Supplementary Information

Catalytic asymmetric total synthesis of diazabicyclooctane β-lactamase inhibitors avibactam and relebactam

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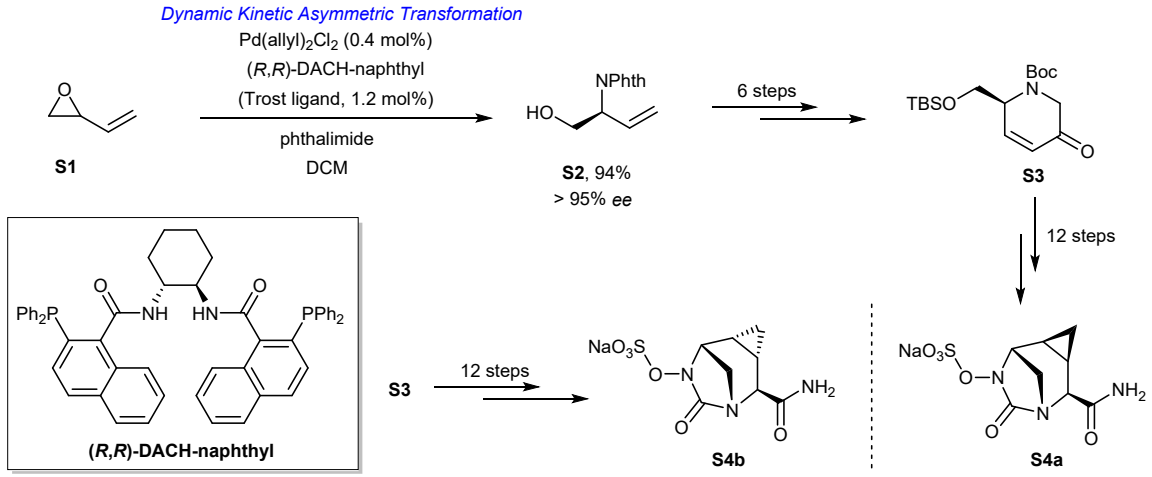
1. General Information

All commercially available reagents were used without further purification. Tetrahydrofuran and toluene were dried with sodium chips and indicated by benzophenone, other anhydrous solvents were purchased from Aladdin. Chromatography was conducted by using 300−400 mesh silica gel. All new compounds were characterized by NMR spectroscopy, high resolution mass spectrometry (HRMS), FT-IR spectroscopy and melting point (if solids). NMR spectra were recorded on a 400 MHz NMR or 600 MHz NMR spectrometer. Reference values for residual solvents were taken as δ = 7.26 ($CDCl_3$) ppm, δ = 2.50 (DMSO-d_6) ppm for ^1H NMR and δ = 77.16 ($CDCl_3$) ppm, δ = 49.00 (MeOH-d_4) ppm, δ = 39.52 (DMSO-d_6) ppm for ^{13}C NMR. Coupling constants (*J*) were given in Hz and multiplicities for coupled signals were denoted as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad 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 microTOF Q III by the ESI method. Melting points (m.p.) were recorded on an SRS-optic melting point apparatus. Chiral HPLC was performed using a Daicel Chiralcel IC column (4.6 × 250 mm) analytical column.

2. A Trost's DYKAT based synthesis of DBOs



Scheme S1. A Trost's DYKAT based synthesis of cyclopropane-fused DBOs

3. Flow Experimental Equipment Information

The continuous flow system was established which including commercially available feeding equipments, continuous reactors and process control unit etc.

The main devices information is as follows:

The feeding equipment: syringe pump (Fusion 4000).

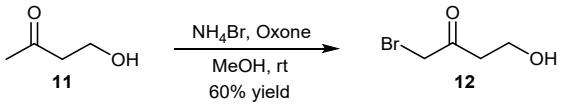
Continuous reactors: PTFE coil reactor (0.8 mm I.D.) and PTFE fittings (RunZe Fluid).

Process control unit: back pressure regulator (75 psi, IDEX Corporation).

4. Experimental Procedures for Reactions in Batch and Continuous Flow

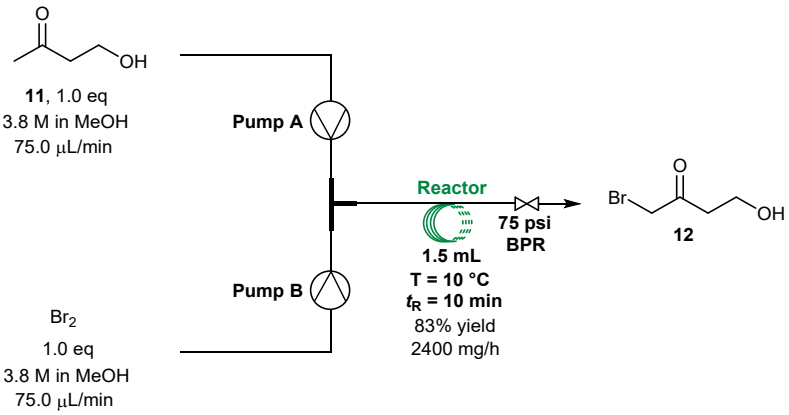
Synthesis of 12

Batch Reaction



Oxone® (15.3 g, 25.0 mmol, 1.1 equiv.) was added to the well stirred solution of ketone **11** (2.0 g, 22.7 mmol, 1.0 equiv.) and NH_4Br (2.4 g, 25.0 mmol, 1.1 equiv.) in MeOH (50.0 mL). The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with saturated aqueous solution of $Na_2S_2O_3$, and extracted with ethyl acetate. Finally, the combined organic layer was washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 10:1) to give compound **12** (2.3 g, 60%) as a pale-yellow oil.

Continuous Flow Reaction

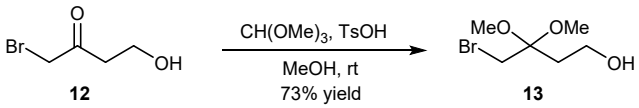


The self-build flow reactor equipment consists of two Fusion 4000 type syringe pumps for reagent/solvent delivery and a 1.5 mL PTFE coil reactor (0.8 mm i.d.). Before the start of the actual experiment, the reactor was primed with MeOH and pre-cooled to 10 °C. The syringe pump A was used to introduce the solution of compound **11** in MeOH (3.8 M, 1.0 equiv., 75.0 μL/min), the syringe pump B was used to introduce the solution of Br_2 (3.8 M, 1.0 equiv., 75.0 μL/min) in MeOH. The two solutions were mixed through a T-shape mixer and pumped through the coil reactor (1.5 mL, internal volume, t_R = 10 min) at 10 °C. A 75 psi BPR was connected at the outlet of coil reactor. The system was allowed to come to steady state by waiting three residence times prior to collecting product. The reaction mixture was collected, then poured into water and extracted with DCM. The combined organic layer was washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 10:1) to give

compound **12** (2400 mg/h, 83%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 2H), 3.90 – 3.88 (m, 2H), 2.91 (t, J = 5.6 Hz, 2H), 2.34 (d, J = 5.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 57.9, 42.1, 34.6. IR (neat) 2965, 2362, 1749, 1539, 1247, 1131 cm^{-1}. HRMS (ESI) m/z calcd for $C_4H_7BrNaO_2$ $[M + Na]^+$: 188.9522, found: 188.9519.

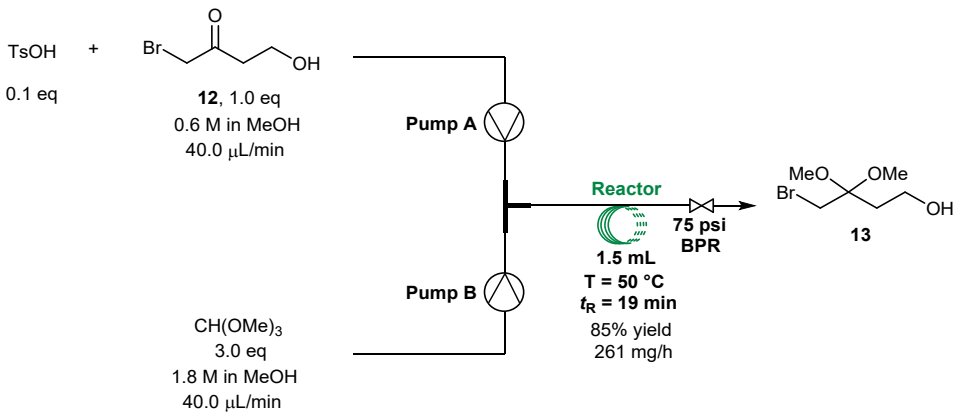
Synthesis of 13

Batch Reaction



To a solution of compound **12** (1.0 g, 6.0 mmol, 1.0 equiv.) in MeOH (20.0 mL) were added trimethoxymethane (2.0 mL, 18.0 mmol, 3.0 equiv.) and TsOH (103.3 mg, 0.6 mmol, 0.1 equiv.). The mixture was stirred at room temperature for 10 h. A saturated aqueous solution of $NaHCO_3$ was added at 0 °C and then concentrated to remove most of the organic phase. The mixture was extracted with ethyl acetate, the combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 10:1) to give compound **13** (931.4 mg, 73%) as a pale-yellow oil.

Continuous Flow Reaction

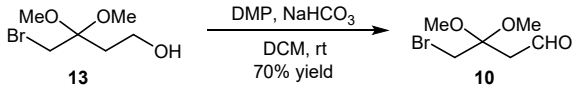


The self-build flow reactor equipment consists of two Fusion 4000 type syringe pumps for reagent/solvent delivery and a 1.5 mL PTFE coil reactor (0.8 mm i.d.). Before the start of the actual experiment, the reactor was primed with MeOH. The syringe pump A was used to introduce the solution of compound **12** (0.6 M, 1.0 equiv.) and TsOH (0.1 equiv.) in MeOH (40.0 μL/min), the syringe pump B was used to introduce the solution of trimethoxymethane (1.8 M, 3.0 equiv., 40.0 μL/min) in MeOH. The two solutions were mixed through a T-shape mixer and pumped through the coil reactor (1.5 mL, internal volume, t_R = 19 min) at 50 °C. A 75 psi BPR was connected at the outlet of coil reactor. The system was allowed to come to steady state by waiting three residence times prior to collecting product. The reaction mixture was collected and a saturated aqueous solution of $NaHCO_3$ was added at 0 °C, then concentrated to remove most of the organic phase. The mixture was extracted with ethyl acetate, the

combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 10:1) to give compound **13** (261 mg/h, 85%) as a pale-yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.74 – 3.71 (m, 2H), 3.47 (s, 2H), 3.25 (s, 6H), 2.22 (t, J = 6.0 Hz, 1H), 2.12 (t, J = 6.0 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 101.4, 58.5, 48.7, 34.5, 32.4. IR (neat) 3054, 2968, 2362, 2342, 1265, 1099, 737 cm^{-1}. HRMS (ESI) m/z calcd for $C_6H_{13}BrNaO_3$ $[M + Na]^+$: 234.9940, found: 234.9945.

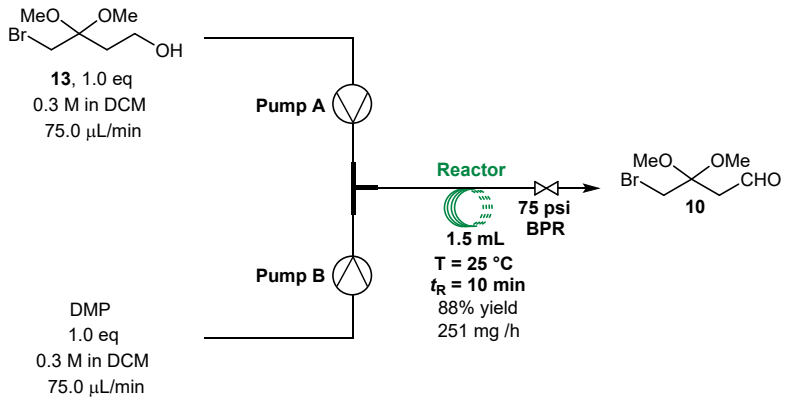
Synthesis of 10

Batch Reaction



To a solution of compound **13** (1.0 g, 4.7 mmol, 1.0 equiv.) in DCM (40.0 mL) were added $NaHCO_3$ (1.2 g, 14.1 mmol, 3.0 equiv) and Dess-Martin periodinane (2.0 g, 4.7 mmol, 1.0 equiv). The mixture was stirred at room temperature for 4 h and then diluted with DCM. Water and a saturated aqueous solution of $Na_2S_2O_3$ were added, then the mixture was vigorously shaken in a separatory funnel until the layers turned completely clear. The layers were separated, and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 50:1) to give compound **10** (693.4 mg, 70%) as a pale-yellow oil.

Continuous Flow Reaction

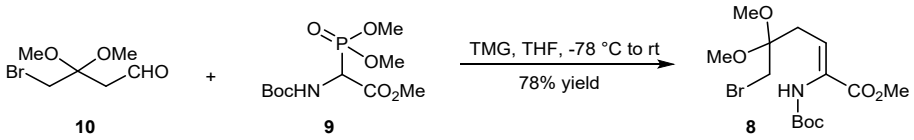


The self-build flow reactor equipment consists of two Fusion 4000 type syringe pumps for reagent/solvent delivery and a 1.5 mL PTFE coil reactor (0.8 mm i.d.). Before the start of the actual experiment, the reactor was primed with DCM. The syringe pump A was used to introduce the solution of compound **13** in DCM (0.3 M, 1.0 equiv., 75.0 µL/min), the syringe pump B was used to introduce the solution of Dess-Martin periodinane in DCM (0.3 M, 1.0 equiv., 75.0 µL/min). The two solutions were mixed through a T-shape mixer and pumped through the coil reactor (1.5 mL, internal volume, t_R = 10 min) at 25 °C. A 75 psi BPR was connected at the outlet of coil reactor. The system was allowed to come to steady state by waiting three residence times prior to collecting product. The reaction mixture was collected, water and a saturated aqueous solution of $Na_2S_2O_3$ were added and the mixture was

vigorously shaken in a separatory funnel until the layers turned completely clear. The layers were separated, and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 50:1) to give compound **10** (251 mg/h, 88%) as a pale-yellow oil. ^1H NMR (600 MHz, $CDCl_3$) δ 9.75 (t, J = 2.4 Hz, 1H), 3.52 (s, 2H), 3.27 (s, 6H), 2.91 (d, J = 3.0 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.1, 99.8, 49.0, 47.0, 32.9. IR (neat) 3056, 2971, 2362, 2342, 1724, 1266, 1099, 1066, 737 cm^{-1}. HRMS (ESI) m/z calcd for $C_6H_{11}BrNaO_3$ $[M + Na]^+$: 232.9784, found: 232.9788.

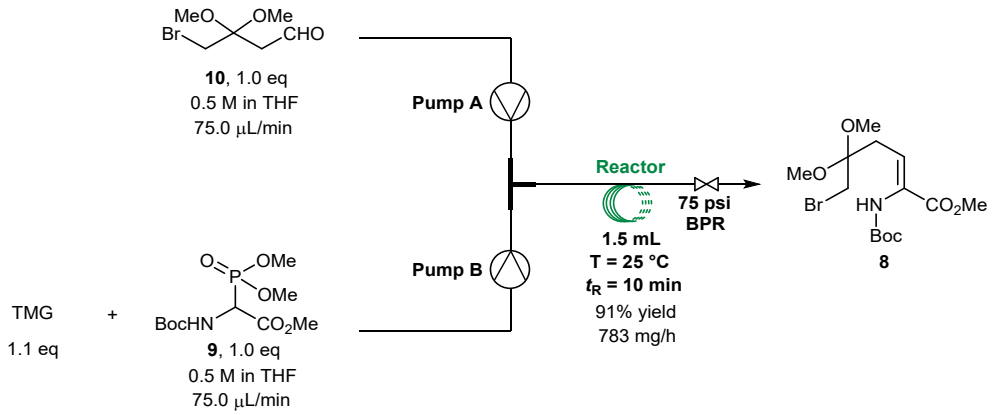
Synthesis of 8

Batch Reaction



To a solution of compound **9** (1.7 g, 5.7 mmol, 1.0 equiv.) in dry THF (15.0 mL) was added TMG (0.8 mL, 6.3 mmol, 1.1 equiv) at –78 °C. After 10 min, a solution of compound **10** (1.2 g, 5.7 mmol, 1.0 equiv.) in dry THF (15.0 mL) was added. The mixture was stirred at room temperature for 3 h, then quenched by addition of water. The mixture was extracted with ethyl acetate, the combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 25:1) to give compound **8** (1.7 g, 78%) as a white solid.

Continuous Flow Reaction

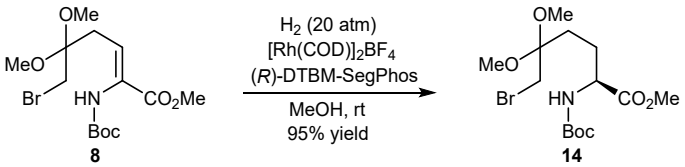


The self-build flow reactor equipment consists of two Fusion 4000 type syringe pumps for reagent/solvent delivery and a 1.5 mL PTFE coil reactor (0.8 mm i.d.). Before the start of the actual experiment, the reactor was primed with THF. The syringe pump A was used to introduce the solution of compound **10** in THF (0.5 M, 1.0 equiv., 75.0 μL/min), the syringe pump B was used to introduce the solution of compound **9** (0.5 M, 1.0 equiv.) and TMG (1.1 equiv.) in THF (75.0 μL/min). The two solutions were mixed through a T-shape mixer and pumped through the coil reactor (1.5 mL, internal

volume, t_R = 10 min) at 25 ℃. A 75 psi BPR was connected at the outlet of coil reactor. The system was allowed to come to steady state by waiting three residence times prior to collecting product. The reaction mixture was collected, quenched by addition of water. The mixture was extracted with ethyl acetate, the combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 25:1) to give compound **8** (783 mg/h, 91%) as a white solid, m.p. = 93.9 – 94.4 ℃. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.38 (t, *J* = 7.2 Hz, 1H), 6.26 (s, 1H), 3.78 (s, 3H), 3.33 (s, 2H), 3.25 (s, 6H), 2.75 (d, *J* = 7.2 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.2, 153.2, 127.8, 127.7, 101.2, 80.9, 52.6, 49.0, 32.4, 32.1, 28.3. IR (neat) 2982, 2360, 2342, 1742, 1697, 1487, 1245, 1216, 1198, 1070, 1047, 951 cm^{-1}. HRMS (ESI) m/z calcd for $C_{14}H_{24}BrNNaO_6$ $[M + Na]^+$: 404.0679, found: 404.0678.

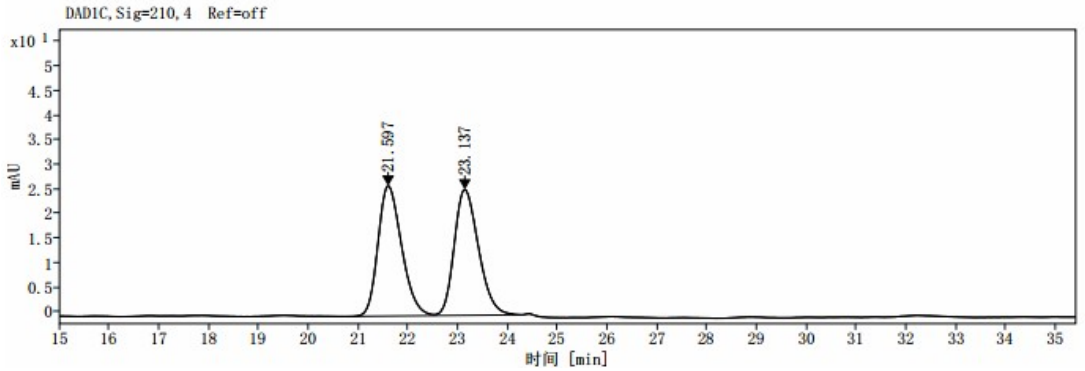
Synthesis of 14

Batch Reaction



A mixture of $[Rh(COD)]_2BF_4$ (21.2 mg, 52.3 μmol, 1.0 mol%) and (*R*)-DTBM-SegPhos (123.4 mg, 104.6 μmol, 2.0 mol%) were dissolved in degassed MeOH (60.0 mL) at argon atmosphere, and the resulting solution was allowed to stirred for 20 min, followed by addition of substrate **8** (2.0 g, 5.2 mmol, 1.0 equiv.). The resulting mixture was transferred to an autoclave, which was purged (3 × 5 atm) and charged with H_2 (20 atm), then the reaction mixture was stirred at room temperature for 48 h. The hydrogen gas was released slowly, and the solution was concentrated and purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 20:1) to afford the product **14** (1.9 g, 95%) as a white solid, m.p. = 84.5 – 86.7 ℃. $[\alpha]_D^{20}$ = –2.23 (c = 1.0, MeOH). The enantiomeric excess was 99.1% *ee*, chiral HPLC conditions: Daicel Chiralcel IC column, 4.6 × 250 mm, 90:10 *n*-hexane/*i*-PrOH, 0.7 mL/min, UV detector at 210 nm, t_{R1} = 21.3 min (major), t_{R2} = 23.1 min (minor). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.11 (d, *J* = 7.8 Hz, 1H), 4.35 – 4.32 (m, 1H), 3.74 (s, 3H), 3.36 – 3.27 (m, 2H), 3.19 (s, 6H), 1.89 – 1.75 (m, 3H), 1.66 – 1.58 (m, 1H), 1.43 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.9, 155.3, 101.2, 80.1, 53.2, 52.5, 48.7, 48.6, 31.1, 28.4, 27.6, 26.5. IR (neat) 2971, 1753, 1703, 1682, 1541, 1366, 1340, 1280, 1254, 1214, 1192, 1170, 1099, 1063, 995 cm^{-1}. HRMS (ESI) m/z calcd for $C_{14}H_{26}BrNNaO_6$ $[M + Na]^+$: 406.0836, found: 406.0835.

