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Supporting Information

Palladium Catalyzed Reductive Heck Coupling and Its Application in Total Synthesis of 17-nor-Excelsinidine

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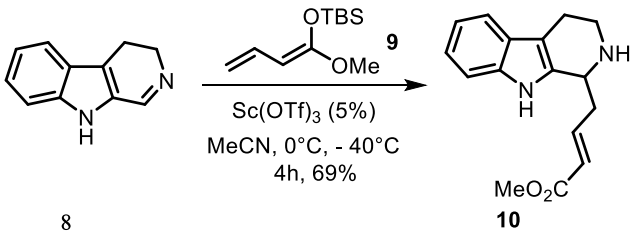
General Informations

All commercial reagents were purchased from Energy Chemical, Shanghai Macklin Biochemical Co Ltd, TCI, J&K Chemical Ltd, Rionlon of the Analytical Reagent, and used without further purification unless specified. Flash column chromatography was performed over silica gel (200-300 mesh) purchased from Qingdao Haiyang Co., China. All reactions were performed using oven-dried (> 100°C) round-bottomed flasks unless otherwise stated. Where appropriate, reactions were carried out under an inert atmosphere of argon with dry sovents, unless otherwise stated. Tetrahydrofuran (THF) was distilled under argon over sodium-benzophenone. Dry acetonitrile (MeCN) was obtained by filtration through drying column on a Glass Technology system. Dichloromethane (CH_2Cl_2), toluene (PhMe), diisopropylamine and 4-methylmorpholine (NMM) were distilled under argon over CaH_2. ^1H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Avance III 400 MHz NMR Spectrometer or a Varian INOVA 600MHz spectrometer. Chemical shifts of ^1H NMR and ^{13}C NMR were recorded in parts per million (ppm, δ) and reported relative to tetramethylsilane (TMS 0.00 ppm) and $CDCl_3$ (H: $\delta = 7.26$, C: $\delta = 77.16$ ppm), CD_3OD (H: $\delta = 4.87$, C: $\delta = 49.00$ ppm) respectively. ^1H NMR splitting patterns are designated as single (s), double (d), triplet (t), quartet (q), double of doublets (dd), doublet of triplets (dt), triplet of doublets (td), and multiplets (m).

Electron ionization mass (EI-MS) spectra were measured on a Shimadzu GCMSQP2010SE spectrometer by direct inlet at 70 eV and the corresponding signals were given in m/z with relative intensity (%) in brackets. High-resolution mass spectra (HRMS) were measured on a Thermo Scientfic Orbitrap Elite Mass Spectrometer by means of the ESI technique. Analytical TLC was performed on silica gel GF254 plates, and the spots were visualized using UV light (254 nm) or phosphomolybdic acid in ethanol (10%).

Experimental Procedures and Data for Compounds

Methyl(E)-4-(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)but-2-enoate 10



8 **10**

Compound **8** was synthesized according to Norman Whittaker.[1]

To a suspension of crude **8** (4.8 g, 28.2 mmol) and $Sc(OTf)_3$ (700 mg, 1.4 mmol) in MeCN (80 mL), **9** (9.1 g, 42.4 mmol) was added with dropwise at 0°C. After 30 min at 0°C, the reaction mixture was allowed to warm up to 40˚C and stirred for 3.5 h. The reaction mixture was cooled to rt and concentrated in vacuo and purified by column chromatography (CH_2Cl_2 : MeOH = 50:1) to afford **10** (5.2 g, 20 mmol, 69%) as a yellow solid.

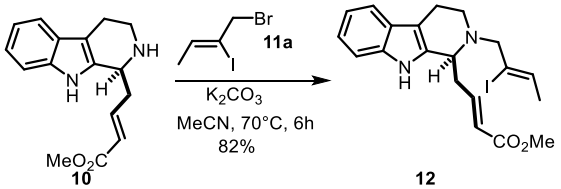
HRMS (ESI$^+$) m/z: calculated for $C_{16}H_{19}N_2O_2^+$ $[M + H]^+$ 271.1441, found 271.1447.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.06 (s, 1H), 7.48 (d, J = 7.7 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.15 (t, J = 8.1 Hz, 1H), 7.10 (t, J = 7.7 Hz, 1H), 7.03-6.98 (m, 1H), 6.05 (d, J = 15.7 Hz,1H), 4.24 (t, J = 8.6 Hz, 1H), 3.73 (s, 3H), 3.32-3.28 (m,1H), 3.02-3.07 (m, 1H), 2.79-2.65 (m, 5H).

^{13}C NMR (151MHz, $CDCl_3$): δ 166.7, 145.2, 135.9, 134.5, 127.4, 124.3, 122.0, 119.6, 118.3, 111.1, 109.8, 51.8, 42.3, 37.9, 29.8, 22.5.

[1]Norman Whittaker. ***J. Chem. Soc. C***, **1969**, 85-89.

Methyl(E)-4-((S)-2-((Z)-2-iodobut-2-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)but-2-enoate 12



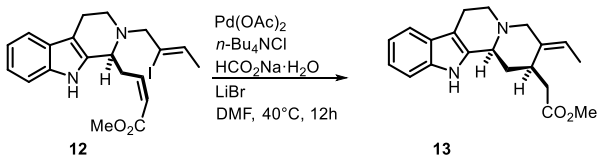
To a solution of **10** (2.7 g, 10.0 mmol) and **11a** (5.2 g, 20.0 mmol) in MeCN (40 mL), K_2CO_3 (2.8 g, 20.0 mmol) was added with portion wise. After 6 h at 70 °C, the reaction mixture was cooled to rt and concentrated in vacuo. The residue was dissolved in H_2O (50 mL) and EtOAc (50 mL). After partitioning, the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by column chromatography (PE : EtOAc = 9:1 ~ 3:1) to afford **12** (3.7 g, 8.2 mmol, 82%) as a yellow solid.

HRMS (ESI$^+$) m/z: calculated for $C_{20}H_{24}IN_2O_2^+$ $[M + H]^+$ 451.0877, found 451.0885.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.19 (bs, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.27-7.08 (m, 4H), 5.93 (d, J = 15.5 Hz, 1H), 5.84 (q, J = 6.4 Hz, 1H), 3.79-3.76 (m, 1H), 3.74 (s, 3H), 3.39 (d, J = 7.8 Hz, 2H), 3.17 (t, J = 9.7 Hz, 1H), 2.96-2.93 (m, 1H), 2.83-2.56 (m, 4H), 1.80 (d, J = 6.4 Hz, 3H).

^{13}C NMR (151MHz, $CDCl_3$): δ 167.1, 147.3, 136.0, 134.0, 132.1, 127.1, 122.6, 121.6, 119.3, 118.1, 111.9, 109.7, 108.3, 65.1, 56.0, 51.5, 43.7, 37.6, 21.7, 17.8.

Methyl2-((2R,12bS,E)-3-ethylidene-1,2,3,4,6,7,12,12b-octahydroindolo-[2,3a]quinolizin-2-yl)acetate 13



A mixture of $Pd(OAc)_2$ (90 mg, 0.4 mmol), n-Bu_4NCl (33.35 g, 120 mmol), $HCO_2Na·H_2O$

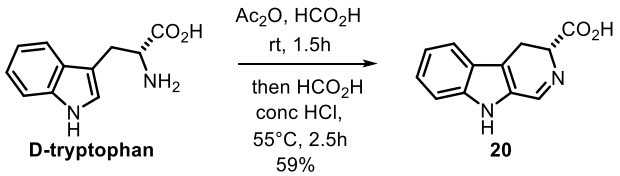
(8.32 g, 80 mmol) and LiBr (1.74 g, 20 mmol) in DMF (80 mL), **12** (1.80 g, 4.0 mmol) in DMF (10 mL) was added under an Argon atmosphere at room temperature for 30 min, and then heated at 40 °C for 12 h. The reaction was then cooled to 0˚C and quenched with *sat*. $NaHCO_3$. The aqueous layer was extracted with EtOAc (4 × 80 mL). The combined filtrates were washed with brine (10 × 100 mL), dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure to give the crude residue, which was purified by silica gel column chromatography eluting with a mixture of DCM / MeOH (v/v = 50:1) to afford **13** (583 mg, 1.8 mmol, 45%) as a yellow foam.

To a solution of $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), *n*-Bu_4NCl (1.67 g, 6.0 mmol), $HCO_2Na·H_2O$ (0.42 g, 4 mmol) and LiBr (87 mg, 1.0 mmol) in DMF (4 mL), **12** (90 mg, 0.20 mmol) in DMF (0.5 mL) was added under an Argon atmosphere at room temperature for 10 min, and then heated at 40 °C for 12 h. The reaction was then cooled to 0 ˚C and quenched with *sat.* $NaHCO_3$. The aqueous layer was extracted with EtOAc (4 × 4 mL). The combined filtrates were washed with brine (5 × 8 mL), dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure to give the crude product as a residue, which was purified by silica gel column chromatography eluting with a mixture of DCM / MeOH (v/v = 50:1) to afford **13** (35.6 mg, 0.11 mmol, 56%) as a yellow foam.

Data for **13**.

See the synthesis of **cis-13**.

(R)-4,9-dihydro-3H-pyrido[3,4-b] indole-3-carboxylic acid hydrochloride 20



To a solution of **D-tryptophan** (5.00 g, 24.48 mmol) in HCO_2H (9.5 mL) was added Ac_2O (2.77 mL). After 1.5 h at rt, HCO_2H (25 mL) and conc HCl (6.5 mL) were added sequentially.

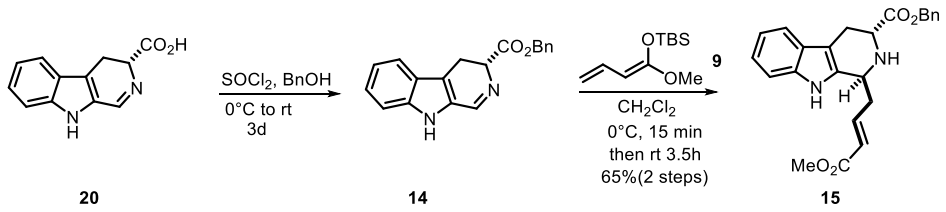
The reaction mixture was heated to 55°C for 2.5 h, cooled to rt and stored at 0°C overnight. The green precipitate was filtered, washed with Et_2O (5 x 10 mL) and dried under high vacuum to give **20** (3.634 g, 14.50 mmol, 59%) as a green solid.

$[\alpha]_D^{23}$: -397.3 (c = 0.75, CH_3OH).

HRMS (ESI$^+$) m/z: calculated for $C_{12}H_{11}N_2O_2^+$ $[M + H]^+$ 215.0815 ,found 215.0819.

^{1}H NMR (400 MHz, CD_3OD): δ 8.92 (d, J = 1.5 Hz, 1H), 7.77 (d, J = 7.2 Hz, 1H), 7.54-7.48 (m, 2H), 7.22 (m, 1H), 5.06 (t, J = 10.0 Hz, 1H), 3.74 (d, J = 4.4 Hz, 1H), 3.73 (d, J = 5.5 Hz, 1H).

(1S,3R)-benzyl1-((E)-4-methoxy-4-oxobut-2-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrio[3,4b]indole-3-carboxylate 15



To a flask with BnOH (130 mL), $SOCl_2$ (9.17 mL, 118.57 mmol) was added over 10 min via syringe pump at 0 °C. Then **20** (3.94 g, 15.717 mmol) was added to the above reaction mixture with portion wise. The reaction mixture was allowed to warm to rt and stirred for 3 days. Et_2O (525 mL) was added and the green precipitate was filtered, washed with Et_2O (5 x 25 mL) and dried under high vacuum to give crude **14** (4.14 g) as a yellow solid which was used in the next without further purification.

To a suspension of crude **14** (4.14 g) in CH_2Cl_2 (63 mL) **9** (7.81 g, 36.44 mmol) was added with dropwise at 0 °C. After 15 min at 0 °C, the reaction mixture was allowed to warm to rt and stirred for 3.5 h. The reaction mixture was quenched with *sat*. $NaHCO_3$. After partitioning, the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by column chromatography (PE: EtOAc = 70:30 ~ 55:45) to afford **15** (4.13 g, 10.21 mmol, 65% over 2

steps) as a light yellow solid.

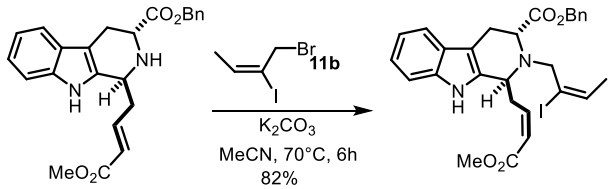
$[\alpha]_D^{25}$**:** - 61.2(c = 0.80, CH_3OH).

HRMS (ESI$^+$) m/z: calculated for $C_{12}H_{25}N_2O_4^+$ $[M + H]^+$ 405.1809, found 405.1815.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (bs, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.29-7.23 (m, 6H), 7.16-7.07 (m, 2H), 7.01 (dt, J = 15.6, 7.6 Hz, 1H), 5.94 (d, J = 15.8 Hz, 1H), 5.14 (s, 2H), 4.36 (t, J = 7.6Hz, 1H), 3.98 (t, J = 6.7 Hz, 1H), 3.72 (s, 3H), 3.11 (dd, J = 15.4, 5.3 Hz, 1H), 3.02 (dd, J = 15.4, 6.7 Hz, 1H), 2.65-2.51 (m, 3H).

^{13}C NMR (101MHz, $CDCl_3$): δ 173.4, 166.7, 145.7, 136.0, 135.5, 133.9, 128.4, 128.1, 127.7, 126.8, 123.4, 121.6, 119.2, 118.0, 111.9, 107.1, 66.5, 52.5, 51.4, 49.2, 38.1, 24.8.

Benzyl(1S,3R)-2-((E)-2-iodobut-2-en-1-yl)-1-((Z)-4-methoxy-4-oxobut-2-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate 16b



15 **16b**

To a solution of **15** (0.81 g, 2.0 mmol) and **11b** (0.52 g, 4.0 mmol) in MeCN (10 mL), K_2CO_3 (0.6 g, 4.0 mmol) was added. After 6 h at 70°C, the reaction mixture was cooled to rt and concentrated in vacuo. The residue was dissolved in H_2O (20 mL) and EtOAc (30 mL). After partitioning, the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by column chromatography (PE: EtOAc = 9:1 ~ 3:1) to afford **16b** (0.96 g, 1.6 mmol, 82%) as a yellow solid.

HRMS (ESI$^+$) m/z: calculated for $C_{28}H_{30}IN_2O_4^+$ $[M + H]^+$ 585.1245, found 585.1254

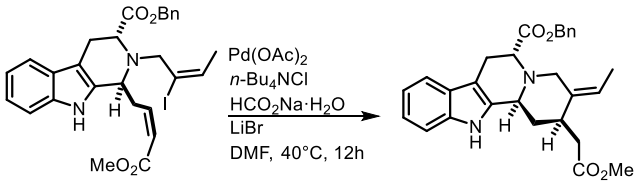
$[\alpha]_D^{23}$**:** -16.7 (c = 0.48, CH_3OH).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.49 (d, J = 7.7 Hz, 1H), 7.31-7.08 (m, 9H), 6.45 (q, J = 7.2 Hz, 1H), 5.87 (d, J = 15.8 Hz, 1H), 5.06 (s, 2H), 4.37 (t, J = 5.5 Hz, 1H), 4.02 (t, J

= 5.5 Hz, 1H), 3.71-3.67 (m, 2H), 3.68 (s, 3H), 3.25-3.20 (m, 1H), 3.11-3.03 (m, 1H), 2.84-2.69 (m, 2H), 1.51 (d, *J* = 7.2 Hz, 3H).

