Electronic Supplementary Material (ESI) for Chemical Communications.

Supplementary Information

The total synthesis of (–)-strempeliopine *via* palladium-catalyzed decarboxylative asymmetric allylic alkylation

Yi An,[a] Mengjuan Wu,[a] Weijian Li,[a] Yaling Li,[a] Zhenzhen Wang,[a] Yansong Xue,[a] Pei Tang*[a] and Fener Chen*[abc]

[a]*Sichuan Research Center for Drug Precision Industrial Technology, West China School of Pharmacy, Sichuan University, Chengdu 610041, China.*
[b]*Engineering Center of Catalysis and Synthesis for Chiral Molecules, Department of Chemistry, Fudan University, Shanghai 200433, China*
[c]*Shanghai Engineering Center of Industrial Asymmetric Catalysis for Chiral Drugs, Shanghai 200433, China*

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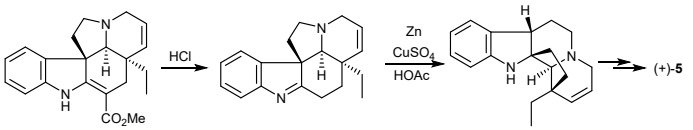
1. General Information

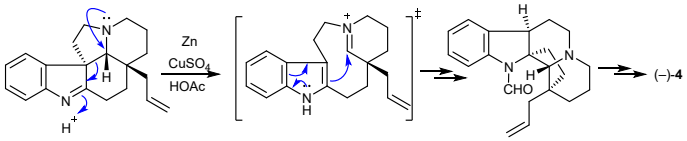
All commercially available reagents were used without further purification. Tetrahydrofuran, toluene, MTBE and 1,4-dioxane were distilled from sodium/benzophenone ketyl. Chromatography was conducted by using 200−300 mesh silica gel. All new compounds gave satisfactory spectroscopic analyses (IR, ^{1}H NMR, ^{13}C NMR, HRMS). NMR spectra were recorded on a 400 MHz NMR. Reference values for residual solvents were taken as δ = 7.26 (Chloroform-*d*) ppm for ^{1}H NMR and δ = 77.16 (Chloroform-*d*) ppm for ^{13}C NMR. Coupling constants (*J*) are given in Hz and are uncorrected and multiplicities for coupled signals were denoted as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad, apt. = apparent and dd = double doublet etc. Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum Two FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on a Bruker TOF Premier, by the ESI method. Optical rotation was obtained from Rudolph Research Analytical Autopol VI automatic polarimeter. Chiral HPLC was performed using a Daicel Chiralcel OJ column (4.6 × 250 mm) analytical column. Unless otherwise noted, all products are isolated yields.

Scheme S1 Synthetic synopsis of *Schizozygine* alkaloids.

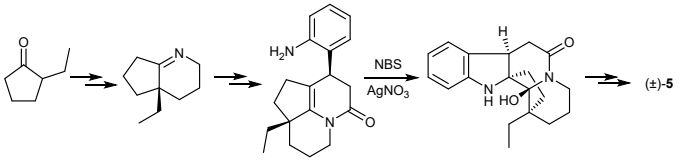
i. Le Men's semi-synthesis of (+)-5 via reductive rearrangement



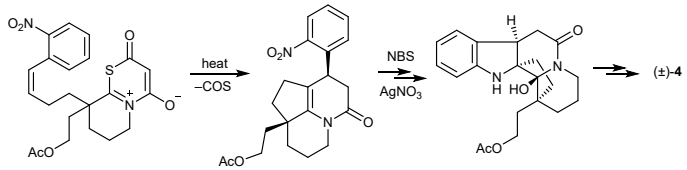
ii. Trojánek's biomimetic synthesis of (–)-4 using Le Men's strategy



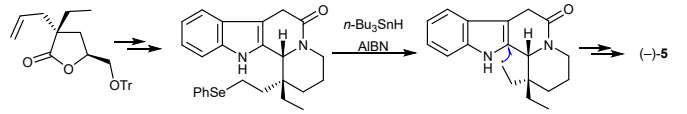
iii. Heathcock's racemic synthesis of (±)-5 via NBS-induced cyclization



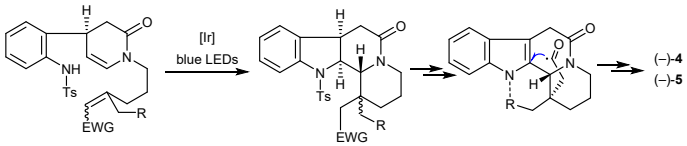
iv. Padwa's racemic synthesis of (±)-4 via intramolecular 1,4-dipolar cycloaddition



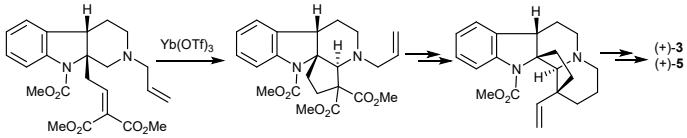
v. Okada's asymmetric synthesis of (–)-5 via reductive radical cyclization



vi. Qin's asymmetric synthesis of (–)-4 and (–)-5 via a cascade photocatalytic radical reaction and radical cyclization



vii. Anderson's asymmetric synthesis of (+)-3 and (+)-5 via [1,4]-hydride transfer/Mannich cyclization



viii. Boger's asymmetric synthesis of (–)-4 via dearomative transannular radical cyclization

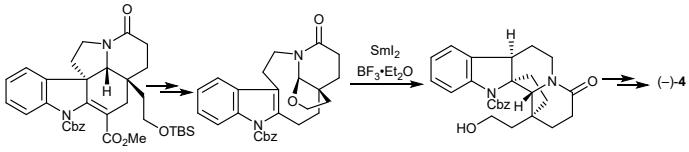
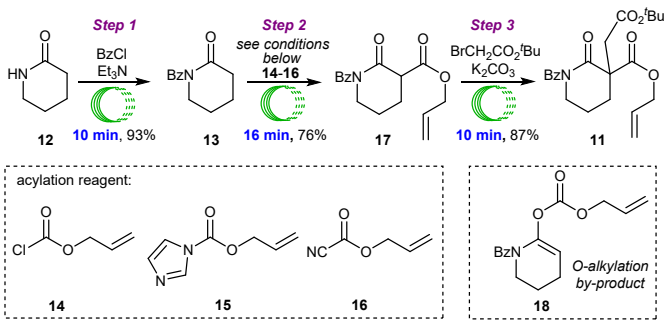


Table S1 Preparation of **11** in continuous flow.



entry	acylation reagent[a]	conditions	selectivity **17**/**18** [b].	yield (%) [c]
1	**14**	LiHMDS (1.2 equiv.), THF, -80 °C, 16 min.	3:4	/
2	**15**	LDA (1.2 equiv.), THF, -80 °C, 16 min.	> 99:1	32
3	**16**	LDA (1.2 equiv.), THF, -80 °C, 16 min.	> 99:1	50
4	**16**	LDA (1.2 equiv.), THF, -40 °C, 16 min.	> 99:1	76

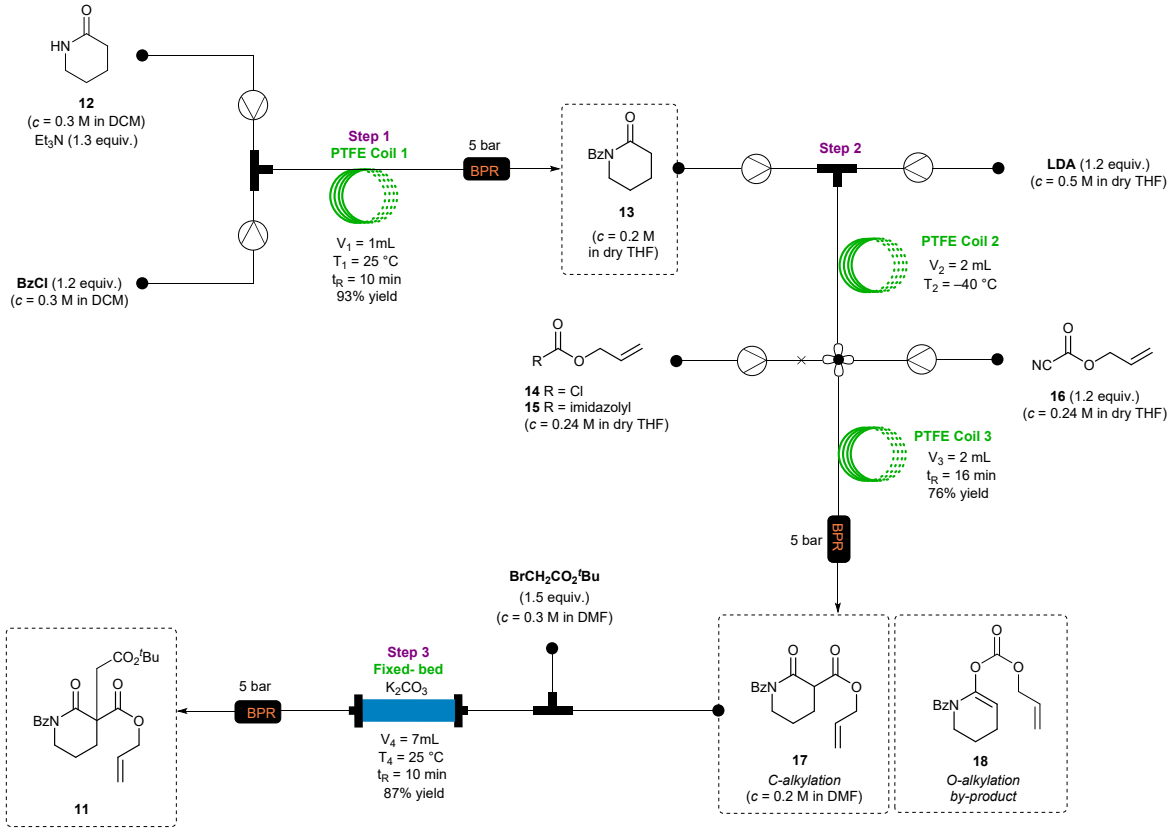
[a] The flow was carried out using acylation reagent (1.2 equiv.).

[b] Selectivity of **17** and **18** was determined by LC-MS. [c] Isolated yield.

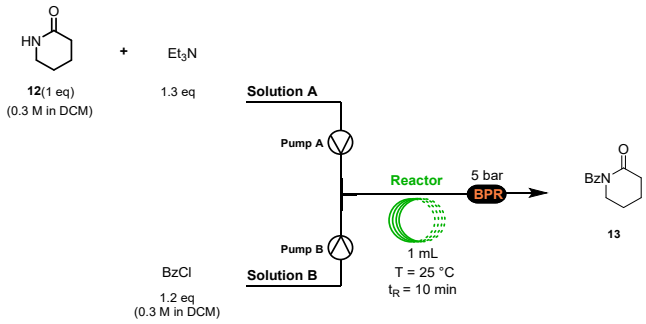
2. Experimental Procedures

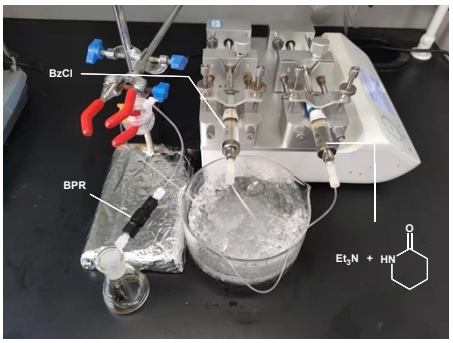
Synthesis of Lactam Substrates: A Continuous-Flow Synthesis Method

Scheme 2 Synthesis of N-benzoyl-β-amido-diester **11** in multistep continuous flow



Synthesis of benzoyl lactam 13





The flow reactor equipment consists of two pumps for reagent/solvent delivery. Before the start of the actual experiment, all reactors were primed with CH_2Cl_2. The Pump A was used to pump the mixture of the starting material **12** and Et_3N which was 8 mL in total. The Pump B was used to pump BzCl. Solutions A and B were mixed at a T-piece and pumped through Reactor. A 5 bar back pressure regulator (BPR) was connected after

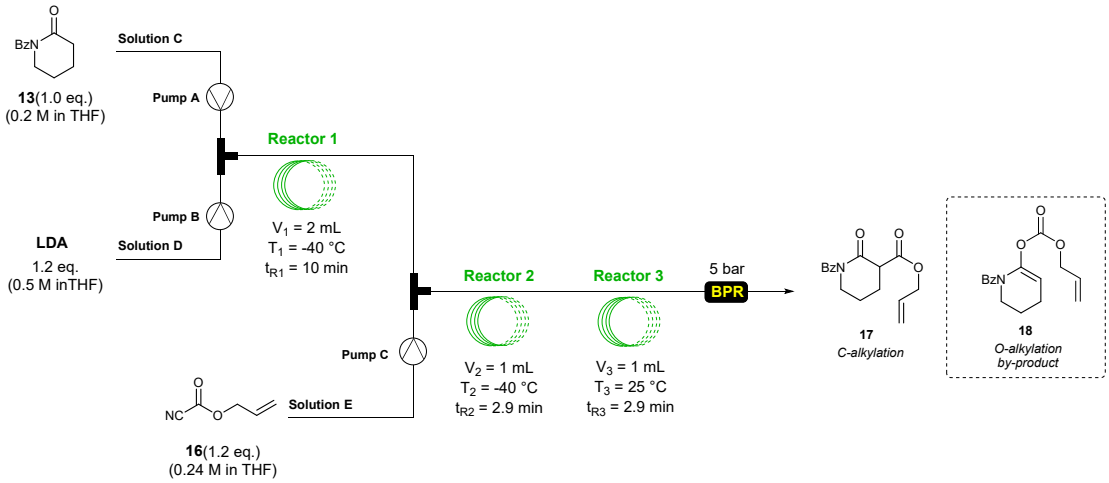
Reactor. After approximately three total system residence times, the output flow from Reactor was collected for 30 mins (3.0 mL). The reactant mixture was concentrated in vacuo and purified using flash chromatography (petroleum ether / ethyl acetate = 3:1) to give pure Benzoyl lactam **13** (77.0 mg, 93%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.53 (d, *J* = 6.8 Hz, 2H), 7.43 (t, *J* = 7.2 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 2H), 3.74 (t, *J* = 5.2 Hz, 2H), 2.49 (t, *J* = 6.8 Hz, 2H), 1.92 – 1.83 (m, 4H); **^{13}C NMR (101 MHz, Chloroform-*d*)** δ 174.49, 173.37, 136.02, 131.28, 127.93, 127.72, 45.95, 34.41, 22.56, 21.23. **HRMS (ESI) *m/z*** $[M + Na]^+$ calcd. for $C_{12}H_{13}NNaO_2^+$ 226.0844, found 226.0838.

Table S1. Solution concentration and flow rates for the synthesis of **13**.

Solution	Pump	Equiv.	Concentration (M)	Flow rate (mL/min)
12	A	1.0 equiv.	0.30	0.045
Et_3N		1.3 equiv.	0.39	
BzCl	B	1.3 equiv.	0.30	0.054

Synthesis of lactam 17



The flow reactor equipment consists of three pumps for reagent/solvent delivery. Before the start of the actual experiment, all reactors were primed with dry THF. Reactor 1 was pre-cooled to -40 °C, Reactor 2 was pre-cooled to -40 °C and Reactor 3 was kept at room temperature. The Pump A was used to pump the solution of

benzoyl lactam **13** and Pump B was used to pump the solution of LDA. Solutions C and D were mixed at a T-piece and pumped through Reactor 1 without back pressure regulator (BPR). The output from Reactor 1 was connected to a second T-piece with an incoming solution of allyl cyanoacetate that was pumped using a Pump C. The collective flow stream was allowed to pump into Reactor 2 and Reactor 3. A 5 bar back pressure regulator (BPR) was connected after Reactor 3. After approximately three total system residence times, the output flow from Reactor 3 was collected for 32 mins (8.0 mL). The reactant mixture was concentrated in vacuo and purified using flash chromatography (petroleum ether / ethyl acetate = 4:1) to give pure lactam **17** (190.0 mg, 0.66 mmol, 76%).

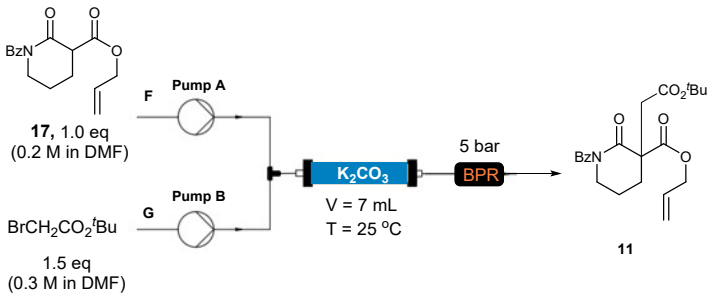
Compound 17: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.69 (d, *J* = 7.6 Hz, 2H), 7.47 (t, *J* = 7.2 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 2H), 6.01– 5.86 (m, 1H), 5.36 (d, *J* = 17.2 Hz, 1H), 5.29 (d, *J* = 10.4 Hz, 1H), 4.69 (d, *J* = 6.0 Hz, 2H), 3.88 – 3.76 (m, 2H), 3.59 (t, *J* = 6.4 Hz, 1H), 2.39 – 2.28 (m, 1H), 2.21 – 2.11 (m, 1H), 2.11 – 2.01 (m, 1H), 2.00 - 1.87 (m, 1H); **^{13}C NMR (101 MHz, Chloroform-*d*)** δ 174.63, 169.66, 169.40, 135.51, 131.97, 131.49, 128.32, 128.23, 119.38, 66.48, 51.14, 46.39, 25.59, 20.72; **HRMS (ESI) *m/z*** $[M + Na]^+$ calcd. for $C_{16}H_{17}NNaO_4^+$ 310.1055, found 310.1051.

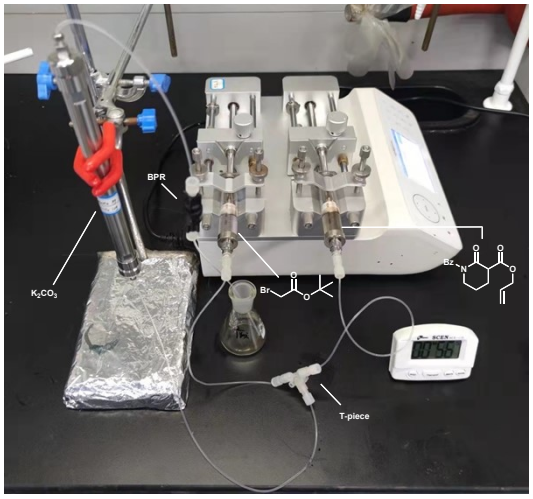
Compound 18: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.53 (d, J = 6.8 Hz, 2H), 7.43 (t, J = 7.2 Hz, 1H), 7.40 – 7.34 (m, 2H), 5.85 – 5.70 (m, 1H), 5.31 – 5.16 (m, 1H), 5.06 (t, J = 3.6 Hz, 1H), 4.46 (d, J = 6.0 Hz, 2H), 3.80 (t, J = 5.2 Hz, 2H), 2.29 (td, J = 10.4, 3.6 Hz, 2H), 1.87 (p, J = 6.0 Hz, 2H); **^{13}C NMR (101 MHz, Chloroform-*d*)** δ 168.98, 152.12, 141.07, 136.09, 130.99, 130.81, 128.33, 127.81, 119.31, 102.38, 77.48, 77.16, 76.84, 69.15, 46.06, 23.22, 21.86; **HRMS (ESI) *m/z*** $[M + H]^+$ calcd. for $C_{16}H_{18}NO_4^+$ 288.1236, found 288.1233.

Table S2. Solution concentration and flow rates for the synthesis of **17**.

