Supporting Information

Construction of Tetracyclic 3-Spirooxindole through Cross Dehydrogenation of Pyridinium: Applications in Facile Synthesis of (±)-Corynoxine and (±)-Corynoxine B

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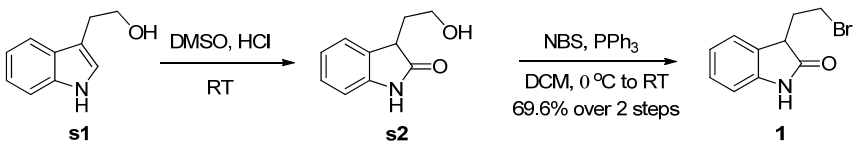
List of Supporting Information

1. General Methods.

Anhydrous THF, Et_2O, toluene and benzene were distilled over sodium and benzophenone ketyl under N_2; Et_3N, DCM and CH_3CN were refluxed with CaH_2 and freshly distilled prior to use; anhydrous MeOH and EtOH were distilled over magnesium under Ar_2; all other solvents and reagents were used from commercial sources without further purifications. All reactions sensitive to air or moisture were carried out under argon or nitrogen atmosphere in dry and freshly distilled solvents under anhydrous conditions, unless otherwise noted.

The silica gel (200-300 meshes) was used for column chromatography. Thin layer chromatographies (TLC) were carried out on GF254 plates (0.25 mm layer thickness). ^{1}H NMR and ^{13}C NMR experiments were performed on Bruker AM-400 and DRX-600 NMR spectrometer at ambient temperature. The residual solvent protons (^{1}H) or the solvent carbons (^{13}C) were used as internal standards. ^{1}H NMR data were presented as follows: chemical shift in ppm downfield from tetramethylsilane (multiplicity, coupling constant, integration). Chemical shifts (δ) were given in ppm with reference to solvent signals [^{1}H NMR: $CDCl_3$ (7.26), CD_3OD (3.31), DMSO-d_6 (2.50); ^{13}C NMR: $CDCl_3$ (77.16), CD_3OD (49.00), DMSO-d_6 (39.52)]. The following abbreviations are used in reporting NMR data: s, singlet; brs, broad singlet; d, doublet; t, triplet; q, quartet; qt, quartet of triplets; dd, doublet of doublets; dt, doublet of triplets; AB, AB quartet; m, multiplet. HRMS (ESI) was taken on Agilent 6540 Q-TOF spectrometer. Melting points were measured on a WRX-5A melting point apparatus and were uncorrected.

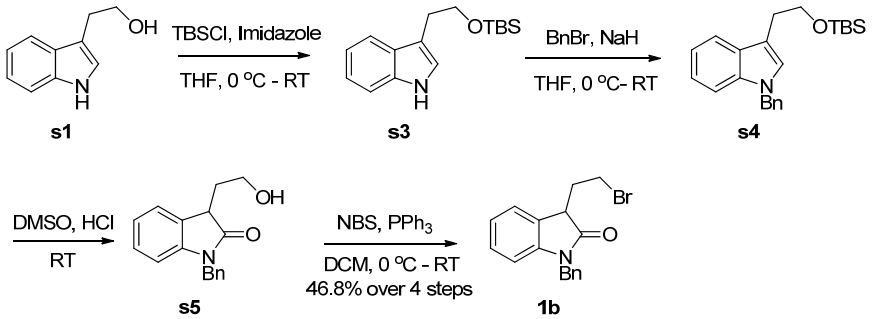
2. General procedure for the synthesis of substrates



s1 **s2** **1**

To a solution of 3-hydroxyethyl oxindole **s1** (3.20 g, 20 mmol) in DMSO (10 mL) was added dropwise conc. HCl (14 mL) at room temperature. The resulting dark

solution was stirred for 3 minutes at room temperature and then poured into ice-water (100 mL). Aqueous sodium hydroxide (30%) was added slowly to bring the pH of the solution to ~7 and the resulting solution was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give the crude oxindole **s2**, which was used without further purification. To an ice-water bath cooled solution of crude product **s2** and PPh_3 (8.90 g, 20 mmol) in DCM (20 mL) was added NBS (3.56 g, 20 mmol) in small portions. The mixture was warmed up to room temperature and allowed to stir for 20 minutes (monitored by TLC), the reaction was quenched with water and extracted with 100 mL of DCM. The combined organic extracts were washed with brine (3 × 50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by chromatography (petroleum ether/ethyl acetate = 4:1) to afford desired product **1** as a slightly yellow solid (3.32 g, 69.6% over 2 steps). M.p.: 117-121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (s, 1H), 7.17 (t, J = 7.4 Hz, 2H), 6.98 (t, J = 7.5 Hz, 1H), 6.86 (d, J = 7.8 Hz, 1H), 3.64 (ddd, J = 19.3, 11.2, 7.0 Hz, 2H), 3.52 (dt, J = 10.0, 7.0 Hz, 1H), 2.51 – 2.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.85, 141.60, 128.51, 128.49, 124.30, 122.70, 110.16, 44.59, 34.04, 30.00; HRMS (ESI) calcd. for $C_{10}H_{11}BrNO$ $[M + H]^+$ 240.0019, found 240.0020.



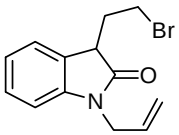
To a solution of 3-hydroxyethyl oxindole **s1** (3.20 g, 20.0 mmol) in 40 mL of THF at 0 °C was slowly added imidazole (1.65 g，24.2 mmol) and TBSCl (3.64 g, 24.2 mmol). The resulting mixture was warmed up to room temperature and allowed to stir for 30 minutes (Monitored by TLC). The reaction was poured into water, extracted with 100 mL of ethyl acetate, washed with brine (3 × 50 mL), dried over

Na_2SO_4, and concentrated under reduced pressure to give crude product **s3** which was not purified for further use.

To a solution of **s3** in 40 mL of THF at 0 ^oC was slowly added NaH (24.2 mmol) and stirred for 10 minutes. Then BnBr (24.2 mmol) was slowly added to the suspension and the resulting mixture was warmed up to room temperature and allowed to stir for 2 h at room temperature. After completion (Monitored by TLC), the reaction was quenched with saturated NH_4Cl (aq.), extracted with 100 mL of ethyl acetate, washed with brine (3 × 50 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give crude product **s4** which was not purified for further use.

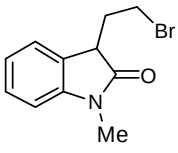
To a solution of above **s4** in DMSO (10 mL) was added dropwise conc. HCl (14 mL) at room temperature. The resulting dark solution was stirred for 30 minutes, and then poured into ice-water (60 mL). Aqueous $NaHCO_3$ was added slowly to bring the PH of the solution to ~7, and extracted with 100 mL of ethyl acetate, washed with brine (3 × 50 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give crude products **s5** which passed a short pad of silica with petroleum ether/ethyl acetate = 4:1 as eluent for further use.

To an ice bath cooled solution of crude product **s5** and PPh_3 (8.90 g, 20 mmol) in DCM (20 mL) was added NBS (3.56 g, 20 mmol) in small portions. The resulting mixture was warmed up to room temperature and allowed to stir for 20 minutes. After completion (monitored by TLC), the reaction was quenched with water and extracted with 100 mL of DCM. The combined organic extracts were washed with brine (3 × 50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography (petroleum ether/ethyl acetate = 10:1) to afford desired product **1b** (3.06 g, 46.8 % over 4 steps) as a slightly yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 6H), 7.19 (t, *J* = 7.7 Hz, 1H), 7.12 – 6.95 (m, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 4.91 (s, 2H), 3.74 (dd, *J* = 11.4, 5.9 Hz, 2H), 3.60 (dd, *J* = 6.4, 3.6 Hz, 1H), 2.47 (dtd, *J* = 21.3, 14.2, 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.20, 143.51, 135.92, 128.95, 128.38, 127.91, 127.82, 127.45, 124.09, 122.73, 109.37, 44.08, 43.89, 34.31, 30.06; MS (ESI): 330 $[M + H]^+$.



1c

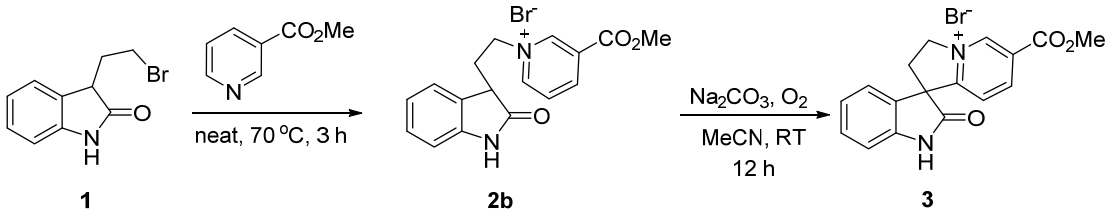
The preparation of **1c** following the same procedures for **1b**. Slightly yellow oil (42.4% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (t, *J* = 7.4 Hz, 2H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 5.82 (tdd, *J* = 15.3, 10.4, 5.3 Hz, 1H), 5.35 – 5.07 (m, 2H), 4.33 (dd, *J* = 4.9, 2.0 Hz, 2H), 3.77 – 3.63 (m, 2H), 3.57 (dt, *J* = 10.0, 7.0 Hz, 1H), 2.43 (ddt, *J* = 28.6, 14.3, 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.78, 143.56, 131.46, 128.35, 127.86, 124.06, 122.64, 117.76, 109.23, 44.03, 42.41, 34.21, 30.02; MS (ESI): 302 [M + Na]$^{+}$.



1d

The preparation of **1d** following the same procedures for **1b**. Yellow oil (50.2% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.23 (m, 3H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 7.7 Hz, 1H), 3.75 – 3.54 (m, 3H), 3.21 (s, 3H), 2.49 – 2.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.02, 144.34, 128.40, 127.84, 123.92, 122.61, 108.29, 44.01, 34.05, 30.09, 26.29; MS (ESI): 254 [M + H]$^{+}$.

3. General procedures for the synthesis of tetracyclic 3-spirooxindole derivatives.

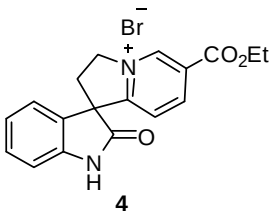


1 **2b** **3**

A suspension of 3-(2-bromo-ethyl)-indole **1a** (1.4 g, 5.9 mmol) and methyl nicotinate (3.23 g, 23.6 mmol) was stirred at 70 °C for 3 h. The mixture was cooled to room temperature. Evaporated the most of solvent at reduced pressure and ethyl ether (30 mL) was added. The mixture was stirred vigorously for 10 min until the pasty material solidified then decanted the organic layer, 10 mL methanol was added to dissolve the residue followed by adding 30 mL ethyl ether under vigorously stirring. This procedure was repeated for three times. The residue yellow wax was dried at 40°C under vacuum to yield pyridinium salt **2b** (1.58 g, 4.2 mmol) as a yellow foam

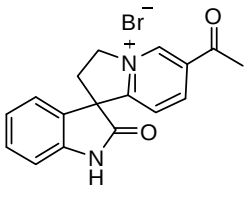
which was used directly without further purification.

To a solution of **2b** (1.58 g，4.2 mmol) and Na_2CO_3 (222 mg，2.1 mmol) in MeCN (20 mL) was stirred at room temperature under an atmosphere of oxygen (1 atm) for 12 h. The mixture was concentrated in vacuum to leave the residue, which was subjected to flash chromatographic separation (dichloromethane/methanol = 20:1) to afford product **3** (1.34 g, 85 %) as a yellow foam. ^{1}H NMR (400 MHz, CD_3OD): δ 9.46 (s, 1H), 9.23 (d, *J* = 5.7 Hz, 1H), 9.04 (d, *J* = 8.0 Hz, 1H), 8.23 (t, *J* = 7.0 Hz, 1H), 7.28 (d, *J* = 7.4 Hz, 1H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 5.00 (dd, *J* = 13.7, 7.0 Hz, 1H), 4.96 (dd, *J* = 13.4, 6.8 Hz, 1H), 4.07 (s, 3H), 3.71 (dd, *J* = 7.9, 4.9 Hz, 1H), 2.93 – 2.79 (m, 1H), 2.77 – 2.55 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 177.02, 163.20, 161.42, 147.94, 145.43, 143.92, 132.03, 131.44, 129.62, 125.96, 124.93, 124.87, 112.06, 61.46, 59.63, 54.18, 49.64, 49.43, 49.21, 49.00, 48.79, 48.57, 48.36, 35.17; HRMS (ESI) calcd for $C_{17}H_{15}N_2O_3$ $[M]^+$ 295.1083, found 295.1077.



4

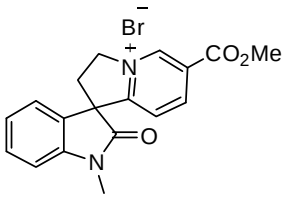
Yellow foam (79% yield), ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.16 (s, 1H), 9.86 (s, 1H), 8.87 (d, *J* = 8.3, 1H), 7.75 (d, *J* = 8.3, 1H), 7.41 (dd, *J* = 13.5, 7.3, 2H), 7.09 (dd, *J* = 11.5, 7.7, 2H), 5.24 (dd, *J* = 14.6, 7.8, 2H), 4.46 (q, *J* = 6.9, 2H), 3.14 – 3.00 (m, 1H), 3.00 – 2.87 (m, 1H), 1.38 (t, *J* = 7.0, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ175.43, 162.02, 159.89, 146.90, 144.77, 142.95, 130.90, 129.50, 129.44, 125.29, 123.96, 123.43, 111.11, 63.13, 59.91, 58.59, 34.10, 14.48; HRMS (ESI) $C_{18}H_{17}N_2O_3$ $[M]^+$ 309.1239, found 309.1238.



5

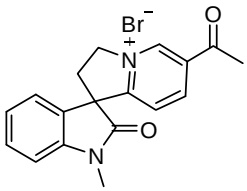
Yellow foam (81% yield), ^{1}H NMR (400 MHz, CD_3OD): δ 9.73 (s, 1H), 8.90 (dd, *J* = 8.3, 1.0, 1H), 7.65 (d, *J* = 8.4, 1H), 7.39 (dt, *J* = 7.9, 5.0, 2H), 7.19 – 6.95 (m, 2H), 5.39 – 5.21 (m, 2H), 3.07 (dd, *J* = 8.5, 6.3, 2H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 192.75, 175.68, 159.57, 145.40, 143.38, 142.55, 135.39, 130.62, 128.30, 124.59, 123.49, 123.47, 110.66, 60.04, 58.17, 48.26, 48.05, 47.84, 47.63, 47.41, 47.20,

46.99, 33.79, 25.85; HRMS (ESI) calcd for $C_{17}H_{15}N_2O_2$ $[M]^+$ 279.1134, found 279.1134.



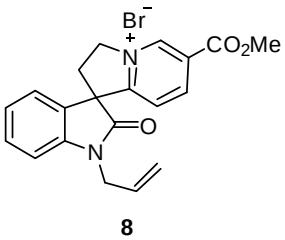
6

Yellow foam (89% yield), ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.88 (s, 1H), 8.79 (d, *J* = 8.3, 1H), 7.91 (d, *J* = 7.4, 1H), 7.52 – 7.33 (m, 2H), 7.16 (t, *J* = 7.6, 1H), 6.96 (d, *J* = 7.8, 1H), 5.90 (t, *J* = 10.8, 1H), 5.43 – 5.16 (m, 1H), 3.97 (s, 3H), 3.54 – 3.48 (m, 1H), 3.24 (s, 3H), 3.01 – 2.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.64, 161.62, 160.36, 146.33, 144.59, 143.79, 131.03, 129.85, 126.91, 126.54, 125.03, 123.41, 109.10, 59.62, 59.08, 53.85, 34.63, 27.11; HRMS (ESI) calcd for $C_{18}H_{17}N_2O_3$ $[M]^+$ 309.1239, found 309.1237.



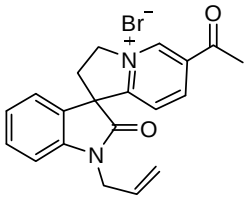
7

Yellow foam (89% yield), ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.67 (s, 1H), 8.80 (d, *J* = 8.2, 1H), 7.70 (d, *J* = 7.4, 1H), 7.46 (t, *J* = 7.8, 1H), 7.36 (d, *J* = 8.3, 1H), 7.19 (t, *J* = 7.6, 1H), 6.99 (d, *J* = 7.9, 1H), 6.06 (t, *J* = 10.6, 1H), 5.53 – 5.22 (m, 1H), 3.41 – 3.30 (m, 1H), 3.27 (s, 3H), 3.04 – 2.94 (m, 1H), 2.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.93, 173.52, 159.78, 145.11, 144.78, 143.85, 134.98, 131.10, 127.08, 125.78, 124.91, 123.21, 109.28, 100.06, 59.45, 58.61, 34.58, 28.18, 27.15; HRMS (ESI) calcd for $C_{18}H_{17}N_2O_2$ $[M]^+$ 293.1290, found 293.1288.



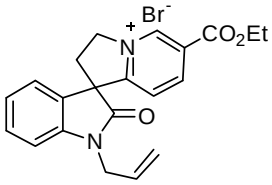
8

Yellow foam (76% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 8.79 (d, *J* = 8.2, 1H), 7.86 (d, *J* = 7.2, 1H), 7.33 (dd, *J* = 25.4, 19.3, 2H), 7.11 (t, *J* = 7.5, 1H), 6.92 (d, *J* = 7.9, 1H), 6.00 – 5.65 (m, 2H), 5.45 – 5.27 (m, 1H), 5.21 (t, *J* = 12.4, 2H), 4.30 (d, *J* = 4.4, 2H), 3.94 (s, 3H), 3.63 – 3.37 (m, 1H), 3.00 – 2.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.40, 161.61, 160.18, 146.39, 144.67, 142.92, 130.86, 130.26, 129.81, 126.86, 126.47, 124.89, 123.24, 118.59, 109.88, 59.51, 59.01, 53.80, 42.95, 34.67; HRMS (ESI) calcd for $C_{20}H_{19}N_2O_3$ $[M]^+$ 335.1396, found 335.1394.