*** ^{13}C NMR (101MHz, $CDCl_3$)**: *δ* 172.8, 166.8, 145.8, 139.9, 136.5, 135.8, 133.8, 128.6, 128.2, 128.1, 127.0, 123.5, 122.0, 120.0, 118.4, 111.1, 107.8, 101.6, 66.4, 56.6, 55.1, 54.1, 51.6, 36.9, 23.5, 16.9.

Benzyl(2R,6R,12bS,Z)-3-ethylidene-2-(2-methoxy-2-oxoethyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-6-carboxylate 17b



16b **17b**

To a solution of $Pd(OAc)_2$ (22 mg, 0.03 mmol), *n*-Bu_4NCl (1.56 g, 5.6 mmol), $HCO_2Na·H_2O$ (0.26 g, 3.8mmol) and LiBr (0.44 g, 5 mmol) in DMF (4 mL) **16b** (0.15 g, 0.25 mmol) was added under Argon atmosphere at room temperature for 30 min, and then the reaction mixture was heated at 40 °C for 12 h. After that, the reaction mixture was then cooled to 0˚C and quenched with *sat.* $NaHCO_3$. The aqueous layer was extracted with EtOAc (4 × 20 mL). The combined filtrates were washed with brine (10 × 25 mL), dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure to give the crude residue, which was purified by silica gel column chromatography eluting with a mixture of PE : EtOAc = 5:1 ~ 3:1 to afford **17b** (55 mg, 0.11 mmol, 45%) as an orange solid.

HRMS (ESI$^+$) m/z: calculated for $C_{28}H_{31}N_2O_4^+$ $[M + H]^+$459.2278, found 459.2281.

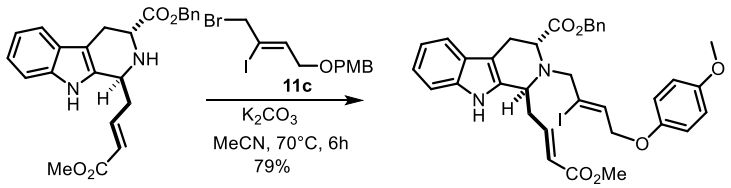
$[\alpha]_D^{25}$: -25.0 (c = 0.76, CH_3OH).

^{1}H NMR (600 MHz, $CDCl_3$): *δ* 7.80 (s, 1H), 7.45 (d, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.26-7.20 (m, 3H), 7.16-7.12 (m, 3H), 7.08 (t, *J* = 6.9 Hz, 1H), 5.19 (q, *J* = 6.2 Hz, 1H), 5.07 (q, *J* = 12.5 Hz, 2H), 4.51 (d, *J* = 11.3 Hz, 1H), 3.96 (dd, *J* = 6.5, 2.0 Hz , 1H), 3.82 (d, *J* = 12.2 Hz, 1H), 3.73 (s, 3H), 3.49 (d, *J* =12.2 Hz, 1H), 3.28- 3.24 (m, 1H), 3.21-3.18 (m, 1H) , 2.79

(m, 1H), 2.74 (dd, *J* = 15.4, 5.8 Hz, 1H), 2.30 (dd, *J* = 15.4, 8.3 Hz, 1H), 2.24 (dt, *J* = 13.4, 2.8 Hz, 1H), 1.67 (d, *J* = 5.8 Hz, 3H), 1.26 (q, *J* = 7.7 Hz, 1H).

^{13}C NMR (151MHz, $CDCl_3$): *δ* 173.5, 172.5, 136.8, 136.3, 136.0, 134.4, 128.6, 128.2, 127.9, 127.3, 121.6, 119.5, 118.2, 115.8, 110.9, 105.8, 66.1, 61.4, 54.0, 53.1, 51.9, 38.7, 38.4, 36.9, 25.3, 13.3.

Benzyl(1S,3R)-2-((Z)-2-iodo-4-(4-methoxyphenoxy)but-2-en-1-yl)-1-((E)-4-methoxy-4-oxobut-2-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate 16c



To a solution of **15** (0.81 g, 2.0 mmol) and **11c** (0.8 g, 2.0 mmol) in MeCN (10 mL), K_2CO_3 (0.6 g, 4.0 mmol) was added with portion wise. After 6 h at 70°C, the reaction mixture was cooled to rt and concentrated in vacuo. The residue was dissolved in H_2O (20 mL) and EtOAc (20 mL). After partitioning, the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by column chromatography (PE : EtOAc= 5:1 ~ 3:1) to afford **16c** (1.1 g, 1.5 mmol, 79%) as a yellow solid.

HRMS (ESI$^+$) m/z: calculated for $C_{35}H_{36}IN_2O_6^+$ $[M + H]^+$707.1613, found 707.1621.

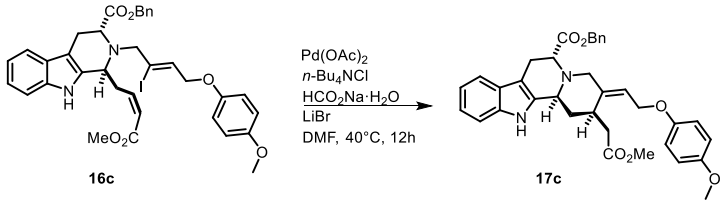
$[\alpha]_D^{25}$: -28.6 (c = 0.77, CH_3OH).

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.83 (d, *J* = 5.5 Hz, 1H), 7.47 (d, *J* = 7.4 Hz, 1H), 7.27-6.99 (m, 9H), 6.83 (s, 4H), 6.18 (t, *J* = 5,1 Hz, 1H), 5.84 (d, *J* = 15.6 Hz, 1H), 5.08 (q, *J* = 5.1Hz, 2H), 4.58 (d, *J* = 5.5 Hz, 2H), 4.26 (t, *J* = 5,5 Hz, 1H), 3.99 (t, *J* = 5,5 Hz, 1H), 3.75 (s, 3H), 3.72 (m, 1H), 3.67 (s, 3H), 3.52 (d, *J* = 13.9 Hz, 1H), 3.18 (m, 1H), 3.05 (m, 1H), 2.68 (t, *J* = 9.7 Hz, 2H).

^{13}C NMR (101MHz, $CDCl_3$): *δ* 172.4, 166.7, 154.2, 145.6, 136.4, 135.8, 133.8, 133.5, 128.6,

128.2, 127.8, 126.9, 123.6, 122.1, 119.7, 118.4, 116.9, 116.0, 114.8, 110.1, 108.2, 107.7, 72.7, 66.4, 62.2, 57.2, 55.8, 55.5, 51.6, 37.2, 23.0.

Benzyl(2R,6R,12bS,E)-2-(2-methoxy-2-oxoethyl)-3-(2-(4-methoxyphenoxy)ethylide-ne)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-6-carboxylate 17c



To a solution of $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), *n*-Bu_4NCl (1.70 g, 6.1 mmol), $HCO_2Na·H_2O$ (0.43 g, 4.05 mmol) and LiBr (0.12 g, 1.35 mmol) in DMF (4 mL) **16c** (0.19 g, 0.27 mmol) was added under Argon atmosphere at room temperature for 30 min, and then heated at 40 °C for 12 h. The reaction was then cooled to 0˚C and quenched with *sat*. $NaHCO_3$. The aqueous layer was extracted with EtOAc (4 × 20 mL). The combined filtrates were washed with brine (10 × 20 mL), dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure to give the crude residue, which was purified by silica gel column chromatography eluting with a mixture of (PE : EtOAc = 5:1 ~ 3:1) to afford **17c** (60 mg, 0.1 mmol, 38%) as a yellow foam.

HRMS (ESI$^+$) m/z: calculated for $C_{35}H_{36}N_2NaO_6^+$ $[M + Na]^+$603.2466, found 603.2472.

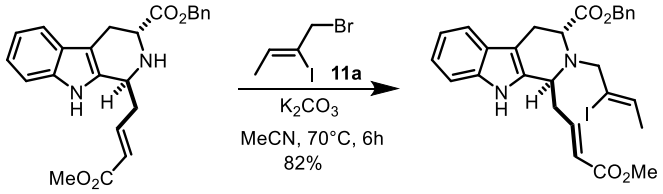
$[\alpha]_D^{25}$**:** -2.0 (c = 0.18, CH_3OH).

^{1}H NMR (600 MHz, $CDCl_3$): *δ* 9.48 (s, 1H) , 7.47 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 8.0Hz, 1H) , 7.29-7.27 (m, 1H) , 7.25-7.18 (m, 4H) , 7.15 (t , *J* = 7.0Hz , 1H), 6.80 (s, 4H), 5.91 (t, *J* = 6.5 Hz , 1H), 5.42 (s, 1H), 5.16 (d, *J* = 12.2 Hz, 1H), 5.06 (d, *J* = 12.2 Hz, 1H) , 4.68 (d, *J* = 6.5 Hz, 1H) , 4.51 (t , *J* = 6.5 Hz, 1H), 3.95-3.85 (m, 2H), 3.77-3.71 (m, 1H), 3.74 (s, 3H), 3.63 (s, 3H), 3.55 (d, *J* = 17.2 Hz, 1H), 3.42-3.40 (m, 1H), 3.30-3.27 (m, 1H), 2.63 (s, 2H), 2.22-2.18 (m, 1H), 2.12-2.08 (m, 1H), 1.56-1.54 (m, 1H), 1.24 (d, *J* = 7.0 Hz, 1H).

^{13}C NMR (151MHz, $CDCl_3$): *δ* 173.1, 167.4, 154.3, 152.4, 136.9, 134.5, 133.1, 128.84, 128.78, 128.7, 128.4, 128.0, 126.4, 123.4, 120.6, 118.4, 116.0, 115.7, 114.8, 111.1, 103.8, 68.3, 64.2,

60.6, 55.9, 52.2, 50.9, 36.5, 31.0, 20.2, 18.6.

(1S,3R)-benzyl-2-((Z)-2-iodobut-2-en-1-yl)-1-((E)-4-methoxy-4-oxobut-2-en-1-yl)2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate 16a



To a solution of **15** (4.13 g, 10.21 mmol) and **11a** (5.33 g, 20.42 mmol) in MeCN (23 mL), K_2CO_3 (2.82 g, 20.42 mmol) was added with portion wise. After 6 h at 70°C, the reaction mixture was cooled to rt and concentrated in vacuo. The residue was dissolved in H_2O (50 mL) and EtOAc (50 mL). After partitioning, the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by column chromatography (PE:EtOAc = 9:1 ~ 3:1) to afford **16a** (4.87 g, 8.33 mmol, 82%) as a yellow solid.

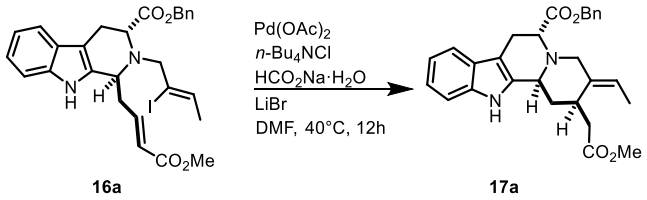
$[\alpha]_D^{25}$**:** - 23.3 (c = 0.30, CH_3OH).

HRMS (ESI$^+$) m/z: calculated for $C_{28}H_{29}IN_2NaO_4^+$ [M + Na]$^+$ 607.1064, found 607.1064.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, J = 9.3 Hz, 1H), 7.47 (d, J = 7.3 Hz, 1H), 7.26-7.00 (m, 10H), 5.89-5.81 (m, 2H), 5.07 (s, 2H), 4.31 (t, J = 5.4 Hz, 1H), 4.00 (t, J = 5.4 Hz, 1H), 3.67 (s, 3H), 3.65 (d, J = 8.8 Hz, 1H), 3.53 (d, J = 14.9 Hz, 1H), 3.19 (dd, J = 15.5, 5.8 Hz, 1H), 3.05 (dd, J = 16.0, 4.0 Hz, 1H), 2.77-2.62 (m, 2H), 1.75 (d, J = 6.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.8, 166.8, 145.9, 136.4, 135.9, 133.7, 132.5, 128.5, 128.1, 127.8, 126.9, 123.4, 121.9, 119.6, 118.3, 111.0, 108.6, 107.7, 66.3, 62.3, 57.0, 55.3, 52.0, 37.0, 23.2, 21.8.

Benzyl(2R,6R,12bS,E)-3-ethylidene-2-(2-methoxy-2-oxoethyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-6-carboxylate 17a



To a solution of $Pd(OAc)_2$ (90 mg, 0.38 mmol), *n*-Bu_4NCl (23.72 g, 84.83 mmol), $HCO_2Na·H_2O$ (5.89 g, 56.55 mmol) and LiBr (1.64 g, 18.85 mmol) in DMF (80 mL), **16a** (2.20 g, 3.77 mmol) in DMF (10 mL) was added under Argon atmosphere at room temperature for 30 min, and then heated at 40 °C for 12 h. The reaction was then cooled to 0˚C and quenched with *sat*. $NaHCO_3$. The aqueous layer was extracted with EtOAc (4 × 80 mL). The combined filtrates were washed with brine (10 × 100 mL), dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure to give the crude product as a residue, which was purified by silica gel column chromatography eluting with a mixture of DCM:MeOH (v/v = 50:1) to afford **17a** (931 mg, 1.92 mmol, 51%) as an orange solid.

To a solution of $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), *n*-Bu_4NCl (1.26 g, 4.5 mmol), $HCO_2Na·H_2O$ (0.31 g, 3 mmol) and LiBr (87 mg, 1 mmol) in DMF (4 mL), **16a** (117 mg, 0.20 mmol) was added under Argon atmosphere at room temperature for 30 min, and then heated at 40 °C for 6 h. The reaction was then cooled to 0˚C and quenched with *sat*. $NaHCO_3$. The aqueous layer was extracted with EtOAc (4 × 4 mL). The combined filtrates were washed with brine (5 × 8 mL), dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure to give the crude product as a residue, which was purified by silica gel column chromatography eluting with a mixture of DCM:MeOH (v/v = 50:1) to afford **17a** (57 mg, 0.12 mmol, 59%) as an orange solid.

$[\alpha]_D^{23}$: -16.1 (c = 0.56, CH_3OH).

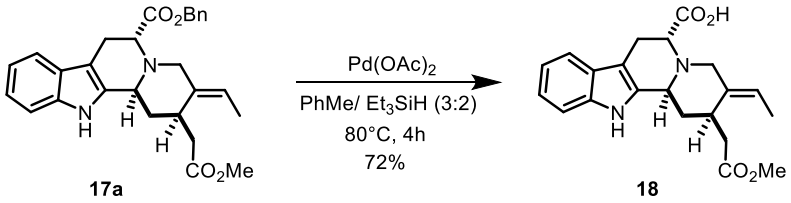
HRMS (ESI$^+$) m/z: calculated for $C_{28}H_{31}N_2O_4^+$ $[M + H]^+$ 459.2278 found 459.2281.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.36 (bs, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.32 (d, J = 7.8 Hz,

1H), 7.25-7.20 (m, 5H), 7.15-7.08 (m, 2H), 5.44 (q, *J* = 6.0 Hz, 1H), 5.14 (d, *J* = 11.8 Hz, 1H), 5.05 (d, *J* = 12.7 Hz, 1H), 4.57 (t, *J* = 6.3 Hz, 1H), 3.95-3.93 (m, 1H), 3.67 (s, 3H), 3.54 (d, *J* = 11.8 Hz, 1H), 3.28-3.16 (m, 4H), 2.37-2.19 (m, 3H), 2.04-1.99 (m, 1H), 1.63 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.8, 172.3, 136.2, 135.9, 135.5, 134.1, 128.5, 128.1, 128.0, 127.4, 121.5, 120.1, 119.4, 118.0, 111.0, 105.3, 66.3, 61.0, 55.1, 51.7, 49.2, 38.1, 32.6, 31.6, 21.8, 12.8.