Solution	Pump	Equiv.	Concentration (M)	Flow rate (mL/min)
13	A	1.0 equiv.	0.20	0.136
LDA	B	1.2 equiv.	0.50	0.064
allyl cyanoacetate	C	1.2 equiv.	0.24	0.136

Synthesis of lactam 11





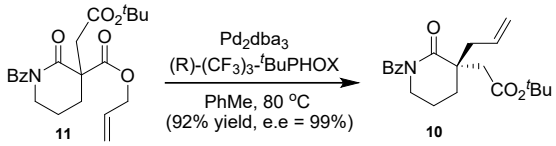
The flow reactor equipment consists of two pumps for reagent/solvent delivery. Before the start of the actual experiment, all reactors were primed with DMF. The Pump A was used to pump the solution of **17**. The Pump B was used to pump the solution of tert-Butyl bromoacetate. Solutions F and G were mixed at a T-piece and pumped through column reactor packed with 20.0 g K_2CO_3. A 5 bar back pressure regulator (BPR) was connected after column reactor. After approximately three total system residence times, the output flow from Reactor was collected for 30 mins (21.0 mL). The reactant mixture was concentrated in vacuo and purified using flash chromatography (petroleum ether / ethyl acetate = 5:1) to give pure **11** (733.0 mg, 87%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.74 (d, *J* = 7.2 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 2H), 6.01 – 5.91 (m, 1H), 5.38 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.31 (d, *J* = 10.0 Hz, 1H), 4.71 (d, *J* = 4.8, 2H), 3.98 – 3.92 (m, 2H), 3.79 (td, J = 12.0, 4.0 Hz, 1H), 3.12 (d, *J* = 16.8 Hz, 1H), 2.67 (d, *J* = 17.2 Hz, 1H), 2.29 – 2.18 (m, 2H), 2.09 – 1.96 (m, 2H), 1.37 (s, 9H); **^{13}C NMR (100 MHz, Chloroform-*d*)** δ 174.79, 171.23, 171.11, 169.48, 136.02, 131.51, 131.25, 128.19, 127.88, 119.64, 81.41, 66.65, 54.17, 46.45, 40.98, 31.67, 28.01, 20.44; **IR (neat, cm^{-1})** 2979, 1718, 1698, 1404, 1219, 1141, 930, 728, 654; **HRMS (ESI) *m/z*** [M + Na]$^+$ calcd. for $C_{22}H_{27}NNaO_6^+$ 424.1736, found 424.1731.

Table S3. Solution concentration and flow rates for the synthesis of **11**.

Solution	Pump	Equiv.	Concentration (M)	Flow rate (mL/min)
17	A	1.0 equiv.	0.20	0.35
tert-Butyl bromoacetate	B	1.5 equiv.	0.30	0.35

Synthesis of benzoyl lactam 10



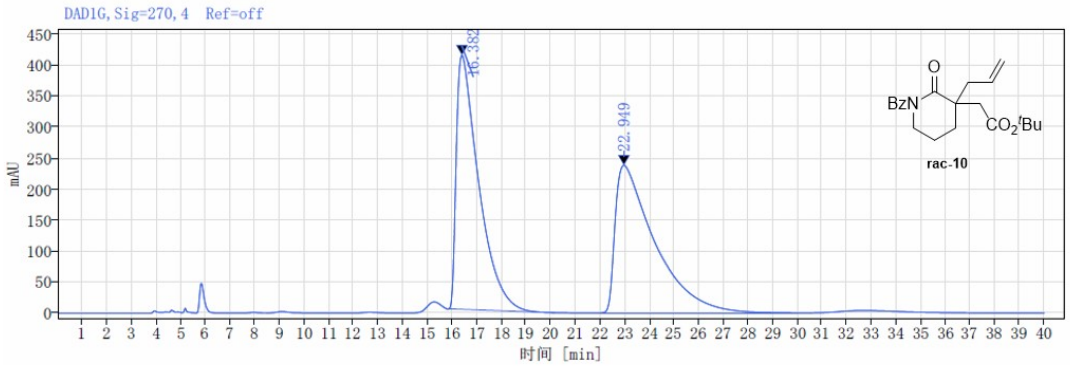
To a dry flask was added (R)-$(CF_3)_3$-^{t}BuPHOX (74.0 mg, 0.125 mmol, 0.125 equiv.) and $Pd_2(dba)_3$ (46.0 mg, 0.05 mmol, 0.05 equiv.). Under argon atmosphere, dry degassed PhMe (22.5 mL) was added through syringe and the mixture was stirred for 30 min at room temperature. Then the mixture was added to a solution of lactam **11** (401.0 mg, 1.00 mmol, 1.00 equiv.) in dry degassed PhMe (7.5 mL). Then the reaction mixture was warmed to 45 °C for 15 h. After completion of the reaction (monitored by TLC), the solvent was removed under reduced pressure. Purification of the residue by column chromatography (petroleum ether / ethyl acetate = 6:1) afforded

the desired product **10** as a yellow oil (329.0 mg, 92%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.55 (d, *J* = 7.2 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 2H), 5.80 – 5.69 (m, 1H), 5.20 – 5.13 (m, 2H), 4.04 – 3.98 (m, 1H), 3.75 (td, *J* = 12.8, 4.0 Hz,1H), 2. 89 (d, *J* = 16.8 Hz, 1H), 2.51 (ddd, *J* = 58.0, 13.6, 7.6 Hz, 2H), 2.21 (d, *J* = 16.8 Hz, 1H), 2.15 – 1.93 (m, 3H), 1.90 – 1.85 (m, 1H), 1.40 (s, 9H); **^{13}C NMR (100 MHz, Chloroform-*d*)** δ 177.24, 175.33, 170.66, 136.90, 132.47, 131.32, 128.10, 127.72, 119.92, 81.08, 46.61, 45.57, 42.89, 42.73, 30.32, 28.23, 20.03; $[\alpha]_D^{20}$ = -15.9 (*c* 0.82, $CHCl_3$, 99% ee); **IR (neat, cm^{-1})** 2950, 1717, 1698, 1277, 1219, 1141, 961, 728, 694, 654; **HRMS (ESI) *m/z*** [M + Na]$^+$ calcd. for $C_{21}H_{27}NNaO_4^+$ 380.1838, found 380.1834.

HPLC for measuring ee value

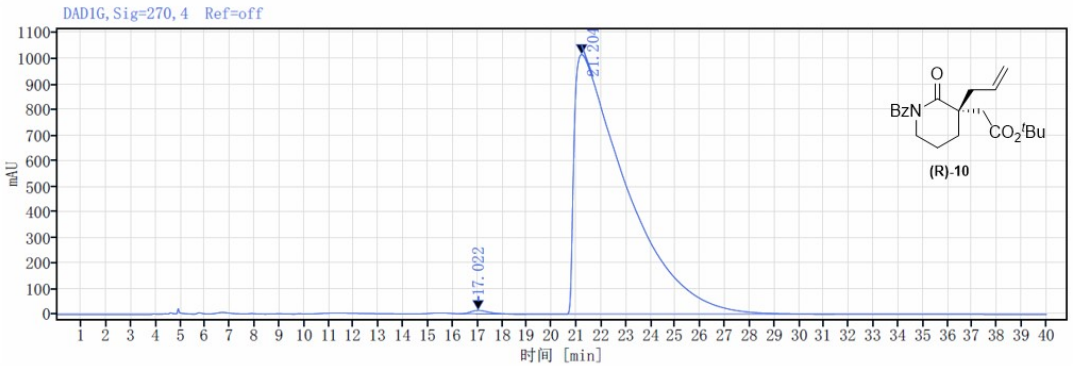
Racemic **10**:



信号: DAD1G, Sig=270, 4 Ref=off

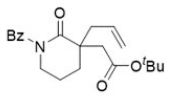
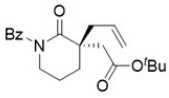
保留时间 [min]	类型	峰宽 [min]	峰面积	高度	峰面积%	名称
16.382	MM m	0.92	25837.68	410.95	49.27	
22.949	MM m	1.53	26606.61	238.70	50.73	
		总和	52444.29			

Enantioenriched 10:

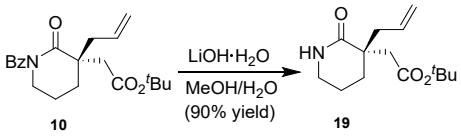


信号: DAD1G, Sig=270, 4 Ref=off

保留时间 [min]	类型	峰宽 [min]	峰面积	高度	峰面积%	名称
17.022	MM m	0.75	695.41	13.98	0.47	
21.204	MM m	2.01	148206.75	1015.04	99.53	
		总和	148902.17			

Entry	Product	Conditions	Retention time (min)	Retention time (min)	% ee
1	 Rac-10	HPLC Chiralpak OJ-H 1% iPrOH in hexanes isocratic, 1.0 mL/min 270 nm	16.38	22.95	0
2	 (R)-10	HPLC Chiralpak OJ-H 1% iPrOH in hexanes isocratic, 1.0 mL/min 270 nm	17.02	21.20	99

Synthesis of lactam 19

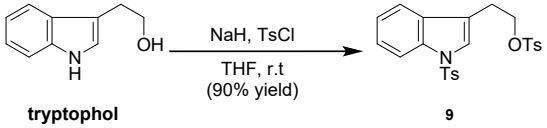


10 **19**

To a solution of lactam **10** (357.0 mg, 1.00 mmol, 1.00 equiv.) in MeOH (25 mL) was added a solution of LiOH•H_2O (63.0 mg, 1.50 mmol, 1.50 equiv.) in H_2O (10 mL) at room temperature. After 12 h, the reaction mixture was concentrated under reduced pressure and diluted with saturated aqueous $NaHCO_3$ and ethyl acetate. The phases were separated, and the aqueous phase was extracted with ethyl acetate, combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, concentrated under vacuum and isolated by using silica flash column chromatography (petroleum ether / ethyl acetate = 2:1) to afford lactam **19** as a white solid (228.0 mg, 90%).

^{1}H NMR (400 MHz, Methanol-d_4) δ 5.84 – 5.73 (m, 1H), 5.13 – 5.08 (m, 2H), 3.35 – 3.23 (m, 2H), 2.79 (d, *J* = 16.0 Hz, 1H), 2.47 – 2.41 (m, 1H), 2.31 – 2.25 (m, 1H), 2.22 (d, *J* = 16.0 Hz, 1H), 1.98 – 1.86 (m, 2H), 1.85 – 1.72 (m, 2H), 1.43 (s, 9H); **^{13}C NMR (100 MHz, Methanol-d_4)** δ 178.24, 172.30, 134.67, 119.25, 81.86, 49.64, 49.43, 49.21, 49.00, 48.79, 48.58, 48.36, 44.15, 43.97, 43.94, 43.25, 30.33, 28.37, 20.29; $[\alpha]_D^{25}$ = +22.8 (*c* 1.1, $CHCl_3$); **IR (neat, cm^{-1})** 2968, 2934, 1727, 1656, 1361, 1153, 1121; **HRMS (ESI) *m/z*** [M + H]$^+$ calcd. for $C_{14}H_{24}NO_3^+$ 254.1756, found 254.1755.

Preparation of compound 9[1]



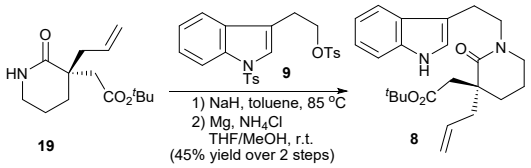
tryptophol **9**

To a suspension of NaH (10.0 g, 250.0 mmol, 60% in mineral oil, 4.0 equiv.) in THF (300 mL) was added a solution of tryptophol (10.0 g, 62.0 mmol, 1.00 equiv.) in THF (100 mL) at 0 °C. The resulting mixture was stirred at room temperature for 1 h and then added a solution of TsCl (47.0 g, 246.0 mmol, 4.0 equiv.) in THF (150 mL). The reaction mixture was stirred overnight at room temperature and quenched by addition of saturated

ammonium chloride solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to purification on silica gel chromatography (petroleum ether / acetone = 5:1) to afford **9** as white solid (21.5 g, 74%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ ppm 7.93 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.32 – 7.27 (m, 3H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.19 – 7.12 (m, 3H), 4.24 (t, *J* = 6.8 Hz, 2H), 3.01 (td, *J* = 6.8, 1.2 Hz, 2H), 2.38 (s, 3H), 2.32 (s, 3H); **^{13}C NMR (100 MHz, Chloroform-*d*)** δ 145.13, 144.93, 135.25, 135.12, 132.52, 130.27, 130.05, 129.83, 127.76, 126.92, 124.87, 124.19, 123.25, 119.15, 117.25, 113.80, 68.85, 25.01, 21.77, 21.70; **IR (neat, cm^{-1})** 3897, 3685, 3673, 3049, 1594, 1377, 1185, 1168, 975, 903, 762, 597, 574. **HRMS (ESI) *m/z*** [M + Na]$^+$ calcd. for $C_{24}H_{23}NNaO_5S_2^+$ 492.0915, found 492.0922.

Synthesis of compound 8



To a suspension of NaH (120.0 mg, 3.0 mmol, 60% in mineral oil, 3.00 equiv.) in toluene (4.0 mL) was added a solution of **19** (253.0 mg, 1.0 mmol, 1.00 equiv.) in toluene (6 mL) at room temperature. The mixture was heated at 85 °C for 1 h. Then a solution of compound **9** (704.0 mg, 1.5 mmol, 1.50 equiv.) in toluene (6.0 mL) was added dropwise to the reaction mixture in 10 min. The resulting mixture was refluxed for 10 h and quenched by adding saturated ammonium chloride solution at 0 °C and extracted by diethyl ether. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was directly used in the next step without further purification. An analytic sample was obtained by column chromatography.

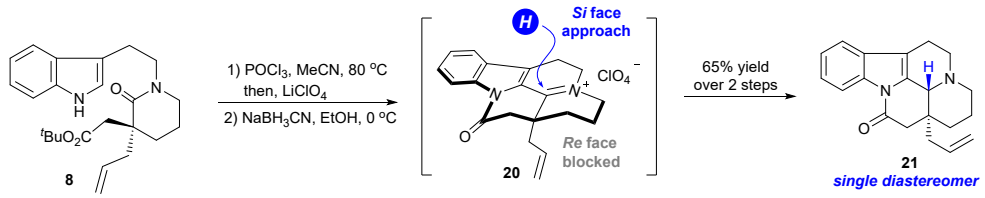
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.99 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.44 (s, 1H), 7.31 (td, *J* = 7.2, 1.2 Hz, 1H), 7.25 – 7.21 (m, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 5.81 – 5.66 (m, 1H), 5.14 – 5.03 (m, 2H), 3.67 – 3.46 (m, 2H), 3.29 (td, *J* = 11.2, 4.4 Hz, 1H), 3.10 – 3.00 (m, 1H), 2.97 – 2.86 (m, 3H), 2.44 (dd, *J* = 13.6, 7.2 Hz, 1H), 2.32 (s, 3H), 2.30 – 2.18 (m, 2H), 2.00 – 1.90 (m, 1H), 1.66 – 1.56 (m, 2H), 1.44 (s, 9H); **^{13}C NMR (100 MHz, Chloroform-*d*)** δ 173.58, 171.03, 144.66, 135.42, 135.23, 133.63, 130.87, 129.73, 126.73, 124.61, 123.46, 123.07, 120.43, 119.65, 118.60, 113.66, 80.35, 49.19, 48.38, 43.47, 43.23, 42.96, 29.27, 28.15, 22.78, 21.48, 19.63.

To a solution of the above crude product in tetrahydrofuran (4.0 mL) and methanol (4.0 mL) was added magnesium granule (245.0 mg, 10.0 mmol, 10.00 equiv.) and NH_4Cl (160.0 mg, 3.0 mmol, 3.00 equiv.) at 0 °C. The resulting mixture was stirred for 4 h at room temperature. Then it was cooled by ice bath, diluted by ethyl acetate (8 mL) and quenched by slowly addition of saturated ammonium chloride solution. The mixture was filtered through Celite and washed with ethyl acetate. The filtrate was extracted with ethyl acetate, combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, concentrated under vacuum and isolated by using silica flash column chromatography (petroleum ether / CH_2Cl_2 / MeOH = 8:8:1) to afford lactam **8** as white solid (179.0 mg, 45% from **19**).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.26 (s, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.21 – 7.15 (m, 1H), 7.14 – 7.09 (m, 1H), 7.06 (s, 1H), 5.79 – 5.68 (m, 1H), 5.10 – 5.05 (m, 2H), 3.77 – 3.69 (m, 1H), 3.59 – 3.51 (m, 1H), 3.21 – 3.16 (m, 1H), 3.03 (t, *J* = 7.6 Hz, 2H), 2.91 (dd, *J* = 16.0, 1.6 Hz, 1H), 2.52 – 2.41 (m, 1H),

2.32 (dd, *J* = 14.0, 7.6 Hz, 1H), 2.25 (dd, *J* = 16.0, 1.6 Hz, 1H), 2.04 – 1.93 (m, 1H), 1.81 – 1.67 (m, 3H), 1.43 (s, 9H); **^{13}C NMR (100 MHz, Chloroform-*d*)** δ 173.35, 171.12, 136.25, 133.79, 127.49, 122.12, 121.81, 119.17, 118.83, 118.51, 113.39, 111.13, 80.36, 48.93, 48.79, 43.51, 43.31, 43.00, 29.28, 28.13, 22.94, 19.61; $[a]_D^{20}$ = -9.5 (*c* 1.6, MeOH); **IR (neat, cm^{-1})** 3267, 2930, 2858, 1719, 1611, 1143, 963, 854, 695, 508; **HRMS (ESI) *m/z*** [M + H]$^+$ calcd. for $C_{24}H_{33}N_2O_3^+$ 397.2491, found 397.2485.

Synthesis of pentacycle 21



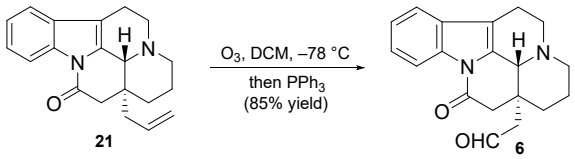
A mixture of lactam **8** (370.0 mg, 1.00 mmol, 1.00 equiv.) and freshly distilled $POCl_3$ (2.7mL, 30.0 mmol, 30.00 equiv.) in dry acetonitrile (1.1 mL) was heated at 80 °C for 3 hours. The reaction mixture was cooled down to room temperature and evaporated in vacuo to remove completely excess of $POCl_3$. The residue was dissolved in CH_2Cl_2 (4.5 mL) and treated with 1 M $LiClO_4$ (aq.) aqueous solution (3.7 mL) for 30 minutes. The reaction mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with 1 M $LiClO_4$ (aq.), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to obtain the iminium salt **20** as a green solid which was directly used in the next step without further purification. An analytic sample was obtained by column chromatography.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.31 (d, *J* = 8.4 Hz, 1H), 7.69 – 7.52 (m, 2H), 7.39 (t, *J* = 7.6 Hz, 1H), 5.69 – 5.42 (m, 1H), 5.25 – 4.94 (m, 2H), 4.42 – 4.17 (m, 1H), 4.03 – 3.78 (m, 3H), 3.49 – 3.32 (m, 1H), 3.20 (d, *J* = 16.8 Hz, 2H), 2.86 (d, *J* = 16.4 Hz, 1H), 2.61 – 2.49 (m, 1H), 2.32 – 2.15 (m, 2H), 1.92 (t, *J* = 13.6 Hz, 2H), 1.81 (d, *J* = 13.2 Hz, 1H); **^{13}C NMR (100 MHz, Chloroform-*d*)** δ 166.90, 164.20, 137.63, 131.32, 128.77, 127.72, 126.60, 125.68, 125.32, 122.62, 122.27, 116.71, 52.40, 51.86, 42.42, 41.23, 40.50, 25.05, 19.53, 17.09.

