Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supplemental Information

Enantioselective total syntheses of (–)-mitragynine, (–)-quinine and (+)-quinidine by Ir-catalyzed asymmetric hydrogenation of all-carbon tetrasubstituted cycloalkenes

Kai Zhang[†,a] Peng Cui[†,a] Miao Miao,[a] Meiqi Zeng,[a] Xu Wang,[a] Minjie Zhang,[a] Qifeng Chen,[a] Hao Song,*[a] Bowen Ke,[a] and Yong Qin*[a,b]

[a]Key Laboratory of Drug-Targeting and Drug Delivery System of the Education Ministry and Sichuan Province, Sichuan Engineering Laboratory for Plant-Sourced Drug and Sichuan Research Center for Drug Precision Industrial Technology, West China School of Pharmacy, Sichuan University, Chengdu 610041, Sichuan Province, China.

[b]Frontiers Medical Center, Tianfu Jincheng Laboratory, Chengdu 610041, Sichuan Province, China.

†These authors contributed equally to this work.

E-mail: songhao@scu.edu.cn; yongqin@scu.edu.cn

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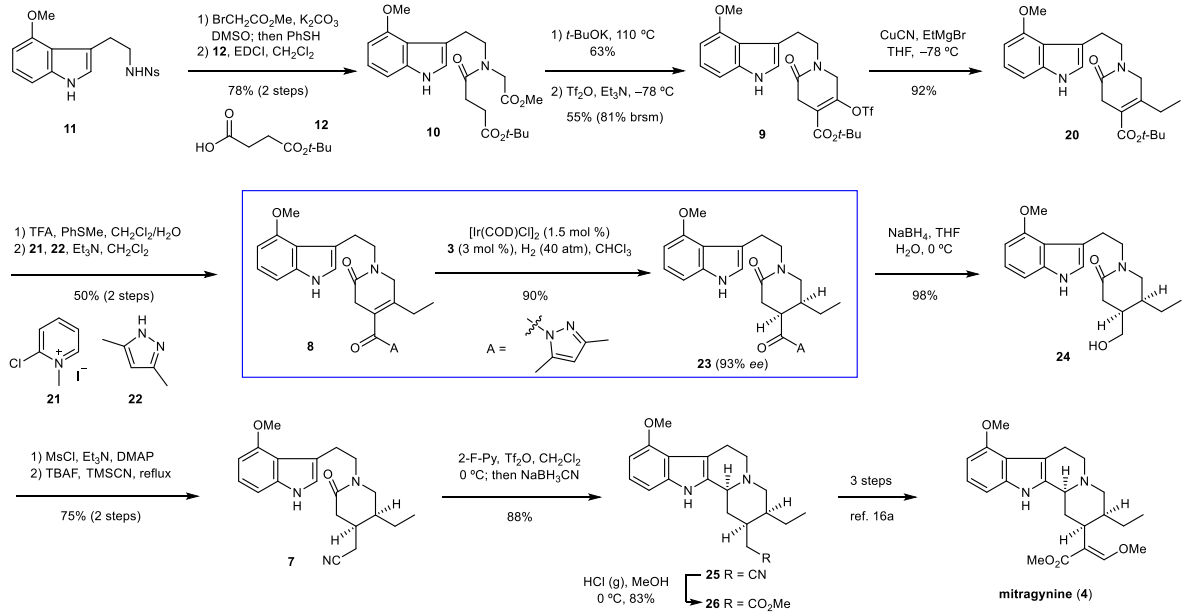
1. General information

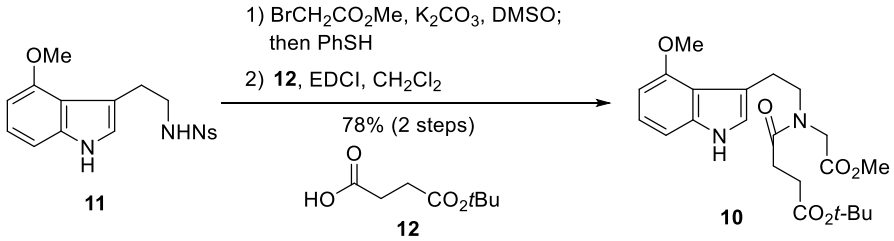
All reactions that require anhydrous conditions were performed in flame-dried glassware under Ar atmosphere and all the commercial reagents were used without purification unless otherwise noted. Solvent purification was conducted according to Purification of Laboratory Chemicals (Peerrin, D. D.; Armarego, W. L. and Perrins, D. R., Pergamon Press: Oxford, 1980). The products were purified by flash column chromatography on silica gel (200-300 meshes) from the Anhui Liangchen Silicon Material Company (China). Reactions were monitored by thin layer chromatography (TLC) supplied by Yantai Chemicals (China). Visualization was accomplished with UV light, exposure to iodine, stained with ethanolic solution of phosphomolybdic acid or basic solution of $KMnO_4$. ^1H NMR and ^{13}C NMR spectra were recorded on Varian INOVA-400/54 and Agilent DD2-600/54 instruments and calibrated by using residual undeuterated chloroform (Chloroform-*d*, ^1H NMR: δ = 7.26, ^{13}C NMR: δ = 77.0), deuterated DMSO (DMSO-d_6, ^1H NMR: δ = 2.50, ^{13}C NMR: δ = 39.50). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, td = triple doublet, dt = double triplet, m = multiplet, and coupling constants (*J*) are reported in Hertz (Hz). Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum Two FT-IR spectrometer. The specific optical rotation was obtained from *Rudolph Research Analytical Autopol VI* automatic polarimeter. High-resolution mass spectra (HRMS) were recorded on Bruker Apex IV FTMS or Thermo Scientific LTQ Orbitrap XL ESI mass spectrometers. LC-MS analysis was performed on HP Agilent 6420 Triple Quad LC/MS. HPLC analysis was performed on HP Agilent 1260 HPLC.

2. Experimental Procedures and Spectroscopic Data of Compounds

2.1 Total synthesis of (–)-mitragynine



2.1.1 Synthesis of compound 10.

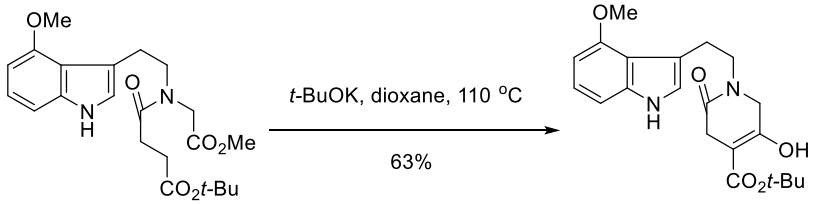


Finely powdered K_2CO_3 (11.0 g, 79.8 mmol, 3.0 equiv.) and methyl bromoacetate (2.77 mL, 29.3 mmol, 1.1 equiv.) were added to a solution of N_b-(4-nitrobenzenesulfonyl)-4-methoxytryptamine **11**(10.0 g, 26.6 mmol, 1.0 equiv.) in DMSO (100 mL). After stirring for 4 h at 25 °C, thiophenol (8.16 mL, 79.8 mmol, 3.0 equiv.) was added and stirring was continued during 2 h. The reaction was quenched with water and the aqueous phase was extracted with EtOAc. The organic layers were combined and washed with water. After drying with anhydrous $MgSO_4$ and removal of the solvent the mixture was used without further purification.

To a solution of the crude mixture in anhydrous CH_2Cl_2 (50 mL), mono-tert-butyl succinate **12** (4.63 g, 26.6 mmol, 1.0 equiv.) and EDCI (5.10 g, 26.6 mmol, 1.0 equiv.) were added successively under argon atmosphere. The resulting mixture was stirred for 1 h at room temperature. The solvent was evaporated and the resulting oil purified by column

chromatography on silica gel (petroleum ether:EtOAc, 3:1, v/v). Product **10** was obtained as pale-yollow amorphous solid (8.67 g, 78% 2 steps). TLC (petroleum ether:EtOAc, 3:1, v/v): R_f = 0.20; ^{1}H NMR (400 MHz, Chloroform-*d*, some signals exist as a pair due to the presence of amide rotamers): δ 8.17 – 8.13 (m, 1H), 7.11 – 7.05 (m, 1H), 6.98 – 6.94 (m, 1H), 6.90 – 6.87 (m, 1H), 6.51 – 6.47 (m, 1H), 4.21 – 4.08 (m, 2H), 3.91 (d, *J* = 4.4 Hz, 3H), 3.77 – 3.65 (m, 5H), 3.12 – 3.02 (m, 2H), 2.68 – 2.48 (m, 4H), 1.44 (d, *J* = 6.4 Hz, 9H). ^{13}C NMR (100 MHz, Chloroform-*d*, some signals exist as a pair due to the presence of amide rotamers): δ 172.4/172.3, 172.2/172.1, 170.1/170.0, 154.5/154.3, 138.1/138.1, 123.0/122.7, 121.3, 117.1/116.9, 113.2/112.4, 104.7/104.7, 99.4/99.2, 80.5/80.3, 55.0/54.9, 52.1/52.0, 51.2, 48.0, 30.6/30.5, 28.0/28.0, 27.8/27.5, 26.3. IR (neat): ν_{max} = 3326, 2978, 2932, 1726, 1639, 1454, 1365, 1254, 1149, 1084, 753, 733 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{22}H_{31}N_2O_6$ $[M+H]^+$ 419.2177, found 419.2175.

2.1.2 Synthesis of compound S1.

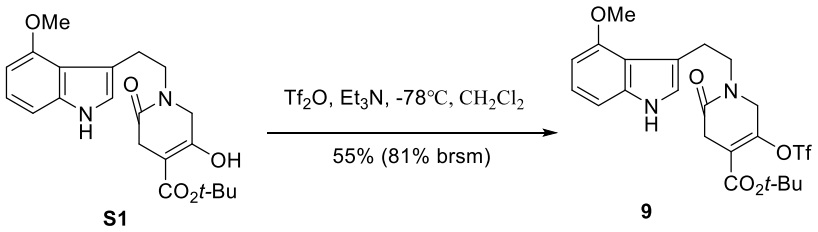


10 **S1**

Under argon atmosphere, compound **10** (8.67 g, 26.6 mmol, 1.0 equiv.) was dissolved in dry dioxane (500 mL). The solution was heated to 110 ^{o}C with an oil bath and *t*-BuOK (39.9 mL, 39.9 mmol, 1.5 equiv., 1.0 M in THF) was added. The resulting mixture was stirred for 30 min at this temperature before it was cooled to room temperature. Next the reaction was cooled with an ice-water bath and saturated NH_4Cl aqueous solution (500 mL) was added. The mixture was extracted with CH_2Cl_2 and the organic layers were combined, dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated and the resulting solid was purified by column chromatography on silica gel (petroleum ether:acetone, 3:1, v/v) to give **S1** was obtained as white powder (6.47g, 63%). TLC (petroleum ether:acetone, 1:1, v/v): R_f = 0.50; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 11.97 (s, 1H), 8.00 (s, 1H), 7.09 (t, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 2.4 Hz, 1H), 6.50 (d, *J* = 7.6 Hz, 1H), 3.97 – 3.94 (m, 5H), 3.73 – 3.69 (m, 2H), 3.16 – 3.12 (m, 4H), 1.51 (s, 9H). ^{13}C NMR (100 MHz, Chloroform-*d*): δ 170.3, 167.0, 162.4, 154.6, 138.1, 122.9, 121.2, 117.1, 113.2, 104.6, 99.4, 95.0, 82.4, 55.0, 49.9, 48.5, 30.1, 28.2, 24.4. IR (neat): ν_{max} = 3250, 2981, 2926, 1680, 1633, 1457, 1402, 1307, 1234, 1150, 810, 742 cm^{-1}. HRMS (ESI): m/z calcd. for

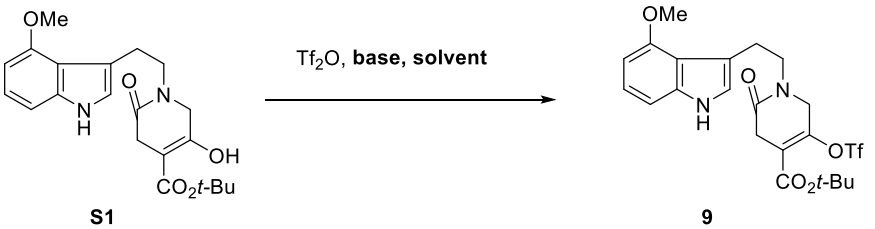
$C_{21}H_{27}N_2O_5$ $[M+H]^+$ 387.1914, found 387.1910.

2.1.3 Synthesis of compound 9.



To a solution of compound **S1** (4.01 g, 10.4 mmol, 1.0 equiv.) in dry CH_2Cl_2 (600 mL), Et_3N (2.17 mL, 15.6 mmol, 1.5 equiv.) was added at –78 ^oC uhder argon. After stirring for 30 min, Tf_2O (0.87 mL, 5.20 mmol, 0.5 equiv.) was added dropwise and stirring was continued during 1 h. An additional Tf_2O (0.87 mL, 5.20 mmol, 0.5 equiv.) was added and the resulting mixture was stirred for 1 h at this temperature. Then saturated $NaHCO_3$ aqueous solution (200 mL) was added and the reaction was allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated and the residue purified by column chromatography on silica gel (CH_2Cl_2:THF, 20:1 to 4:1 v/v). Product **9** was obtained as white powder (2.96 g, 55%, 81% brsm) with recovering of **S1** (1.29 g). TLC (CH_2Cl_2:THF, 4:1 v/v): R_f = 0.60; ^1H NMR (400 MHz, Chloroform-*d*): δ 8.07 (s, 1H), 7.09 (t, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 2.0 Hz, 1H), 6.51 (d, *J* = 7.6 Hz, 1H), 3.98 (t, *J* = 4.4 Hz, 2H), 3.93 (s, 3H), 3.71 (t, *J* = 7.2 Hz, 2H), 3.36 (t, *J* = 4.4 Hz, 2H), 3.12 (t, *J* = 7.6 Hz, 2H), 1.52 (s, 9H). ^{13}C NMR (100 MHz, Chloroform-*d*): δ 164.5, 161.1, 154.4, 141.9, 138.2, 123.0, 118.2 (q, *J* = 220 Hz), 121.3, 120.4, 116.9, 112.6, 104.7, 99.5, 84.1, 55.0, 48.9, 48.6, 32.6, 27.9, 24.4. IR (neat): ν_{max} = 3294, 2982, 2934, 1720, 1647, 1428, 1211, 1139, 1099, 869, 742 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{22}H_{26}F_3N_2O_7S$ $[M+H]^+$ 519.1407, found 519.1405.

Table S1 Screening of conditions for the preparation of compound 9.

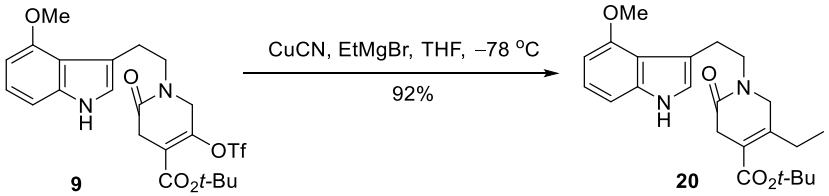


Entry	Base	Solvent	Conv. (%)[a]	Yield (%)[a]

1	Et_3N	CH_2Cl_2	50	33
2	DIPEA	CH_2Cl_2	10	7
3	Py	CH_2Cl_2	25	<5
4	2,6-lutidine	CH_2Cl_2	33	15
5	DBU	CH_2Cl_2	60	30
6	Daboc	CH_2Cl_2	<10	trace
7	Et_3N	THF	<5	trace
8	Et_3N	MeCN	<5	trace
9	Et_3N	PhMe	<5	trace
10	Et_3N	$CHCl_3$	30	10
11	Et_3N	Et_2O	<5	trace
12	Et_3N	DMF	<10	trace
13[b]	Et_3N	CH_2Cl_2	trace	/
14[c]	Et_3N	CH_2Cl_2	68	55

[a] Conversions and yields were calculated based on the isolated material. [b] $PhN(Tf)_2$ was used instead of Tf_2O. [c] Tf_2O was added by two portions as indicated in the above experimental procedure.

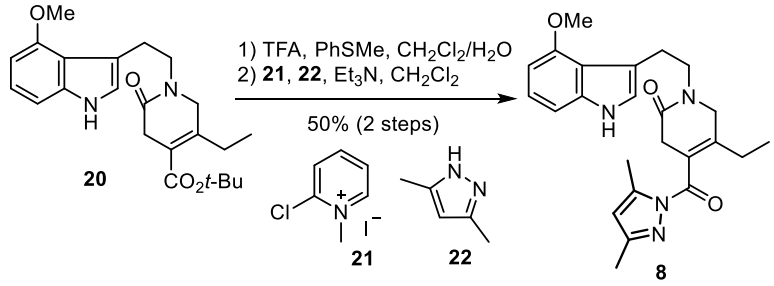
2.1.4 Synthesis of compound 20.



To a suspension of CuCN (2.70 g, 30.1mmol, 3.9 equiv.) in anhydrous THF (200 mL), EtMgBr (19.3 mL, 19.3 mmol, 2.5 equiv., 1.0 M in THF) was added at –78 °C under argon and the resulting mixture was stirred for 1 h before the solution of compound S5 (4.00 g, 7.72 mmol, 1.0 equiv.) in anhydrous THF (40 mL) was added. After stirring for 2 h, the reaction was quenched with saturated NH_4Cl aqueous solution and warmed to room tempareture. The mixture was filtered by Celite. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (CH_2Cl_2:acetone, 10:1 to 3:1 v/v) to afford **20** (2.83 g, 92%) as a white powder. TLC (CH_2Cl_2:acetone, 1:1 v/v) :

R_f = 0.60; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.02 (s, 1H), 7.09 (t, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 2.0 Hz, 1H), 6.50 (d, *J* = 7.6 Hz, 1H), 3.95 (s, 3H), 3.83 (t, *J* = 4.0 Hz, 2H), 3.72 (t, *J* = 6.8 Hz, 2H), 3.19 – 3.12 (m, 4H), 2.34 (q, *J* = 7.2 Hz, 2H), 1.49 (s, 9H), 0.98 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*): δ 167.3, 165.2, 154.5, 144.2, 138.1, 122.8, 121.2, 121.2, 117.2, 113.3, 104.6, 99.4, 81.1, 55.0, 53.2, 48.2, 33.5, 28.1, 24.7, 24.5, 12.9. IR (neat): ν_{max} = 3272, 2976, 2932, 1699, 1634, 1457, 1367, 1249, 1158, 1099, 848, 740 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{23}H_{31}N_2O_4$ $[M+H]^+$ 399.2278, found 399.2279.

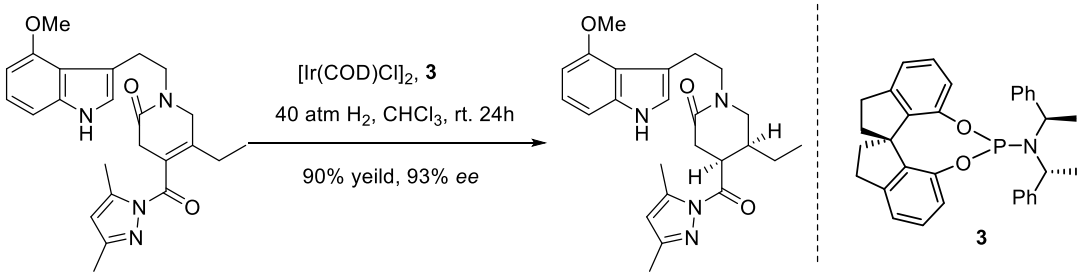
2.1.5 Synthesis of compound 8.



PhSMe (16 mL) and water (16 mL) were added to a solution of **20** (2.00 g, 5.02 mmol, 1.0 equiv.) in CH_2Cl_2 (16 mL). Then the resulting mixture was cooled with an ice-water bath followed by addition of TFA (32 mL) before warmed to room tempareture. The reaction was stirred vigorously overnight and then cooled to 0 ^{o}C with an ice bath. Next the pH of the reaction was adjusted to 3 or 4 with saturated $NaHCO_3$ aqueous solution and the layers were separated. The aqueous layer was extracted with CH_2Cl_2:MeOH (5:1, v/v) , the combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The solvent was evaporated and the residue was dissolved in dry CH_2Cl_2 (50 mL) under argon protection. Next 3,5-dimethylpyrazole (961 mg, 10.0 mmol, 2.0 equiv.), Et_3N (1.67 mL, 12.0 mmol, 2.4 equiv.) and Mukaiyama reagent (1.54 g, 6.02 mmol, 1.2 equiv.) were added successively. The resulting mixture was stirred overnight at 25 ^{o}C. The solvent was evaporated and the resulting oil purified by column chromatography on silica gel (petroleum ether:EtOAc, 1:1 to 1:3 v/v). Product **8** was obtained as a white powder (1.05 g, 50% 2 steps). TLC (petroleum ether: EtOAc, 1:3 v/v): R_f = 0.40; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.00 (s, 1H), 7.09 (t, *J* = 8.0 Hz, 1H), 6.98 – 6.95 (m, 2H), 6.52 (d, *J* = 8.0 Hz, 1H), 5.98 (s, 1H), 3.97 (s, 3H), 3.92 (t, *J* = 4.0 Hz, 2H), 3.75 (t, *J* = 7.2 Hz, 2H), 3.36 (t, *J* = 4.0 Hz, 2H), 3.18 (t, *J* = 7.6 Hz, 2H), 2.56 (s, 3H), 2.21 (s, 3H), 2.05 (q, *J* = 7.6 Hz, 2H), 0.95 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*): δ 168.1, 166.4, 154.6, 152.8, 144.1, 138.1, 137.4,

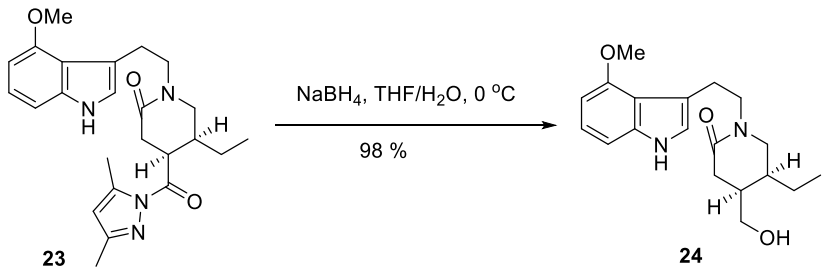
124.9, 122.8, 121.3, 117.2, 113.4, 111.4, 104.6, 99.4, 55.1, 51.9, 48.7, 34.3, 25.1, 24.5, 14.2, 13.8, 12.6. IR (neat): ν_{max} = 3270, 2973, 2929, 1699, 1633, 1456, 1377, 1338, 966, 872, 742 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{24}H_{29}N_4O_3$ $[M+H]^+$ 421.2234, found 421.2235.

2.1.6 Synthesis of compound 23.



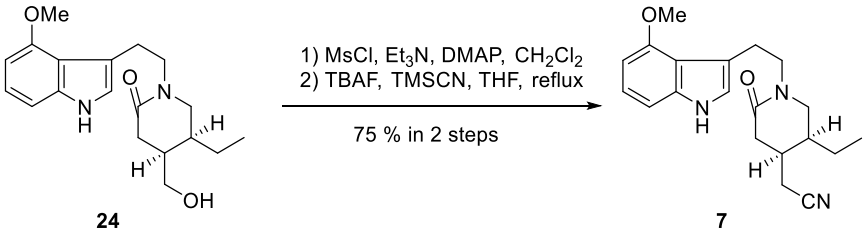
To a 50 mL flask were successively added $[Ir(COD)Cl]_2$ (23.8 mg, 35.7 μmol, 1.5 mol %), **3** (35.7 mg, 71.4 μmol, 3.0 mol%), dry degassed $CHCl_3$ (12 mL) under argon atmosphere. The resulting mixture was stirred at 25 ^oC. After 1 h, the solution of **8** (1.00 g, 2.38 mmol, 1.0 equiv) in dry degassed $CHCl_3$ (12 mL) was added and the reaction flask was placed in autoclave under 40 atm H_2. The reaction was stirred for 24 h at 25 ^oC before the H_2 was released. The $CHCl_3$ was evaporated and the resulting oil purified by column chromatography on silica gel (petroleum ether: EtOAc, 1:3, v/v). Product **23** was obtained as a white powder (904 mg, 90% yield, 93% *ee*). TLC (petroleum ether: EtOAc, 1:3 v/v) : R_f = 0.40; optical rotation: $[\alpha]_D^{25}$ = –9.8 (c = 0.9, chloroform)**.** ^1H NMR (400 MHz, Chloroform-*d*): δ 8.15 (s, 1H), 7.07 (t, *J* = 8.0 Hz, 1H), 6.98 – 6.94 (m, 2H), 6.49 (d, *J* = 8.0 Hz, 1H), 5.96 (s, 1H), 4.36 – 4.32 (m, 1H), 3.95 (s, 3H), 3.72 – 3.68 (m, 2H), 3.46 – 3.36 (m, 2H), 3.14 (t, *J* = 8.0 Hz, 2H), 2.82 (dd, *J* = 18.0, 8.0 Hz, 1H), 2.59 – 2.52 (m, 4H), 2.22 – 2.16 (m, 4H), 1.43 – 1.21 (m, 2H), 0.82 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 173.4, 168.1, 154.6, 152.0, 144.2, 138.1, 122.7, 121.4, 117.3, 113.5, 111.4, 104.6, 99.2, 55.0, 50.2, 49.3, 40.4, 37.3, 32.0, 24.6, 20.8, 14.6, 13.8, 12.0. IR (neat): ν_{max} = 3261, 2967, 2925, 2851, 1731, 1627, 1457, 1436, 1214, 1175, 1021, 743 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{24}H_{31}N_4O_3$ $[M+H]^+$ 423.2391, found 423.2390. The enantiomeric excess of **16** was determined by HPLC analysis on Chiralpak AD-H column. Conditions: hexane/isopropanol = 90/10, flow rate = 1.0 mL/min, uv-vis detection at λ = 254 nm, t_R = 26.0 min (major), 34.6 min (minor).