(2R,6R,12bS,E)-3-ethylidene-2-(2-methoxy-2-oxoethyl)-1,2,3,4,6,7,12,12-boctahydroindolo[2,3-a]quinolizine-6-carboxylic acid 18.



To a solution of **17a** (490 mg, 1.07 mmol) and $Pd(OAc)_2$ (72 mg, 0.32 mmol) in PhMe (30 mL), Et_3SiH (20 mL) was added in one portion at 80°C. After 4 h at 80°C, the reaction mixture was concentrated in vacuo. The residue was dissolved in MeOH and filtered on celite. After removal of the solvent in vacuo, the crude residue was purified by column chromatography (CH_2Cl_2:MeOH = 95:5 ~ 4:1) to afford **18** (284 mg, 0.77 mmol, 72%) as a yellow solid.

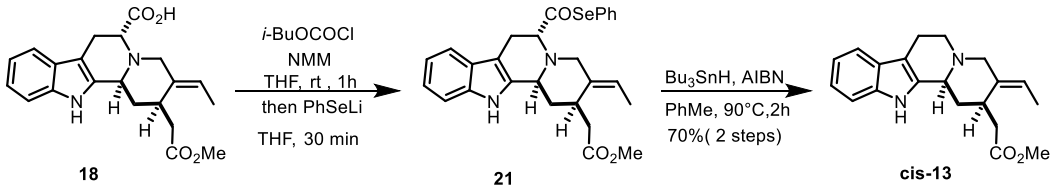
$[\alpha]_D^{25}$: -5.714 (c = 0.35, CH_3OH).

HRMS (ESI$^+$) m/z: calculated for $C_{21}H_{25}N_2O_4^+$ $[M + H]^+$ 369.1809, found369.1815.

^{1}H NMR (600 MHz, CD_3OD): δ 7.44 (d, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.10 (t, *J* = 7.3 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 5.73 (q, *J* = 6.9 Hz, 1H), 5.20 (bs, 1H), 4.04 (t, *J* = 5.5 Hz, 1H), 3.88-3.82 (m, 2H), 3.55 (s, 3H), 3.45-3.27 (m, 4H), 2.45-2.40 (m, 2H), 2.31 (dd, *J* = 15.5, 7.6 Hz, 1H), 2.07 (dd, *J* = 15.4, 7.6 Hz, 1H), 1.65 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, CD_3OD): δ 173.7, 138.2, 131.6, 129.4, 127.6, 123.4, 120.6, 119.2, 112.4, 105.6, 65.0, 54.2, 53.1, 51.7, 37.7, 31.6, 30.8, 21.8, 13.3.

Methyl2-((2R,12bS,E)-3-ethylidene-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3a]quinolizin-2-yl)acetate cis-13.



To a solution of **18** (391 mg, 1.06 mmol) in THF (10.6 mL), isobutyl chloroformate (172 μL, 1.33 mmol) was added with dropwise at rt, followed by 4-methylmorpholine (138 μL, 1.22 mmol). The reaction mixture was stirred at rt for 1 h. Simultaneously to a solution of phenylselenol (153 μL, 1.27 mmol) in THF (5.3 mL), *n*-BuLi (511 μL, 2.4 M in hexanes, 1.27 mmol) was added with dropwise at rt. After 5 min at rt, the solution of PhSeLi was transferred to the mixed anhydride system via cannulation. The reaction mixture was then stirred at rt for 30 min and quenched with H_2O (15 mL). The aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by column chromatography (PE:EtOAc = 9:1 ~ 85:15) to afford nearly pure **21** (446 mg) as an orange foam which was used in the next step without further purification.

To a solution of **21** (361 mg) in degassed benzene (6.2 mL), Bu_3SnH (763 μL, 2.84 mmol) and AIBN (23 mg, 0.14 mmol) in degassed benzene (1 mL) was added at 80 °C over 1 h via syringe pump. Then the reaction mixture was stirred at 80 °C for 1 h. After cooling to rt, the mixture was directly submitted to column chromatography (CH_2Cl_2:MeOH= 98:2 ~ 92:8) to afford **cis-13** (253 mg, 0.78 mmol, 74% over 2 steps) as a yellow foam.

$[\alpha]_D^{25}$: +10.0 (c = 0.10, CH_3OH).

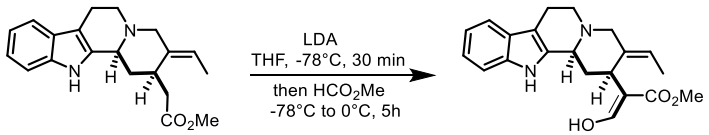
HRMS (ESI$^+$) m/z: calculated for $C_{20}H_{25}N_2O_2^+$ $[M+H]^+$ 325.1911, found 325.1916.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (bs, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.17-7.14 (M, 1H), 7.12-7.09 (m, 1H), 5.48 (q, J = 6.8 Hz, 1H), 4.30 (bs, 1H), 3.70 (s, 3H), 3.56 (d, J = 12.4 Hz, 1H), 3.27 (dd, J = 12.4, 5.2 Hz, 1H), 3.17-3.10 (m, 2H), 3.06- 2.99 (m, 1H), 2.97 (d, J = 12.4 Hz, 1H), 2.65 (d, J = 15.8 Hz, 1H), 2.31 (dt, J = 14.2, 3.8 Hz, 1H), 2.21-

2.11 (m, 3H), 1.65 (d, J = 6.8 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.0, 136.1, 135.9, 133.8, 127.7, 121.5, 120.9, 119.5, 118.1, 111.9, 107.5 53.4, 53.2, 51.8, 51.3, 37.4, 31.3, 30.9, 18.1, 12.8.

(+)-geissoschizine (1)



13 **(+)-geissoschizine (1)**

To a solution of diisopropylamine (162 µL, 1.15 mmol) in THF (0.6 mL) *n*-BuLi (743 µL, 1.55 M in THF, 1.15 mmol) was added with dropwise at -78 °C. After 30 min at 0 °C, the reaction mixture was recooled to 78 °C and a solution of **13** (101 mg, 0.31 mmol) in THF (3.2 mL) was added to the LDA system with dropwise. After 30 min at -78 °C, methyl formate (1.61 mL, 26.15 mmol) was added with dropwise in neat form. The reaction mixture was stirred at -78 °C for 3 h, slowly warmed to 0 °C over 2 h and quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (10 mL × 3), and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography PE:EA= 3:1) to afford (+)-geissoschizine (**1**) (76 mg, 0.22 mmol, 70%).

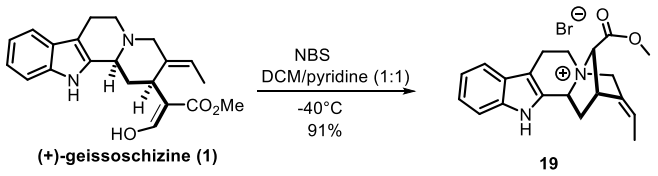
$[\alpha]_D^{23}$: +40.0 (c = 0.10, CH_3OH).

HRMS (ESI$^+$) m/z: calculated for $C_{21}H_{25}N_2O_3^+$ $[M + H]^+$ 353.1860, found 353.1866.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (bs, 1H), 7.89 (s, 1H), 7.48 (d, J = 8.6 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.19-7.09 (m, 2H), 5.42 (q, J = 7.2 Hz, 1H), 4.52 (d, J = 11.5 Hz, 1H), 3.96 (dt, J = 13.7, 2.4 Hz, 1H), 3.87-3.80 (m, 1H), 3.71 (s, 3H), 3.24-3.17 (m, 2H), 3.11-3.03 (m, 1H), 2.82 (dd, J = 15.3, 4.2 Hz, 1H), 2.74-2.65 (m, 2H), 2.10 (t, J = 13.7 Hz, 1H), 1.83 (d, J = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.7, 161.7, 136.6, 133.3, 132.9, 126.6, 122.1, 121.9, 119.8, 118.4, 111.1, 108.2, 107.7, 59.2, 53.7, 51.3, 50.6, 33.9, 27.8, 20.5, 13.3.

(5S,12bS,13S,E)-3-ethylidene-13-(methoxycarbonyl)-1,2,3,4,6,7,12,12b-octahydro-2,5methanoindolo[2,3-a]quinolizin-5-ium bromide 19.



To a solution of (+)-Geissoschizine (20 mg, 0.057 mmol) in CH_2Cl_2 (2.4 mL) pyridine (2.4 mL) was added at rt. After 5 min of stirring, the light yellow solution was cooled to −40 °C, NBS (10.2 mg, 0.057 mmol) in DCM (0.5 mL) was added with dropwise to the above mixture. The resulting orange solution was stirred at −40 °C for 25 min, and quenched with a mixture of saturated aqueous $Na_2S_2O_3$ (3 mL) and saturated aqueous $NaHCO_3$ (3 mL). The mixture was allowed to warm to ambient temperature, and partitioned between saturated aqueous $NaHCO_3$ (10 mL) and DCM (10 mL). The aqueous layer was extracted with DCM (2 x 10 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography (CH_2Cl_2:MeOH = 98:2 ~ 92:8) to afford **19** (21 mg, 0.052 mmol, 91%) as a yellow foam.

$[\alpha]_D^{23}$: -60.0 (c = 0.10, CH_3OH).

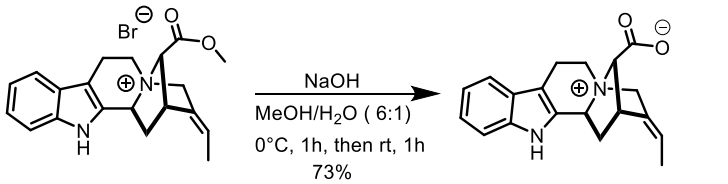
HRMS (ESI^+) m/z: calculated for $C_{20}H_{23}N_2O_2^+$ $[M+H]^+$ 323.1754, found 323.1754.

HRMS (ESI^-) m/z: calculated for Br^- $[M]^-$79.9178, found 79.9187.

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.55 (s, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.12-7.08 (m, 1H), 7.04-6.94 (m, 2H), 5.72 (bs, 1H), 5.43 (q, J = 7.0 Hz, 1H), 5.21 (d, J = 14.2 Hz, 1H), 4.33-4.29 (m, 1H), 4.24-4.10 (m, 2H), 4.02 (s, 1H), 3.75 (s, 3H), 3.61 (d, J = 4.2Hz, 1H), 2.69 (dd, J = 12.6, 8.6 Hz, 1H), 2.62-2.54 (m, H), 2.46-2.34 (m, 2H), 1.59 (d, J = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.3, 137.2, 130.1, 129.1, 124.9, 122.6, 120.4, 119.6, 118.4, 112.1, 102.9, 70.2, 68.9, 65.5, 53.6, 51.8, 42.4, 34.7, 17.9, 14.4.

(−)-17-nor-excelsinidine (7)



19 **(-)-17-nor-excelsinidine (7)**

To a solution of **19**(20 mg, 0.050 μmol) in MeOH/H_2O 6:1 (0.6 mL), NaOH (*solid*, 16 mg, 0.40 mmol) was added with one-portion at 0 °C. After 1 h at 0 °C, the reaction mixture was allowed to warm to rt and stirred at rt for 1h. The mixture was directly submitted to preparative TLC (CH_2Cl_2:MeOH= 92:8) to afford (-)-17-nor-excelsinidine (11 mg, 0.036 mmol, 73%) as an off-white solid.

$[\alpha]_D^{23}$**:** -100.0 (c = 0.17, CH_3OH).

HRMS (ESI$^+$) m/z: calculated for $C_{19}H_{21}N_2O_2^+$ $[M+H]^+$309.1598, found 309.1598.

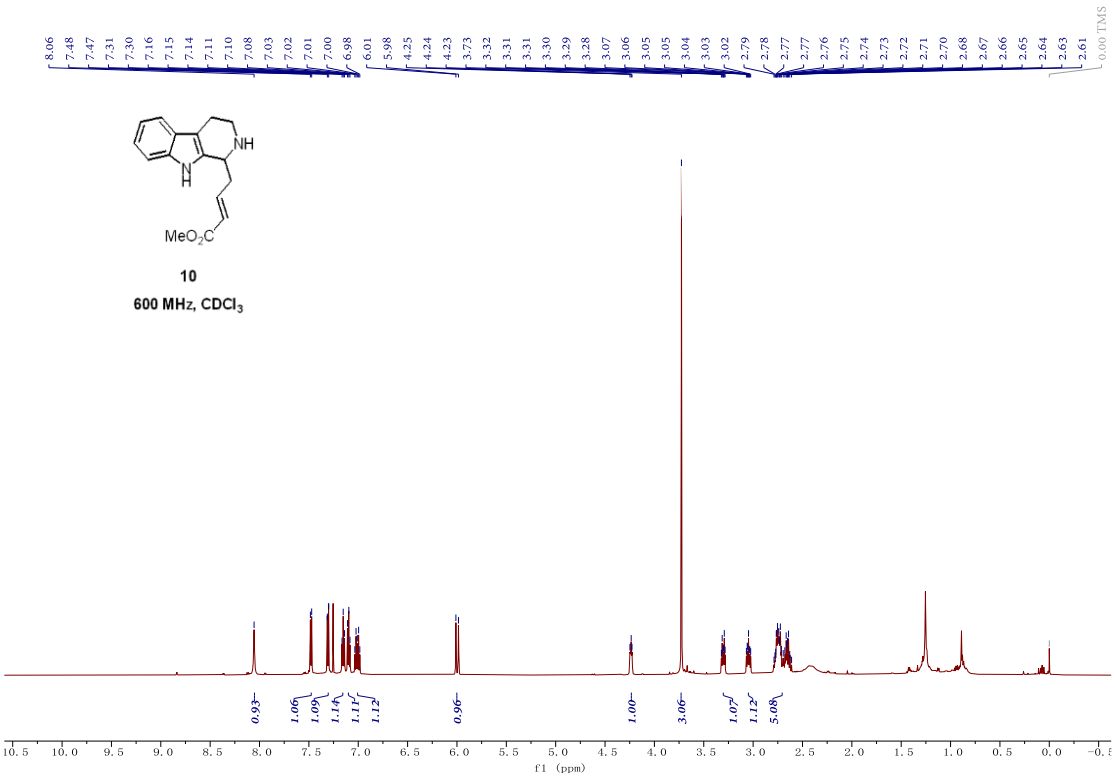
^{1}H NMR (600 MHz, CD_3OD): *δ* 7.49 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.17 (dt, *J* = 7.6, 1.32 Hz, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 5.53 (q, *J* = 6.8 Hz, 1H), 5.12 (t, *J* = 6.8 Hz, 1H), 4.82-4.77 (m, 2H), 4.12-4.09 (m, 2H), 3.82 (s, 1H), 3.69 (dt, *J* = 12.24, 4.8 Hz, 1H), 3.13-3.09 (m, 1H), 3.06-3.0 (m,1H), 2.36 (dd, *J* = 6.9, 2.6 Hz, 2H), 1.77 (dt, *J* = 6.9, 2.1 Hz, 3H).