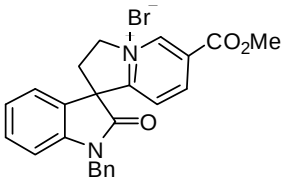
9

Yellow foam (86% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.55 (s, 1H), 8.75 (d, *J* = 8.2, 1H), 7.65 (d, *J* = 7.4, 1H), 7.37 (t, *J* = 7.7, 1H), 7.30 (d, *J* = 8.3, 1H), 7.13 (t, *J* = 7.6, 1H), 6.92 (d, *J* = 7.9, 1H), 6.11 – 5.88 (m, 1H), 5.84 – 5.74 (m, 1H), 5.49 – 5.30 (m, 1H), 5.22 (t, *J* = 14.0, 2H), 4.30 (d, *J* = 5.2, 2H), 3.37 – 3.16 (m, 1H), 3.02 – 2.89 (m, 1H), 2.89 – 2.72 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.75, 173.36, 159.98, 145.09, 143.10, 135.07, 131.11, 130.33, 127.02, 126.01, 125.04, 122.99, 118.89, 110.13, 100.38, 59.51, 58.86, 58.66, 43.12, 34.80, 28.25; HRMS (ESI) calcd for $C_{20}H_{19}N_2O_3$ $[M]^+$ 319.1447, found 319.1444.



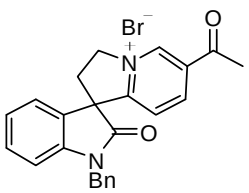
10

Yellow foam (86% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 8.79 (d, *J* = 8.2, 1H), 8.01 (d, *J* = 7.4, 1H), 7.41 (t, *J* = 7.7, 1H), 7.35 (d, *J* = 8.3, 1H), 7.20 (t, *J* = 7.6, 1H), 6.96 (d, *J* = 7.9, 1H), 5.94 (t, *J* = 10.6, 1H), 5.83 (ddd, *J* = 15.8, 10.5, 5.2, 1H), 5.30 (m, 3H), 4.54 – 4.40 (m, 2H), 4.34 (d, *J* = 5.2, 2H), 3.65 (dd, *J* = 22.6, 9.9, 1H), 2.92 (dd, *J* = 12.7, 6.9, 1H), 1.43 (t, *J* = 7.1, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.60, 161.03, 160.47, 146.36, 144.47, 143.02, 131.00, 130.33, 126.98, 126.86, 125.20, 123.19, 118.78, 109.86, 63.56, 59.74, 59.17, 43.05, 34.83, 14.26; HRMS (ESI) calcd for $C_{21}H_{21}N_2O_3$ $[M]^+$ 349.1552, found 349.1550.



11

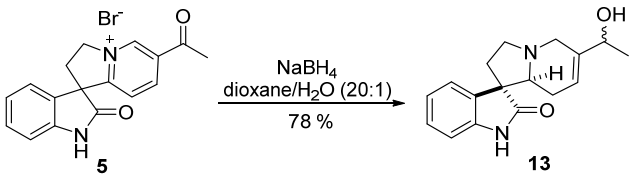
Yellow foam (91% yield), ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.82 (s, 1H), 8.75 (d, *J* = 8.2, 1H), 7.93 (d, *J* = 7.4, 1H), 7.25 (dt, *J* = 16.5, 6.5, 7H), 7.10 (t, *J* = 7.6, 1H), 6.84 (d, *J* = 7.9, 1H), 6.00 – 5.83 (m, 1H), 5.43 – 5.23 (m, 1H), 4.98 – 4.74 (m, 2H), 3.96 (s, 3H), 3.67 – 3.50 (m, 1H), 3.02 – 2.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.99, 161.60, 160.49, 146.43, 144.70, 142.96, 134.83, 130.98, 130.01, 129.24, 128.37, 127.37, 126.94, 126.91, 125.20, 123.19, 109.99, 59.74, 59.22, 53.93, 44.54, 34.81; HRMS (ESI) calcd for $C_{24}H_{21}N_2O_3$ $[M]^+$ 385.1552, found 385.1548.



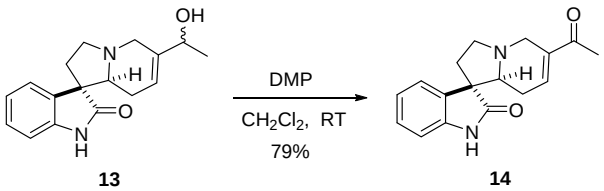
12

Yellow foam (87% yield), ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.53 (s, 1H), 8.72 (d, *J* = 8.1, 1H), 7.56 (d, *J* = 7.2, 3H), 7.26 (ddd, *J* = 19.2, 16.1, 7.7, 9H), 7.10 (t, *J* = 7.3, 1H), 6.85 (d, *J* = 7.9, 1H), 6.07 – 5.87 (m, 1H), 5.46 – 5.29 (m, 1H), 4.85 (q, *J* = 15.5, 3H), 3.36 – 3.17 (m, 1H), 2.97 (m, 1H), 2.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.67, 173.72, 159.82, 145.10, 144.82, 142.97, 135.18, 134.69, 131.00, 129.19, 128.35, 127.31, 126.94, 125.75, 124.99, 122.77, 110.13, 59.52, 58.54, 44.50, 34.64, 27.78; HRMS (ESI) calcd for $C_{24}H_{21}N_2O_2$ $[M]^+$ 369.1603, found 369.1599.

4. Procedures for the synthesis of (±)-conynoxine and (±)-conynoxine B

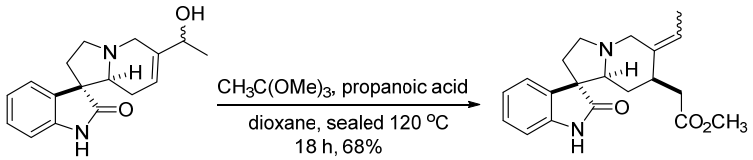


To a solution of coupling product 5 (1.20 g, 3.35 mmol) in a mixture of dioxane and water (20:1, 20 mL) at room temperature was added $NaBH_4$ (0.51 g, 13.40 mmol). After refluxing for 2 h, the reaction mixture was poured into saturated NH_4Cl aqueous solution, the resulting solution was extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with brine (3 × 100 mL), dried over Na_2SO_4, after removal of the solvent, the residue was purified by flash column chromatography on silica gel (dichloromethane/methanol = 50:1) to give **13** (0.72 g, 78%) as yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 7.39 (d, *J* = 7.4 Hz, 1H), 7.19 (t, *J* = 7.2 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 7.7 Hz, 1H), 5.58 (d, *J* = 20.0 Hz, 1H), 4.26 (dt, *J* = 19.3, 6.4 Hz, 1H), 3.73 (d, *J* = 15.3 Hz, 1H), 3.59 (d, *J* = 15.5 Hz, 1H), 3.53 – 3.37 (m, 1H), 3.04 – 2.82 (m, 1H), 2.78 (dt, *J* = 10.6, 5.4 Hz, 1H), 2.67 – 2.55 (m, 1H), 2.51 – 2.34 (m, 1H), 2.26 – 2.03 (m, 2H), 1.36 – 1.19 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.03, 140.36, 127.97, 125.38, 122.70, 119.82, 118.25, 109.69, 70.48, 69.79, 68.02, 67.95, 56.54, 54.48, 53.03, 51.91, 35.46, 35.37, 26.59, 22.29, 21.66; HRMS (ESI) calcd. for $C_{17}H_{21}N_2O_2$ $[M + H]^+$ 285.1598, found 285.1602.



The alcohol **13** (20 mg, 0.070 mmol) was diluted with CH_2Cl_2 (2 mL). Dess-Martin periodinane (36 mg, 0.084 mmol) was then added and the reaction was allowed to stir at room temperature for 2.5 h. The reaction was quenched with $NaHCO_3/Na_2S_2O_3$ (5:1) and diluted with Et_2O. The reaction mixture was allowed to stir for an additional 10 minutes. The layers were then separated and the aqueous layer

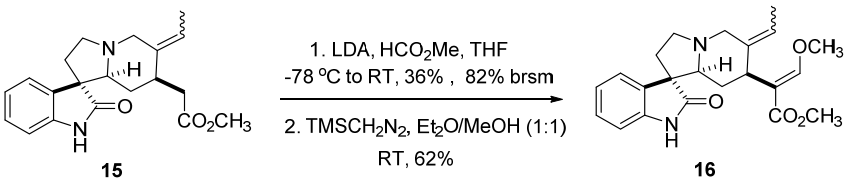
was extracted with Et_2O (2 × 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered and concentrated in *vacuo*. The aldehyde was dried further by passing through a small column of silica gel (dichloromethane/methanol = 60:1) to give **14** (16 mg, 79 %) as soft yellow foam. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.35 (d, *J* = 7.4, 1H), 7.22 (td, *J* = 7.7, 0.9, 1H), 7.04 (t, *J* = 7.2, 1H), 6.90 (d, *J* = 7.7, 1H), 6.76 (s, 1H), 3.98 (d, *J* = 16.4, 1H), 3.57 – 3.47 (m, 1H), 2.94 (dd, *J* = 16.4, 3.2, 1H), 2.77 (dd, *J* = 9.7, 4.6, 1H), 2.69 (dd, *J* = 17.4, 9.2, 1H), 2.49 (ddd, *J* = 13.0, 9.7, 3.2, 1H), 2.35 – 2.20 (m, 3H), 2.11 (ddd, *J* = 16.0, 12.9, 4.6, 1H), 2.00 – 1.85 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 197.50, 181.03, 140.16, 138.19, 138.11, 133.10, 128.18, 125.28, 122.91, 109.67, 66.45, 56.50, 54.01, 51.27, 35.08, 27.67, 25.44; HRMS (ESI) calcd. For $C_{17}H_{19}N_2O_2$ $[M + H]^+$ 283.1441, found 283.1448.



13 **15**

A solution of **13** (1.00 g, 3.52 mmol), trimethyl orthoacetate (2.25 mL, 17.60 mmol) propanoic acid (80 μL, 1.06 mmol) in 1,4-dioxane (20 mL) was charged with argon and then was sealed and stirred at 120 °C for 18 h. After cooling to room temperature and removal of solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel (dichloromethane/methanol = 50:1) to give **15** (0.82 g, 68 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.12 (dd, *J* = 36.3, 13.1 Hz, 1H), 7.34 (t, *J* = 7.3 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 6.97 (dd, *J* = 9.9, 5.0 Hz, 1H), 6.89 (d, *J* = 7.7 Hz, 1H), 5.42 – 4.97 (m, 1H), 3.95 (dd, *J* = 73.0, 12.2 Hz, 1H), 3.67 – 3.49 (m, 3H), 3.32 (t, *J* = 8.3 Hz, 1H), 2.71 (dt, *J* = 21.8, 10.2 Hz, 2H), 2.63 – 2.32 (m, 6H), 2.32 – 2.14 (m, 1H), 2.14 – 1.97 (m, 2H), 1.58 (dd, *J* = 16.3, 7.2 Hz, 4H), 1.27 (dt, *J* = 10.9, 10.4 Hz, 2H), 1.09 (d, *J* = 13.2 Hz, 1H), 0.74 (dd, *J* = 23.3, 11.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.40, 182.28, 173.24, 172.92, 140.52, 136.40, 135.31, 133.69, 133.53, 127.72, 127.67, 125.31, 125.16, 122.46, 120.60, 115.78, 109.75, 67.12, 56.65, 54.13, 53.98, 53.27, 51.68, 51.45, 49.51, 38.79, 38.25, 37.52, 37.09, 35.80, 35.42, 33.21, 31.02, 13.26, 13.08; HRMS (ESI) calcd. for

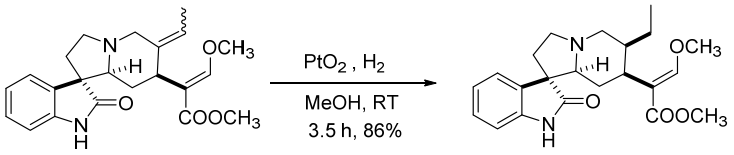
$C_{20}H_{25}N_2O_3$ $[M + H]^+$ 341.1860, found 341.1869.



To a solution of **15** (1.00 g, 2.94 mmol) in THF (20 mL) was added lithium diisopropylamine (4.4 mL, 8.80 mmol, 2.0 M in THF) at -78°C under argon atmosphere. The mixture was stirred at the same temperature for 1 h and then methyl formate (3.24 mL, 29.40 mmol) was added. The mixture was warmed up to 0 °C and subsequently allowed to stir at room temperature for additional 12 h. The reaction solution was the poured into 30 mL of water and the pH was adjusted to 12 by the addition of solid KOH. The aqueous solution which resulted was extracted with 30 mL of ethyl ether. The organic layer was washed with brine (3 × 30 mL), dried over Na_2SO_4, and evaporated solvent *in vacuo* leading to the recovery of 0.50 g of the starting material **15**. The aqueous solution remained which was acidified with 2*N* citric acid aqueous solution to adjust PH to 3 and extracted with DCM. The organic layer was dried over Na_2SO_4, and evaporated solvent *in vacuo* to give 0.39 g (36%, 82% based on recovered starting material) formyl intermediate as a mixture of formyl and enol tautomers.

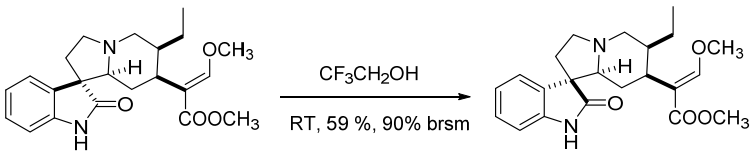
To a stirred solution of the above mixture (0.39 g, 1.06 mmol) in 20 mL of the mixture solvent (Et_2O/MeOH = 1:1) at room temperature was added (trimethylsilyl)diazomethane (2.65 mL, 5.30 mmol, 2.0 M solution in hexane). After stirring at room temperature for 5 h, the mixure was concentrated *in vacuo*, the residue was submitted to chromatography on silica gel (dichloromethane/methanol = 50:1) to give **16** (242 mg, 62 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (s, 1H), 7.43 (d, *J* = 7.3, 1H), 7.29 (s, 1H), 7.14 (t, *J* = 7.6, 1H), 6.98 (t, *J* = 7.5, 1H), 6.88 (d, *J* = 7.7, 1H), 5.00 (d, *J* = 5.9, 1H), 4.11 (d, *J* = 12.4, 1H), 3.66 (s, 3H), 3.58 (s, 3H), 3.34 (dd, *J* = 15.7, 9.1, 2H), 2.65 (d, *J* = 10.4, 1H), 2.60 – 2.48 (m, 2H), 2.41 (dd, *J* = 11.0, 9.4, 1H), 2.09 (dt, *J* = 12.8, 8.5, 1H), 1.80 – 1.67 (m, 1H), 1.61 (d, *J* = 6.5, 3H), 1.06 (d, *J* = 11.4, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.53, 168.64,

160.23, 140.38, 133.91, 132.99, 127.55, 125.41, 122.30, 116.39, 110.52, 109.58, 72.40, 61.49, 56.99, 54.59, 53.57, 51.23, 35.78, 30.23, 13.23; HRMS (ESI) calcd. for $C_{22}H_{27}N_2O_4$ $[M + H]^+$ 383.1965, found 383.1972.



16 **corynoxine**

A mixture of **16** (100 mg, 0.29 mmol) and PtO_2 (83%, 10 mg) in MeOH (2 mL) was stirred at room temperature under an atmosphere of hydrogen (1 atm) for 6 h. The mixture was filtered through a pad of Celite, and the filtrate was concentrated. The residue was purified by flash column chromatography on silica gel (dichloromethane/acetone = 10:1) to give (±)-corynoxine (86 mg, 86 %) as an amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (s, 1H), 7.47 (d, *J* = 7.3, 1H), 7.29 (s, 1H), 7.23 – 7.17 (m, 1H), 7.12 – 7.04 (m, 1H), 6.87 (d, *J* = 7.7, 1H), 3.62 (s, 3H), 3.54 (s, 3H), 3.29 – 3.16 (m, 2H), 2.80 (d, *J* = 13.3, 1H), 2.53 – 2.35 (m, 3H), 2.23 – 2.12 (m, 1H), 2.10 – 2.00 (m, 1H), 1.92 – 1.80 (m, 1H), 1.74 – 1.65 (m, 1H), 1.52 (d, *J* = 11.0, 1H), 1.19 – 1.08 (m, 1H), 0.96 (d, *J* = 13.0, 1H), 0.90 (t, *J* = 7.4, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ 182.10, 169.23, 160.31, 140.18, 134.76, 127.33, 125.00, 122.37, 111.83, 109.45, 73.16, 61.19, 57.46, 54.70, 54.01, 51.27, 40.33, 38.98, 34.96, 25.45, 19.39, 13.04; HRMS (ESI) calcd. for $C_{22}H_{29}N_2O_4$ $[M + H]^+$ 385.2128, found 385.2121.