2.1.7 Synthesis of compound 24.



To a solution of compound **23** (500 mg, 1.18 mmol, 1.0 equiv) in THF (40 mL) and water (10 mL), $NaBH_4$ (89.3 mg, 2.36 mmol, 2.0 equiv) was added slowly at 0 °C. The reaction was stirred for 6 h before saturated NH_4Cl aqueous solution was added. The resulting mixture was extracted with EtOAc, the combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The solvent was evaporated and the resulting oil purified by column chromatography on silica gel (CH_2Cl_2: acetone, 2:1 to 1:2 v/v) afforded product **24** as white foam (382 mg, 98%). TLC (CH_2Cl_2: acetone, 2:1 v/v): R_f = 0.30; optical rotation: $[\alpha]_D^{25}$ = –5.9 (c = 0.5, chloroform). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.53 (s, 1H), 7.06 (t, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.87 (d, *J* = 2.4 Hz, 1H), 6.47 (d, *J* = 7.6 Hz, 1H), 3.92 (s, 3H), 3.75 – 3.70 (m, 1H), 3.61 – 3.54 (m, 2H), 3.43 (dd, *J* = 10.8, 8.0 Hz, 1H), 3.18 (dd, *J* = 12.4, 5.2 Hz, 1H), 3.12 – 3.03 (m, 3H), 2.89 (brs, 1H), 2.40 (t, *J* = 6.0 Hz, 2H), 2.14 – 2.06 (m, 1H), 1.85 – 1.78 (m, 1H), 1.42 – 1.17 (m, 2H), 0.86 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*): δ 169.4, 154.5, 138.2, 122.5, 121.5, 117.2, 113.0, 104.8, 99.1, 61.7, 55.0, 50.8, 49.3, 37.7, 36.4, 33.7, 24.5, 20.6, 12.0. IR (neat): ν_{max} = 3281, 2923, 2878, 1614, 1501, 1457, 1418, 1339, 1229, 1028, 742 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{19}H_{27}N_2O_3$ $[M+H]^+$331.2016, found 331.2015.

2.1.8 Synthesis of compound 7.

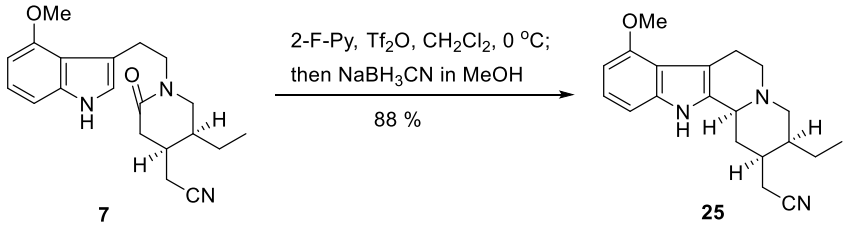


Under argon atmosphere, compound **24** (330 mg, 1.00 mmol, 1.0 equiv.) was dissolved in dry CH_2Cl_2 (30 mL) and Et_3N (208 μL, 1.50 mmol, 1.5 equiv.), DMAP (12.2 mg, 0.100 mmol, 0.1 equiv.), MsCl (92.9 μL, 1.20 mmol, 1.2 equiv.) were added successively. The resulting mixture was stirred for 6 h at 25 °C. The reaction was quenched by addition of saturated NH_4Cl aqueous solution and the aqueous layer was extracted with CH_2Cl_2, the combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The

solvent was removed and the residue was purified by flash column chromatography on silica gel (CH_2Cl_2: acetone, 2:1 v/v) afforded a white foam.

To a solution of this white foam in THF (25 mL), TMSCN (375μL, 3.00 mmol, 3.0 equiv.) was added followed by addition of TBAF (3.00 mL, 3.00 mmol, 3.0 equiv., 1.0 M in THF). The reation was warmed to 70 ^{o}C with an oil bath and stirred for 5 h. Then the reaction was allowed to cool to room tempareture and quenched by addition of water. The resulting mixture was extracted with EtOAc, the combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under reduce pressure and the residue was purified by column chromatography on silica gel (CH_2Cl_2:acetone, 10:1 to petroleum ether:EtOAc, 2:1 v/v). Product **7** was obtained as a white foam (254 mg, 75% 2 steps). TLC (CH_2Cl_2: acetone, 2:1 v/v): R_f = 0.80; optical rotation: $[\alpha]_D^{25}$ = +21.5 (c = 0.7, chloroform). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.17 (s, 1H), 7.08 (t, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 2.0 Hz, 1H), 6.50 (d, *J* = 8.0 Hz, 1H), 3.94 (s, 3H), 3.82 – 3.75 (m, 1H), 3.61 – 3.54 (m, 1H), 3.23 (dd, *J* = 12.8, 5.2 Hz, 1H), 3.13 (t, *J* = 7.2 Hz, 2H), 3.01 (dd, *J* = 12.8, 7.2 Hz, 1H), 2.53 (dd, *J* = 16.8, 5.6 Hz, 1H), 2.40 – 2.28 (m, 2H), 2.22 (dd, *J* = 16.8, 6.4 Hz, 1H), 2.05 (dd, *J* = 16.8, 8.4 Hz, 1H), 1.89 – 1.81 (m, 1H), 1.29 – 1.18 (m, 2H), 0.88 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*): δ 167.0, 154.5, 138.1, 122.8, 121.4, 118.3, 117.2, 113.1, 104.7, 99.4, 55.0, 49.6, 49.1, 37.3, 35.9, 33.1, 24.4, 20.2, 17.9, 11.7. IR (neat): ν_{max} = 3245, 2962, 2926, 2862, 1626, 1499, 1457, 1340, 1233, 1099, 744 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{20}H_{26}N_3O_2$ $[M+H]^+$ 340.2020, found 340.2025.

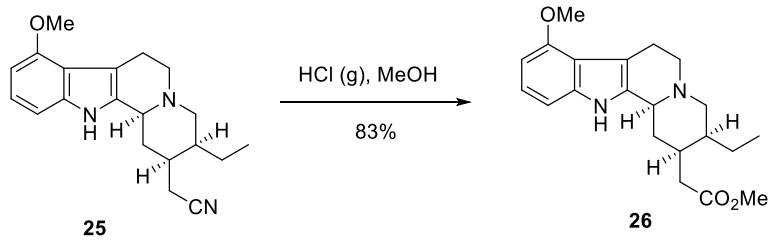
2.1.9 Synthesis of compound 25.



To a solution of compound **7** (293 mg, 0.864 mmol, 1.0 equiv.) in dry CH_2Cl_2 (20 mL), 2-F-Py (149 μL, 1.73 mmol, 2.0 equiv.) was added at 0 ^{o}C under argon. After stirring for 10 min, Tf_2O (218 μL, 1.30 mmol, 1.5 equiv.) was added and the reaction was stirred for 30 min before a solution of $NaBH_3CN$ (217 mg, 3.46 mmol, 4.0 equiv.) in methol was added dropwise. The resulting mixture was stirred for 30 min. Then the reaction was quenched by addition of saturated $NaHCO_3$ aqueous solution and extracted with CH_2Cl_2. The combined

organic layers were dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated and the resulting oil purified by column chromatography on silica gel (petroleum ether:EtOAc, 4:1 to 1:1, v/v) afforded product **25** (246 mg, 88%) as a white powder. TLC (petroleum ether: EtOAc, 2:1 v/v): R_f = 0.30; optical rotation: $[\alpha]_D^{25}$ = –50.4 (c = 0.3, chloroform). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.78 (s, 1H), 7.03 (t, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.47 (d, *J* = 7.6 Hz, 1H), 3.88 (s, 3H), 3.24 (d, *J* = 8.8 Hz, 1H), 3.14 – 2.92 (m, 4H), 2.58 (td, *J* = 11.6, 4.0 Hz, 1H), 2.39 – 2.26 (m, 3H), 2.20 – 2.11 (m, 1H), 1.98 (dt, *J* = 12.8, 3.6 Hz, 1H), 1.71 – 1.61 (m, 2H), 1.57 – 1.48 (m, 1H), 1.21 – 1.12 (m, 1H), 0.95 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*): δ 154.4, 137.3, 132.4, 122.2, 119.1, 117.4, 108.2, 104.3, 99.8, 59.5, 56.9, 55.3, 53.4, 39.2, 37.2, 31.5, 23.7, 21.3, 17.7, 12.2. IR (neat): ν_{max} = 3360, 2926, 2807, 1455, 1382, 1343, 1260, 1108, 742 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{20}H_{26}N_3O$ $[M+H]^+$ 324.2070, found 324.2069.

2.1.10 Synthesis of compound 26.

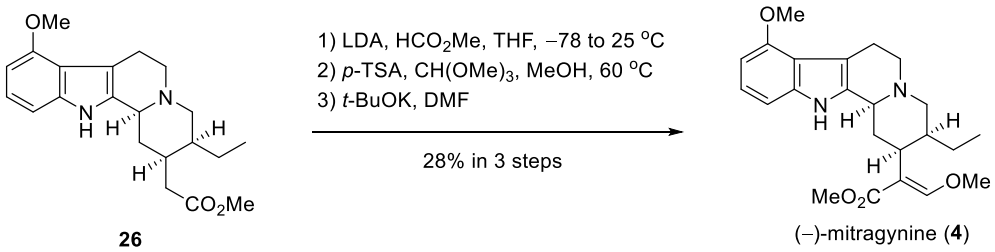


25 **26**

Under argon, dry HCl gas was bubbled into a solution of cyanide **25** (200 mg, 0.619 mmol, 1.0 equiv.) in dry MeOH (50 mL) at 0^{o}C over a period of 5 h. After removing the ice bath, the reaction was stirred at room temperature for 5 h. The solvent was evaporated in vacuo and the residue was dissolved in water (30 mL) and EtOAc (20 mL). The mixture was allowed to be stirred vigorously overnight and extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue obtained was subjected to flash column chromatography (petroleum ether:EtOAc, 2:1 v/v) to give 26 (183 mg, 83%) as a pale-yellow oil. TLC (petroleum ether: EtOAc, 1:1 v/v): R_f = 0.60; optical rotation: $[\alpha]_D^{25}$ = –36.7 (c = 0.8, chloroform). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.75 (s, 1H), 7.00 (t, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.45 (d, *J* = 7.6 Hz, 1H), 3.87 (s, 3H), 3.72 (s, 3H), 3.26 (d, *J* = 8.8 Hz, 1H), 3.15 – 3.06 (m, 1H), 3.01 – 2.91 (m, 3H), 2.62 – 2.54 (m, 1H), 2.40 – 2.33 (m, 2H), 2.31 – 2.26 (m, 2H), 1.93 – 1.85 (m, 1H), 1.71 – 1.63 (m, 1H), 1.56 – 1.47 (m, 2H), 1.31 – 1.19 (m, 1H), 0.92 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, Chloroform-*d*): δ 173.6, 154.5, 137.3, 133.1, 121.9, 108.0, 104.2, 99.7, 59.8, 58.0, 55.3, 53.6, 51.6, 39.9, 38.0, 36.7, 31.8, 23.7, 18.2, 12.5.IR (neat): ν_{max} =

2953, 2928, 1736, 1460, 1434, 1256, 1106, 772 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{21}H_{29}N_2O_3$ $[M+H]^+$ 357.2173, found 357.2176.

2.1.11 Synthesis of (–)-mitragynine (4).[1]



26 (–)-mitragynine (**4**)

Under argon, to a solution of ester **26** (150 mg, 0.421 mmol, 1.0 equiv.) in dry THF (15 mL) was added LDA (2.53 mL, 2.53 mmol, 6.0 equiv., 1.0 M in THF) dropwise at –78 ℃.[1] After 30 min, methyl formate (2.08 mL, 33.7 mmol, 80.0 equiv.) was added. The resulting mixture was then warmed to room temperature and stirred overnight. The reaction was quenched by addition of saturated NH_4Cl aqueous solution and extracted with EtOAc. The combined organic phases dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was dissolved in dry MeOH (15 mL) to which was added $CH(OMe)_3$ (138 μL, 1.26 mmol, 3.0equiv.) and *p*-TsOH H_2O (239 mg, 1.26 mmol, 3.0 equiv.), and the mixture was stirred at 60 ℃ for 48 h. The resulting mixture was quenched with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted three times with $CHCl_3$. The combined organic layer was washed with brine, and dried over Na_2SO_4, and concentrated under reduce pressure. The crude materials were subjected to flash column chromatography (CH_2Cl_2:acetone, 30:1 to 10:1 v/v) to give 67.6 mg of desired dimethoxyacetal intermediate and 60 mg of ester S11. Desired intermediate (67.6 mg, 0.157 mmol, 1.0 equiv.) was dissolved in dry degassed DMF (5 mL) to which was added *t*-BuOK (88.1 mg, 0.786 mmol, 5.0 equiv.) at room temperature under Ar atmosphere. The reaction mixture was stirred for 5 h at room temperature. The resulting mixture was quenched with saturated aqueous NH_4Cl solution. The aqueous layer was extracted four times with $CHCl_3$. The combined organic layer was dried over Na_2SO_4, and concentrated under reduce pressure. The crude materials were purified by column chromatography on silica gel (petroleum ether: EtOAc, 4:1 to 1:1 v/v) afforded (–)-mitragynine as an amorphous pale-yellow solid (46.9 mg, 28% 3 steps). TLC (petroleum ether:EtOAc, 2:1 v/v) : R_f = 0.30; optical rotation: $[\alpha]_D^{25}$ = –92.5 (c = 0.4, chloroform), lit.[2], –136.9 (chloroform). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.68 (s, 1H), 7.43 (s, 1H), 6.99 (t, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.45 (d, *J* = 7.6

Hz, 1H), 3.87 (s, 3H), 3.73 (s, 3H), 3.71 (s, 3H), 3.17 – 3.09 (m, 2H), 3.06 – 2.90 (m, 4H), 2.56 – 2.44 (m, 3H), 1.82 – 1.73 (m, 2H), 1.66 – 1.62 (m, 1H), 1.23 – 1.16 (m, 1H), 0.87 (t, J = 7.6 Hz, 3H). ^{13}C NMR (150 MHz, Chloroform-*d*): δ 169.2, 160.5, 154.5, 137.2, 133.7, 121.8, 117.7, 111.5, 107.9, 104.2, 99.8, 61.5, 61.3, 57.8, 55.3, 53.8, 51.3, 40.7, 39.9, 29.9, 23.9, 19.1, 12.9. IR (neat): ν_{max} = 2953, 2927, 1700, 1641, 1460, 1255, 1106, 769 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{23}H_{31}N_2O_4$ $[M+H]^+$ 399.2278, found 399.2275.

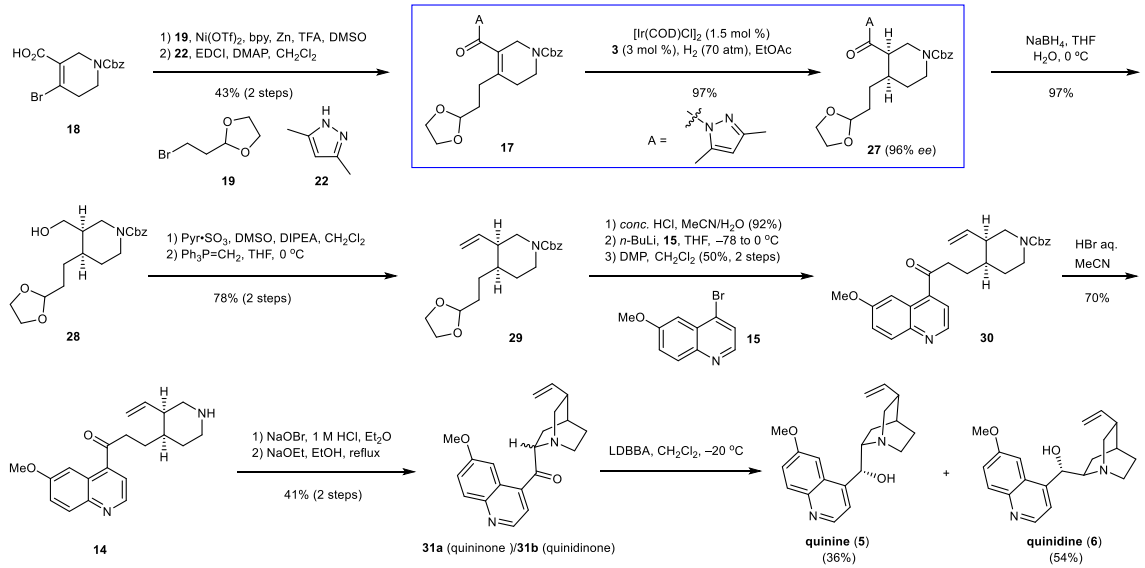
Table S2. Comparison of ^{1}H NMR (Chloroform-*d*) spectroscopic data of the synthetic (–)-mitragynine in the literature and in our study.

A: lit.[2] Natural **(–)-Mitragynine** δ_H [ppm, mult, J (Hz)], 500 MHz	B: Our Synthetic **(–)-Mitragynine** δ_H [ppm, mult, J (Hz)], 400 MHz	Error (B – A) $\Delta\delta$/ppm
7.71 (br s, 1H)	7.68 (s, 1H)	–0.03
7.43 (s, 1H)	7.43 (s, 1H)	0
6.99 (t, J = 7.9 Hz, 1H)	6.99 (t, J = 8.0 Hz, 1H)	0
6.90 (d, J =8.0 Hz, 1H)	6.90 (d, J = 8.0 Hz, 1H)	0
6.46 (d, J = 7.7 Hz, 1H)	6.45 (d, J = 7.6 Hz, 1H)	–0.01
3.88 (s, 3H)	3.87 (s, 3H)	–0.01
3.73 (s, 3H)	3.73 (s, 3H)	0
3.71 (s, 3H)	3.71 (s, 3H)	0
3.18 – 3.07 (m, 2H)	3.17 – 3.09 (m, 2H)	/
3.07 – 2.99 (m, 2H)		
2.97 (dd, J = 15.5, 4.0 Hz, 1H)	3.06 – 2.90 (m, 4H)	/
2.92 (dd, J = 11.3, 5.8 Hz, 1H)		
2.57 – 2.48 (m, 2H)	2.56 – 2.44 (m, 3H)	/
2.45 (dd, J = 11.7, 2.8 Hz, 1H)		
1.84 – 1.73 (m, 2H)	1.82 – 1.73 (m, 2H)	/
1.65 – 1.61 (m, 1H)	1.66 – 1.62 (m, 1H)	/
1.24 – 1.15 (m, 1H)	1.23 – 1.16 (m, 1H)	/
0.87 (t, J = 7.4 Hz, 3H)	0.87 (t, J = 7.6 Hz, 3H)	0

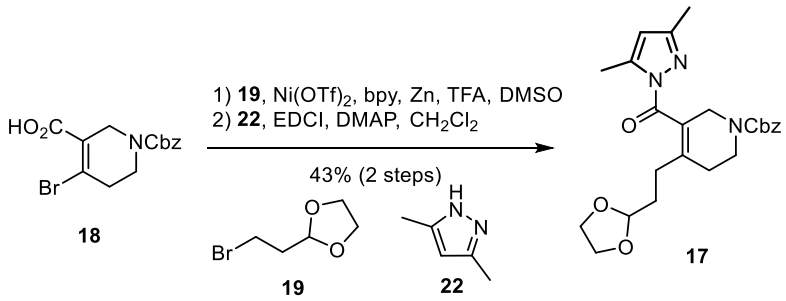
Table S3. Comparison of ^{13}C NMR (Chloroform-*d*) spectroscopic data of the synthetic (–)-mitragynine in the literature and in our study.

A: lit.[2] Natural **(–)-Mitragynine** δ (ppm), 100 MHz	B: Our Synthetic **(–)-Mitragynine** δ (ppm), 100 MHz	Error (B – A) $\Delta\delta$/ppm
169.4	169.2	–0.2
160.7	160.5	–0.2
154.6	154.5	–0.1
137.4	137.2	–0.2
133.9	133.7	–0.2
121.9	121.8	–0.1
117.8	117.7	–0.1
111.6	111.5	–0.1
108.0	107.9	–0.1
104.3	104.2	–0.1
99.9	99.8	–0.1
61.7	61.5	–0.2
61.4	61.3	–0.1
57.9	57.8	–0.1
55.5	55.3	–0.2
53.9	53.8	–0.1
51.5	51.3,	–0.2
40.8	40.7	–0.1
40.1	39.9	–0.2
30.1	29.9	–0.2
24.1	23.9	–0.2
19.2	19.1	–0.1
13.0	12.9	–0.1

2.2. Total synthesis of (–)-quinine and (+)-quinidine.



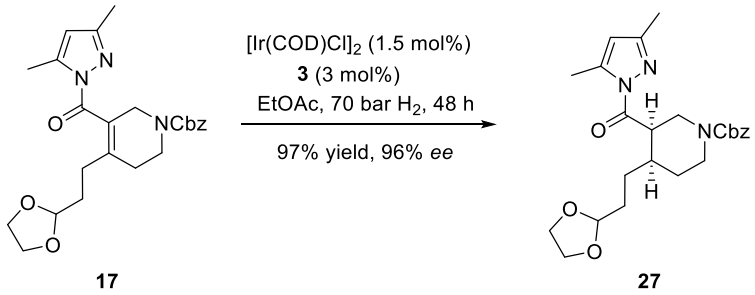
2.2.1 Synthesis of compound 17.



To a 100 mL oven dried flask, compound **18** (680 mg, 2.00 mmol, 1.0 equiv.), $Ni(OTf)_2$ (143 mg, 0.400 mmol, 0.2 equiv.), zinc powder (256 mg, 4.00 mmol, 2.0 equiv.), 2,2'-bipyridine (62.5 mg, 0.400 mmol, 0.2 equiv.) and dry degassed DMSO (40 mL) were added under argon atmosphere. Next TFA (34.0 μL, 0.200 mmol, 0.1 equiv.) and 2-(2-bromoethyl)-1,3-dioxolane (469 μL, 4.00 mmol, 2.0 equiv.) were added at 0 ^oC. The resulting mixture was warmed to 25 ^oC and stirred for 12 h. Then the reaction was cooled with an ice-water bath before 1 N HCl (40 mL) was added. The resulting mixture was stirred until there was no zinc powder residue, then extracted with MTBE and dried over anhydrous $MgSO_4$. The solvent was removed by evaporation and the residue was dried in vacuo. The crude product was dissolved in dry CH_2Cl_2 (50 mL) under argon, and 3,5-dimethylpyrazole (385 mg, 4.00 mmol, 2.0 equiv.), EDCI (767 mg, 4.00 mmol, 2.0 equiv.), DMAP (244 mg, 2.00 mmol, 1.0 equiv.) were successively added. The reaction was stirred overnight at 25 ^oC. The solvent was removed by evaporation and the residue was

chromatographed on silica gel (petroleum ether:*i*-PrOH, 30/1 v/v) to afford **17** (377 mg, 43% 2 steps) as colorless oil. TLC (petroleum ether:EtOAc, 1:1, v/v): R_f = 0.40; ^{1}H NMR (400 MHz, Chloroform-*d*, some signals exist as a pair due to the presence of amide rotamers): δ 7.35 – 7.31 (m, 5H), 5.96 (s, 1H), 5.14 (s, 2H), 4.78 (t, *J* = 4.8 Hz, 1H), 4.30 (s, 2H), 3.98 – 3.72 (m, 4H), 3.66 (t, *J* = 6.0 Hz, 2H), 2.55 (s, 3H), 2.29 (s, 2H), 2.18 (brs, 5H), 1.82 – 1.76 (m, 2H). ^{13}C NMR (150 MHz, Chloroform-*d*, some signals exist as a pair due to the presence of amide rotamers): δ 155.2/155.0, 152.6, 144.1, 139.7, 139.1, 136.7, 134.8, 128.5, 128.0/127.9, 127.1, 111.3/111.3, 103.8, 67.2, 64.8, 44.4/44.2, 40.4/40.1, 31.6, 29.0, 28.5/28.1, 14.2/14.2, 13.8. IR (neat): ν_{max} = 2962, 2927, 1736, 1691, 1601, 1398, 1339, 1301, 1233, 1212, 1116, 757 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{24}H_{30}N_3O_5$ $[M+H]^+$ 440.2180, found 440.2176.

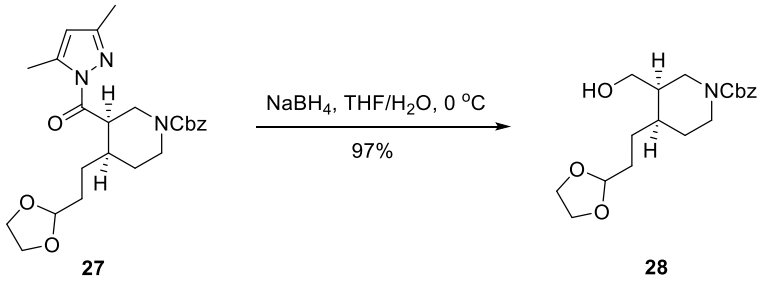
3.2 Synthesis of compound 27.