^{13}C NMR (151 MHz, CD_3OD): *δ* 169.3, 138.9, 134.2, 131.0, 126.9, 123.6, 120.8, 119.4, 119.4, 112.5, 105.5, 72.9, 70.5, 66.7, 52.3, 43.5, 35.3, 18.9, 14.4.

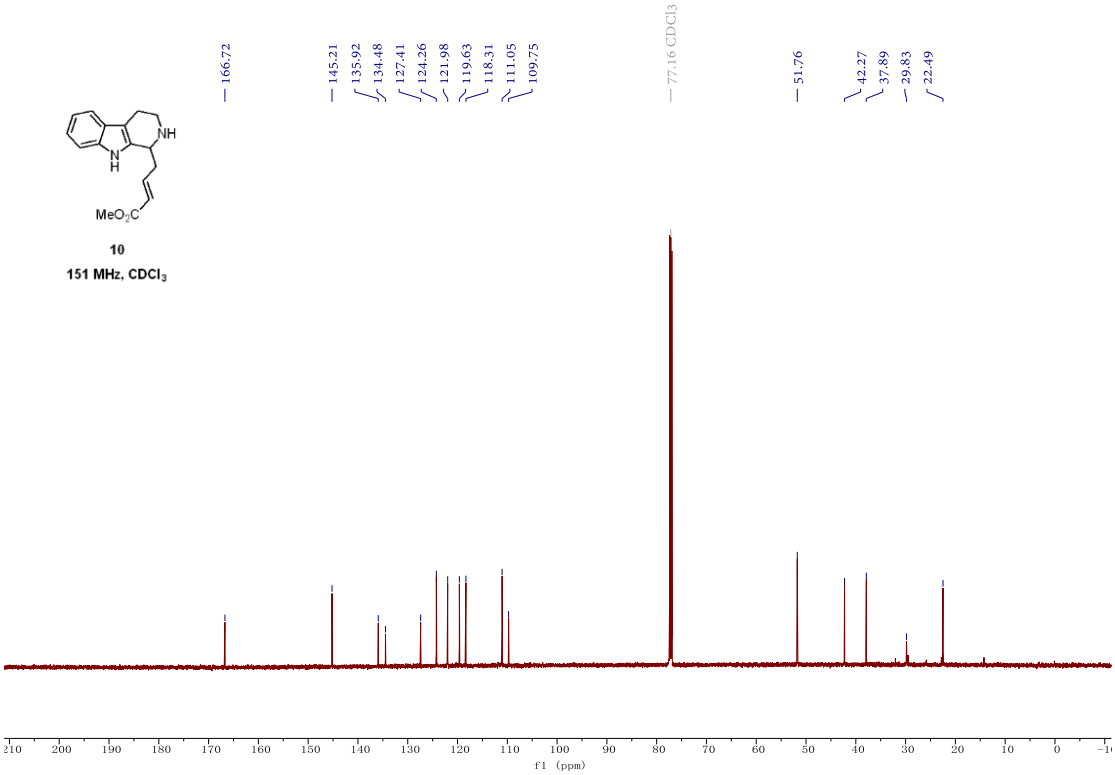
NMR Spectra

NMR of compound 10

^{1}H NMR of 10 (600 MHz, $CDCl_3$)

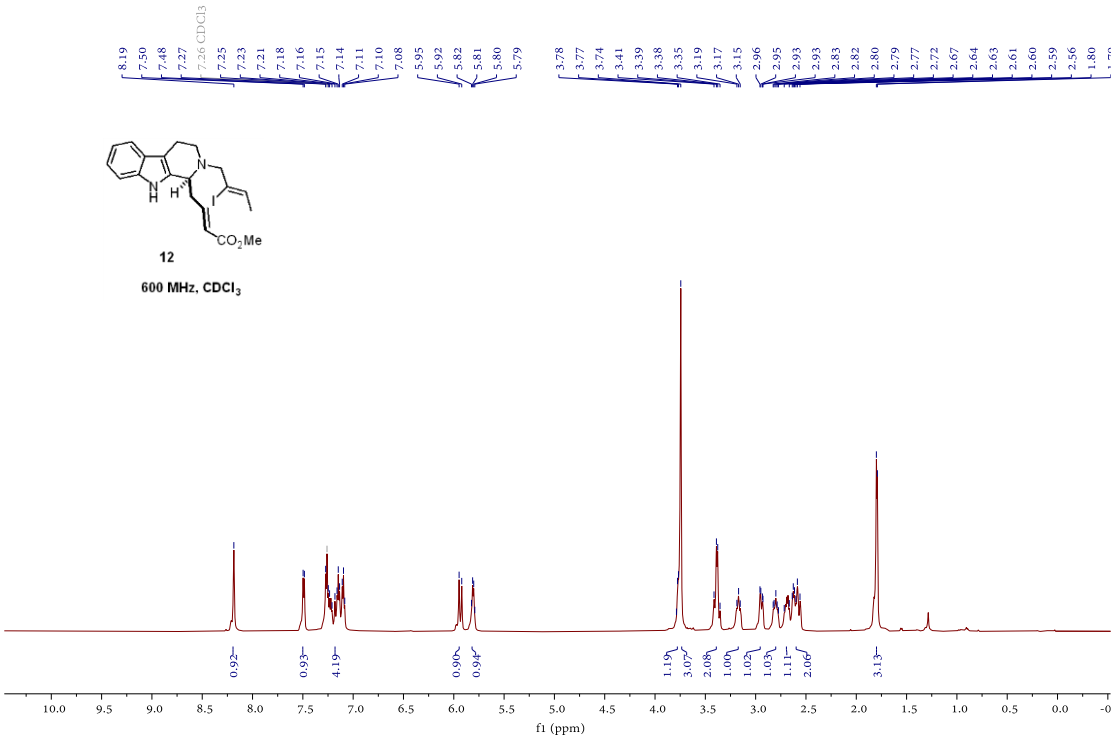


^{13}C NMR of 10 (151 MHz, $CDCl_3$)

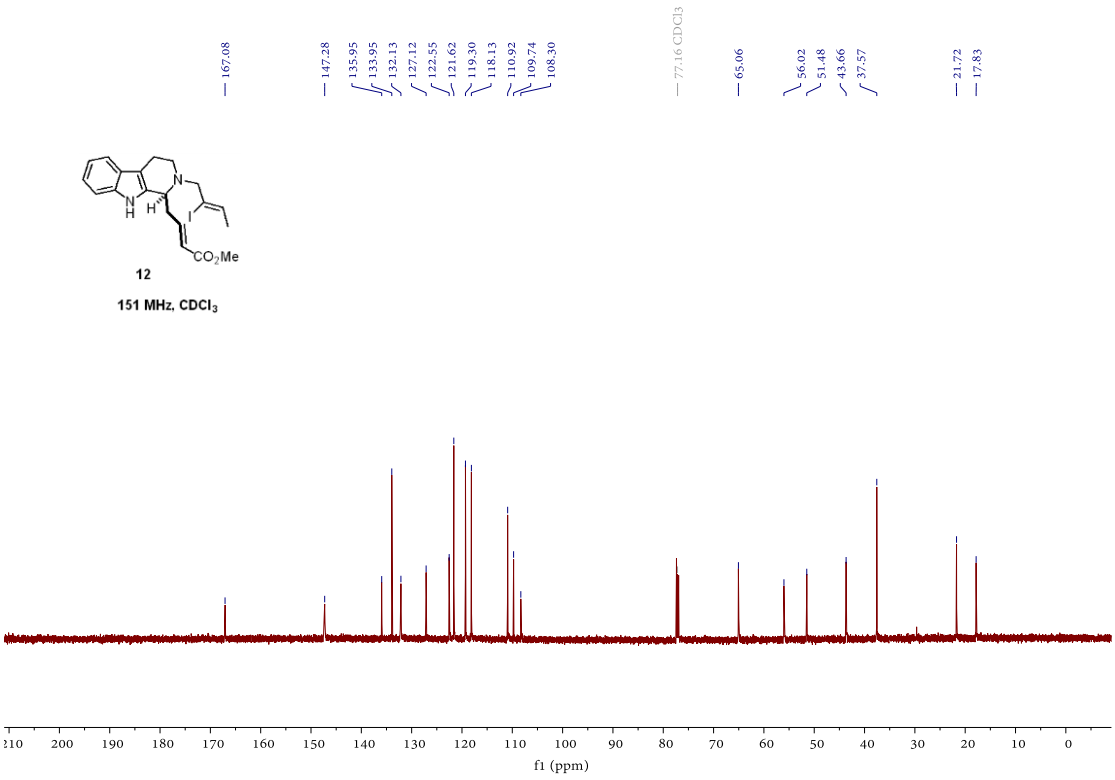


NMR of compound 12

^{1}H NMR of 12 (600 MHz, $CDCl_3$)

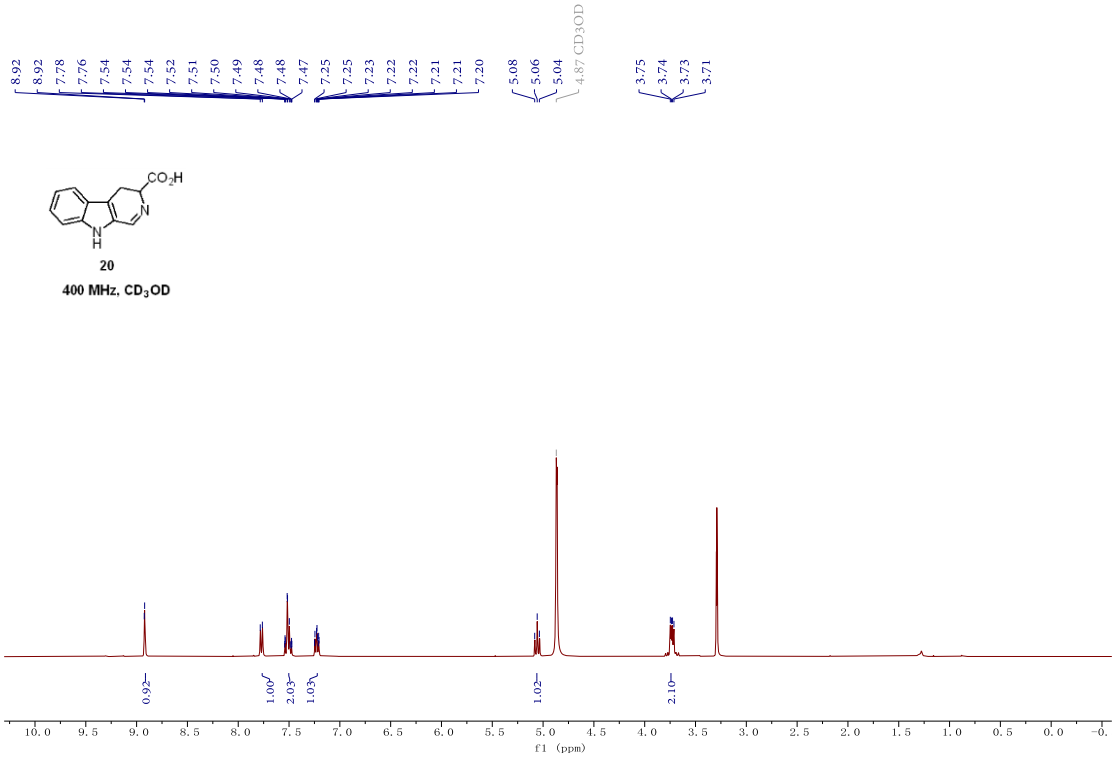


^{13}C NMR of 12 (151 MHz, $CDCl_3$)



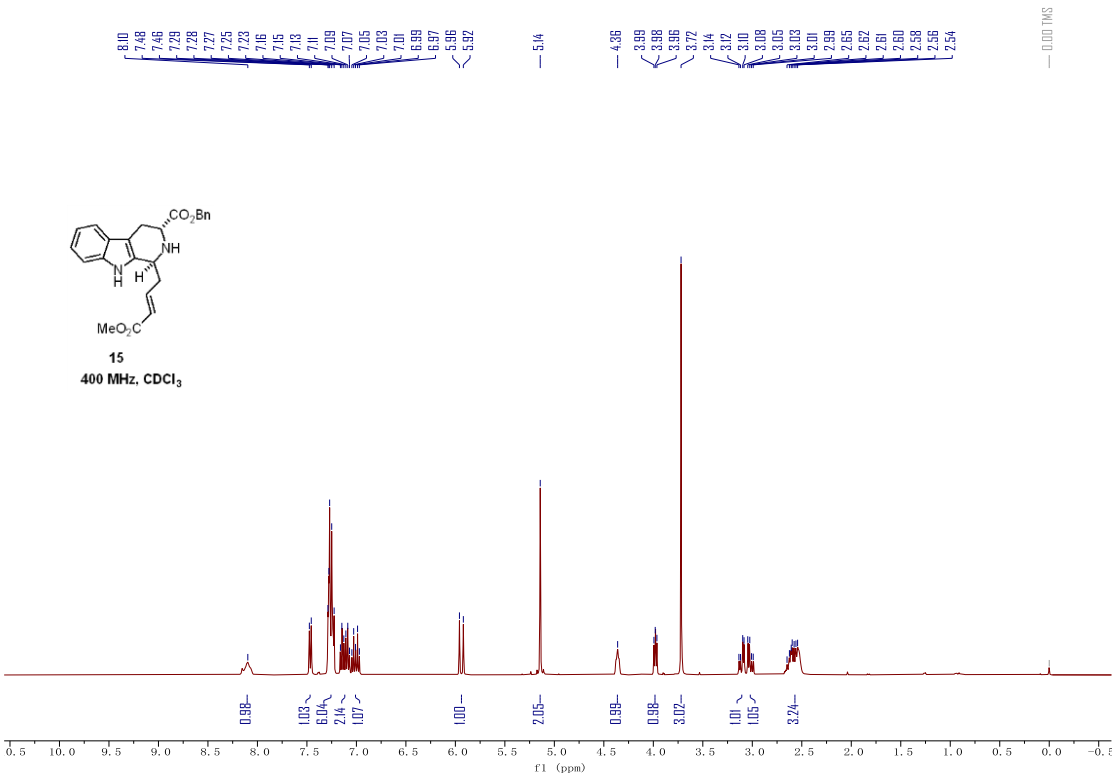
NMR of compound 20

^{1}H NMR of 20 (400 MHz, CD_3OD)