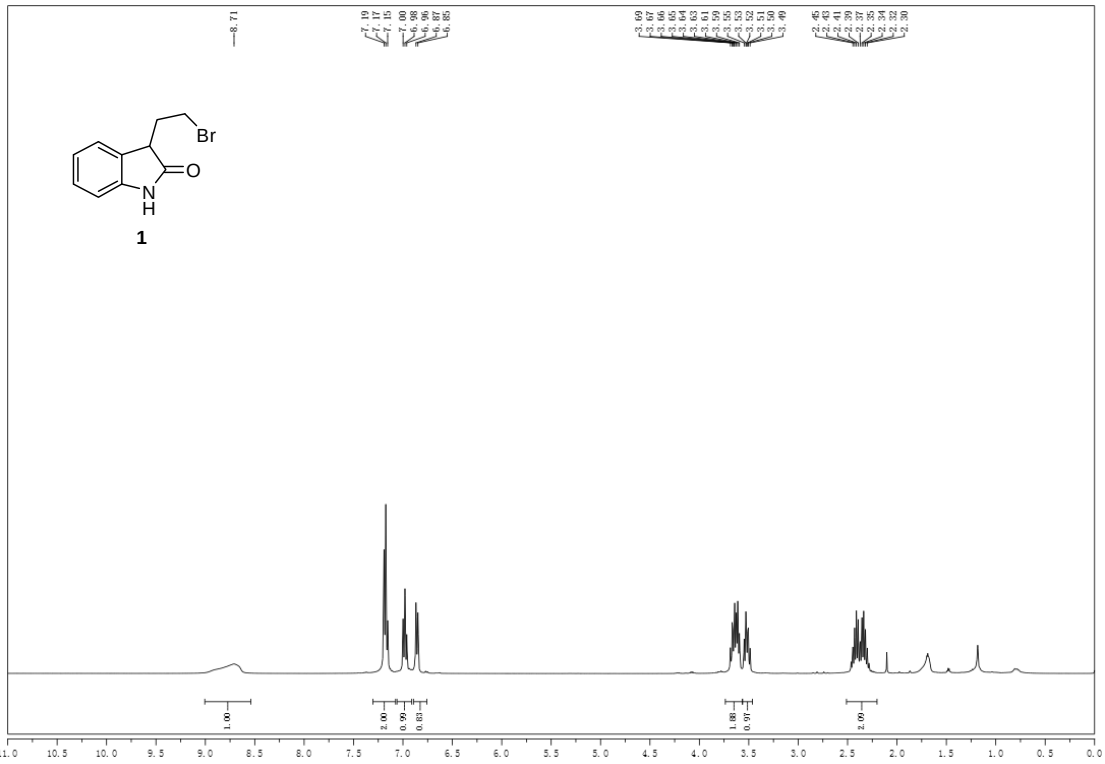


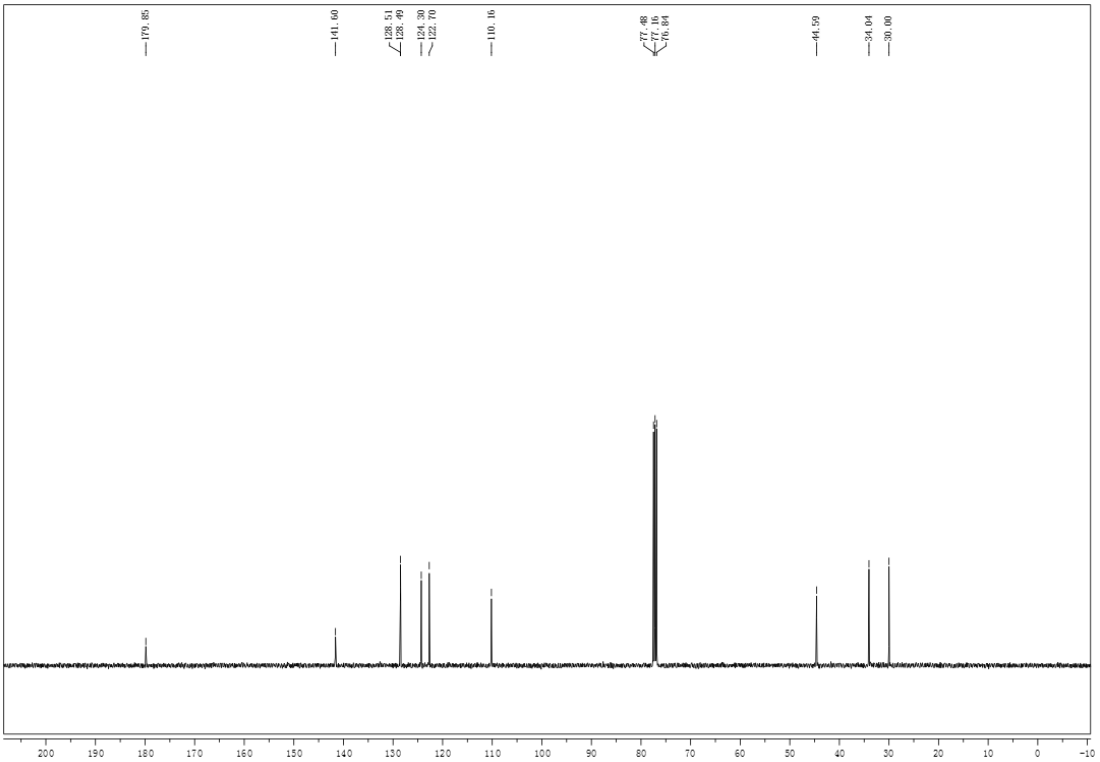
corynoxine **corynoxine B**

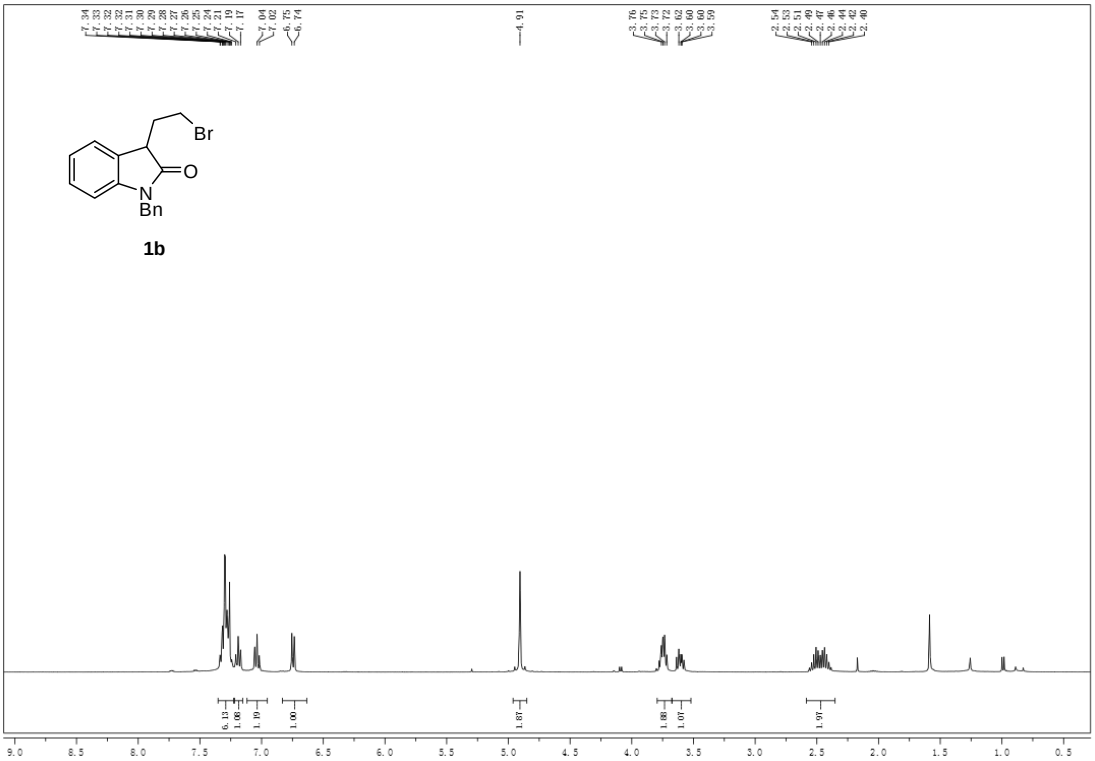
A solution of (±)-corynoxine (16 mg, 0.04 mmol) in 2,2,2-trifluoroenthanol (2 mL) was stirred at room temperature for 6 h. After removal of solvent in vacuo, the residue was purified by flash column chromatography on silica gel (dichloromethane : methanol = 50:1) to give (±)-corynoxine B (9.4 mg, 59 %, 90 % brsm) as an

amorphous solid, and recovery 5.0 mg of (±)-corynoxine. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (s, 1H), 7.29 (s, 1H), 7.17 (dd, *J* = 14.8, 7.4, 2H), 7.01 (t, *J* = 7.4, 1H), 6.86 (d, *J* = 7.6, 1H), 3.61 (s, 3H), 3.59 (s, 3H), 3.31 (dd, *J* = 22.9, 9.6, 2H), 2.64 (d, *J* = 13.0, 1H), 2.55 – 2.45 (m, 1H), 2.37 (dt, *J* = 24.5, 10.1, 2H), 2.20 (d, *J* = 10.8, 1H), 2.09 – 1.97 (m, 2H), 1.89 – 1.73 (m, 2H), 1.49 (d, *J* = 10.1, 1H), 1.18 (dd, *J* = 12.9, 7.0, 1H), 1.04 (d, *J* = 12.2, 1H), 0.87 (t, *J* = 7.3, 4H), 0.87 (t, *J* = 7.3, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.84, 169.23, 160.53, 141.23, 133.83, 127.85, 123.23, 122.48, 111.55, 109.33, 76.82, 61.64, 56.51, 55.12, 55.06, 51.37, 40.48, 40.20, 34.20, 25.08, 19.29, 13.48; HRMS (ESI) calcd. for $C_{22}H_{29}N_2O_4$ $[M + H]^+$ 385.2122, found 385.2121.

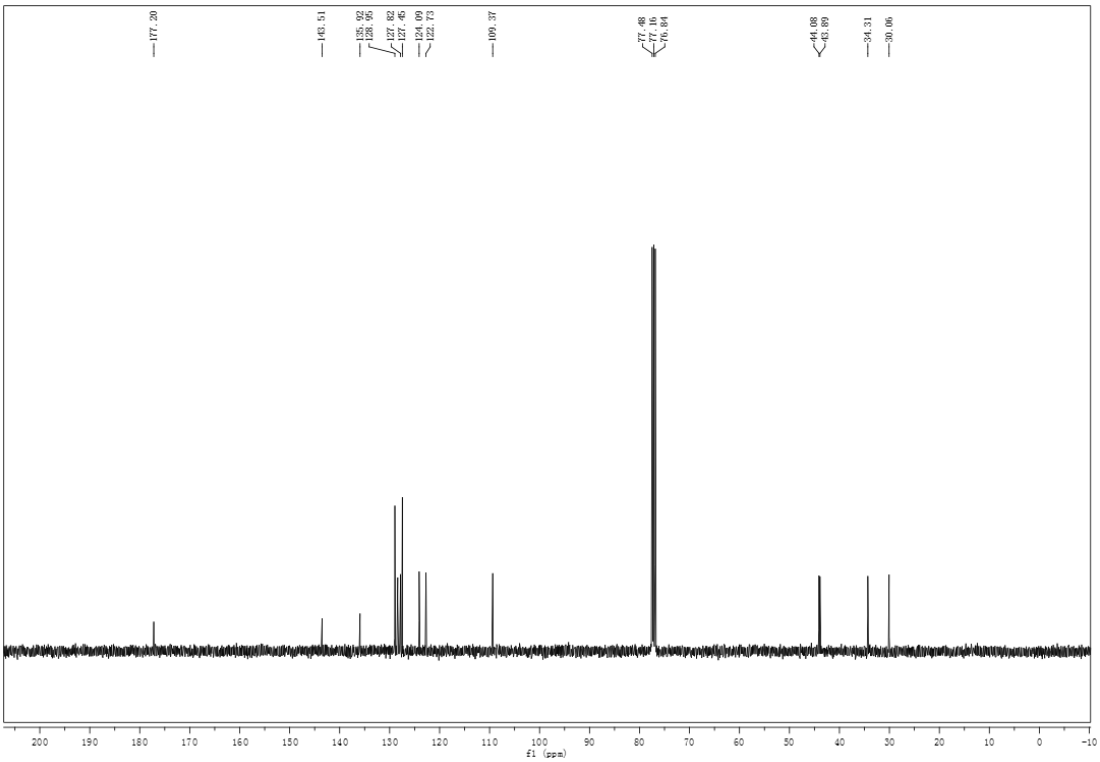
5. Copies of ^{1}H NMR and ^{13}C NMR spectra

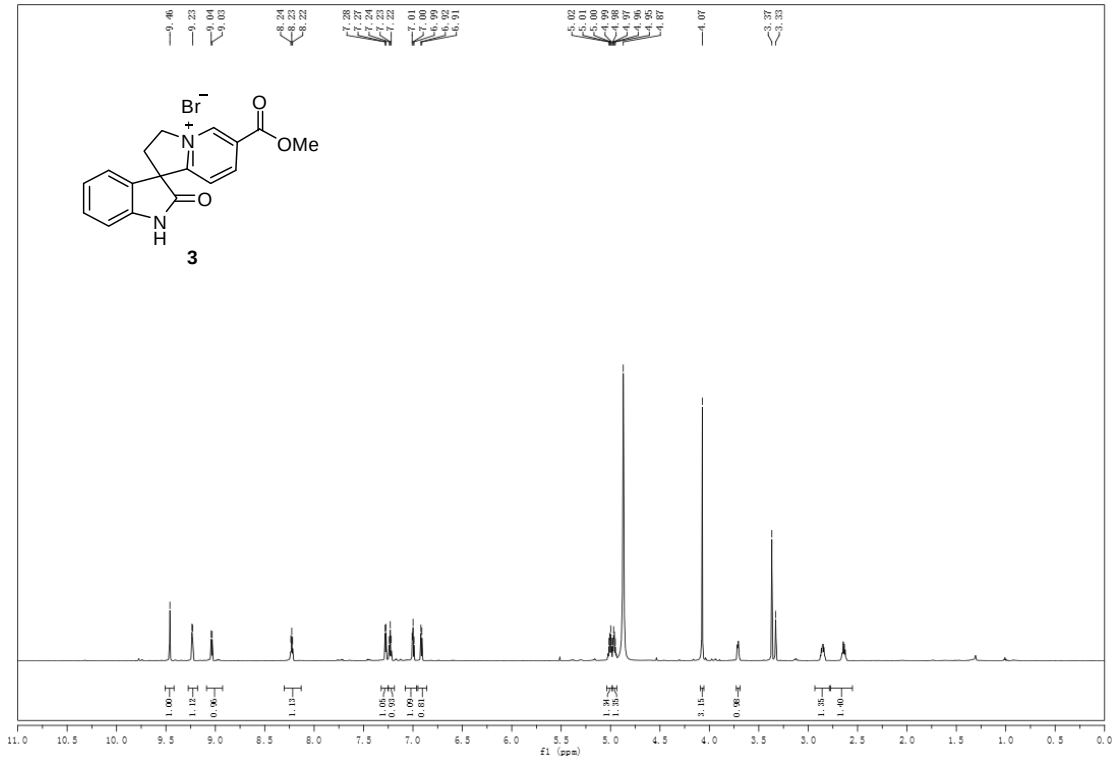






1b

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3.37
3.33
Br
O
OMe
N
O
N
H
3
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1.05
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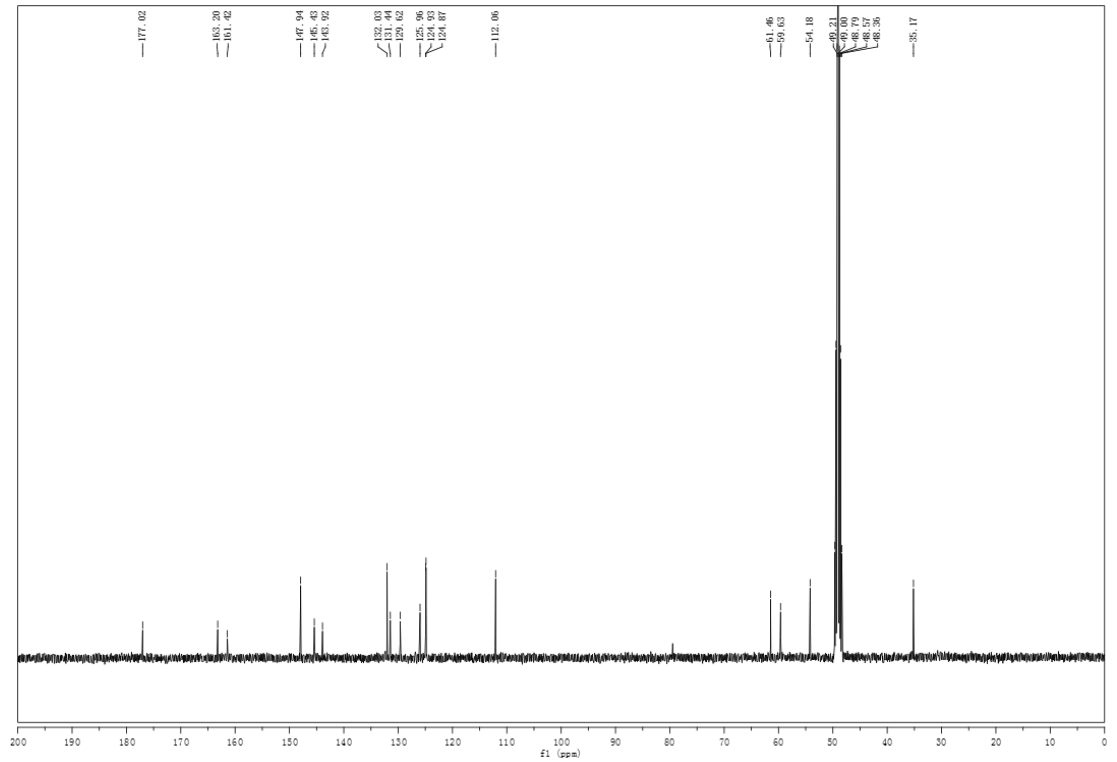
1.40
f1 (ppm)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49.00
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48.36
35.17
f1 (ppm)