Under argon, $[Ir(COD)Cl]_2$ (11.8 mg, 17.6 μmol, 1.5 mol %) and **3** (17.7 mg, 35.2 μmol, 3.0 mol %) were dissolved in dry degassed EtOAc (5 mL), the mixture was stirred for 1 h at 25 ^{o}C. Next a solution of compound **17** (516 mg, 1.18 mmol, 1.0 equiv.) in dry degassed EtOAc (5 mL) was added. The resulting mixture was placed in autoclave and charged with hydrogen to 70 atm, the reaction was stirred for 48 h at 25 ^{o}C. After releasing hydrogen, the reaction solvent was removed and the residue was purified by flash column chromatography on silica gel (petroleum ether:EtOAc, 2:1 v/v). Product **27** (499 mg, 97%) was obtained as colorless oil with 96% *ee*. TLC (petroleum ether:EtOAc, 2:1 v/v): R_f = 0.35; Optical rotation: $[\alpha]_D^{25}$ = +47.6 (c = 1.1, chloroform). ^{1}H NMR (400 MHz, Chloroform-*d*, some signals exist as a pair due to the presence of amide rotamers): δ 7.34 – 7.12 (m, 5H), 5.88 (d, *J* = 25.2 Hz, 1H), 5.04 (d, *J* = 38.3 Hz, 2H), 4.77 (t, *J* = 3.6 Hz, 1H), 4.21 (dd, *J* = 14.0, 4.0 Hz, 1H), 4.13 – 3.75 (m, 6H), 3.41 – 3.32 (m, 1H), 3.17 – 3.10 (m, 1H), 2.42 (d, *J* = 16.0 Hz, 3H), 2.20 – 2.07 (m, 4H), 1.99 (s, 1H), 1.71 – 1.52 (m, 5H). ^{13}C NMR (100 MHz, Chloroform-*d*, some signals exist as a pair due to the presence of amide

rotamers): δ 172.9/172.8, 155.3/155.1, 151.6, 143.8, 137.0/136.6, 128.4/128.3, 127.7/127.4, 111.0, 104.4, 66.9, 64.8, 45.5, 43.3/43.1, 42.0/41.7, 37.3, 31.5, 27.5/27.1, 25.6/25.5, 14.5, 13.8. IR (neat): ν_{max} = 2926, 2867, 1722, 1699, 1432, 1322, 1235, 1123, 962, 760 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{24}H_{32}N_3O_5$ $[M+H]^+$ 442.2336, found 442.2337. The enantiomeric excess of **29** was determined by HPLC analysis on Chiralpak AS-H column. Conditions: hexane/isopropanol = 50/50, flow rate = 0.5 mL/min, uv-vis detection at λ = 254 nm, t_R = 10.2 min (minor), 13.3 min (major).

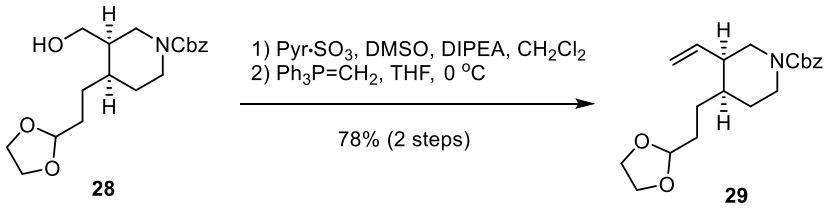
3.3 Synthesis of compound 28.



27 **28**

To a solution of compound **27** (400 mg, 0.91 mmol, 1.0 equiv.) in THF (16 mL) and water (4 mL), $NaBH_4$ (172 mg, 4.55 mmol, 5.0 equiv.) was added at 0 °C. After stirring for 12 h, additional $NaBH_4$ (172 mg, 4.55 mmol, 5.0 equiv.) was added and stirred for 24 h. The reaction was quenched by addition of saturated NH_4Cl aqueous solution and the aqueous phase was extracted with EtOAc. The organic layers were combined, dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated and the resulting oil purified by column chromatography on silica gel (petroleum ether:*i*-PrOH, 20:1 to 15:1 v/v) afforded **28** (306mg, 97%) as colorless oil. TLC (petroleum ether:EtOAc, 1:1 v/v): R_f = 0.20; optical rotation: $[\alpha]_D^{25}$ = +19.3 (c = 0.4, chloroform). ^{1}H NMR (400 MHz, Chloroform-*d*, some signals exist as a pair due to the presence of amide rotamers): δ 7.39 – 7.30 (m, 5H), 5.14 (s, 2H), 4.83 (t, *J* = 4.4 Hz, 1H), 4.30 – 4.10 (m, 2H), 3.99 – 3.80 (m, 4H), 3.57 – 3.33 (m, 2H), 2.92 – 2.78 (m, 3H), 1.95 – 1.64 (m, 4H), 1.47 – 1.28 (m, 4H).^{13}C NMR (100 MHz, Chloroform-*d*, some signals exist as a pair due to the presence of amide rotamers): δ 156.6, 136.6, 128.5, 128.1, 127.9, 104.3, 67.4, 64.9, 58.4/57.4, 45.7, 45.1, 39.9/39.3, 37.8/37.6, 31.3, 27.7, 26.9/26.4. IR (neat): ν_{max} = 3458, 2926, 2872, 1696, 1679, 1436, 1240, 1030, 804, 699 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{19}H_{28}NO_5$ $[M+H]^+$ 350.1962, found 350.1963.

3.4 Synthesis of compound 29.

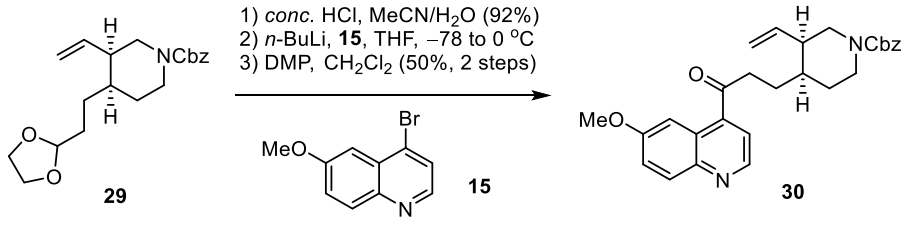


Under argon, to a solution of compound **28** (357 mg, 1.02 mmol, 1.0 equiv.) in dry CH_2Cl_2 (15 mL), anhydrous DMSO (0.86 mL, 12.3 mmol, 12.0 equiv.), DIPEA (1.43 mL, 8.16 mmol, 8.0 equiv.), pyridine sulfur trioxide (974 mg, 6.12 mmol, 6.0 equiv.) were added successively. The resulting mixture was stirred for 2 h at 25 °C. Then Et_2O (150 mL) was added, the resulting mixture was successively washed with 1N HCl aqueous solution, saturated $NaHCO_3$ aqueous solution and brine. The organic phase was dried with anhydrous $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the crude aldehyde was used directly.

To a oven dried 50 mL round-bottom flask with a stir bar, methyltriphenylphosphonium bromide (1.83 g, 5.10 mmol, 5.0 equiv.) and anhydrous THF (20 mL) were charged under argon. The solution was cooled to –78 °C and *n*-BuLi (1.64 mL, 4.08 mmol, 4.0 equiv., 2.5 M in hexane) was added dropwise. Then the reaction was allowed to be warmed to 25 °C. After stirring for 30 min, the suspension of ylide was recooled to –78 °C, a solution of crude aldehyde in anhydrous THF (5 mL) was added. The resulting mixture was warmed to 0 °C and stirred for 5 h. The reaction was quenched by addition of saturated NH_4Cl aqueous solution and the aqueous phase was extracted with EtOAc. The organic layers were combined, dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated and the resulting oil purified by column chromatography on silica gel (petroleum ether:EtOAc, 5:1 v/v) afforded **29** (274 mg, 78% 2 steps) as colorless oil. TLC (petroleum ether:EtOAc, 2:1 v/v): R_f = 0.50; optical rotation: $[\alpha]_D^{25}$ = +38.7 (c = 1.0, chloroform). ^{1}H NMR (400 MHz, Chloroform-*d*, some signals exist as a pair due to the presence of amide rotamers): δ 7.34 – 7.28 (m, 5H), 5.82 – 5.73 (m, 1H), 5.16 – 5.07 (m, 4H), 4.81 (t, *J* = 4.4 Hz, 1H), 4.20 – 4.05 (m, 2H), 3.99 – 3.79 (m, 4H), 3.04 (d, *J* = 12.0 Hz, 1H), 2.92 – 2.81 (m, 1H), 2.39 – 2.28 (m, 1H), 1.72 – 1.56 (m, 3H), 1.48 – 1.20 (m, 4H). ^{13}C NMR (100 MHz, Chloroform-*d*, some signals exist as a pair due to the presence of amide rotamers): δ 155.5, 136.9, 135.4/135.3, 128.4, 127.8/127.7, 117.1, 104.5, 66. 9, 64.8, 49.0/48.5, 44.0, 42.4/42.3, 38.6, 31.1, 27.6/27.4, 27.2/26.9. IR (neat): ν_{max} = 2929, 2859, 1695, 1433, 1236, 1100, 1024, 998, 698 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{20}H_{28}NO_4$

[M+H] $^{+}$ 346.2013, found 346.2012.

3.5 Synthesis of compound 30.

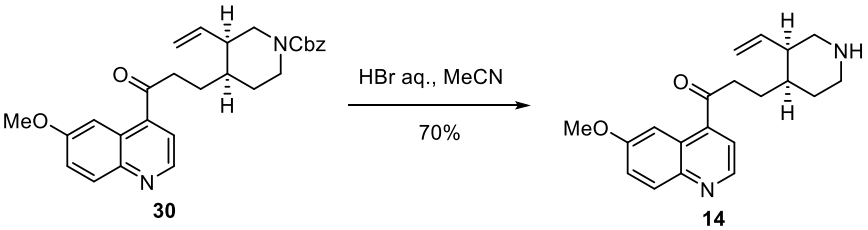


To a solution of compond **29** (250 mg, 0.725 mmol, 1.0 equiv.) in MeCN (5 mL), water (5 mL) and *conc.* HCl (5 mL) were added, the reaction was stirred for 2 h at 25 ^{o}C. Next water (15 mL) was added, the resulting mixture was extracted with EtOAc. The combined organic layers were washed with saturated $NaHCO_3$ aqueous solution and brine, dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated and the residue purified by column chromatography on silica gel (petroleum ether:EtOAc, 5:1 v/v) afforded intermediate (201 mg, 92%) as colorless oil. TLC (petroleum ether:EtOAc, 2:1 v/v): R_f = 0.45; optical rotation: $[\alpha]_D^{25}$ = +50.0 (c = 0.7, chloroform). ^{1}H NMR (400 MHz, Chloroform-*d*, some signals exist as a pair due to the presence of amide rotamers) δ 9.76 (s, 1H), 7.35 – 7.30 (m, 5H), 5.83 – 5.74 (m, 1H), 5.16 – 5.07 (m, 4H), 4.22 – 4.06 (m, 2H), 3.03 (d, *J* = 12.4 Hz, 1H), 2.93 – 2.80 (m, 1H), 2.51 – 2.31 (m, 3H), 1.59 – 1.31 (m, 5H). ^{13}C NMR (100 MHz, Chloroform-*d*, some signals exist as a pair due to the presence of amide rotamers) δ 202.2, 155.5, 136.8, 135.1, 128.4, 127.9/127.8, 117.5, 67.0, 49.0/48.6, 43.9, 42.4/42.2, 38.1, 27.5/27.3, 25.2/25.0. IR (neat): ν_{max} = 2928, 2858, 1693, 1433, 1236, 1095, 998, 698 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{18}H_{24}NO_3$ $[M+H]^+$ 302.1751, found 302.1752.

Under argon, compound **15** (316 mg, 1.33 mmol, 2.0 equiv.) was dissolved in anhydrous Et_2O (15 mL) and cooled to –78 ^{o}C. After 5 min, *n*-BuLi (0.48 mL, 1.20 mmol, 1.8 equiv., 2.5 N in hexane) was added dropwise and stirred for 1h. A solution of intermediate (200 mg, 0.664 mmol, 1.0 equiv.) in anhydrous Et_2O (5 mL) was added. The reaction was stirred for another 1 h before warmed to 0 ^{o}C. After stirring overnight, water was added, the aqueous phase was extracted with EtOAc. The organic layers were combined, dried with anhydrous Na_2SO_4 and filtered. The solvent was evaporated and the crude alchol was redissolved in CH_2Cl_2 (15 mL). Next DMP (564 mg, 1.33 mmol, 2.0 equiv.) was added and the resulting suspension was stirred for 30 min at 25 ^{o}C. Then

saturated $NaHCO_3$ (10 mL) aqueous solution and saturated $Na_2S_2O_3$ (10 mL) aqueous solution were added to the reaction, the resulting mixture was stirred vigorously until became clear. The layers was separated and aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried with anhydrous Na_2SO_4 and filtered. The solvent was evaporated and the crude product was purified by column chromatography on silica gel (petroleum ether:EtOAc, 2:1 v/v) afforded **30** (152 mg, 50 % 2 steps) as colorless oil. TLC (petroleum ether:EtOAc, 1:1 v/v): R_f = 0.30; optical rotation: $[\alpha]_D^{25}$ = +28.7 (c = 0.6, chloroform). ^{1}H NMR (400 MHz, Chloroform-*d*, some signals exist as a pair due to the presence of amide rotamers): δ 8.86 (d, *J* = 4.4 Hz, 1H), 8.04 (d, *J* = 9.2 Hz, 1H), 7.82 (d, *J* = 2.8 Hz, 1H), 7.58 (d, *J* = 4.4 Hz, 1H), 7.43 – 7.30 (m, 6H), 5.87 – 5.78 (m, 1H), 5.17 – 5.08 (m, 4H), 4.22 – 4.05 (m, 2H), 3.93 (s, 3H), 3.12 – 2.86 (m, 4H), 2.45 – 2.32 (m, 1H), 1.74 – 1.67 (m, 3H), 1.52 – 1.43 (m, 2H). ^{13}C NMR (100 MHz, Chloroform-*d*, some signals exist as a pair due to the presence of amide rotamers): δ 203.7, 159.4, 155.5, 146.9, 145.7, 140.3, 136.8, 135.3/135.1, 131.4, 128.4, 127.9/127.8, 125.1, 122.8, 120.0, 117.5, 102.9, 67.0, 55.6, 49.0/48.6, 43.9, 42.6/42.2, 39.1, 38.3, 27.7, 27.4/27.1. IR (neat): ν_{max} = 2933, 2858, 1693, 1618, 1431, 1238, 1095, 999, 698 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{28}H_{31}N_2O_4$ $[M+H]^+$ 459.2278, found 459.2278.

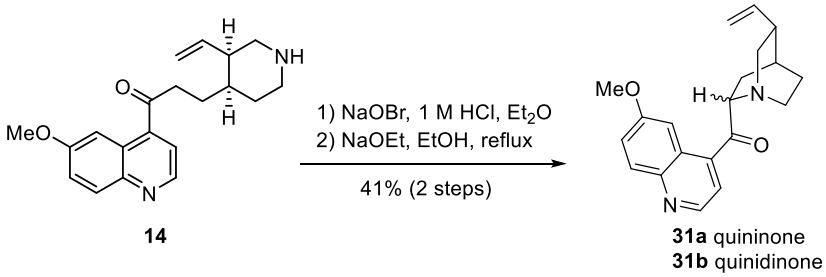
3.7 Synthesis of *d*-quinotoxine 14.



To a solution of ketone **30** (152 mg, 0.332 mmol, 1.0 equiv.) in MeCN (5 mL), HBr (10 mL, 48% in water w/w) was added, the resulting mixture was stirred overnight at 25 ^{o}C. Then the reaction was poured into saturated $NaHCO_3$ aqueous solution and the pH was adjusted to 9 by addition of $NaHCO_3$ solid at 0 ^{o}C. The resulting mixture was extracted with EtOAc and the organic layers were combined, dried with anhydrous Na_2SO_4, filtered. The solvent was evaporated and the residue was purified by column chromatography on silica gel (CH_2Cl_2: MeOH, 10:1, with 0.1% NH_3 v/v). Product **14** (75.3 mg, 70 %) was obtained as pale-yellow oil. TLC (CH_2Cl_2:MeOH, 10:1 v/v): R_f = 0.30; optical rotation: $[\alpha]_D^{25}$ = +31.7 (c = 0.2, EtOH). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.86 (d, *J* = 4.4 Hz, 1H),

8.04 (d, *J* = 9.2 Hz, 1H), 7.81 (d, *J* = 2.8 Hz, 1H), 7.58 (d, *J* = 4.4 Hz, 1H), 7.41 (dd, *J* = 9.2, 2.4 Hz, 1H), 6.17 – 6.08 (m, 1H), 5.17 – 5.11 (m, 2H), 3.94 (s, 3H), 3.13 – 2.96 (m, 4H), 2.86 (dd, *J* = 12.4, 3.2 Hz, 1H), 2.70 – 2.64 (m, 1H), 2.34 – 2.31 (m, 1H), 1.72 – 1.69 (m, 4H), 1.55 – 1.42 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 204.2, 159.4, 147.0, 145.7, 140.6, 137.2, 131.4, 125.2, 122.9, 120.0, 116.7, 103.0, 55.6, 52.0, 46.3, 43.0, 39.3, 38.3, 29.0, 27.8. IR (neat): ν_{max} = 2924, 2852, 1688, 1618, 1505, 1243, 1028, 854, 748 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{20}H_{25}N_2O_2$ $[M+H]^+$ 325.1911, found 325.1912.

3.8 Synthesis of quininone/quinidinone (35a/b)[3].



14

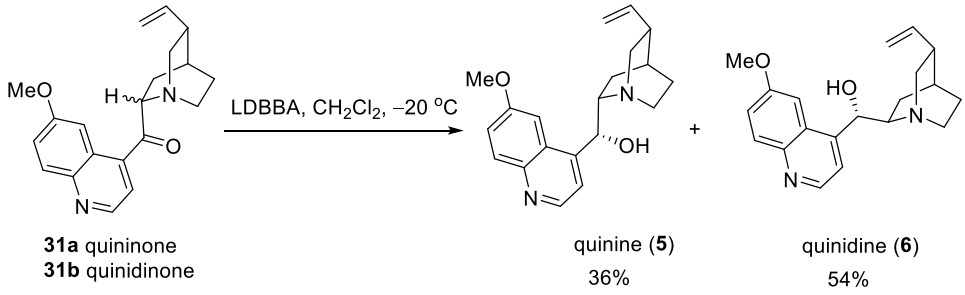
31a quininone
31b quinidinone

Quininone/quinidinone was prepared according to the reported procedure.[2] A fresh solution of sodium hypobromite was prepared as follows: NaOH (59.3 mg, 1.48 mmol, 3.0 equiv.) was dissolved in 1 mL water. The basic solution was cooled to 0 ^{o}C and bromine (25.3 μL, 0.494 mmol, 1.0 equiv) was added with vigorous stirring. The solution turned yellow upon consumption of the bromine. The solution was then allowed to stir for 15 minutes at 0 ^{o}C.

A round-bottomed flask containing *d*-quinotoxine **14** (160 mg, 0.494 mmol, 1.0 equiv.) was charged with 1N HCl (0.50 mL, 0.500 mmol, 1.0 equiv.) and ether (5 mL) and stirred vigorously. The freshly prepared solution of sodium hypobromite was then added dropwise *via* syringe. Stirring was continued for 10 minutes. The ether layer was then separated, dried over Na_2SO_4, and filtered into a round-bottomed flask. The flask was stoppered and allowed to stand 24 h in the dark. The ether was filtered and the solvent was removed by rotary evaporation to yield an unstable yellow oil (135 mg, 0.335 mmol, 68% crude yield) that was immediately dissolved in anhydrous EtOH (10 mL). The solution was heated to reflux and NaOEt (3.5 mL, 0.836 mmol, 2.5 equiv., 2.4 M in EtOH) was added. After 10 min, the reaction was cooled to room tempareture and 1 N HCl solution was added to adjust pH to 3. The EtOH was evaporated and the aqueous layer was then made basic through the addition of 1 N NaOH solution and extracted with ether. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column

chromatography on silica gel (CH_2Cl_2:MeOH, 20:1 with 1% NH_3 v/v). The mixture (65 mg, 41% 2 steps) of quininone and quinidinone were obtained as yellow oil.

3.9 Synthesis of quinine and quinidine.[4]



Under argon, the mixture of quininone and quinidinone (30 mg, 0.093 mmol, 1.0 equiv.) were dissolved in dry CH_2Cl_2 (4 mL) and LDBBA (0.93 mL, 0.556 mmol, 6.0 equiv., 0.6 M in THF) was added at –20 °C. After being stirred for 1 h at same temperature, the reaction was quenched by adding saturated aqueous $NaHCO_3$ solution. The mixture was then extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. Purification of the crude product by prep. TLC (CH_2Cl_2: MeOH, 20:1 with 1% NH_3 v/v) gave (–)-quinine (10.8 mg, 36%) and (+)-quinidine (16.3 mg, 54%) as white solid.

(–)-Quinine:

TLC (CH_2Cl_2: MeOH, 10:1 v/v), R_f = 0.20; optical rotation: $[\alpha]_D^{25}$ = –139.5 (c = 0.5, EtOH). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.48 (d, *J* = 4.4 Hz, 1H), 7.89 (d, *J* = 9.2 Hz, 1H), 7.44 (d, *J* = 4.4 Hz, 1H), 7.28 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.22 (d, *J* = 2.8 Hz, 1H), 5.76 – 5.70 (m, 1H), 5.47 (s, 1H), 4.96 – 4.88 (m, 2H), 4.75 (s, 1H), 3.89 (s, 3H), 3.45 – 3.38 (m, 1H), 3.12 – 3.01 (m, 2H), 2.64 – 2.52 (m, 2H), 2.23 (s, 1H), 1.78 – 1.67 (m, 3H), 1.54 – 1.46 (m, 2H). ^{13}C NMR (100 MHz, Chloroform-d): δ 157.6, 147.9, 147.4, 144.1, 141.9, 131.4, 126.6, 121.4, 118.4, 114.3, 101.4, 72.1, 60.0, 57.0, 55.6, 43.2, 40.0, 27.9, 27.7, 21.9. IR (neat): ν_{max} = 3149, 2933, 2857, 1623, 1591, 1508, 1240, 1029, 822 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{20}H_{25}N_2O_2$ $[M+H]^+$ 325.1911, found 325.1911.

(+)-Quinidine:

TLC (CH_2Cl_2: MeOH, 10:1 v/v), R_f = 0.25; optical rotation: $[\alpha]^{25}_D$= +220 (c = 0.6, EtOH).^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.61 (d, *J* = 4.4 Hz, 1H), 7.95 (d, *J* = 9.2 Hz, 1H), 7.50 (d, *J* = 4.4 Hz, 1H), 7.30 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 6.05 – 5.96 (m, 1H), 5.55 (d, *J* = 4.0 Hz, 1H), 5.04 – 5.00 (m, 2H), 4.02 (s, 1H), 3.86 (s, 3H),

3.29 – 3.24 (m, 1H), 3.06 (td, *J* = 9.2, 4.4 Hz, 1H), 2.91 – 2.80 (m, 2H), 2.78 – 2.70 (m, 1H), 2.21 (q, *J* = 8.4 Hz, 1H), 2.04 – 1.89 (m, 1H), 1.76 – 1.67 (m, 1H), 1.53 – 1.37 (m, 2H), 1.20 – 1.12 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*): δ 157.6, 147.7, 147.5, 144.1, 140.6, 126.6, 121.4, 118.4, 114.4, 101.2, 72.1, 59.8, 55.5, 50.2, 49.6, 40.1, 28.2, 26.4, 21.3. IR (neat): ν_{max} = 3069, 2930, 2868, 1619, 1588, 1508, 1260, 1041, 819 cm^{-1}. HRMS (ESI): m/z calcd. for $C_{20}H_{25}N_2O_2$ $[M+H]^+$ 325.1911, found 325.1912.

