exact mass calculated for $[M+H]^+$ ($C_{24}H_{33}N_2O_6$) = 445.2333, found 445.2338.

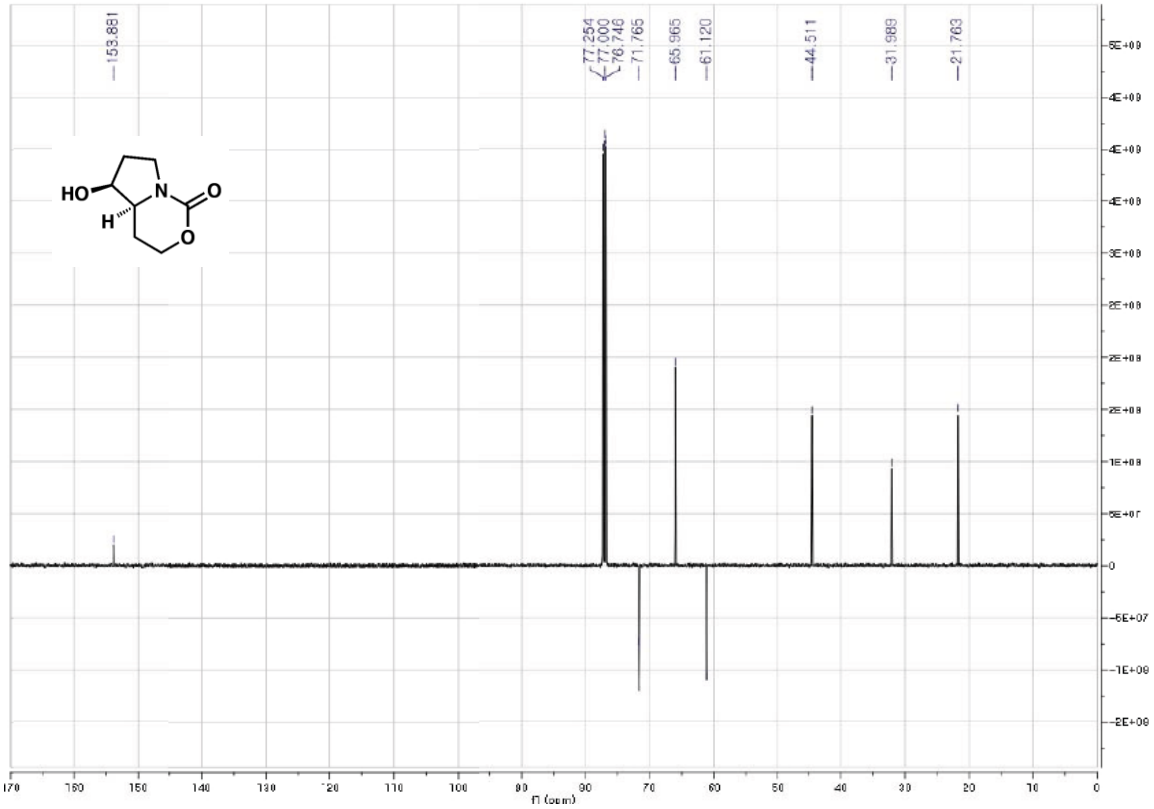
**Diol (S1)**



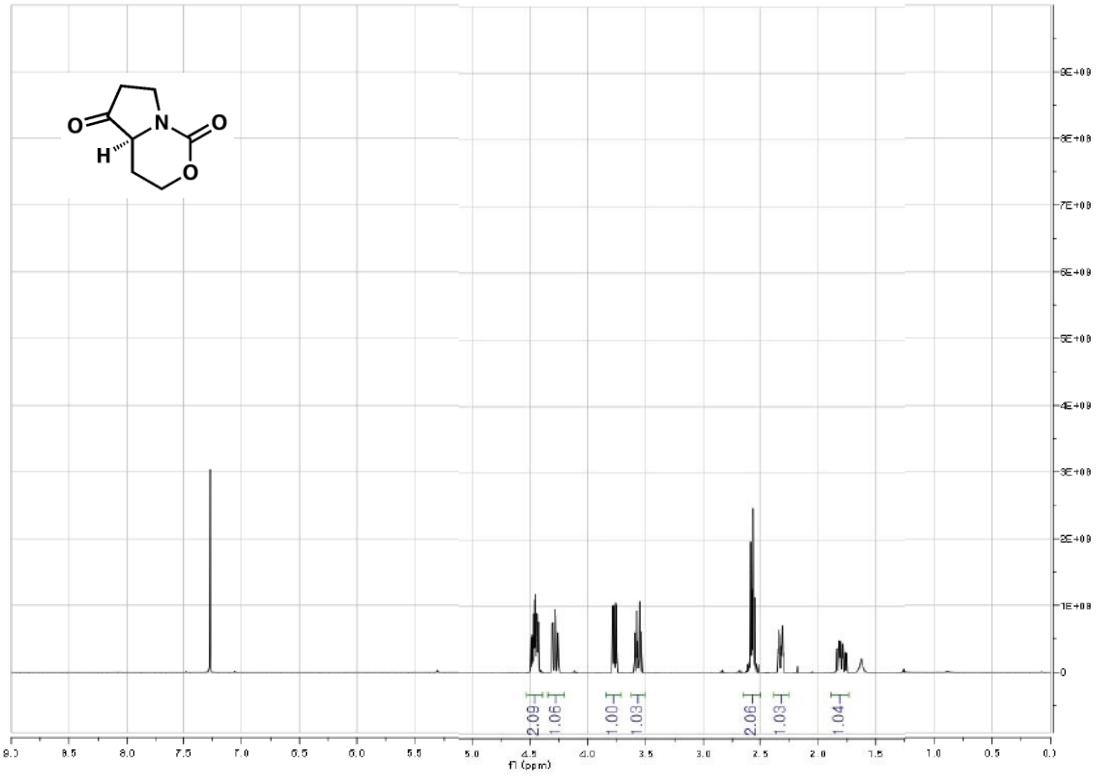



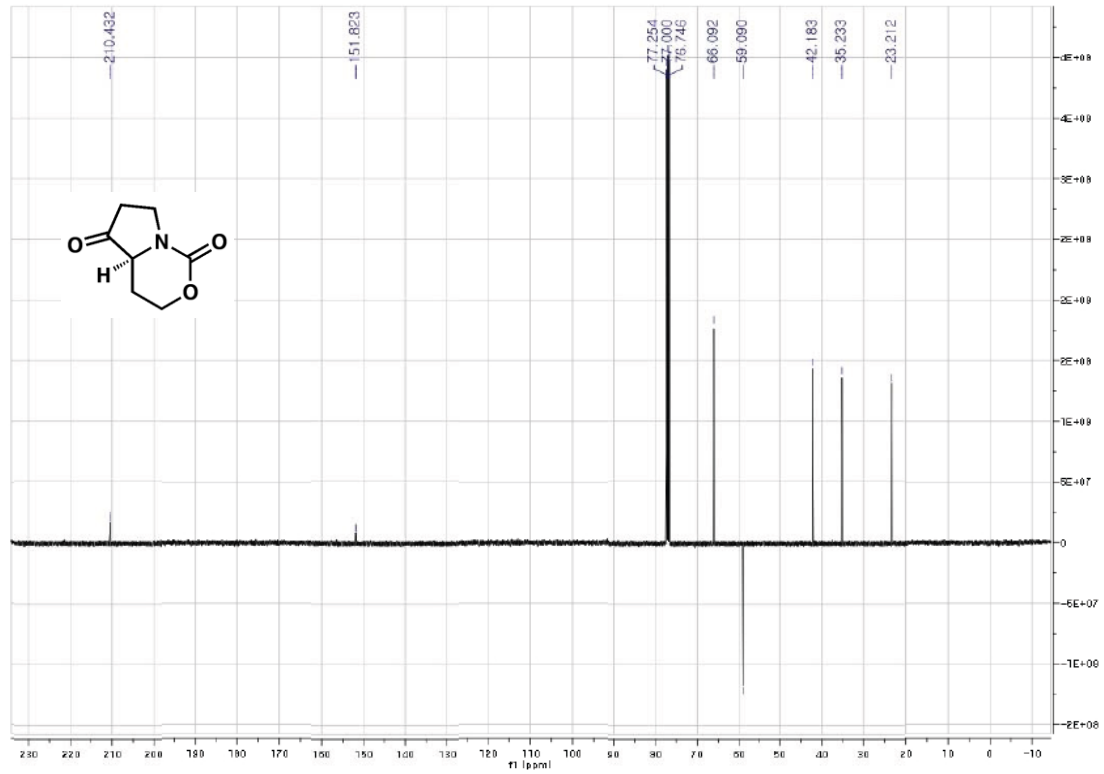
## 5-Hydroxy-hexahydropyrrolo[1,2-*c*][1,3]oxazin-1-one (S2)