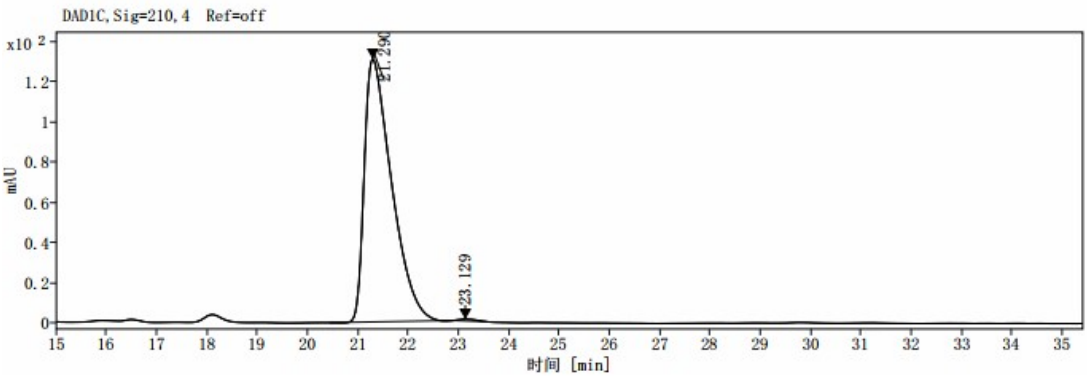
Table S1. HPLC Spectrum of *rac*-14



Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
21.597	BV	1.64	873.54	26.45	50.19
23.137	VB	1.73	866.82	25.55	49.81
		Totals	1740.36		

Chiral HPLC conditions: Daicel Chiralcel IC column, 4.6 × 250 mm, 90:10 *n*-hexane/*i*-PrOH, 0.7 mL/min, UV detector at 210 nm. t_{R1} = 21.6 min, t_{R2} = 23.1 min.

Table S2. HPLC Spectrum of (–)-14



Ret Time [min]	Type	Width [min]	Area [mAU * s]	Height [mAU]	Area%
21.290	MM m	0.57	4932.12	130.65	99.57
23.129	MM m	0.31	21.24	0.865	0.43
		Totals	4953.36		

Chiral HPLC conditions: Daicel Chiralcel IC column, 4.6 × 250 mm, 90:10 *n*-hexane/*i*-PrOH, 0.7 mL/min, UV detector at 210 nm. t_{R1} = 21.3 min (major), t_{R2} = 23.1 min (minor).

Synthesis of 15

Batch Reaction

Table S3. Optimization of the reaction conditions of piperidine ring formation

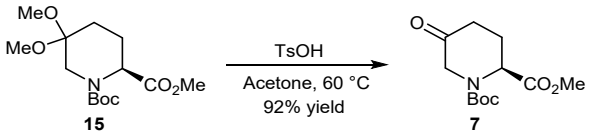
entry	Base	Solvent	**T (ºC)**	**t (h)**	Result
1	LiHMDS	THF	–20	12	< 5% yield
2	MeONa	MeOH	rt	18	No Reaction
3	KHMDS	THF	–78	12	< 5% yield
4	K_2CO_3	$CHCl_3$	65	12	No Reaction

5	DIPEA	THF	rt	12	No Reaction
6	LDA	THF	–78	16	Complicated
7	*n*-BuLi	THF	–78	16	Complicated
8	NaH	DMF	rt	12	73% yield

The compound **14** (5.0 g, 13.0 mmol, 1.0 equiv.) was dissolved in dry DMF (100.0 mL) and NaH (60% dispersion in mineral oil, 780.7 mg, 19.5 mmol, 1.5 equiv.) was added portionwise at 0 ℃ under an argon atmosphere. The bubbling solution was stirred at room temperature until full consumption of the starting material. After addition of water, the aqueous phase was extracted with DCM. The combined organic layer was washed with water, brine and dried over Na_2SO_4, then concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 20:1) to give compound **15** (2.9 g, 73%) as a pale-yellow oil. $[\alpha]_D^{20}$ = –54.2 (c = 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ (rotamers, 1:0.76) 4.90 (d, *J* = 6.0 Hz, 1H), 4.70 (d, *J* = 6.4 Hz, 0.76H), 4.25 (dd, *J* = 14.0, 2.8 Hz, 0.76H), 4.12 (dd, *J* = 14.0, 2.4 Hz, 1H), 3.70 – 3.69 (2 s, 5.28H), 3.19 – 3.16 (2 s, 10.56H), 2.81 (d, *J* = 14.4 Hz, 1H), 2.70 (d, *J* = 14.0 Hz, 0.76H), 2.15 – 2.05 (m, 1.76H), 2.00 – 1.85 (m, 3.52H), 1.45 – 1.41 (2 s, 15.84H), 1.35 – 1.27 (m, 1.76H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (rotamers) 172.2, 172.0, 155.2, 155.1, 97.3, 97.1, 80.6, 54.4, 53.0, 52.4, 52.3, 48.6, 48.4, 47.90, 47.88, 45.6, 45.3, 28.9, 28.5, 28.4, 23.4, 23.2. IR (neat) 2985, 2362, 2342, 1741, 1694, 1265, 1153, 1101, 1054, 738, 704 cm^{-1}. HRMS (ESI) m/z calcd for $C_{14}H_{25}NNaO_6$ $[M + Na]^+$: 326.1574, found: 326.1575.

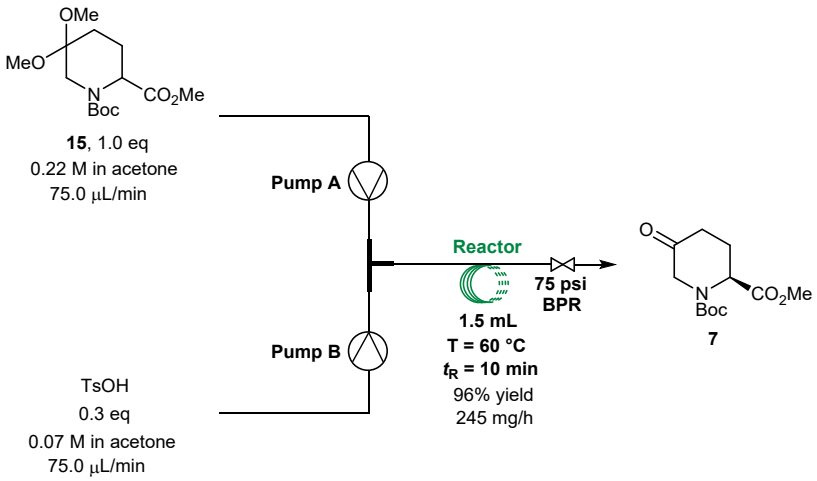
Synthesis of 7

Batch Reaction



TsOH (0.5 g, 3.0 mmol, 0.3 equiv.) was added to a solution of the ketal **15** (3.0 g, 9.9 mmol, 1.0 equiv.) in wet acetone (125.0 mL). After being stirred for 2 h at 60 ℃, the solvent was evaporated and a saturated aqueous solution of $NaHCO_3$ was added. The mixture was extracted with ethyl acetate, the combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 20:1) to give compound **7** (2.3 g, 92%) as a pale-yellow oil.

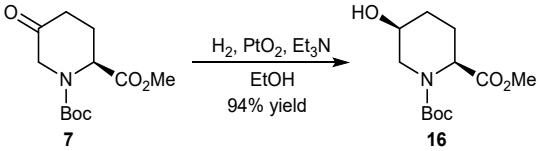
Continuous Flow Reaction



The self-build flow reactor equipment consists of two Fusion 4000 type syringe pumps for reagent/solvent delivery and a 1.5 mL PTFE coil reactor (0.8 mm i.d.). Before the start of the actual experiment, the reactor was primed with acetone. The syringe pump A was used to introduce the solution of compound **15** in acetone (0.22 M, 1.0 equiv., 75.0 μL/min), the syringe pump B was used to introduce the solution of TsOH (0.07 M, 0.3 equiv., 75.0 μL/min) in acetone. The two solutions were mixed through a T-shape mixer and pumped through the coil reactor (1.5 mL, internal volume, t_R = 10 min) at 60 °C. A 75 psi BPR was connected at the outlet of coil reactor. The system was allowed to come to steady state by waiting three residence times prior to collecting product. The reaction mixture was collected and the solvent was evaporated, then a saturated aqueous solution of $NaHCO_3$ was added. The mixture was extracted with ethyl acetate, the combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 20:1) to give compound **7** (245 mg/h, 96%) as a pale-yellow oil. $[\alpha]_D^{20}$ = –5.4 (c = 1.0, MeOH) [Lit.[1] $[\alpha]_D^{20}$ = –4.8 (c = 0.5, MeOH)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ (rotamers, 1:1) 4.80 (t, *J* = 6.8 Hz, 1H), 4.57 (t, *J* = 6.8 Hz, 1H), 4.40 – 4.24 (m, 2H), 3.93 – 3.83 (m, 2H), 3.75 (s, 6H), 2.53 – 2.23 (m, 6H), 2.23 – 1.99 (m, 2H), 1.43 (2 s, 18H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (rotamers) 205.5, 172.5, 172.1, 154.7, 154.3, 81.4, 81.3, 54.4, 52.9, 52.41, 52.39, 52.3, 50.9, 35.9, 35.7, 28.20, 28.16, 23.7, 23.6. IR (neat) 2958, 2359, 2341, 1747, 1532, 1241, 1051, 1008, 750 cm^{-1}. HRMS (ESI) m/z calcd for $C_{12}H_{19}NNaO_5$ $[M + Na]^+$: 280.1155, found: 280.1155.

Synthesis of 16

Batch Reaction

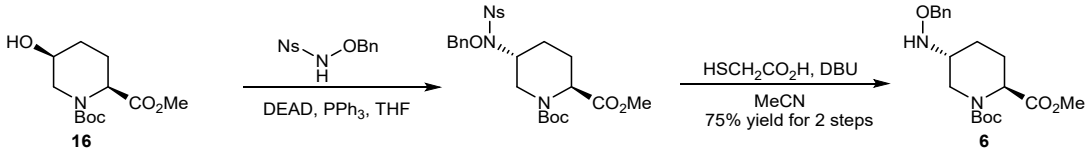


To a stirred solution of the ketone **7** (1.5 g, 5.8 mmol, 1.0 equiv.) in EtOH (25.0 mL) were added PtO_2 (66.2 mg, 0.3 mmol, 5.0 mol%) and triethylamine (0.8 mL, 5.8 mmol, 1.0 equiv.). The resulting mixture was stirred for 36 h at room temperature under H_2 (1 atm, balloon) and then filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 10:1) to give compound **16** (1.4 g, 94%) as a pale-yellow oil. $[\alpha]_D^{20}$ = –20.4 (c = 1.0,

MeOH) [Lit.[1] $[\alpha]_D^{20}$ = –17.7 (c = 1.3, MeOH)]. ^{1}H NMR (400 MHz, DMSO-d_6) δ (rotamers, 1:1) 4.97 – 4.95 (m, 2H), 4.67 (dd, J = 6.0, 2.0 Hz, 1H), 4.58 (dd, J = 6.4, 2.4 Hz, 1H), 3.94 – 3.87 (m, 2H), 3.67 (2 s, 6H), 2.58 – 2.52 (m, 1H), 2.42 – 2.36 (m, 1H), 2.13 – 2.03 (m, 2H), 1.83 – 1.73 (m, 2H), 1.65 – 1.64 (m, 2H), 1.38 (2 s, 18H), 1.06 – 0.92 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (rotamers) 171.6, 171.4, 154.7, 154.4, 79.5, 79.4, 65.1, 53.6, 52.4, 52.12, 52.09, 48.5, 47.6, 30.1, 29.9, 28.0, 27.9, 24.8, 24.6. IR (neat) 2973, 2950, 1739, 1435, 1423, 1367, 1244, 1215, 1112, 1068, 995, 879, 864 cm^{-1}. HRMS (ESI) m/z calcd for $C_{12}H_{21}NNaO_5$ $[M + Na]^+$: 282.1312, found: 282.1312.

Synthesis of 6

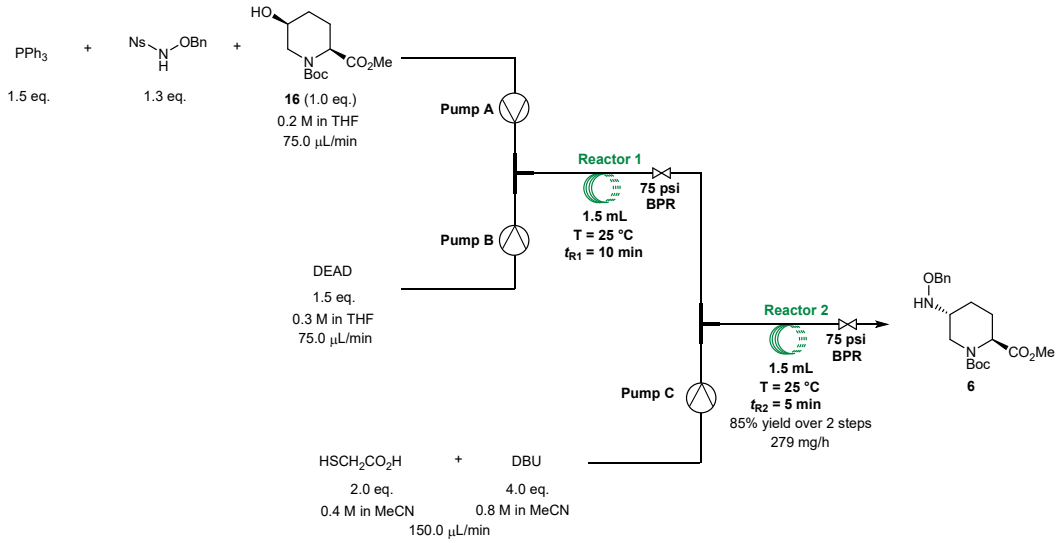
Batch Reaction



Triphenylphosphine (7.7 g, 29.5 mmol, 1.5 equiv.) and N-nitrosulfonyl-O-benzyl hydroxylamine (7.9 g, 25.6 mmol, 1.3 equiv.) were added to a solution of compound **16** (5.1 g, 19.7 mmol, 1.0 equiv.) in THF (250.0 mL). DEAD (4.3 mL, 29.5 mmol, 1.5 equiv.) was added dropwise at 0 °C and the reaction mixture was stirred for 24 h at room temperature and concentrated in vacuo. The residue was directly used in the next step without further purification.

To a stirred solution of the crude above and DBU (11.8 mL, 78.7 mmol, 4.0 equiv.) in CH_3CN (250.0 mL) was added mercaptoacetic acid (2.7 mL, 39.3 mmol, 2.0 equiv.). The resultant solution was stirred for 1 h and then diluted with Et_2O (15.0 mL). The organic phase was washed with a saturated aqueous solution of $NaHCO_3$ and the aqueous phase was extracted with Et_2O. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (petroleum ether/acetone = 30:1) to give compound **6** (5.4 g, 75% for 2 steps) as a pale-yellow oil.

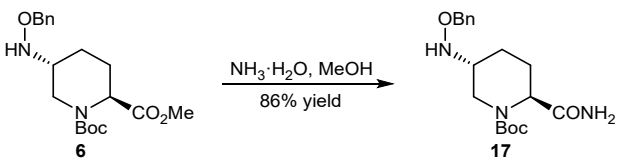
Continuous Flow Reaction



The self-build flow reactor equipment consists of two Fusion 4000 type syringe pumps for reagent/solvent delivery and two 1.5 mL PTFE coil reactors (0.8 mm i.d.). Before the start of the actual experiment, all reactors were primed with THF. The syringe pump A was used to introduce the solution of compound **16** (0.2 M, 1.0 equiv.), N-nitrosulfonyl-O-benzyl hydroxylamine (1.3 equiv.) and triphenylphosphine (1.5 equiv.) in THF (75.0 μL/min), the syringe pump B was used to introduce the solution of DEAD in THF (0.3 M, 1.5 equiv., 75.0 μL/min). The two solutions were mixed through a T-shape mixer and pumped through the coil reactor 1 (1.5 mL, internal volume, t_{R1} = 10 min) at 25 ℃. A 75 psi BPR was connected at the outlet of coil reactor 1. The reaction mixture in THF from the reactor 1 output was combined with the solution of DBU (0.8 M, 4.0 equiv.) and mercaptoacetic acid (0.4 M, 2.0 equiv.) in acetonitrile (150.0 μL/min) at T-piece connector, entering the reactor 2 (1.5 mL, internal volume, t_{R2} = 5 min) at 25 ℃. A 75 psi BPR was connected at the outlet of coil reactor 2. The system was allowed to come to steady state by waiting three residence times prior to collecting product. The reaction mixture was collected and concentrated in vacuo, then purified using flash chromatography (petroleum ether/acetone = 30:1) to give compound **6** (279 mg/h, 85%) for 2 steps as a white solid. $[\alpha]_D^{20}$ = –17.0 (c = 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.20 (m, 5H), 4.76 – 4.67 (m, 2H), 4.17 (d, *J* = 13.2 Hz, 1H), 3.72 (s, 3H), 3.20 – 3.10 (m, 2H), 2.07 – 1.84 (m, 2H), 1.78 – 1.50 (m, 1H), 1.55 – 1.52 (m, 2H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, MeOH-d_4) δ (rotamers) 173.6, 157.9, 157.4, 139.3, 129.6, 129.3, 128.7, 81.7, 77.4, 56.3, 55.0, 54.5, 52.7, 43.7, 42.6, 28.6, 23.6, 22.3. IR (neat) 3055, 2982, 2362, 2342, 1740, 1683, 1265, 1152, 738, 704 cm^{-1}. HRMS (ESI) m/z calcd for $C_{19}H_{28}N_2NaO_5$ [M + Na]$^+$: 387.1890, found: 387.1890.

Synthesis of 17

Batch Reaction

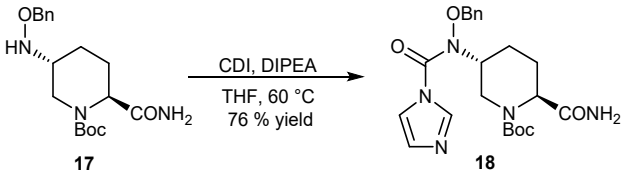


The 28% ammonium hydroxide (300.0 mL) was added to compound **6** (3.1 g, 8.5 mmol, 1.0 equiv.) in

MeOH (40.0 mL). The solution was stirred at room temperature. After 48 h, the solvent was evaporated in vacuo to give compound **17** (2.6 g, 86%) as a white foam. $[\alpha]_D^{20}$ = –15.6 (c = 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.26 (m, 5H), 6.15 (s, 1H), 6.03 (s, 1H), 5.44 (s, 1H), 4.79 – 4.65 (m, 3H), 4.25 (d, *J* = 14.0 Hz, 1H), 3.14 (t, *J* = 2.8 Hz, 1H), 2.99 (d, *J* = 14.0 Hz, 1H), 2.07 – 1.90 (m, 1H), 1.90 – 1.70 (m, 2H), 1.59 (m, 1H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 155.8, 138.0, 128.5, 128.5, 127.9, 81.0, 76.7, 53.6 (2 C), 42.5, 28.5, 22.9, 20.1. IR (neat) 2977, 2362, 1683, 1417, 1393, 1366, 1265, 1154, 736 cm^{-1}. HRMS (ESI) m/z calcd for $C_{18}H_{27}N_3NaO_4$ $[M + Na]^+$: 372.1894, found: 372.1892.

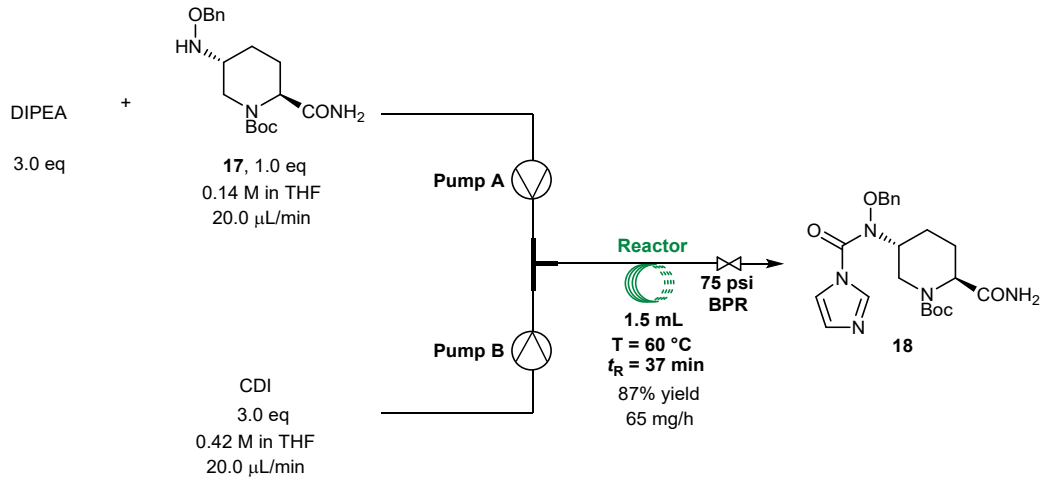
Synthesis of 18

Batch Reaction



To a solution of compound **17** (3.0 g, 8.6 mmol, 1.0 equiv.) in THF (100.0 mL) were added DIPEA (4.5 mL, 25.8 mmol, 3.0 equiv.) and CDI (4.2 g, 25.8 mmol, 3.0 equiv.). The reaction mixture was stirred at 60 °C overnight. The reaction mixture was diluted with ethyl acetate and washed four times with 1:1 brine:water, then the organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give crude compound **18** (2.9 g, 76%) as a yellow foam. The residue was directly used in the next step without further purification.

Continuous Flow Reaction

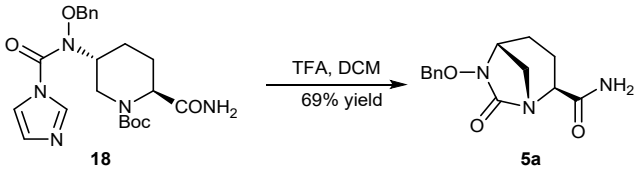


The self-build flow reactor equipment consists of two Fusion 4000 type syringe pumps for reagent/solvent delivery and a 1.5 mL PTFE coil reactor (0.8 mm i.d.). Before the start of the actual experiment, the reactor was primed with THF. The syringe pump A was used to introduce the solution of compound **17** (0.14 M, 1.0 equiv.) and DIPEA (3.0 equiv.) in THF (20.0 µL/min), the syringe pump

B was used to introduce the solution of CDI in THF (0.42 M, 3.0 equiv., 20.0 μL/min). The two solutions were mixed through a T-shape mixer and pumped through the coil reactor (1.5 mL, internal volume, t_R = 37 min) at 60 °C. A 75 psi BPR was connected at the outlet of coil reactor. The system was allowed to come to steady state by waiting three residence times prior to collecting product. The reaction mixture was collected, diluted with ethyl acetate and washed four times with 1:1 brine:water, then the organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give compound **18** (65 mg/h, 87%) as a white foam, which was used in the next step without further purification.