Table S4. Comparison of ^{1}H NMR (Chloroform-*d*) spectroscopic data of the synthetic (–)-quinine and natural (–)-quinine

A: authentic sample δ [ppm, mult, *J* (Hz)], 400 MHz	B: synthetic sample δ [ppm, mult, *J* (Hz)], 400 MHz	Error (B–A) $\Delta\delta$/ppm
8.46(d, *J* = 4.4 Hz, 1H)	8.48 (d, *J* = 4.4 Hz, 1H)	0.02
7.89 (d, *J* = 9.2 Hz, 1H)	7.89 (d, *J* = 9.2 Hz, 1H)	0
7.43 (d, *J* = 4.4 Hz, 1H)	7.44 (d, *J* = 4.4 Hz, 1H)	0.01
7.26 (dd, *J* = 9.2, 2.8 Hz, 1H)	7.28 (dd, *J* = 9.2, 2.8 Hz, 1H)	0.02
7.22 (d, *J* = 2.8 Hz, 1H)	7.22 (d, *J* = 2.8 Hz, 1H)	0
5.76 – 5.67 (m, 1H)	5.76 – 5.70 (m, 1H)	/
5.46 (s, 1H)	5.47 (s, 1H)	0.01
4.96 – 4.88 (m, 2H)	4.96 – 4.88 (m, 2H)	/
4.88 (s, 1H)	4.75 (s, 1H)	–0.13
3.88 (s, 3H)	3.89 (s, 3H)	0.01
3.45 – 3.38 (m, 1H)	3.45 – 3.38 (m, 1H)	/
3.11 – 3.01 (m, 2H)	3.12 – 3.01 (m, 2H)	/
2.64 – 2.57 (m, 2H)	2.64 – 2.52 (m, 2H)	/
2.23 (s, 1H)	2.23 (s, 1H)	0
1.78 – 1.66 (m, 3H)	1.78 – 1.67 (m, 3H)	/
1.53 – 1.43 (m, 2H)	1.54 – 1.46 (m, 2H)	/

Table S5. Comparison of ^{13}C NMR (Chloroform-*d*) spectroscopic data of the synthetic (–)-quinine and natural (–)-quinine

A: authentic sample δ (ppm), 100 MHz	B: synthetic sample δ (ppm), 100 MHz	Error (B–A) $\Delta\delta$/ppm
157.6	157.6	0
148.0	147.9	–0.1
147.4	147.4	0
144.0	144.1	0.1
141.9	141.9	0
131.3	131.4	0.1
126.6	126.6	0
121.4	121.4	0
118.4	118.4	0
114.3	114.3	0
101.4	101.4	0
72.0	72.1	0.1
60.0	60.0	0
57.0	57.0	0
55.6	55.6	0
43.2	43.2	0
40.0	40.0	0
27.9	27.9	0
27.7	27.7	0
21.9	21.9	0

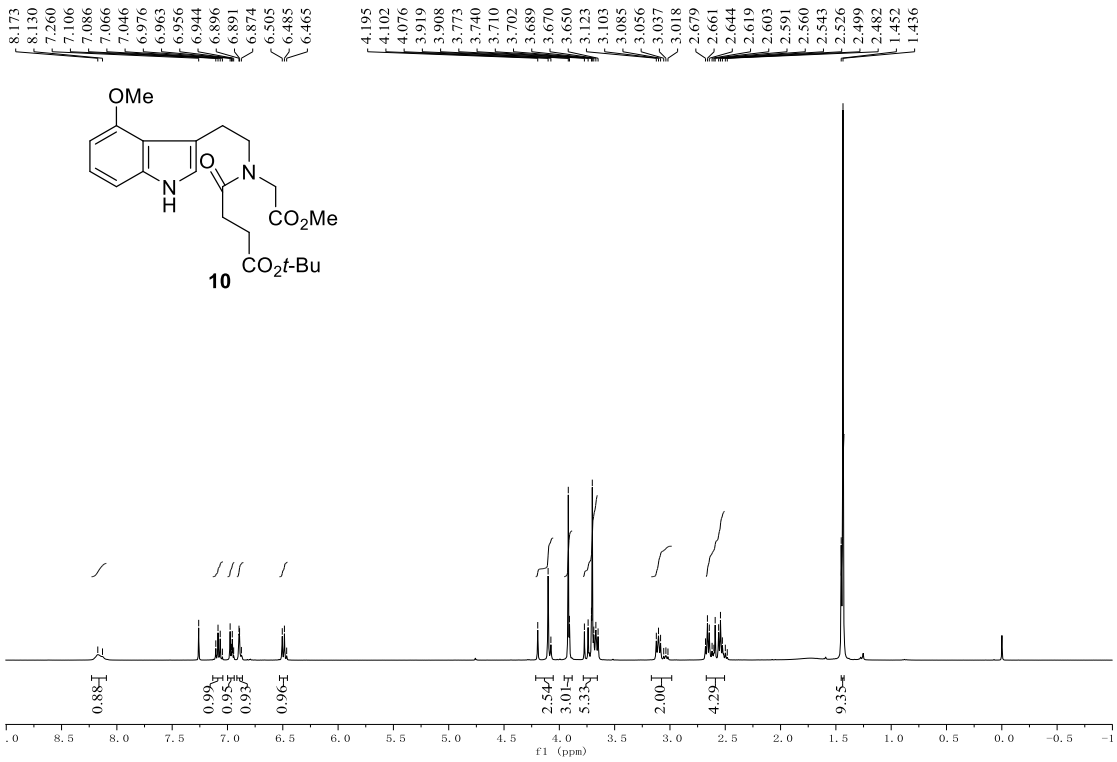
Table S6. Comparison of ^{1}H NMR (Chloroform-*d*) spectroscopic data of the synthetic (+)-quinidine and natural (+)-quinidine

A: authentic sample δ [ppm, mult, J (Hz)], 400 MHz	B: synthetic sample δ [ppm, mult, J (Hz)], 400 MHz	Error (B–A) $\Delta\delta$/ppm
8.60 (d, J = 4.4 Hz, 1H)	8.61 (d, J = 4.4 Hz, 1H)	0.01
7.95 (d, J = 9.2 Hz, 1H)	7.95 (d, J = 9.2 Hz, 1H)	0
7.50 (d, J = 4.4 Hz, 1H)	7.50 (d, J = 4.4 Hz, 1H)	0
7.30 (dd, J = 9.2, 2.8 Hz, 1H)	7.30 (dd, J = 9.2, 2.8 Hz, 1H)	0
7.18 (d, J = 2.8 Hz, 1H)	7.18 (d, J = 2.4 Hz, 1H)	0
6.05 – 5.96 (m, 1H)	6.05 – 5.96 (m, 1H)	/
5.54 – 5.51 (m, 1H)	5.55 (d, J = 4.0 Hz, 1H)	/
5.04 – 5.00 (m, 2H)	5.04 – 5.00 (m, 2H)	/
3.95 (s, 1H)	4.02 (s, 1H)	0.07
3.87 (s, 3H)	3.86 (s, 3H)	–0.01
3.28 – 3.22 (m, 1H)	3.29 – 3.24 (m, 1H)	/
3.06 (td, J = 9.2, 4.4 Hz, 1H)	3.06 (td, J = 9.2, 4.4 Hz, 1H)	0
2.96 – 2.81 (m, 2H)	2.91 – 2.80 (m, 2H)	/
2.78 – 2.69 (m, 1H)	2.78 – 2.70 (m, 1H)	/
2.21 (q, J = 8.4 Hz, 1H)	2.21 (q, J = 8.4 Hz, 1H)	0
2.03 – 1.88 (m, 1H)	2.04 – 1.89 (m, 1H)	/
1.76 – 1.67 (m, 1H)	1.76 – 1.67 (m, 1H)	/
1.52 – 1.37 (m, 2H)	1.53 – 1.37 (m, 2H)	/
1.21 – 1.13 (m, 1H)	1.20 – 1.12 (m, 1H)	/

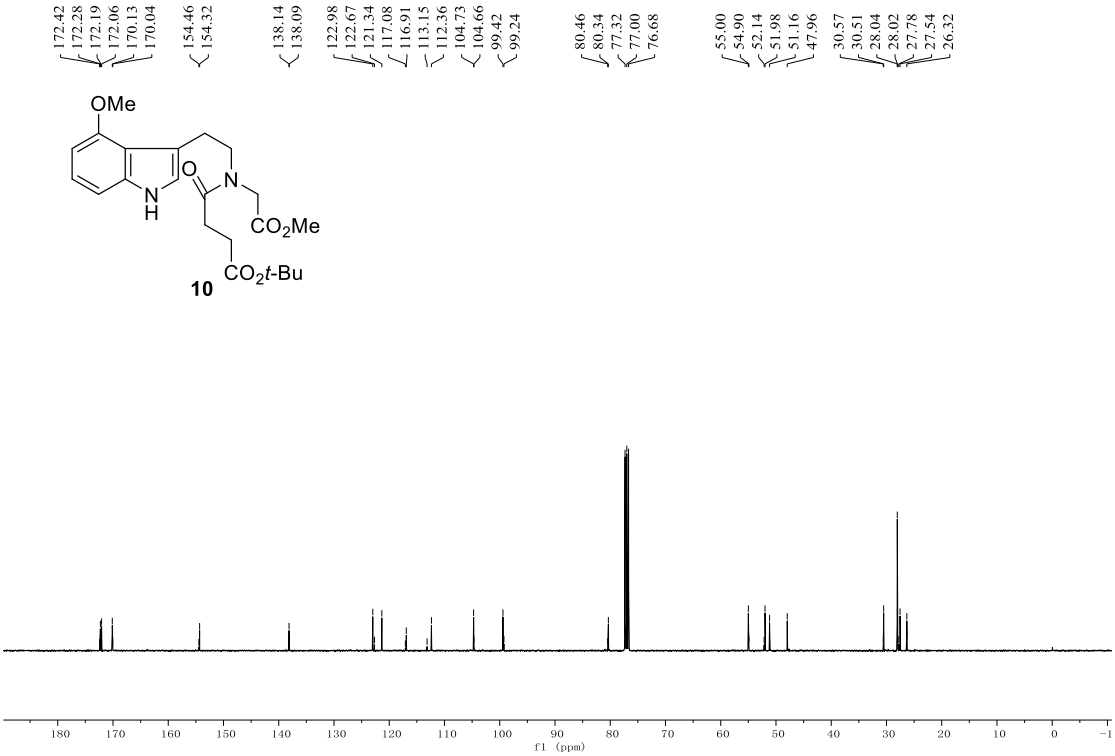
Table S7. Comparison of ^{13}C NMR (Chloroform-*d*) spectroscopic data of the synthetic (+)-quinidine and natural (+)-quinidine

A: authentic sample δ (ppm), 100 MHz	B: synthetic sample δ (ppm), 100 MHz	Error (B–A) $\Delta\delta$/ppm
157.6	157.6	0
147.8	147.7	-0.1
147.5	147.5	0
144.1	144.1	0
140.7	140.6	-0.1
131.5	131.5	0.1
126.6	126.6	0
121.4	121.4	0
118.4	118.4	0
114.4	114.4	0
101.3	101.2	-0.1
72.1	72.1	0
59.8	59.8	0
55.5	55.5	0
50.2	50.2	0
49.6	49.6	0
40.1	40.1	0
28.2	28.2	0
26.5	26.4	-0.1
21.4	21.3	-0.1

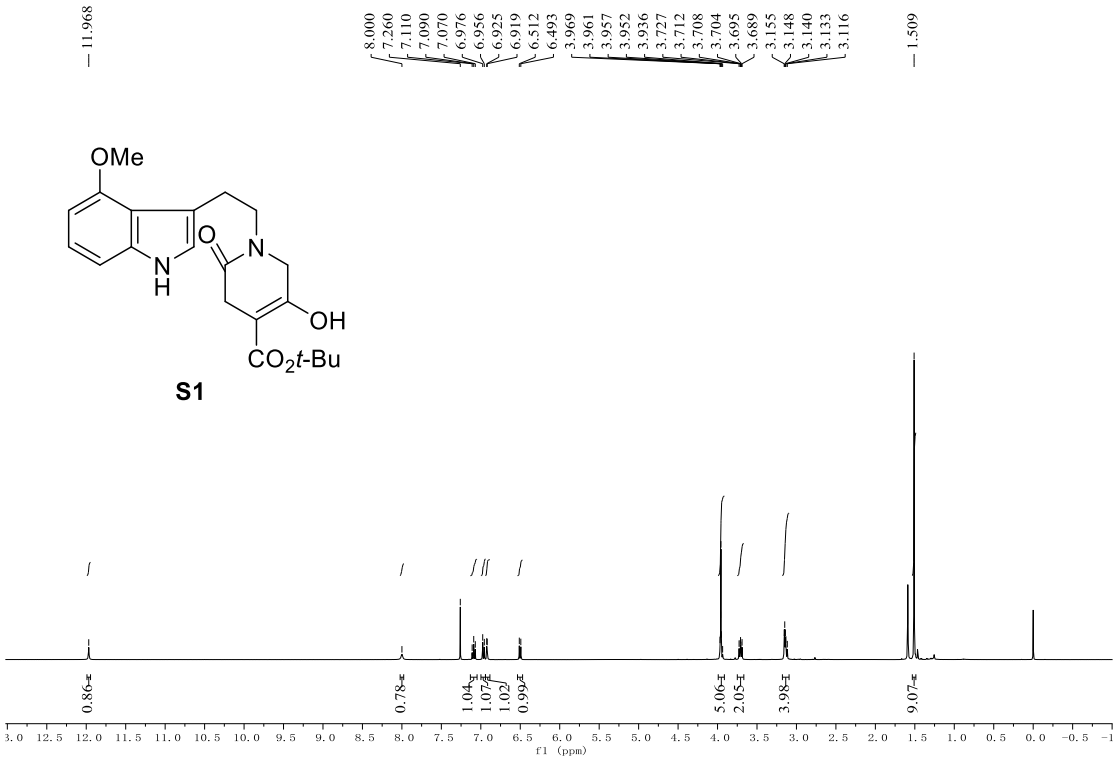
3. ^{1}H and ^{13}C NMR Spectra of Compounds



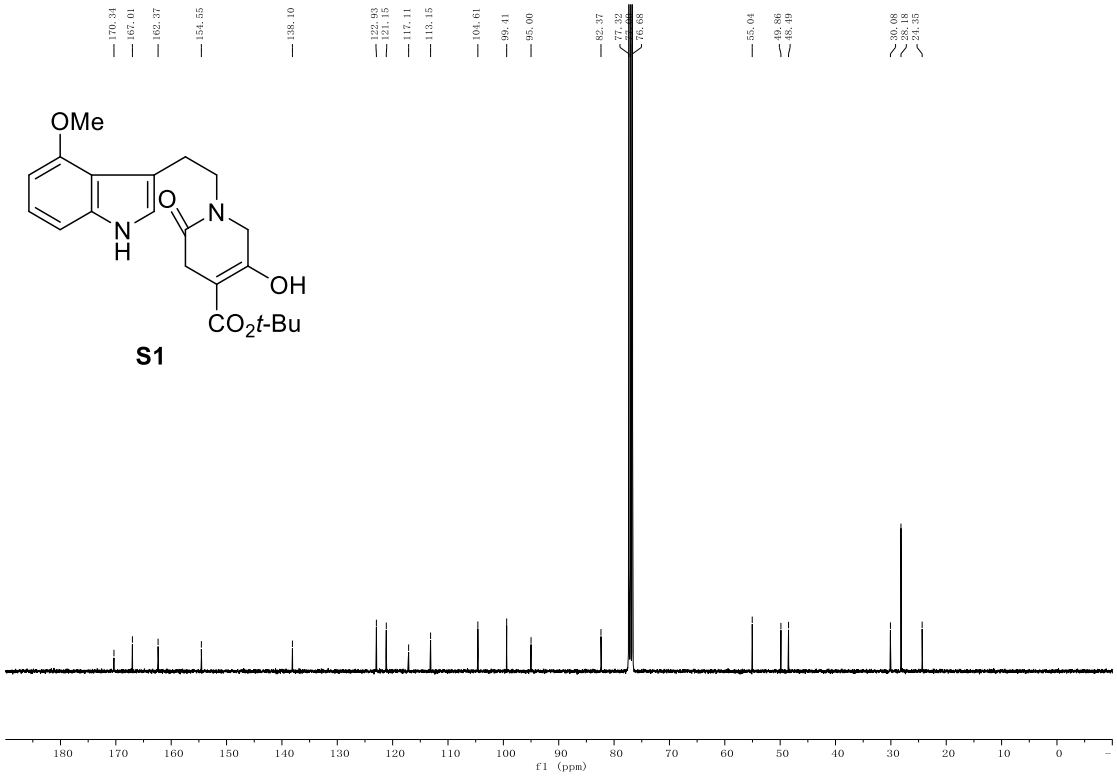
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of compound **10**



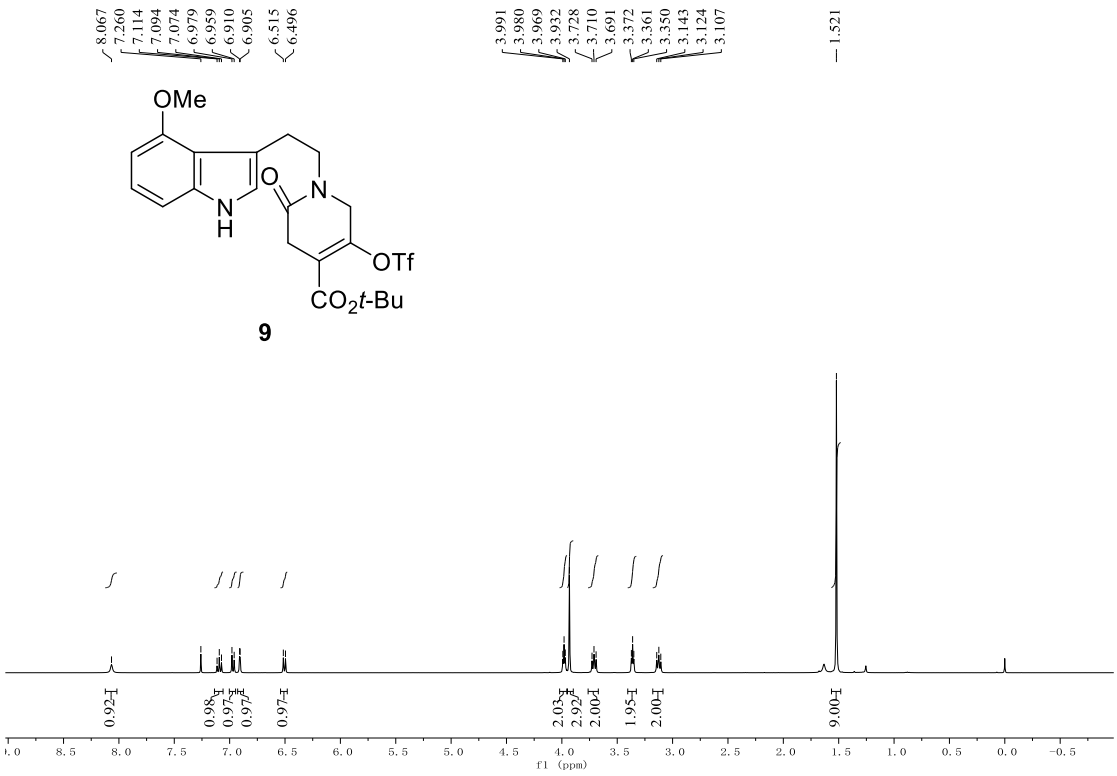
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of compound **10**



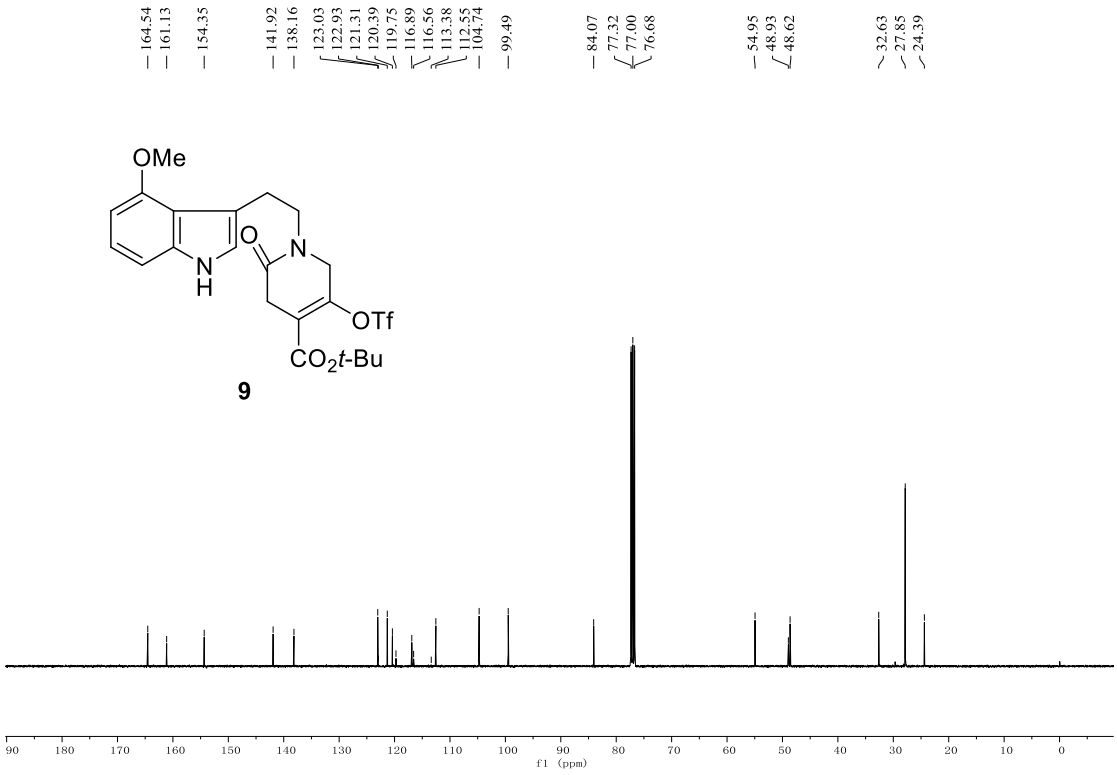
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of compound **S1**



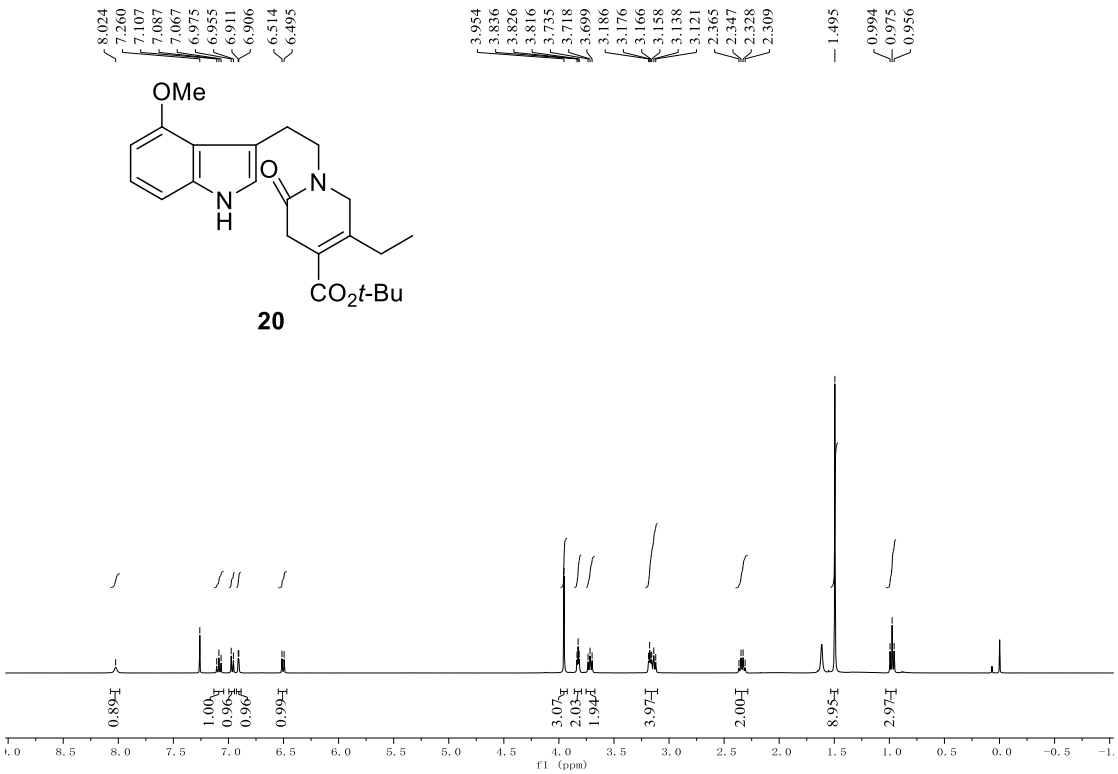
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of compound **S1**



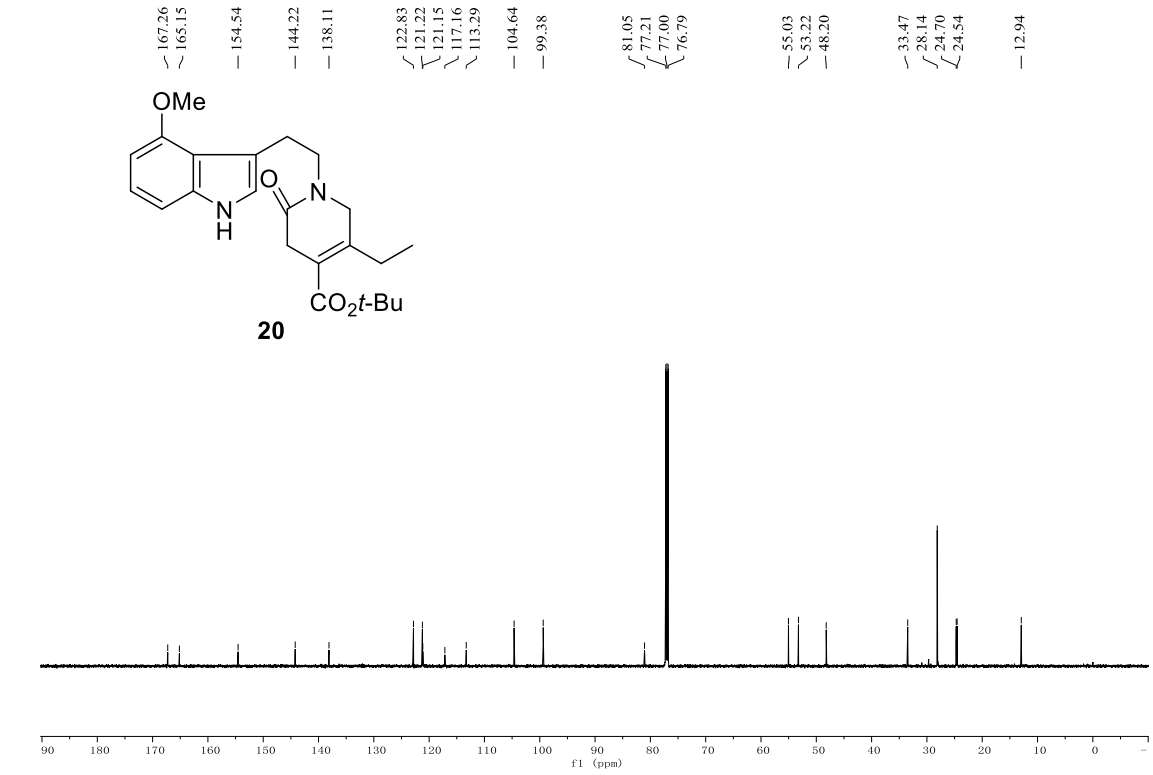
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of compound **9**



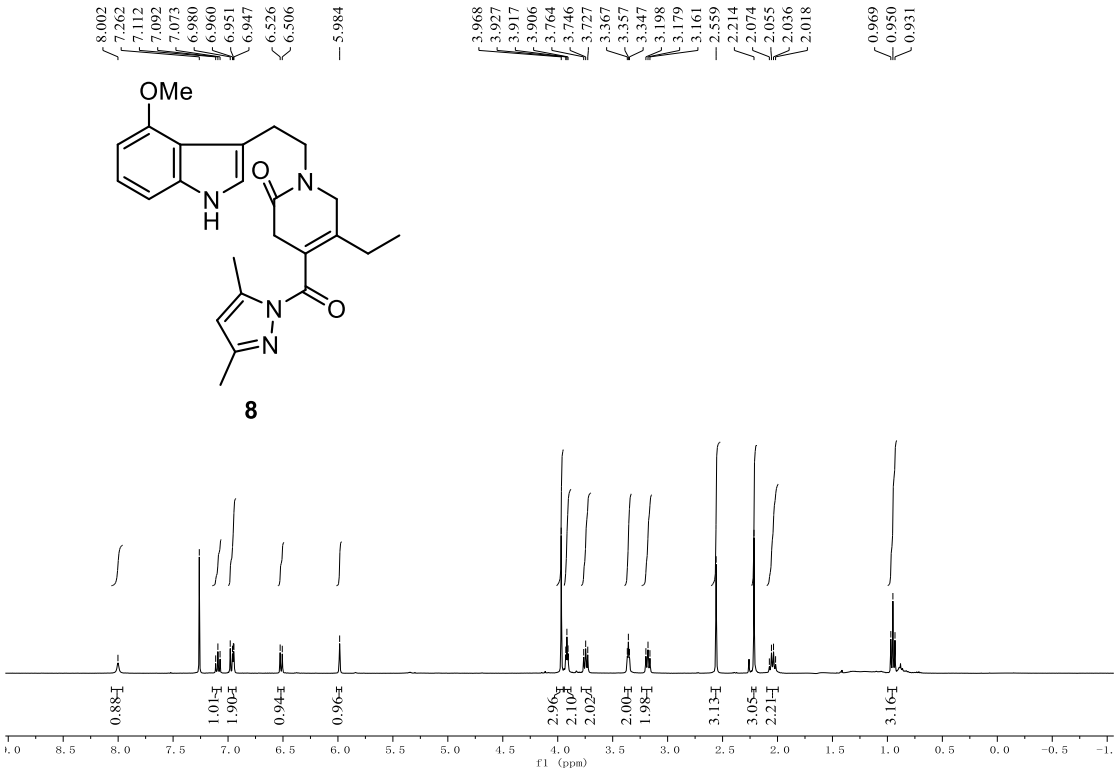
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of compound **9**