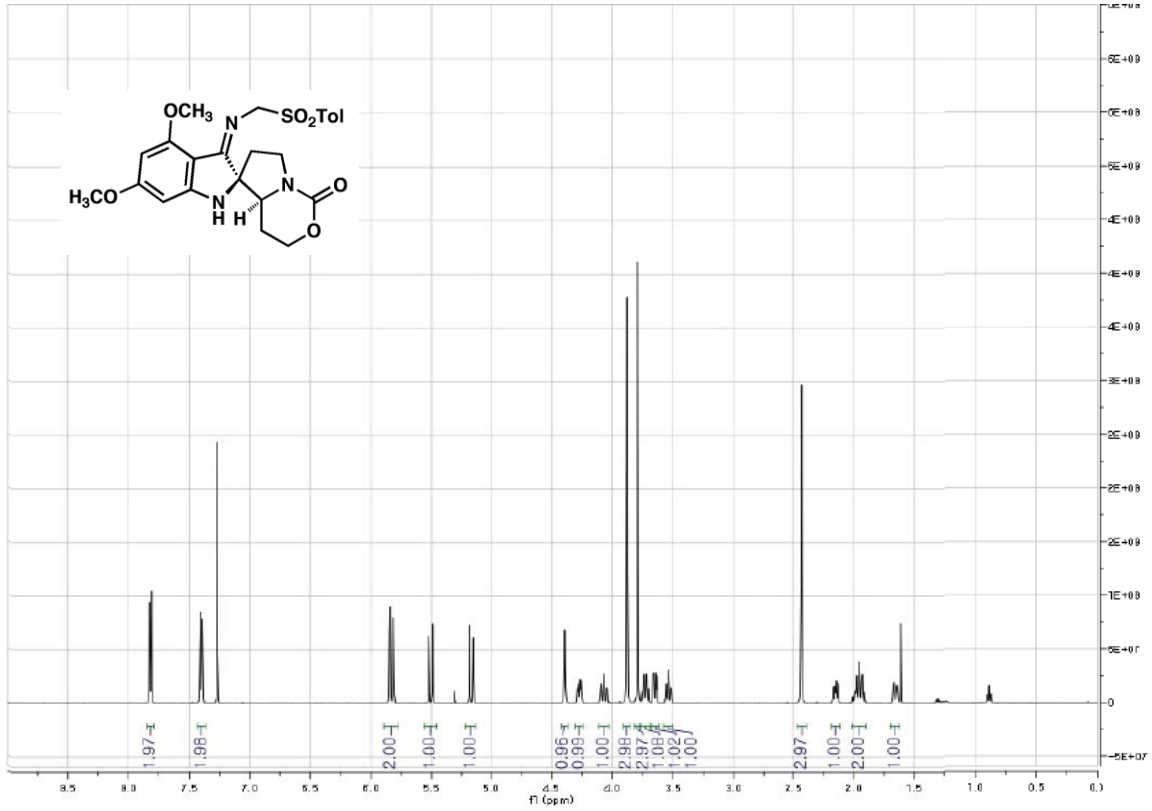



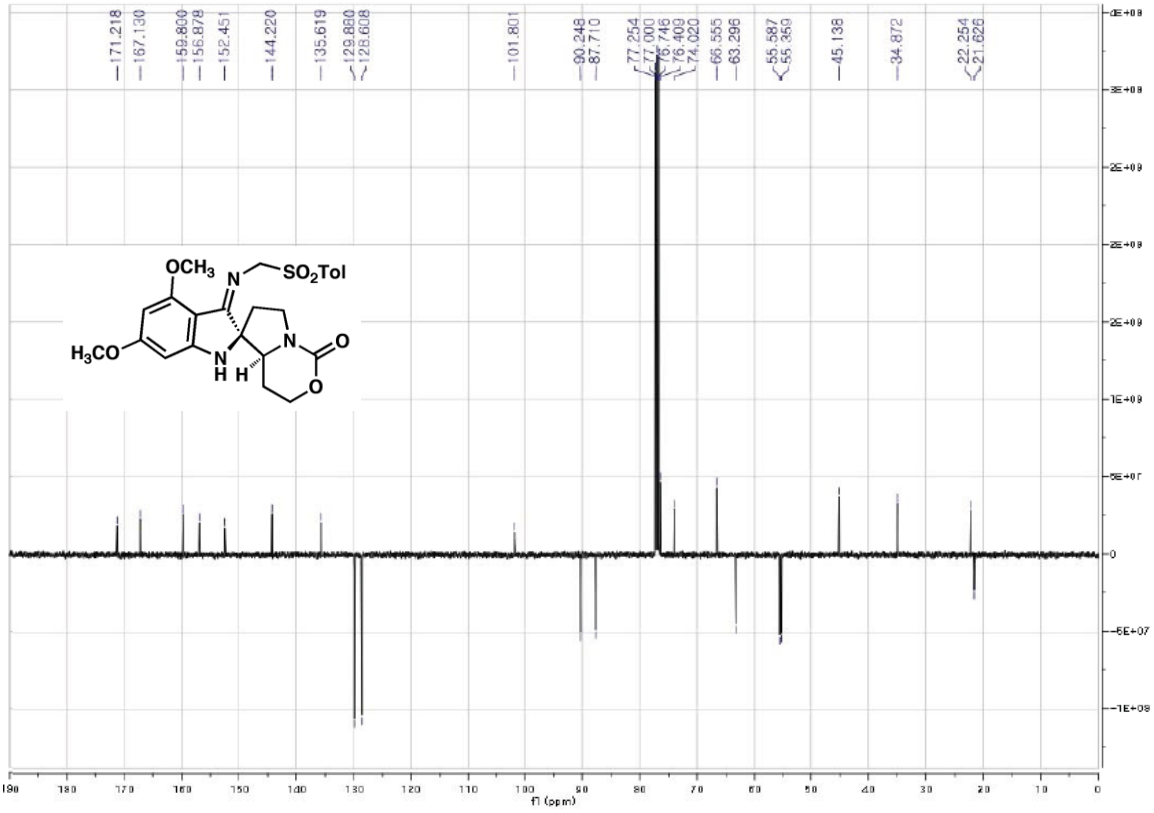
## **Carbamate** (7)