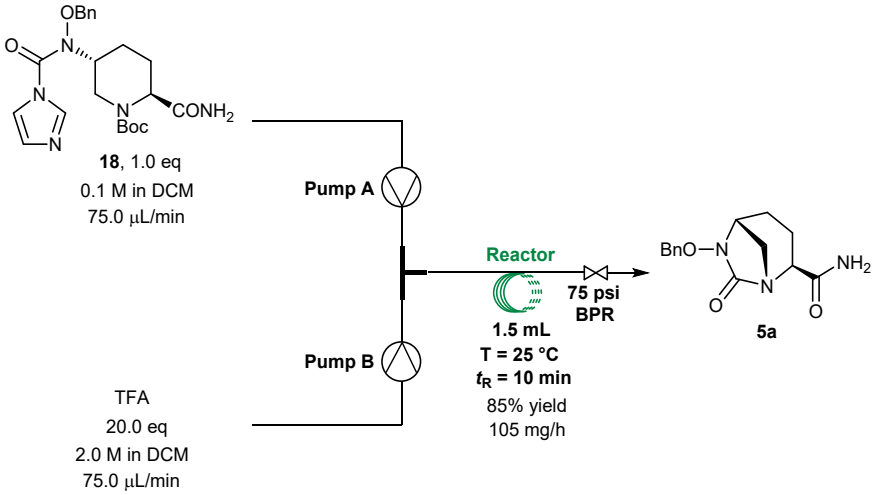
Synthesis of 5a

Batch Reaction



Trifluoroacetic acid (9.0 mL, 117.2 mmol, 20.0 equiv.) was added at 0 °C to a solution of compound **18** (2.6 g, 5.9 mmol, 1.0 equiv.) in DCM (90.0 mL). The reaction mixture was stirred at room temperature for 1 h. A saturated aqueous solution of $NaHCO_3$ was added at 0 °C, the mixture was extracted with ethyl acetate, the combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 30:1) to give compound **5a** (1.1 g, 69%) as a white solid.

Continuous Flow Reaction

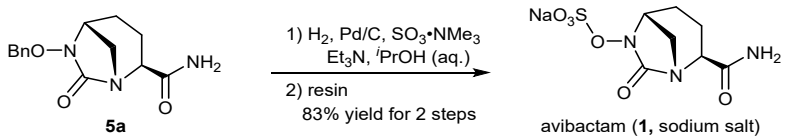


The self-build flow reactor equipment consists of two Fusion 4000 type syringe pumps for reagent/solvent delivery and a 1.5 mL PTFE coil reactor (0.8 mm i.d.). Before the start of the actual experiment, the reactor was primed with DCM. The syringe pump A was used to introduce the solution

of compound **18** in DCM (0.1 M, 1.0 equiv., 75.0 μL/min), the syringe pump B was used to introduce the solution of trifluoroacetic acid in DCM (2.0 M, 20.0 equiv., 75.0 μL/min). The two solutions were mixed through a T-shape mixer and pumped through the coil reactor (1.5 mL, internal volume, t_R = 10 min) at 25 ℃. A 75 psi BPR was connected at the outlet of coil reactor. The system was allowed to come to steady state by waiting three residence times prior to collecting product. The reaction mixture was collected, quenched by a saturated aqueous solution of $NaHCO_3$, and the mixture was extracted with ethyl acetate. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 30:1) to give compound **5a** (105 mg/h, 85%) as a white solid. $[\alpha]_D^{20}$ = –28.1 (c = 1.0, $CHCl_3$) [Lit.[2] $[\alpha]_D^{20}$ = –23.6 (c = 0.7, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 5H), 6.64 (s, 1H), 6.10 – 6.05 (m, 1H), 5.05 – 4.87 (m, 2H), 3.94 – 3.91 (m, 1H), 3.31 – 3.29 (m, 1H), 3.03 – 2.99 (m, 1H), 2.76 (d, J = 11.6 Hz, 1H), 2.39 – 2.24 (m, 1H), 2.05 – 1.82 (m, 2H), 1.65 – 1.53 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 167.7, 135.7, 129.3, 128.9, 128.6, 78.3, 60.5, 58.0, 47.8, 20.9, 17.4. IR (neat) 3296, 3252, 2975, 2943, 1740, 1651, 1595, 1450, 1356, 1327, 1209, 1063, 1024, 849, 705 cm^{-1}. HRMS (ESI) m/z calcd for $C_{14}H_{17}N_3NaO_3$ $[M + Na]^+$: 298.1162, found: 298.1163.

Synthesis of 1

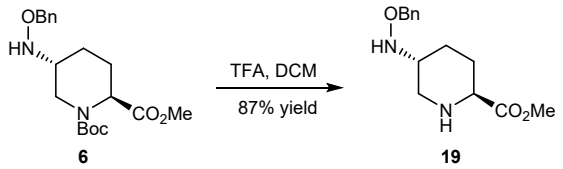
Batch Reaction



To a solution of compound **5a** (900.0 mg, 3.3 mmol, 1.0 equiv.) in isopropanol (10.0 mL) and water (10.0 mL) was added sulfur trioxide trimethylamine complex (509.6 mg, 3.7 mmol, 1.1 equiv.), triethylamine (90.9 μL, 0.7mmol, 0.2 equiv.), 10% Pd/C (180.0 mg, 20.0 wt%). The resulting mixture was stirred for 14 h at room temperature under H_2 (1 atm, balloon) and then filtered, washed with water and concentrated under reduced pressure. The crude product was solubilized in water, filtered, eluted on Amberlite 732-Na resin with H_2O and concentrated under vacuum. The residue was redissolved in EtOH, filtered and the filtrate was concentrated to give product **1** (779.3 mg, 83%) as a white solid, m.p. = 257.1 – 260.5 ℃ (Lit.[2] m.p. = 259.1 – 262.4 ℃). $[\alpha]_D^{20}$ = –44.6 (c = 1.0, MeOH/H_2O = 1/1) [Lit.[2] $[\alpha]_D^{20}$ = –46.4 (c = 0.8, MeOH/H_2O = 1/1)]. ^{1}H NMR (400 MHz, D_2O) δ 4.24 (dd, J = 6.4, 3.2 Hz, 1H), 4.09 (d, J = 7.2 Hz, 1H), 3.37 (d, J = 12.0 Hz, 1H), 3.15 (d, J = 12.0 Hz, 1H), 2.32 – 2.16 (m, 1H), 2.14 – 2.08 (m, 1H), 2.03 – 1.89 (m, 1H), 1.89 – 1.71 (m, 1H). ^{13}C NMR (100 MHz, D_2O) δ 174.7, 169.4, 60.3, 59.8, 47.2, 19.8, 18.1. IR (neat) 3419, 2988, 2362, 2342, 1748, 1652, 1456, 1119, 764 cm^{-1}. HRMS (ESI) m/z calcd for $C_7H_{10}N_3O_6S$ $[M – Na]^–$: 264.0296, found: 264.0300.
NMR data is consistent with data reported in the literature.[2]

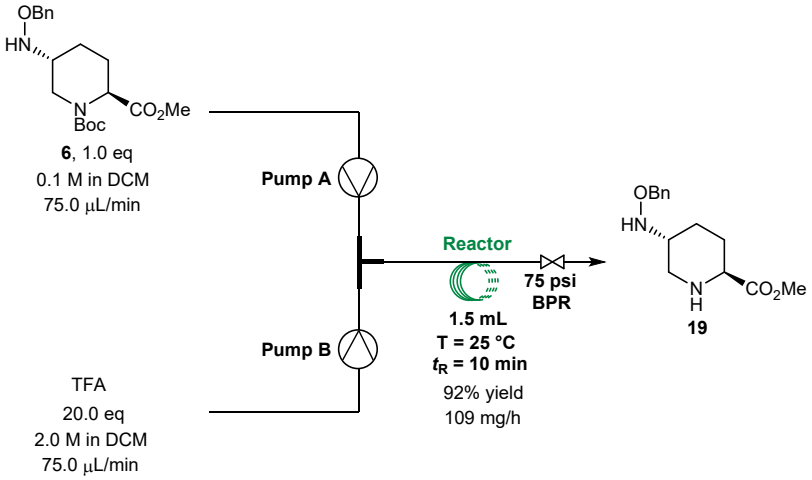
Synthesis of 19

Batch Reaction



Trifluoroacetic acid (27.3 mL, 356.7 mmol, 20.0 equiv.) was added at 0 ℃ to a solution of compound **6** (6.5 g, 17.8 mmol, 1.0 equiv.) in DCM (260.0 mL). The reaction mixture was stirred at room temperature for 3 h. A saturated aqueous solution of $NaHCO_3$ was added at 0 ℃, the mixture was extracted with ethyl acetate, the combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 10:1) to give compound **19** (4.1 g, 87%) as a pale-yellow oil.

Continuous Flow Reaction

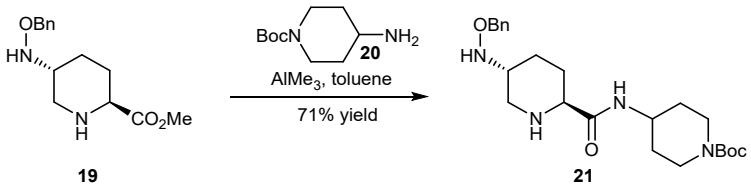


The self-build flow reactor equipment consists of two Fusion 4000 type syringe pumps for reagent/solvent delivery and a 1.5 mL PTFE coil reactor (0.8 mm i.d.). Before the start of the actual experiment, the reactor was primed with DCM. The syringe pump A was used to introduce the solution of compound **6** in DCM (0.1 M, 1.0 equiv., 75.0 μL/min), the syringe pump B was used to introduce the solution of trifluoroacetic acid in DCM (2.0 M, 20.0 equiv., 75.0 μL/min). The two solutions were mixed through a T-shape mixer and pumped through the coil reactor (1.5 mL, internal volume, t_R = 10 min) at 25 ℃. A 75 psi BPR was connected at the outlet of coil reactor. The system was allowed to come to steady state by waiting three residence times prior to collecting product. The reaction mixture was collected, quenched by a saturated aqueous solution of $NaHCO_3$. The mixture was extracted with ethyl acetate, and the combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate = 10:1) to give compound **19** (109 mg/h, 92%) as a pale-yellow oil. $[\alpha]_D^{20}$ = –12.3 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 5H), 5.42 (s, 1H), 4.66 (s, 2H), 3.71 (s, 3H), 3.38 – 3.36 (m, 1H), 3.29 (dd, *J* = 11.2, 3.2 Hz, 1H), 2.99 – 2.97 (m, 1H), 2.43 (dd, *J* = 12.0, 9.6 Hz, 1H), 2.08 – 2.04 (m, 1H), 1.97 – 1.89 (m, 1H), 1.54 – 1.51 (m, 1H), 1.34 – 1.23 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 137.8,128.5, 128.4, 127.9, 76.9, 58.4, 57.1, 52.1,

49.5, 28.1, 28.0. IR (neat) 3163, 2945, 2857, 1744, 1455, 1435, 1361, 1212, 1194, 1047, 1006, 750, 701 cm^{-1}. HRMS (ESI) m/z calcd for $C_{14}H_{21}N_2O_3$ $[M + H]^+$: 265.1547, found: 265.1548.

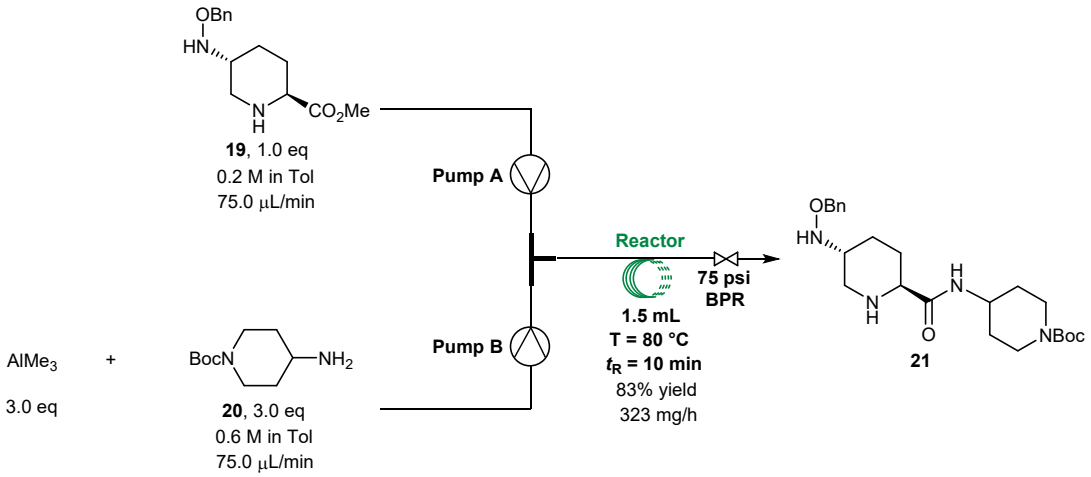
Synthesis of 21

Batch Reaction



To a solution of **20** (4.5 g, 22.7 mmol, 3.0 equiv.) in dry toluene (40.0 mL) was added $AlMe_3$ (2 M in toluene, 11.4 mL, 22.7 mmol, 3.0 equiv.) dropwise at 0 ℃. After 10 min, the mixture was stirred at room temperature for 1 h. Then a solution of compound **19** (2.0 g, 7.6 mmol, 1.0 equiv.) in dry toluene (40.0 mL) was added dropwise at 0 ℃. The mixture was stirred at 50 ℃ for 12 h, then quenched by addition of water. The mixture was extracted with ethyl acetate, the combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH = 100:1) to give compound **21** (2.3 g, 71%) as a white solid.

Continuous Flow Reaction

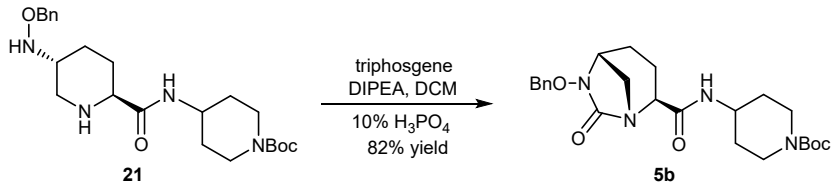


The self-build flow reactor equipment consists of two Fusion 4000 type syringe pumps for reagent/solvent delivery and a 1.5 mL PTFE coil reactor (0.8 mm i.d.). Before the start of the actual experiment, the reactor was primed with toluene. The syringe pump A was used to introduce the solution of compound **19** in toluene (0.2 M, 1.0 equiv., 75.0 μL/min), the syringe pump B was used to introduce the solution of **20** (0.6 M, 3.0 equiv.) and trimethylaluminium (0.6 M, 3.0 equiv.) in toluene (75.0 μL/min). The two solutions were mixed through a T-shape mixer and pumped through the coil reactor (1.5 mL, internal volume, t_R = 10 min) at 80 ℃. A 75 psi BPR was connected at the outlet of coil reactor. The system was allowed to come to steady state by waiting three residence times prior to collecting product. The reaction mixture was collected in a separate round-bottom flask, quenched by addition of

water. The mixture was extracted with ethyl acetate, the combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH = 100:1) to give compound **21** (323 mg/h, 83%) as a white solid, m.p. = 113.4 – 114.5 ℃ (Lit.[3] m.p. = 117.5 – 118.0 ℃). $[\alpha]_D^{20}$ = 12.97 (c = 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 5H), 6.77 (d, *J* = 8.0 Hz, 1H), 4.64 (s, 2H), 4.06 – 3.91 (m, 2H), 3.91 – 3.81 (m, 1H), 3.29 – 3.24 (m, 1H), 3.14 (dd, *J* = 10.4, 3.2 Hz, 1H), 2.96 – 2.93 (m, 1H), 2.86 – 2.80 (m, 2H), 2.45 (dd, *J* = 12.0, 9.6 Hz, 1H), 2.08 – 2.04 (m, 1H), 1.91 – 1.78 (m, 3H), 1.42 (s, 9H), 1.34 – 1.21 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 154.7, 137.7, 128.5, 128.4, 127.9, 79.7, 76.9, 59.6, 56.8, 49.0, 46.2, 42.5, 31.9, 28.5, 28.2, 27.6. IR (neat) 2968, 2362, 1749, 1538, 1455, 1247, 1135, 1053 cm^{-1}. HRMS (ESI) m/z calcd for $C_{23}H_{36}N_4NaO_4$ [M + Na]$^+$: 455.2629, found: 455.2630.

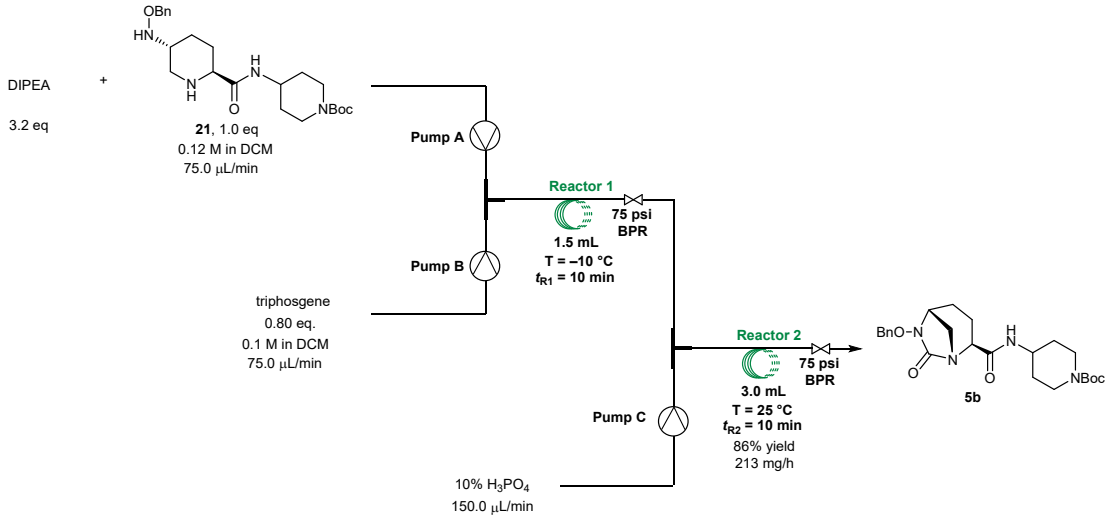
Synthesis of 22

Batch Reaction



To a solution of compound **21** (5.6 g, 12.9 mmol, 1.0 equiv.) in DCM (80.0 mL) was added DIPEA (7.2 mL, 41.4 mmol, 3.2 equiv.). The mixture was cooled to –18 ℃ and then charged with triphosgene (3.1 g, 10.4 mmol, 0.8 equiv.) in three portions. The mixture was stirred at –5 to 5 ℃ for 30 min then charged with 10 % H_3PO_4 aqueous. The mixture was stirred at room temperature overnight. A saturated aqueous solution of $NaHCO_3$ was added at 0 ℃, the mixture was extracted with DCM, the combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH = 150:1) to give compound **5b** (4.9 g, 82%) as a white solid.

Continuous-Flow Reaction



The self-build flow reactor equipment consists of two Fusion 4000 type syringe pumps for reagent/solvent delivery, a 1.5 mL PTFE coil reactor 1 (0.8 mm i.d.) and a 3.0 mL PTFE coil reactor 2 (0.8 mm i.d.). Before the start of the actual experiment, all reactors were primed with DCM. The syringe pump A was used to introduce the solution of compound **21** (0.12M, 1.0 equiv.) and DIPEA (3.2 equiv.) in DCM (75.0 μL/min), the syringe pump B was used to introduce the solution of triphosgene in DCM (0.1 M, 0.8 equiv., 75.0 μL/min). The two solutions were mixed through a T-shape mixer and pumped through the coil reactor 1 (1.5 mL, internal volume, t_{R1} = 10 min) at –10 °C. A 75 psi BPR was connected at the outlet of coil reactor 1. The reaction mixture in DCM from the reactor 1 output was combined with the 10 % H_3PO_4 aqueous (150.0 μL/min) at T-piece connector, entering the reactor 2 (3.0 mL, internal volume, t_{R2} = 10 min) at 25 °C. A 75 psi BPR was connected at the outlet of coil reactor 2. The system was allowed to come to steady state by waiting three residence times prior to collecting product. The reaction mixture was collected, a saturated aqueous solution of $NaHCO_3$ was added at 0 °C, the mixture was extracted with DCM, the combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH = 150:1) to give compound **5b** (213 mg/h, 86%) as a white solid. $[\alpha]_D^{20}$ = 17.27 (c = 0.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.32 (m, 5H), 6.59 (d, *J* = 8.4 Hz, 1H), 5.06 – 4.88 (m, 2H), 4.02 – 3.99 (m, 2H), 3.92 – 3.87 (m, 2H), 3.30 – 3.28 (m, 1H), 2.98 – 2.88 (m, 1H), 2.85 – 2.82 (m, 2H), 2.65 (d, *J* = 11.6 Hz, 1H), 2.36 (dd, *J* = 14.8, 6.8 Hz, 1H), 2.04 – 1.80 (m, 4H), 1.64 – 1.52 (m, 1H), 1.44 (s, 9H), 1.34 – 1.22 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 167.3, 154.7, 135.6, 129.3, 128.9, 128.6, 79.8, 78.3, 60.4, 57.8, 47.5, 46.8, 32.0, 31.8, 28.4, 20.8, 17.3. IR (neat) 2925, 2861, 1749, 1682, 1514, 1454, 1422, 1364, 1316, 1300, 1217, 1166, 1197, 1062, 974, 893, 743, 692, 526 cm^{-1}. HRMS (ESI) m/z calcd for $C_{24}H_{34}N_4NaO_5$ [M + Na]$^+$: 481.2421, found: 481.2420.

Synthesis of 2

Batch Reaction

To a stirred solution of compound **5b** (1.5 g, 3.3 mmol, 1.0 equiv.) in THF (30.0 mL) was added $Pd(OH)_2/C$ (300.0 mg, 20 wt%) and the resulting solution was transferred to an autoclave, which was purged (3 × 5 atm) and charged with H_2 (20 atm), then the reaction mixtures were stirred at room temperature for 12 h. The hydrogen gas was released slowly, and the solution was concentrated to give crude product as a white foam, which was directly used in next step without further purification.