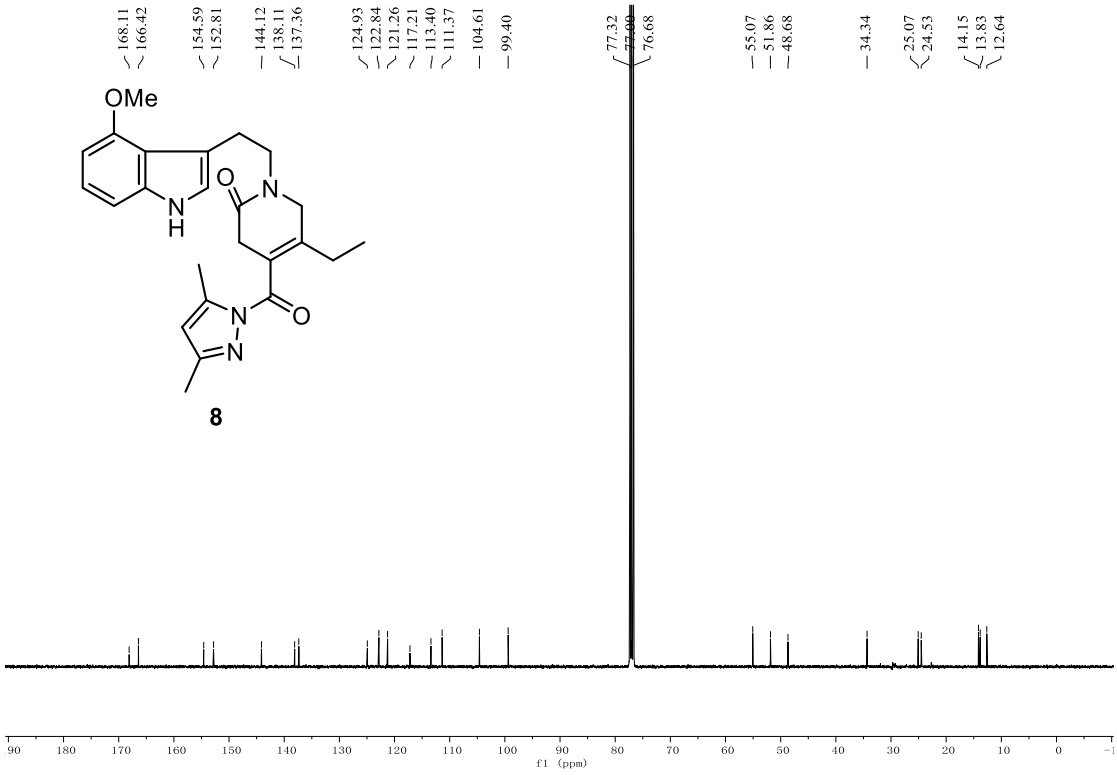
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of compound **20**



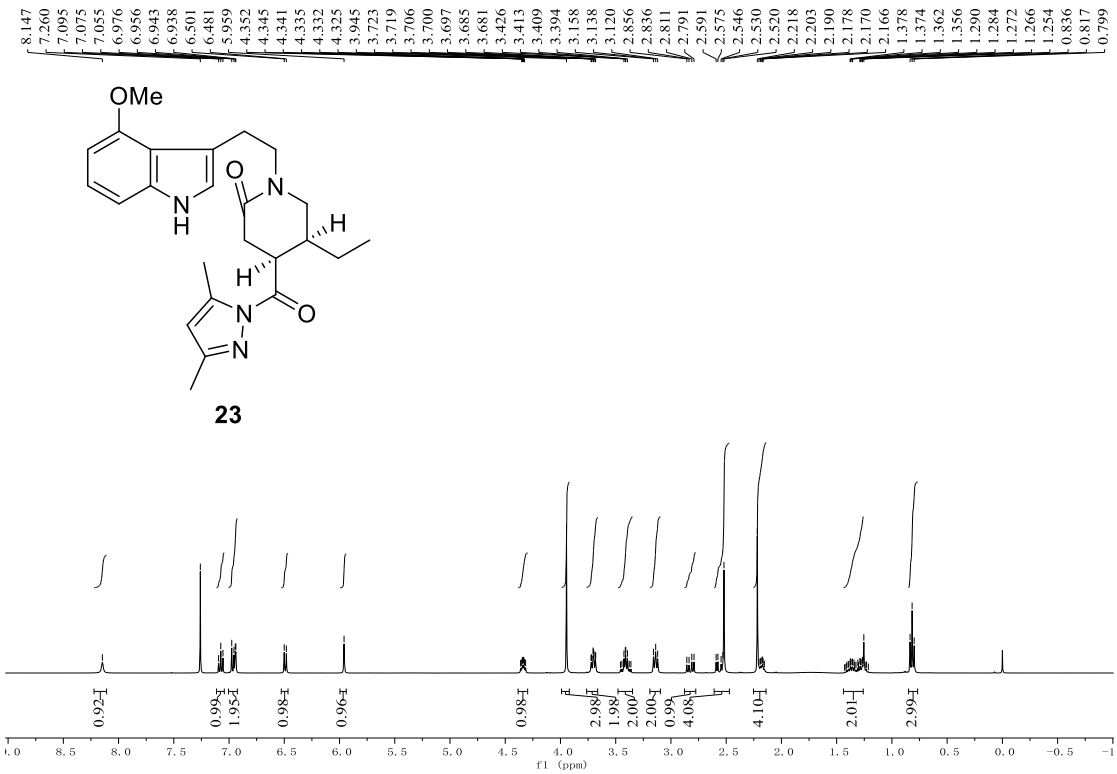
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of compound **20**



^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of compound **8**

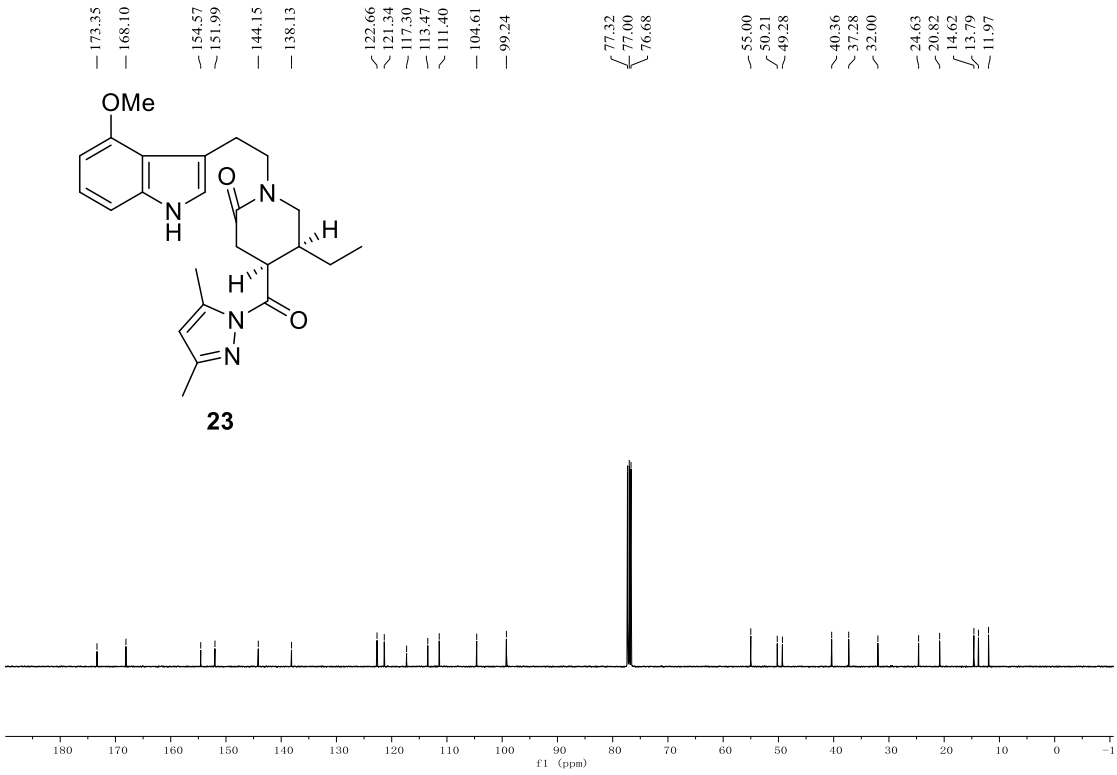


^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of compound **8**



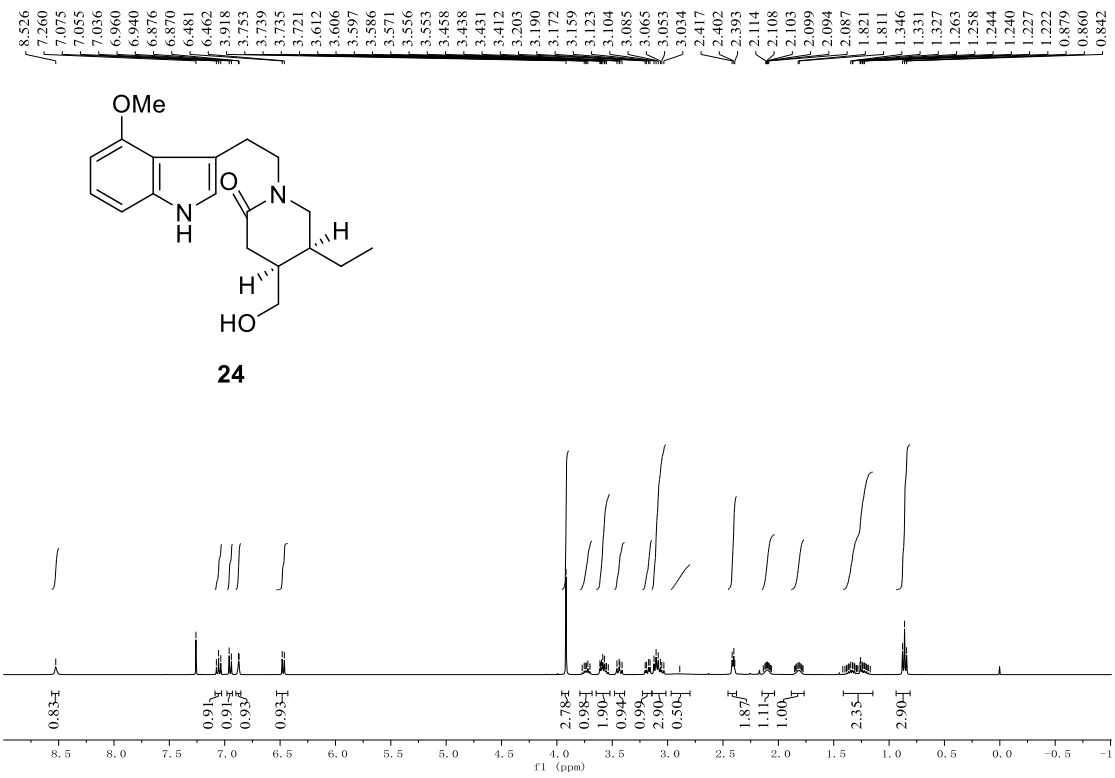
23

^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of compound **23**



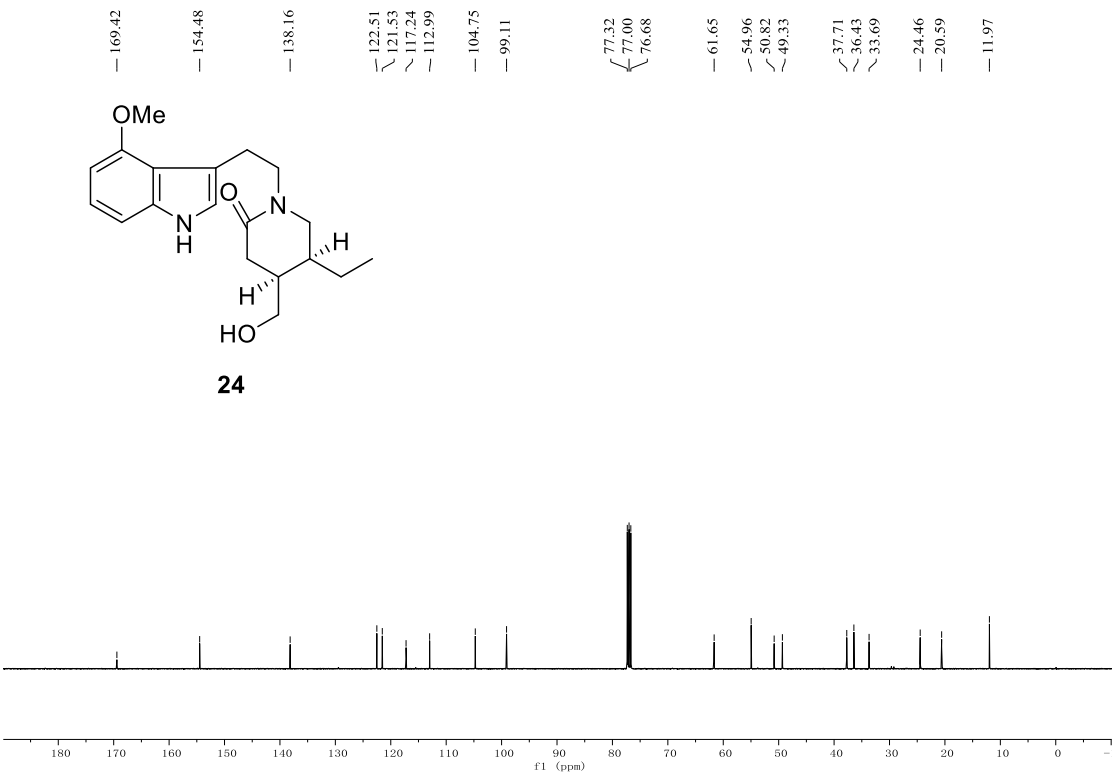
23

^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of compound **23**



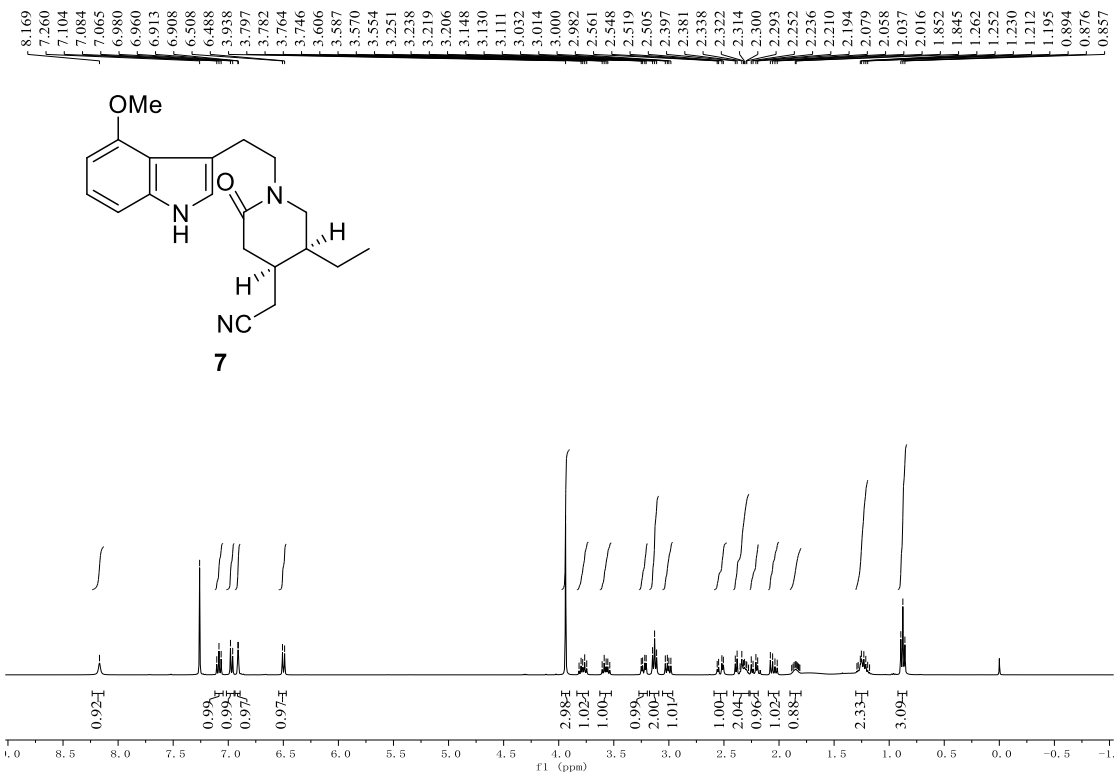
24

^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of compound **24**

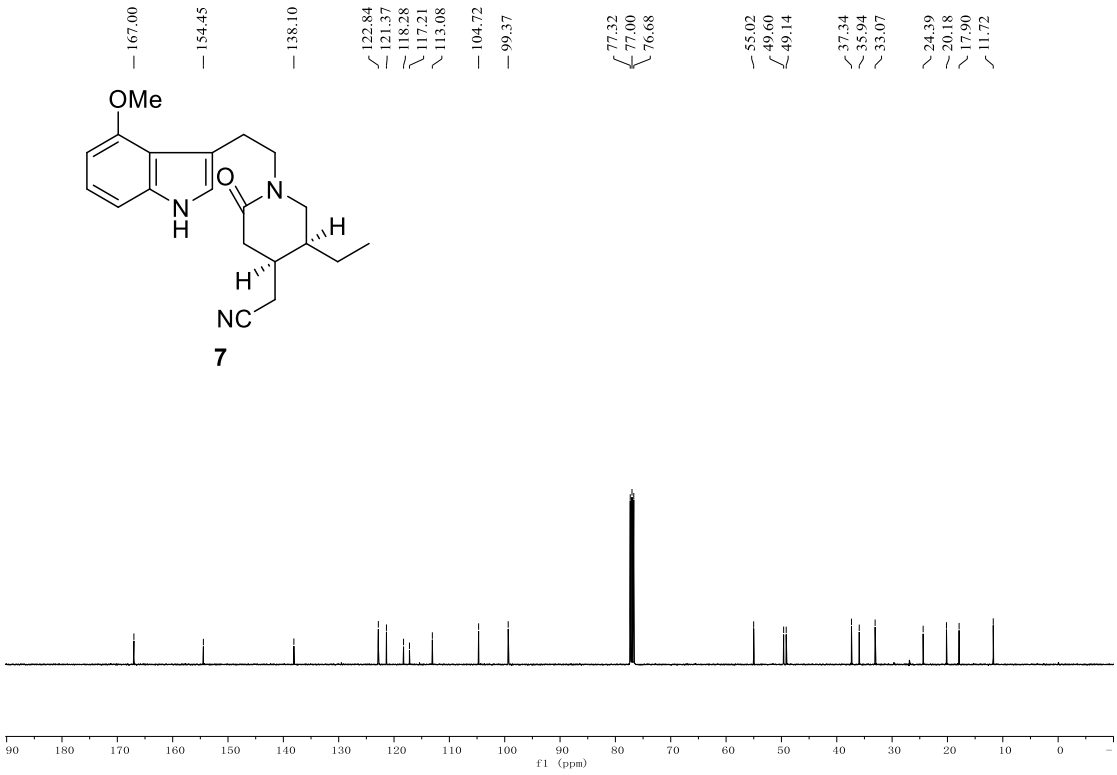


24

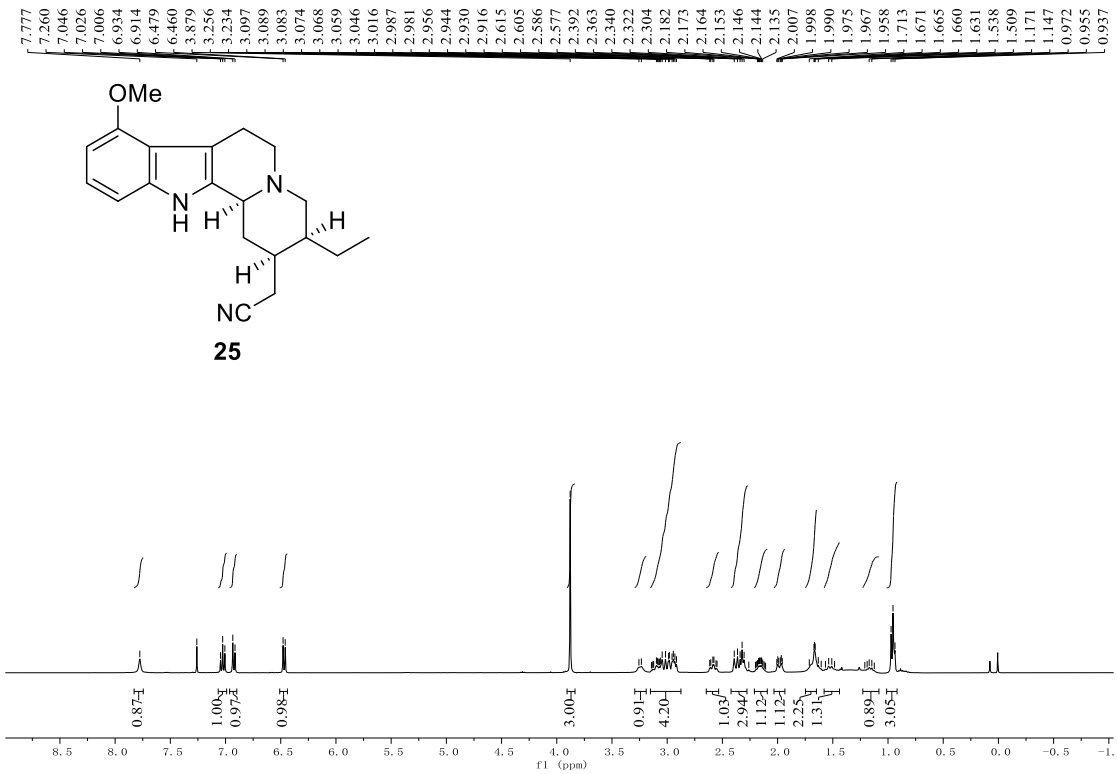
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of compound **24**



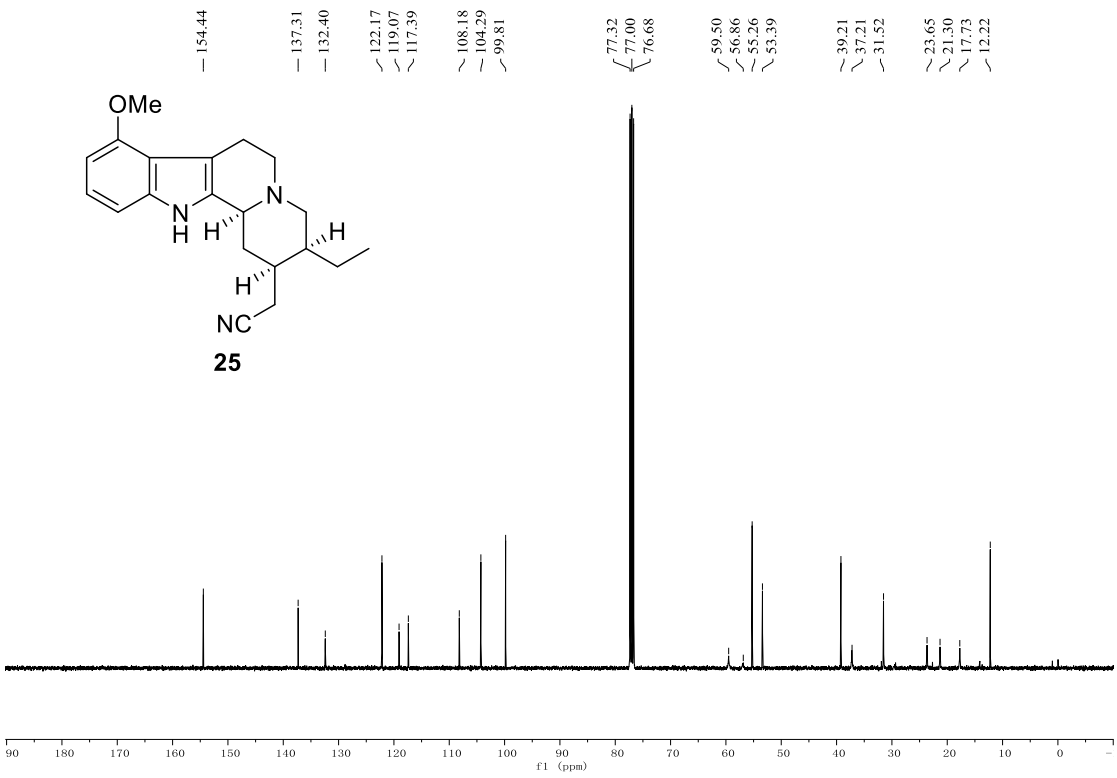
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of compound **7**