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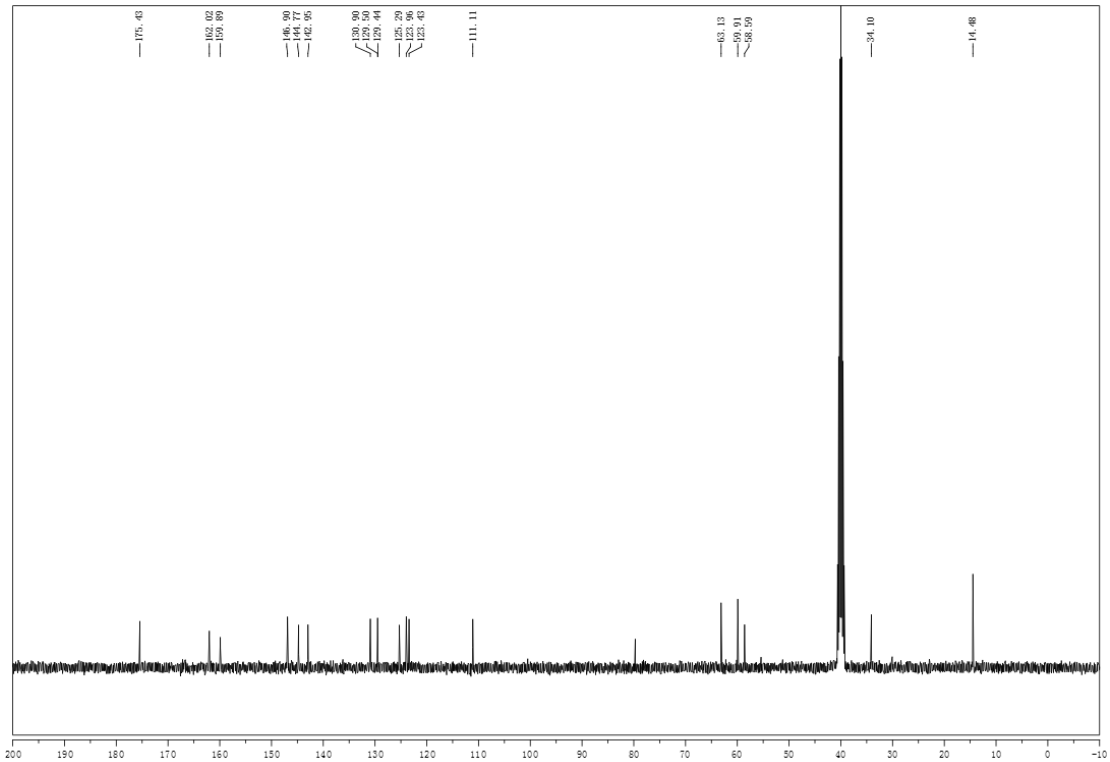
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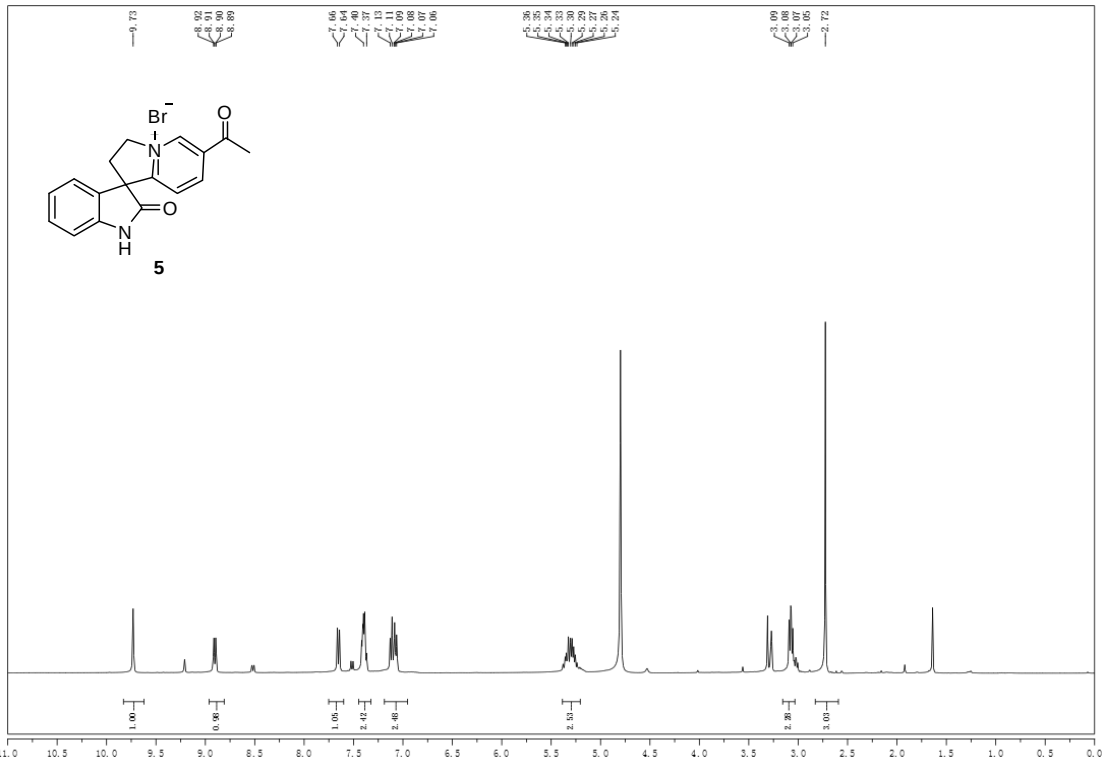
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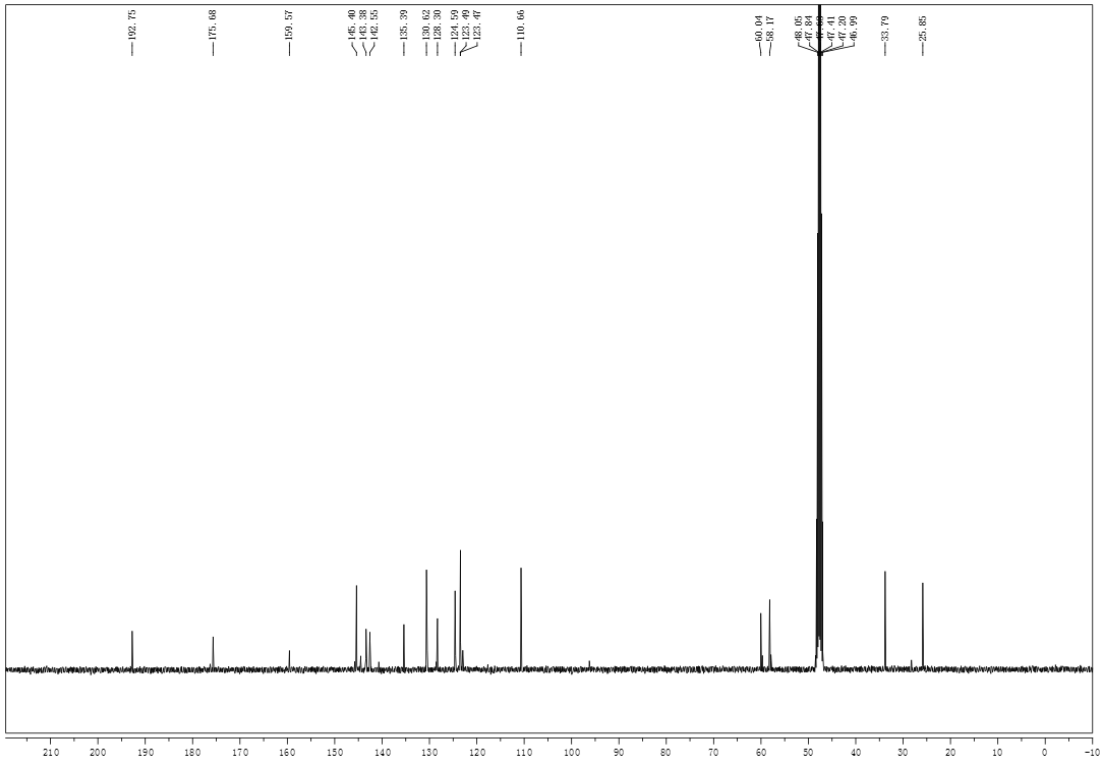

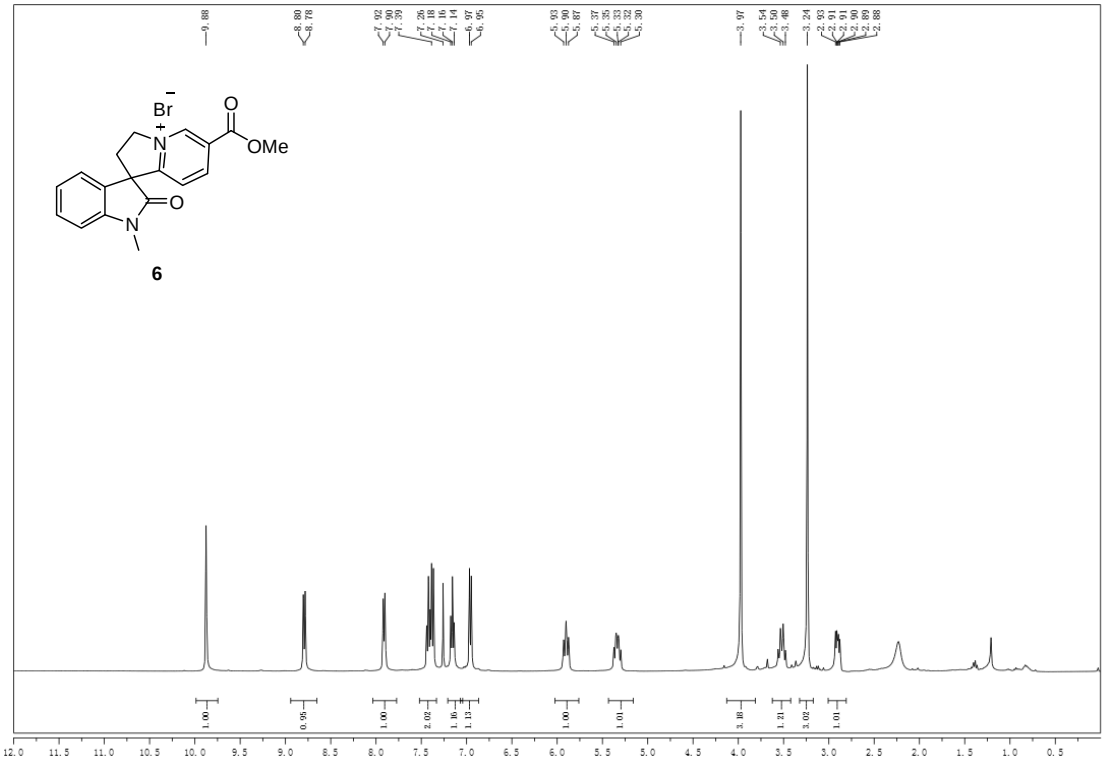
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OMe
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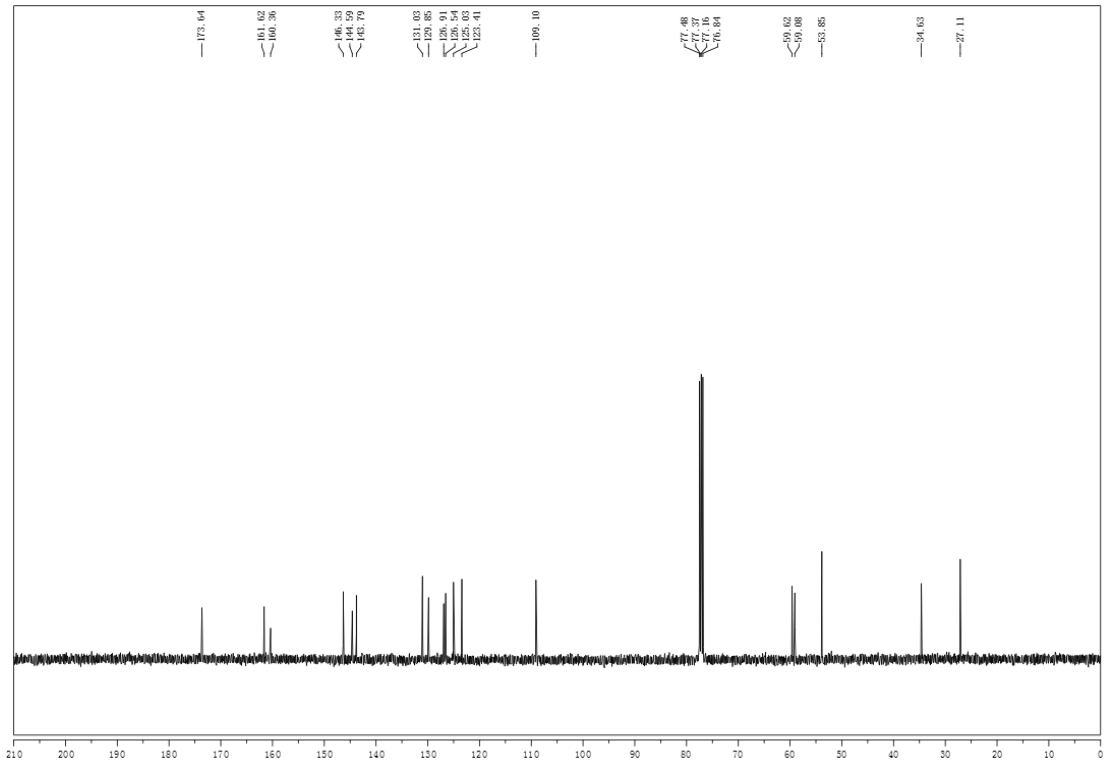
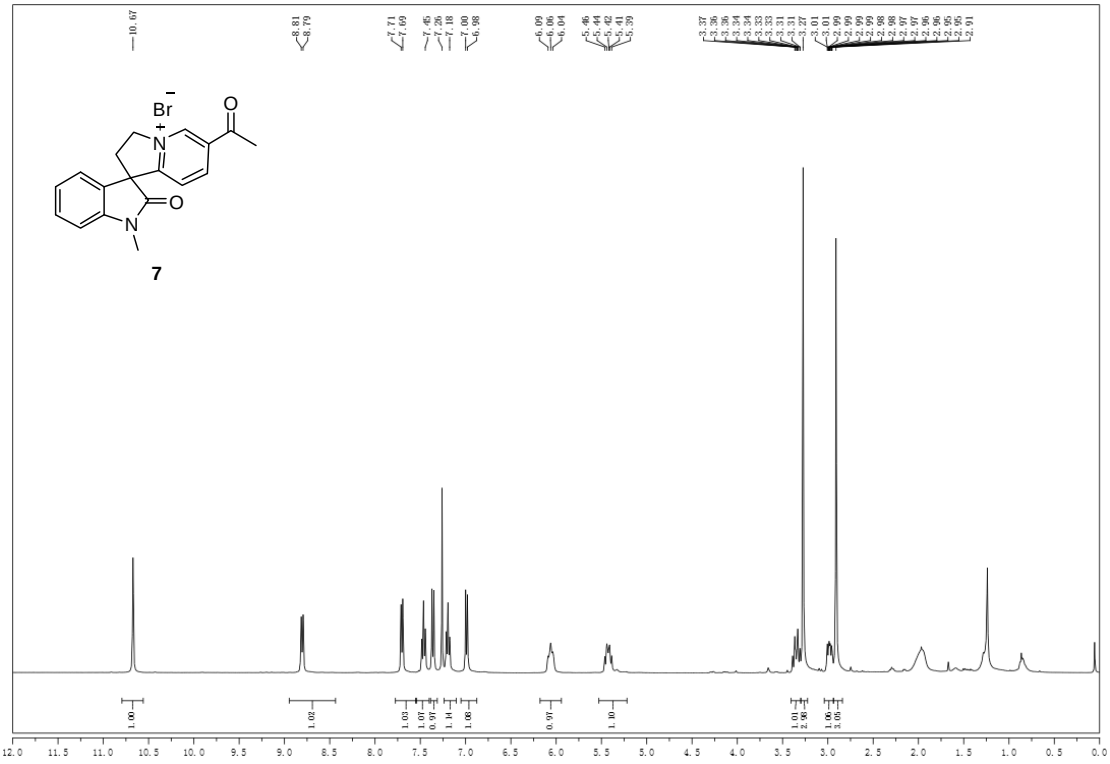
O
N
6