To a solution of the crude product above in pyridine (50.0 mL) was added sulfur trioxide trimethylamine complex (4.2 g, 26.2 mmol, 8.0 equiv.), the reaction mixture was stirred at room temperature for 12 h and concentrated in vacuum. The residue was redissolved in DCM (80.0 mL), 0.5 M K_2HPO_4 (10.4 mL, 5.2 mmol, 1.6 equiv.) was added over 5 minutes. Bu_4NHSO_4 (1.2 g, 3.6 mmol, 1.1 equiv.) was then added over 5 minutes. After stirring for 30 minutes, the mixture was extracted with DCM, the combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure, which used with an assumed yield of 100% in the next step.

The solution of $Bu_4N^+SO_4^-$ salt (2.3 g, 3.3 mmol, 1.0 equiv.) was cooled in an ice bath, and TMSI (0.7 mL, 4.9 mmol, 1.5 equiv.) was added dropwise. The reaction mixture was stirred for 2 h, then quenched with water to afford a slurry. The slurry was warmed to room temperature and agitated for 12 h. Tetrabutylammonium acetate (295.9 mg, 1.0 mmol, 0.3 equiv.) was slowly added. The slurry was agitated for 1 h. Filter to collect the solid, and the solid was washed with MeCN/water (94/6) to afford the product **2** (888.9 mg, 78% for 4 steps) as a white solid. $[\alpha]_D^{20}$ = –26.7 (c = 1.0, $CHCl_3$) [Lit.[4] $[\alpha]_D^{25}$ = –23.3 (c = 1.0, $CHCl_3$)]. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 1H), 8.20 (d, J = 7.6 Hz, 1H), 8.17 (s, 1H), 4.00 (s, 1H), 3.94 – 3.85 (m, 1H), 3.73 (d, J = 6.4 Hz, 1H), 3.27 (d, J = 12.8 Hz, 2H), 3.05 – 2.91 (m, 4H), 2.05 – 1.95 (m, 1H), 1.94 – 1.79 (m, 3H), 1.71 – 1.61 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.1, 166.1, 59.3, 57.6, 46.4, 43.8, 42.3, 28.1, 27.9, 20.5, 18.4. IR (neat) 2920, 2359, 1742, 1526, 1451, 1238, 1023, 1007, 749, 578 cm^{-1}. HRMS (ESI) m/z calcd for $C_{12}H_{21}N_4O_6S$ $[M + H]^+$: 349.1176, found: 349.1175.

NMR data is consistent with data reported in the literature.[4]

5. Supplemental References

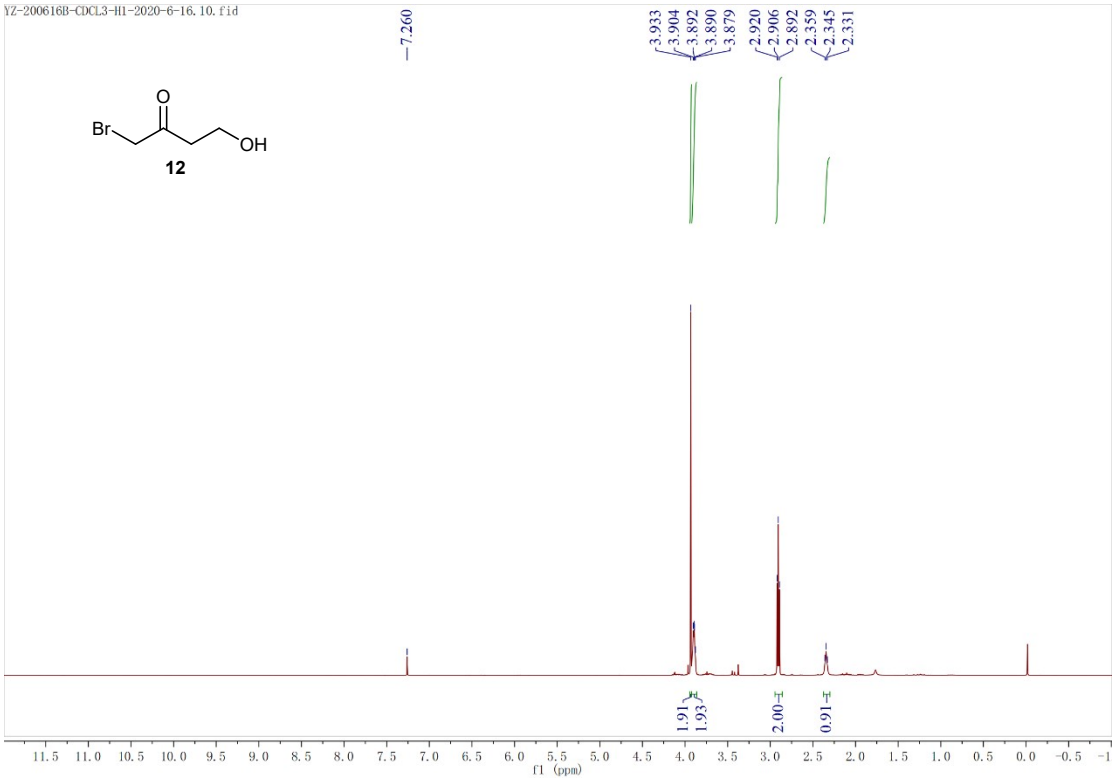
1 Z. Edoo, L. Iannazzo, F. Compain, I. Li de la Sierra Gallay, H. van Tilbeurgh, M. Fonvielle, F. Bouchet, E. Le Run, J.-L. Mainardi, M. Arthur, M. Ethève-Quelquejeu and J.-E. Hugonnet, *Chem. Eur. J.*, 2018, **24**, 8081–8086.

2 T. Wang, L. -D. Du, D. -j. Wan, X. Li, X. -Z. Chen and G. -F. Wu, *Org. Process Res. Dev.*, 2018, **22**, 1738–1744.

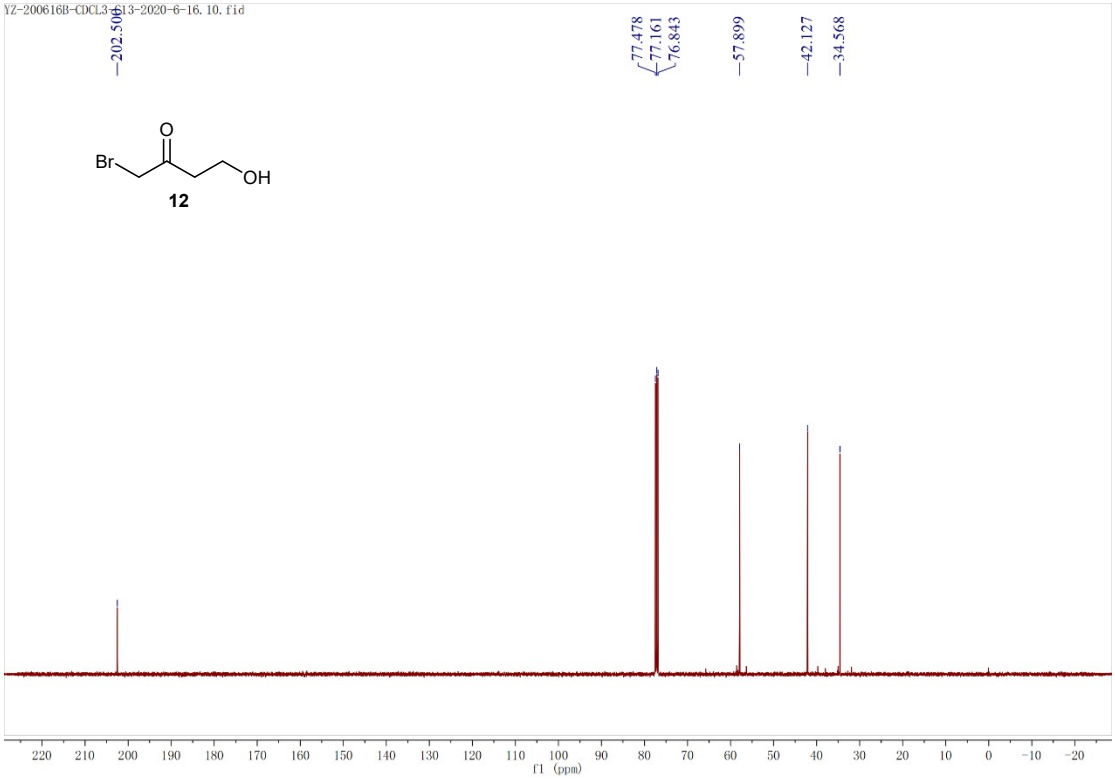
3 S. P. Miller, Y.-L. Zhong, Z. Liu, M. Simeone, N. Yasuda, J. Limanto, Z. Chen, J. Lynch and V. Capodanno, *Org. Lett.*, 2014, **16**, 174–177.

4 I. K. Mangion, R. T. Ruck, N. Rivera, M. A. Huffman and M. Shevlin, *Org. Lett.*, 2011, **13**, 5480–5483.

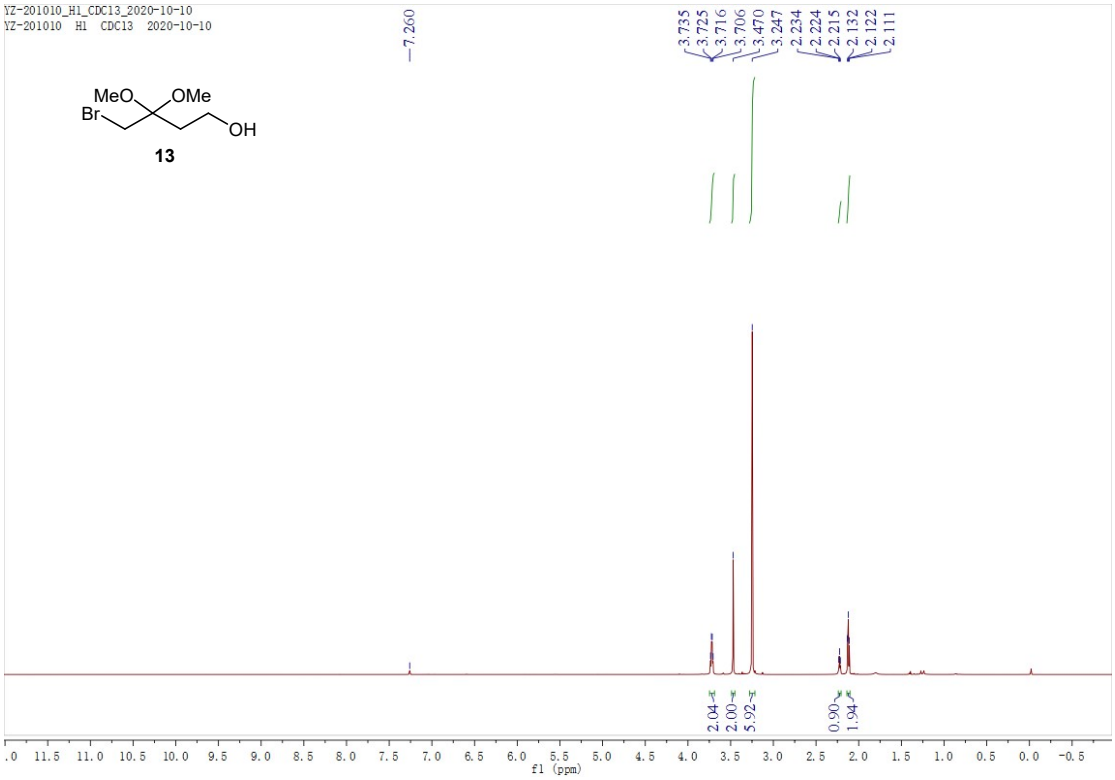
6. NMR Spectra



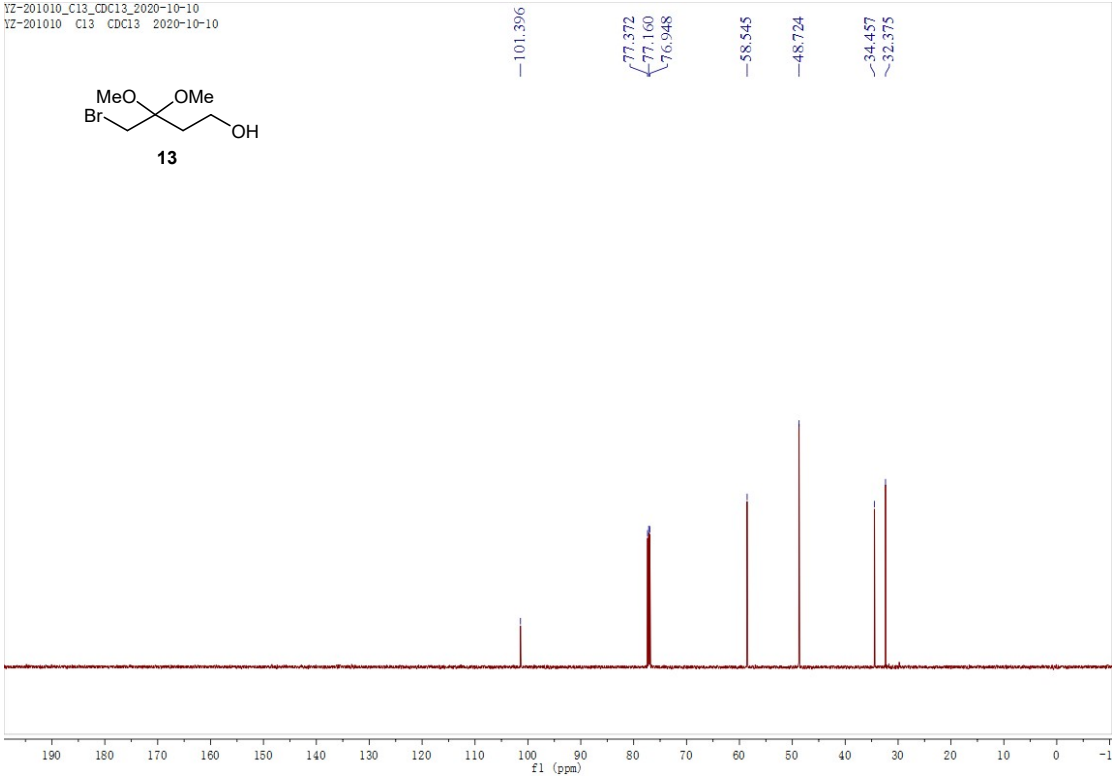
^{1}H-NMR Spectrum (400 MHz, $CDCl_3$) of Compound 12



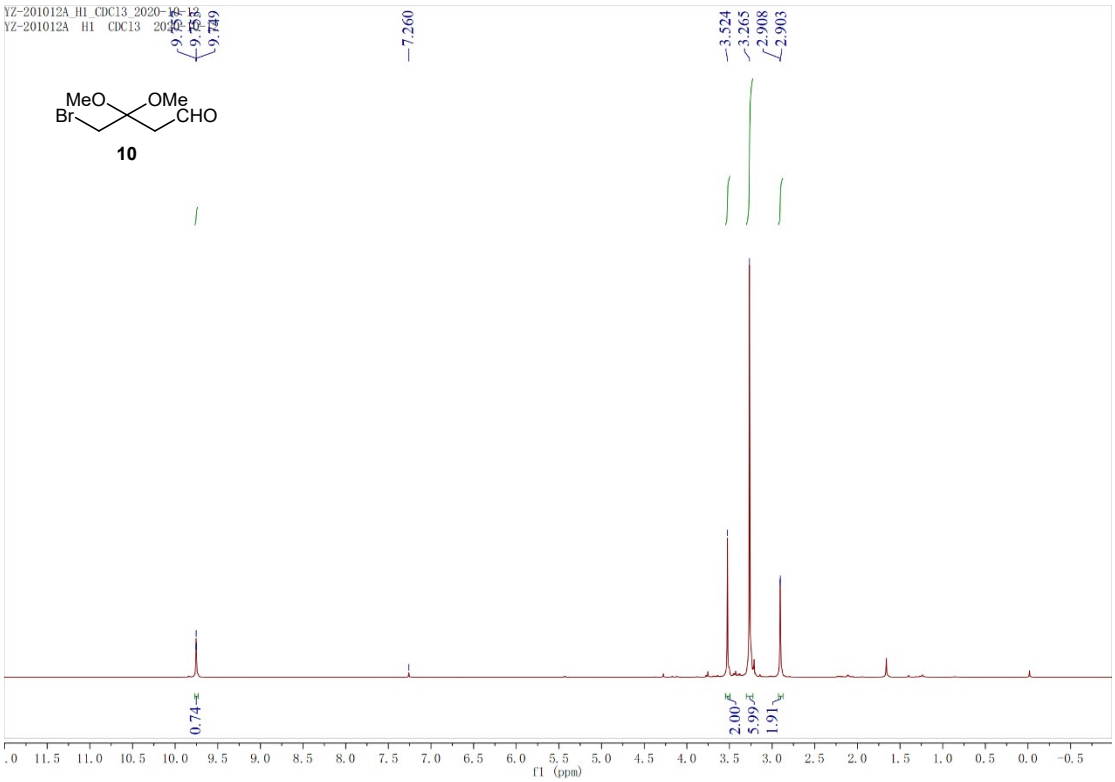
^{13}C-NMR Spectrum (100 MHz, $CDCl_3$) of Compound 12



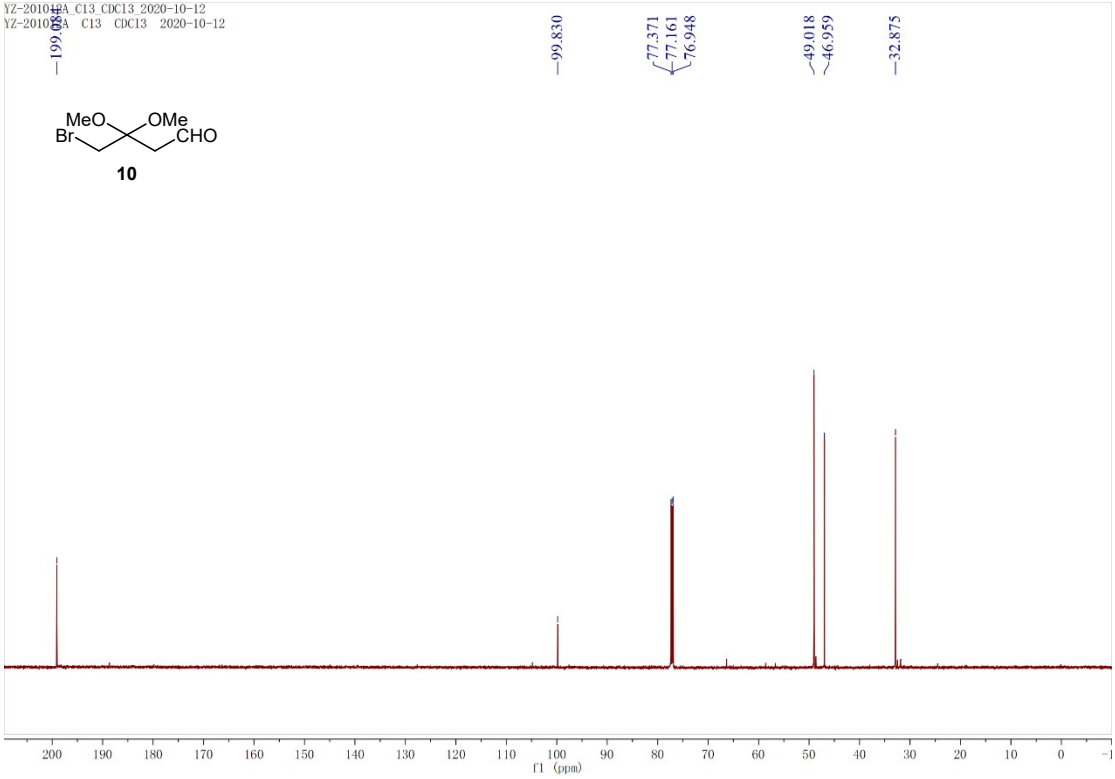
^{1}H-NMR Spectrum (600 MHz, $CDCl_3$) of Compound 13



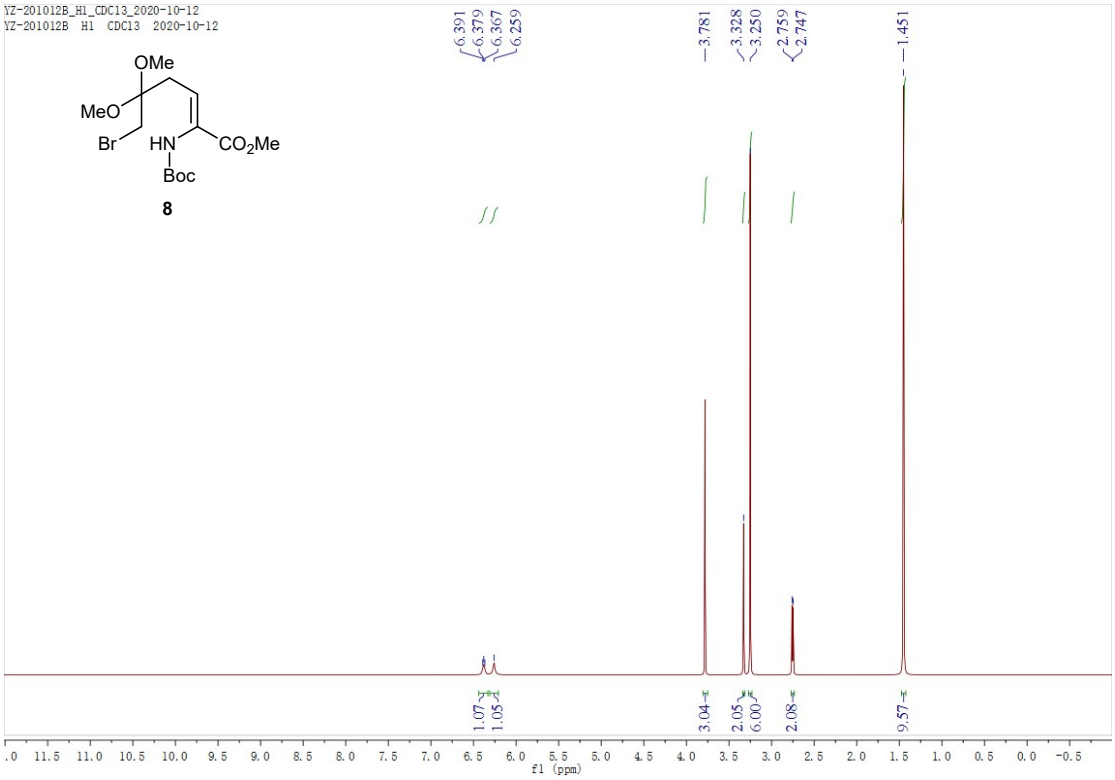
^{13}C-NMR Spectrum (150 MHz, $CDCl_3$) of Compound 13