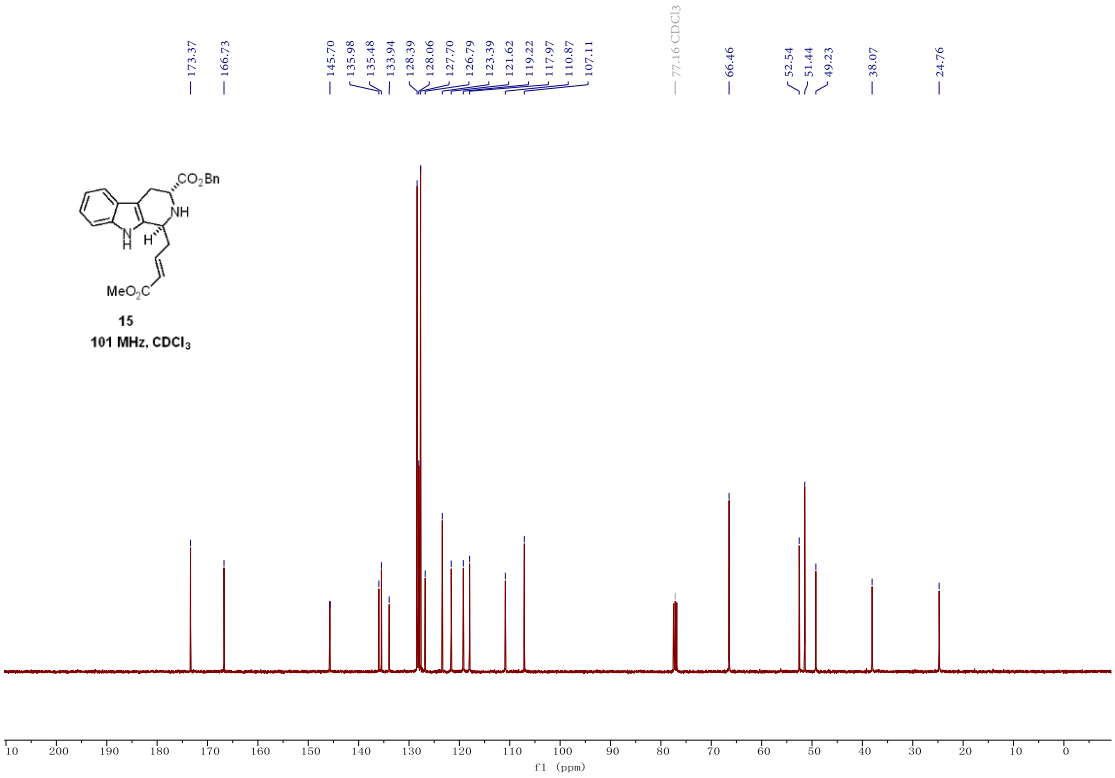


NMR of compound 15

^{1}H NMR of 15 (400 MHz, $CDCl_3$)

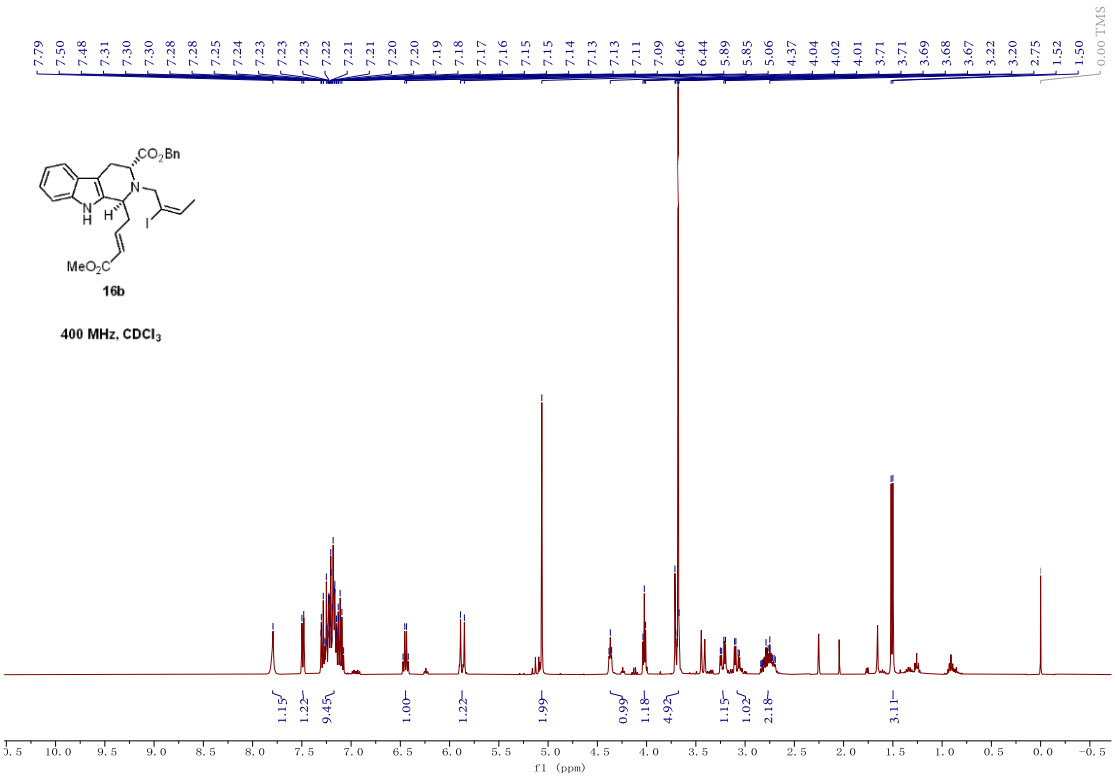


^{13}C NMR of 15 (101 MHz, $CDCl_3$)

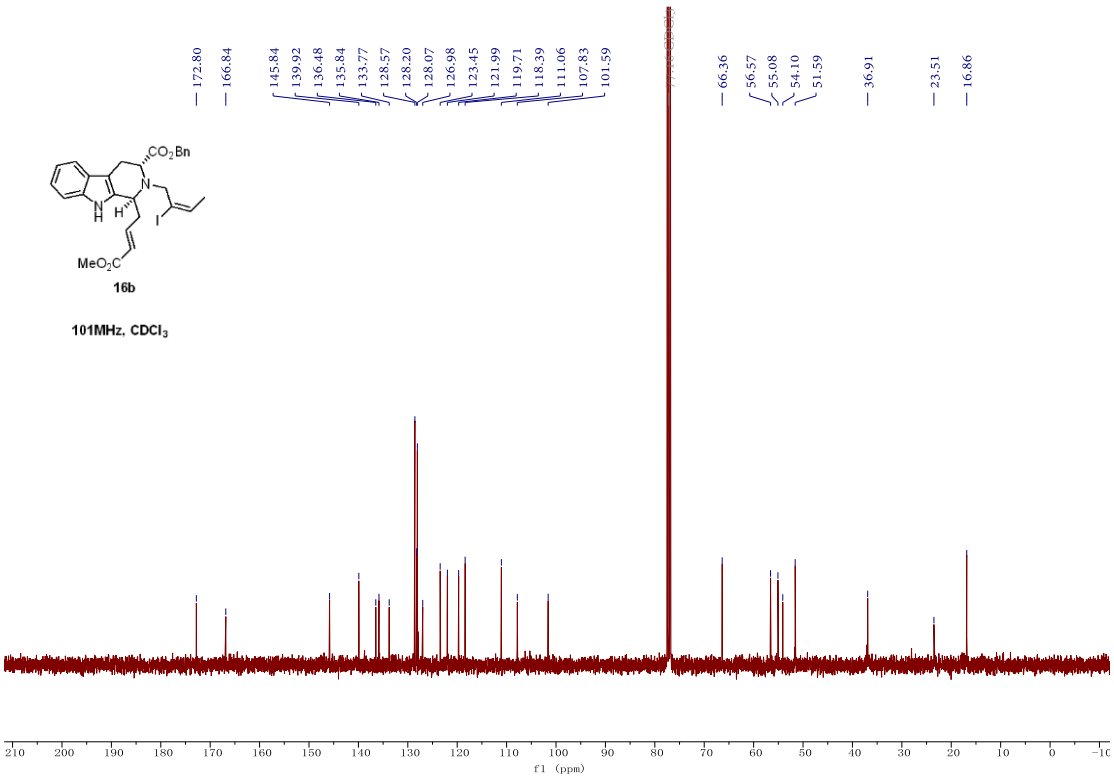


NMR of compound 16b

^{1}H NMR of 16b (400 MHz, $CDCl_3$)

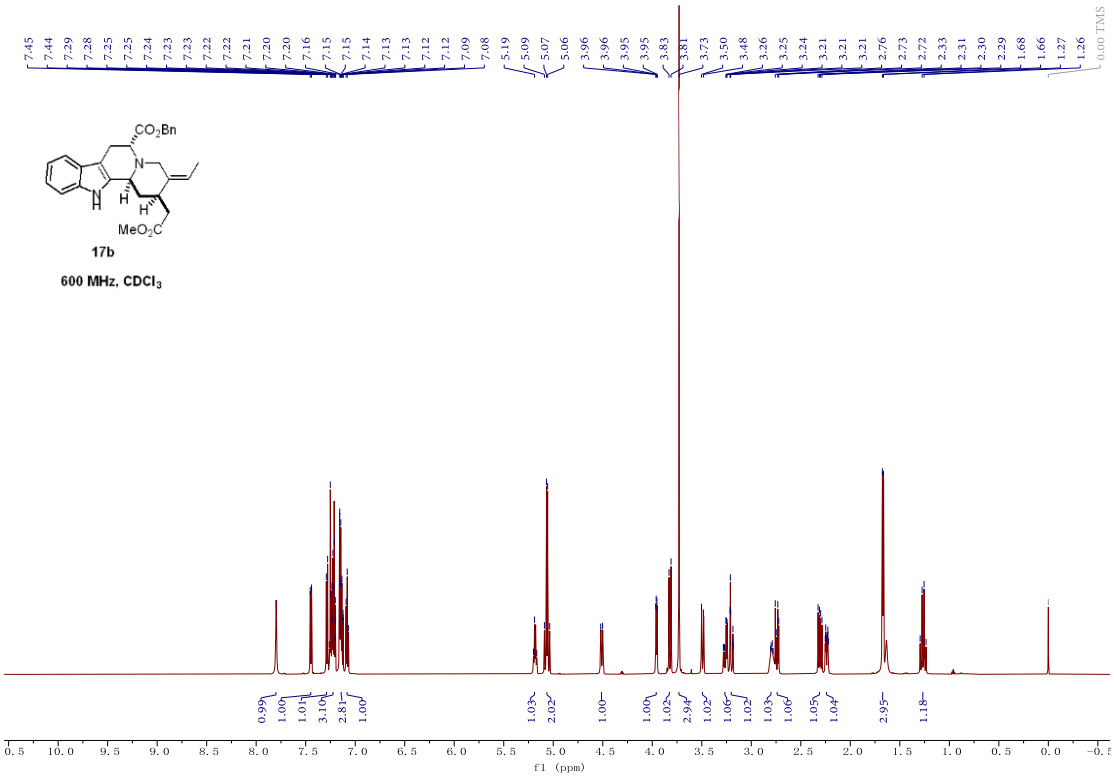


^{13}C NMR of 16b (101 MHz, $CDCl_3$)

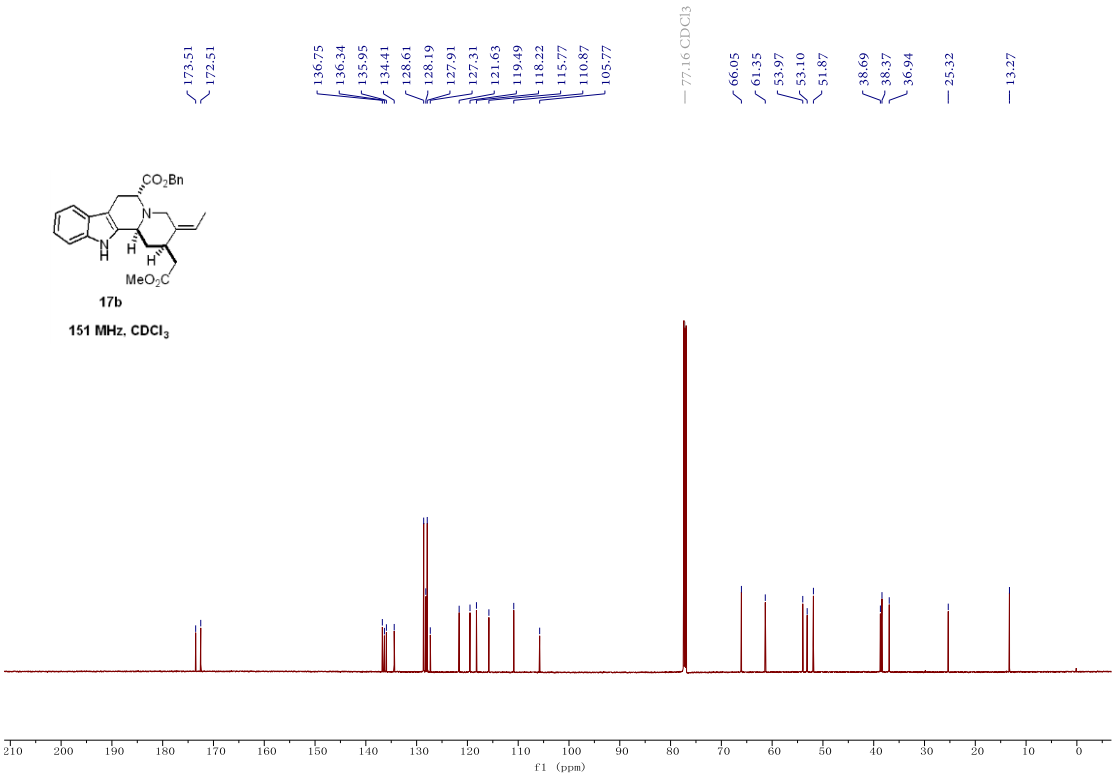


NMR of compound 17b

^{1}H NMR of 17b (600 MHz, $CDCl_3$)

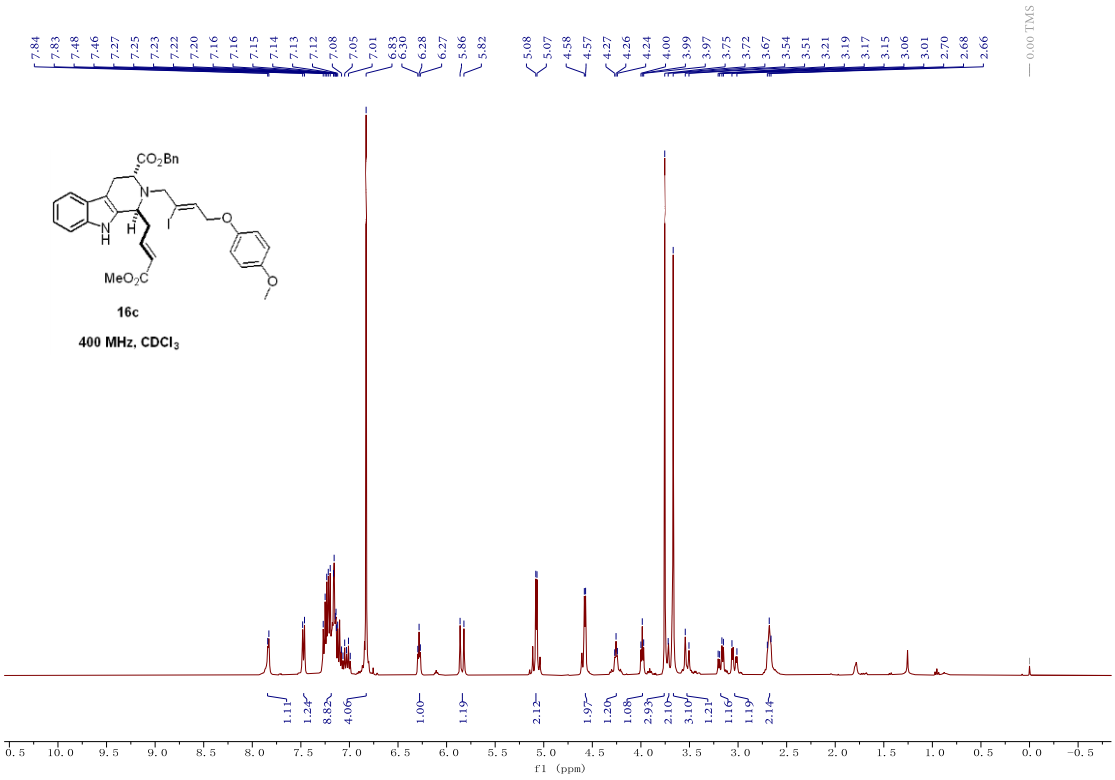


^{13}C NMR of 17b (151 MHz, $CDCl_3$)