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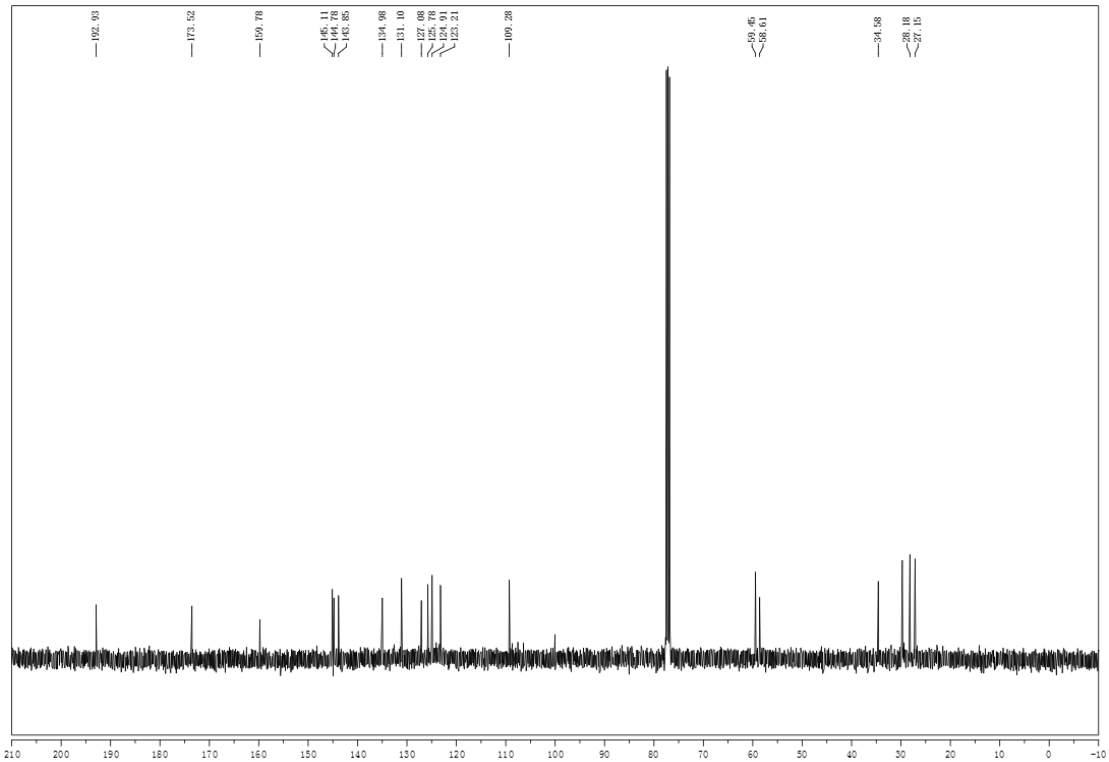
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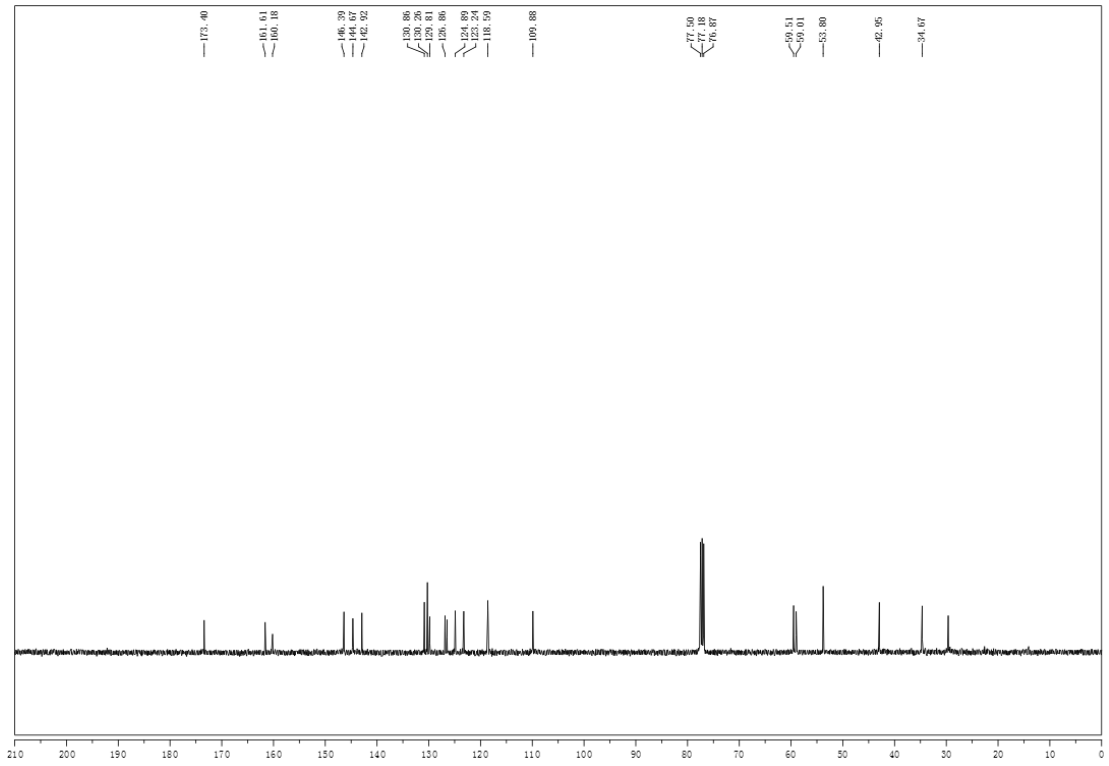
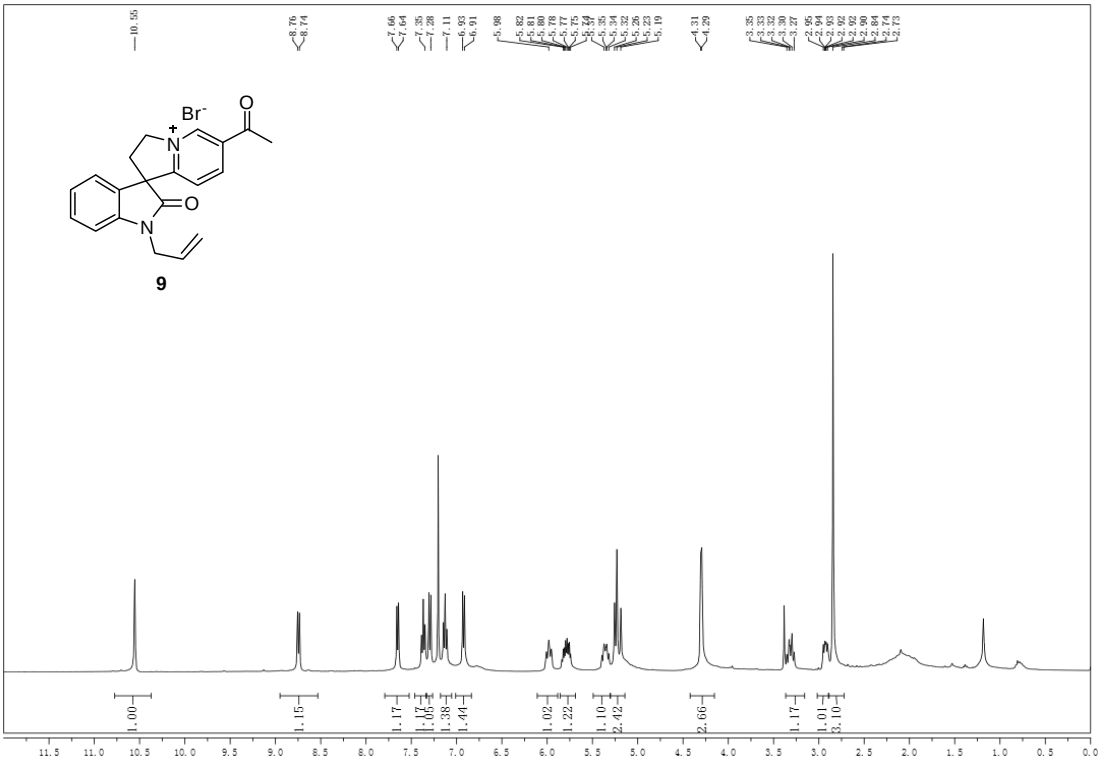
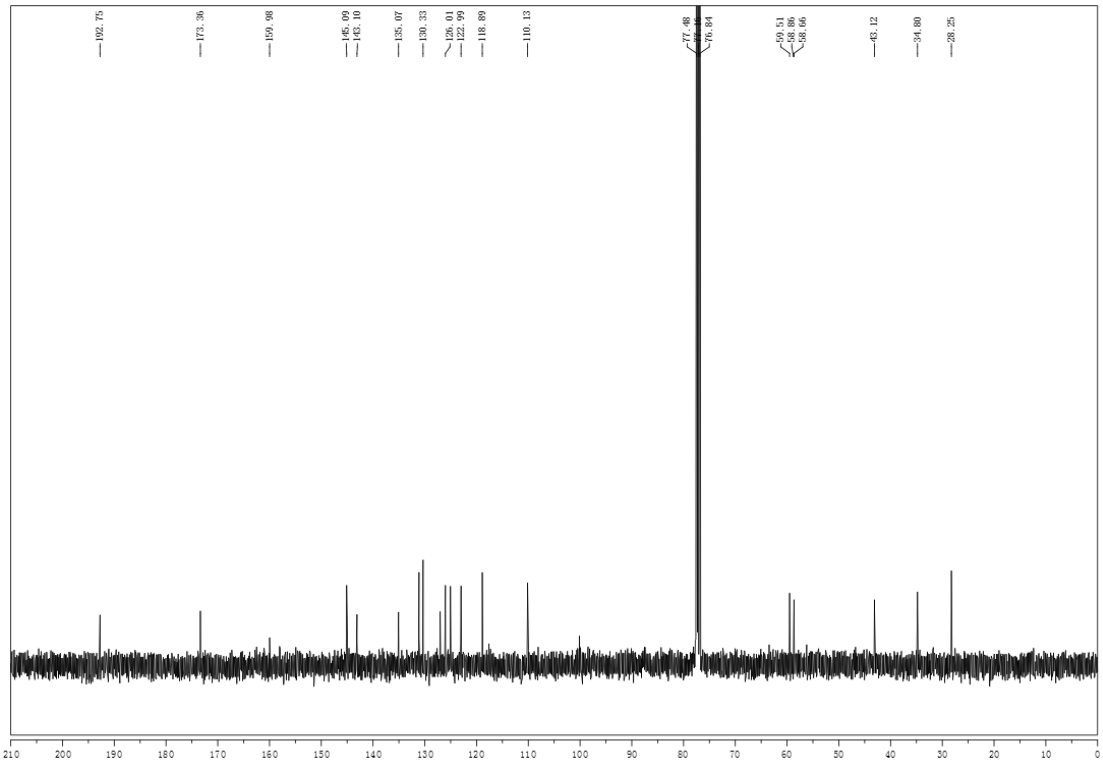
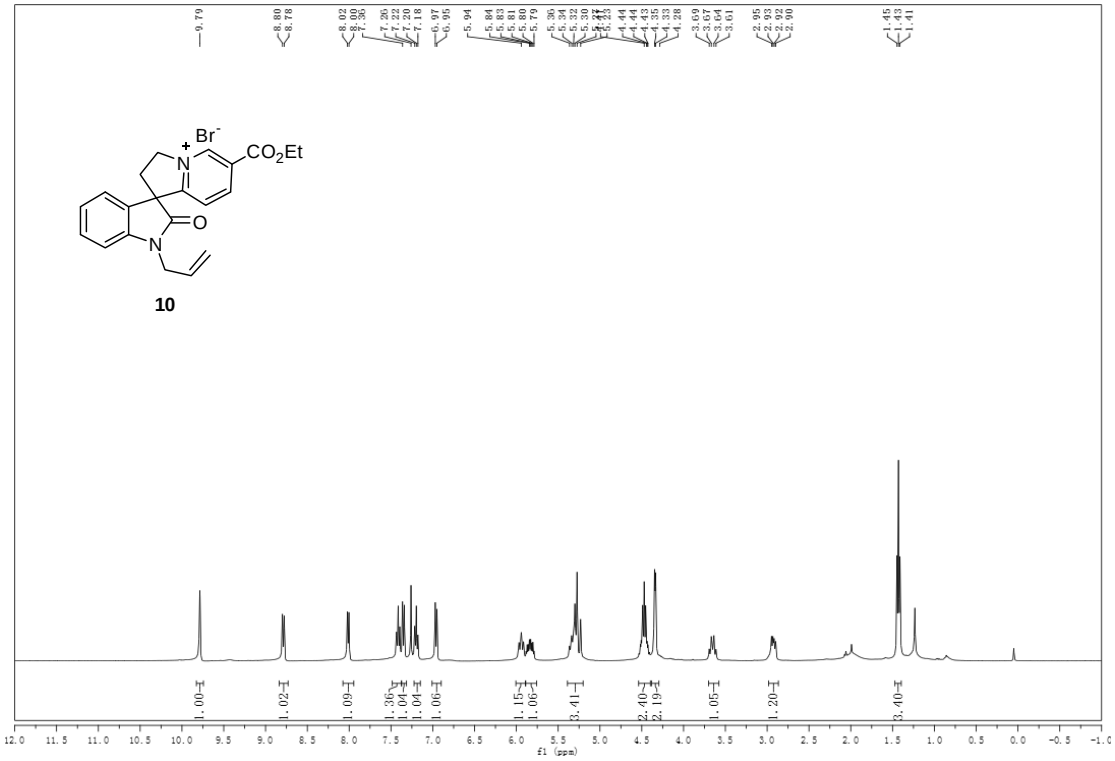
27.15