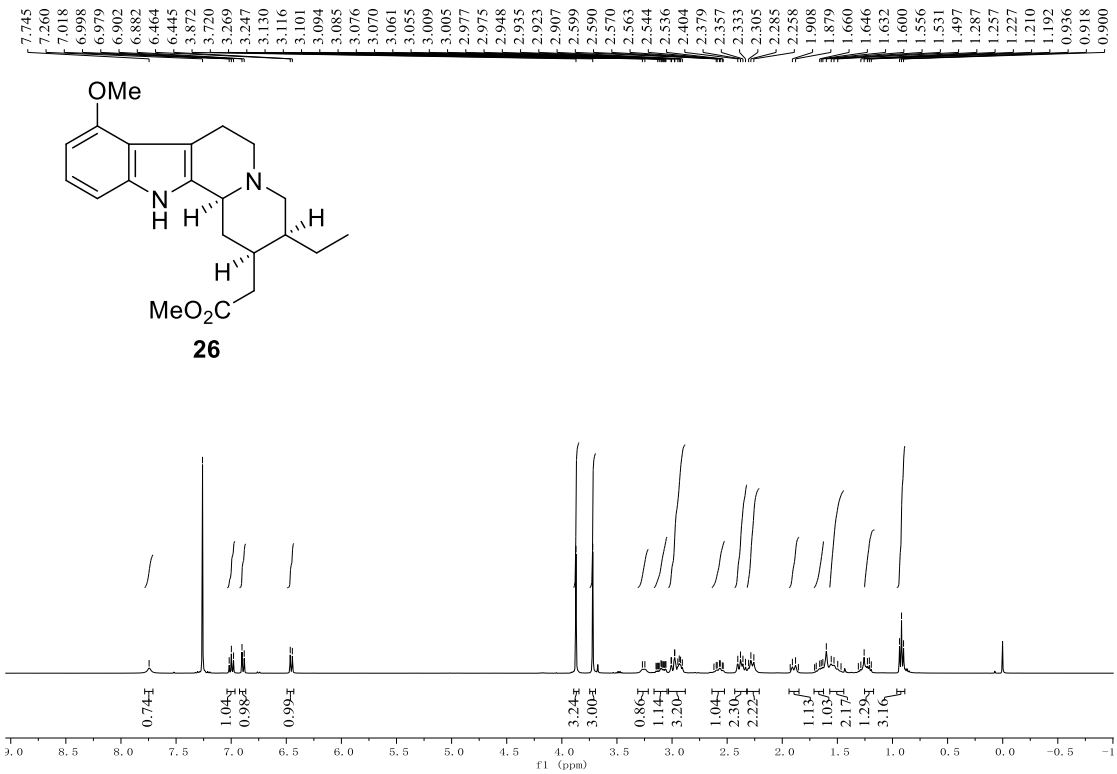
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of compound **7**



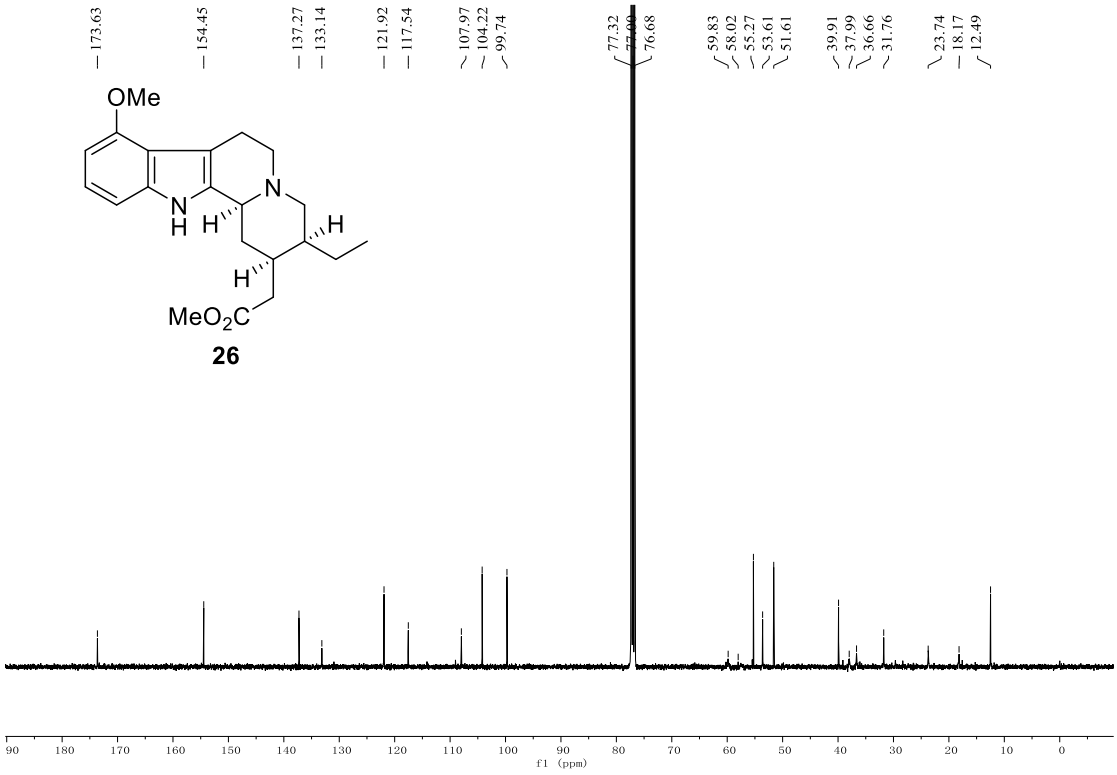
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of compound **25**



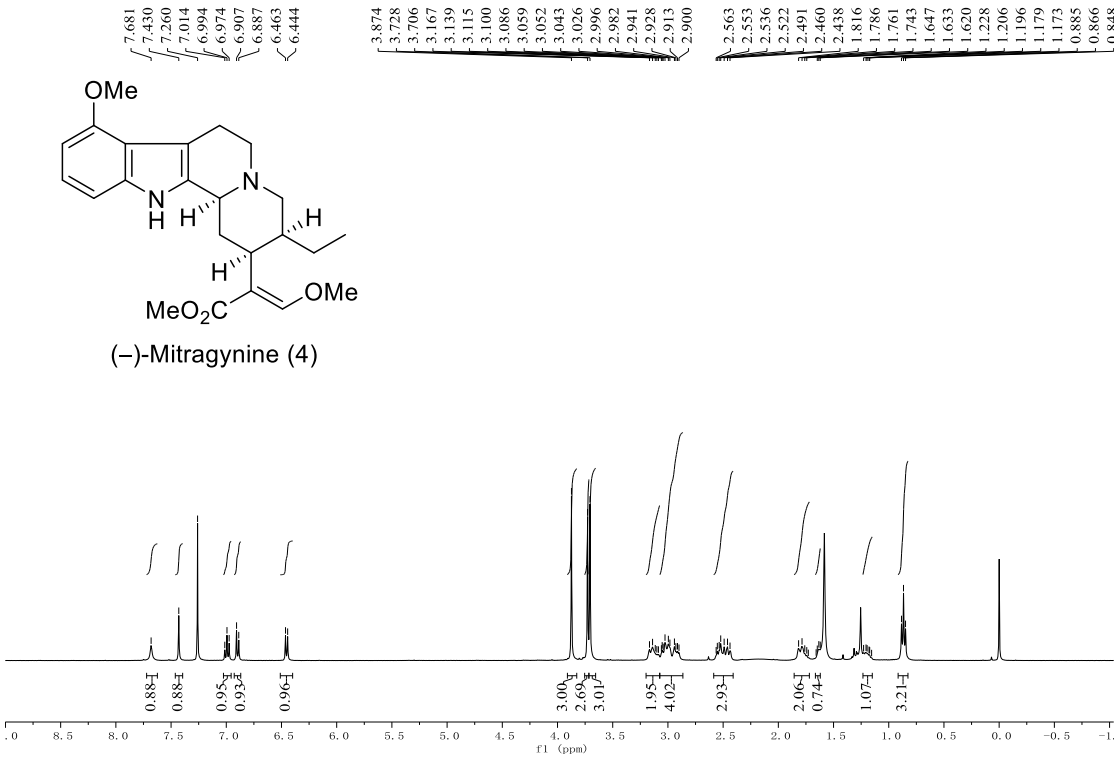
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of compound **25**



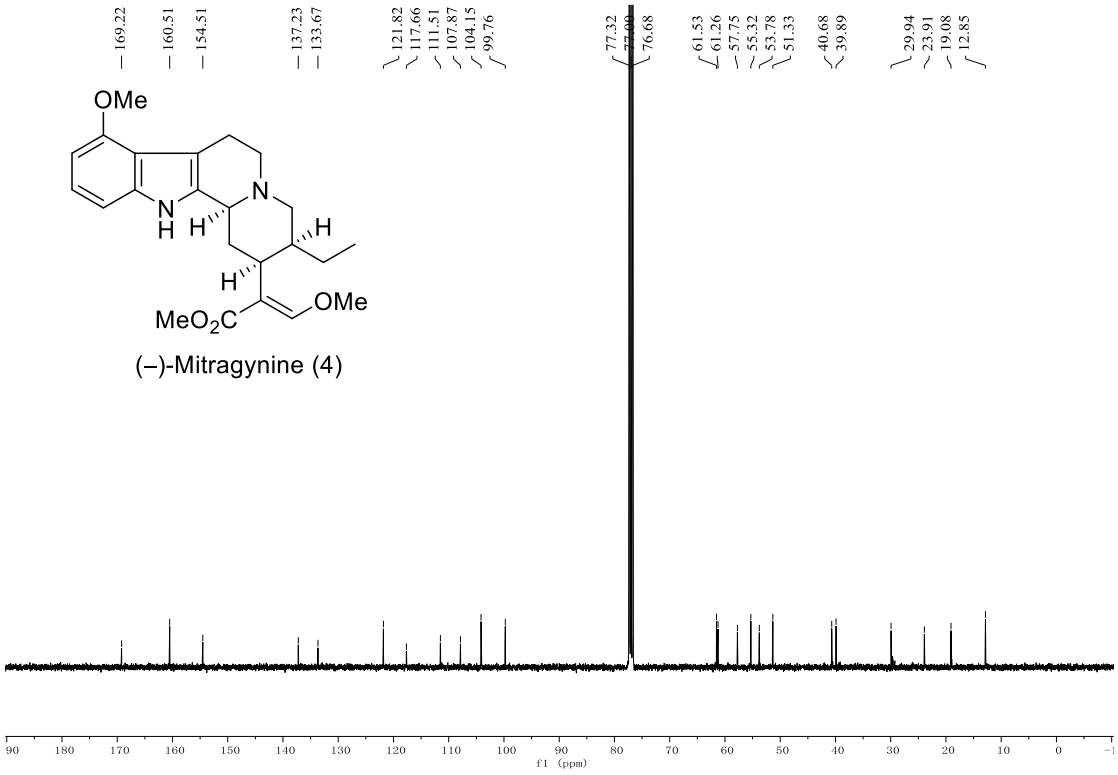
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of compound **26**



^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of compound **26**

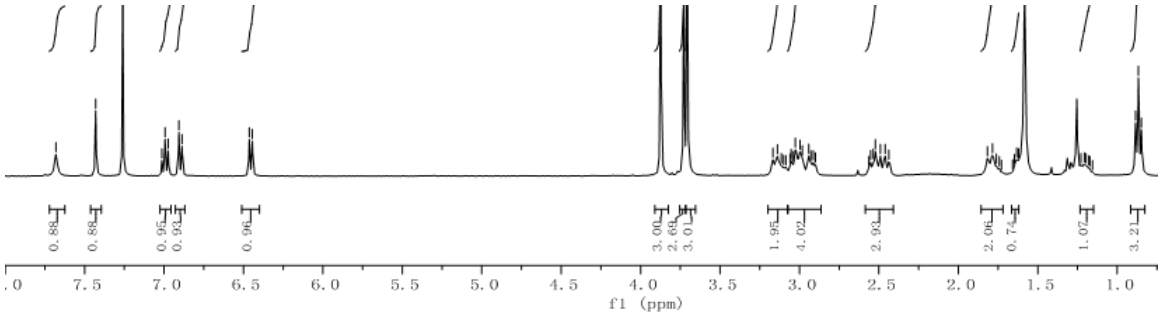


^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of (-)-Mitragynine (4)

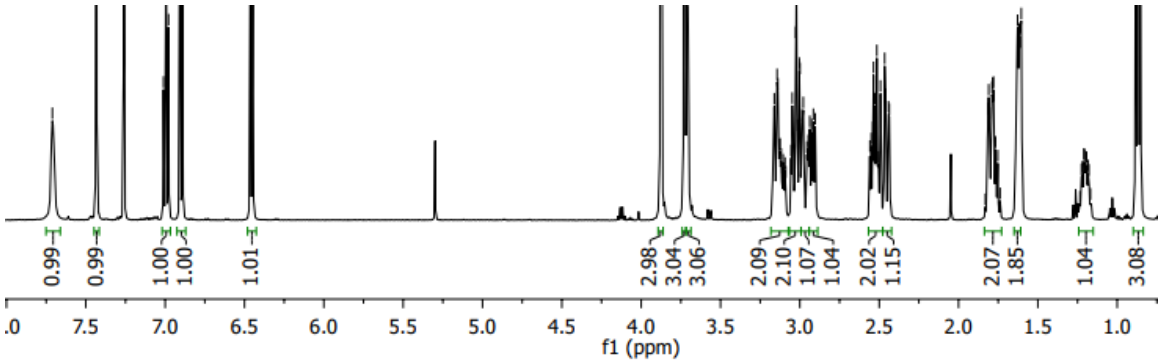


^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of (-)-Mitragynine (4)

^{1}H NMR of our synthetic (-)-Mitragynine (4)

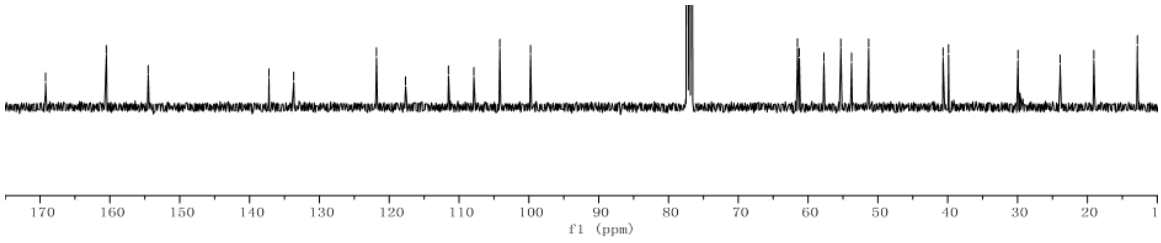


^{1}H NMR of natural (-)-Mitragynine (4)

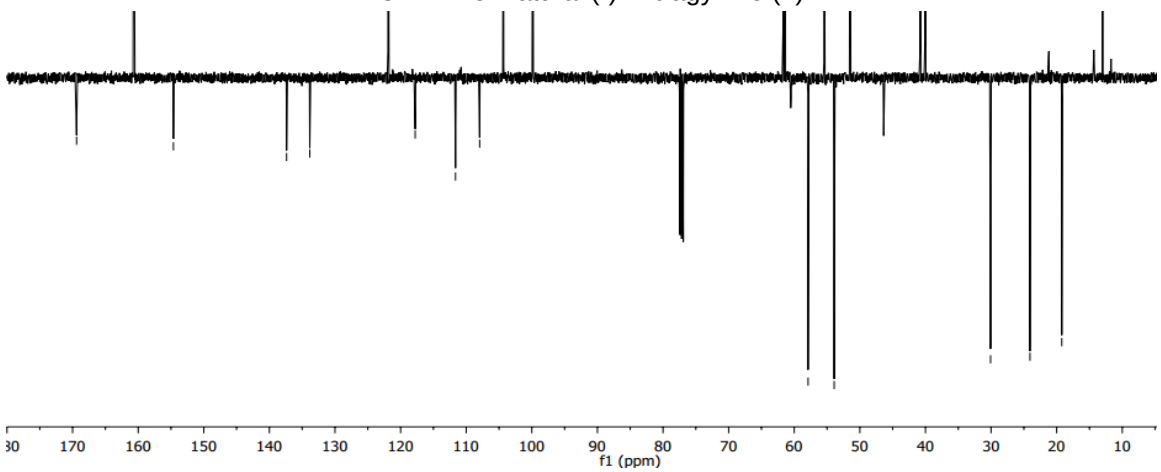


Comparison of ^{1}H NMR (Chloroform-*d*) spectrum between natural (-)-Mitragynine (4) and our synthetic (-)-Mitragynine (4)

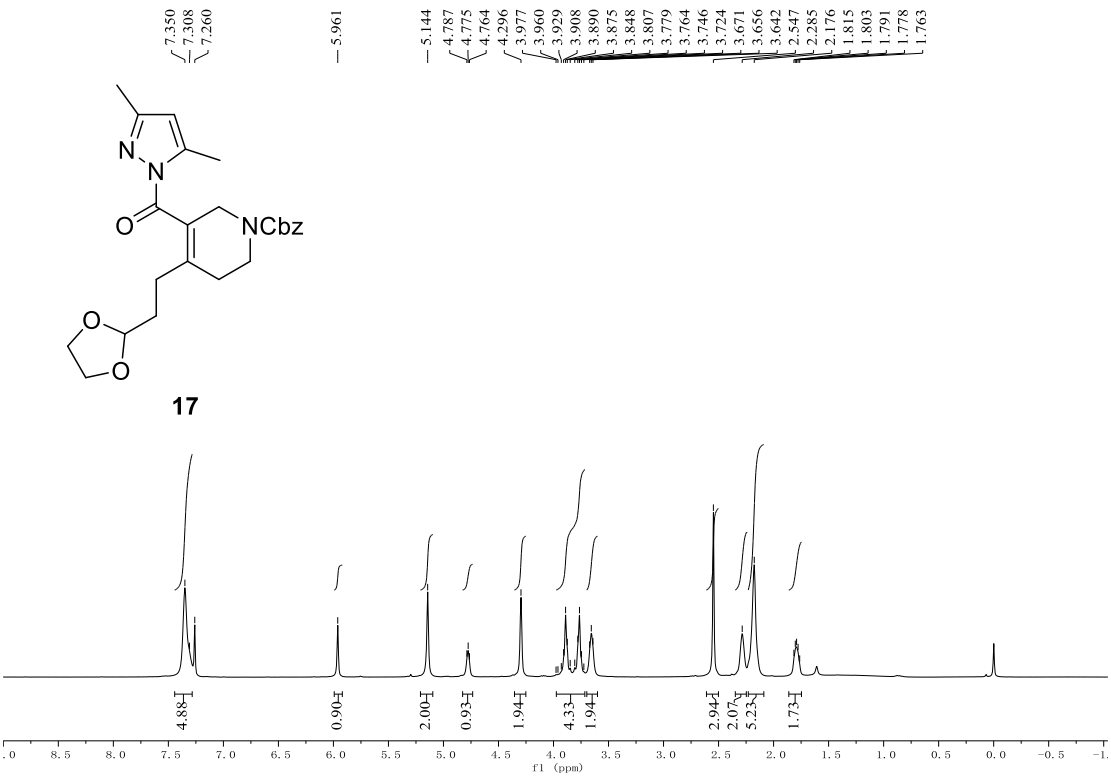
^{13}C NMR of our synthetic (-)-Mitragynine (4)



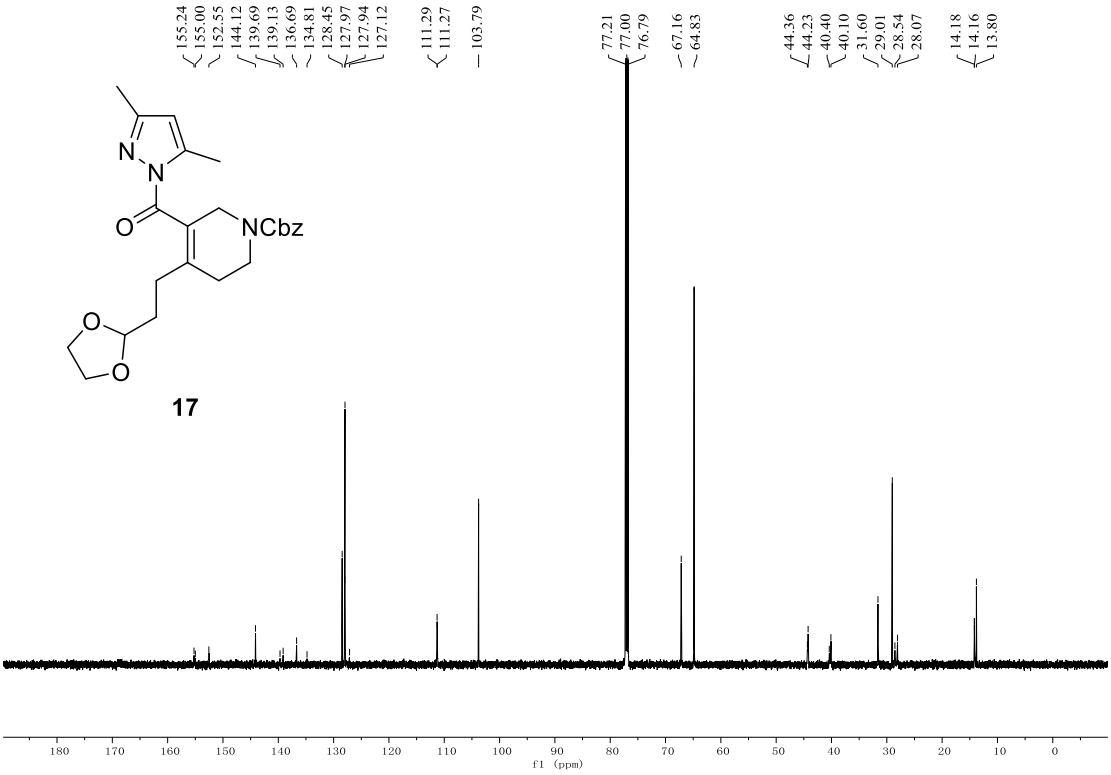
^{13}C NMR of natural (-)-Mitragynine (4)



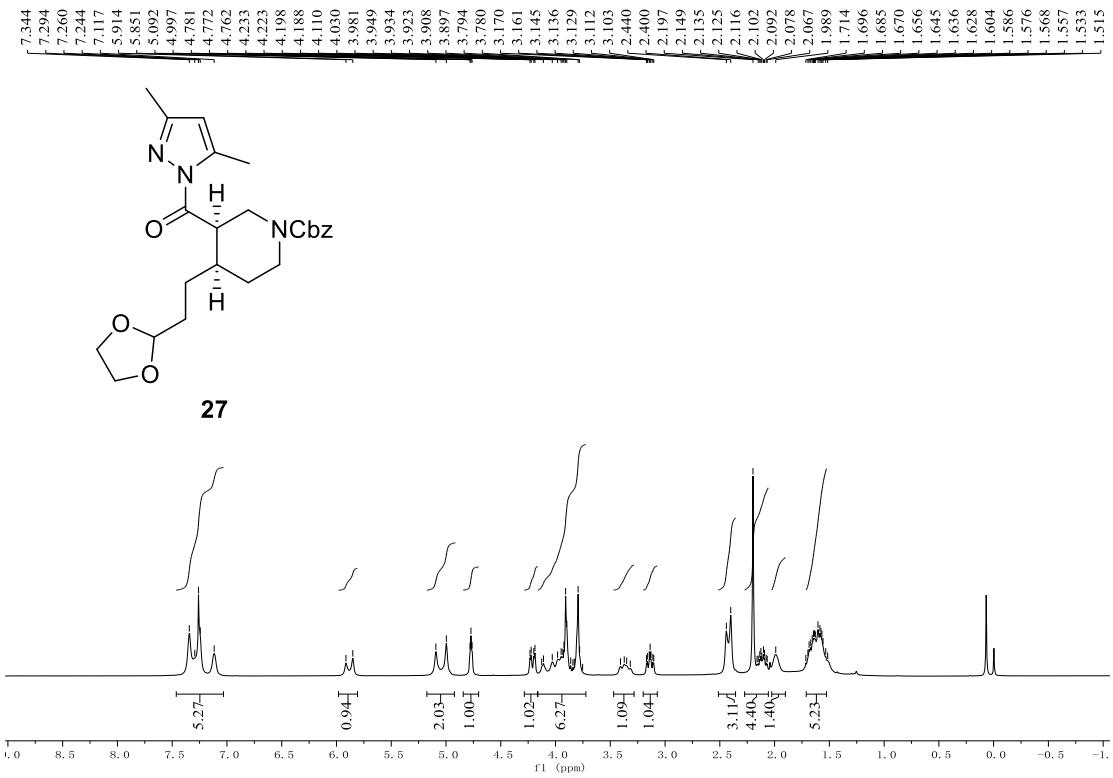
Comparison of ^{13}C NMR (Chloroform-*d*) spectrum between natural (–)-mitragynine and our synthetic (–)-mitragynine



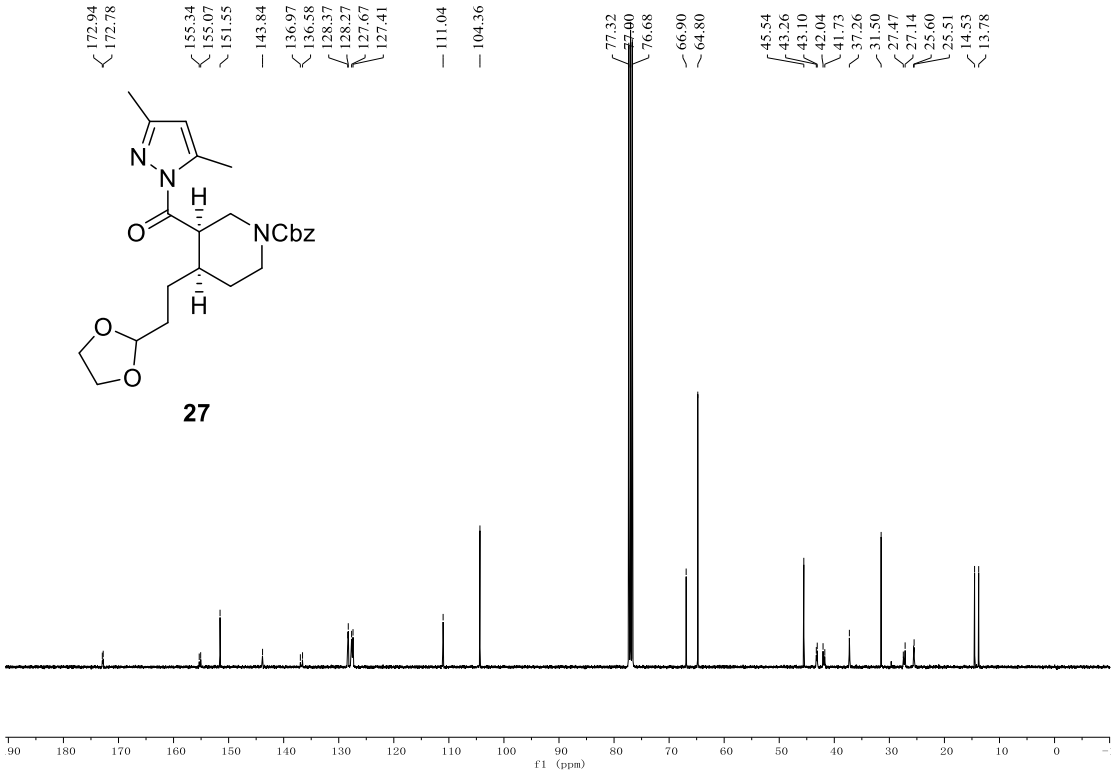
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of compound **17**