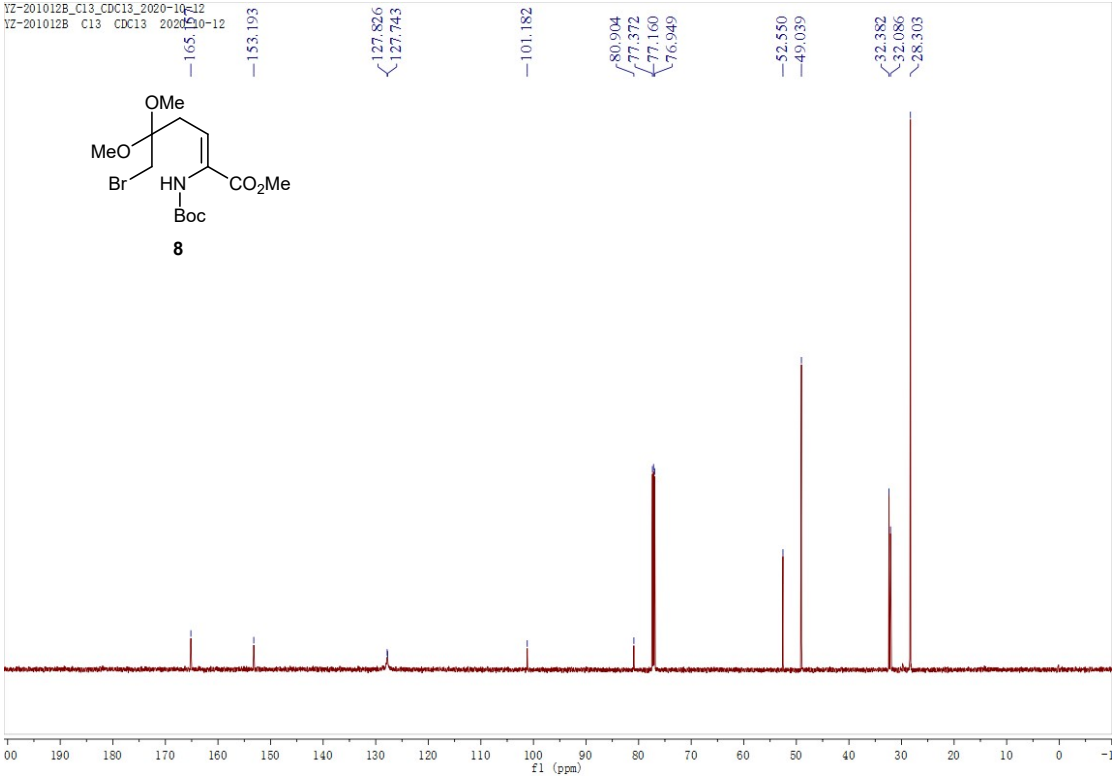
^{1}H-NMR Spectrum (600 MHz, $CDCl_3$) of Compound 10



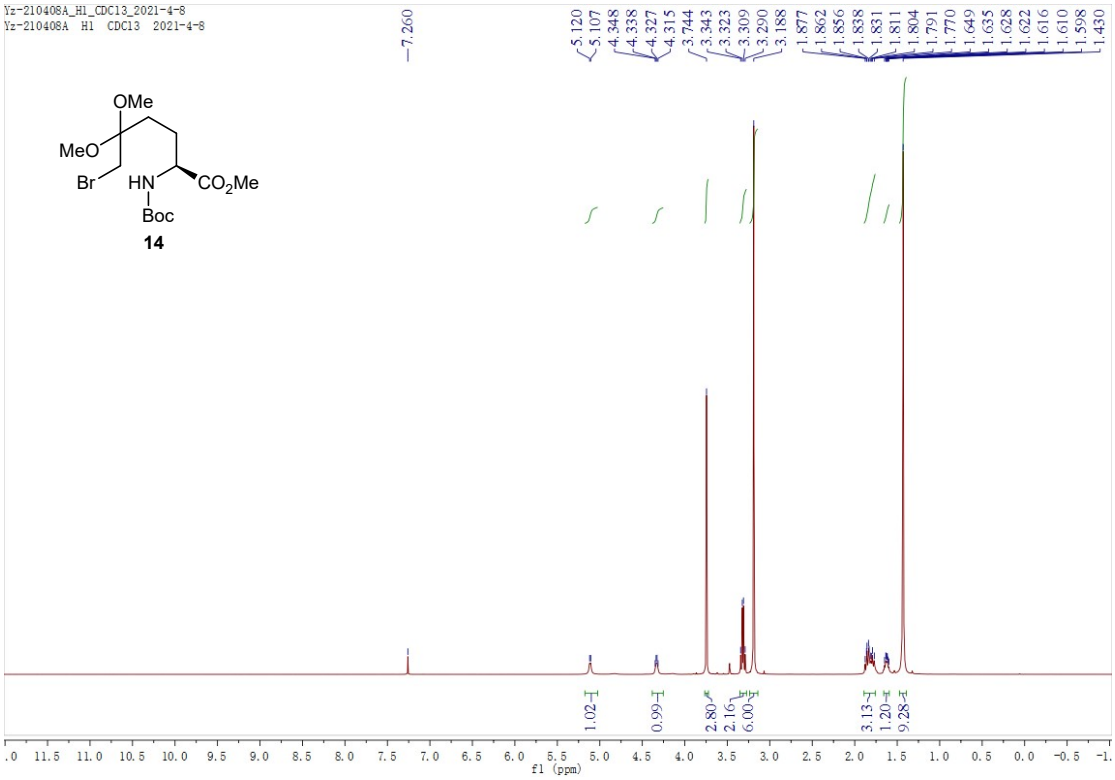
^{13}C-NMR Spectrum (150 MHz, $CDCl_3$) of Compound 10



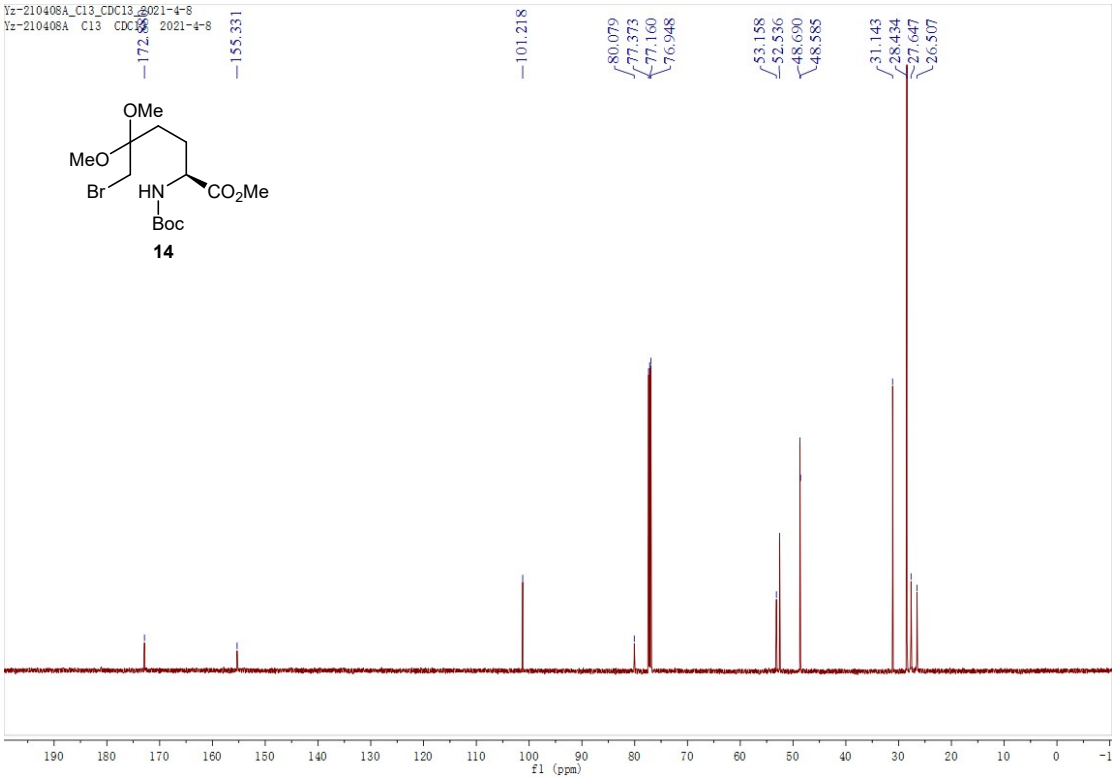
^{1}H-NMR Spectrum (600 MHz, $CDCl_3$) of Compound 8



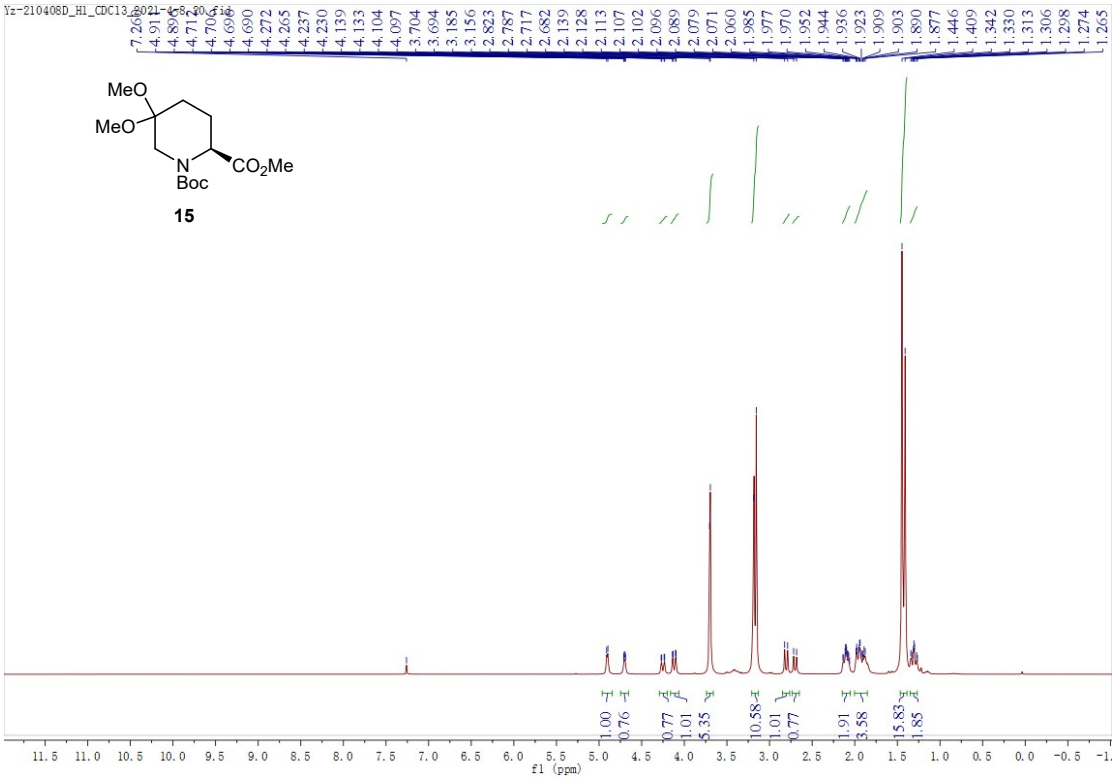
^{13}C-NMR Spectrum (150 MHz, $CDCl_3$) of Compound 8



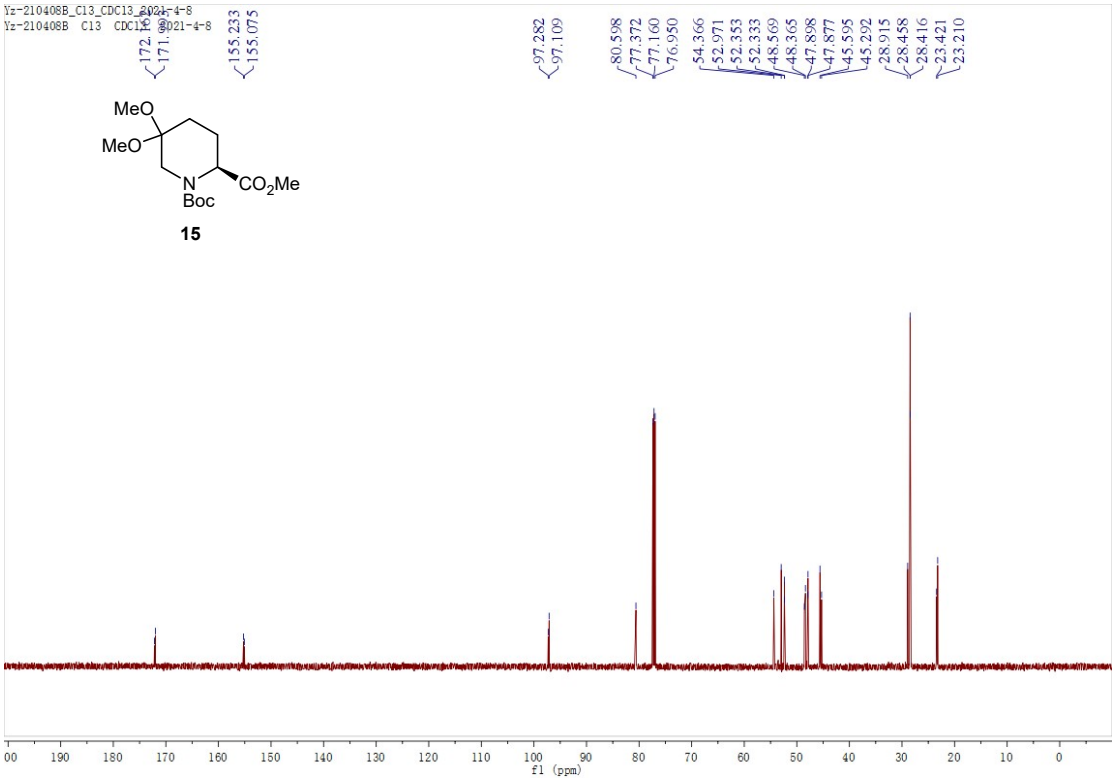
^{1}H-NMR Spectrum (600 MHz, $CDCl_3$) of Compound 14



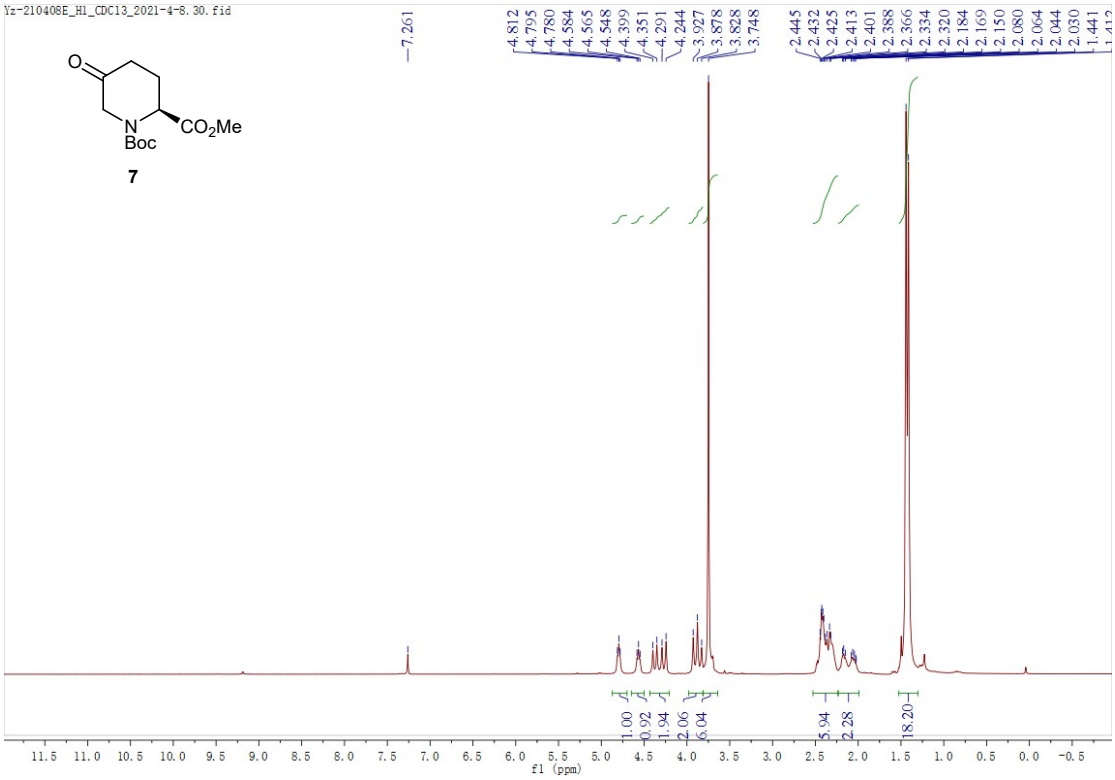
^{13}C-NMR Spectrum (150 MHz, $CDCl_3$) of Compound 14



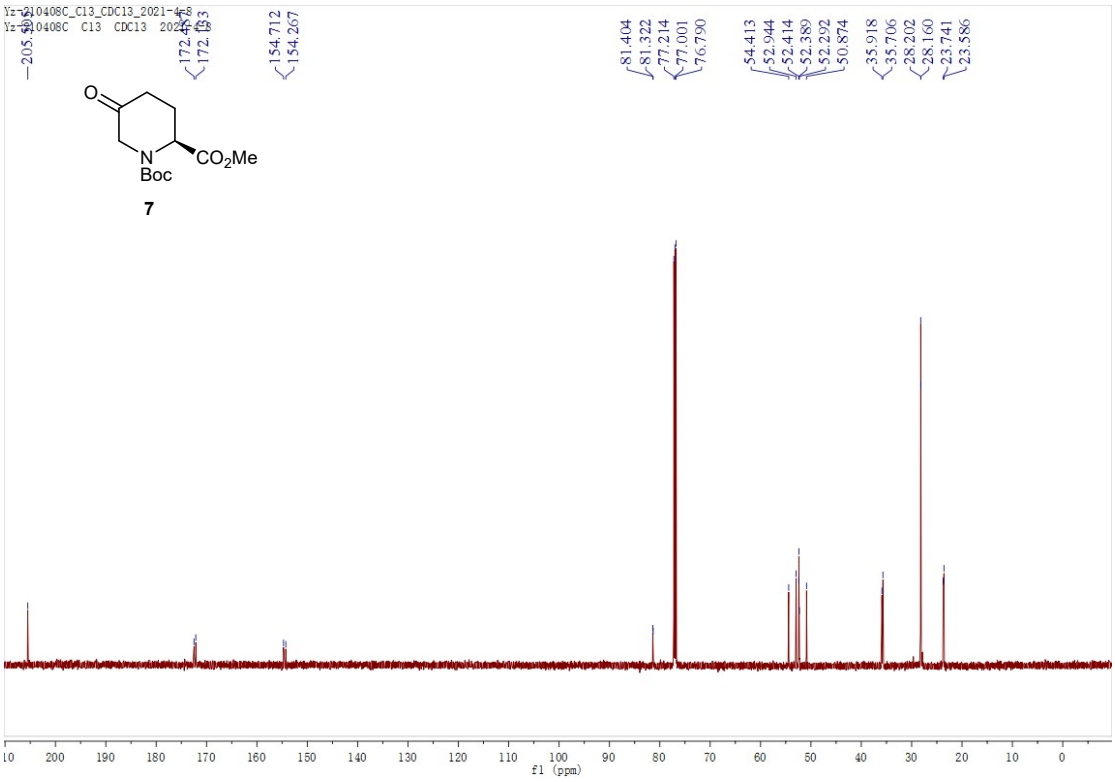
^{1}H-NMR Spectrum (400 MHz, $CDCl_3$) of Compound 15



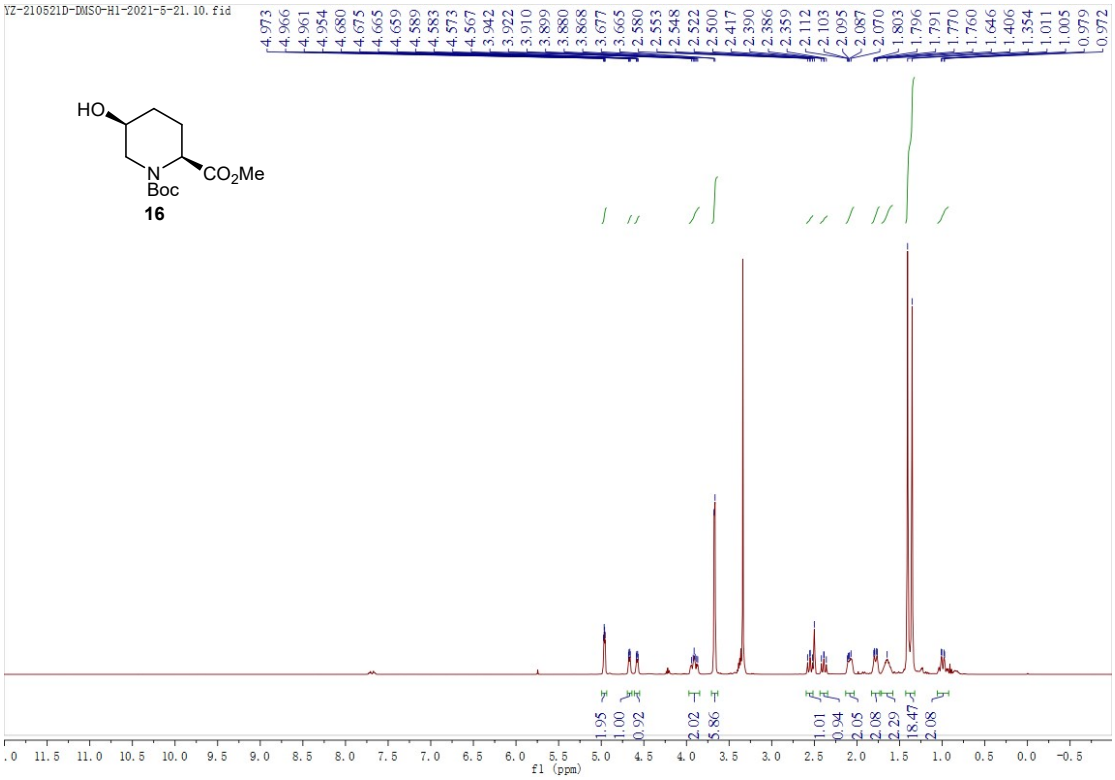
^{13}C-NMR Spectrum (150 MHz, $CDCl_3$) of Compound 15