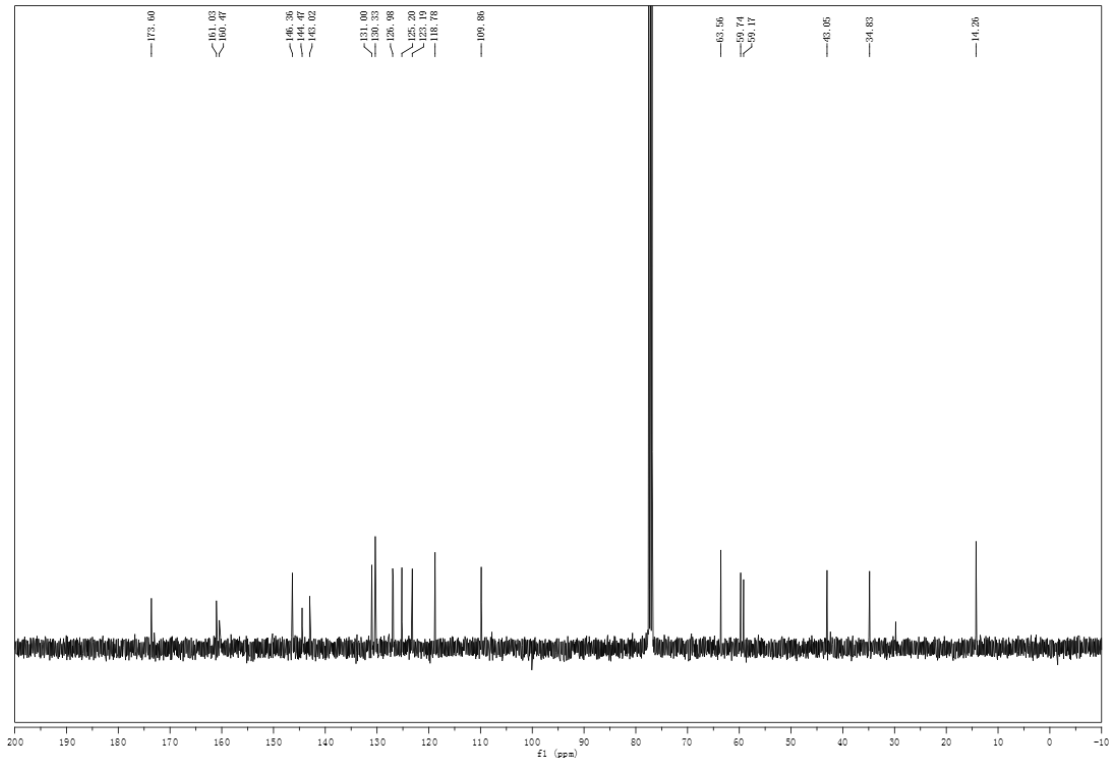

Br
O
OMe
N
O
N
8

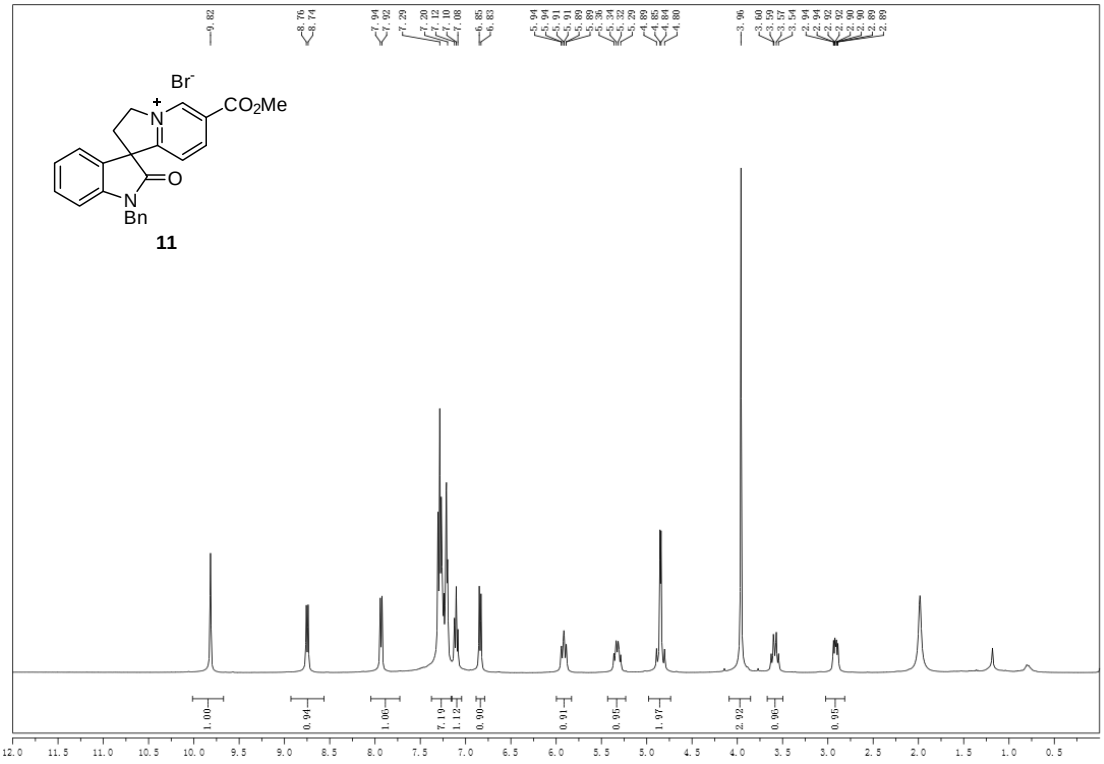


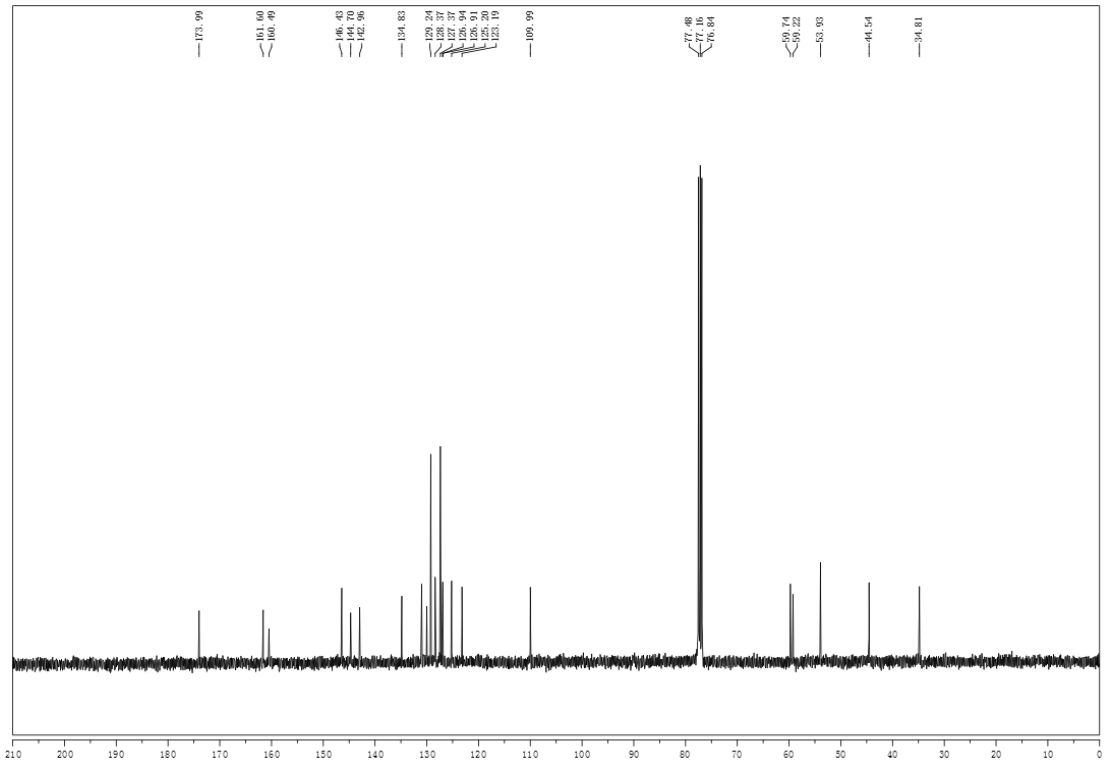

Br⁻
O
N
O
N
9

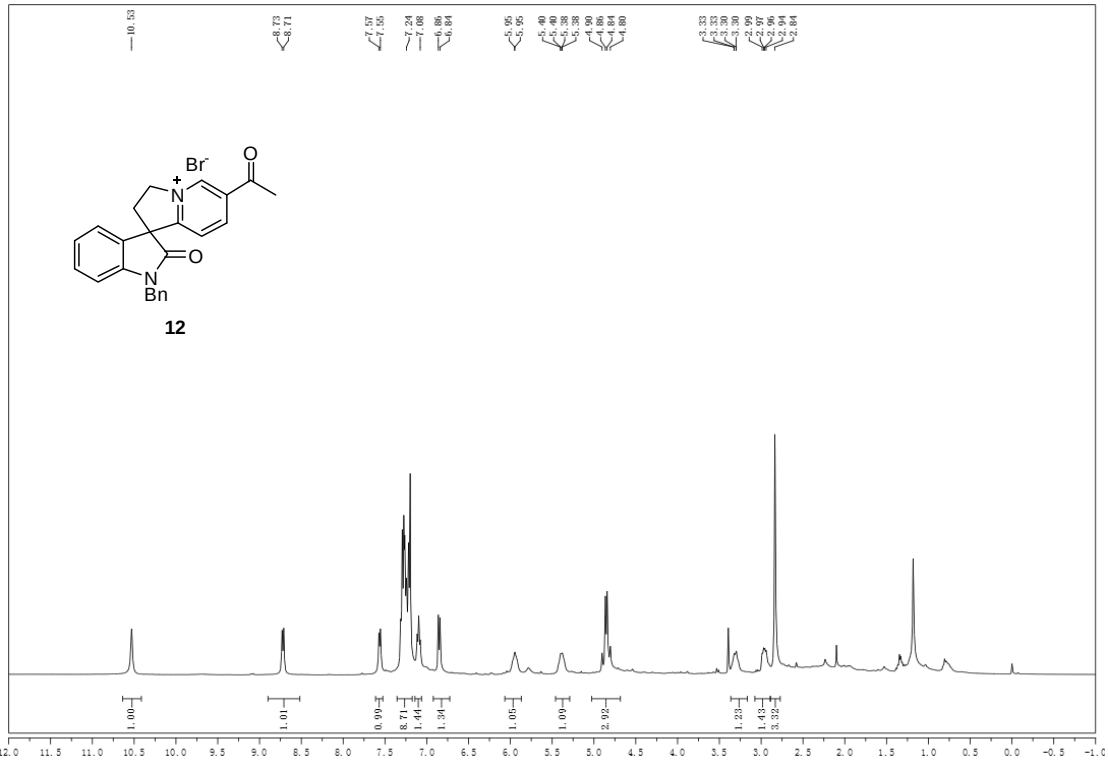



Br-
CO2Et
N
O
N
10
f1 (ppm)

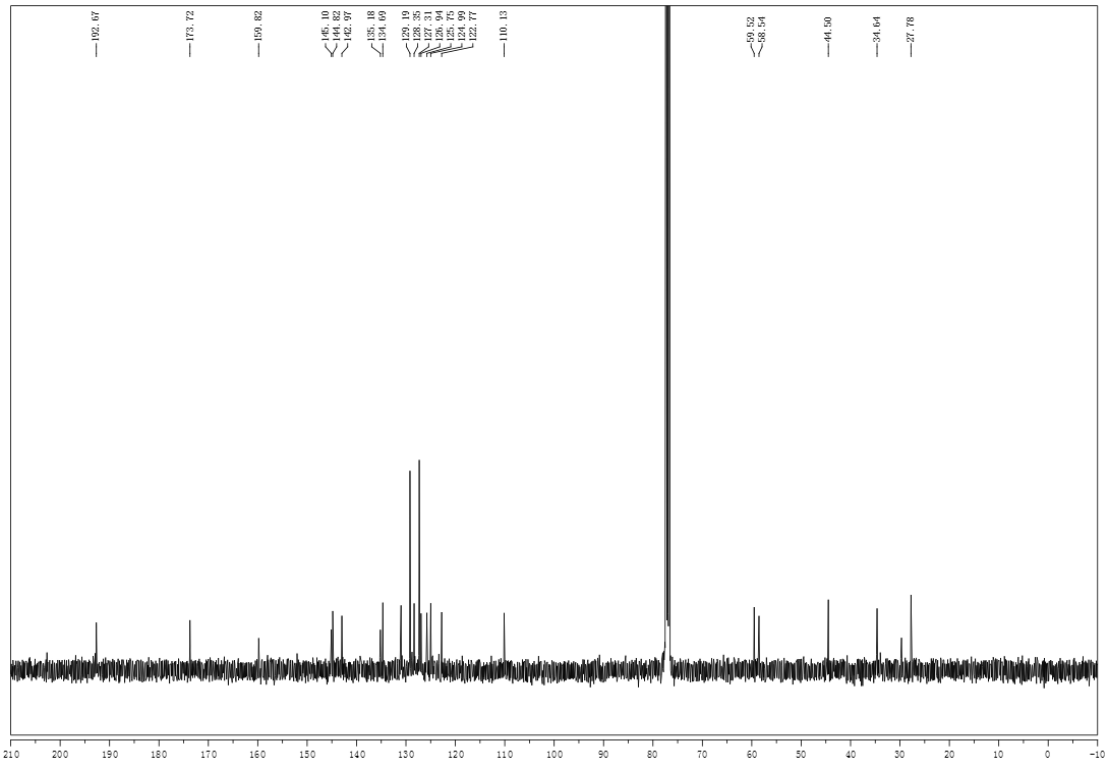

f1 (ppm)

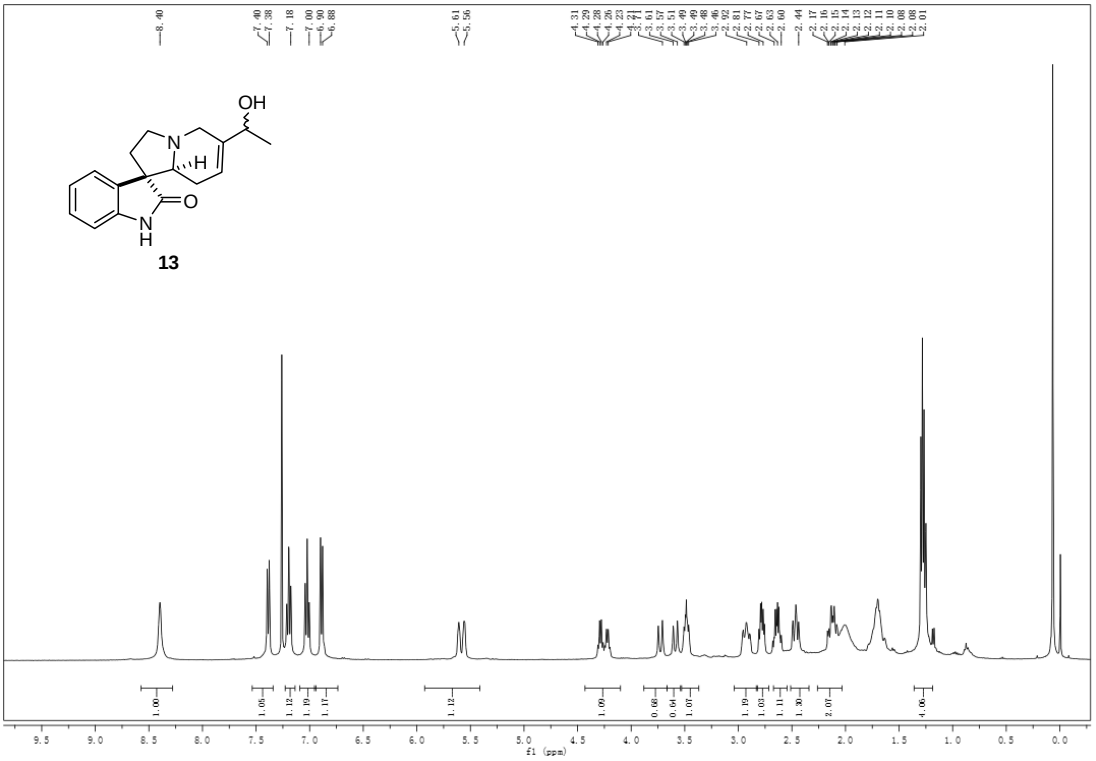

Br-
CO2Me
N
O
N
Bn
11



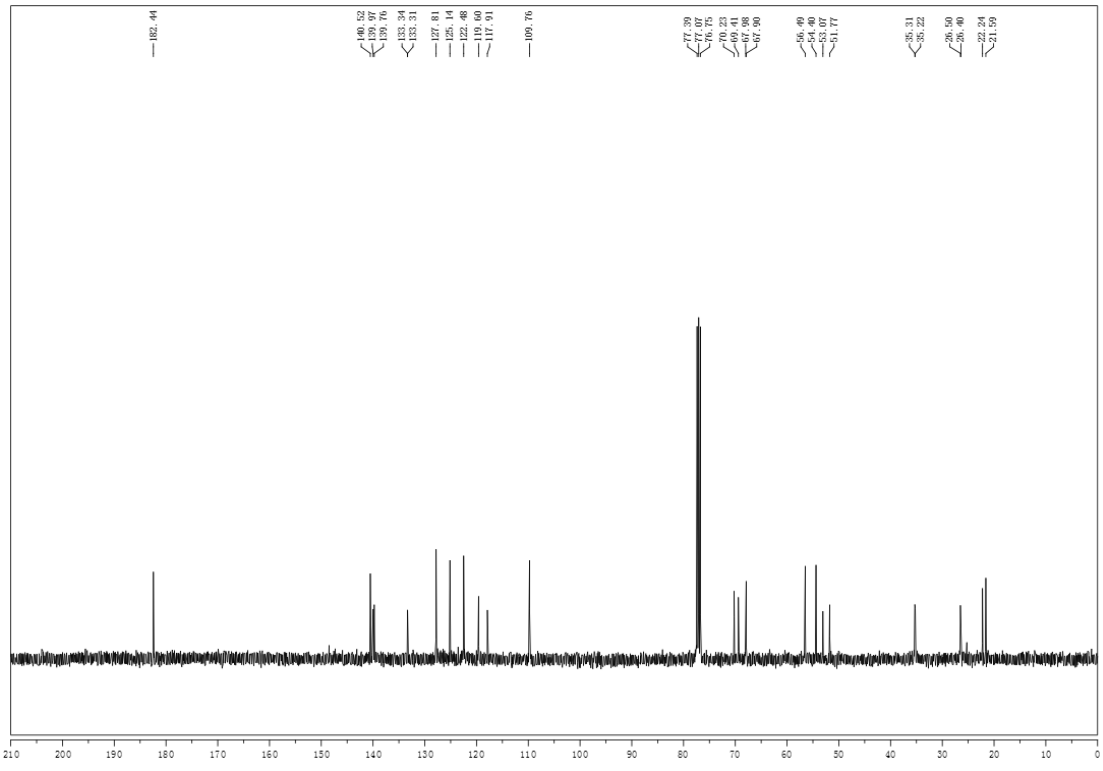

10.53
8.73
8.71
7.57
7.55
7.24
7.08
6.86
6.84
5.95
5.95
5.40
5.40
5.38
5.38
4.90
4.86
4.84
4.80
3.33
3.33
3.30
3.30
2.99
2.97
2.96
2.94
2.94
Br-
O
N+
O
N
Bn
1.00
1.01
0.99
8.71
1.44
1.34
1.05
1.09
2.92
1.23
1.43
3.32

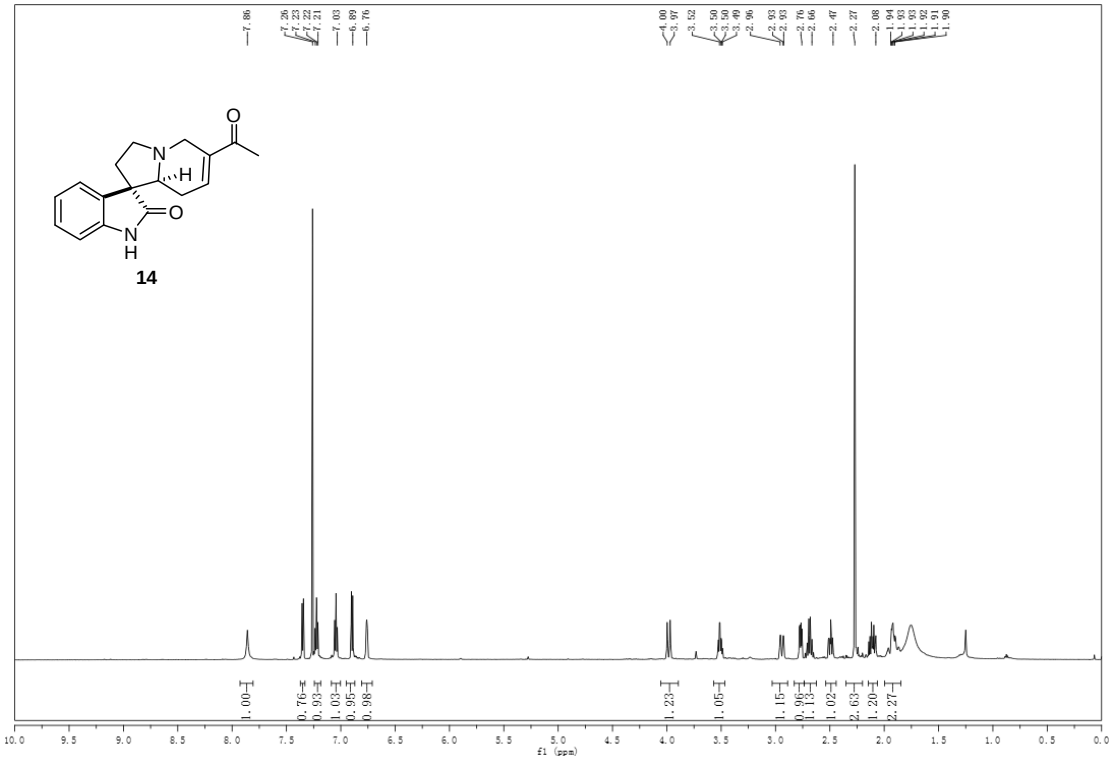
12

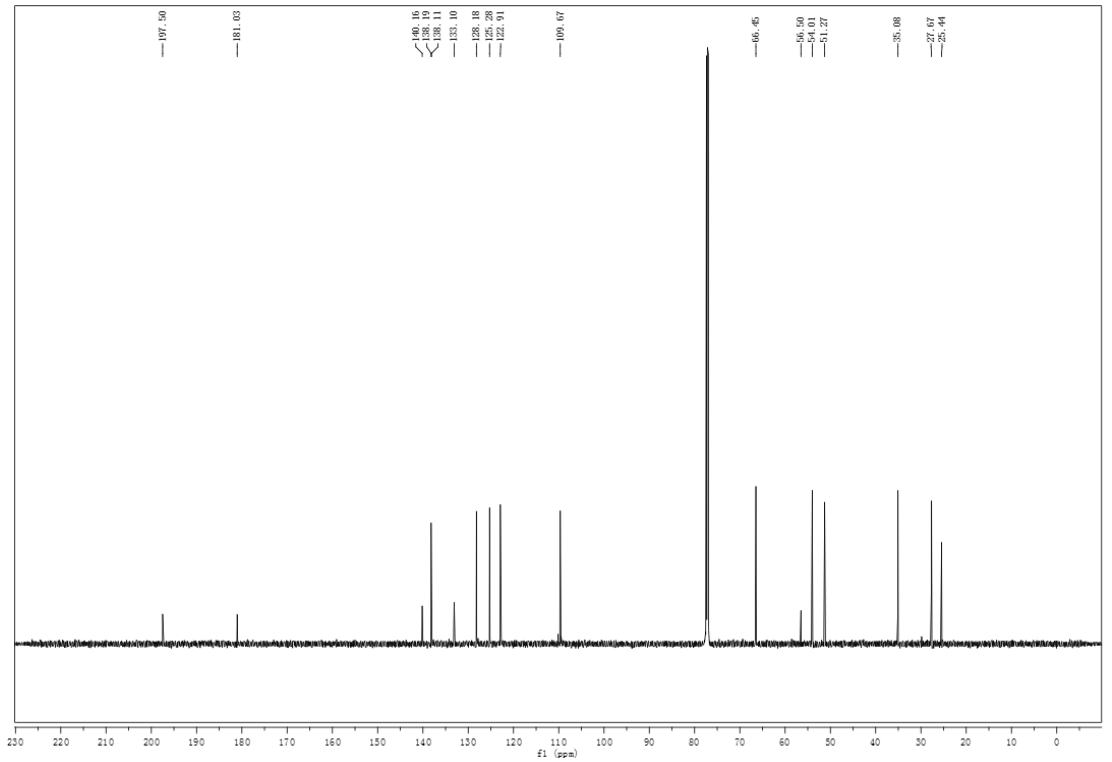

192.67
173.72
159.82
146.10
144.82
142.97
135.18
134.69
129.19
128.35
127.31
126.94
125.75
124.99
122.77
110.13
59.52
58.54
44.50
34.64
27.78