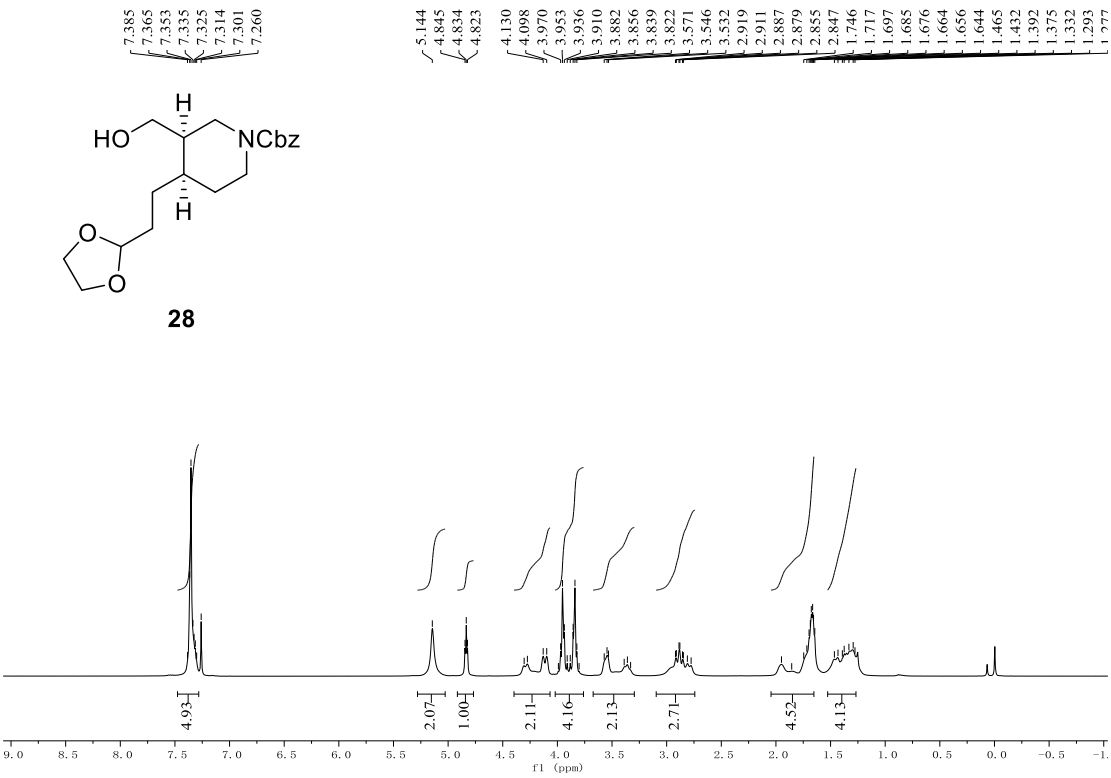
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of compound **17**



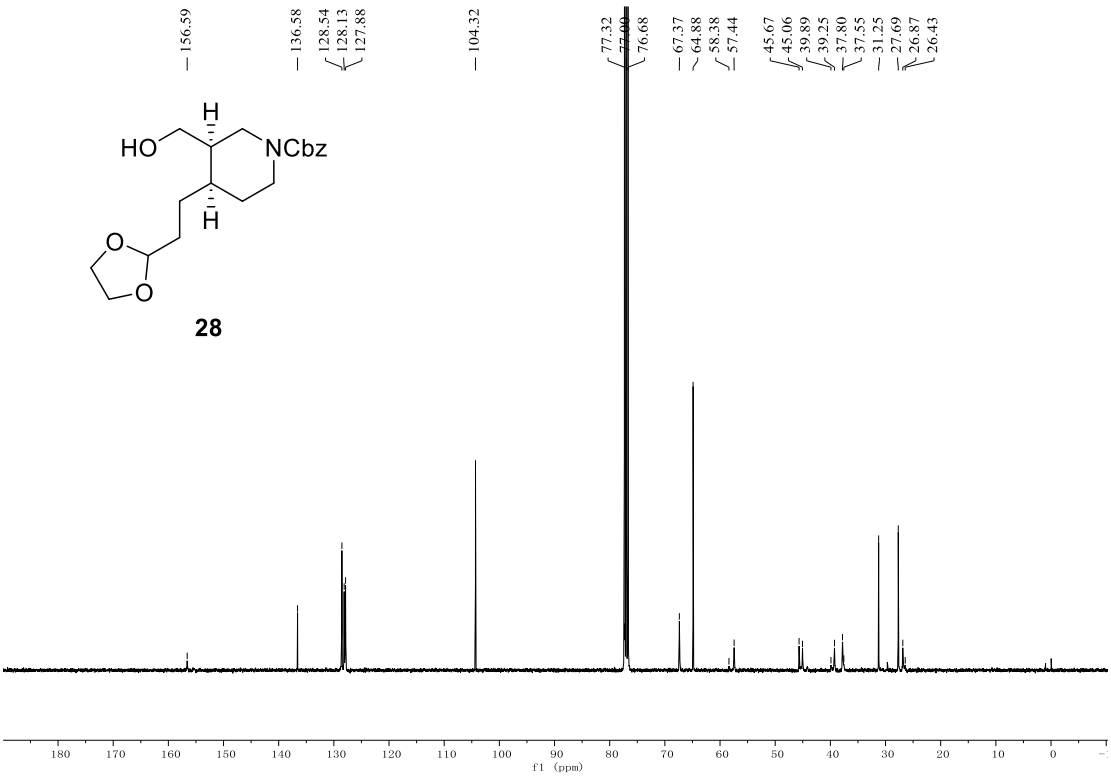
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of compound **27**



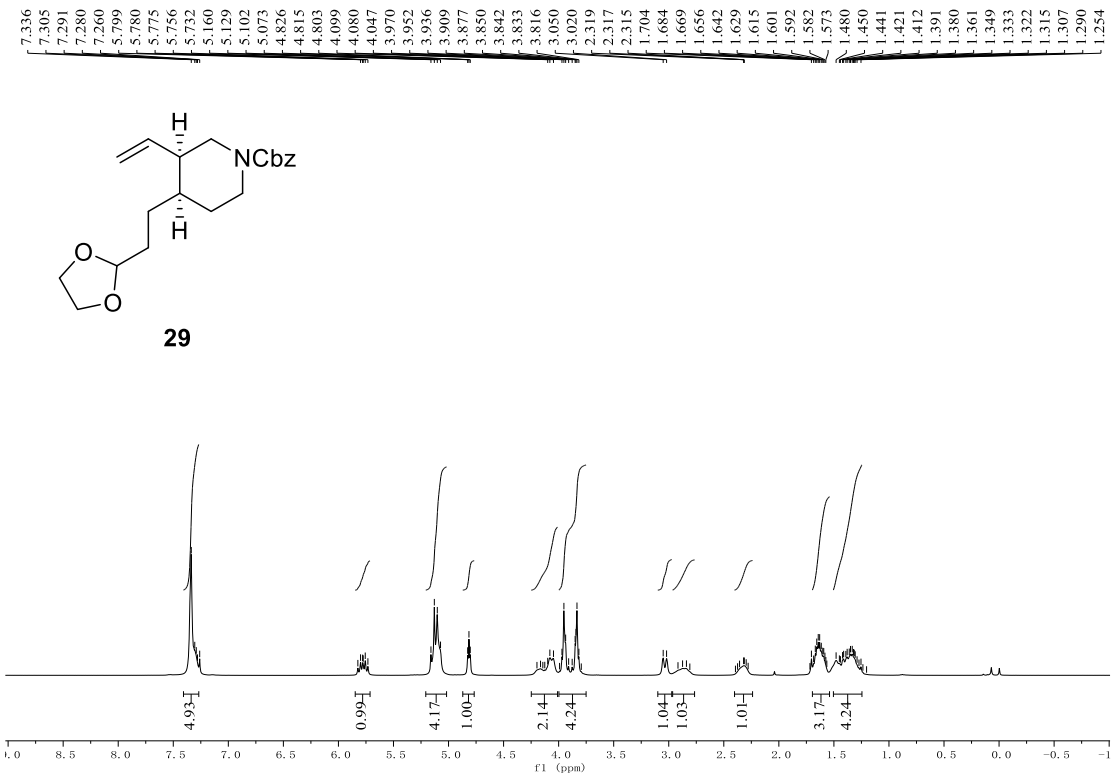
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of compound **27**



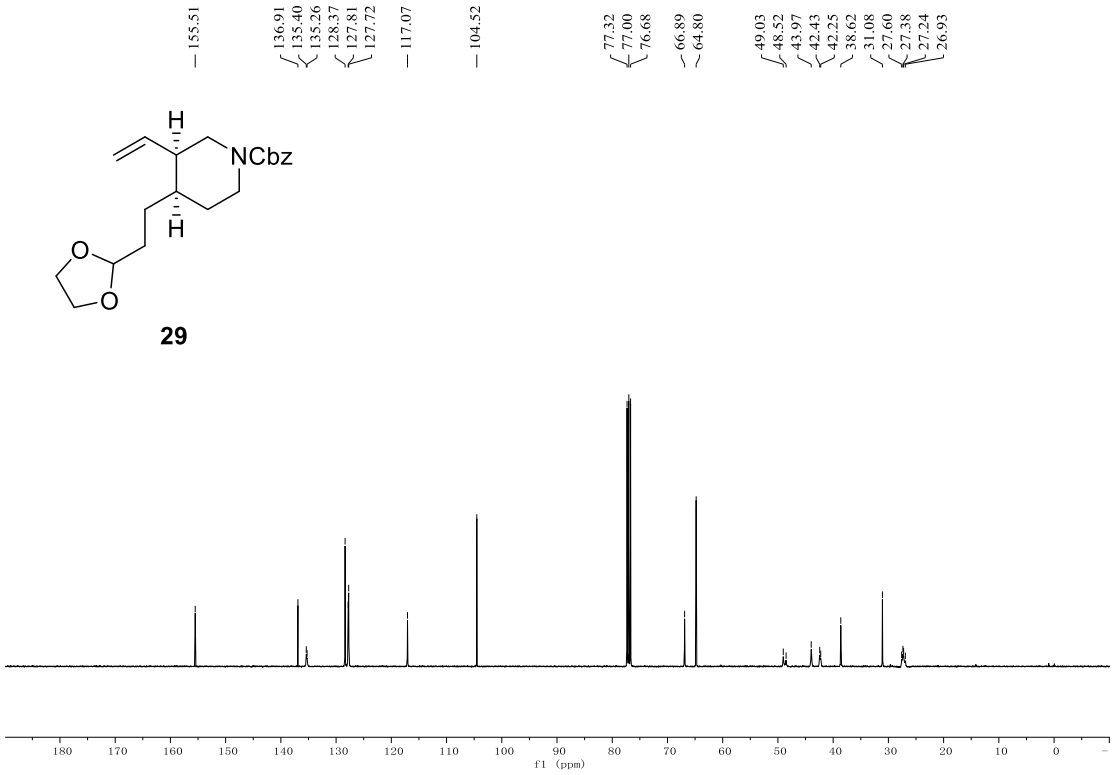
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of compound **28**



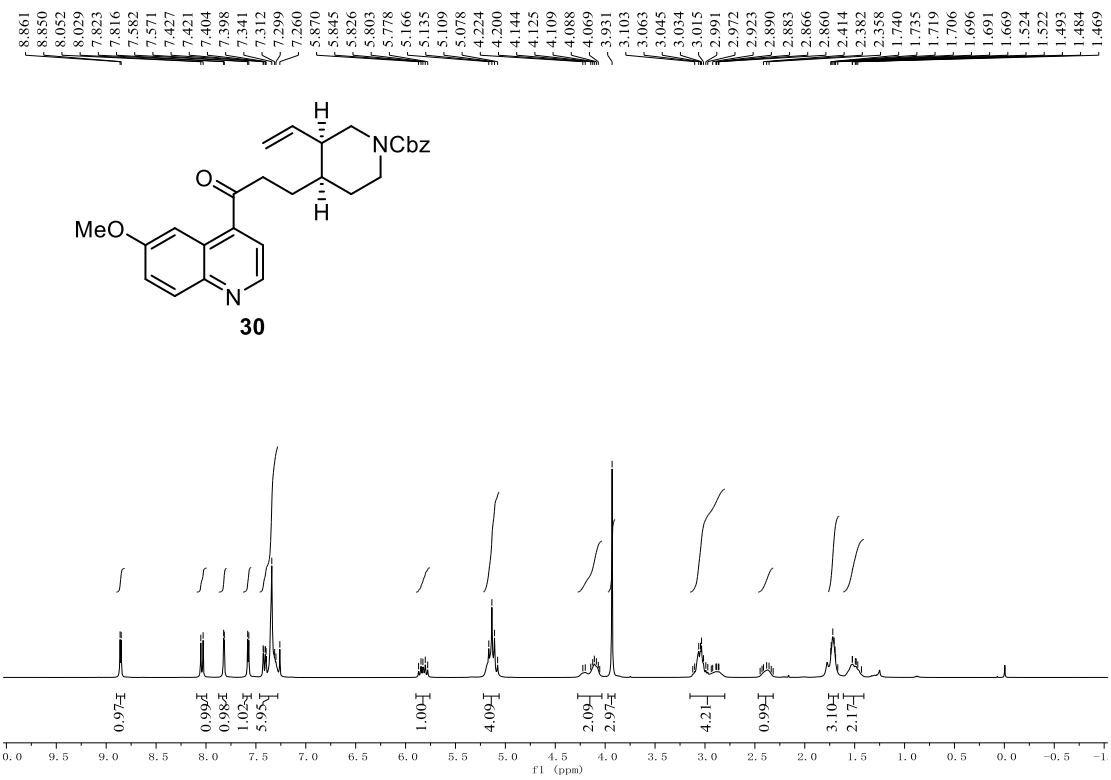
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of compound **28**



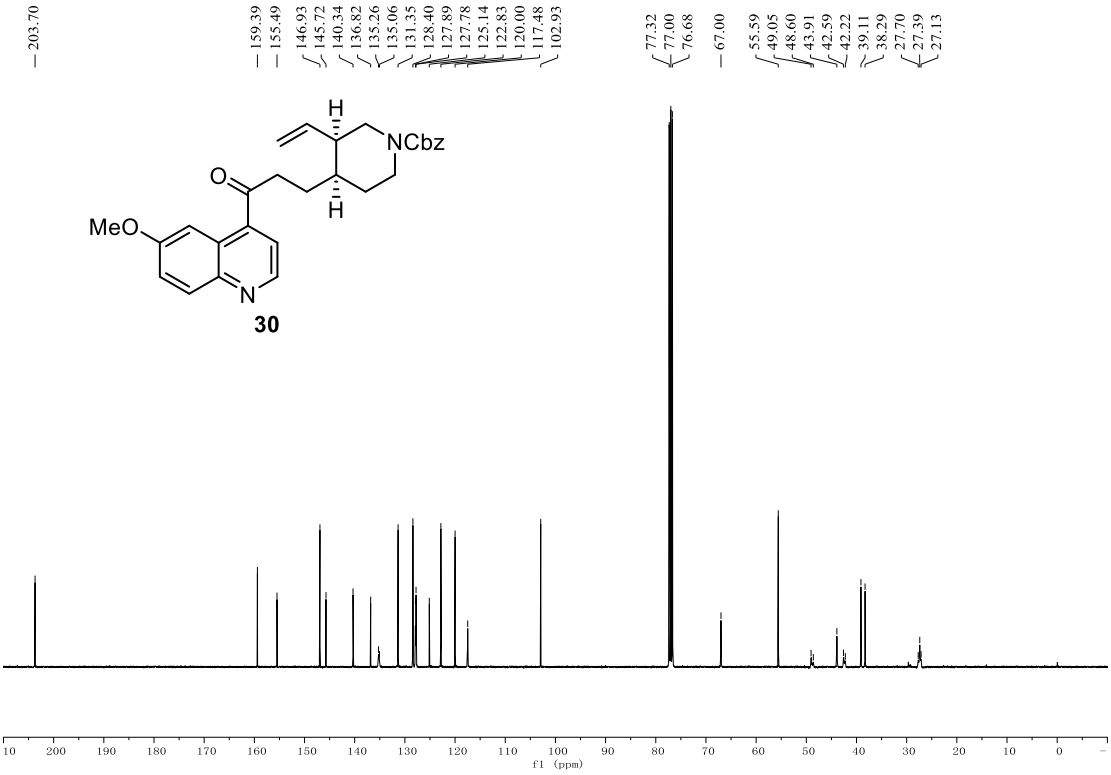
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of compound **29**



^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of compound **29**

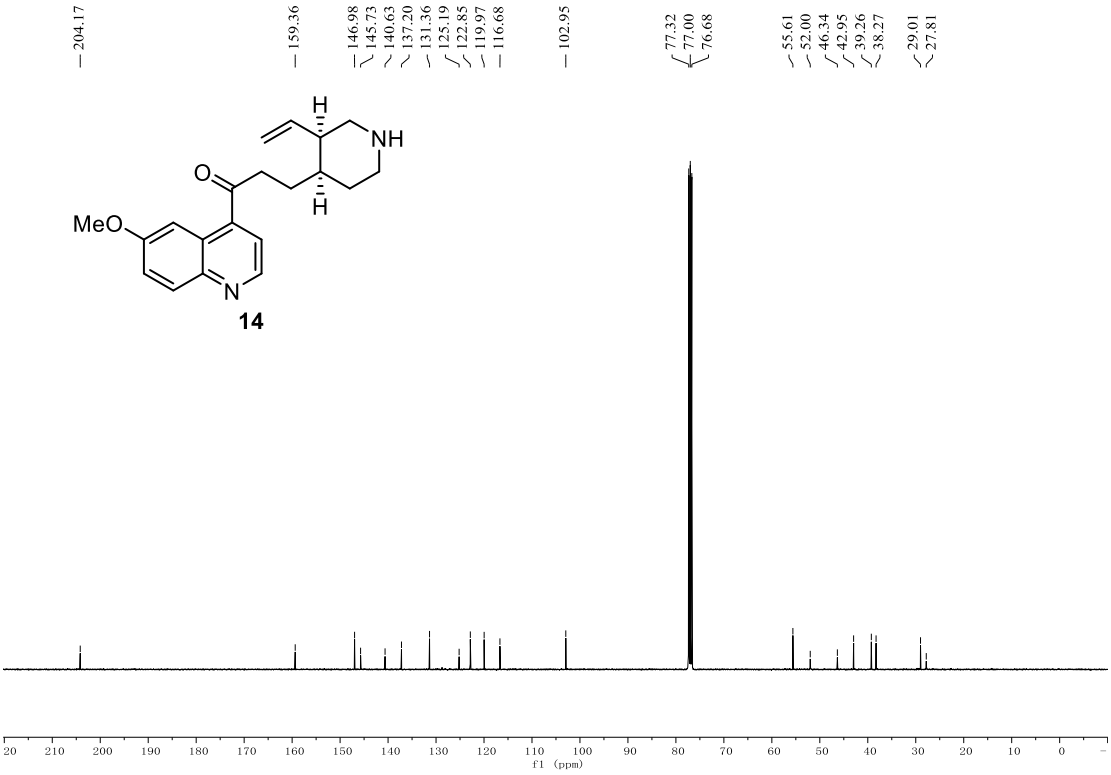


^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of compound **30**

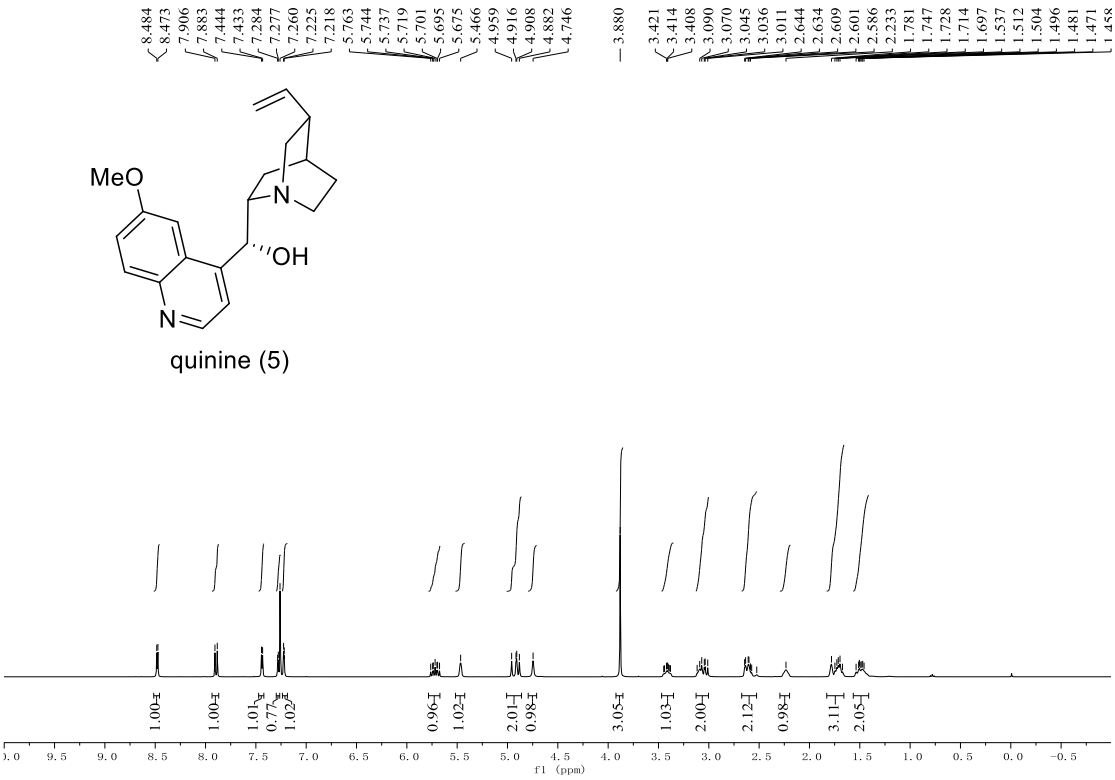


^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of compound **30**

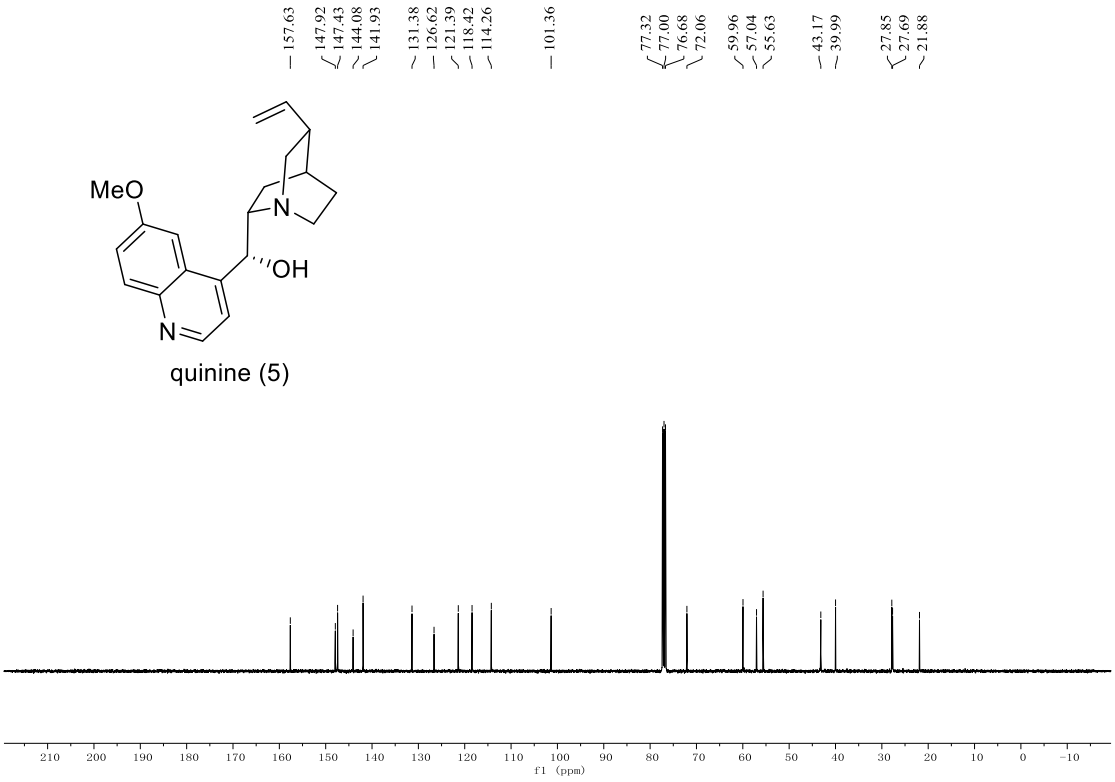
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of compound **14**