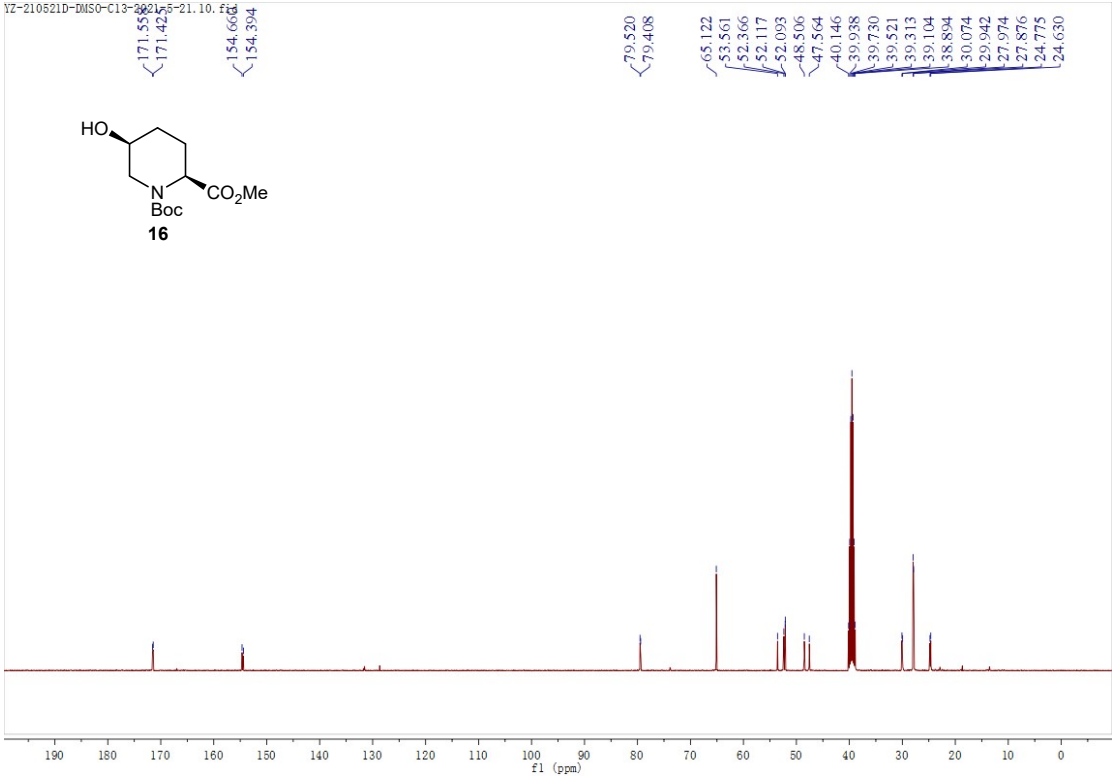
^{1}H-NMR Spectrum (400 MHz, $CDCl_3$) of Compound 7



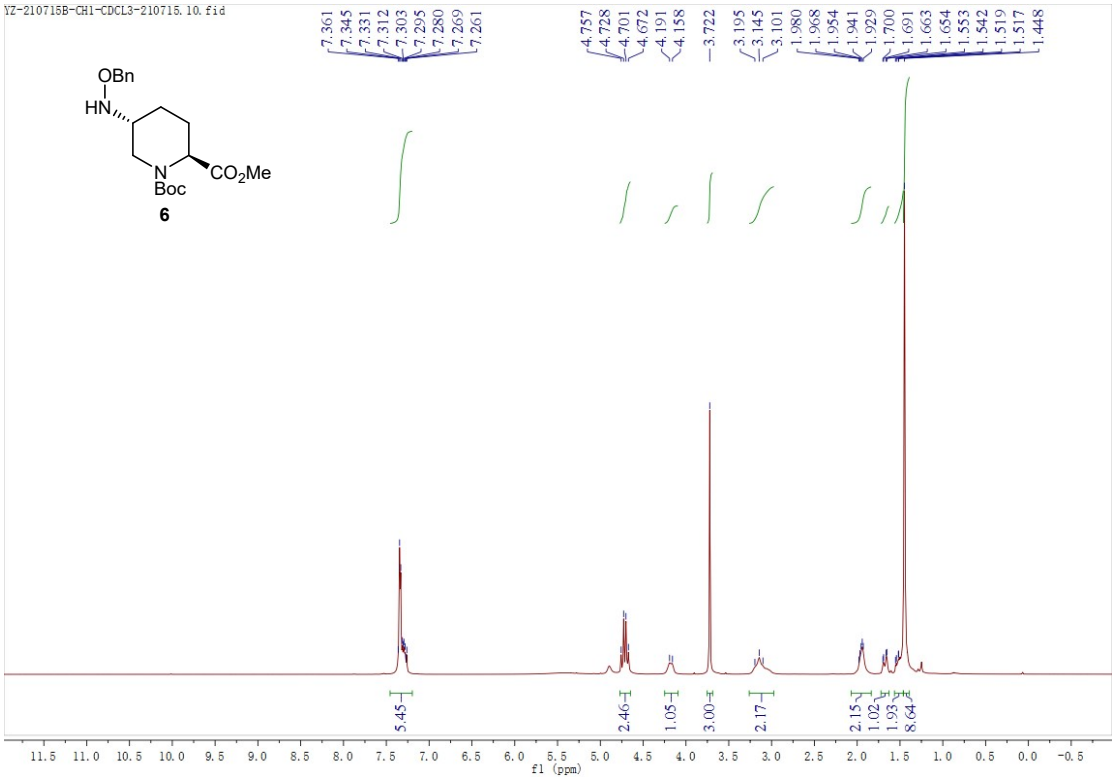
^{13}C-NMR Spectrum (150 MHz, $CDCl_3$) of Compound 7



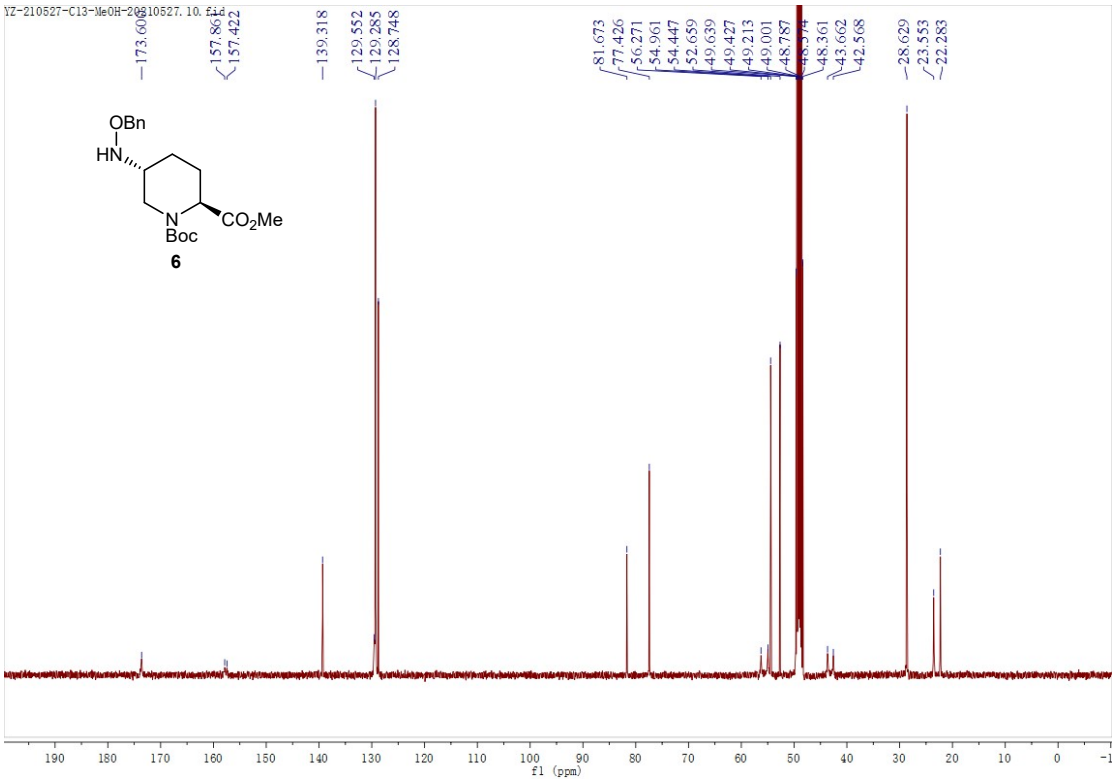
^{1}H-NMR Spectrum (400 MHz, DMSO-d_6) of Compound 16



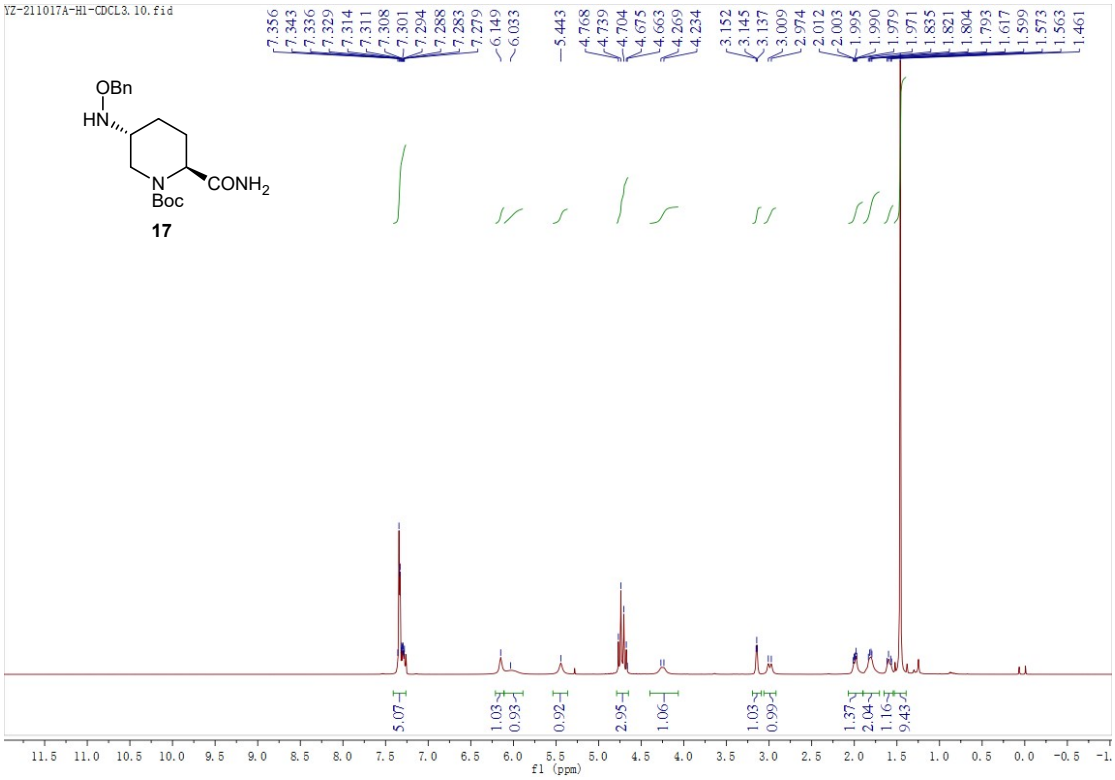
^{13}C-NMR Spectrum (100 MHz, DMSO-d_6) of Compound 16



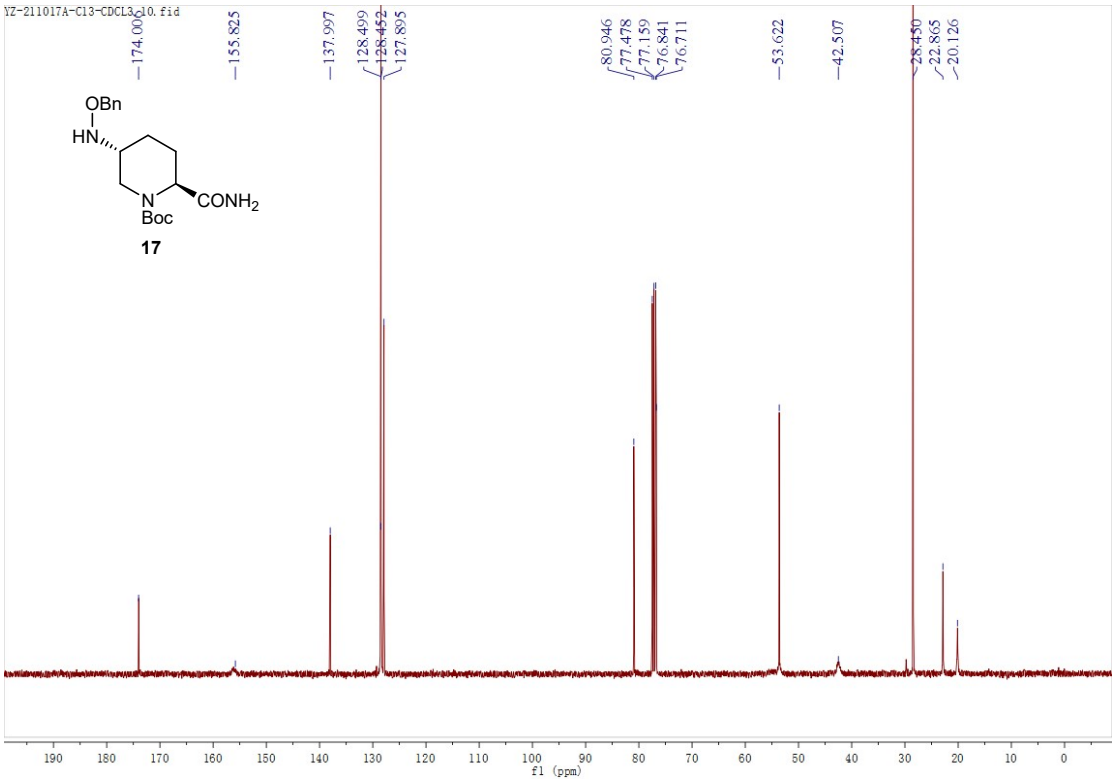
^{1}H-NMR Spectrum (400 MHz, $CDCl_3$) of Compound 6



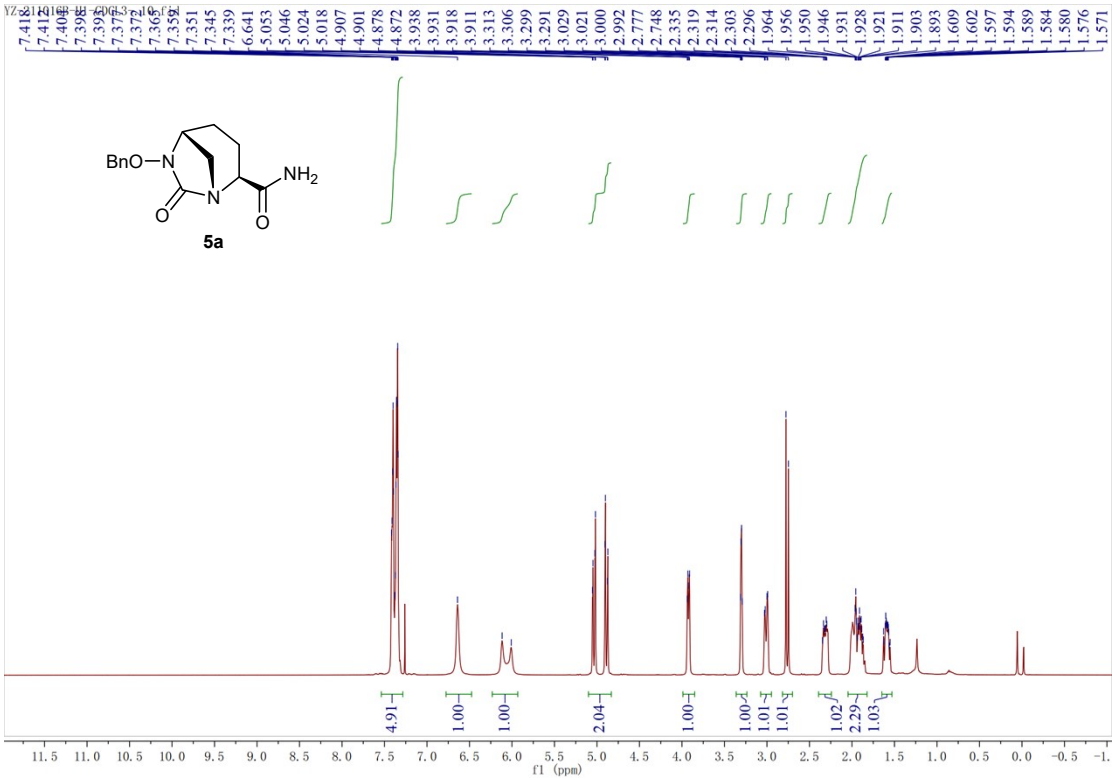
^{13}C-NMR Spectrum (100 MHz, MeOH- d_4) of Compound 6



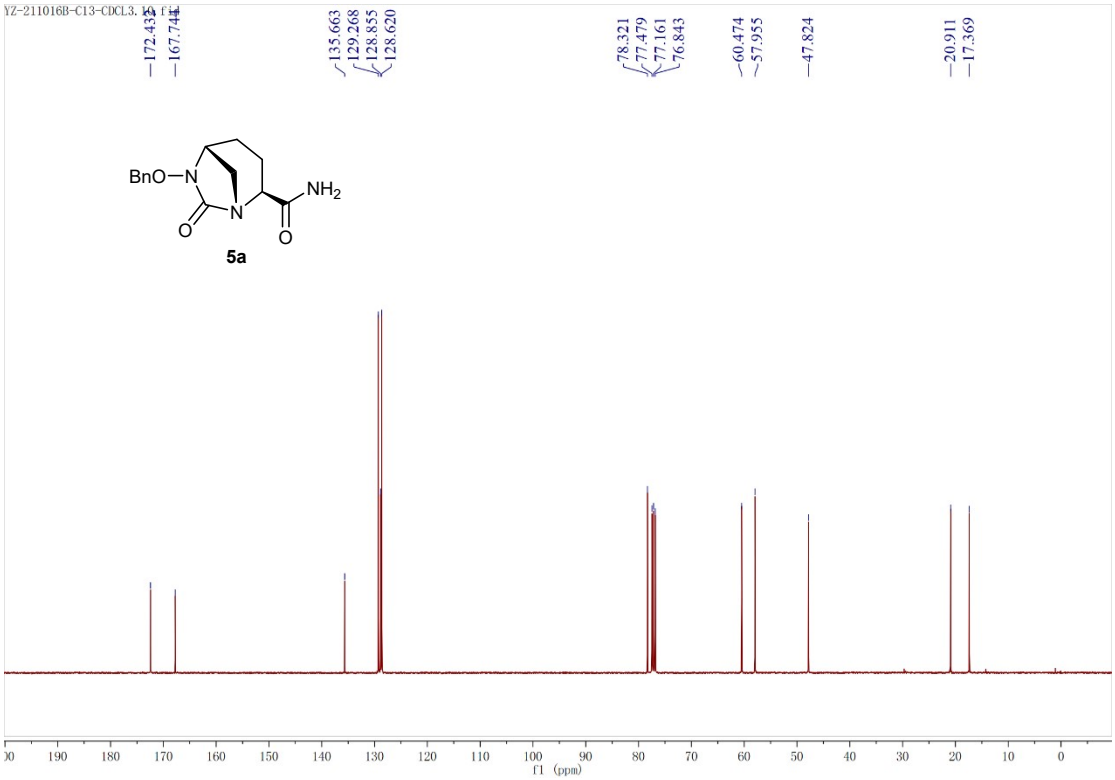
^{1}H-NMR Spectrum (400 MHz, $CDCl_3$) of Compound 17



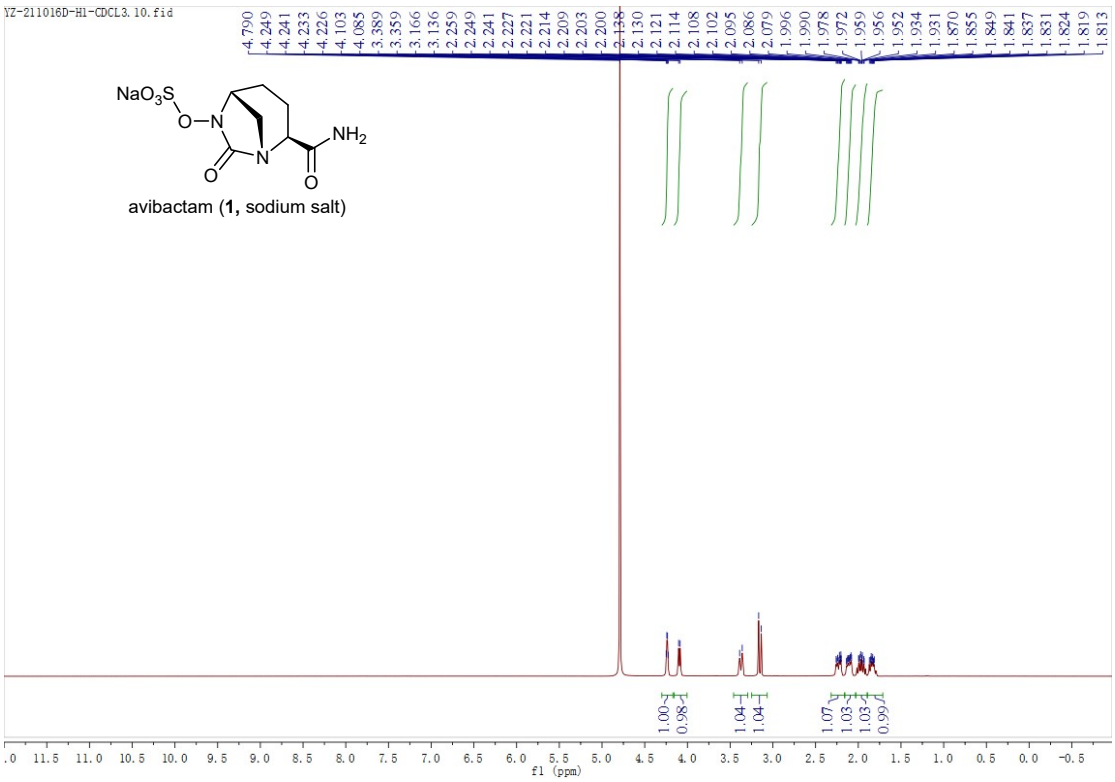
^{13}C-NMR Spectrum (100 MHz, $CDCl_3$) of Compound 17