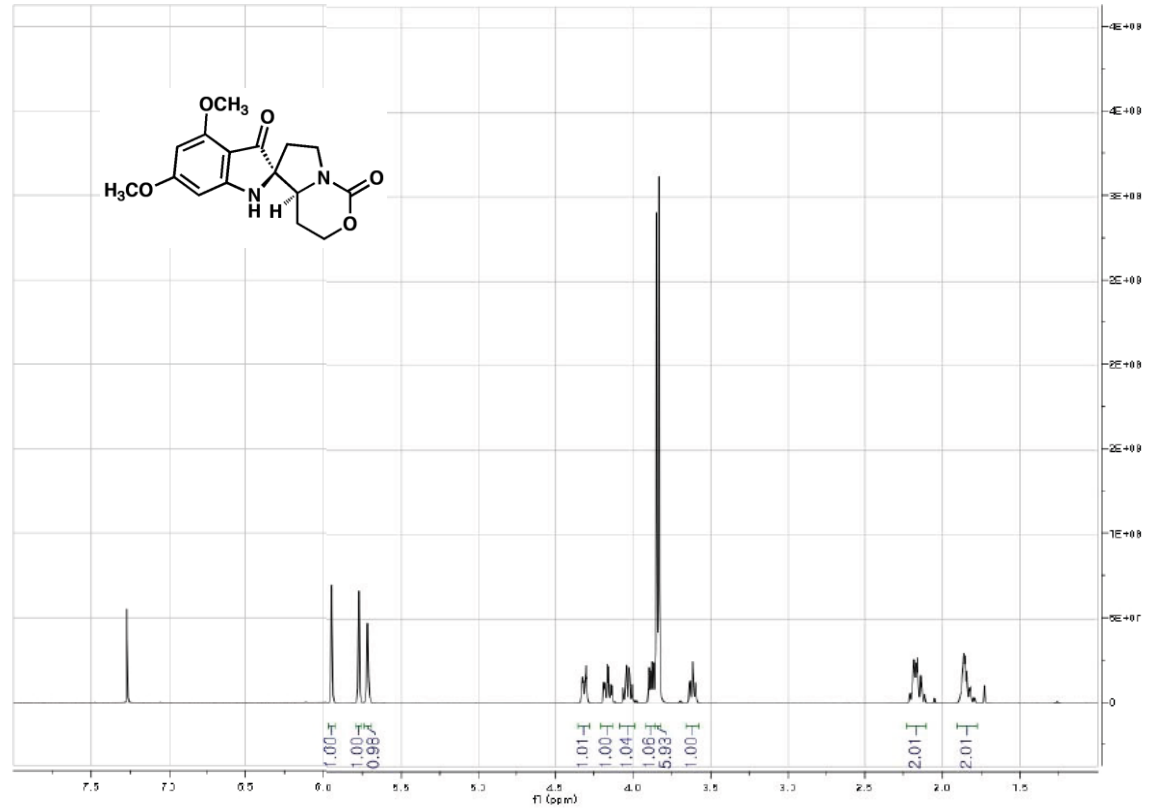



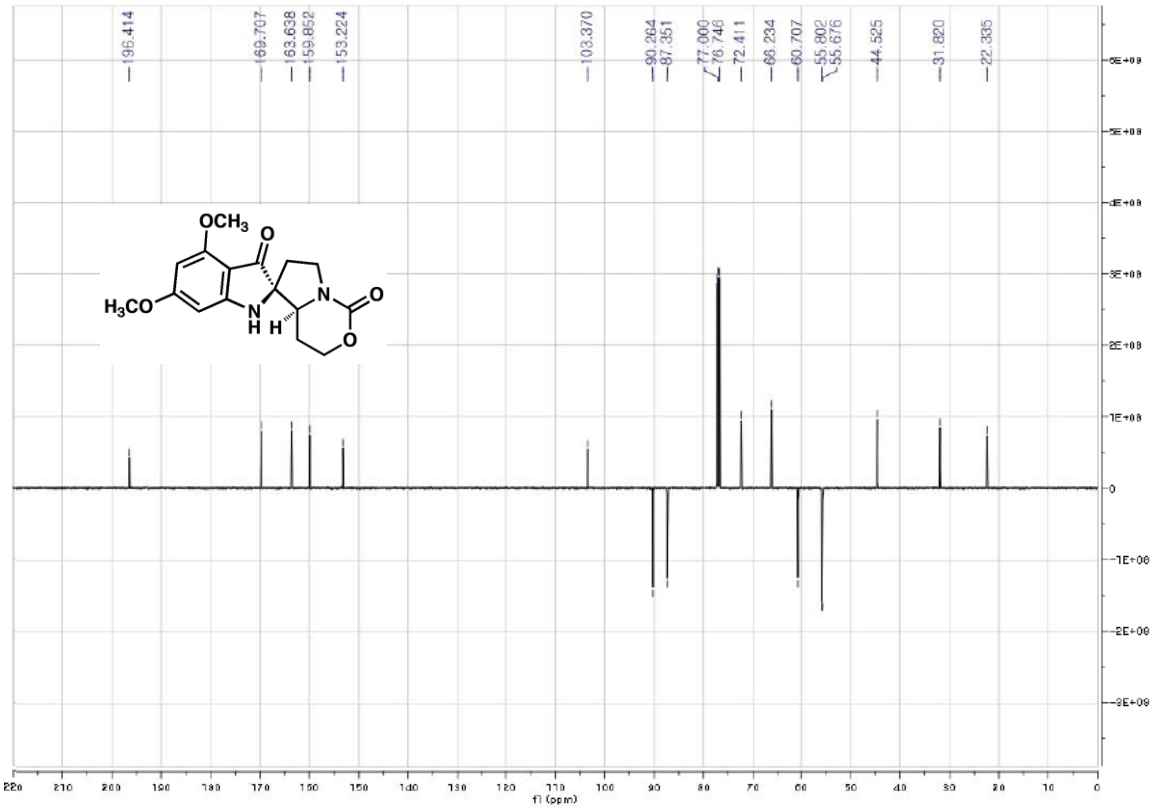
## Interrupted Ugi product (S3)