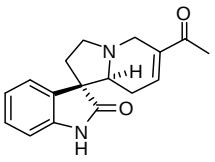


13



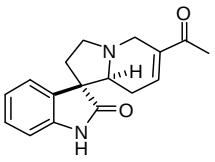

7.86
7.26
7.23
7.22
7.21
7.03
6.89
6.76
4.00
3.97
3.52
3.50
3.50
3.49
2.96
2.93
2.93
2.76
2.66
2.47
2.27
2.08
1.94
1.93
1.92
1.91
1.90
O
N
H
O
N
H
14
1.00
0.76
0.93
1.03
0.95
0.98
1.23
1.05
1.15
0.96
1.13
1.02
2.63
1.20
2.27
f1 (ppm)


197.50
181.03
140.16
138.19
136.11
133.10
128.18
125.28
122.91
109.67
66.45
56.50
54.01
51.27
35.08
27.67
25.44
f1 (ppm)



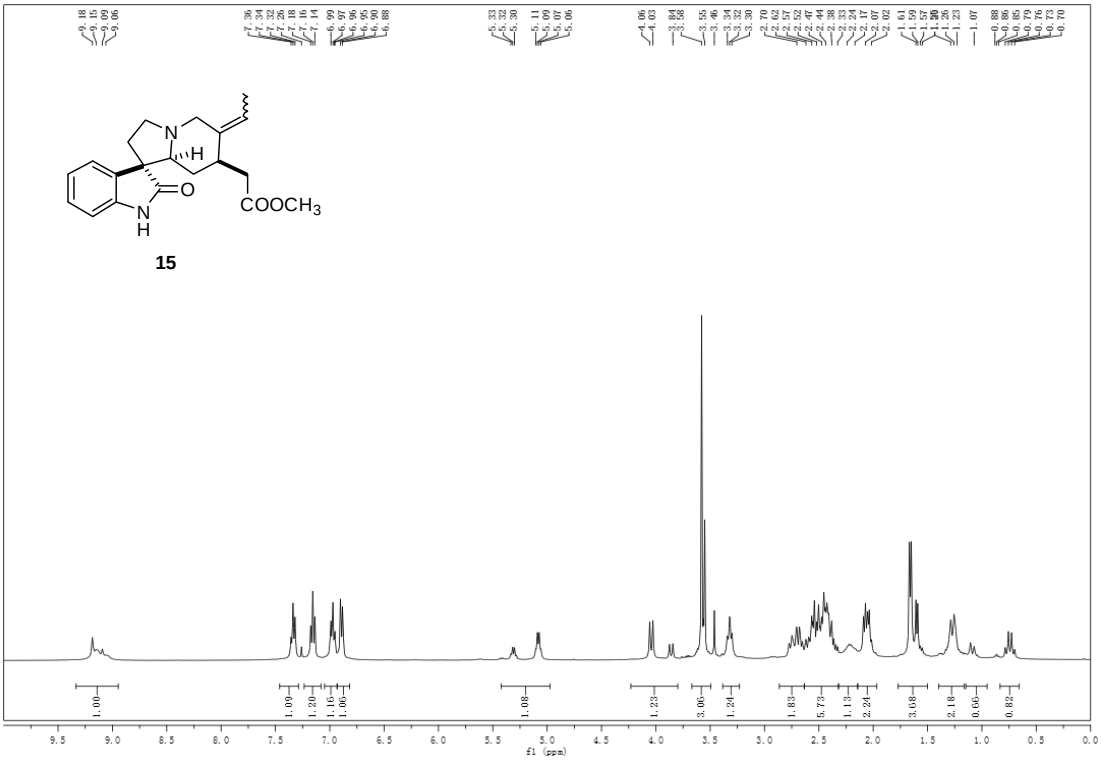
14

^{1}H -^{1}H COSY

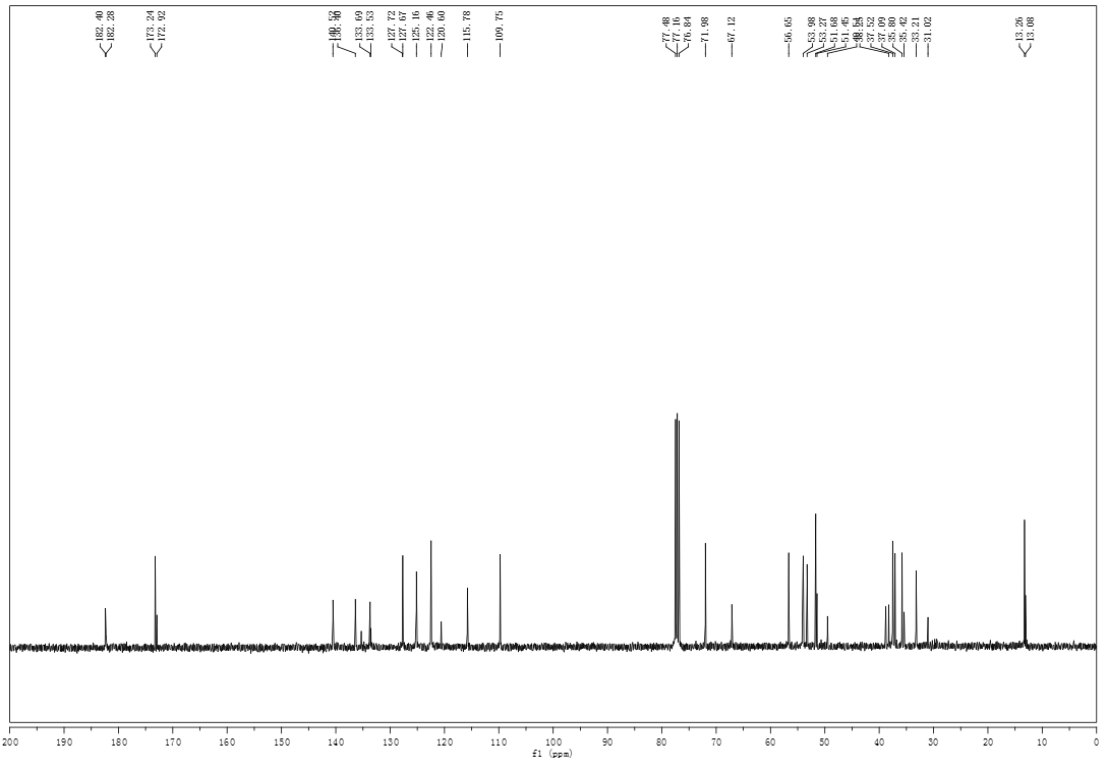


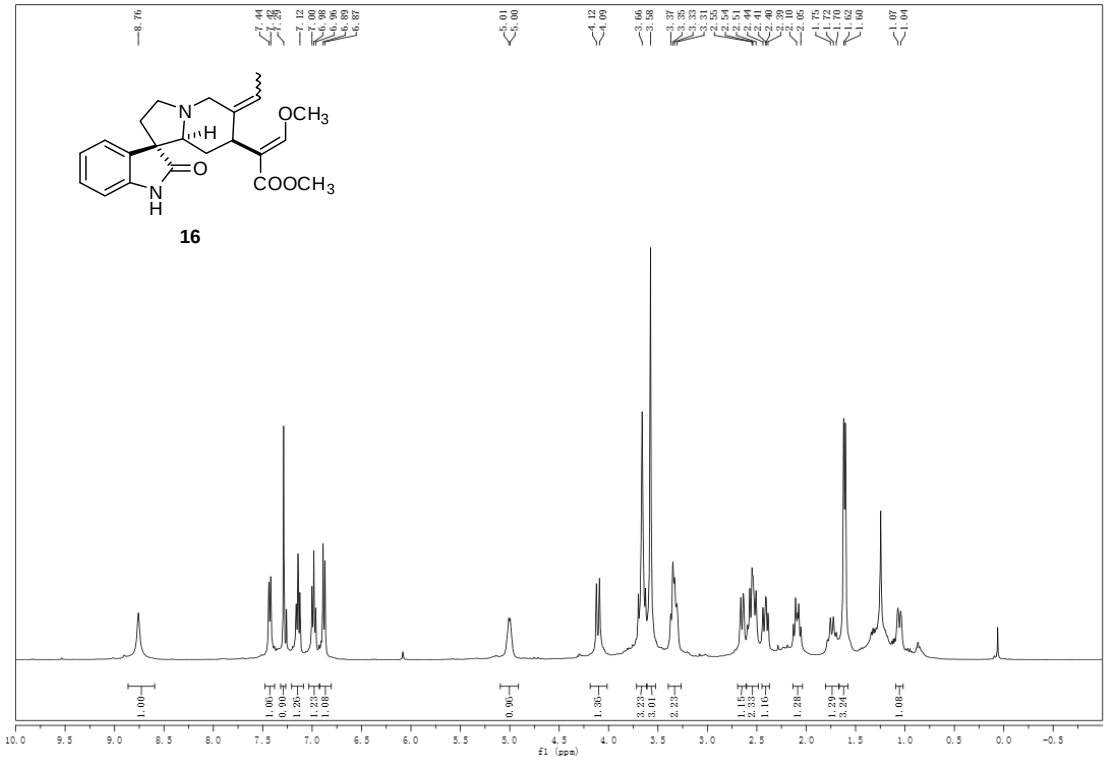
14

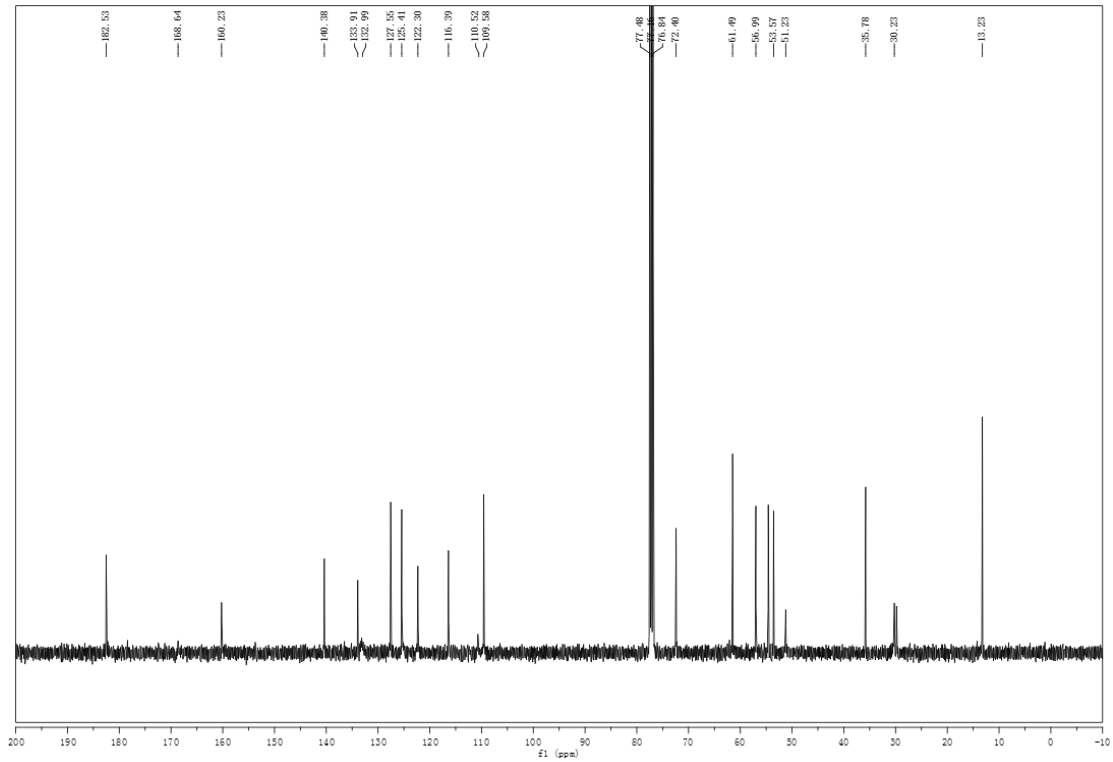
ROESY

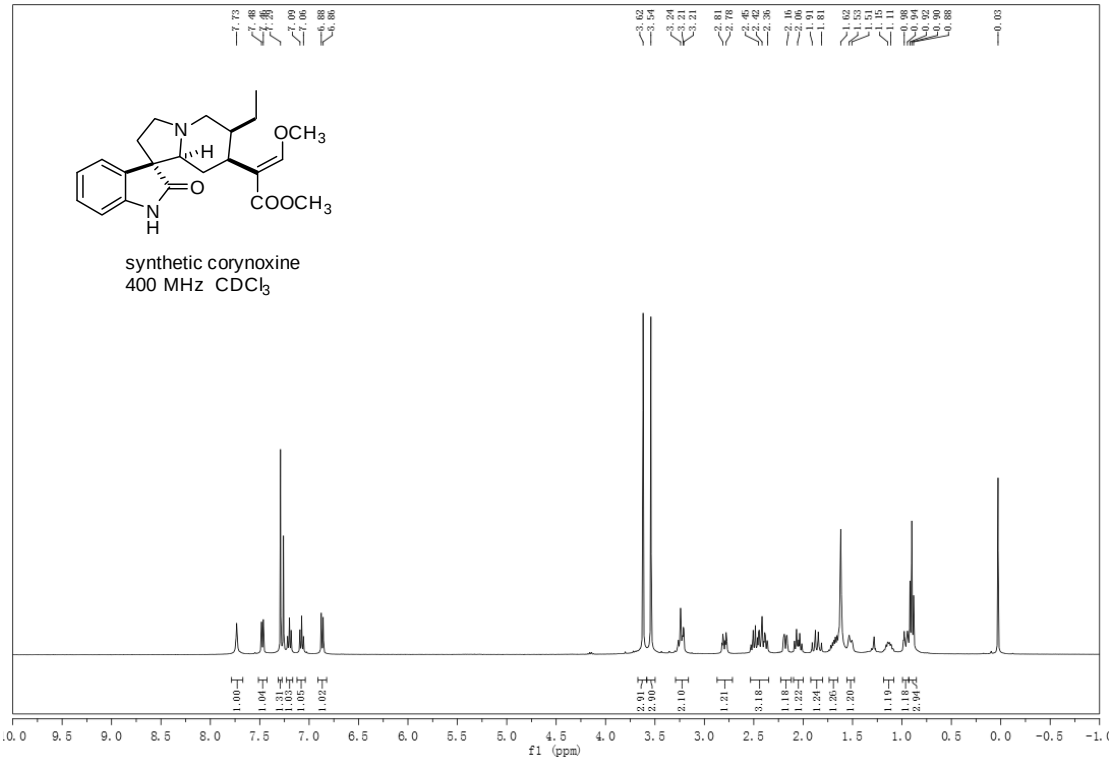


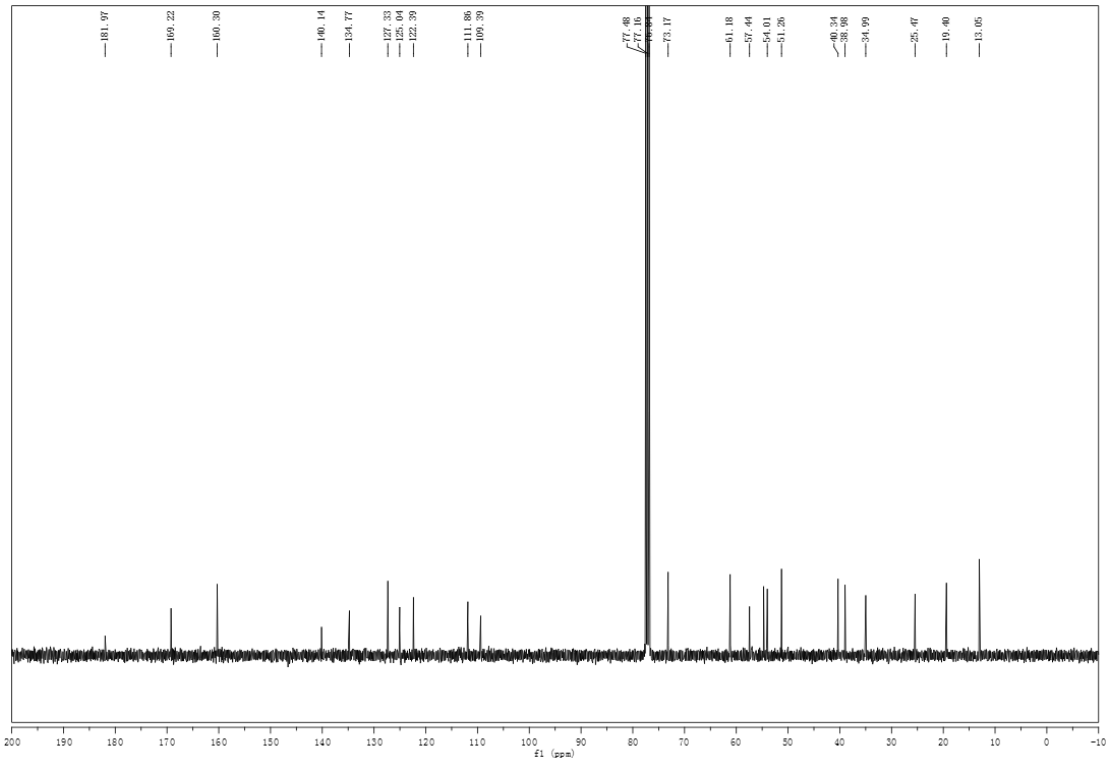
15

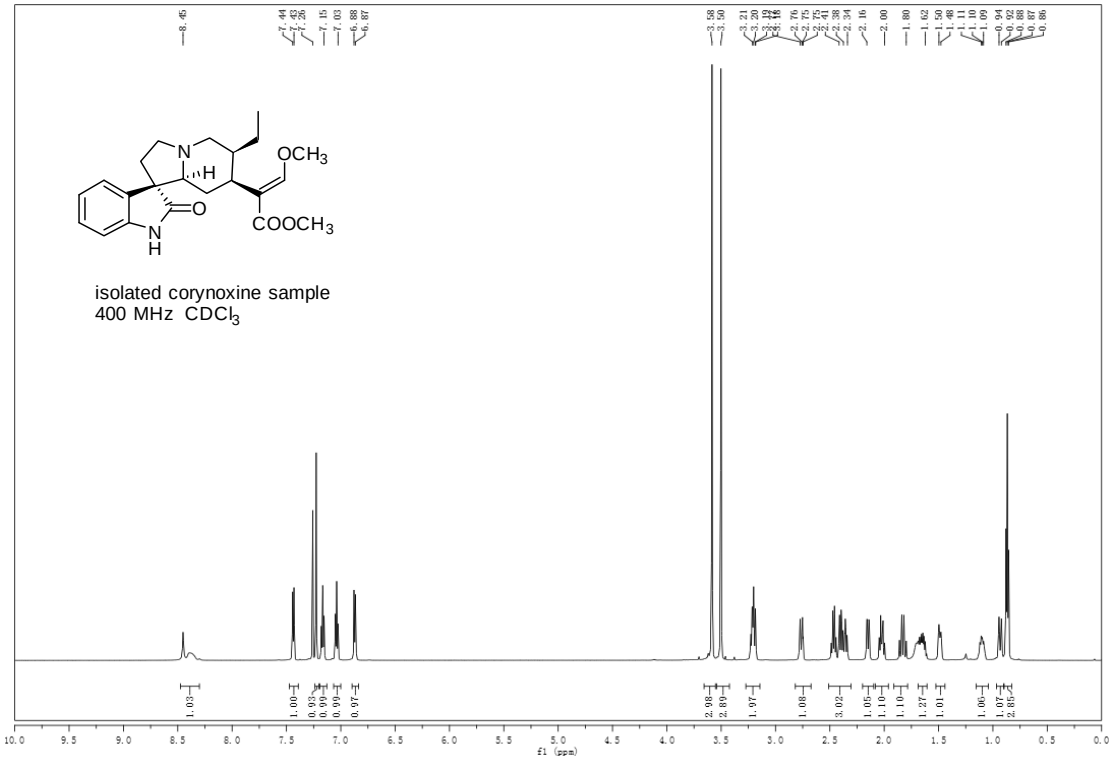


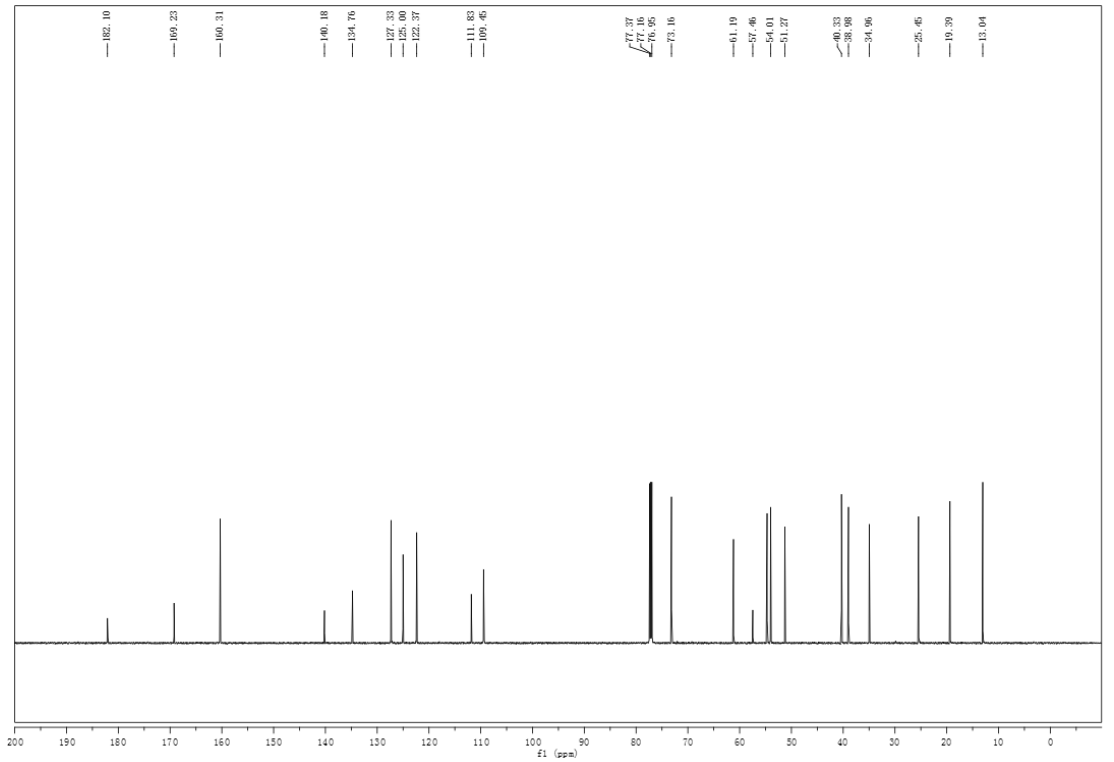

8.76
7.44
7.43
7.26
7.12
7.00
6.98
6.96
6.89