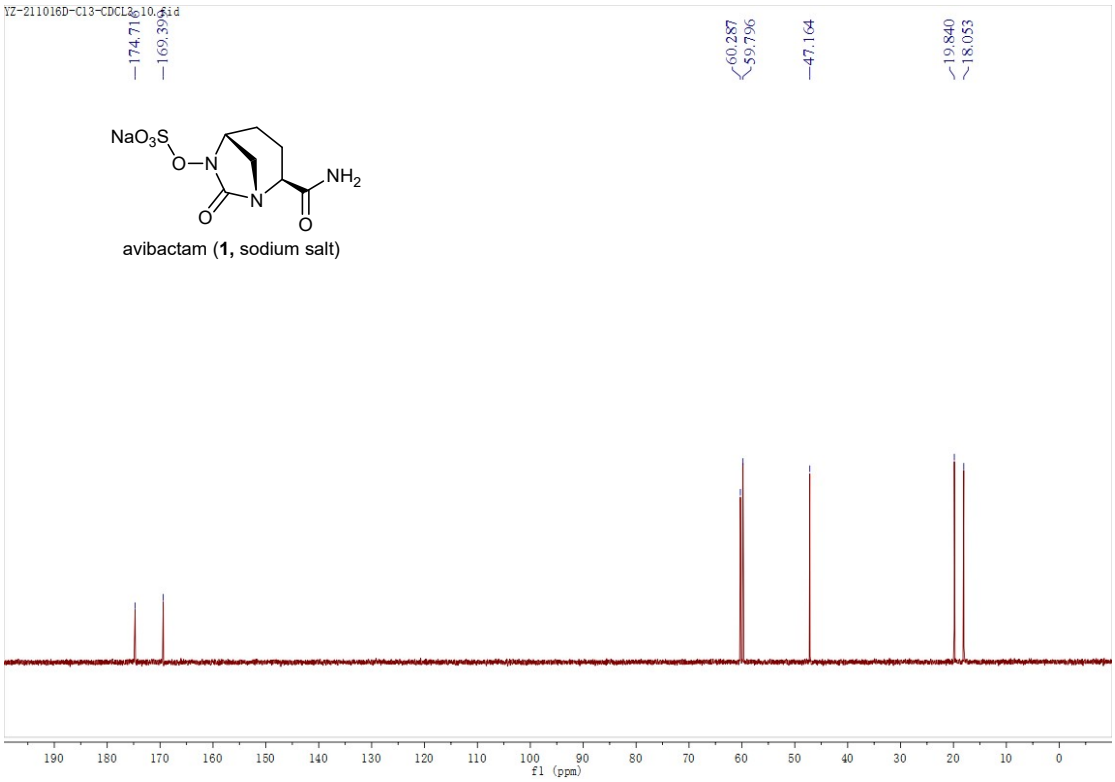
^{1}H-NMR Spectrum (400 MHz, $CDCl_3$) of Compound 5a



^{13}C-NMR Spectrum (100 MHz, $CDCl_3$) of Compound 5a



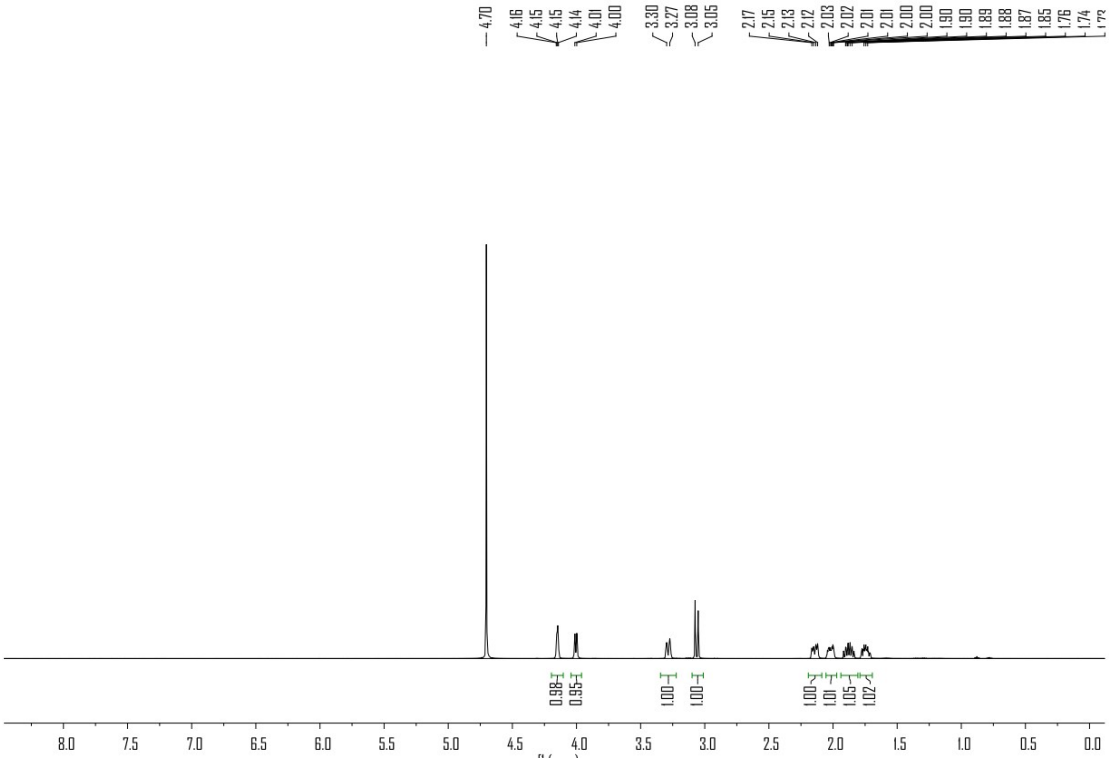
^{1}H-NMR Spectrum (400 MHz, D_2O) of Compound 1



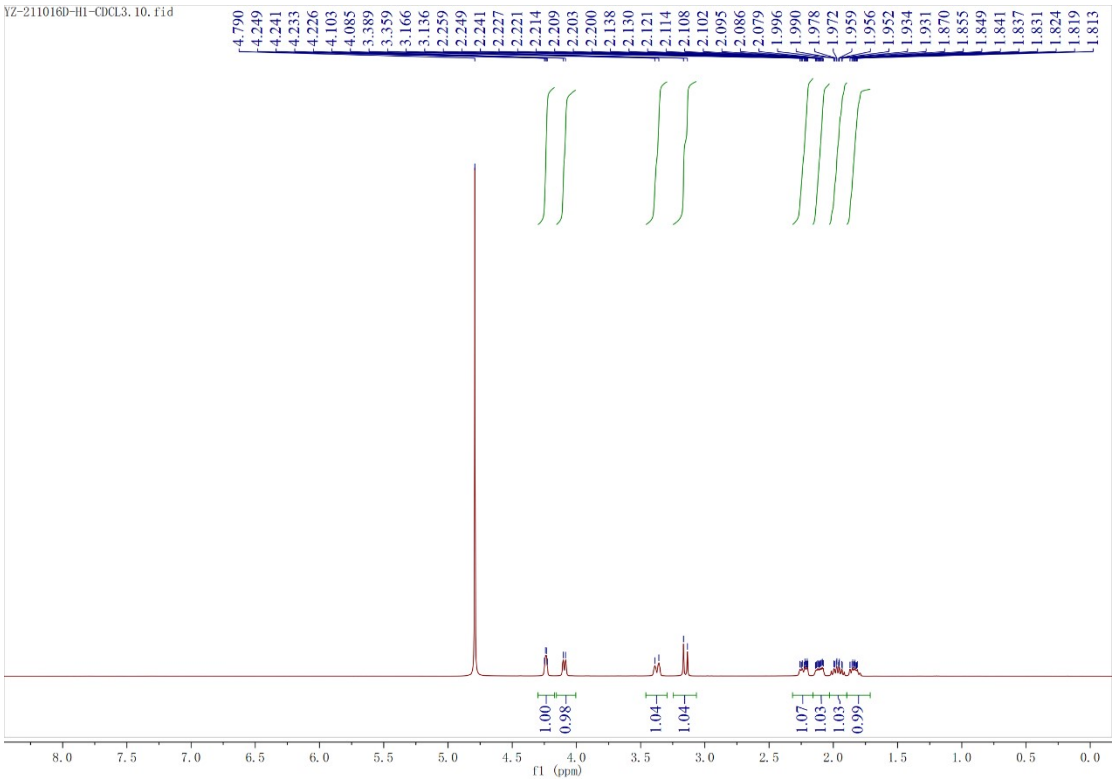
^{13}C-NMR Spectrum (100 MHz, D_2O) of Compound 1

Comparison of ^{1}H spectrums between the synthesized avibactam by Wu's group and the synthesized avibactam by our group.

The synthesized avibactam by Wu's group

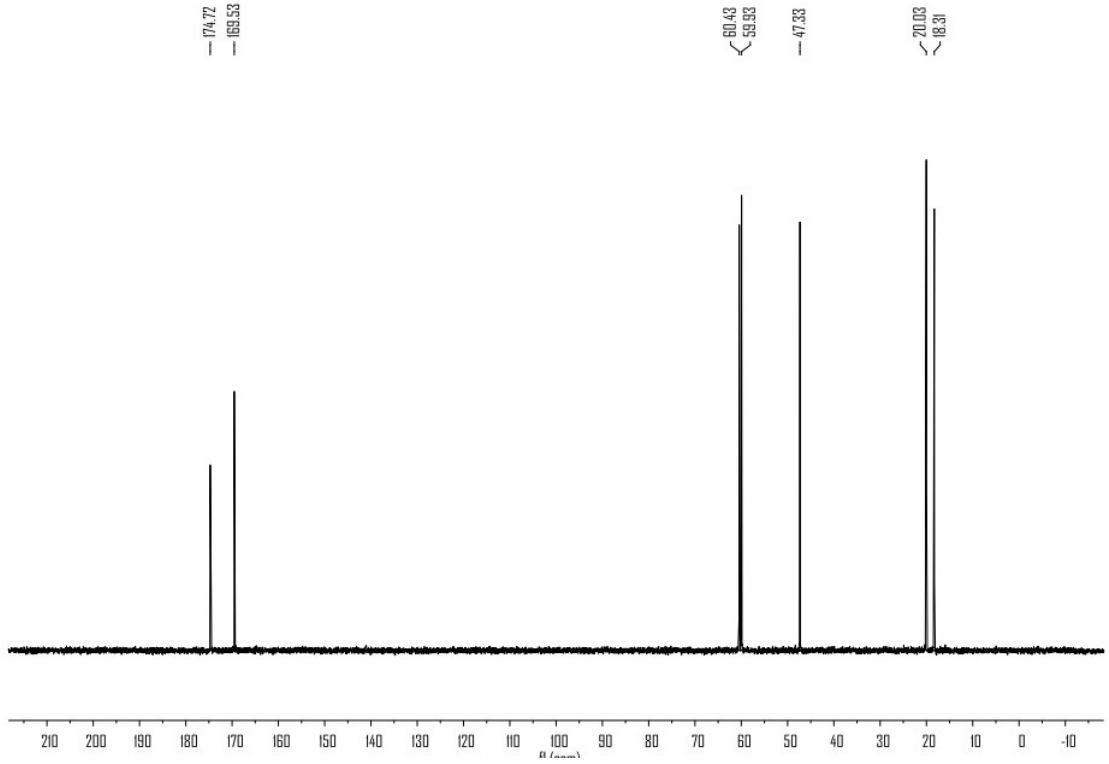


The synthesized avibactam by our group

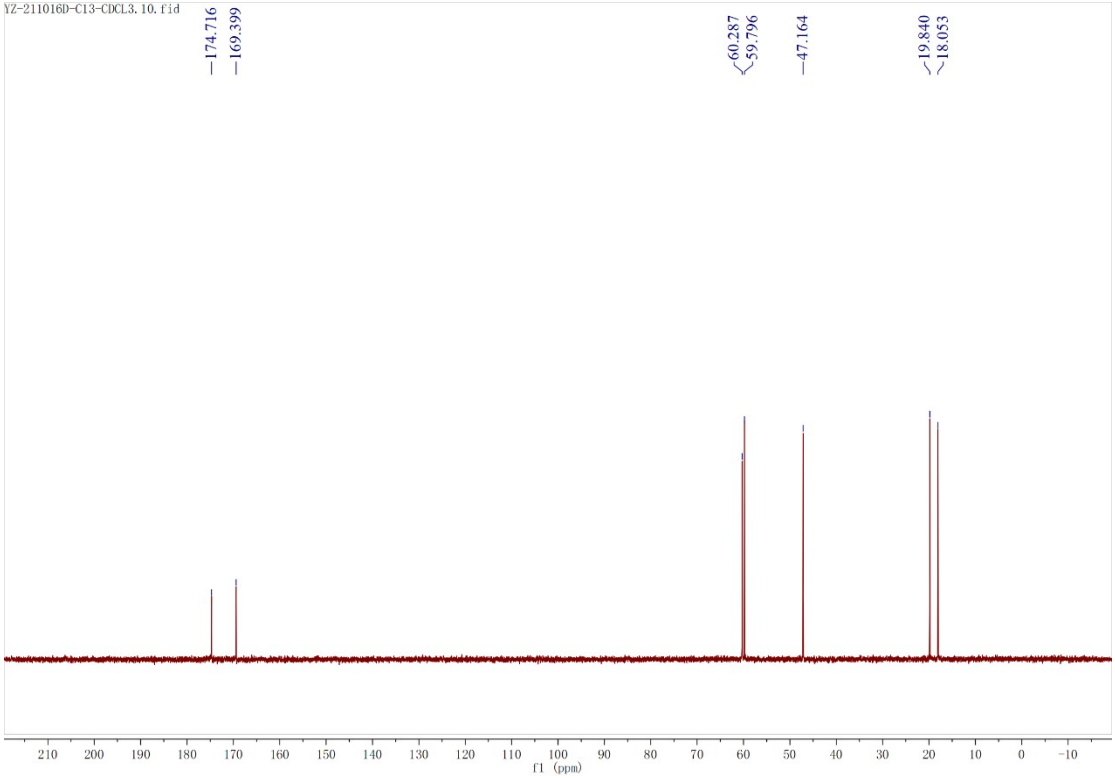


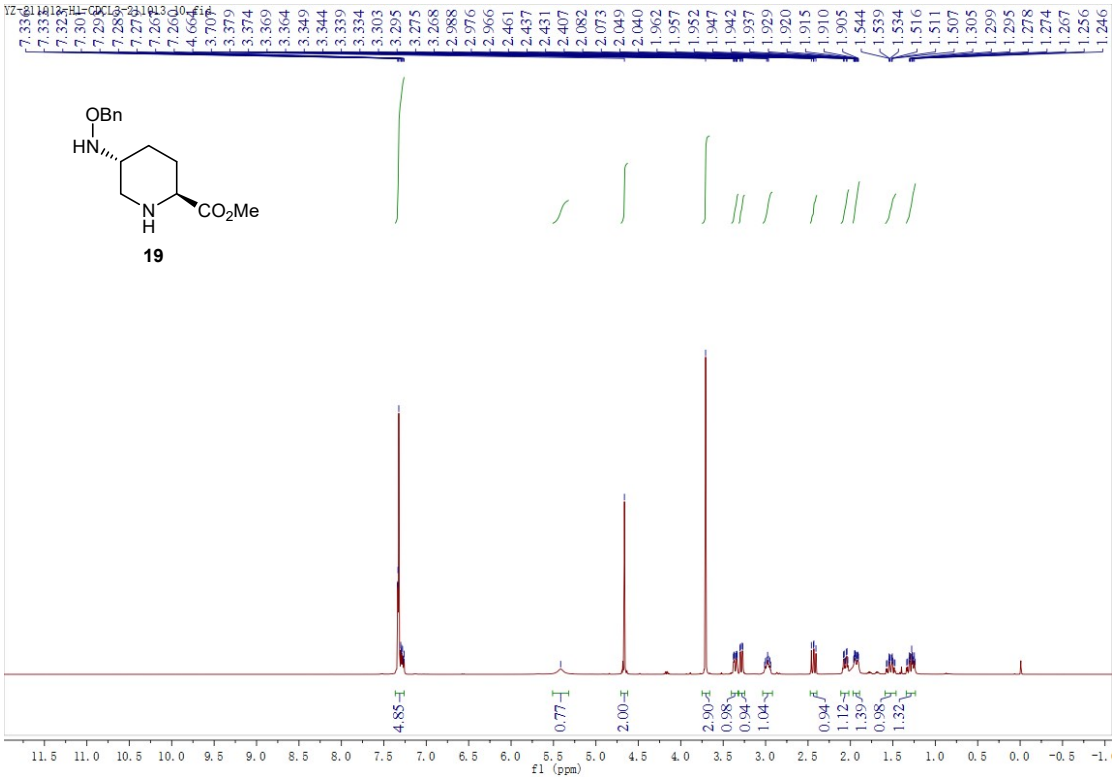
Comparison of ^{13}C spectrums between the synthesized avibactam by Wu's group and the synthesized avibactam by our group.

The synthesized avibactam by Wu's group

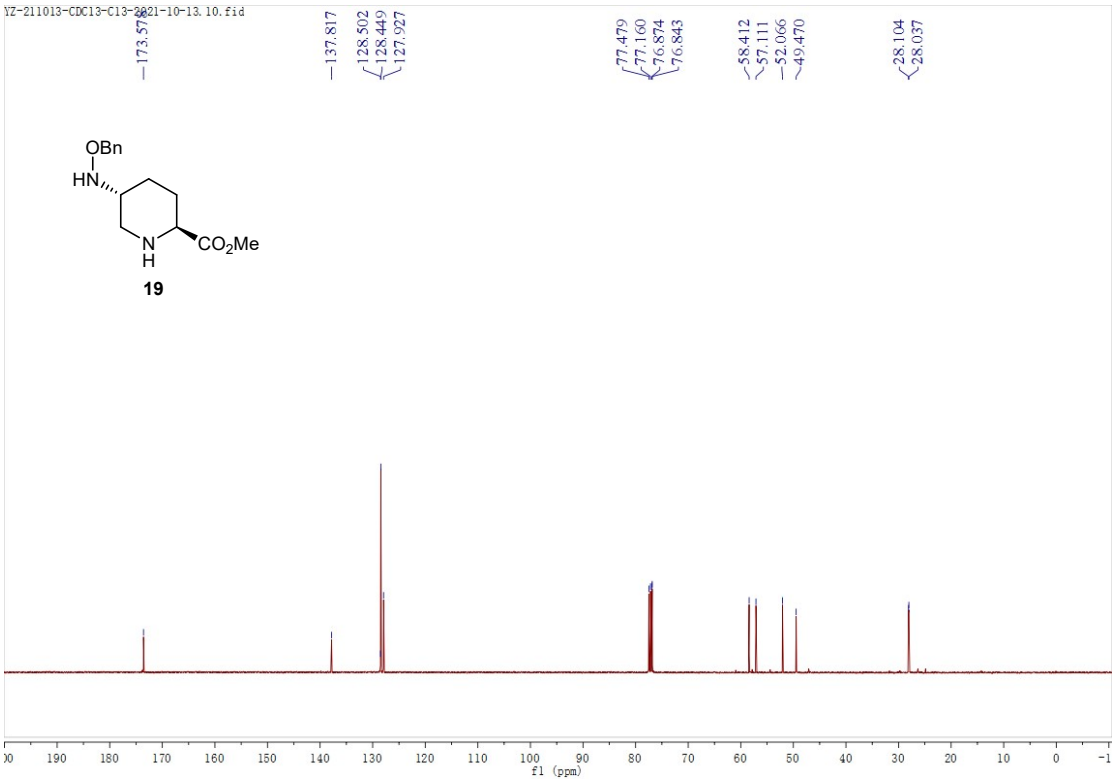


The synthesized avibactam by our group

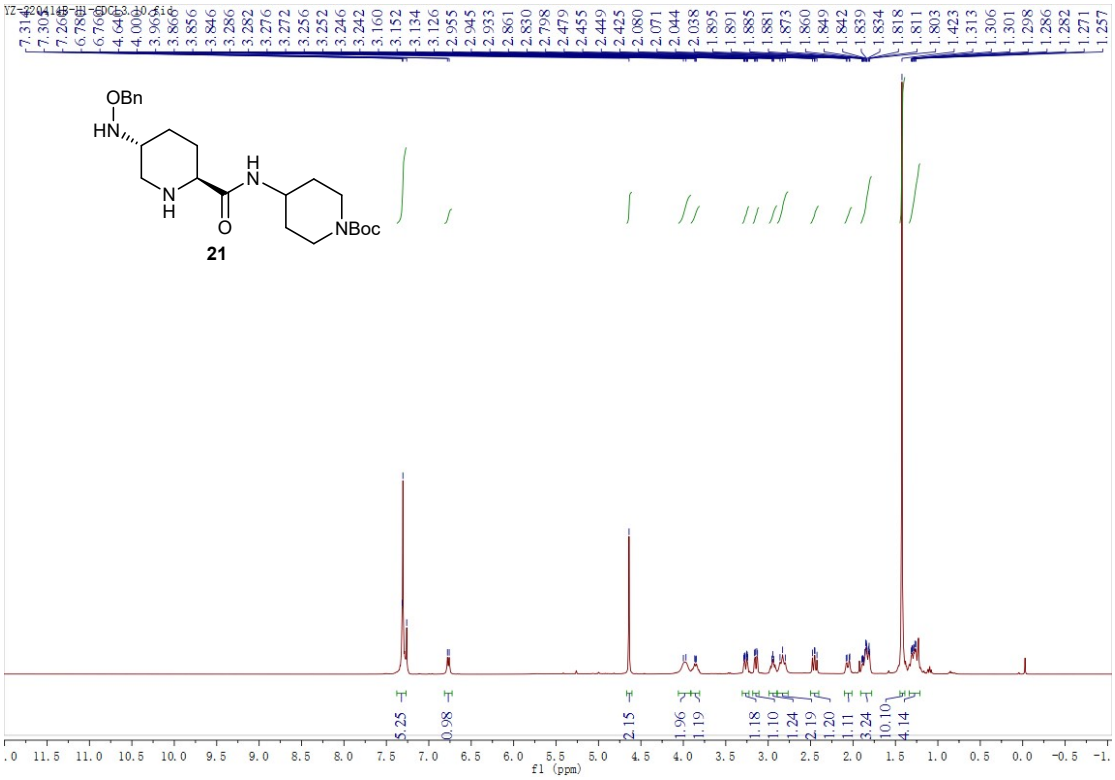




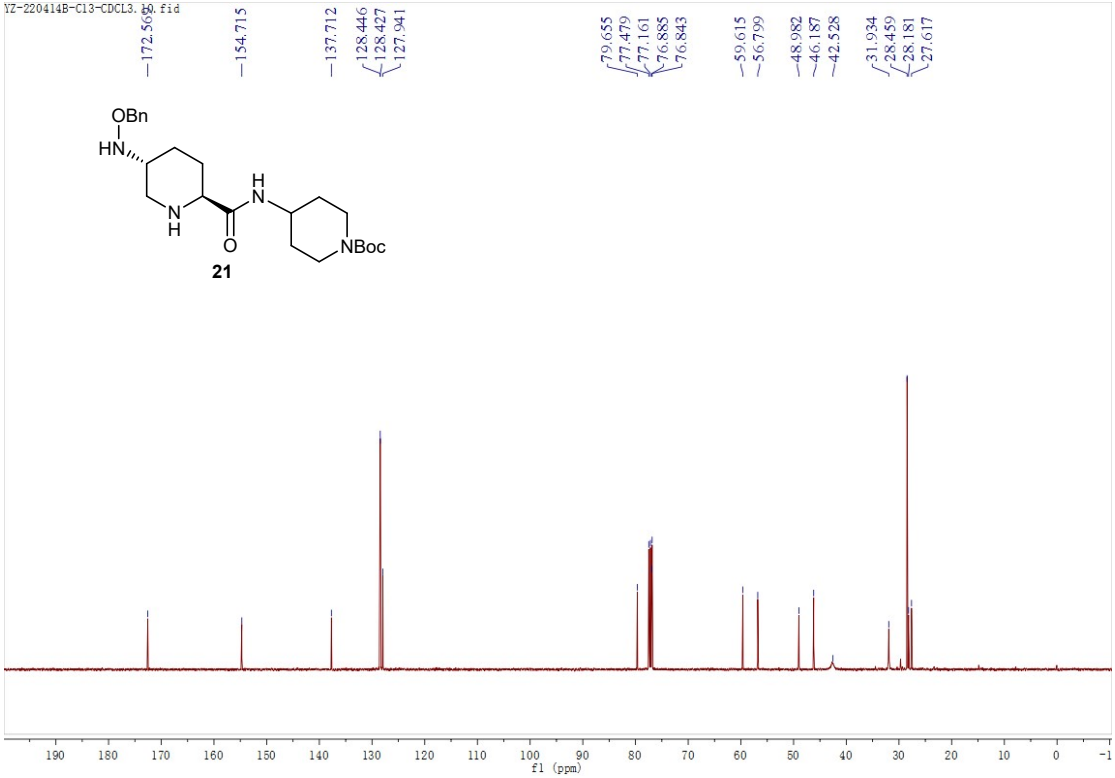
^{1}H-NMR Spectrum (400 MHz, $CDCl_3$) of Compound 19