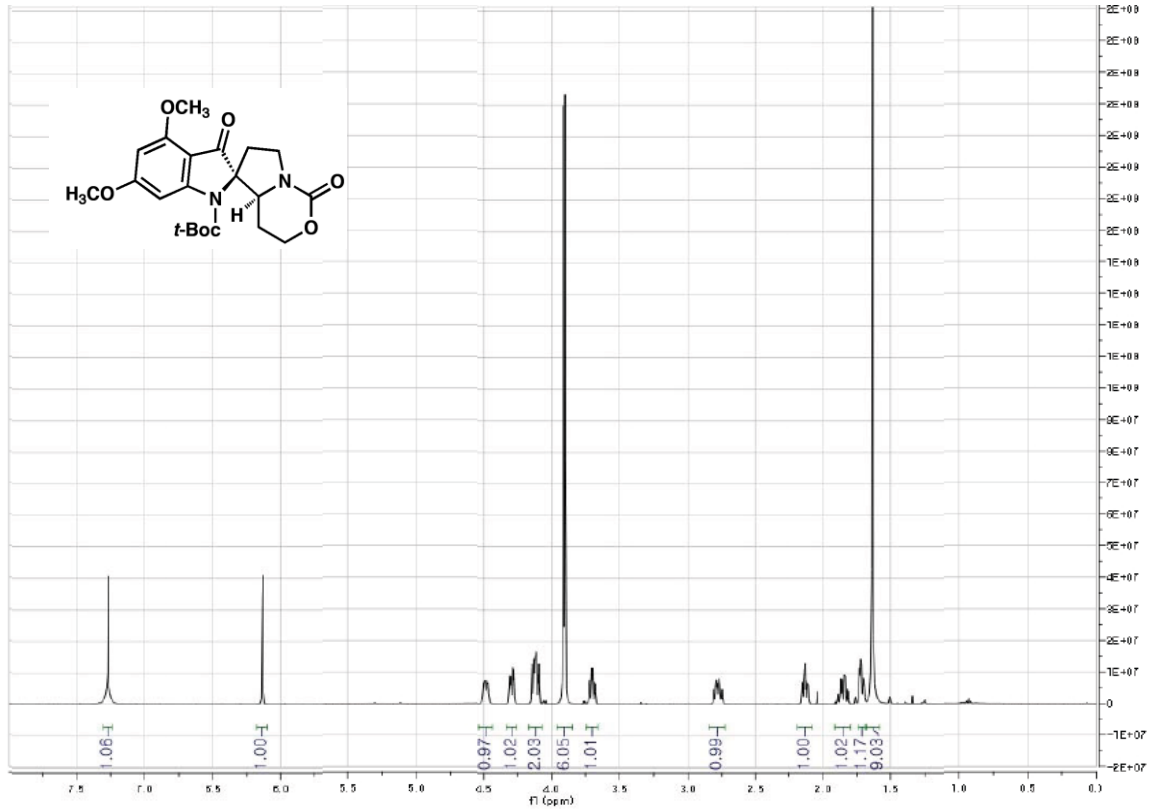



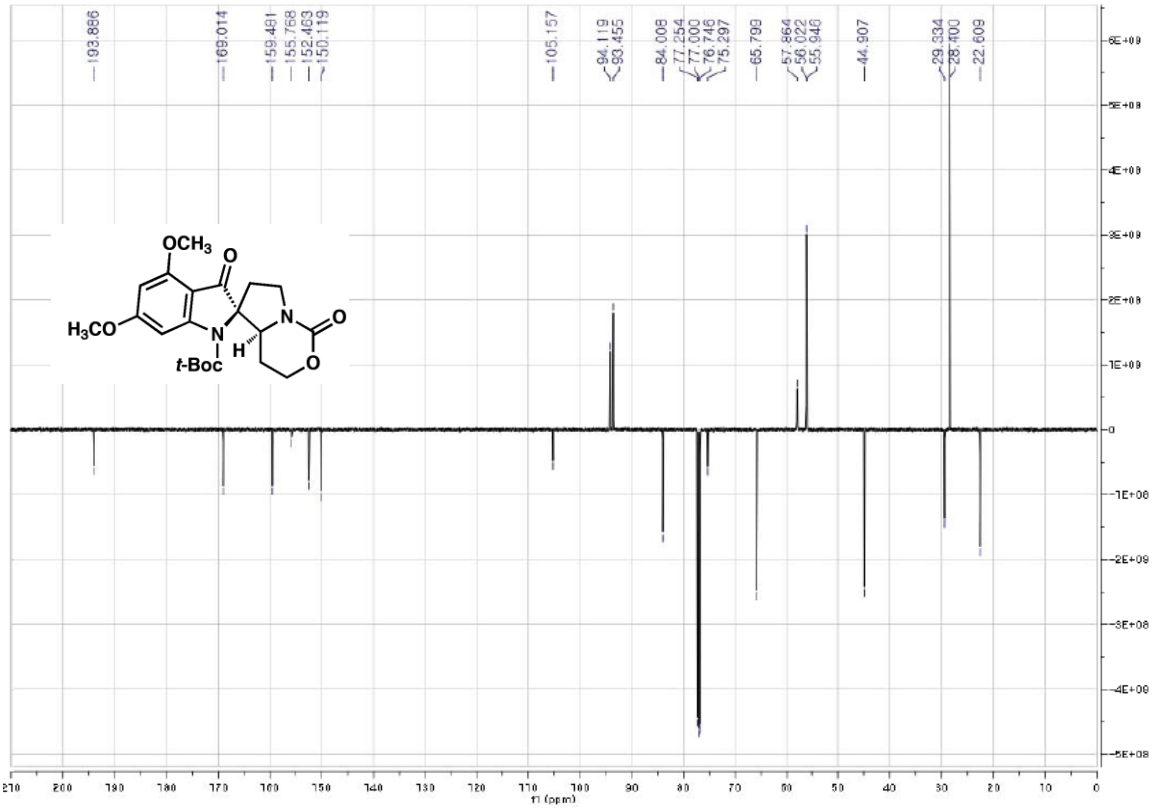
## Indoxyl (8)



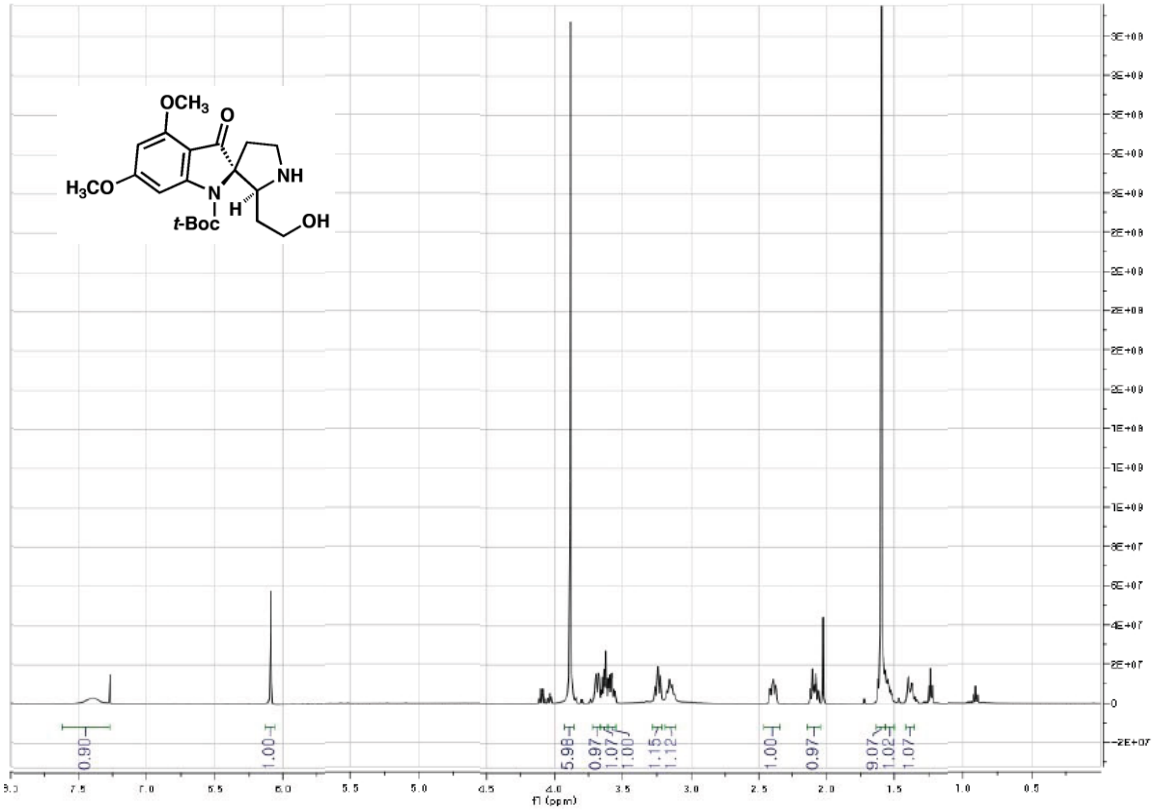



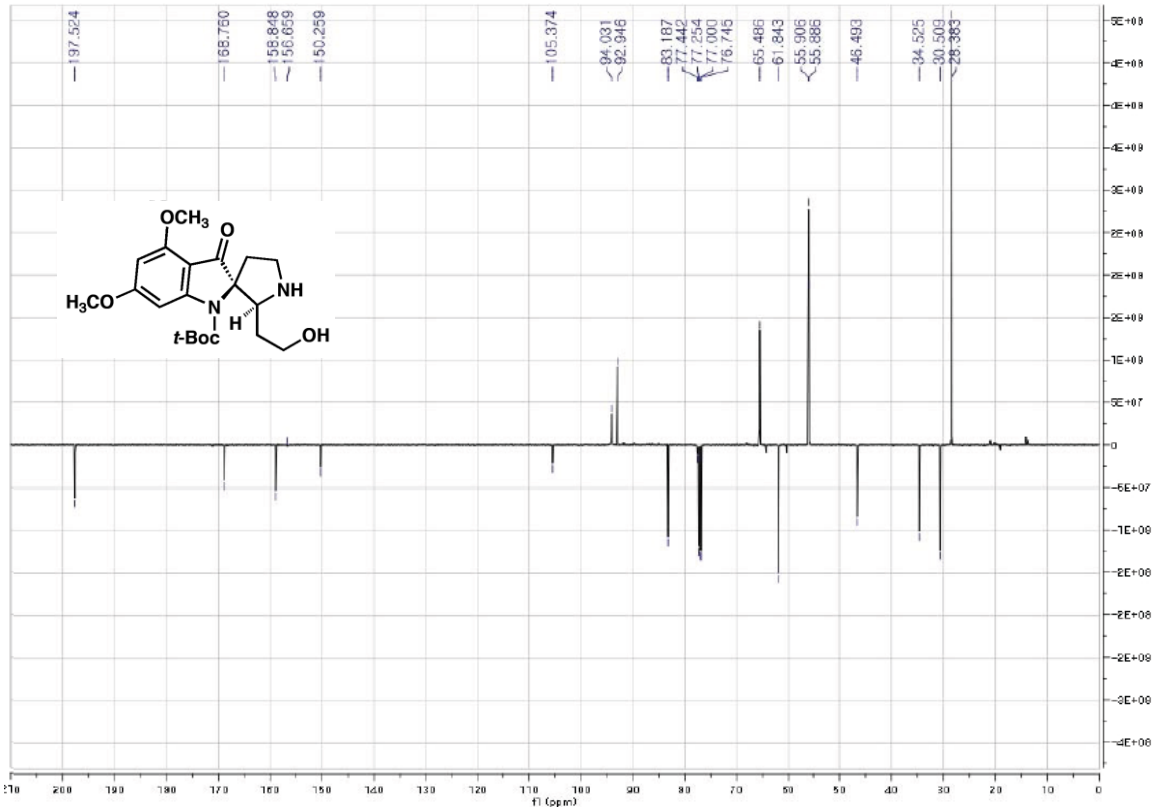
## Boc-protected indoxyl (S4)