The iminium salt **20** was added portionwise to a solution of $NaBH_3CN$ (754.0 mg, 12.0 mmol, 12.0 equiv.) in EtOH (50.0 mL, 0.02 M) at 0 °C. After being stirred at 0 °C for 2 h, the reaction mixture was quenched with 2 M HCl and evaporated in vacuo. The crude product was redissolved in CH_2Cl_2 and saturated aqueous Na_2CO_3 solution and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (petroleum ether / ethyl acetate = 5:1) to afford the singer isomer **21** (199.0 mg, 65% from **8**) as a white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.34 (dd, *J* = 6.8, 1.6 Hz, 1H), 7.39 (dd, *J* = 6.8, 2.0 Hz, 1H), 7.34 – 7.20 (m, 2H), 5.66 (ddt, J = 17.6, 10.0, 7.6 Hz, 1H), 5.09 – 4.89 (m, 2H), 3.11 – 3.00 (m, 2H), 2.92 (t, *J* = 2.8 Hz, 1H), 2.90 – 2.80 (m, 1H), 2.75 (d, *J* = 16.8 Hz, 1H), 2.67 – 2.53 (m, 2H), 2.47 (td, *J* = 11.2, 4.0 Hz, 1H), 2.33 – 2.20 (m, 2H), 1.93 (qt, *J* = 13.2, 4.4 Hz, 1H), 1.81 (dt, *J* = 13.2, 3.2 Hz, 1H), 1.65 – 1.54 (m, 1H), 1.51 (dd, *J* = 14.8, 7.2 Hz, 1H), 1.19 – 1.06 (m, 1H); **^{13}C NMR (100 MHz, Chloroform-*d*)** δ 167.21, 134.97, 132.88, 129.77, 124.04, 123.75, 118.63, 118.08, 116.20, 112.94, 65.04, 55.21, 52.04, 44.38, 39.22, 33.10, 32.25, 21.24, 21.12. $[a]_D^{20}$ = +184.35 (*c* 0.46, $CHCl_3$); **IR (neat, cm^{-1})** 2979, 2949, 1719, 1699, 1365, 1316, 1148, 929; **HRMS (ESI) *m/z*** [M + H]$^+$ calcd. for $C_{20}H_{23}N_2O^+$ 307.1810, found 307.1800.

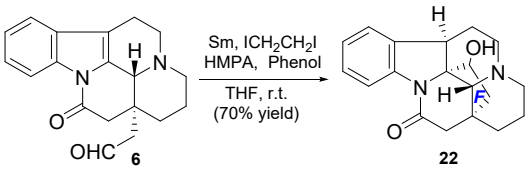
Synthesis of aldehyde 6



Pentacycle **21** (306.0 mg, 1.0 mmol, 1.00 equiv.) was dissolved in 15 mL of CH_2Cl_2. The mixture was cooled to -78 °C. Ozone was bubbled into the mixture while keeping the temperature at -78 °C. When the color turned to blue, the ozone bubbling was stopped. O_2 was bubbled until the mixture turned to colorless, PPh_3 (314.0 mg, 1.2 mmol, 1.20 equiv.) was added. The mixture was stirred at -78 °C for 1 h then warmed to 0 °C naturally. After being stirred at 0 °C for 1 h, The reaction mixture was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure and purified by flash column chromatography (petroleum ether / ethyl acetate = 3:1) to afford the aldehyde **6** (262.0 mg, 85%) as a white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.67 (s, 1H), 8.30 (d, *J* = 4.8 Hz, 1H), 7.38 (d, *J* = 4.4 Hz, 1H), 7.30 – 7.26 (m, 1H), 7.26 – 7.22 (m, 1H), 3.08 – 3.05 (m, 1H), 3.04 – 3.03 (m, 1H), 3.03 – 2.93 (m, 2H), 2.98 – 2.94 (m, 1H), 2.85 – 2.77 (m, 1H), 2.61 (d, *J* =10.8 Hz, 1H), 2.52 – 2.48 (m, 1H), 2.47 – 2.43 (m, 1H), 2.28 (td, *J* = 8.0, 2.4 Hz, 1H), 2.11 (d, *J* = 8.8 Hz, 1H), 1.93 – 1.86 (m, 2H), 1.63 (d, *J* = 9.6 Hz, 1H), 1.30 (tq, *J* = 9.2, 4.4 Hz, 1H); **^{13}C NMR (100 MHz, Chloroform-*d*)** δ 201.04, 166.60, 135.10, 132.09, 129.77, 124.55, 124.16, 118.40, 116.40, 113.78, 65.10, 55.10, 51.94, 44.72, 43.29, 39.23, 33.04, 21.55, 21.20. $[a]_D^{20}$ = +99.3 (*c* 1.3, $CHCl_3$); **IR (neat, cm^{-1})** 2932, 1716, 1699, 1463, 1316, 1149, 915; **HRMS(ESI) *m/z*** [M + H]$^+$ calcd. for $C_{19}H_{21}N_2O_2^+$ 309.1603, found 309.1598.

Synthesis of compound 22

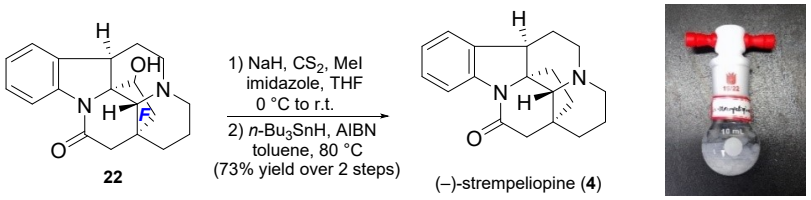


Samarium (376.0 mg, 2.5 mmol, 2.50 equiv.) and 1,2-diiodoethane (677.0 mg, 2.4 mmol, 2.40 equiv.) were suspended in freshly distilled anhydrous THF (25 mL) under a N_2 atmosphere and stirred for 2 h at room temperature. To the resulting dark blue solution HMPA (1.8 mL, 10.0 mmol, 10 equiv.) was added. The aldehyde **6** (308.0 mg, 1.0 mmol, 1.00 equiv.) and phenol (188.0 mg, 2.0 mmol, 2.0 equiv.) dissolved in THF (20 mL), were then added in one portion to the deep blue solution at 50 °C. After 18h the reaction was quenched with saturated aqueous solution of sodium bicarbonate, the organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined ether extracts were washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure and purified by flash column chromatography (petroleum ether / ethyl acetate = 2:1) to afford compound **22** (230.0 mg, 70%) as a white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.26 – 7.16 (m, 2H), 7.07 (td, *J* = 7.2, 0.8 Hz, 1H), 3.99 – 3.89 (m, 2H), 3.12 (td, *J* = 11.6, 6.4 Hz, 1H), 2.94 – 2.85 (m, 1H), 2.56 – 2.47 (m, 2H), 2.45 – 2.34 (m, 2H), 2.24 (dd, *J* = 15.2, 7.2 Hz, 1H), 2.18 – 2.01 (m, 3H), 1.91 – 1.60 (m, 4H), 1.38 – 1.22 (m, 2H); **^{13}C NMR (100 MHz, Chloroform-*d*)** δ 167.11, 141.58, 134.15, 127.96, 124.60, 124.55, 116.98, 78.84, 75.06, 66.25, 53.99, 50.42, 50.04, 44.32, 40.71, 36.18, 30.34, 26.88, 21.53. $[a]_D^{25}$ = +18.3 (*c* 1.1, $CHCl_3$); **IR (neat, cm^{-1})** 3405,

2890, 1694, 1463, 1374, 1139, 962; **HRMS (ESI)** ***m/z*** [M + H]$^+$ calcd. for $C_{19}H_{23}N_2O_2^+$ 311.1760, found 311.1753.

Synthesis of (-)-strempeliopine (4)



Under N_2 atmosphere, a solution of **22** (47.0 mg, 0.15 mmol, 1.00 equiv.) and imidazole (11.0 mg, 0.17 mmol, 1.10 equiv.) in anhydrous THF (17.0 mL) was treated with NaH (27.0 mg, 0.68 mmol, 60% in mineral oil, 40.00 equiv). The mixture was allowed to stir at room temperature for 1.0 h before it was cooled to 0 °C followed by the addition of CS_2 (182.0 µL, 3.0 mmol, 20.00 equiv). The reaction mixture was stirred at 0 °C for 1 h and then treated with MeI (187.0 µL, 3.0 mmol, 20.00 equiv), and the reaction mixture was allowed to be warmed to room temperature. After 1 h, the reaction mixture was quenched with the addition of saturated aqueous NH_4Cl solution, and the mixture was extracted with ethyl acetate. The combined organic phase was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was directly used in the next step without further purification.

Under N_2 atmosphere, to a mixture of the above crude product and AIBN (12.0 mg, 0.075 mmol, 0.50 equiv.) in dry PhMe (4.6 mL) was added *n*-Bu_3SnH (102.0 µL, 0.38 mmol, 2.50 equiv.). The reaction was stirred at 80 °C for 30 min and concentrated in vacuo. Flash chromatography (petroleum ether / ethyl acetate = 2:1) provided (-)-strempeliopine **4** (33.0 mg, 73%) as a white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 (d, *J* = 8.0 Hz, 1H), 7.22 (t, *J* = 7.8, Hz, 2H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.05 (td, *J* = 7.4, 1.1 Hz, 1H), 3.25 (t, *J* = 7.2 Hz, 1H), 2.96 (ddd, *J* = 11.6, 6.0, 2.0 Hz, 1H), 2.90 – 2.81 (m, 1H), 2.62 (d, *J* = 18.2 Hz, 1H), 2.46 (dd, *J* = 18.4, 2.4 Hz, 1H), 2.34 – 2.25 (m, 3H), 2.24 – 2.18 (m, 1H), 2.15 – 2.07 (m, 1H), 2.06 – 2.03 (m, 1H), 2.03 (s, 1H), 2.01 – 1.92 (m, 1H)，1.90 – 1.81 (m, 1H)，1.74 – 1.70 (m, 1H)，1.59 (ddd, *J* = 13.6, 4.8, 2.4 Hz, 1H)，1.53 – 1.46 (m, 1H)，1.30 – 1.24 (m, 1H). **^{13}C NMR (100 MHz, Chloroform-*d*)** δ 169.26, 142.13, 133.25, 128.12, 124.01, 123.75, 115.92, 72.33, 69.72, 54.25, 50.67, 50.44, 43.14, 42.05, 38.88, 31.92, 32.41, 26.32, 21.91. $[a]_D^{20}$ = -26.3 (*c* 0.8, MeOH). Literature: $[a]_D^{20}$ = -24 (*c* 0.23, MeOH)[2]; $[a]_D^{20}$ = -27.6 (*c* 0.03, MeOH)[3]; **IR (neat, cm^{-1})** 2890, 1666, 1563, 1469, 1393, 1277, 1139, 962, 751, 509; **HRMS (ESI)** ***m/z*** [M + H]$^+$ calcd. for $C_{19}H_{23}N_2O^+$ 295.1810, found 295.1797.

Comparison of ^{1}H NMR ($CDCl_3$) chemical shifts (ppm)		
Synthetic (-)-strempeliopine[2] (400 MHz)	synthetic (-)-strempeliopine[3] (600 MHz)	Our synthetic (-)-strempeliopine (400 MHz)
1.28 (td, *J* = 13.2, 4.4 Hz, 1H)	1.28 (td, *J* = 13.3, 4.7 Hz, 1H)	1.30 - 1.24 (m, 1H)
1.53 - 1.45 (m, 1H)	1.53 - 1.47 (m, 1H)	1.53 - 1.46 (m, 1H)
1.59 (d, *J* = 12.8 Hz, 1H)	1.59 (ddd, *J* = 13.7, 4.8, 2.4 Hz, 1H)	1.59 (ddd, *J* = 13.6, 4.8, 2.4 Hz, 1H)
1.74 (d, *J* = 13.6 Hz, 1H)	1.73 (dt, *J* = 13.7, 3.4 Hz, 1H)	1.74 - 1.70 (m, 1H)
1.92 - 1.77 (m, 1H)	1.85 (qt, *J* = 13.0, 4.1 Hz, 1H)	1.90 - 1.81 (m, 1H)
2.00 - 1.93 (m, 1H)	2.01 - 1.93 (m, 1H)	2.01 - 1.92 (m, 1H)
2.03 (s, 1H)	2.03 (s, 1H)	2.03 (s, 1H)
2.07 - 2.04 (m, 1H)	2.06 - 2.01 (m, 1H)	2.06 - 2.03 (m, 1H)
2.14 - 2.07 (m, 1H)	2.09 (dq, *J* = 14.1, 6.2 Hz, 1H)	2.15 - 2.07 (m, 1H)

2.24 - 2.17 (m, 1H)	2.26 - 2.19 (m, 1H)	2.24 - 2.18 (m, 1H)
2.35 - 2.25 (m, 3H)	2.35 - 2.26 (m, 3H)	2.34 - 2.25 (m, 3H)
2.46 (d, *J* = 18.4 Hz, 1H)	2.46 (dd, *J* = 18.2, 2.4 Hz, 1H)	2.46 (dd, *J* = 18.4, 2.4 Hz, 1H)
2.63 (d, *J* = 18.4 Hz, 1H)	2.62 (d, *J* = 18.2 Hz, 1H)	2.62 (d, *J* = 18.2 Hz, 1H)
2.86 (d, *J* = 10.8 Hz, 1H)	2.85 (dt, *J* = 11.2, 3.2 Hz, 1H)	2.90 - 2.81 (m, 1H)
2.97 (dt, *J* = 11.6, 6.8 Hz, 1H)	2.96 (ddd, *J* = 11.2, 7.9, 5.9 Hz, 1H)	2.96 (ddd, *J* = 11.6, 6.0, 2.0 Hz, 1H)
3.25 (t, *J* = 7.2 Hz, 1H)	3.25 (t, *J* = 7.2 Hz, 1H)	3.25 (t, *J* = 7.2 Hz, 1H)
7.06 (t, *J* = 7.6 Hz, 1H)	7.05 (td, *J* = 7.4, 1.1 Hz, 1H)	7.05 (td, *J* = 7.4, 1.1 Hz, 1H)
7.16 (d, *J* = 7.2 Hz, 1H)	7.16 (d, *J* = 7.4 Hz, 1H)	7.16 (d, *J* = 7.6 Hz, 1H)
7.22 (t, *J* = 7.6 Hz, 1H)	7.22 (t, *J* = 7.7 Hz, 1H)	7.22 (t, *J* = 7.8, Hz, 2H)
8.05 (d, *J* = 8.0 Hz, 1H)	8.05 (d, *J* = 8.0 Hz, 1H)	8.04 (d, J = 8.0 Hz, 1H)

Comparison of ^{13}C NMR ($CDCl_3$) chemical shifts (ppm)		
Synthetic (-)-strempeliopine[2] (151 MHz)	synthetic (-)-strempeliopine[3] (151 MHz)	Our synthetic (-)-strempeliopine (151 MHz)
169.3	169.2	169.3
142.3	142.2	142.1
133.3	133.3	133.3
128.2	128.1	128.1
124.1	124.0	124.0
123.8	123.7	123.8
116.0	115.9	115.9
72.4	72.4	72.3
69.8	69.8	69.7
54.4	54.3	54.2
50.38	50.7	50.7
50.5	50.5	50.5
43.2	43.2	43.2
42.2	42.1	42.1
39.0	38.9	38.9
32.0	32.0	32.0
31.5	31.5	31.4
26.4	26.4	26.4
22.0	22.0	22.0

3. Supplemental References

1. H.Adachi, K. K. Palaniappan, A. A. Ivanov, N. Bergman, Z. G. Gao and K. A. Jacobson, *J. Med. Chem.* 2007, **50**, 1810.
2. Q. Zhou, X. Dai, H. Song, H. He, X. Wang, X. Liu and Y. Qin, *Chem. Commun.*, 2018, **54**, 9510.
3. X. Zeng and D. L. Boger, *J. Am. Chem. Soc.* 2021, **143**, 12412.