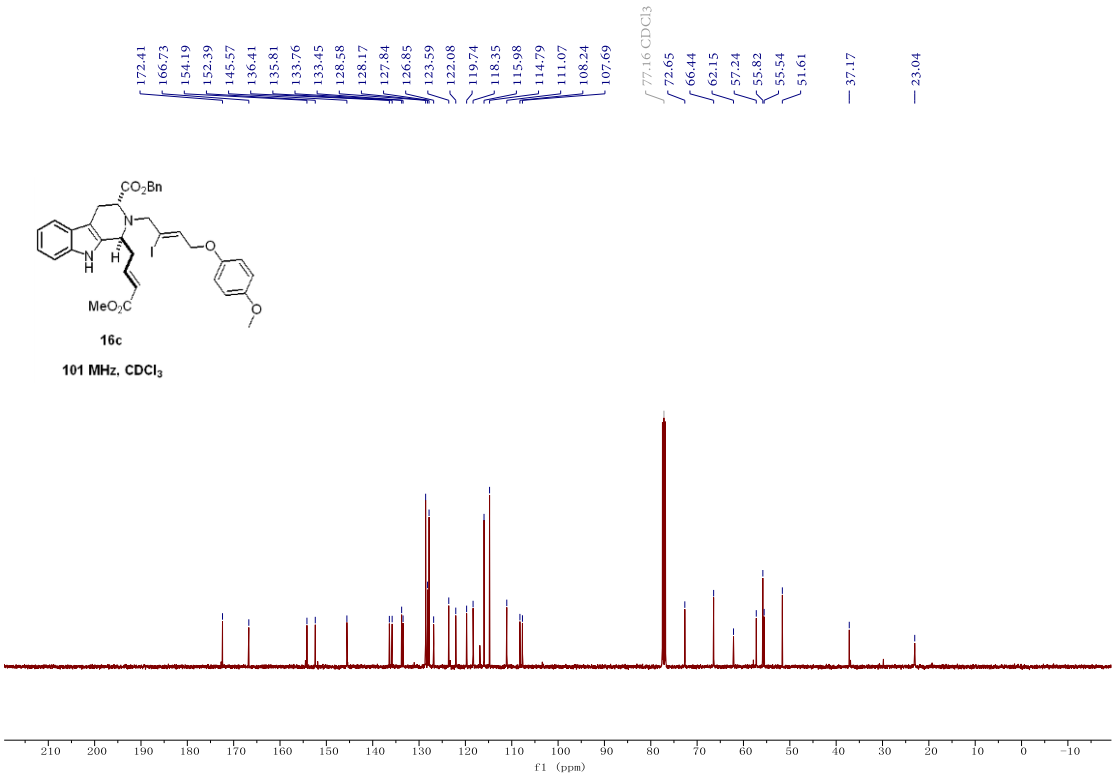


NMR of compound 16c

^{1}H NMR of 16c (400 MHz, $CDCl_3$)

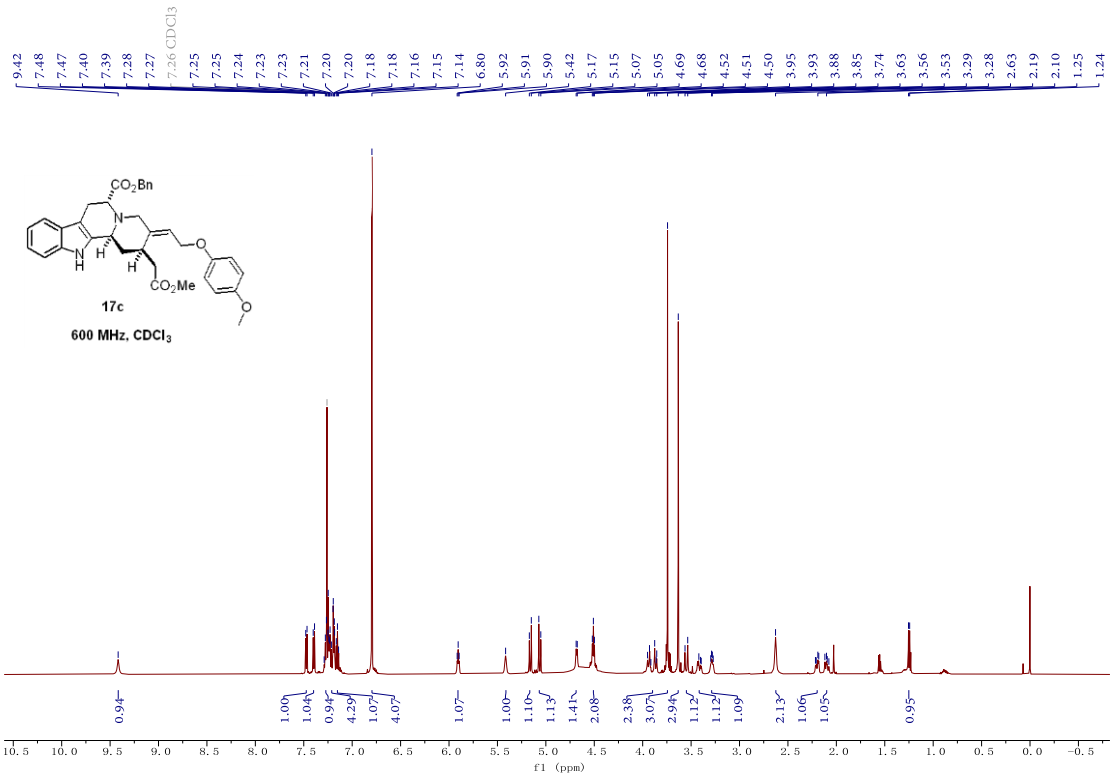


^{13}C NMR of 16c (101 MHz, $CDCl_3$)

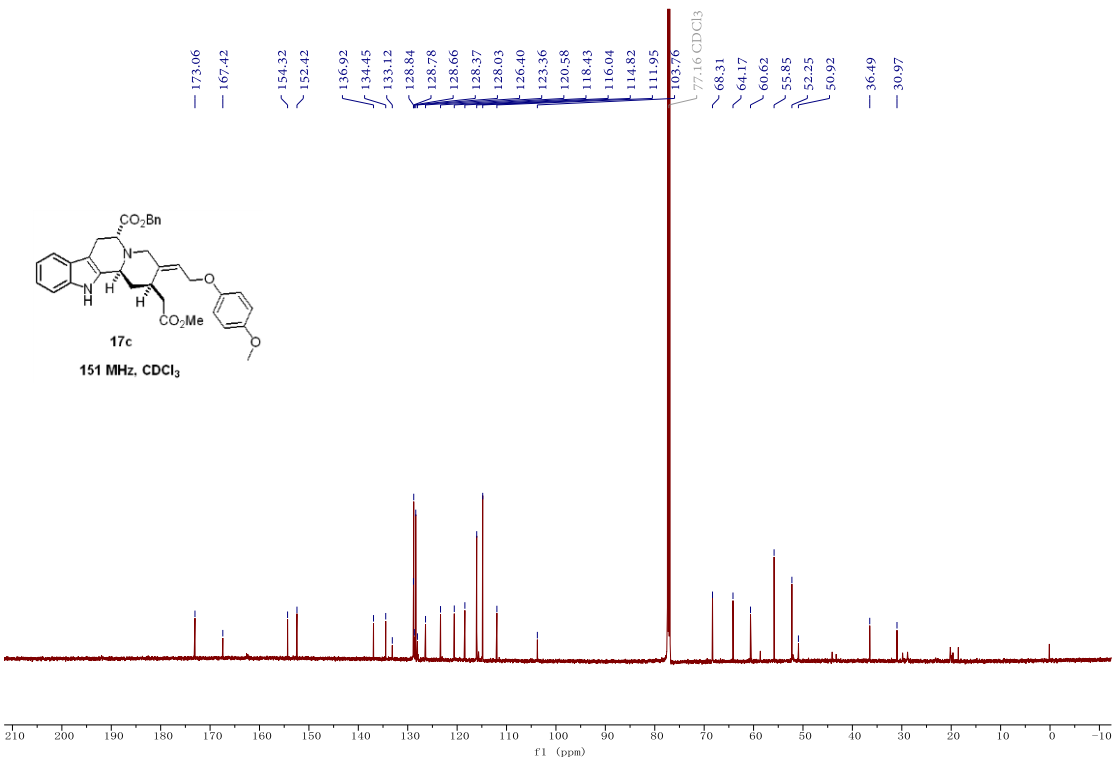


NMR of compound 17c

^{1}H NMR of 17c (600 MHz, $CDCl_3$)

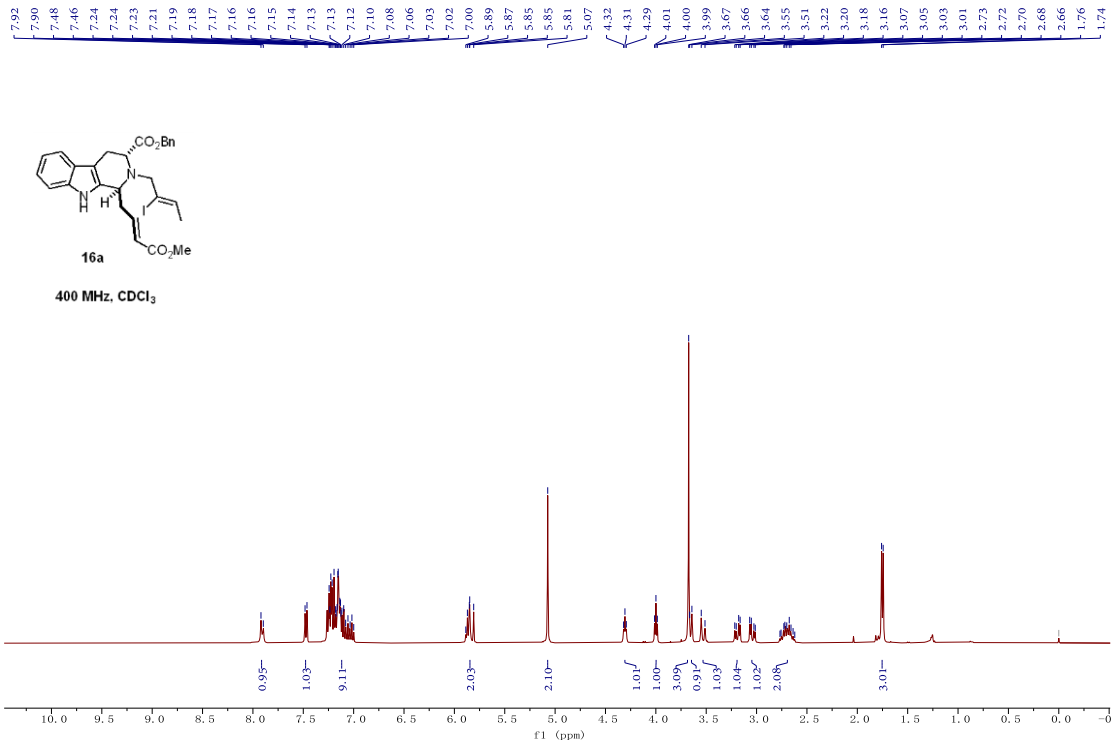


^{13}C NMR of 17c (151 MHz, $CDCl_3$)

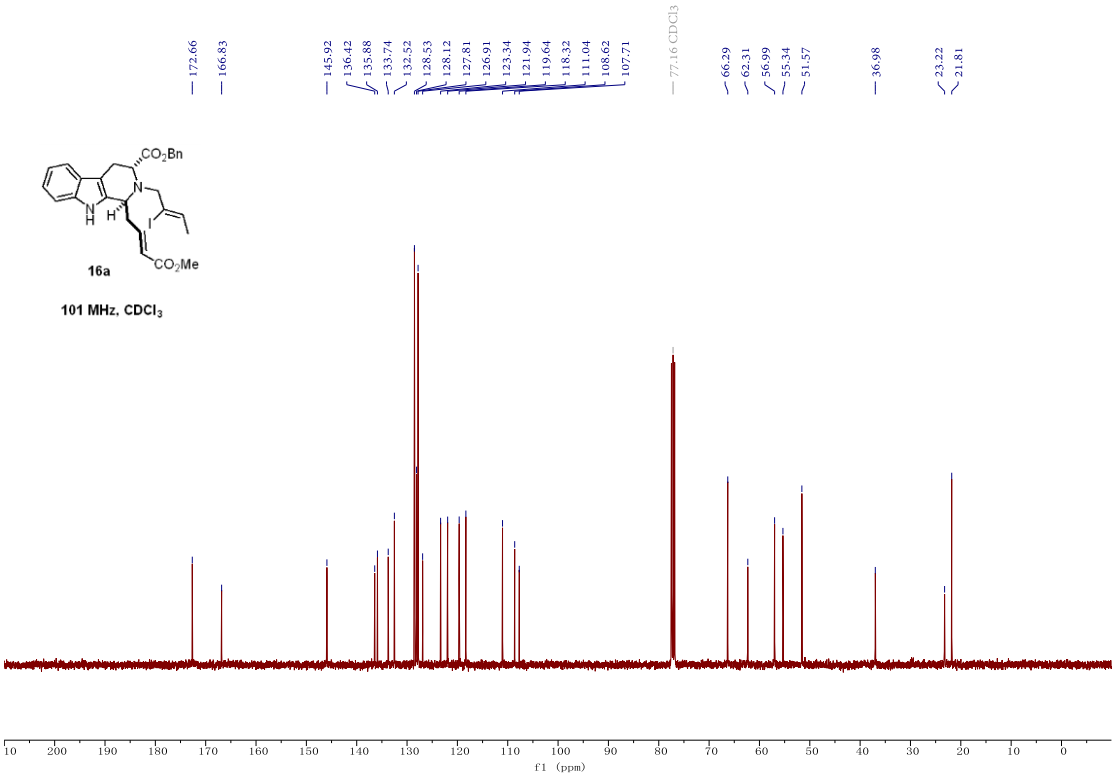


NMR of compound 16a

^{1}H NMR of 16a (400 MHz, $CDCl_3$)