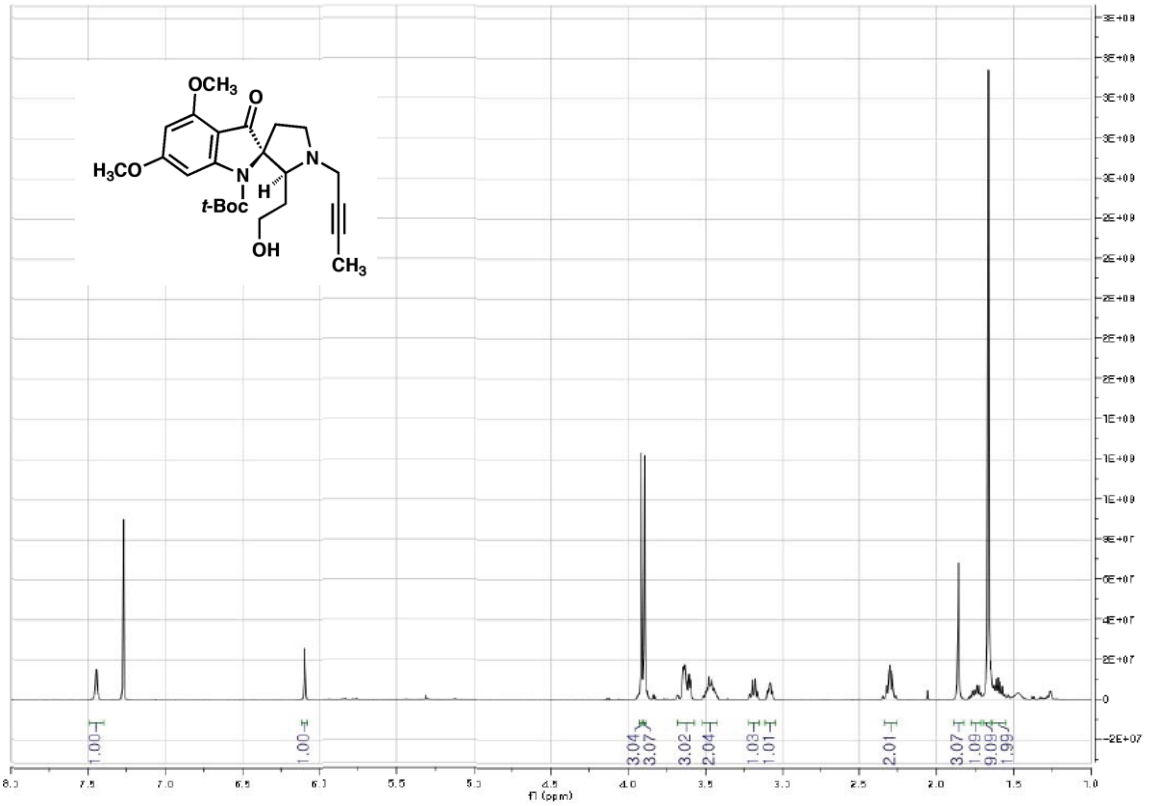



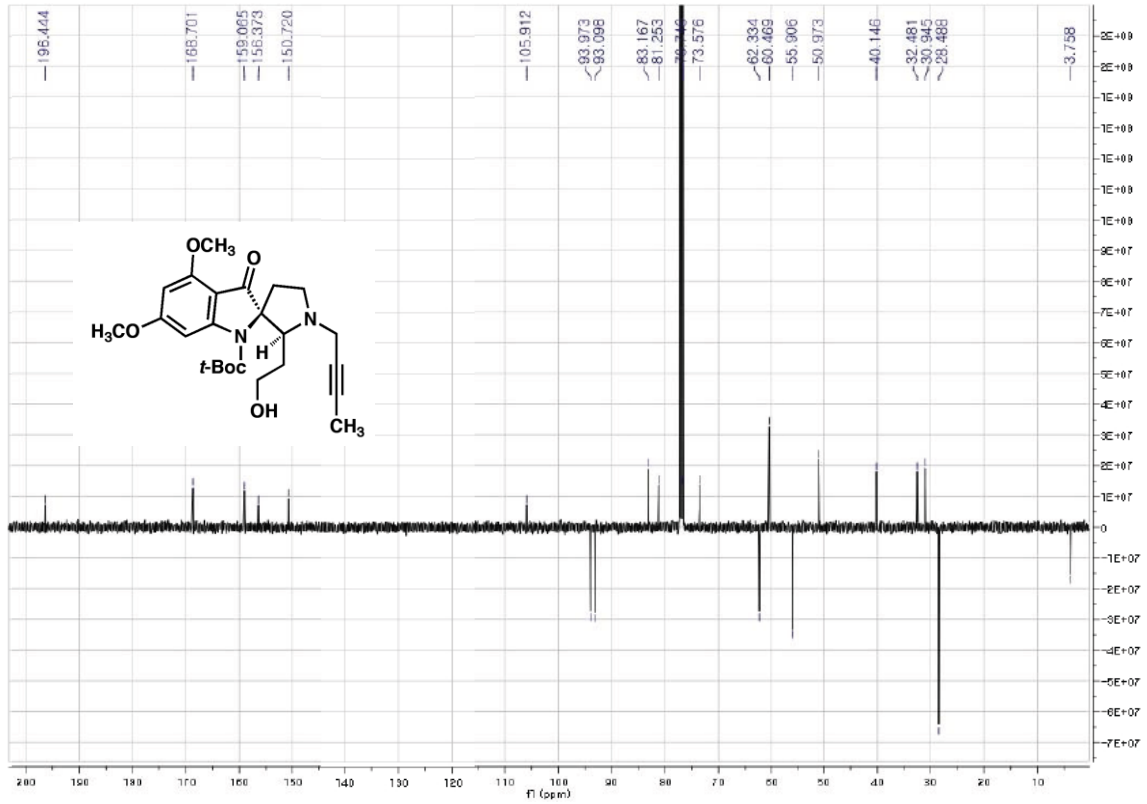
## Amino alcohol (S5)