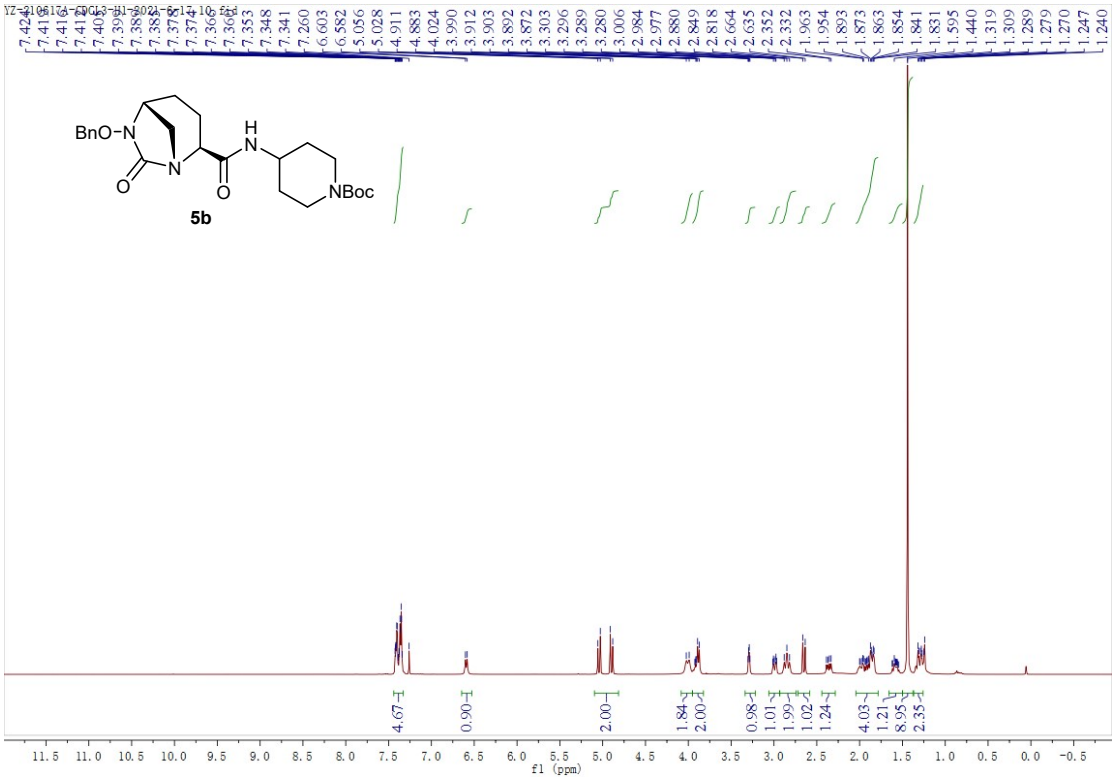
^{13}C-NMR Spectrum (100 MHz, $CDCl_3$) of Compound 19



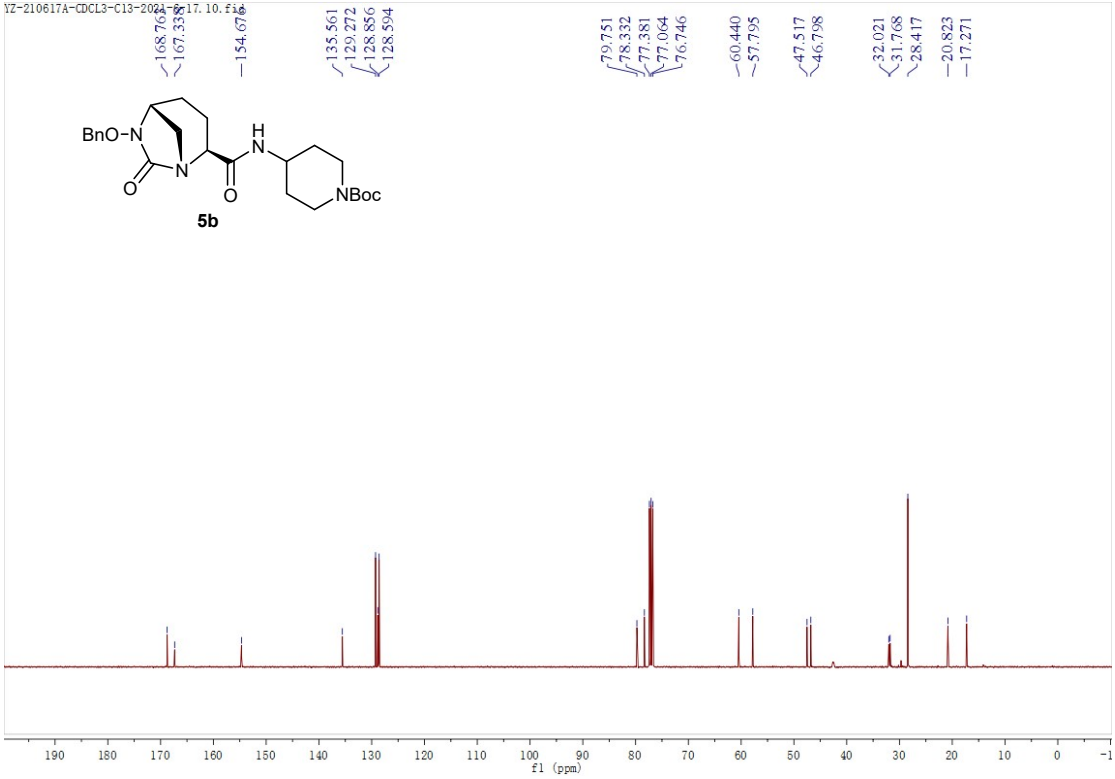
^{1}H-NMR Spectrum (400 MHz, $CDCl_3$) of Compound 21



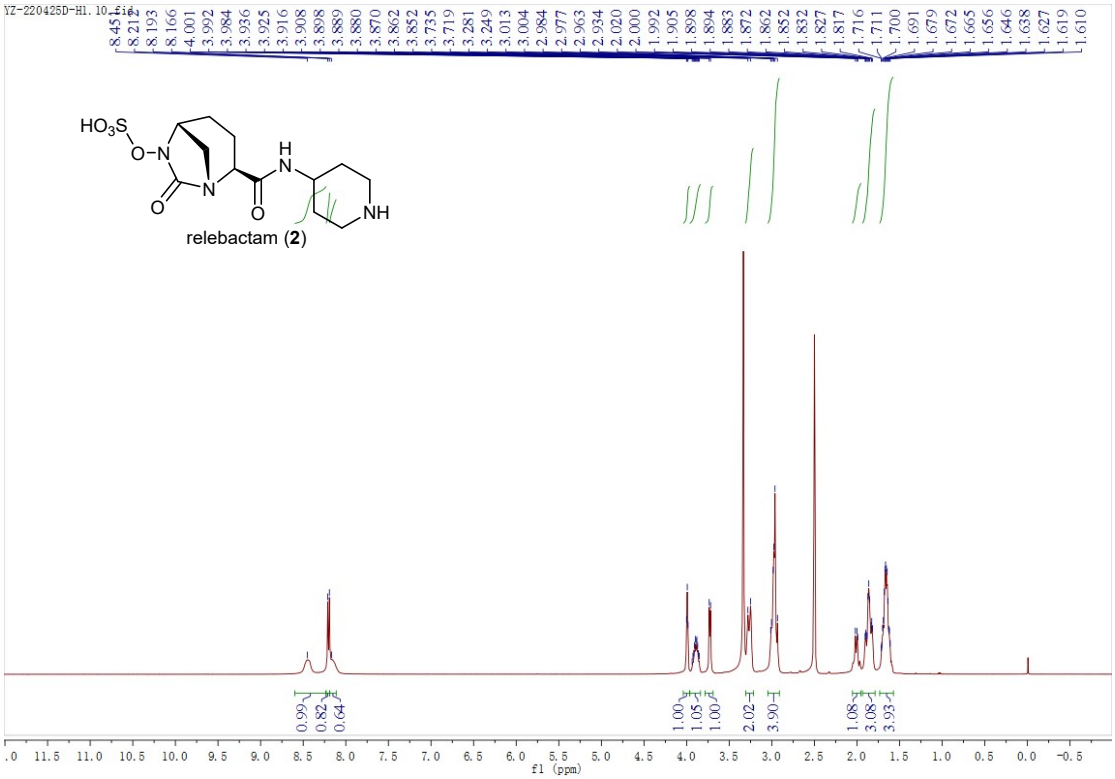
^{13}C-NMR Spectrum (100 MHz, $CDCl_3$) of Compound 21



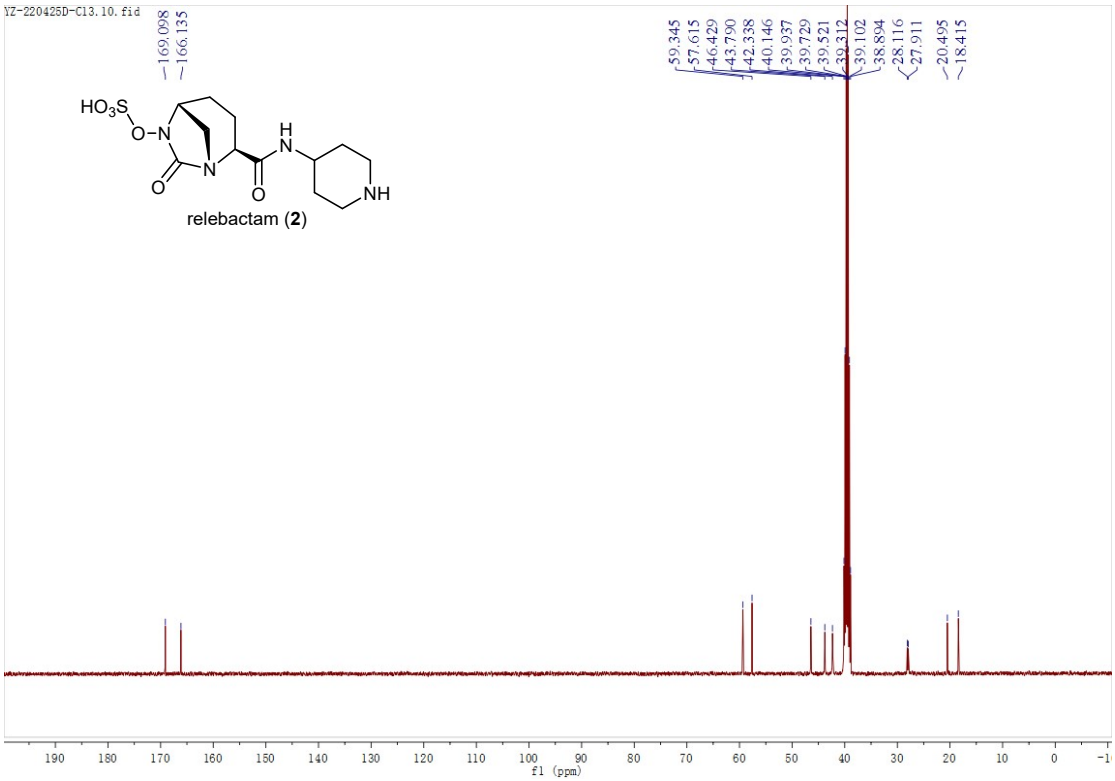
^{1}H-NMR Spectrum (400 MHz, $CDCl_3$) of Compound 5b



^{13}C-NMR Spectrum (100 MHz, $CDCl_3$) of Compound 5b



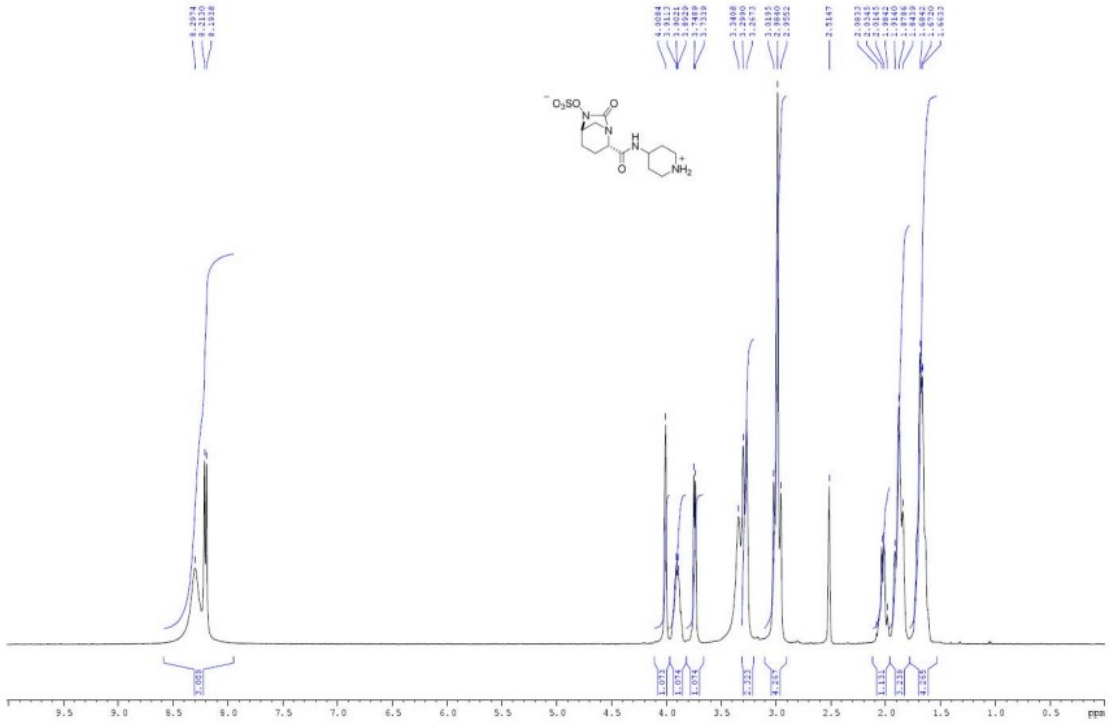
^{1}H-NMR Spectrum (400 MHz, DMSO-d_6) of Compound 2



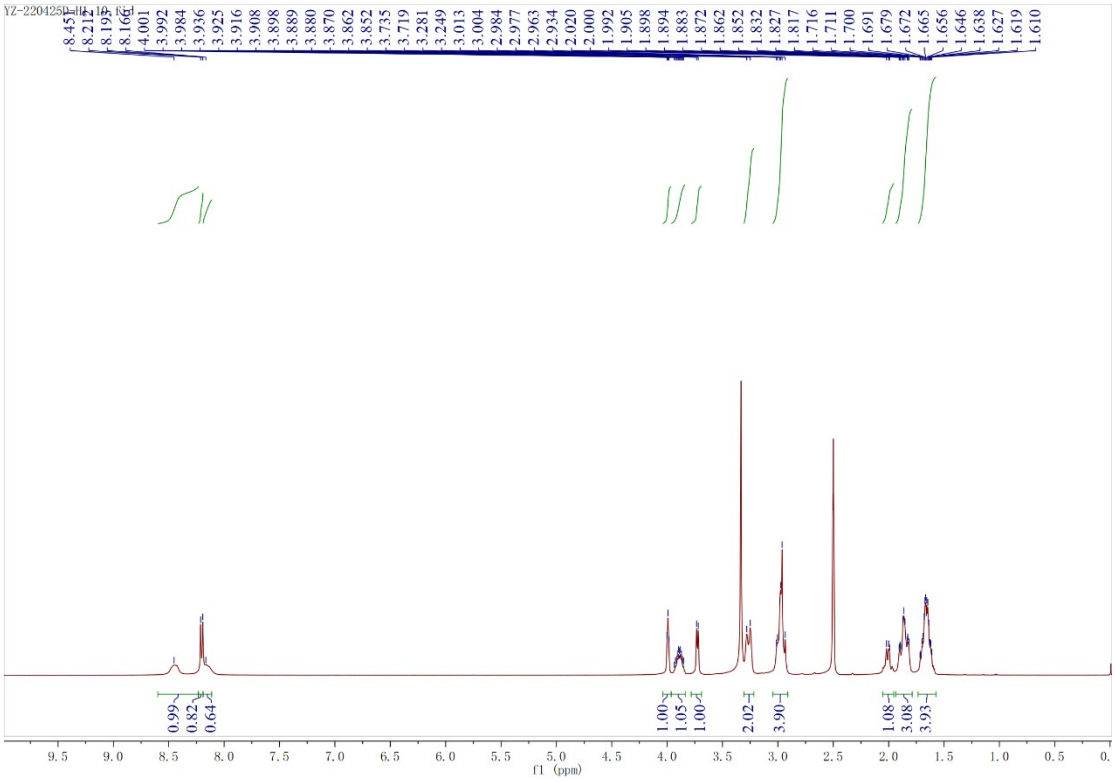
^{13}C-NMR Spectrum (100 MHz, DMSO-d_6) of Compound 2

Comparison of ^{1}H spectrums between the synthesized relebactam by Mangion's group and the synthesized avibactam by our group.

The synthesized relebactam by Mangion's group

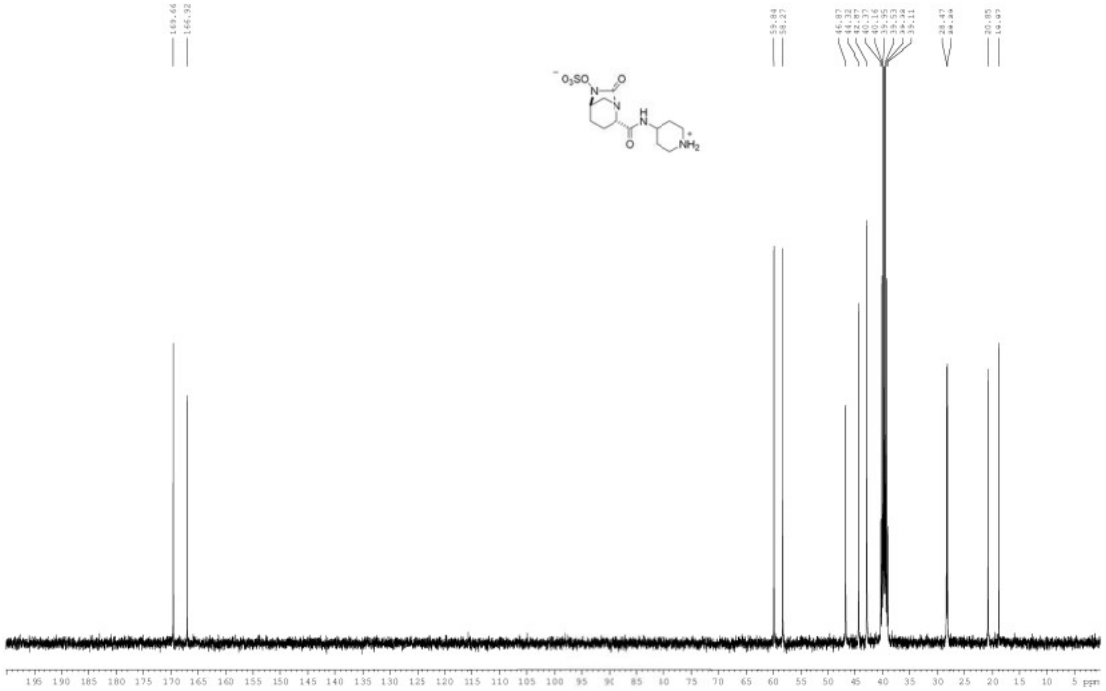


The synthesized relebactam by our group



Comparison of ^{13}C spectrums between the synthesized relebactam by Mangion's group and the synthesized avibactam by our group.

The synthesized relebactam by Mangion's group



The synthesized relebactam by our group