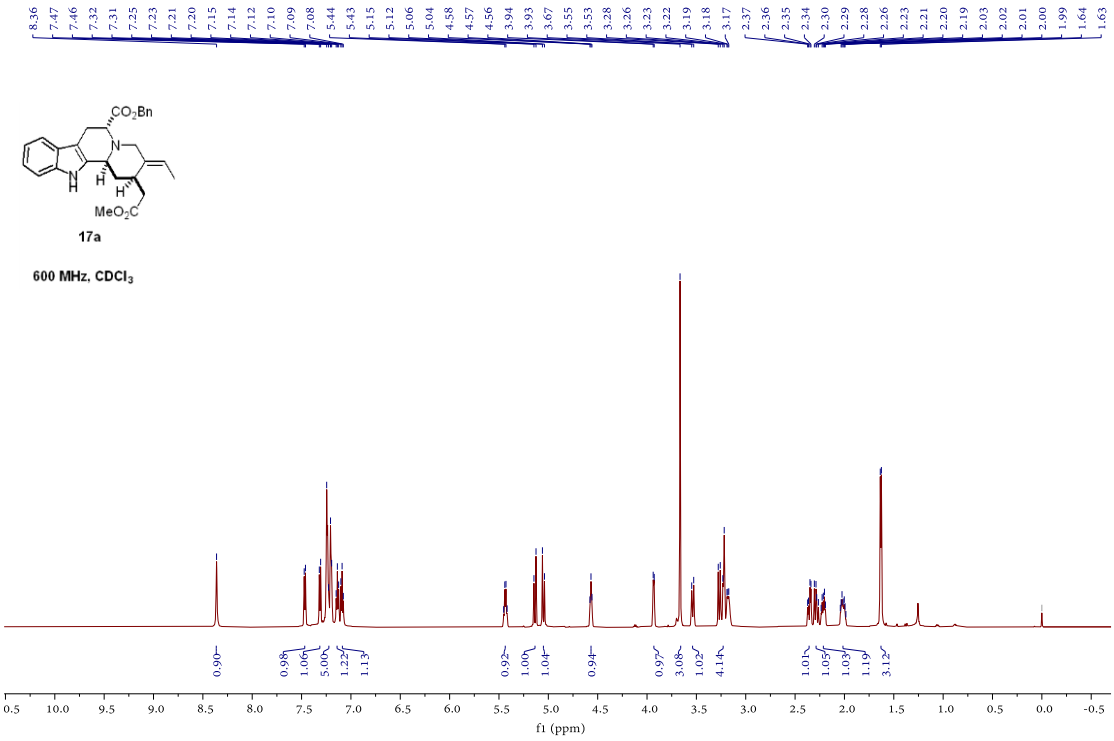


^{13}C NMR of 16a (101 MHz, $CDCl_3$)

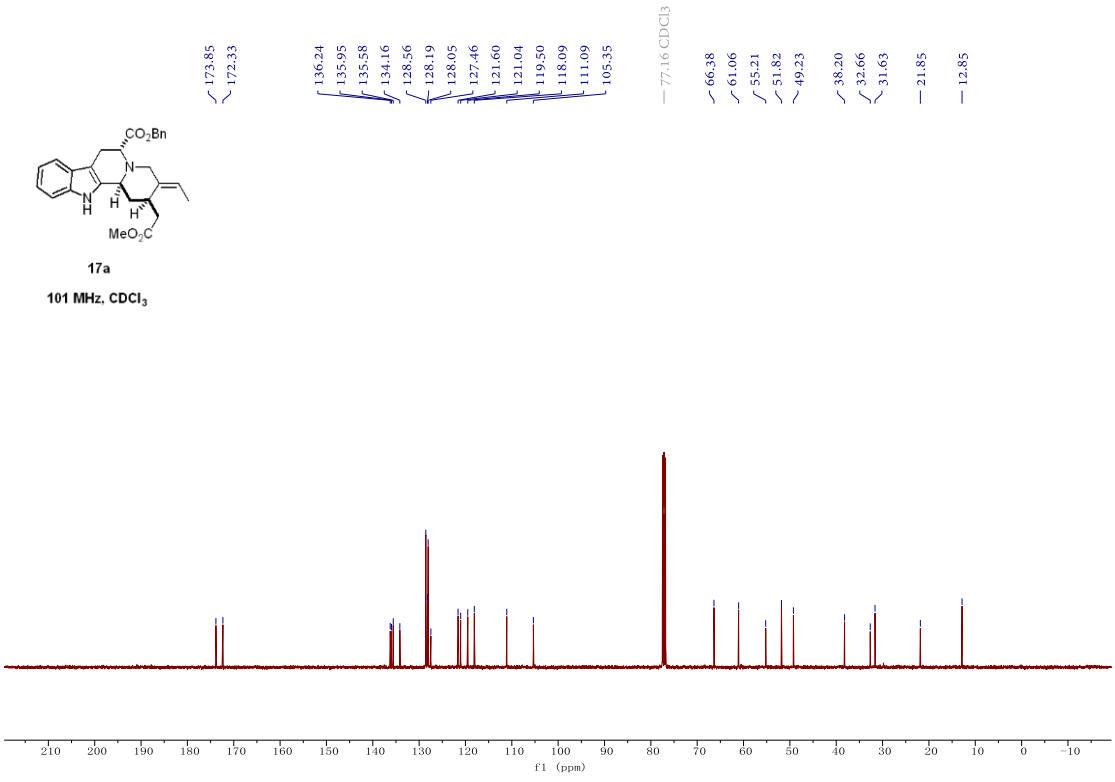


NMR of compound 17a

^{1}H NMR of 21 (600 MHz, $CDCl_3$)

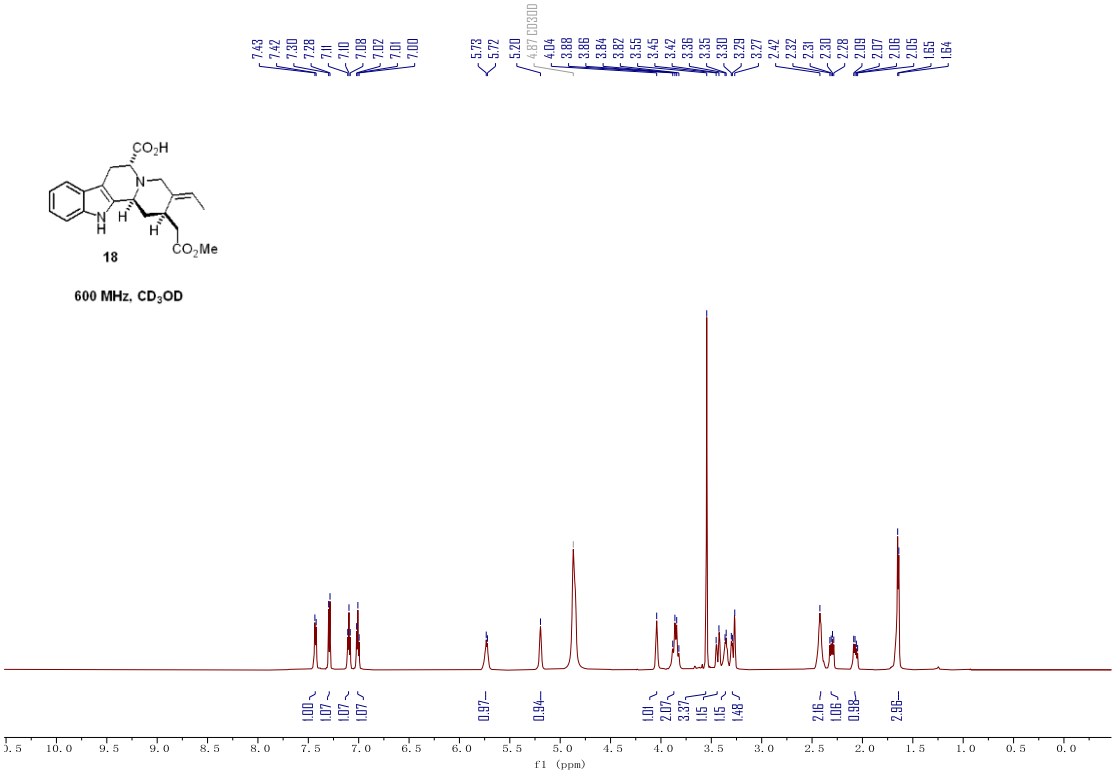


^{13}C NMR of 17a (101 MHz, $CDCl_3$)

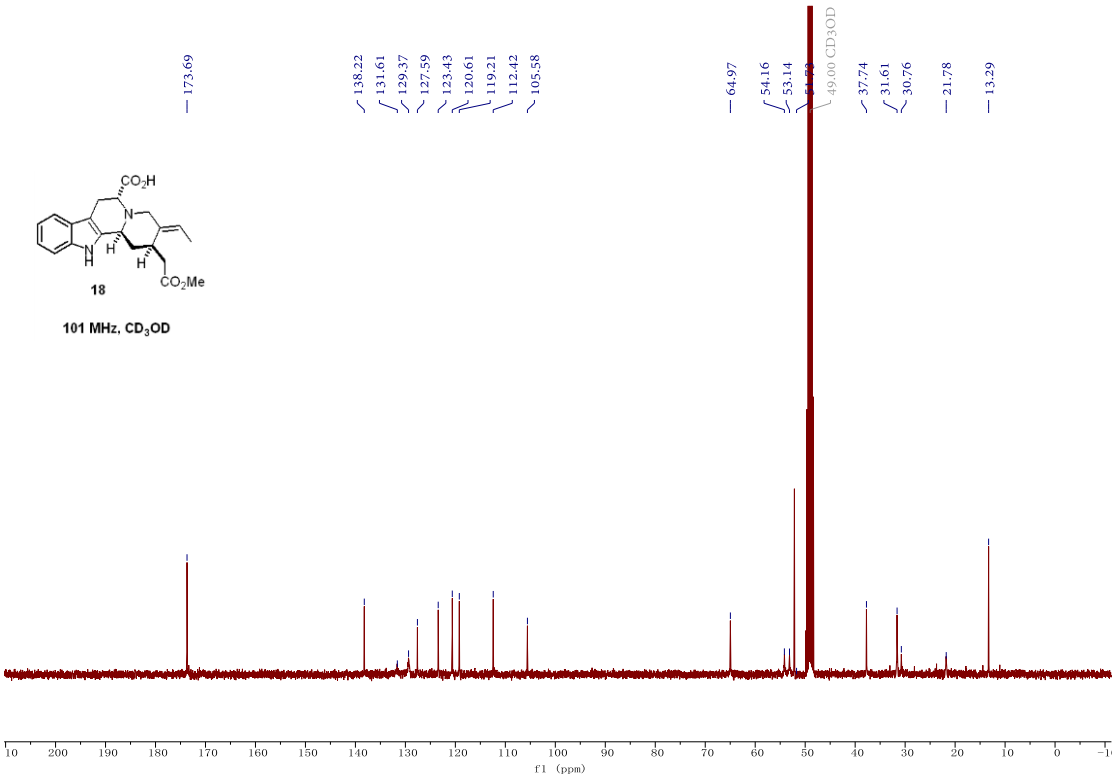


NMR of compound 18

^{1}H NMR of 18 (600 MHz, CD_3OD)

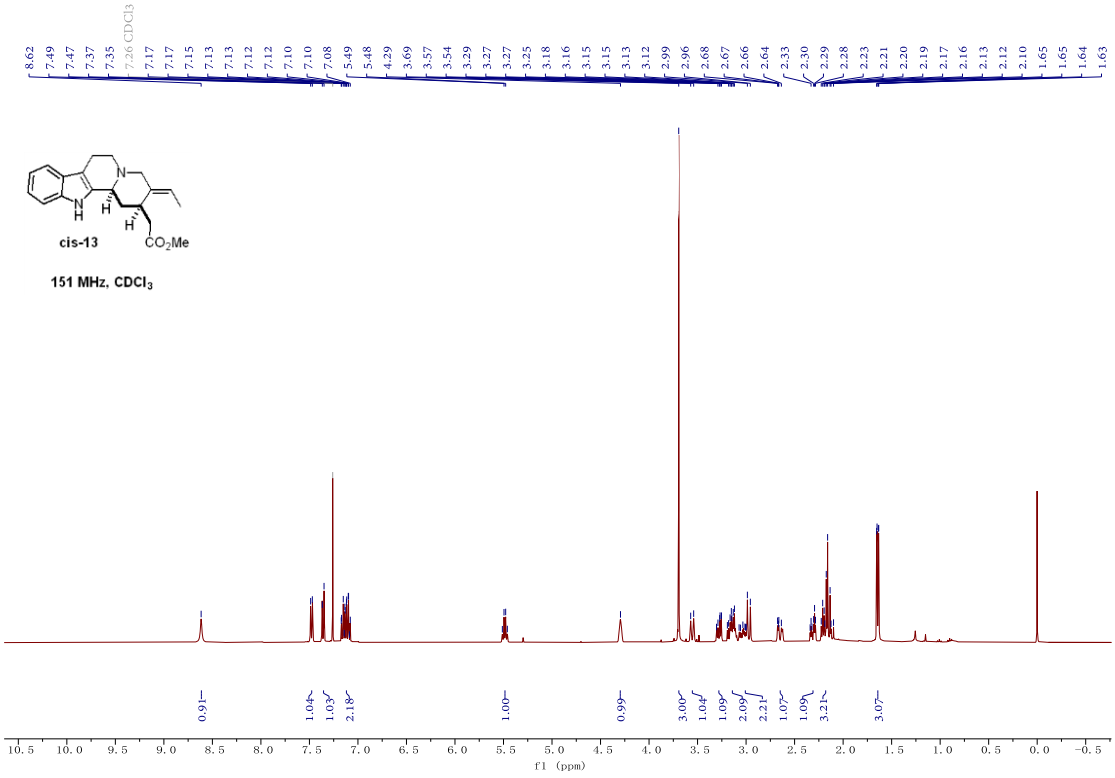


^{13}C NMR of 18 (101 MHz, CD_3OD)

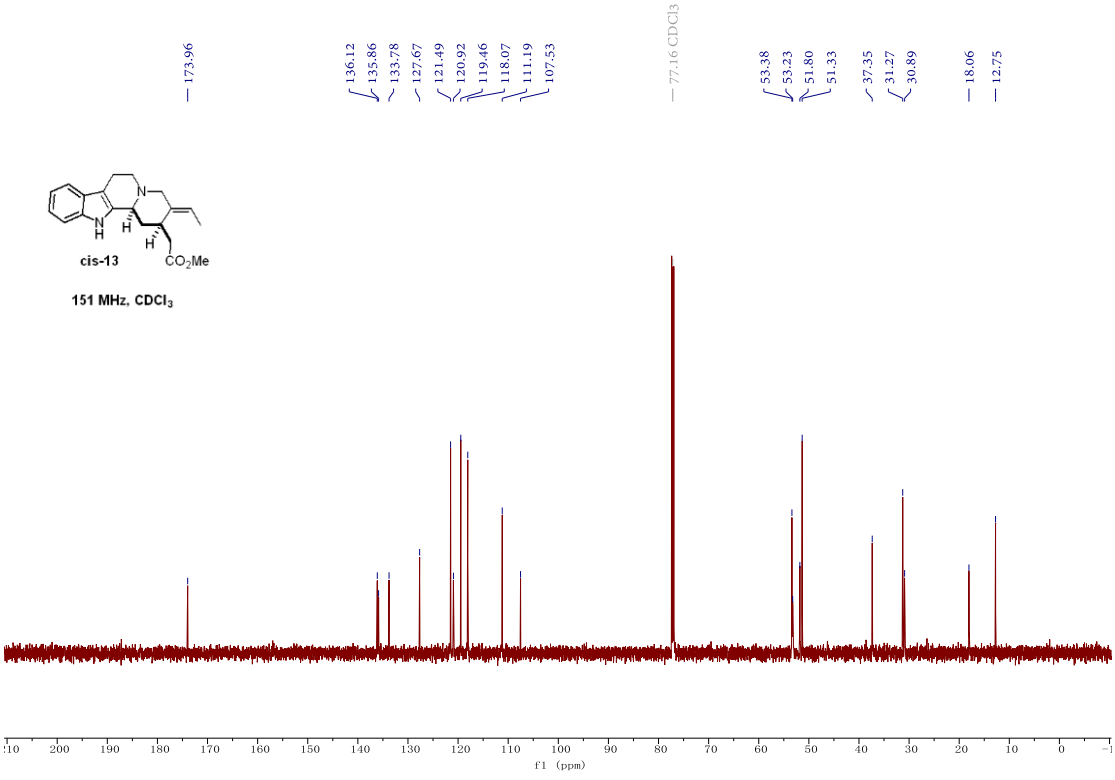


NMR of compound cis-13

^{1}H NMR of cis-13 (400 MHz, $CDCl_3$)