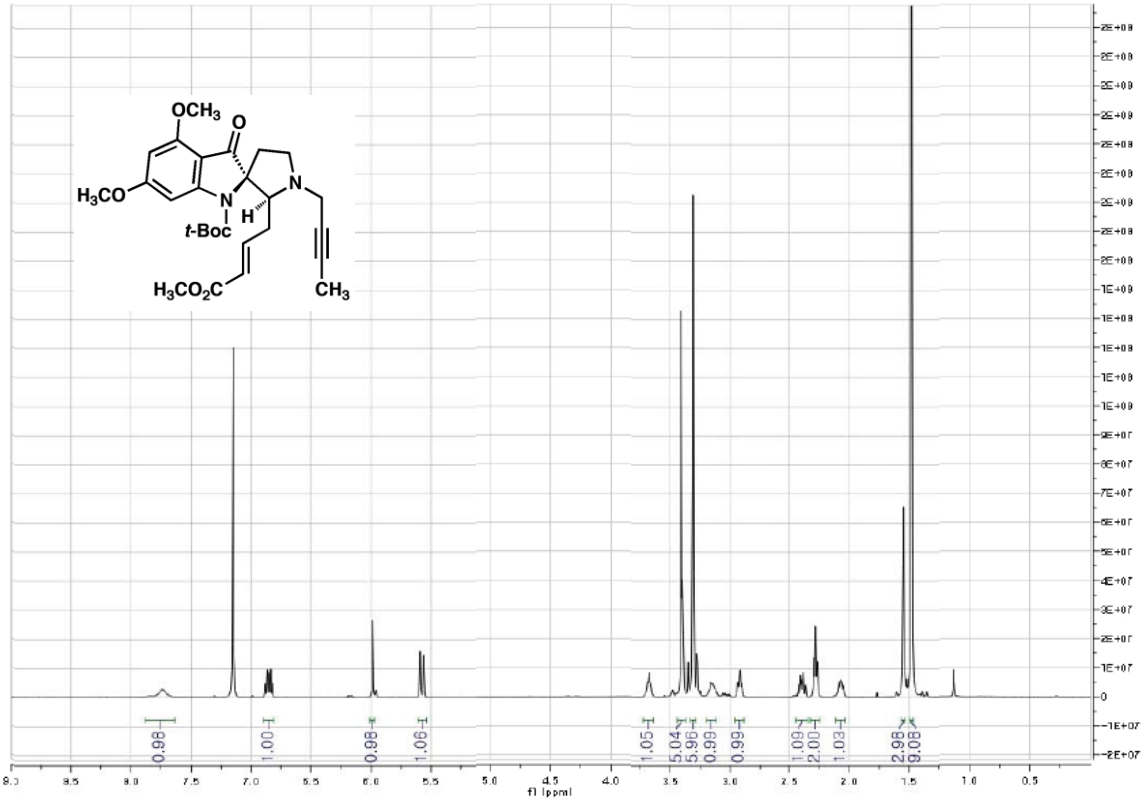



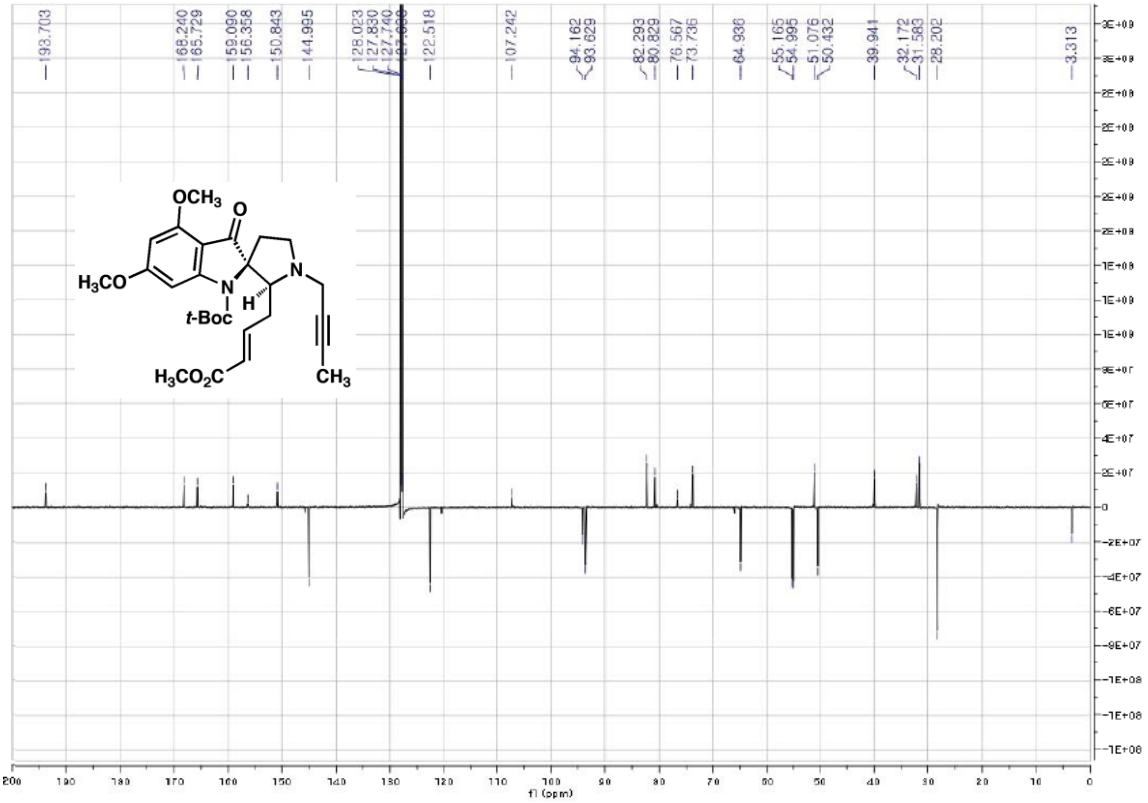
## Alkynyl alcohol (9)