4. NMR Spectra

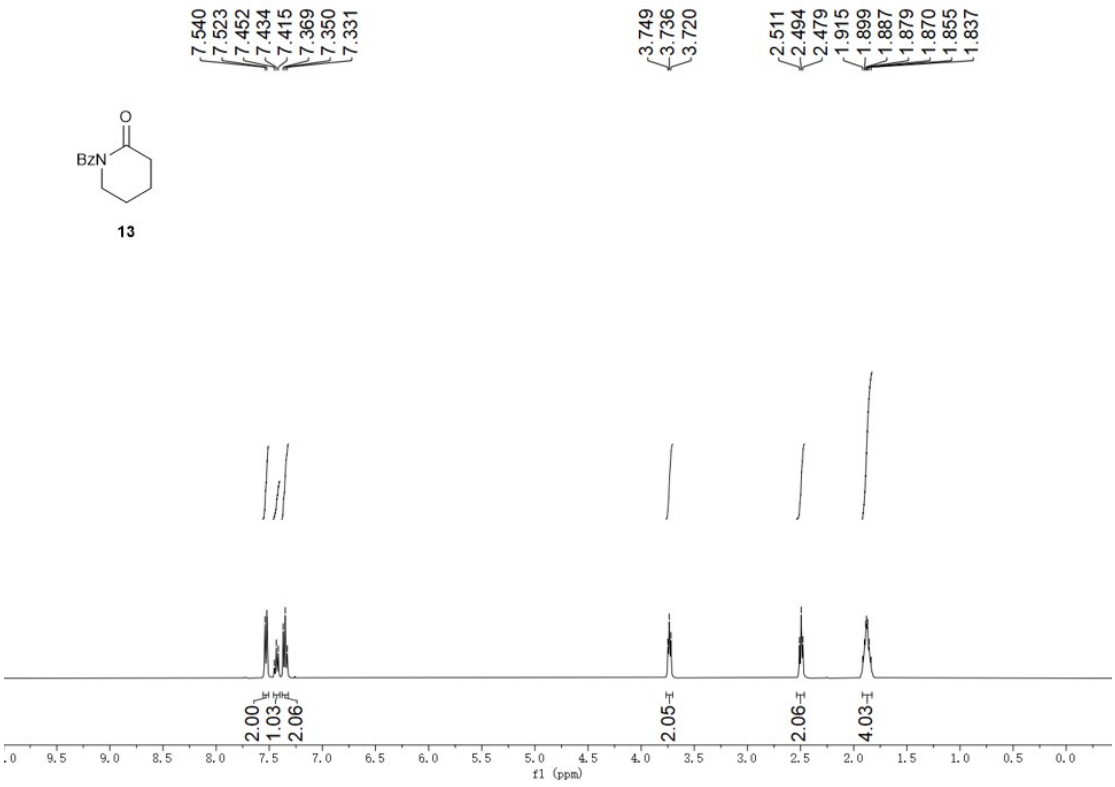


Figure S1: ^{1}H NMR spectrum of **13**

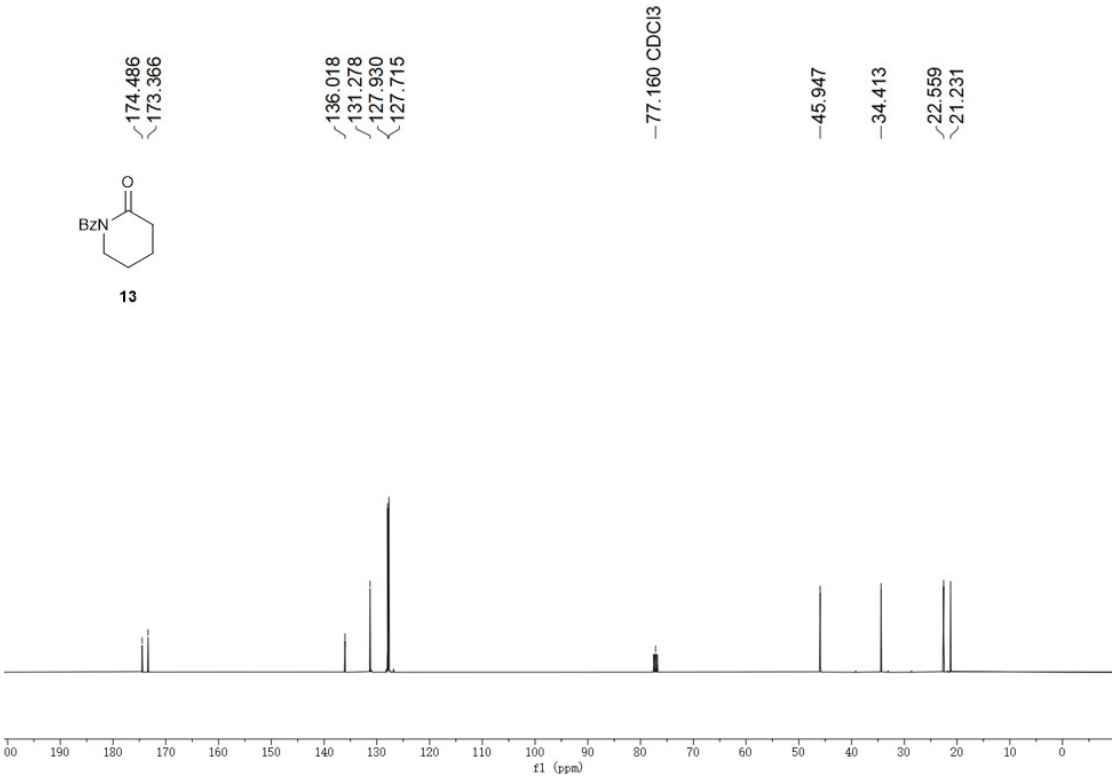


Figure S2: ^{13}C NMR spectrum of **13**

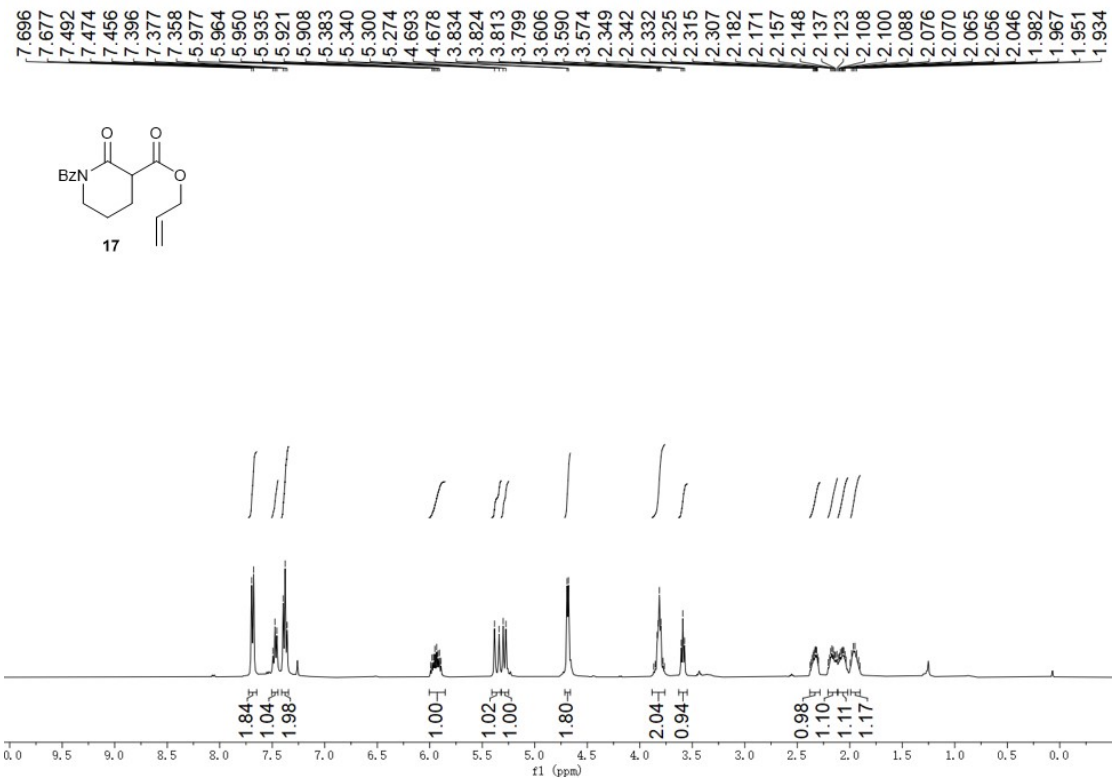


Figure S3: ^{1}H NMR spectrum of **17**

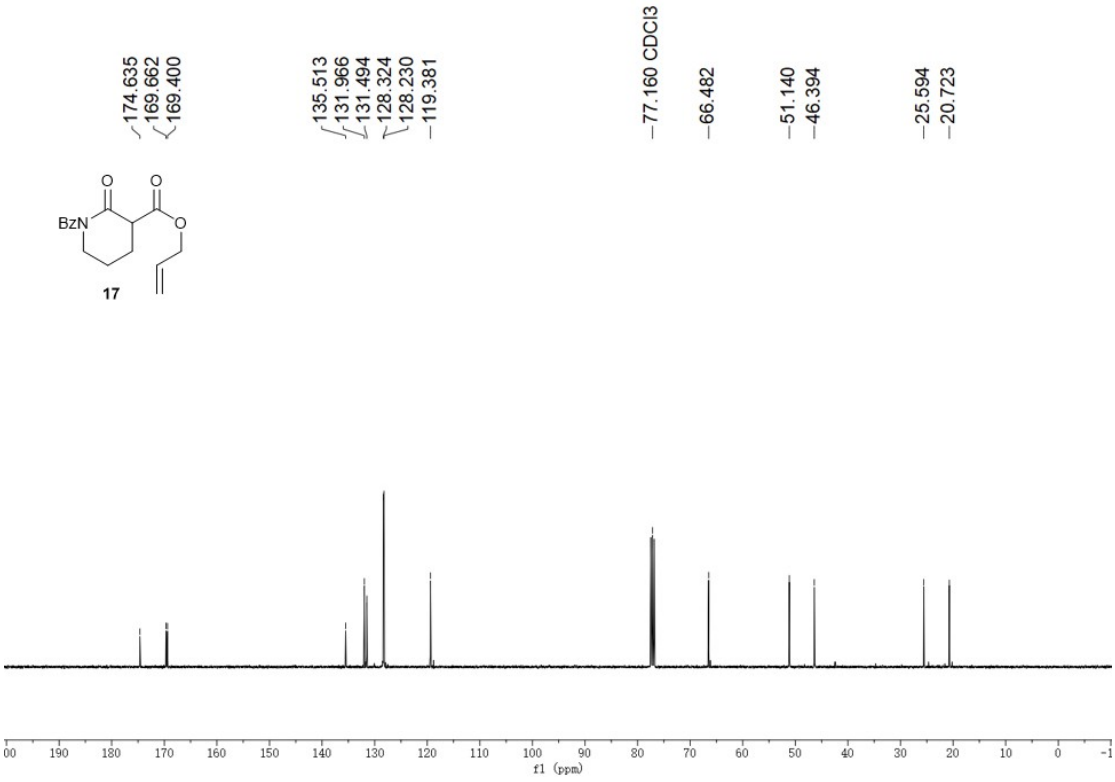


Figure S4: ^{13}C NMR spectrum of **17**

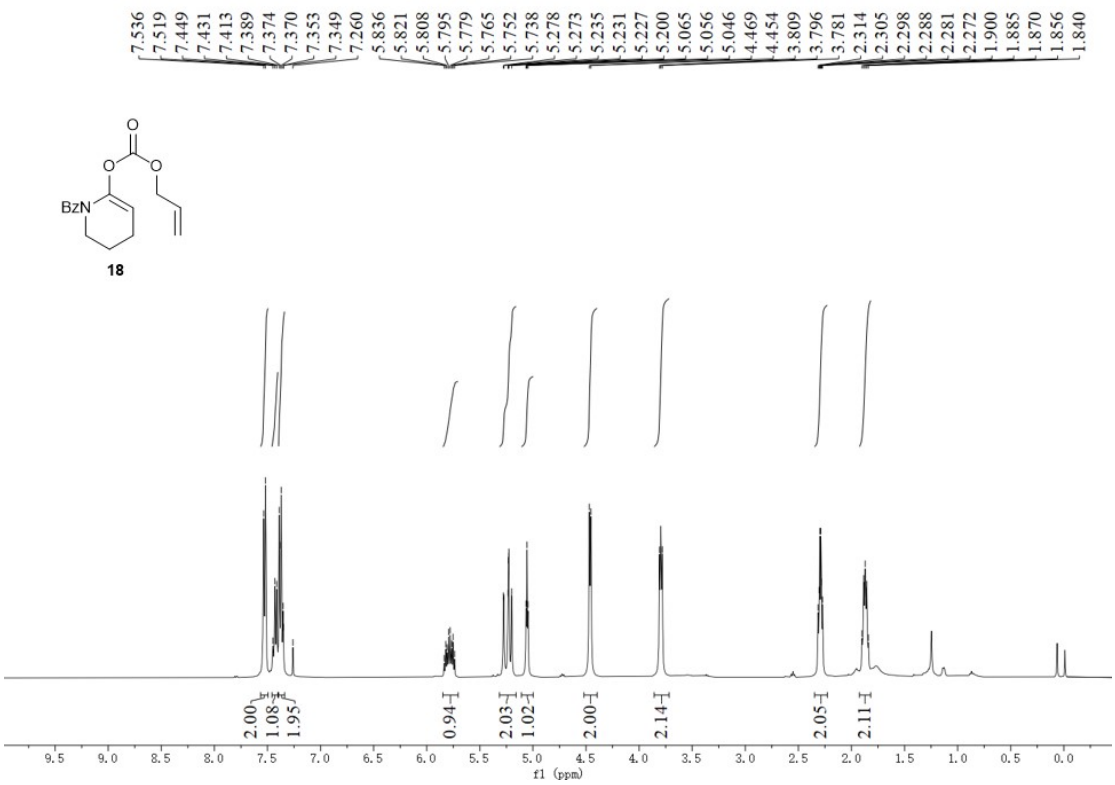


Figure S5: ^{1}H NMR spectrum of **18**

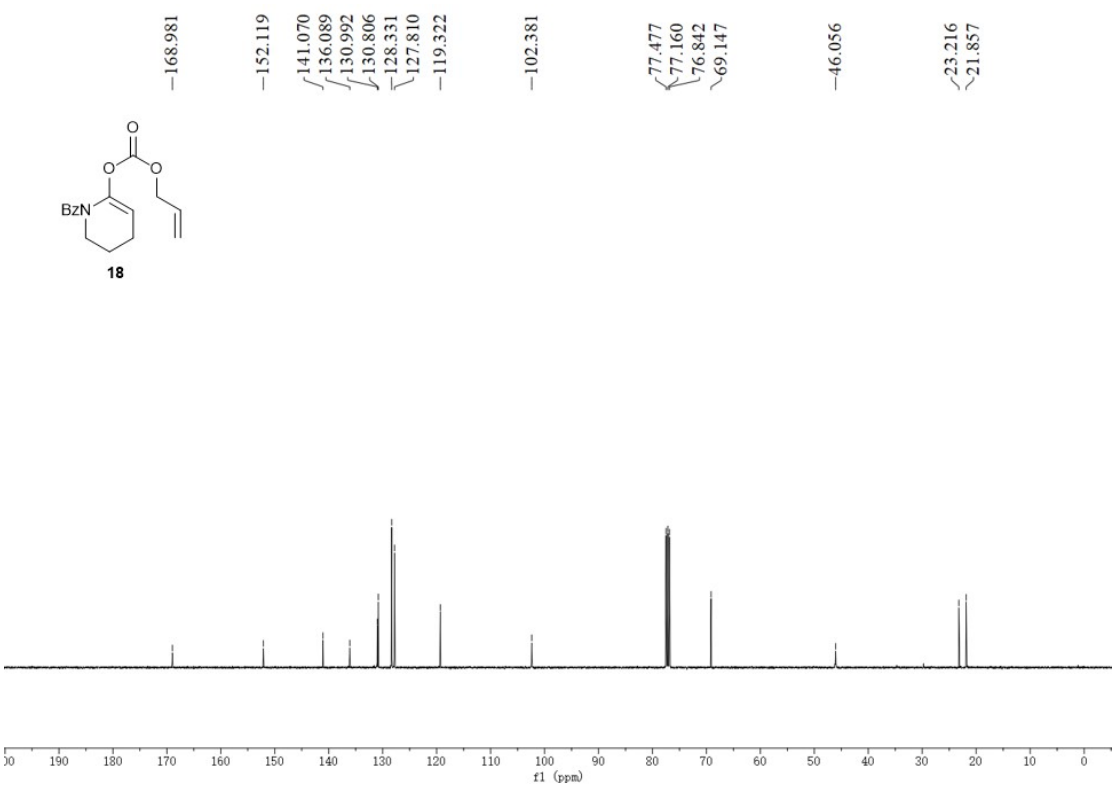


Figure S6: ^{13}C NMR spectrum of **18**

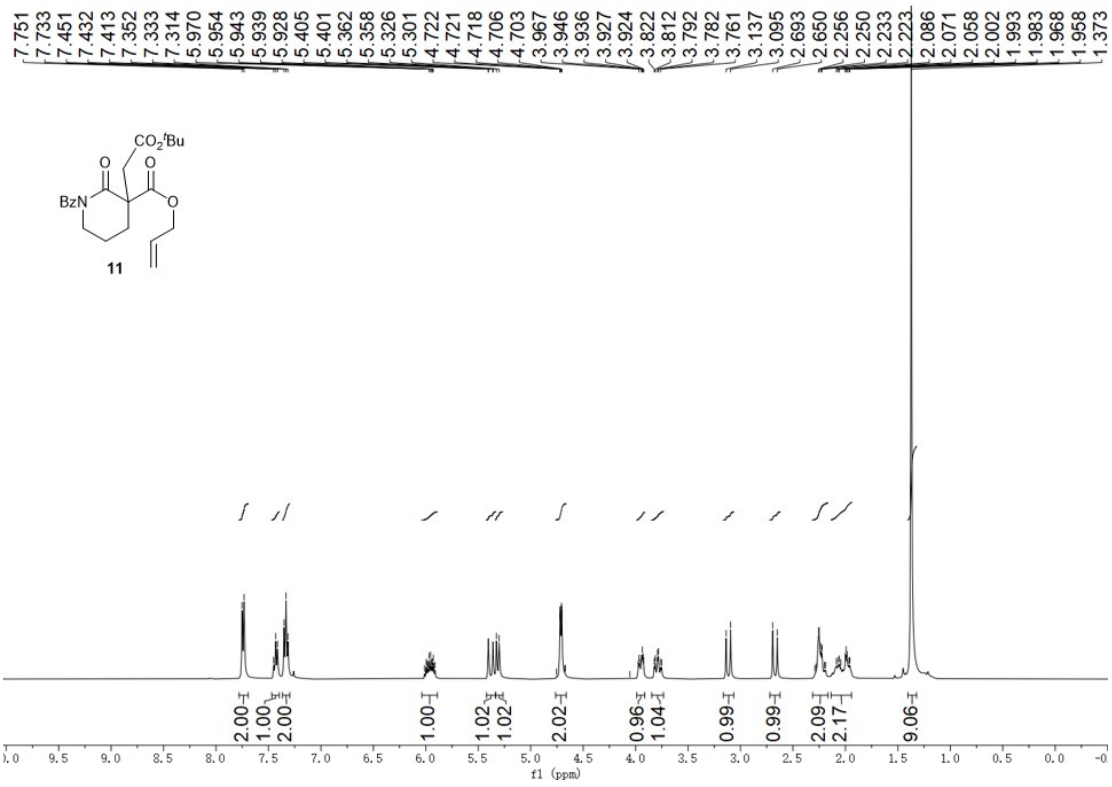


Figure S7: ^{1}H NMR spectrum of **11**

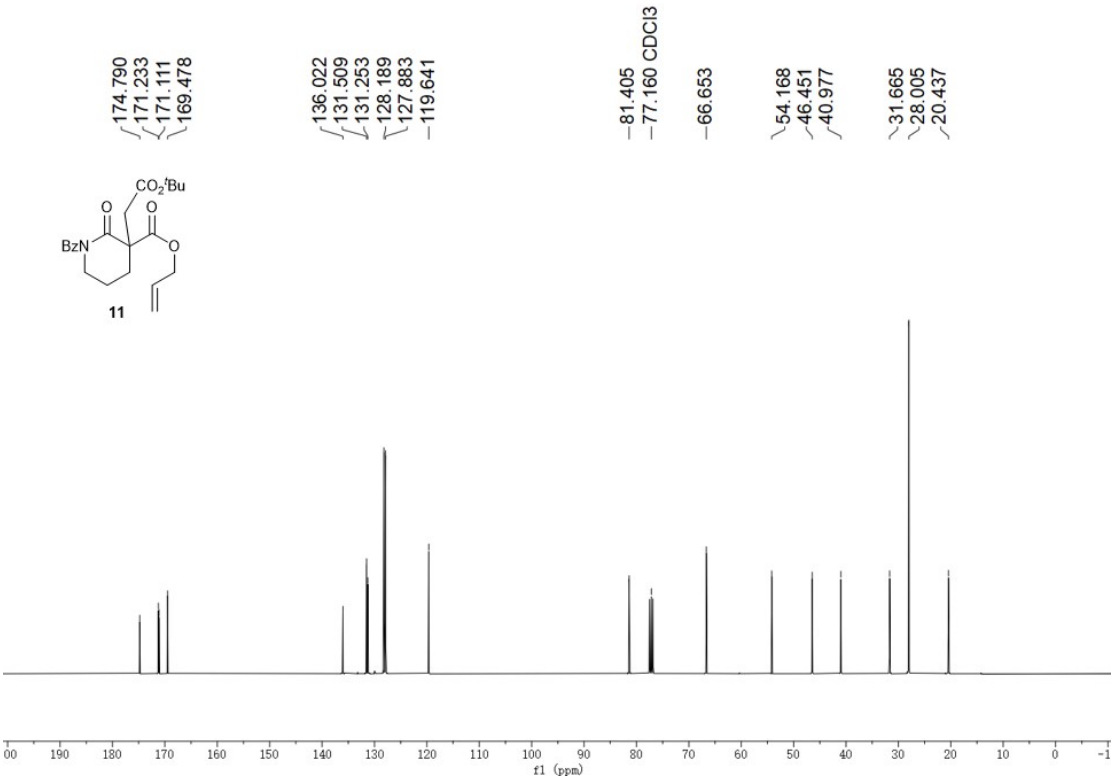


Figure S8: ^{13}C NMR spectrum of **11**

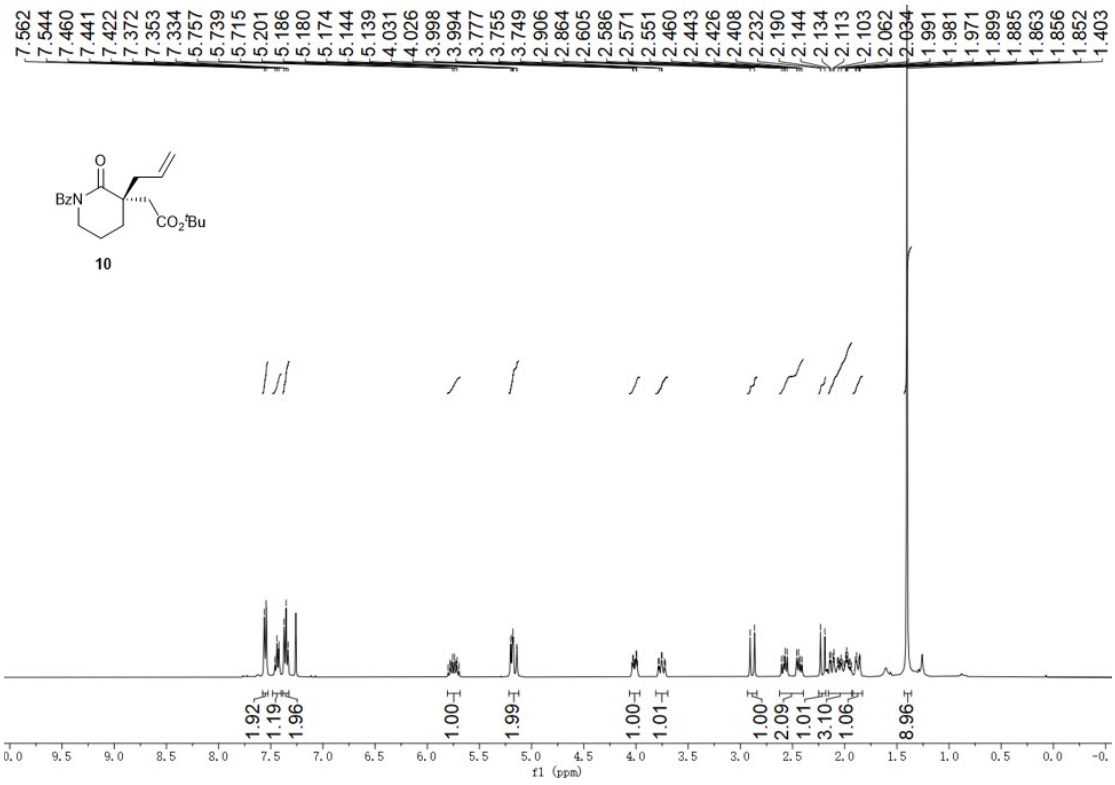