6.87
5.01
5.00
4.12
4.09
3.66
3.58
3.37
3.35
3.33
3.31
2.55
2.54
2.51
2.44
2.41
2.40
2.39
2.10
2.05
1.75
1.72
1.70
1.62
1.60
1.07
1.04
OCH3
N
H
O
N
H
COOCH3
16
1.00
1.06
0.99
1.26
1.23
1.08
0.96
1.36
3.23
3.01
2.23
1.15
2.33
1.16
1.28
1.29
3.24
1.08
f1 (ppm)

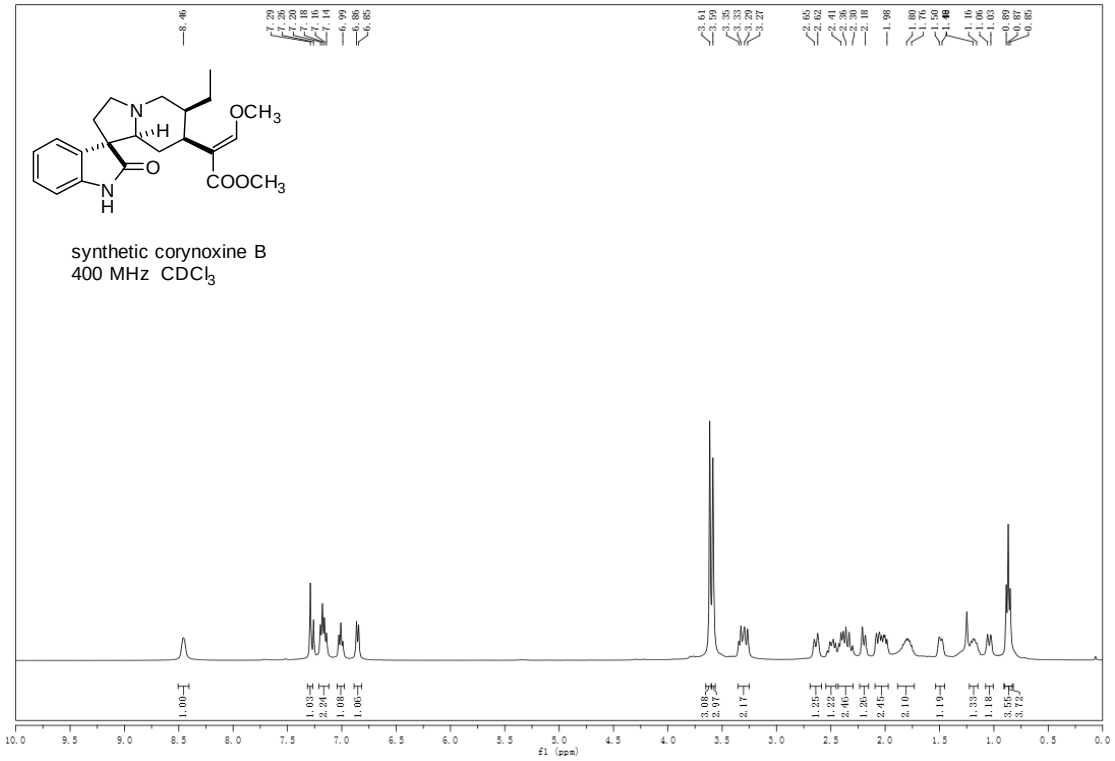

182.53
168.64
160.23
140.38
133.91
132.99
127.55
125.41
122.30
116.39
110.52
109.58
77.48
77.16
76.84
72.40
61.49
56.99
53.57
51.23
35.78
30.23
13.23
f1 (ppm)

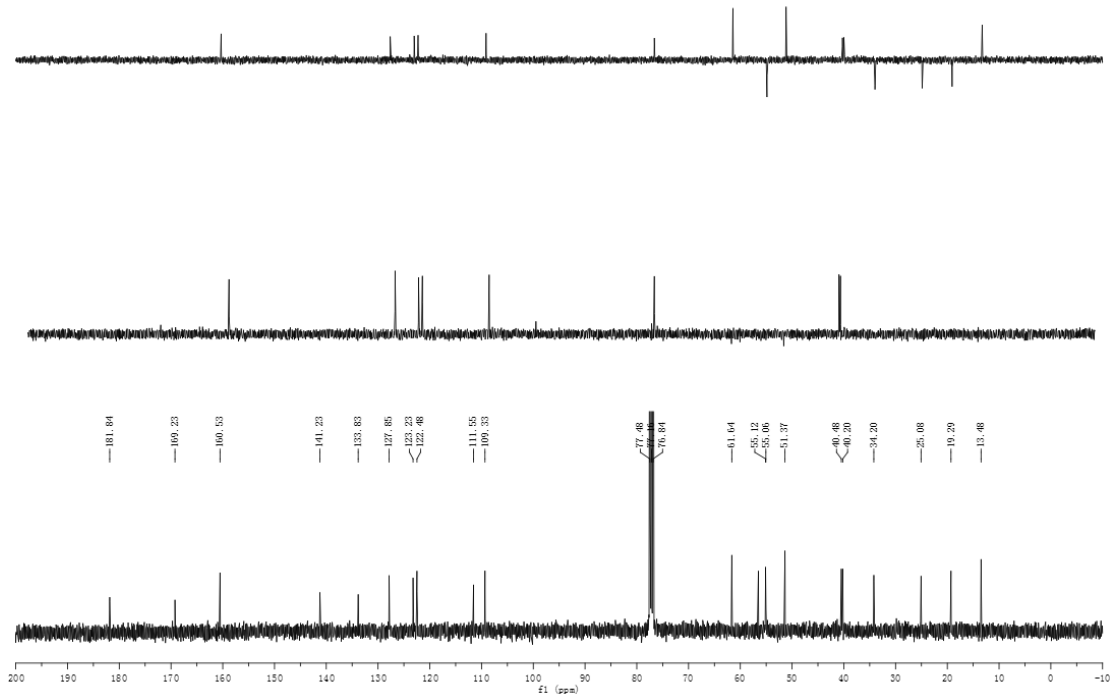

OCH3
N
H
O
N
H
COOCH3
synthetic corynoxine
400 MHz CDCl3
f1 (ppm)

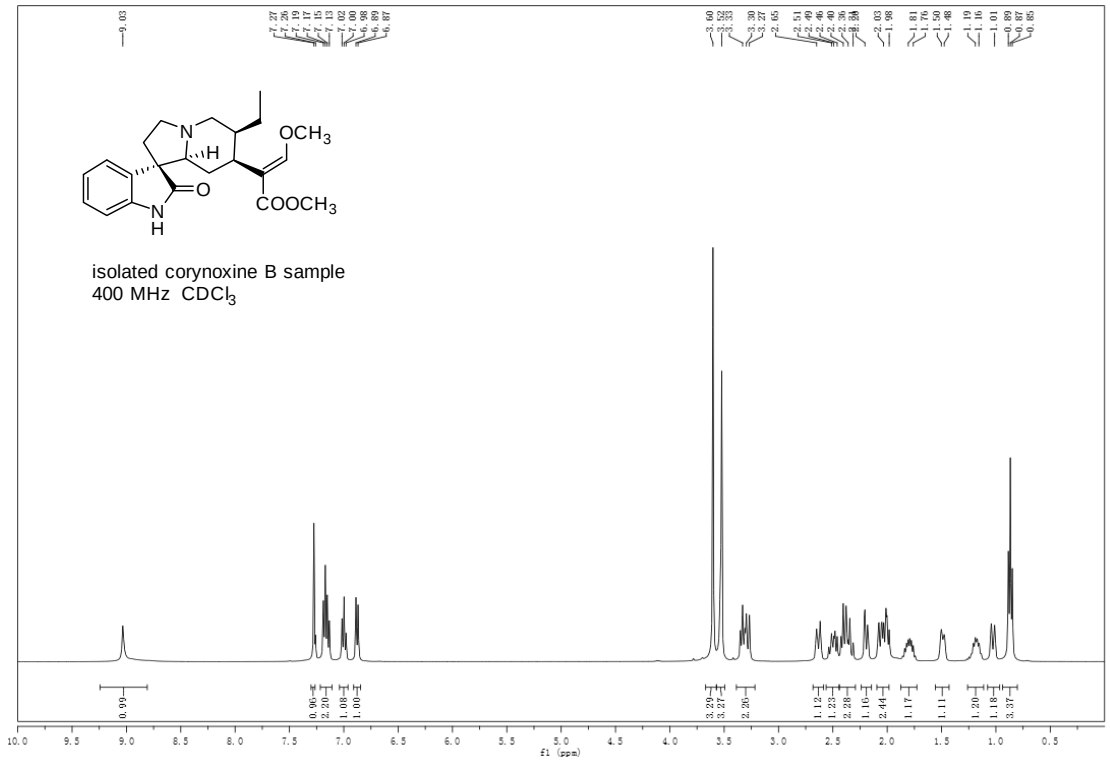

f1 (ppm)

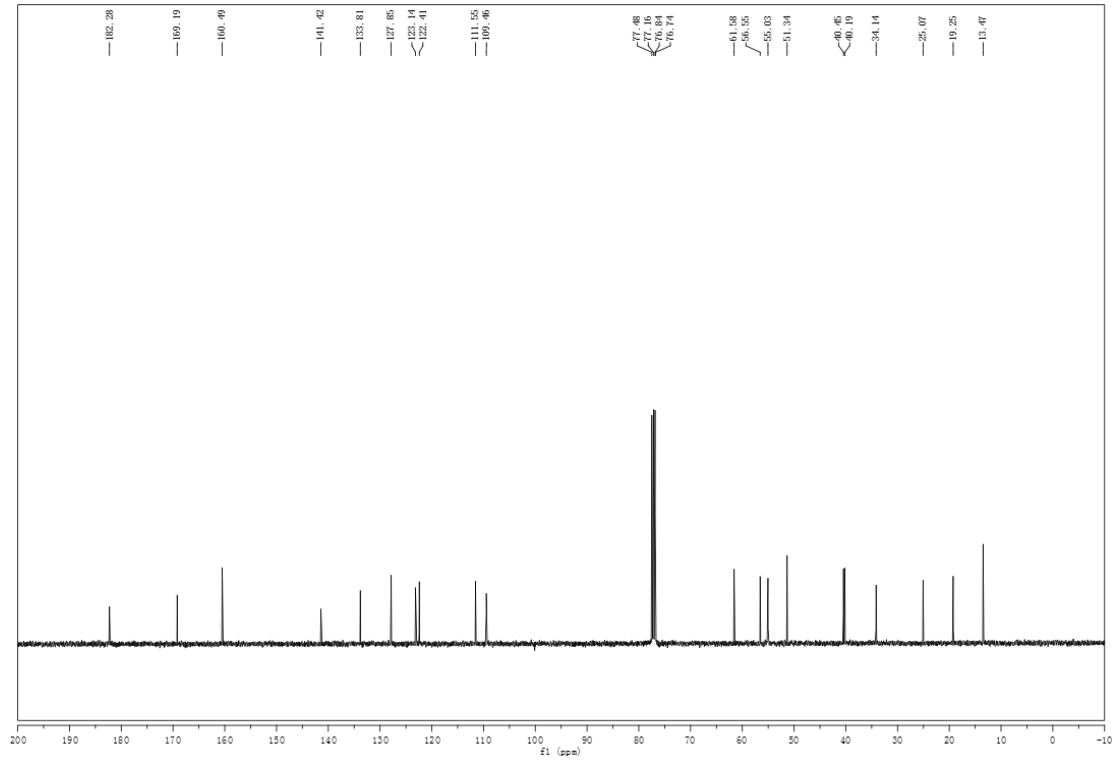

isolated corynoxine sample
400 MHz CDCl3
f1 (ppm)


f1 (ppm)


synthetic corynoxine B
400 MHz CDCl3
f1 (ppm)


f1 (ppm)


OCH3
COOCH3
N
H
O
N
H
isolated corynoxine B sample
400 MHz CDCl3
f1 (ppm)


f1 (ppm)