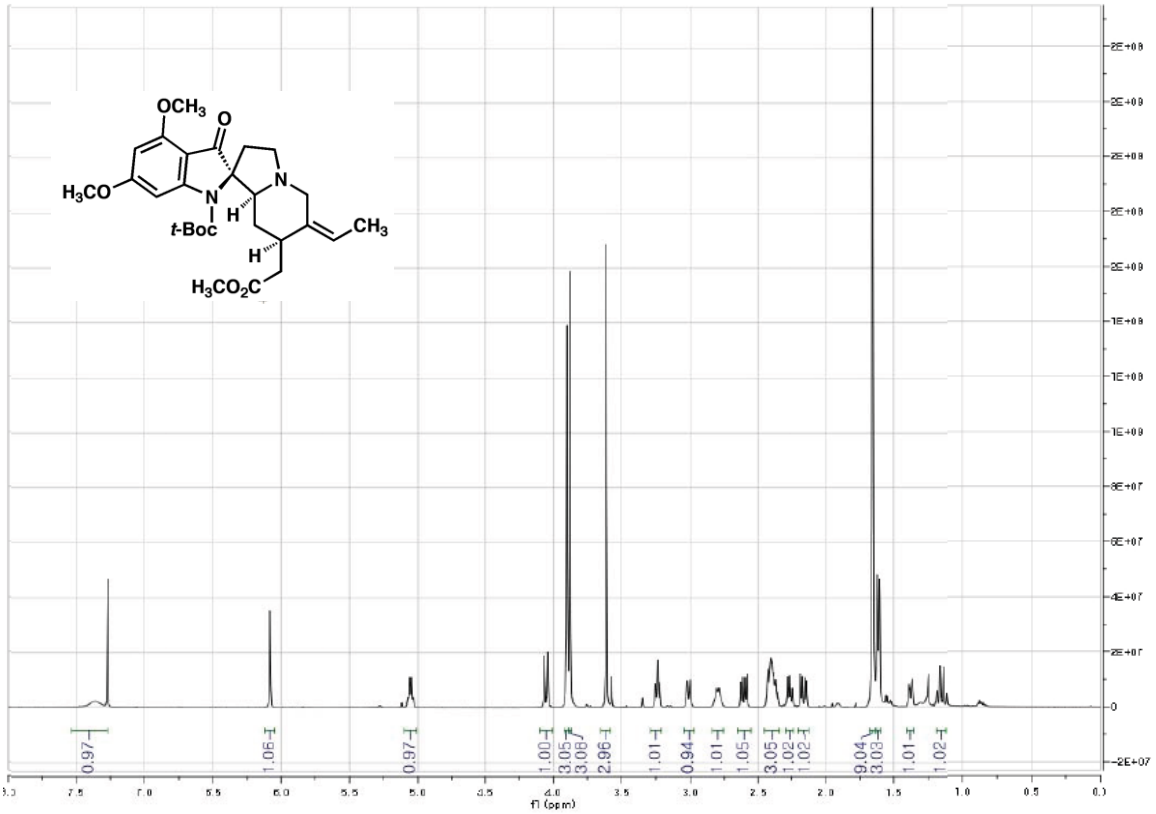



## 1,7-Enyne (10)

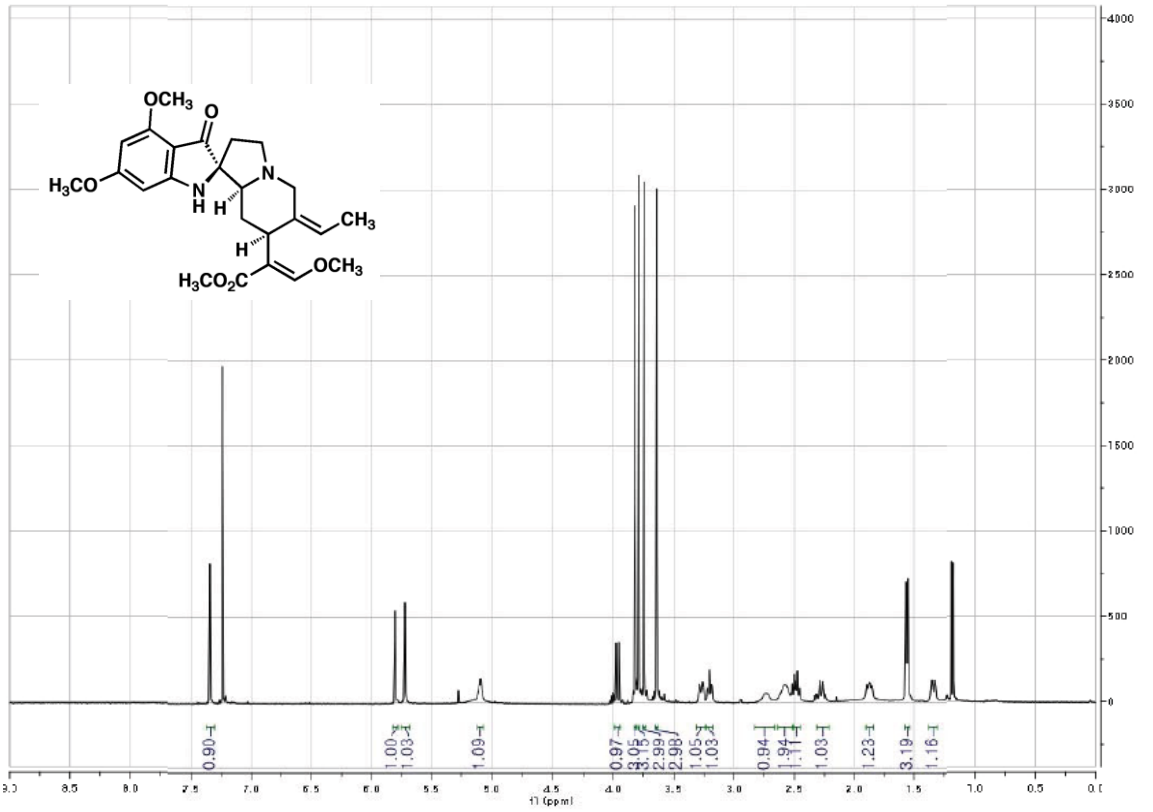


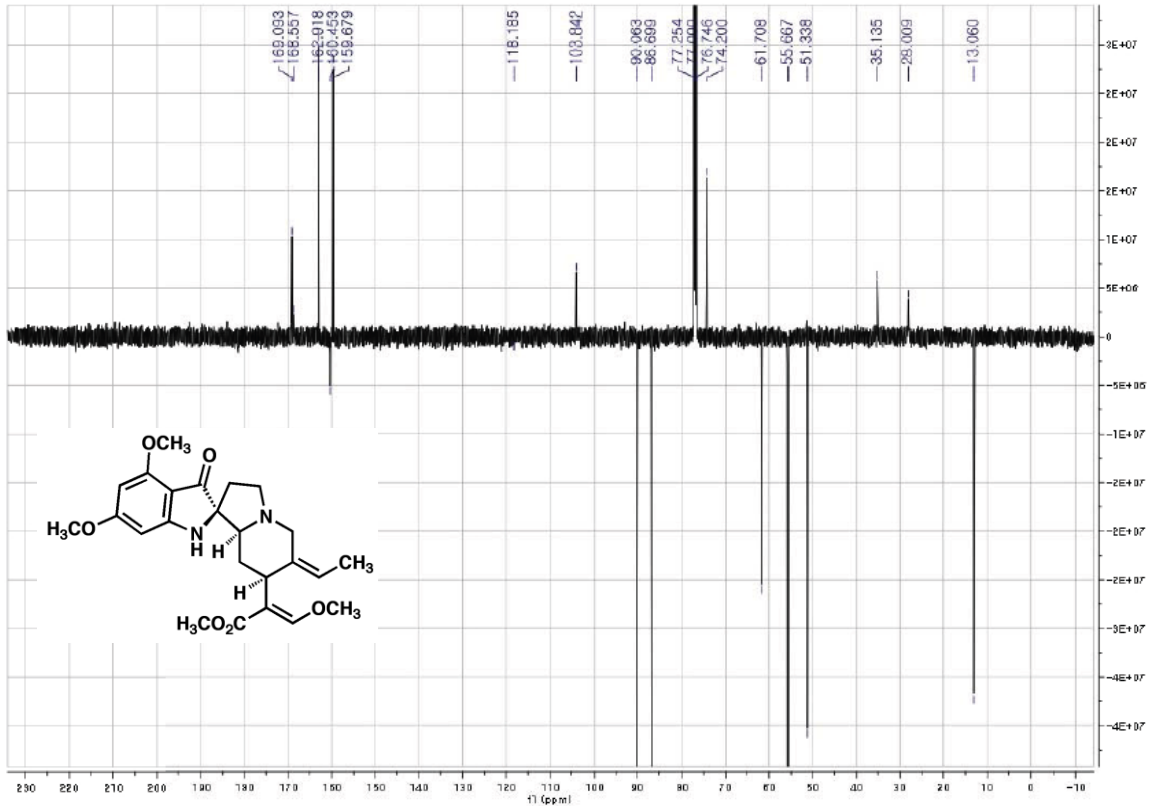



## Tetracyclic piperidine (12)

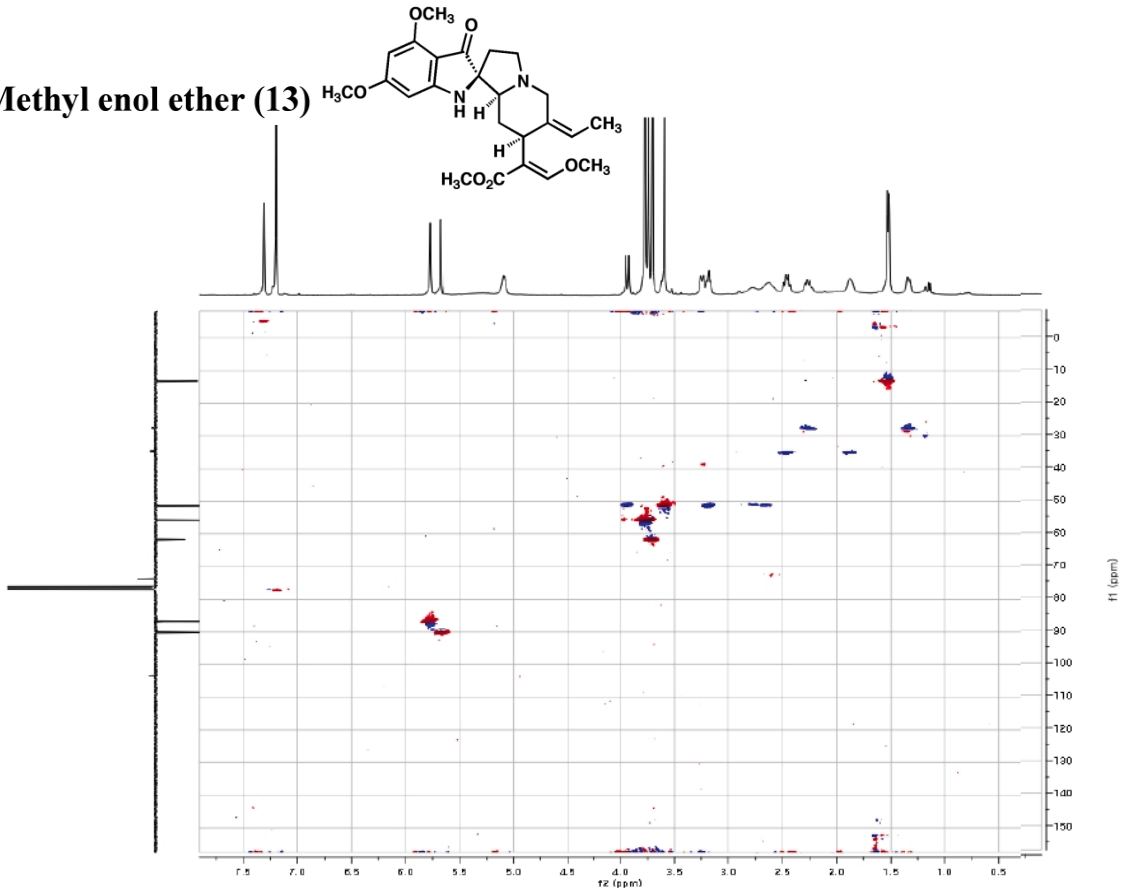


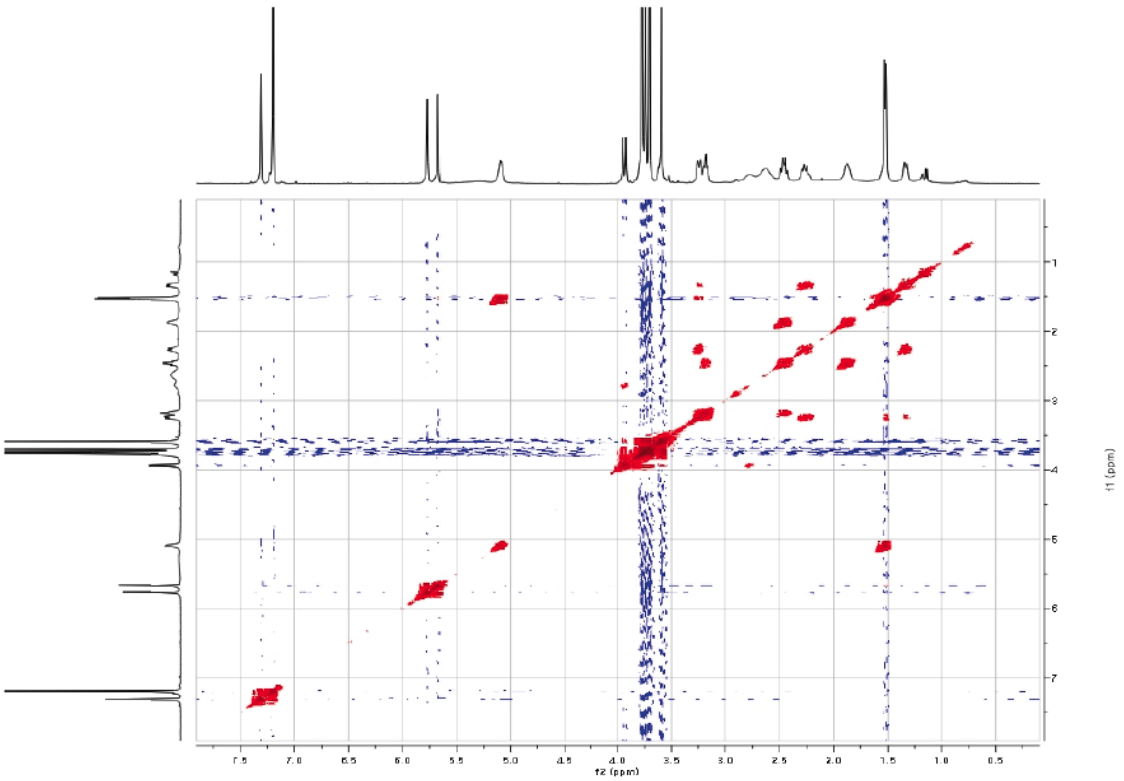