Figure S9: ^{1}H NMR spectrum of **10**

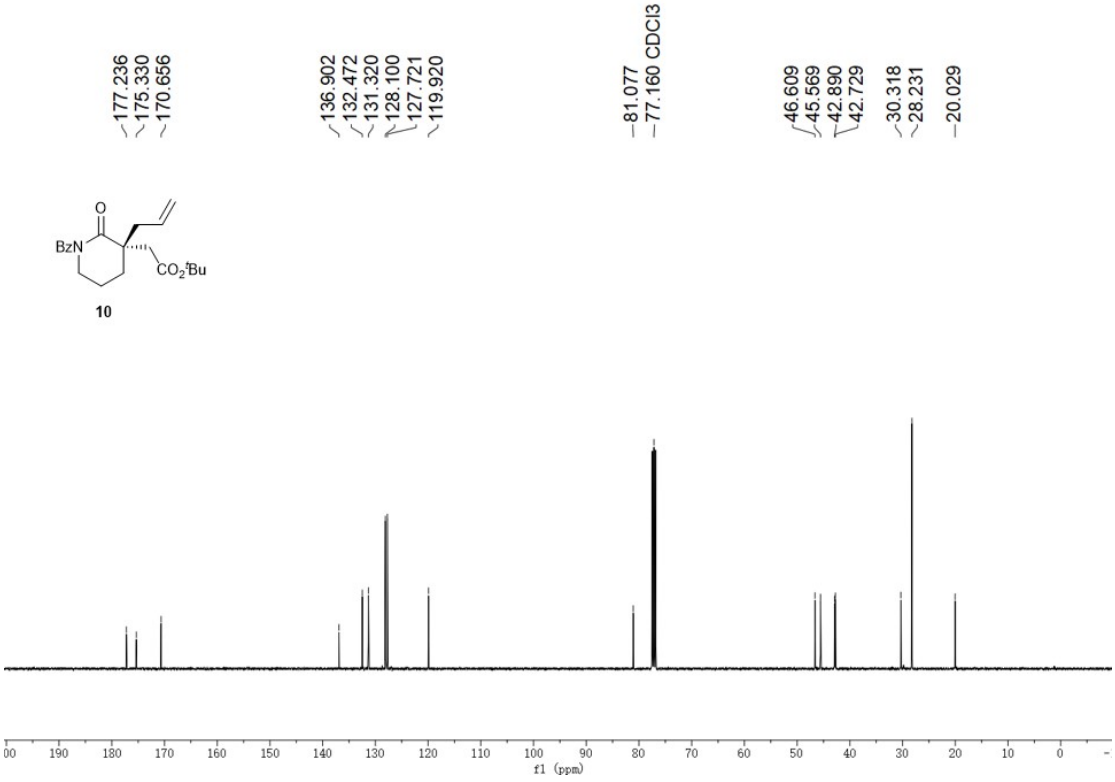


Figure S10: ^{13}C NMR spectrum of **10**

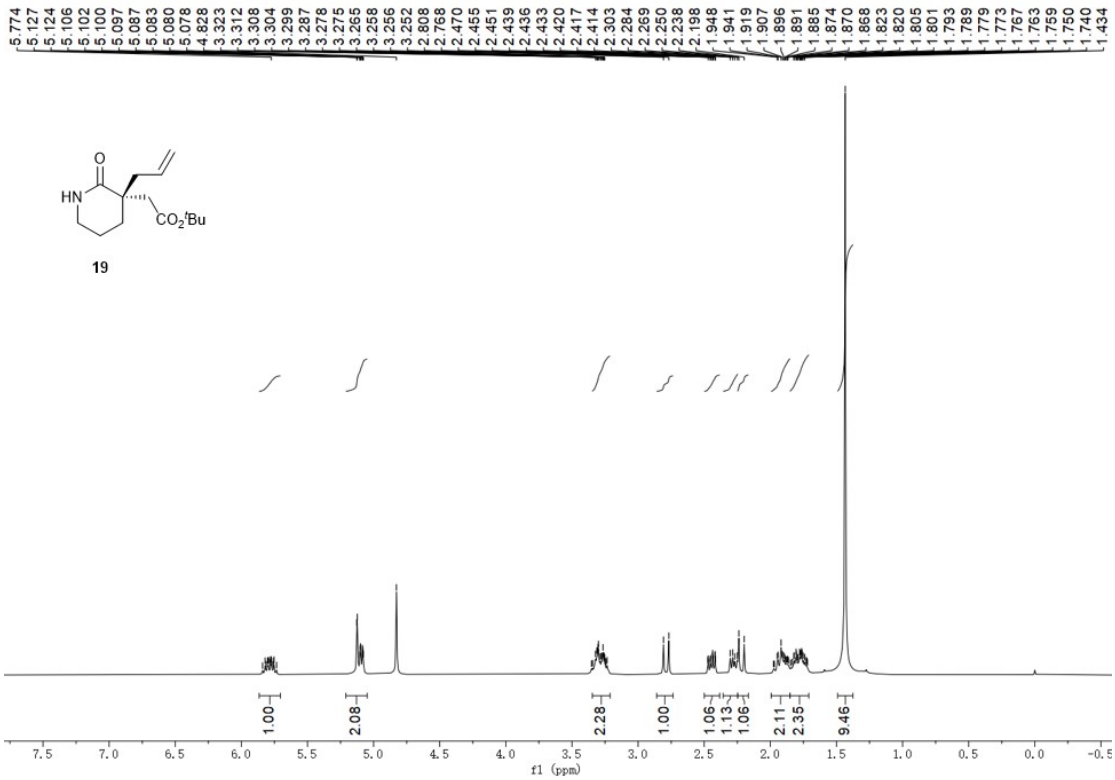


Figure S11: ^{1}H NMR spectrum of **19**

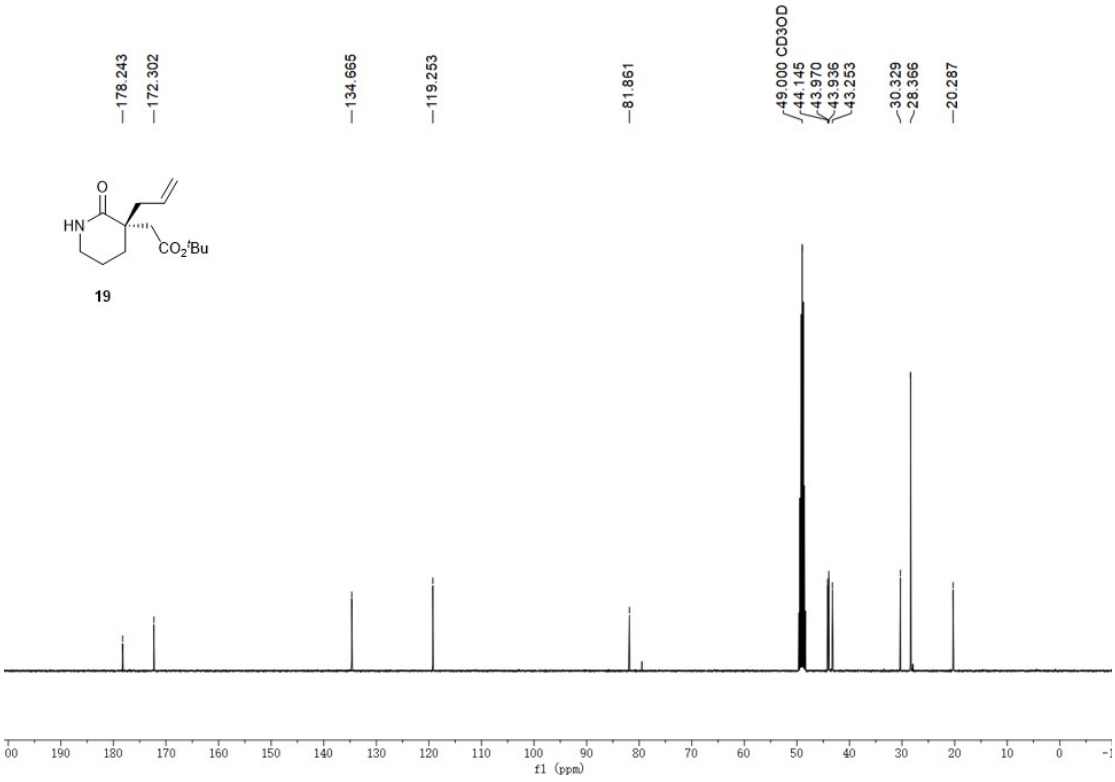


Figure S12: ^{13}C NMR spectrum of **19**

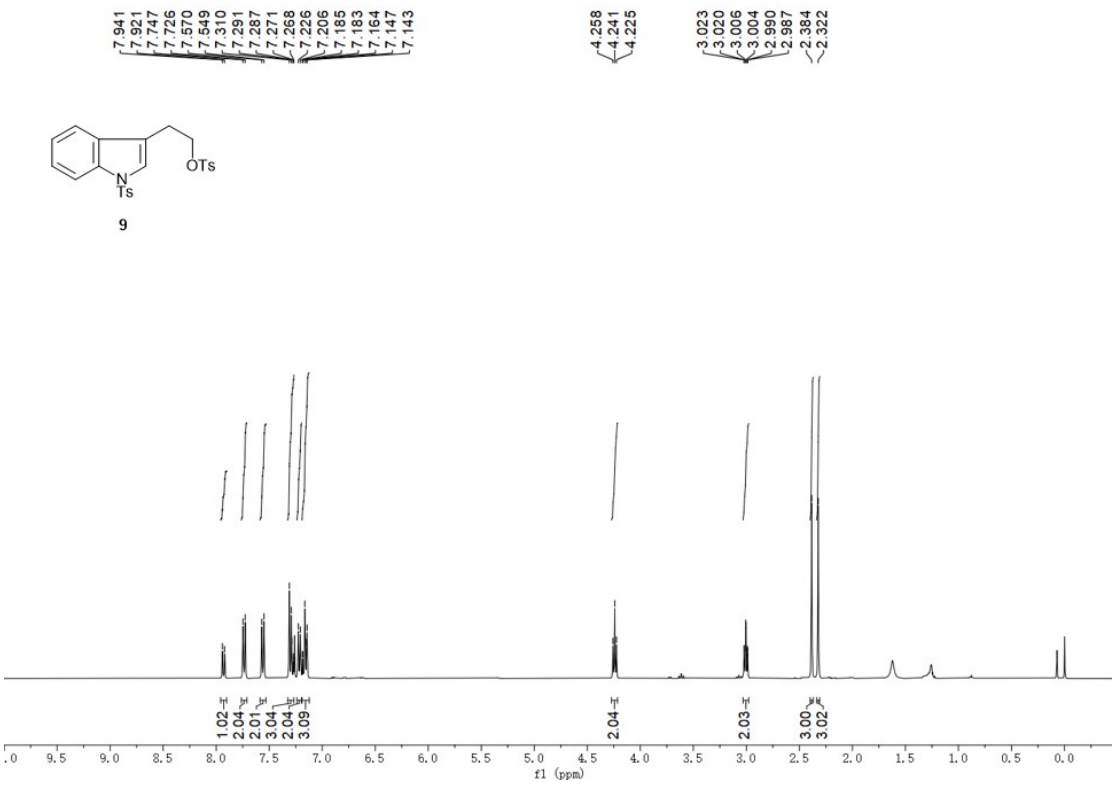


Figure S13: ^{1}H NMR spectrum of **9**

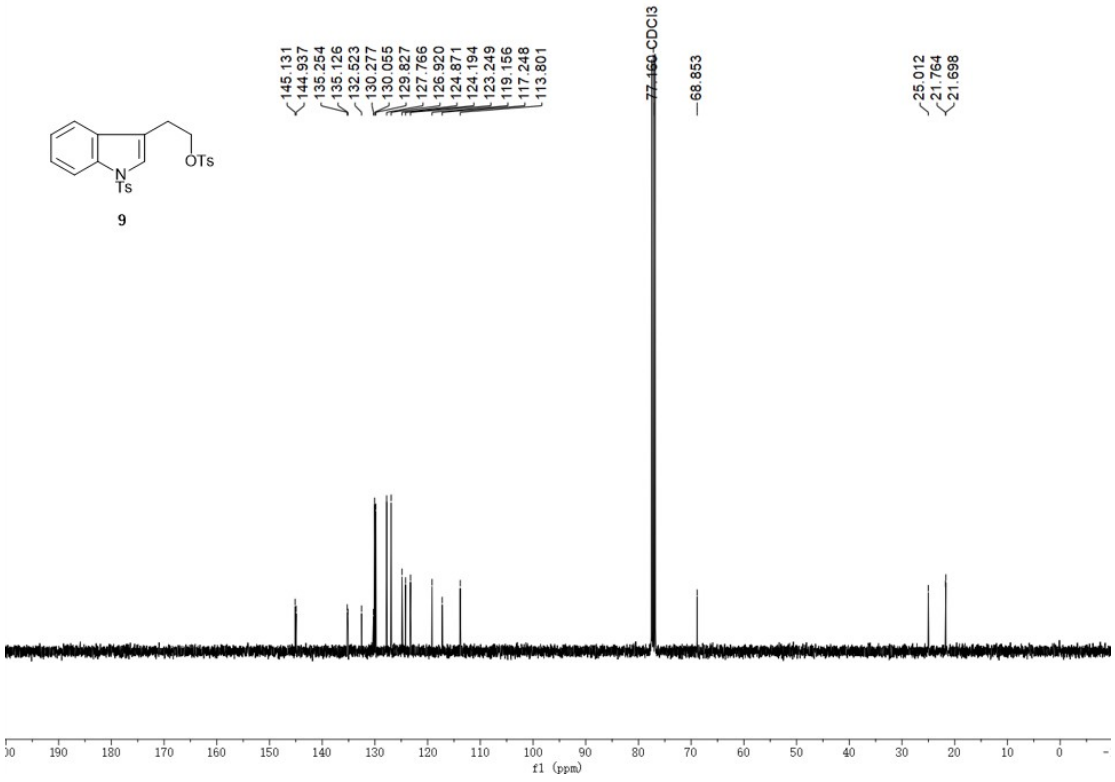


Figure S14: ^{13}C NMR spectrum of **9**

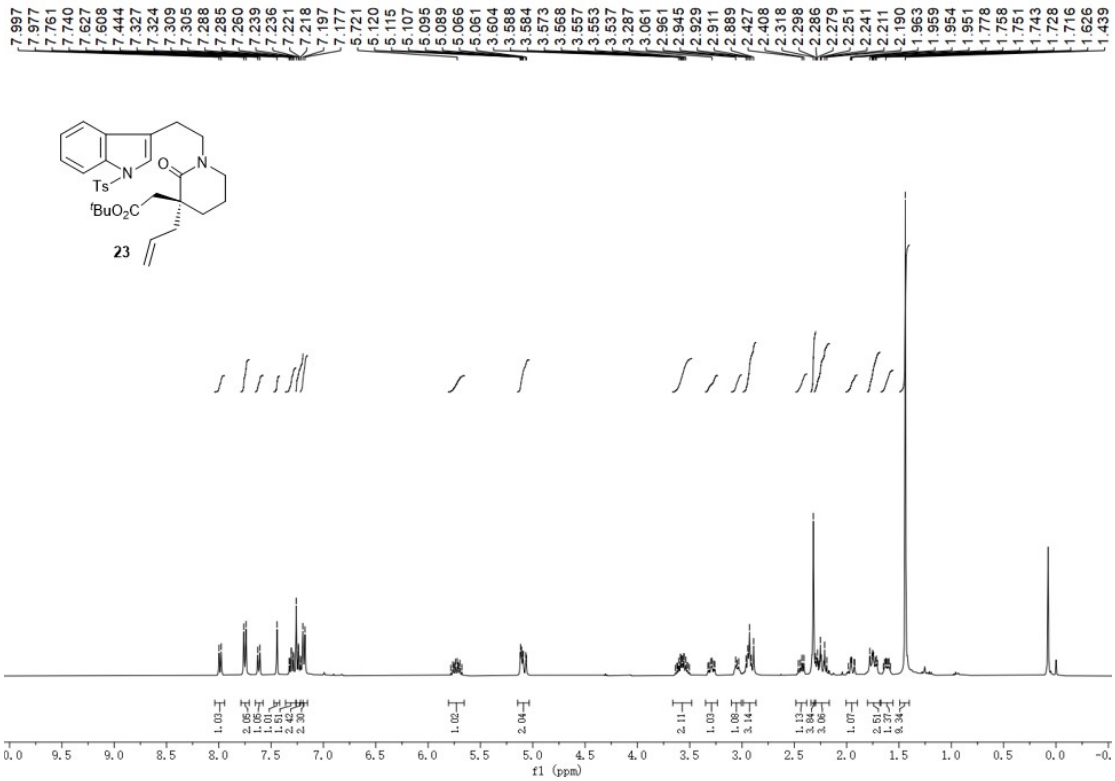


Figure S15: ^{1}H NMR spectrum of **23**

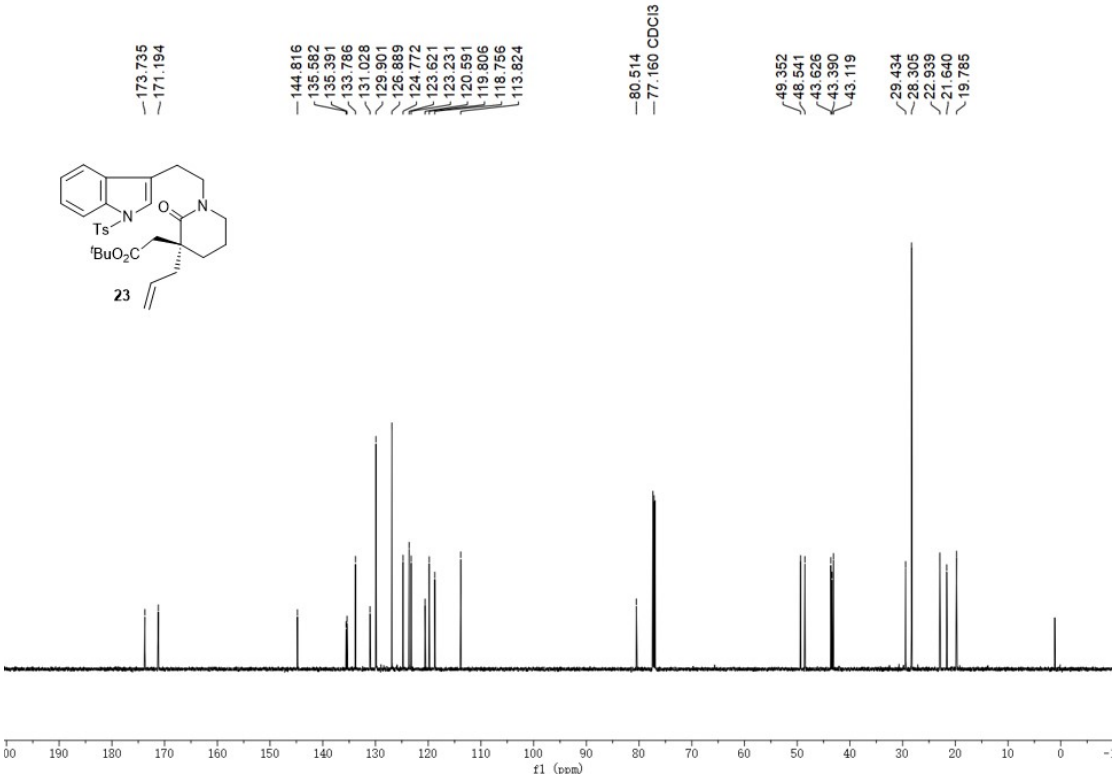


Figure S16: ^{13}C NMR spectrum of **23**

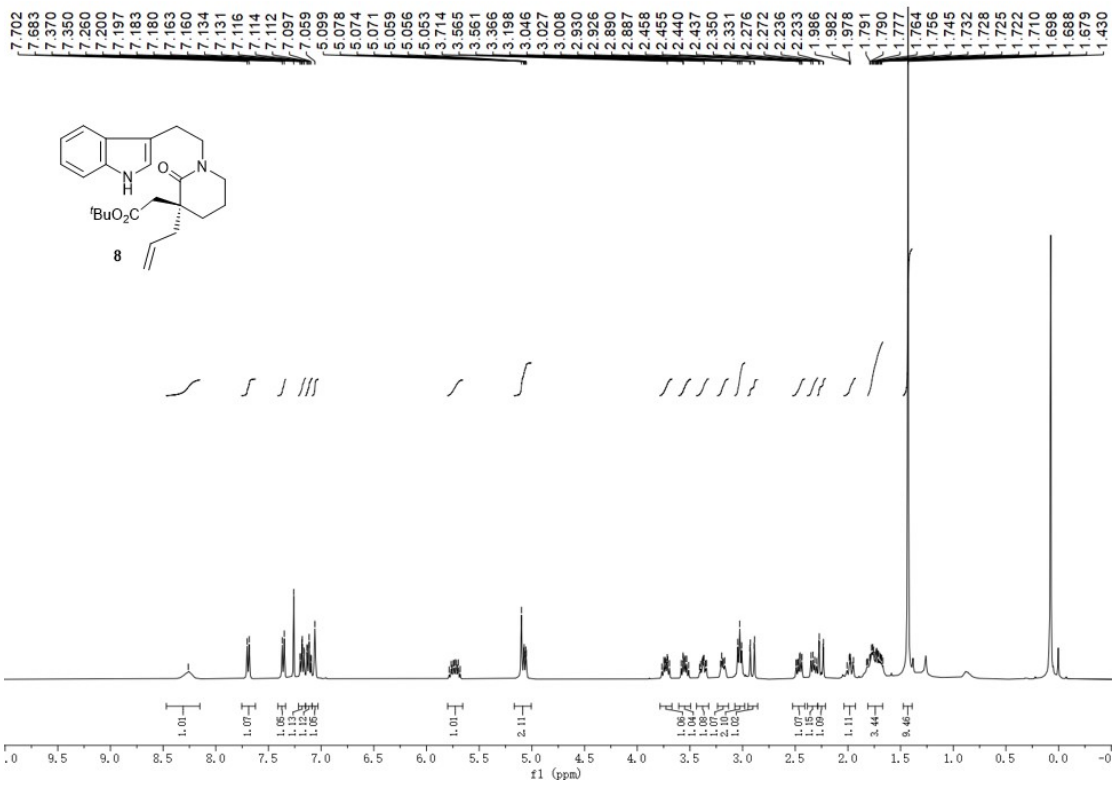


Figure S17: ^{1}H NMR spectrum of **8**