^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of compound **14**

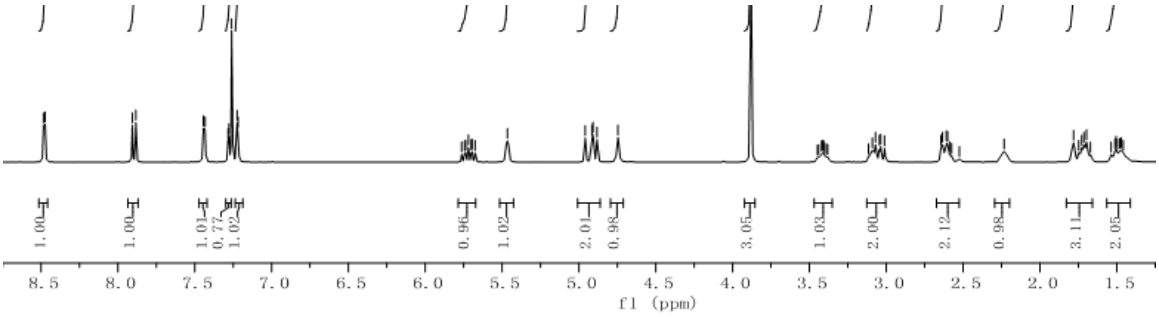


^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of quinine (5)

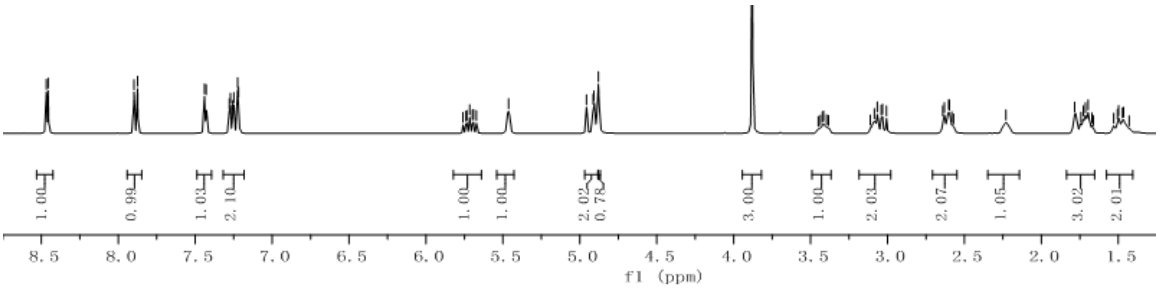


^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of quinine (5)

^{1}H-NMR of our synthetic quinine (5)

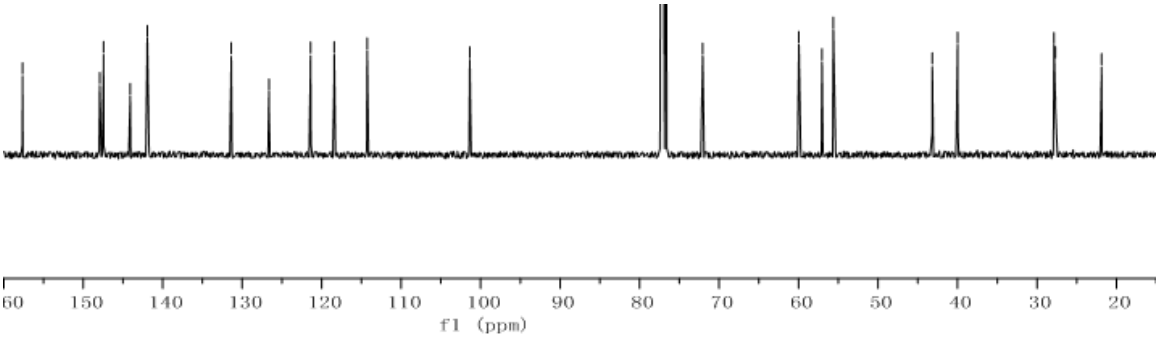


^{1}H-NMR of natural quinine (5)

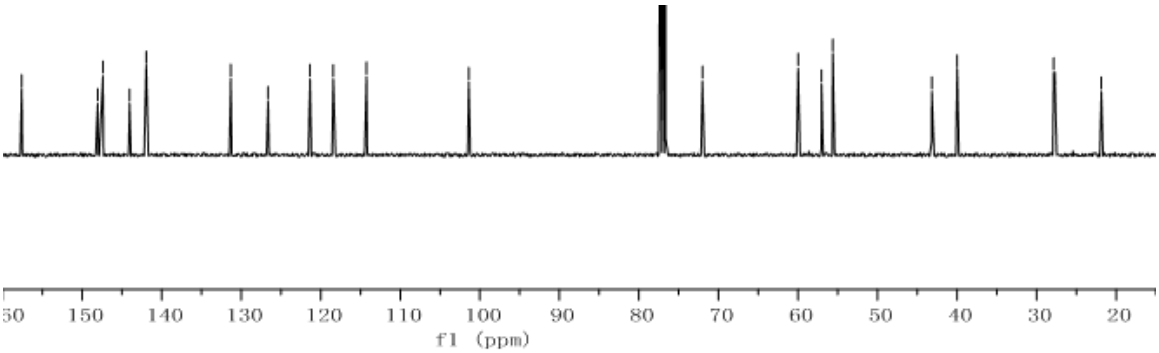


Comparison of ^{1}H NMR (Chloroform-*d*) spectrum between natural quinine (5) and our synthetic quinine

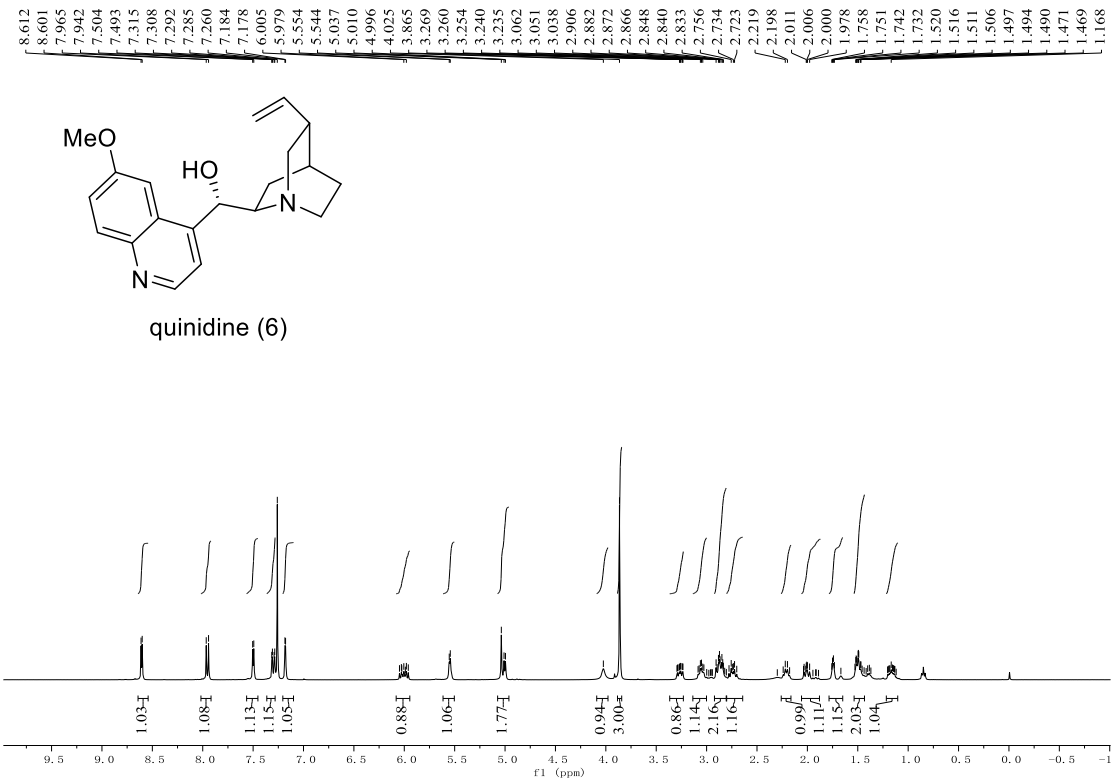
^{13}C-NMR of our synthetic quinine (5)



^{13}C-NMR of natural quinine (5)

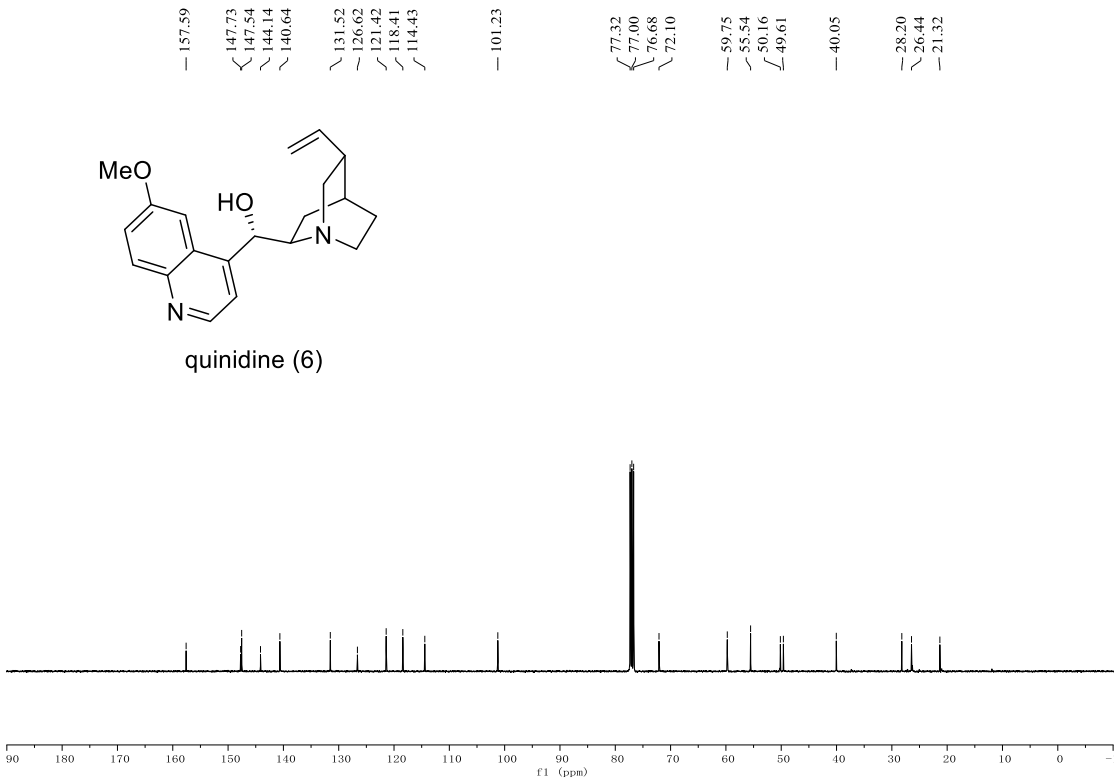


Comparison of ^{13}C NMR (Chloroform-*d*) spectrum between natural quinine (5) and our synthetic quinine (5)



quinidine (6)

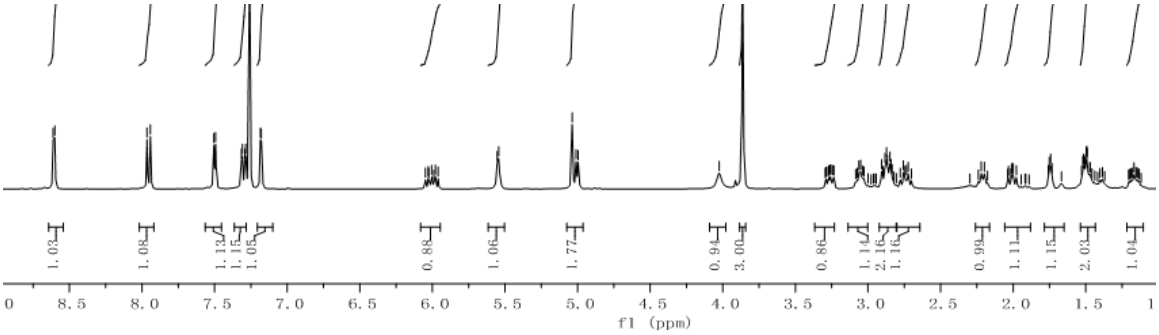
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of quinidine (6)



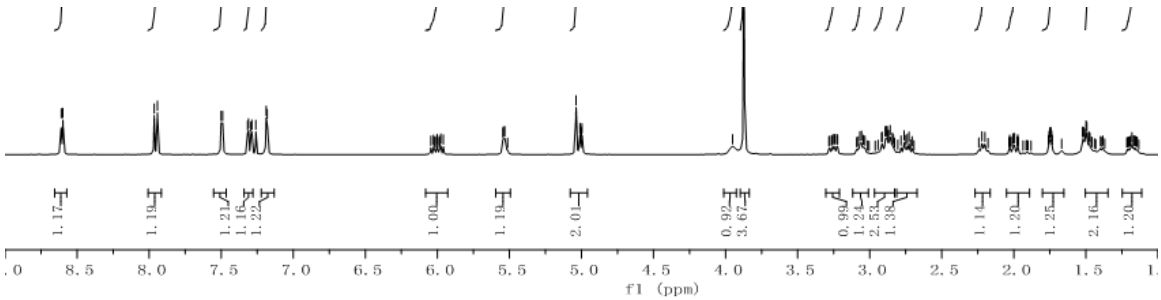
quinidine (6)

^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of quinidine (6)

^{1}H-NMR of our synthetic quinidine (6)

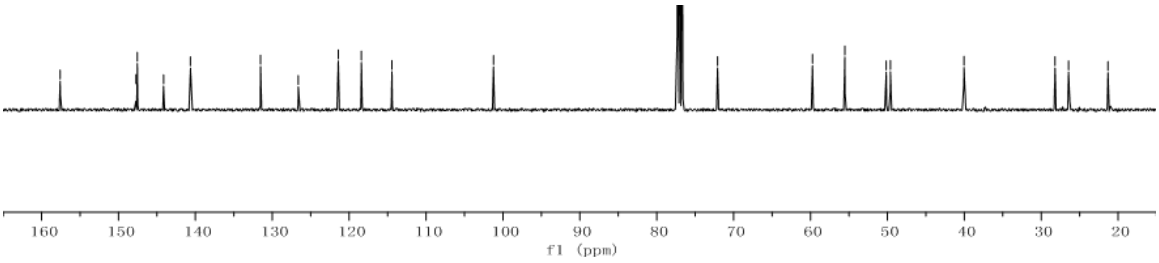


^{1}H-NMR of natural quinidine (6)

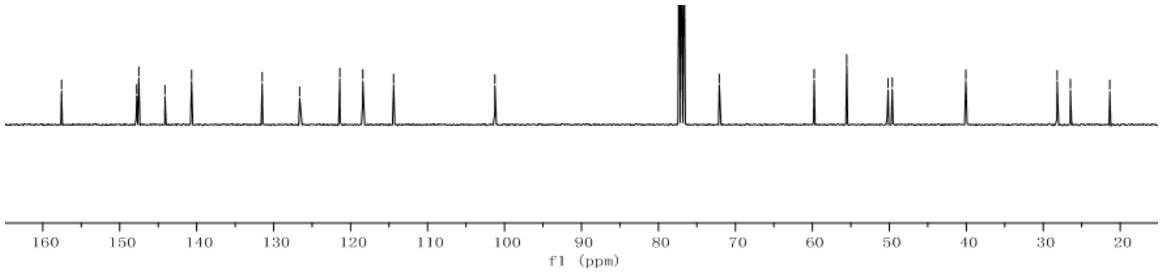


Comparison of ^{1}H NMR (Chloroform-*d*) spectrum between natural quinidine (6) and our synthetic quinidine (6)

^{13}C-NMR of our synthetic quinidine (6)

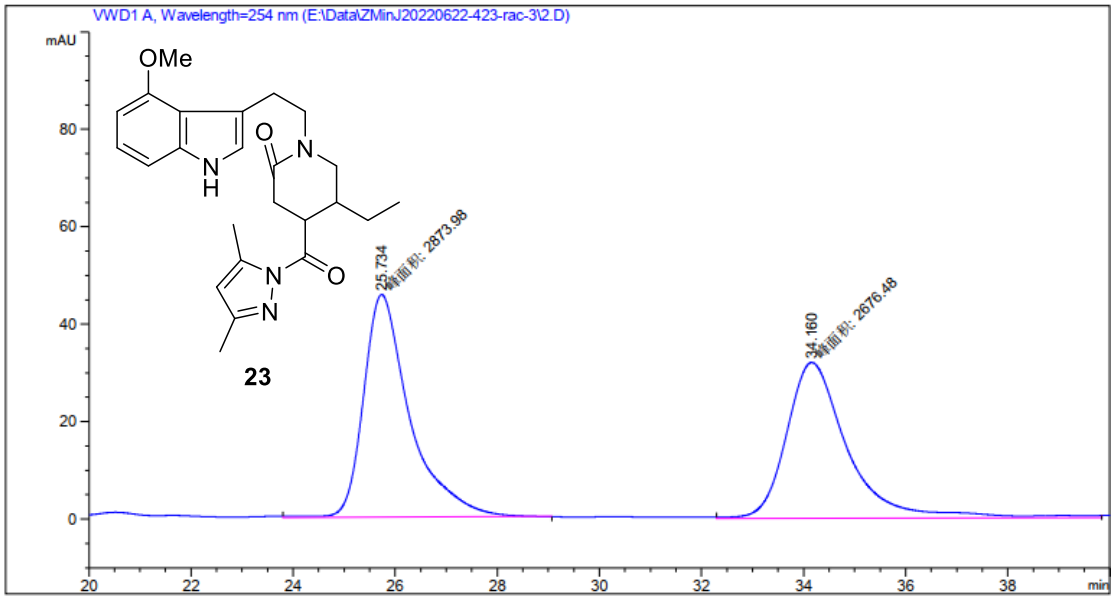


^{13}C-NMR of natural quinidine (6)

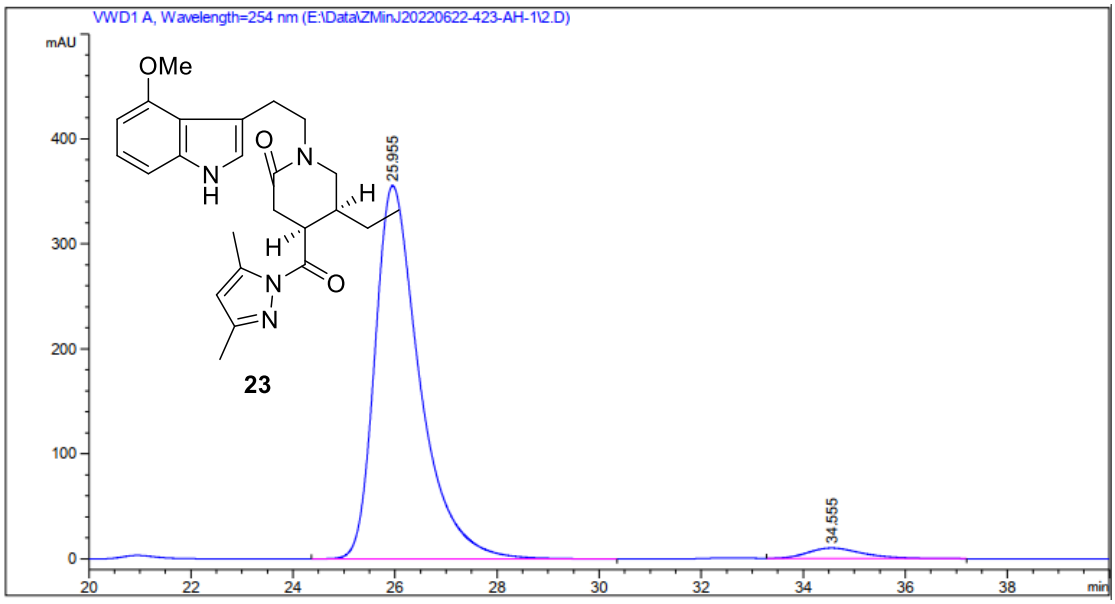


Comparison of ^{13}C NMR (Chloroform-*d*) spectrum between natural quinidine (6) and our synthetic quinidine (6)

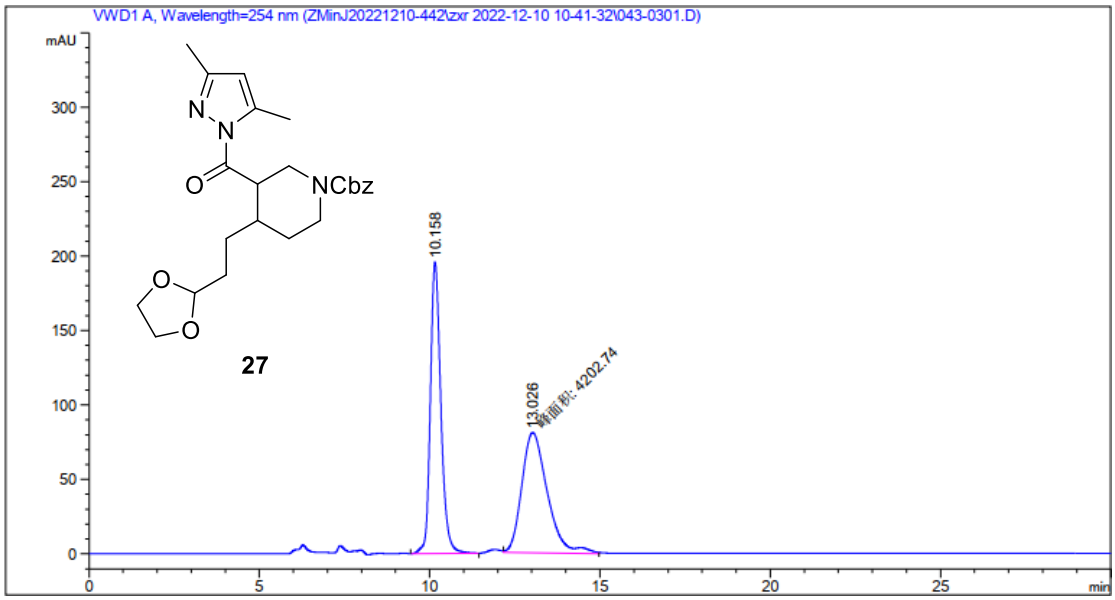
4. HPLC Chromatograms of Compounds



Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
25.734	MM	1.05	2873.98	45.66	51.78
34.160	MM	1.39	2676.49	31.99	48.22



Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
25.955	BB	0.91	21652.40	355.44	96.69
34.555	BB	1.10	740.18	9.95	3.31



Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
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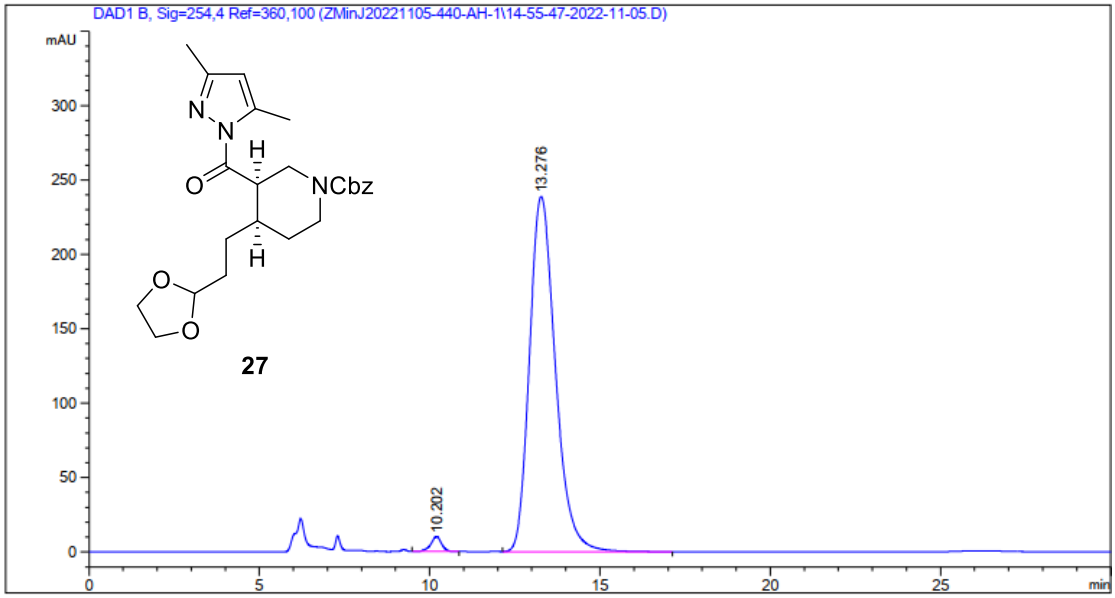
13.026	MM	0.87	4202.74	80.70	50.2



Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
10.20	BB	0.33	222.03	10.18	1.73
13.28	BB	0.81	12590.30	238.67	98.27

5. References

1. H. Takayama, M. Maeda, S. Ohbayashi, M. Kitajima, S.-I. Sakai, N. Aimi, The First Total Synthesis of (−)-Mitragynine, An Analgesic Indole Alkaloid in Mitragyna Speciosa. *Tetrahedron Lett.* 1995, **36**, 9337– 9340.
2. A. C. Kruegel, M. M. Gassaway, A. Kapoor, A. Váradi, S. Majumdar, M. Filizola, J. A. Javitch and D. Sames, Synthetic and receptor signaling explorations of the mitragyna alkaloids: mitragynine as an atypical molecular framework for opioid receptor modulators, *J. Am. Chem. Soc.* 2016, **138**, 6754–6764.
3. A. C. Smith, R. M. Williams, Rabe Rest in Peace: Confirmation of the Rabe–Kindler Conversion of d-Quinotoxine Into Quinine: Experimental Affirmation of the Woodward–Doering Formal Total Synthesis of Quinine. *Angew. Chem. Int. Ed.* 2008, **47**, 1736–1740.
4. W. Liu, W. Qin, X. Wang, F. Xue, X.-Y. Liu, Y. Qin, Bioinspired Synthesis of (+)-Cinchonidine Using Cascade Reactions. *Angew. Chem. Int. Ed.* 2018, **57**, 12299–12302.