## Methyl enol ether (13)



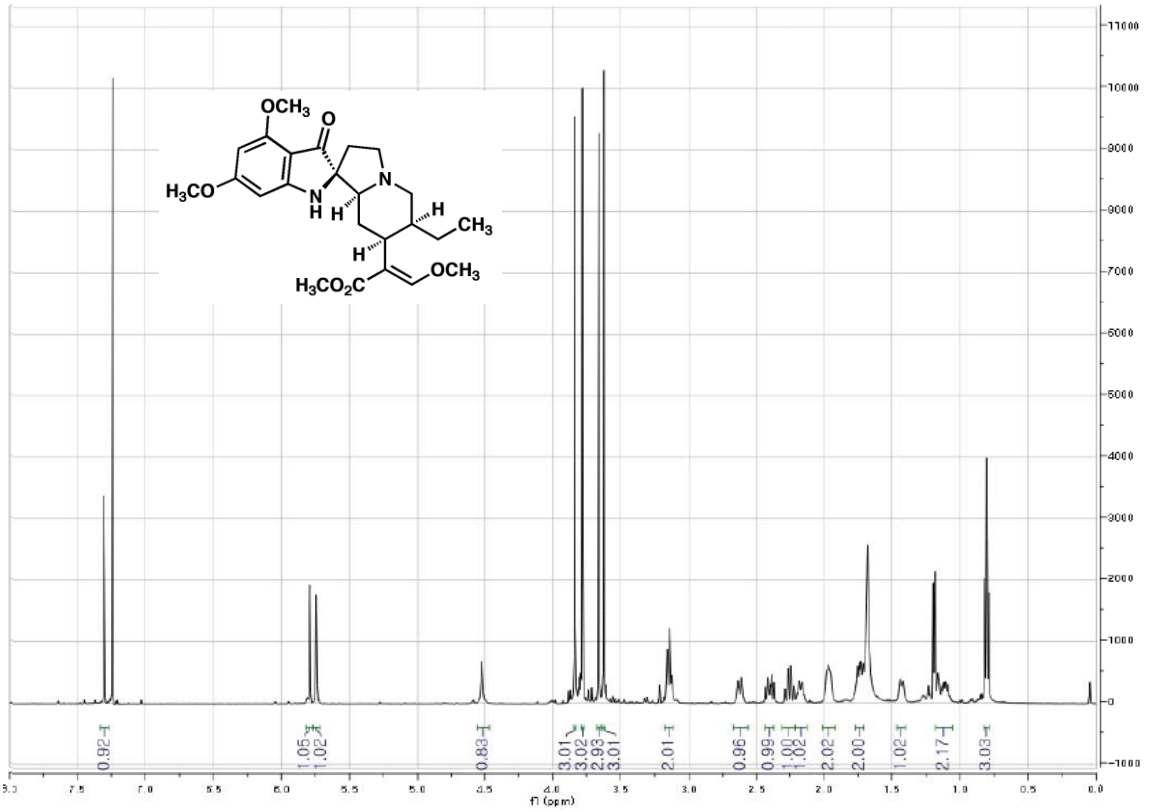



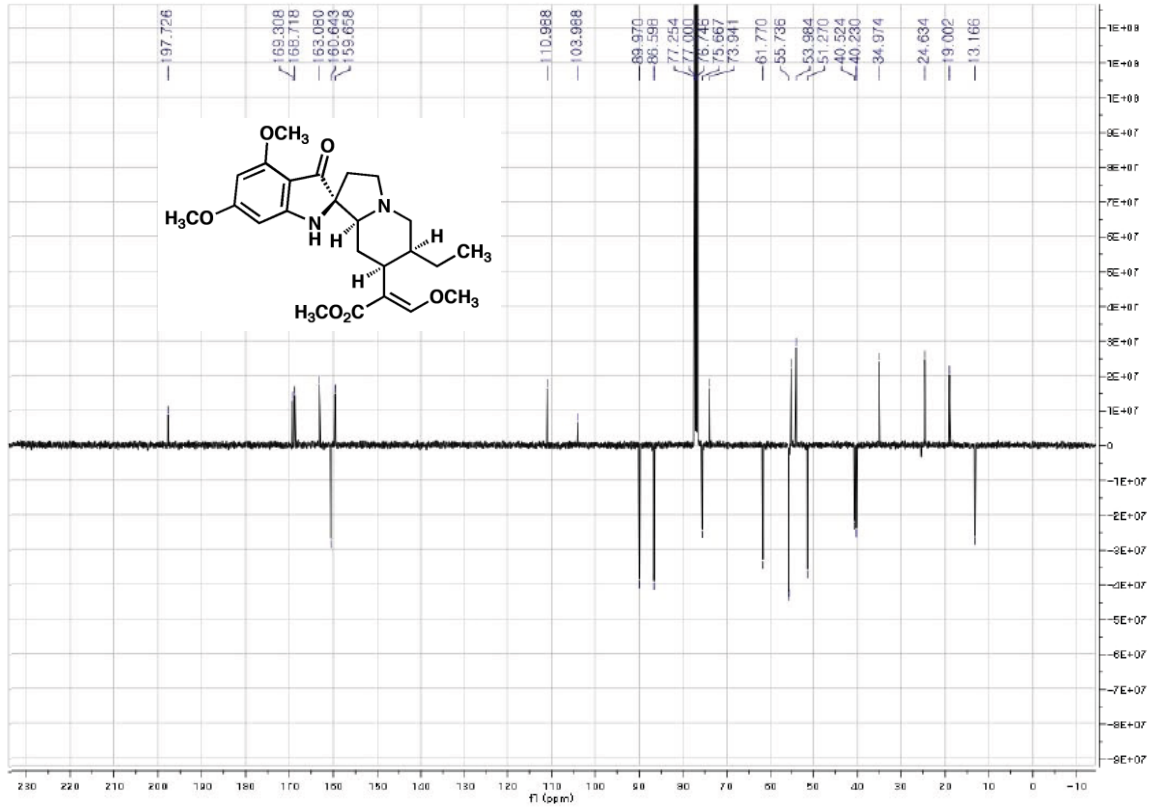
**Methyl enol ether (13)**



## 11-Methoxy mitragynine pseudoindoxyl (5)



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