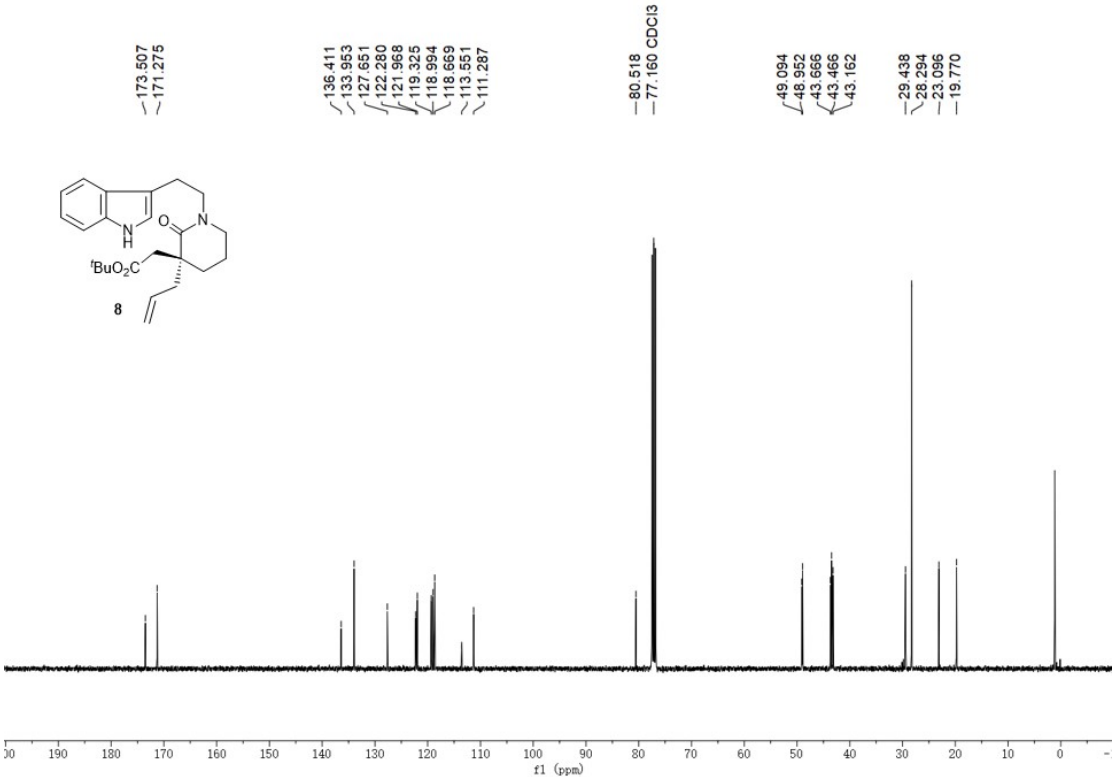


Figure S18: ^{13}C NMR spectrum of **8**

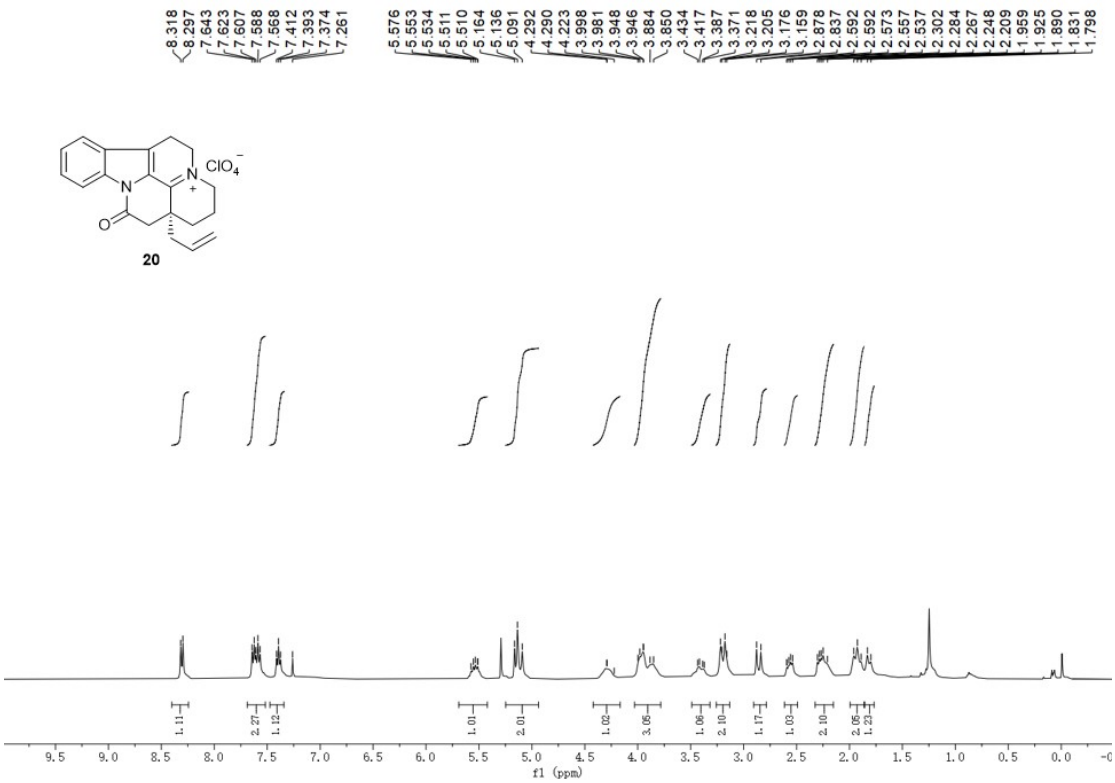


Figure S19: ^{13}C NMR spectrum of **20**

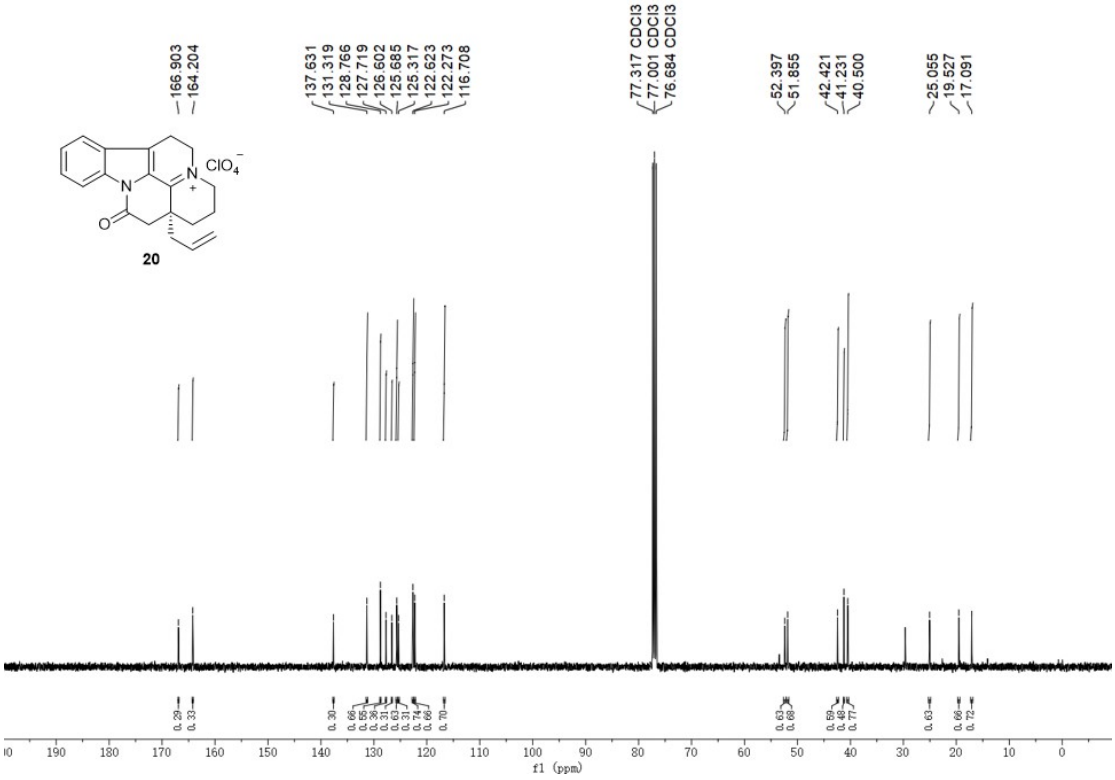


Figure S20: ^{13}C NMR spectrum of **20**

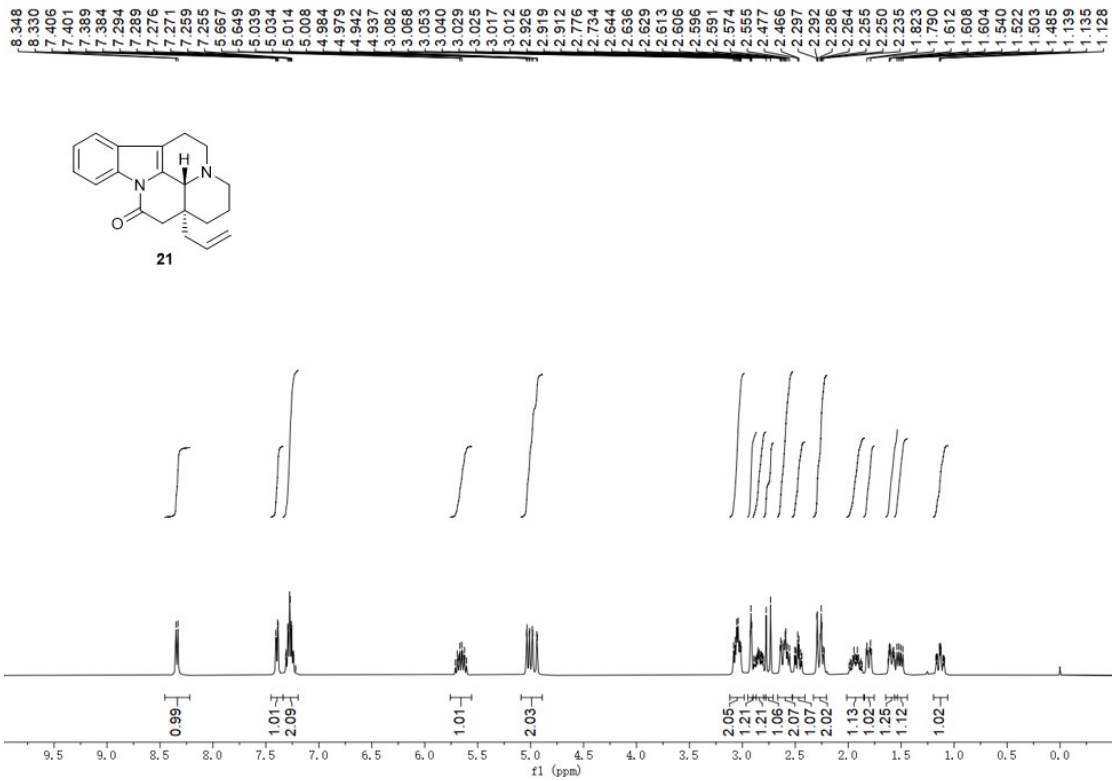


Figure S21: ^{1}H NMR spectrum of **21**

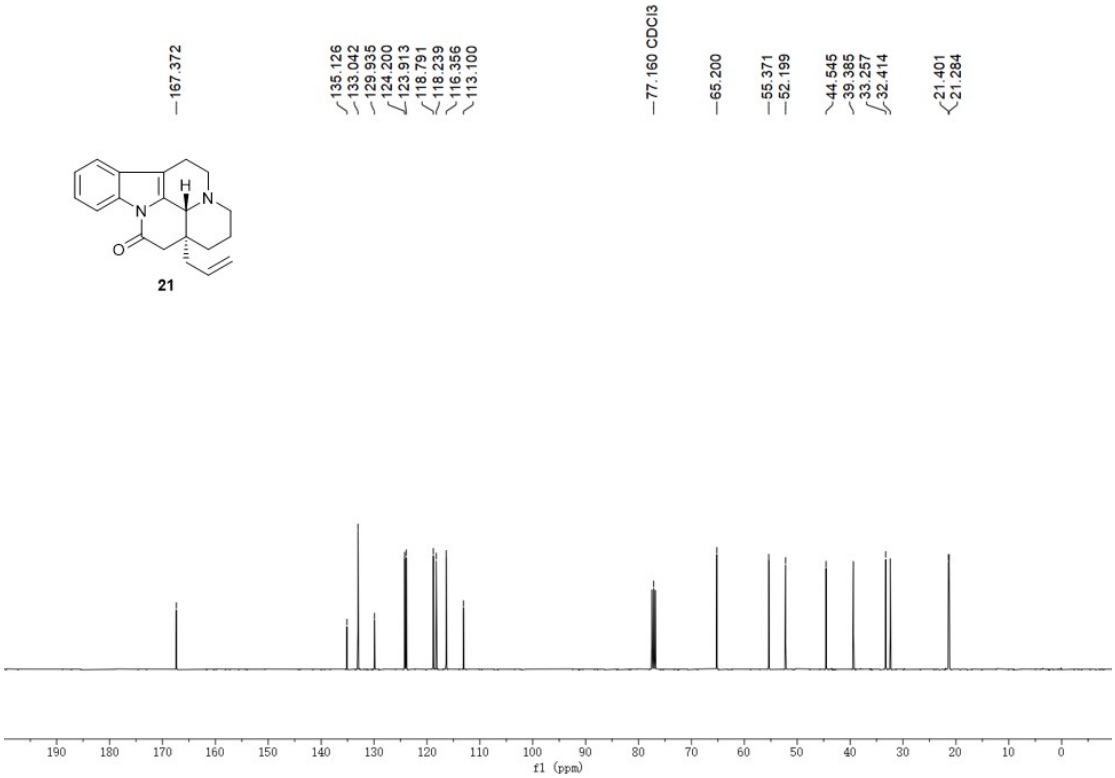


Figure S22: ^{13}C NMR spectrum of **21**

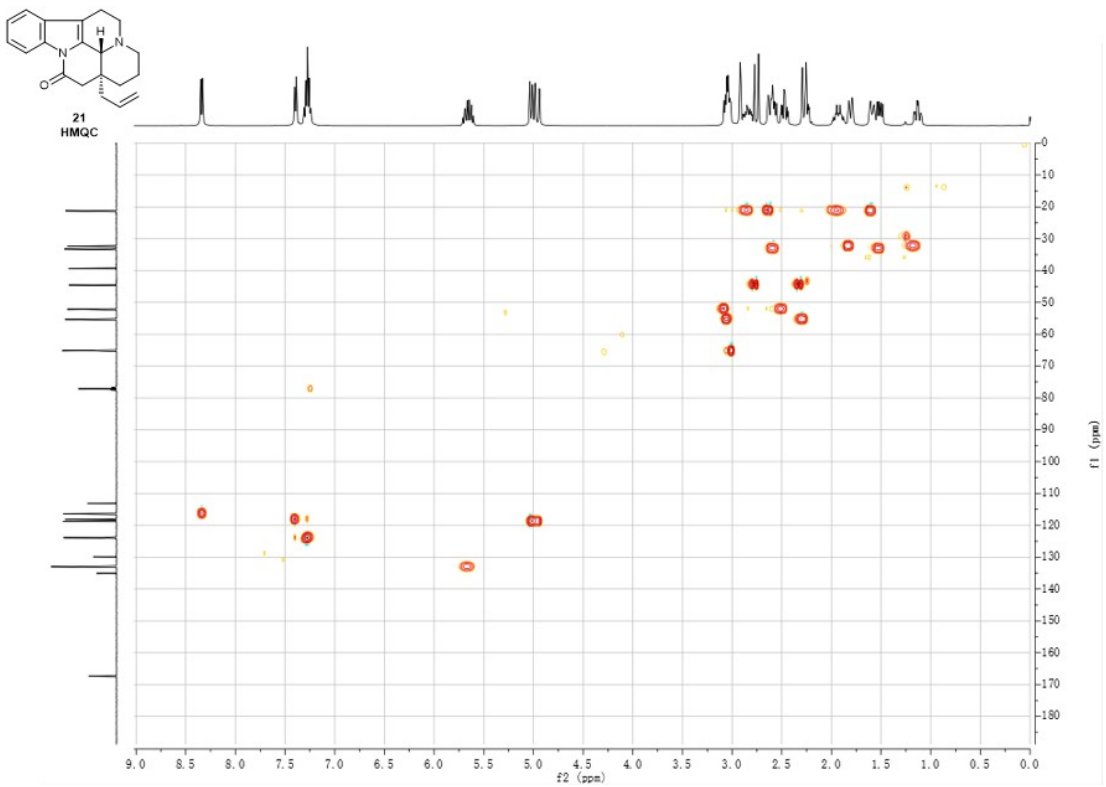


Figure S23: HMQC spectrum of **21**

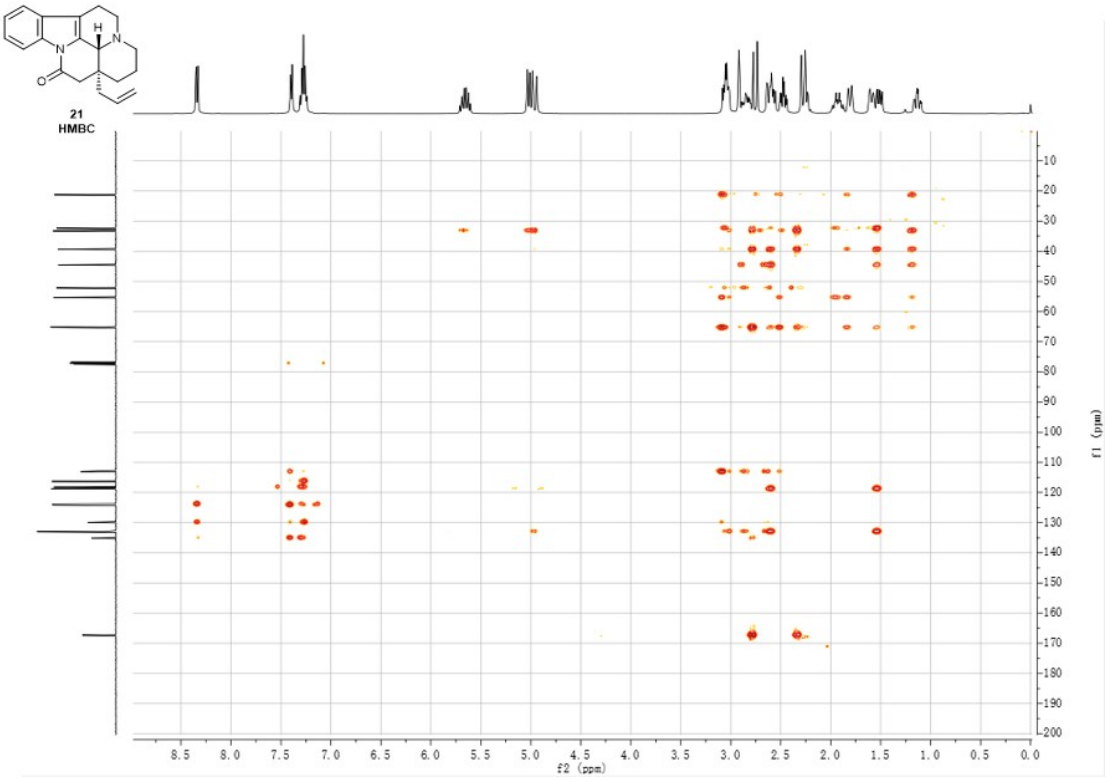


Figure S24: HMBC spectrum of **21**

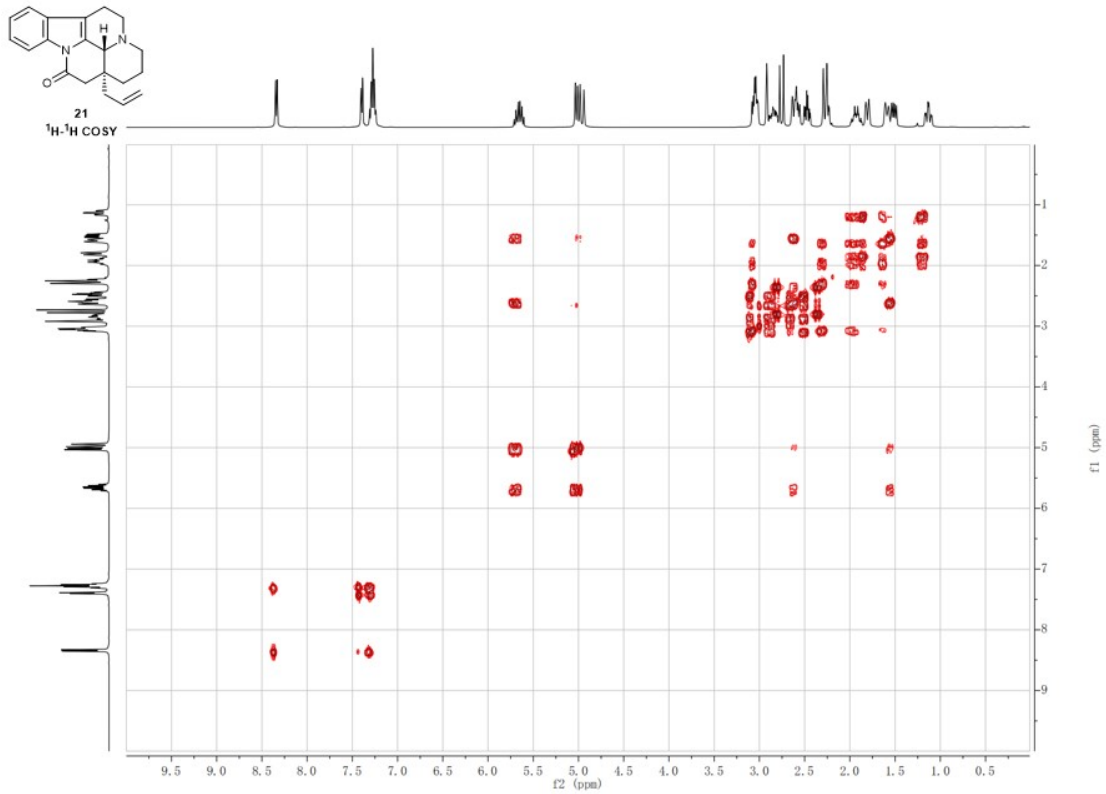


Figure S25: ^{1}H-^{1}H COSY spectrum of **21**

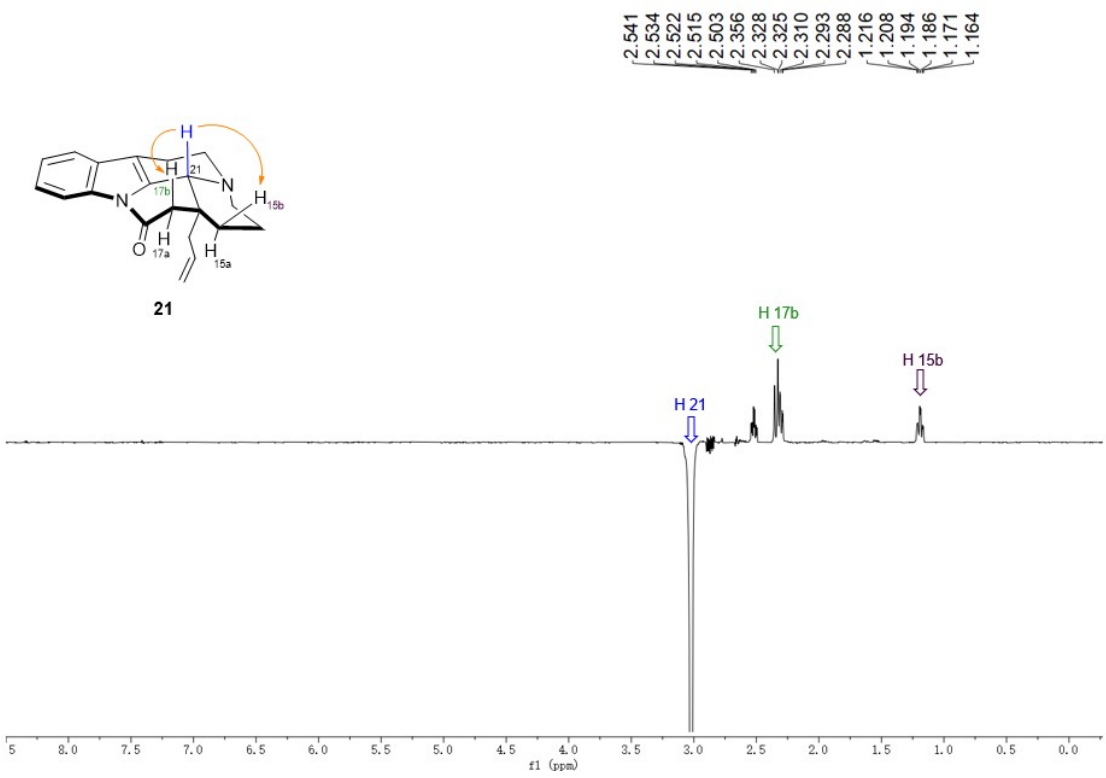


Figure S26: NOEds spectrum of **21**