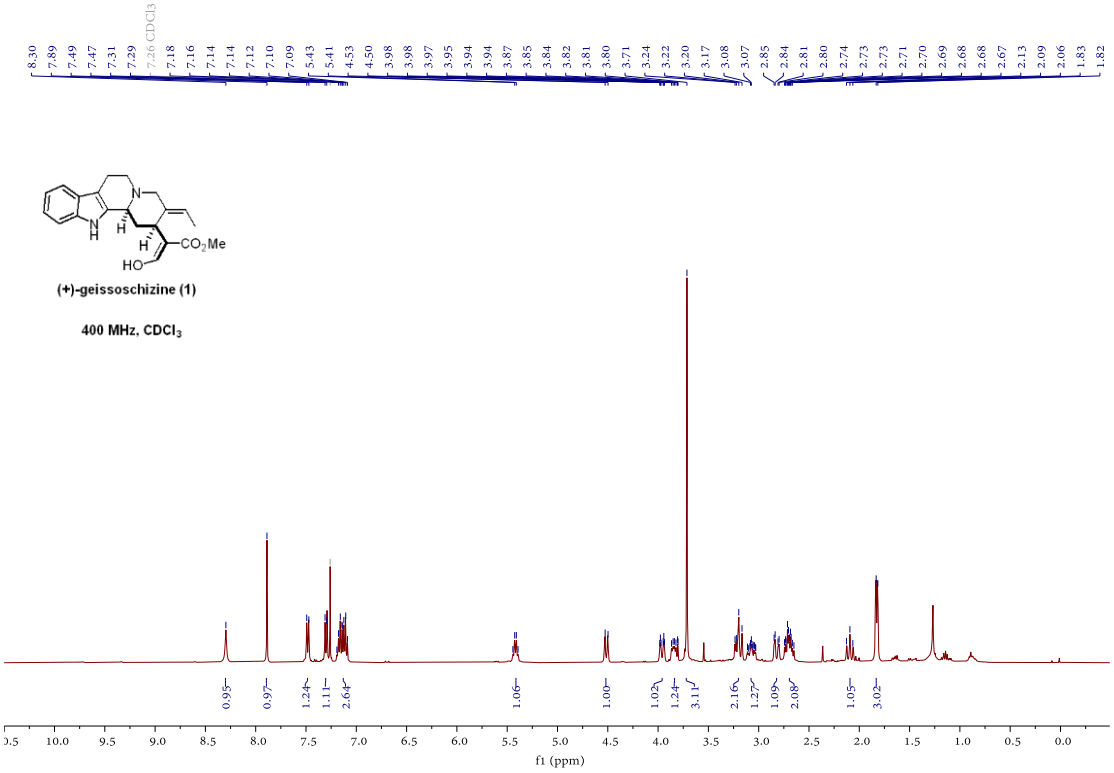


^{13}C NMR of 13 (151 MHz, $CDCl_3$)

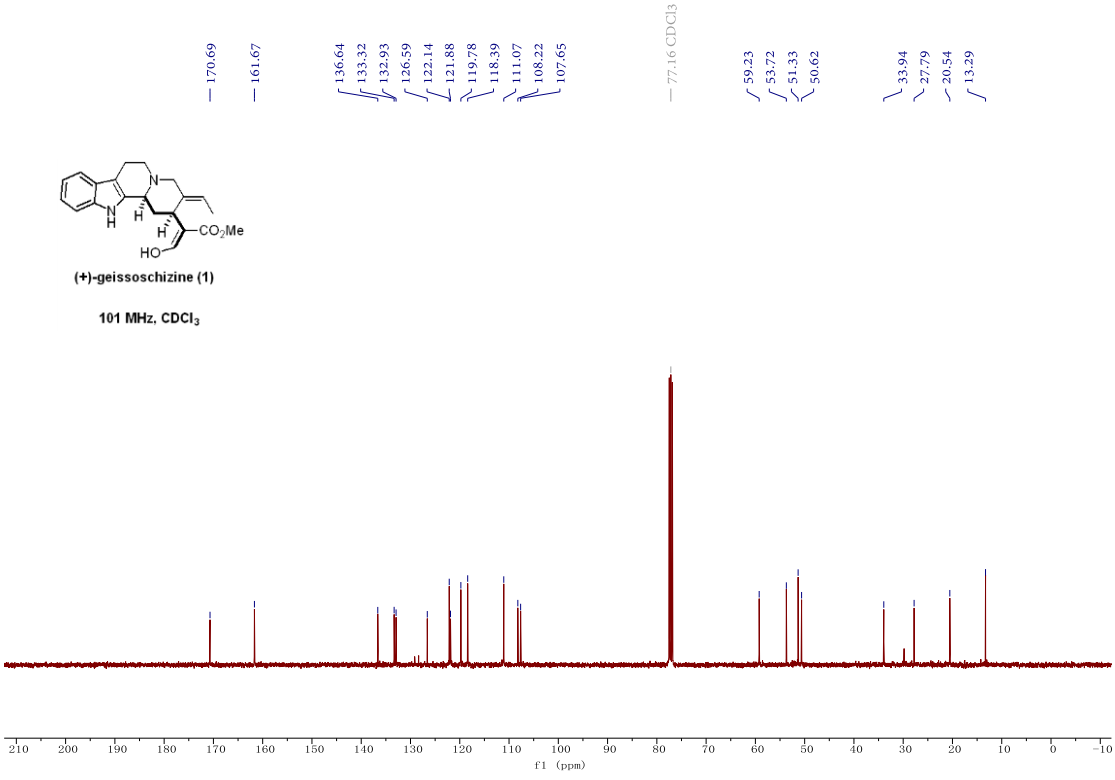


NMR of compound (+)-geissoschizine (1)

^{1}H NMR of (+)-geissoschizine (1) (400 MHz, $CDCl_3$)

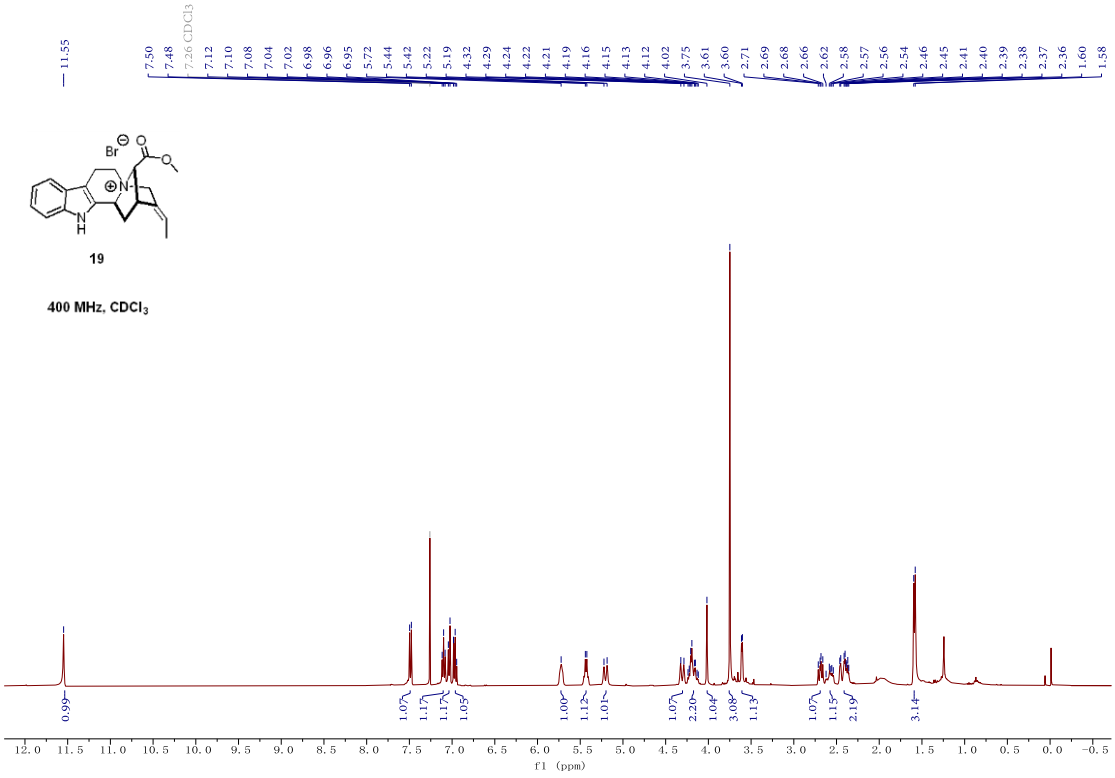


^{13}C NMR of (+)-geissoschizine (1) (101 MHz, $CDCl_3$)

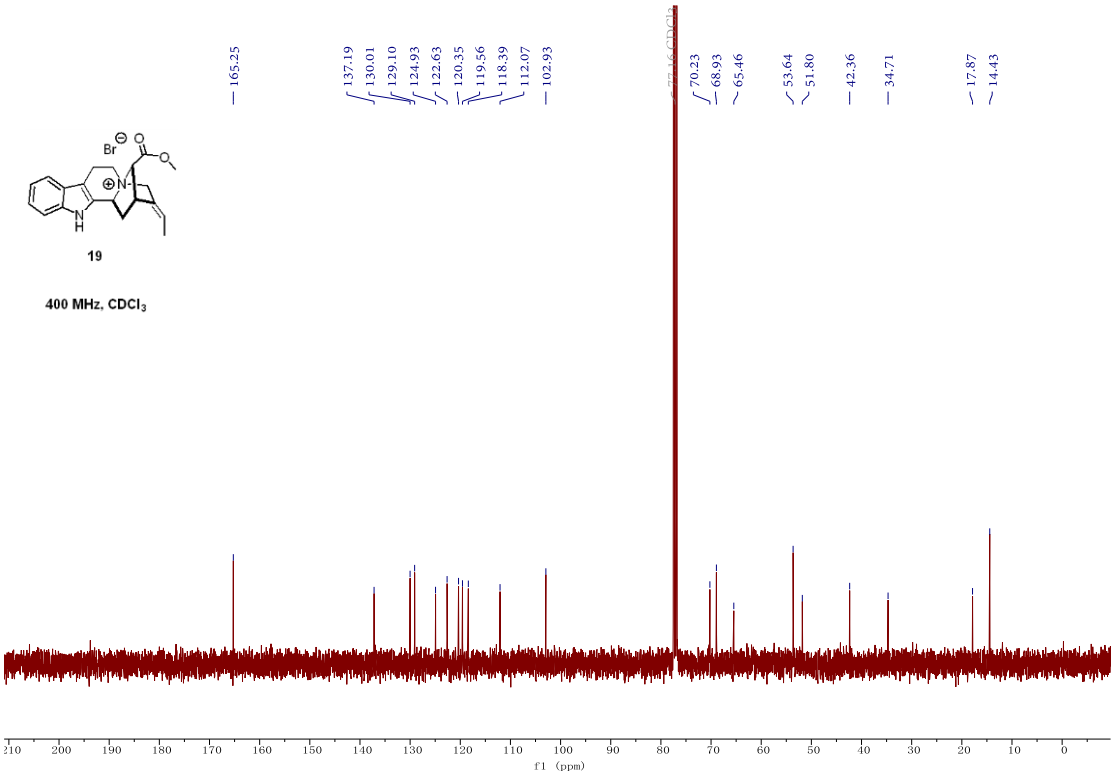


NMR of compound 19

^{1}H NMR of 19(400 MHz, $CDCl_3$)

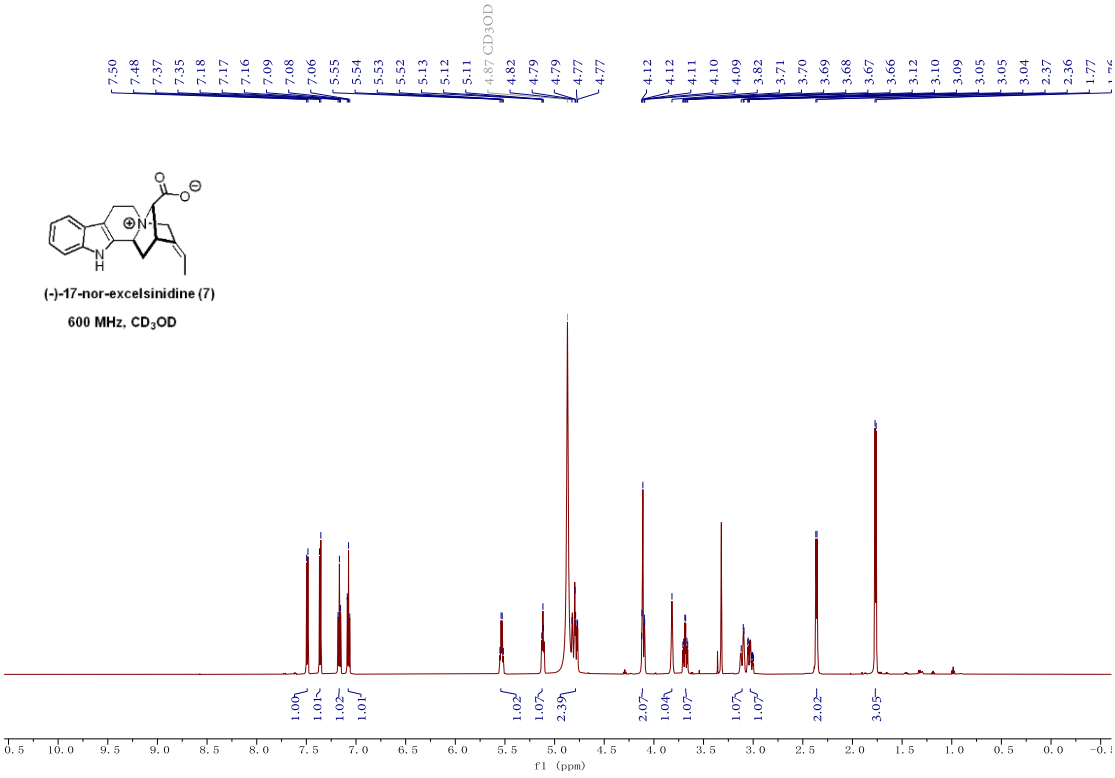


^{13}C NMR of (-)-19(101 MHz, $CDCl_3$)



NMR of compound (-)-17-nor-excelsinidine (7)

^{1}H NMR of (-)-17-nor-excelsinidine (7) (600 MHz, CD_3OD)



^{13}C NMR of (-)-17-nor-excelsinidine (7) (151 MHz, CD_3OD)