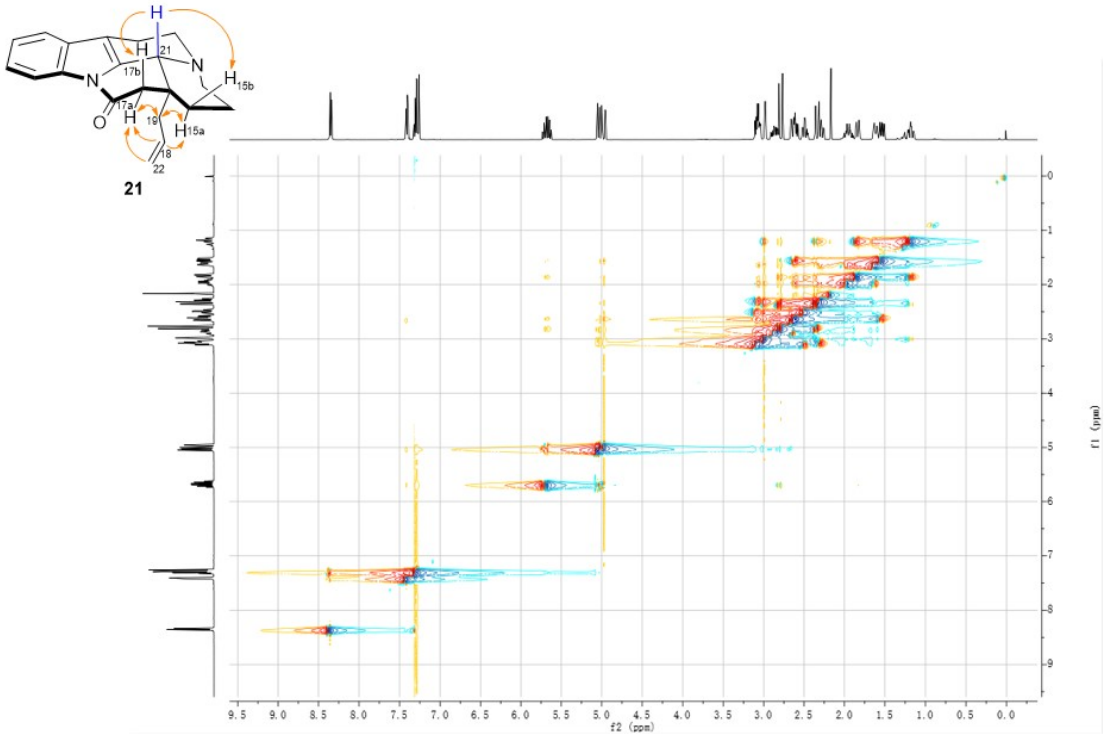


Figure S27: 2D NOESY spectrum of **21**

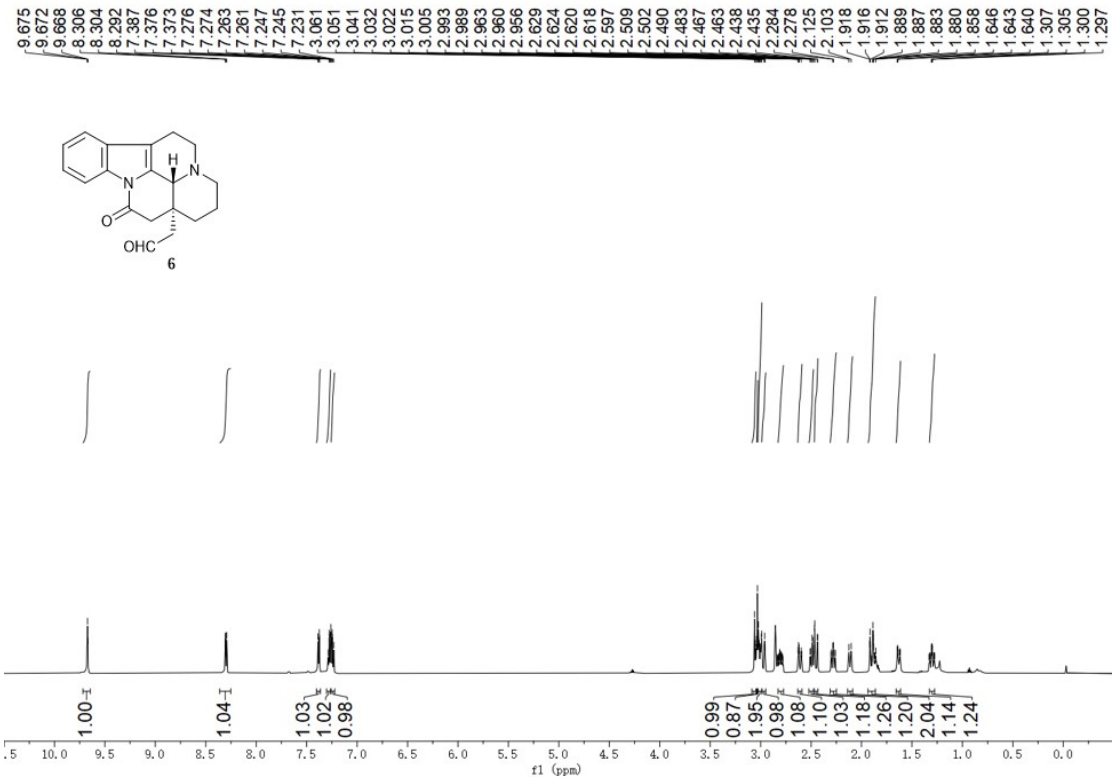


Figure S28: ^{1}H NMR spectrum of **6**

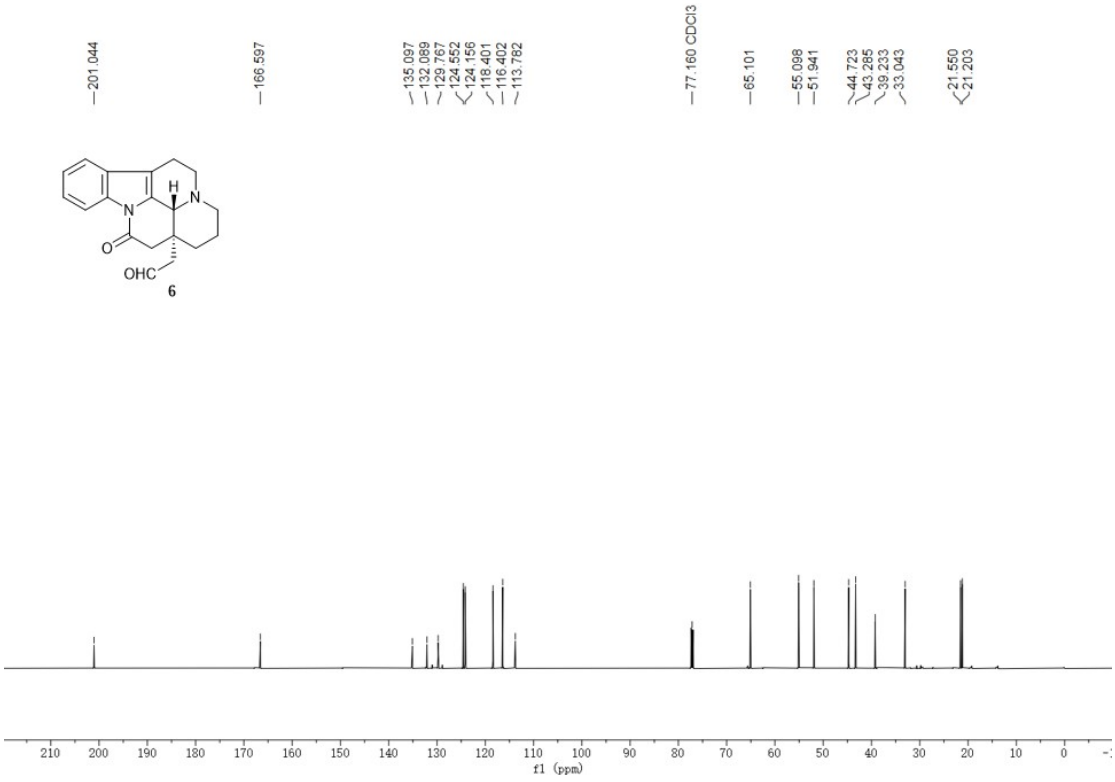


Figure S29: ^{13}C NMR spectrum of **6**

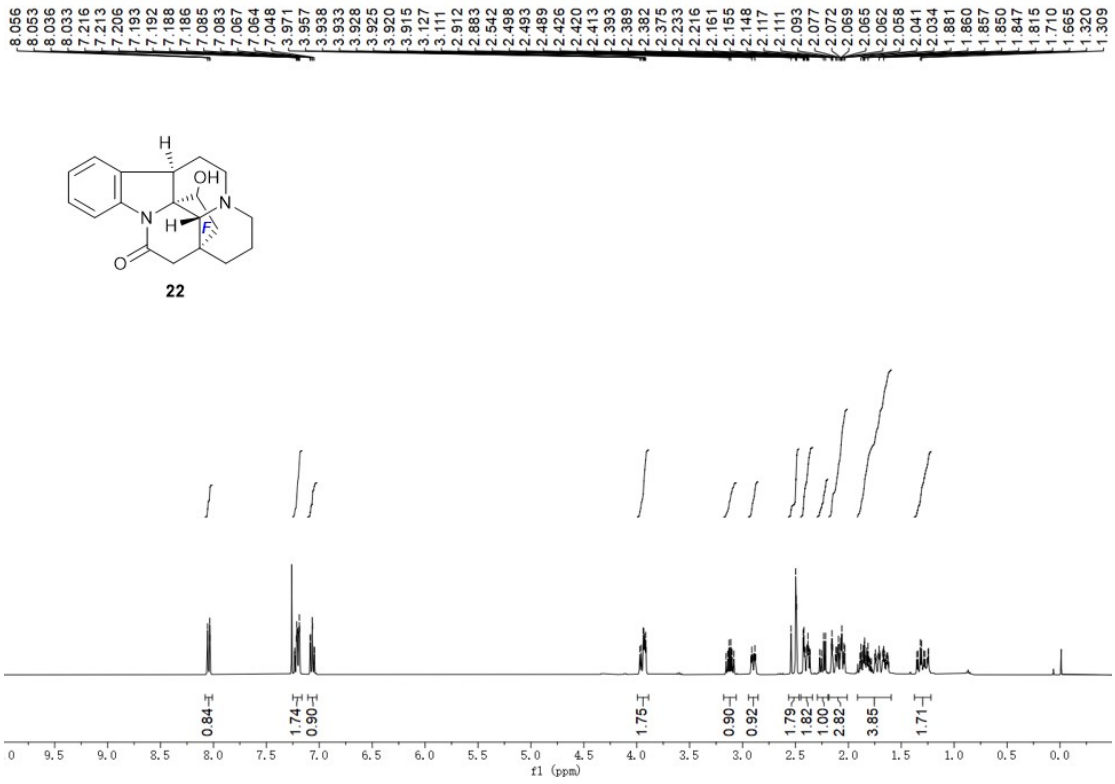


Figure S30: ^{1}H NMR spectrum of **22**

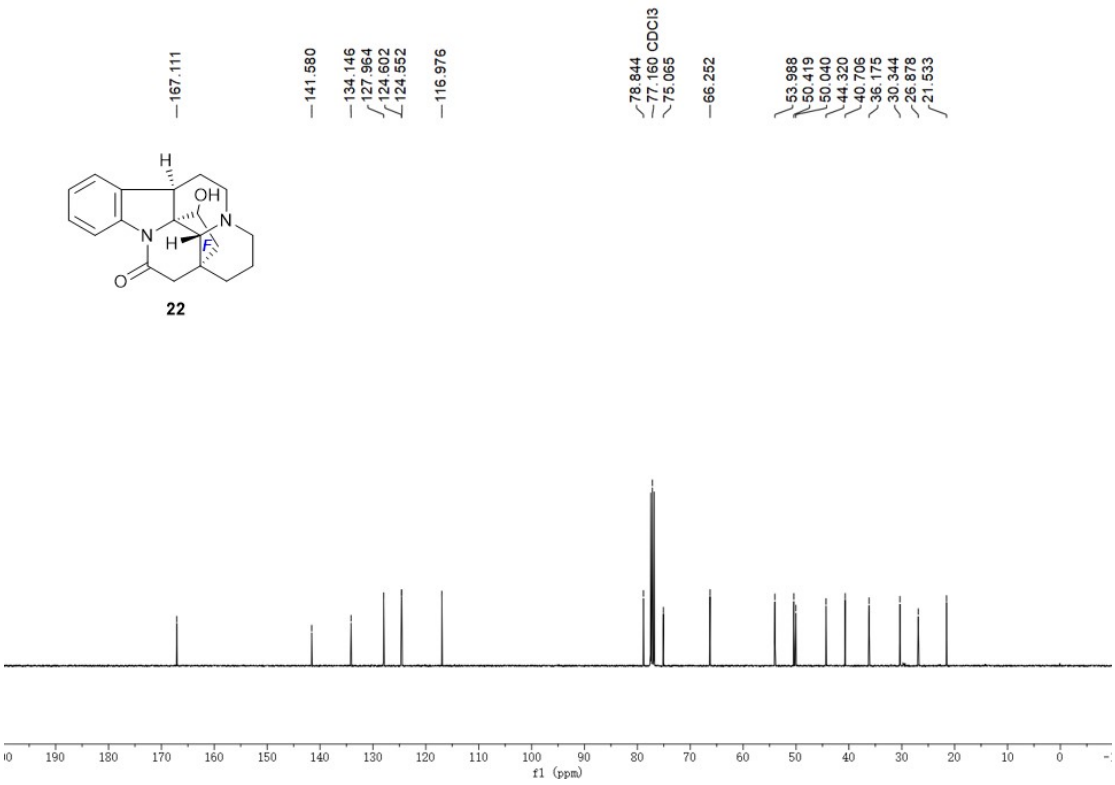


Figure S31: ^{13}C NMR spectrum of **22**

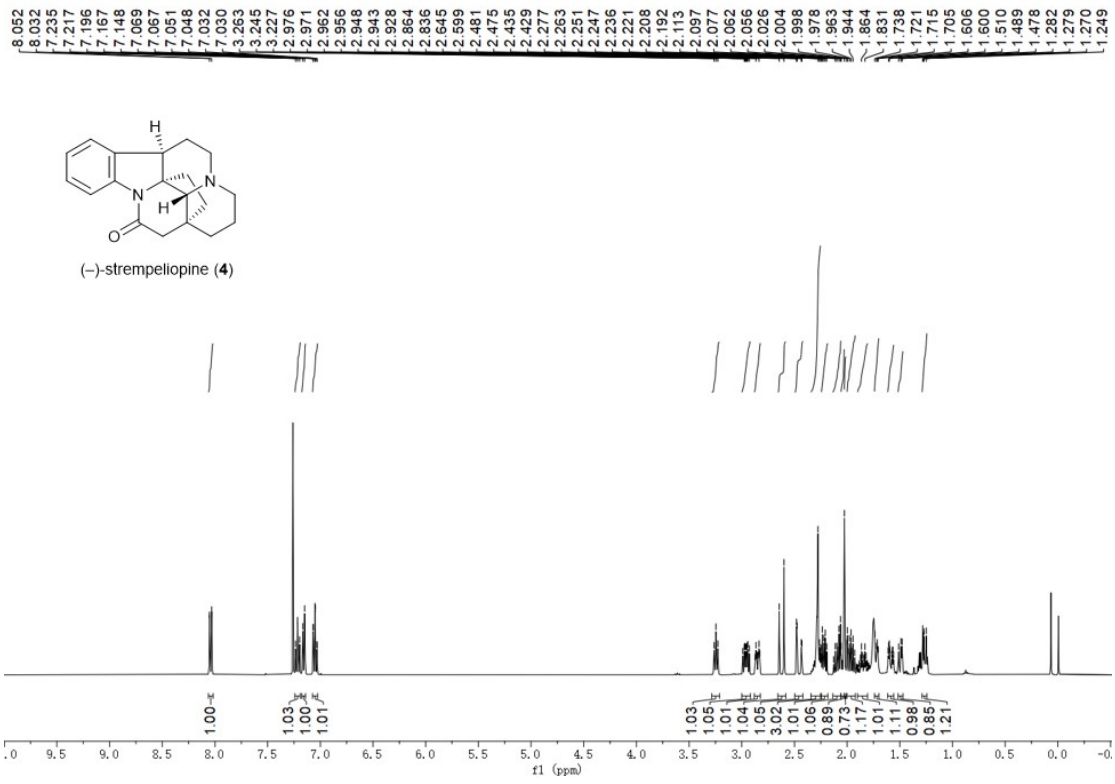


Figure S32: ^{1}H NMR spectrum of **4**

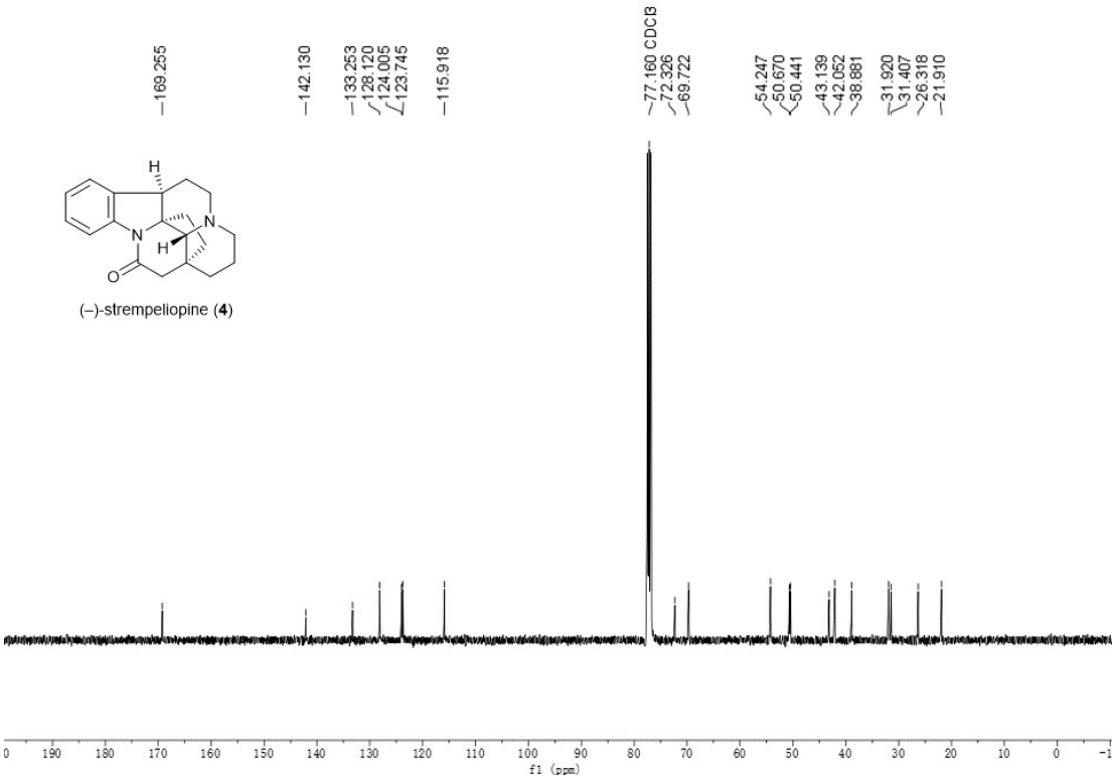


Figure S33: ^{13}C NMR spectrum of **4**

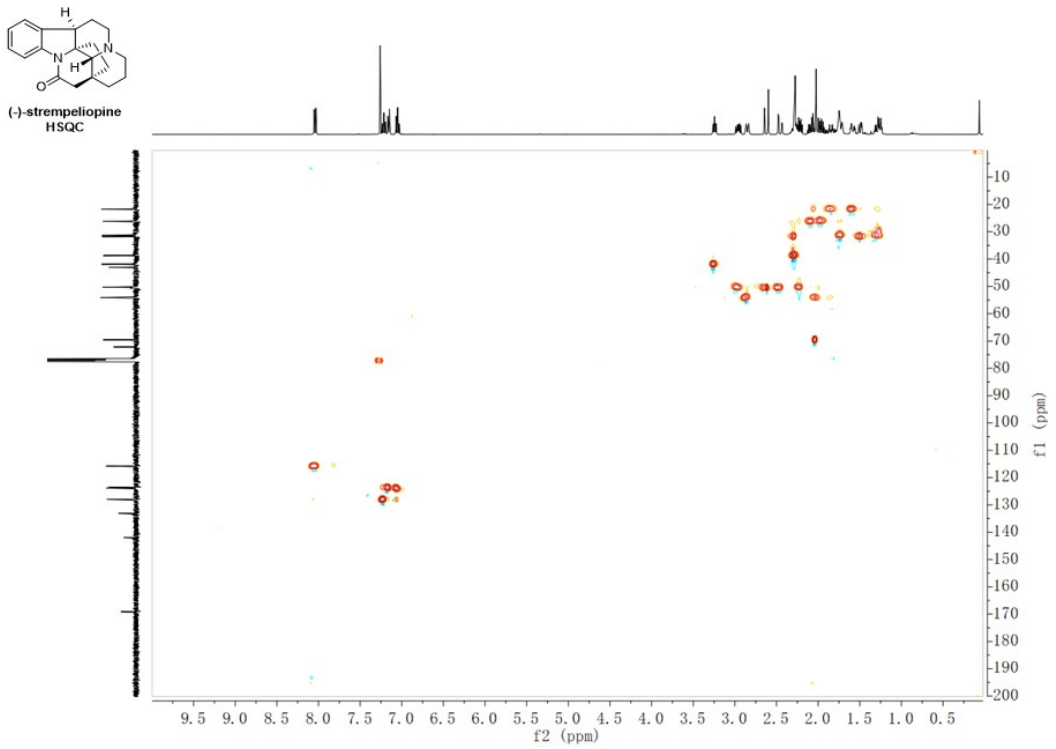


Figure S34: HSQC spectrum of **4**

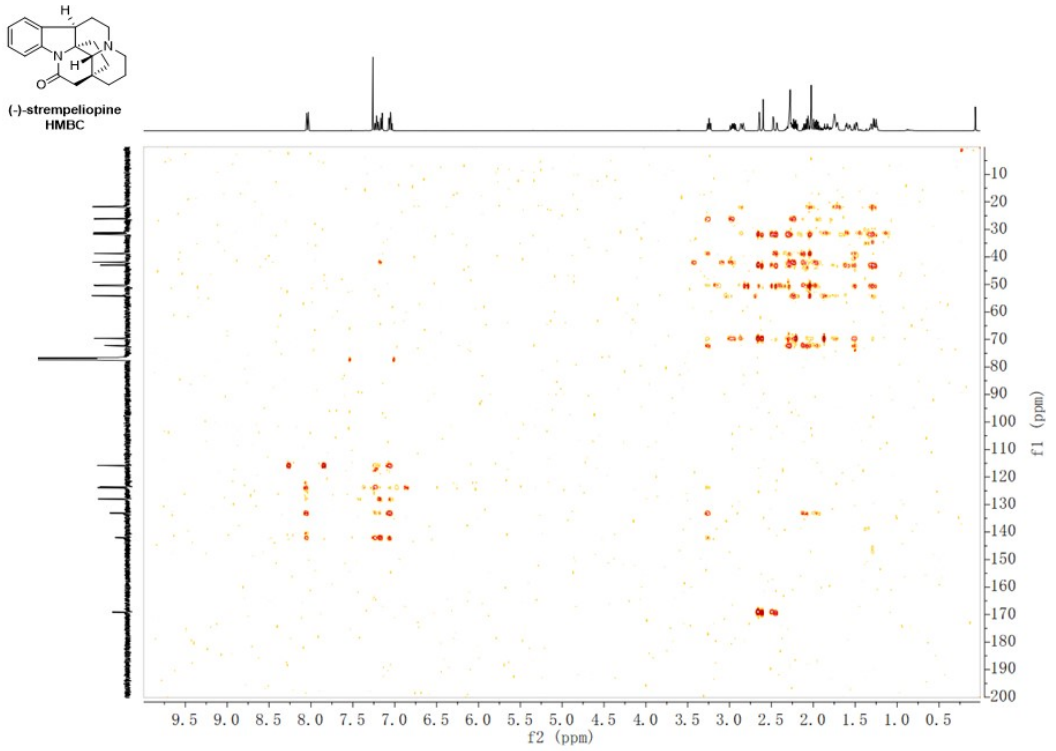


Figure S35: HMBC spectrum of **4**

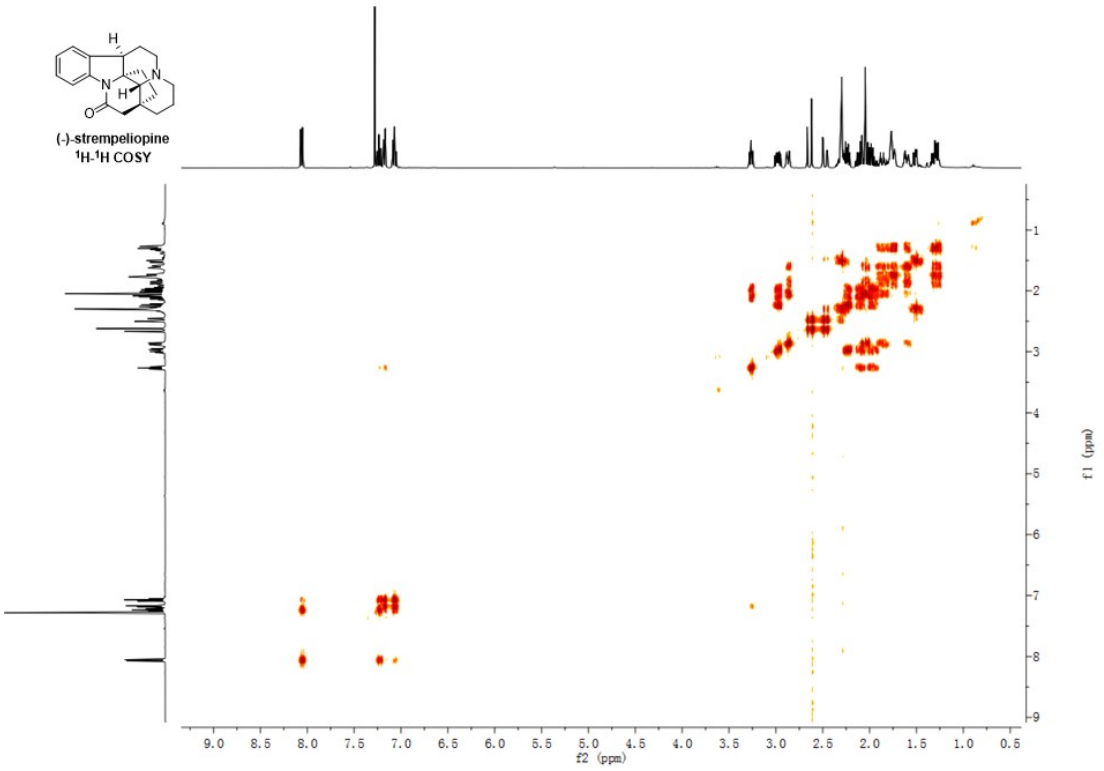
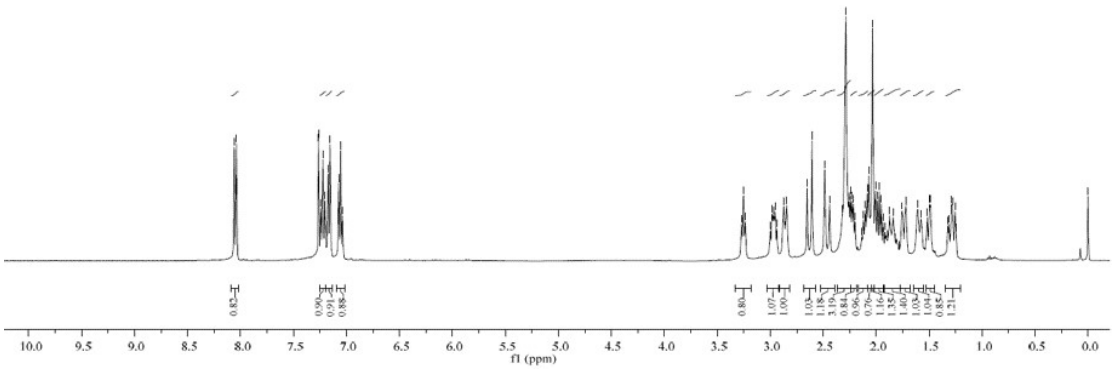


Figure S36: ^{1}H-^{1}H COSY spectrum of **4**

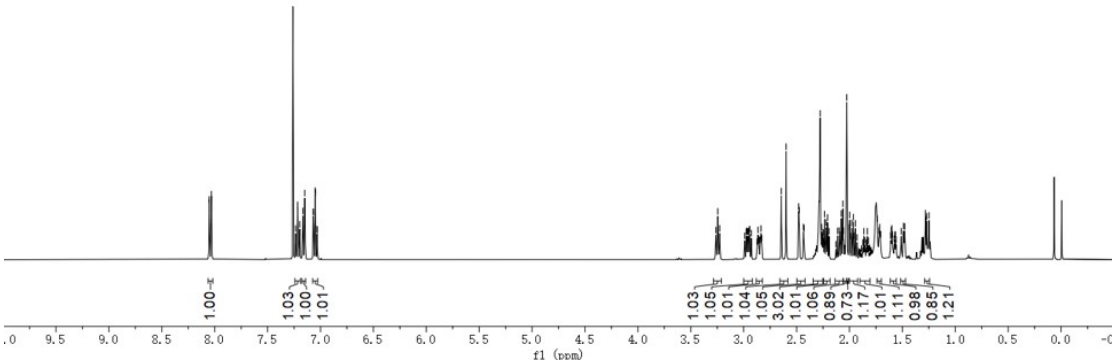
Comparison of ^{1}H spectrum between the synthesized (-)-strempeliopine by Qin's group and

the synthesized (-)-strempeliopine by our group.

The synthesized (-)-strempeliopine by Qin's group

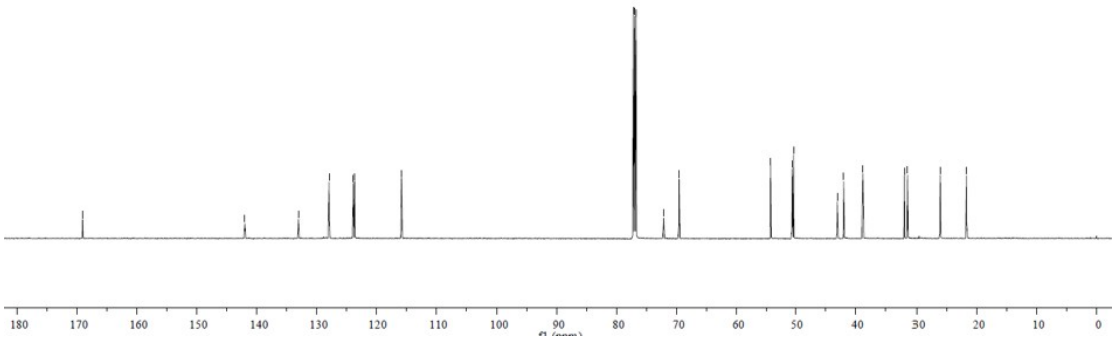


The synthesized (-)-strempeliopine by our group



Comparison of ^{13}C spectrum between the synthesized (-)-strempeliopine by Qin's group and the synthesized (-)-strempeliopine by our group.

The synthesized (-)-strempeliopine by Qin's group



The synthesized (-)-strempeliopine by our group