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Supporting Information

Enantioselective Total Synthesis of (-)-Kainic Acid and (+)-Acromelic Acid C via Rh(I)-Catalyzed Asymmetric Enyne Cycloisomerization

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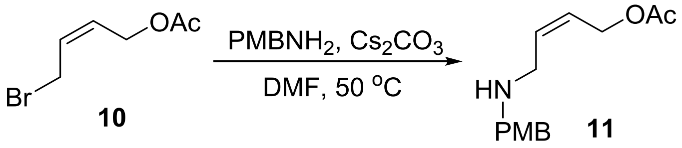
Table of Contents

1. General Information

All oxygen or moisture sensitive reactions were carried out under inert atmosphere (nitrogen or argon) with rigid exclusion of moisture. All the commercially available reagents and catalysts were used without further purification. Reaction solvents were purchased in anhydrous form, except for THF (tetrahydrofuran) which was distilled from Na/benzophenone. Flash column chromatography was performed using the indicated solvents on Qingdao Haiyang silica gel (200-300 mesh). Analytical thin-layer chromatography (TLC) was carried out using pre-coated sheets (Sanpontgroup silica gel, 0.2 mm) which, after development, were visualized at 254 nm, and/or staining in *p*-anisole, ninhydrin or phosphomolybdic acid solution followed by heating. NMR spectra were recorded on Bruker AscendTM 500MHz or Bruker AscendTM 400MHz spectrometers. Chemical shifts were reported in parts per million (ppm), relative to either a tetramethylsilane (TMS) internal standard or the signals of the residual solvent. Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad), coupling constants (Hz) and integration. High-resolution ESI mass spectra were obtained using a Q-Exactive mass spectrometer. Optical rotations were recorded on a Rudolph AutoPol I Polarimeter.

2. Experimental Procedures

2.1 Synthesis of the Common Intermediate 6



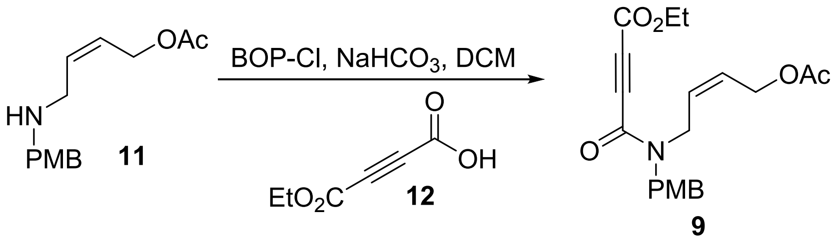
To a stirred solution of allylic bromide **10**[1] (5.0 g, 26.0 mmol) in dry DMF (125 mL) was added Cs_2CO_3 (17.0 g, 52.2 mmol) and $PMBNH_2$ (13.6 mL, 104.1 mmol) at room temperature. Then the reaction was heated to 50 °C and stirred for 2 h. The resulting mixture was diluted with ethyl acetate (500 mL) and washed with water (5 x 100 mL) and brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography to give allylic amine **11** (5.4 g, 84%) as a light yellow oil.

TLC: $R_f = 0.40$ (ethyl acetate : methanol = 10:1);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 5.78 (dtt, J = 11.0, 6.7, 1.3 Hz, 1H), 5.65 (dtt, J = 11.1, 6.8, 1.5 Hz, 1H), 4.62 (d, J = 6.3 Hz, 2H), 3.81 (s, 3H), 3.73 (s, 2H), 3.38 – 3.30 (m, 2H), 2.07 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 158.7, 133.1, 132.2, 129.3, 125.4, 113.8, 60.3, 55.3, 52.9, 45.6, 21.0.

HRMS (ESI): calculated for $C_{14}H_{20}NO_3^+$ $[M+H]^+$: 250.1438, found 250.1431.



To a stirred solution of allylic amine **11** (1.0 g, 4.0 mmol) in DCM (150 mL) at 0 °C was added acid **12** (1.4 g, 9.9 mmol), $NaHCO_3$ (1.7 g, 20.2 mmol) and BOP-Cl (2.6 g, 10.2 mmol). The reaction was allowed to warm to room temperature and stirred for 12 h. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated *in vacuo*. The resulting residue was then diluted with ethyl acetate (200 mL), washed with water (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography to afford enyne **9** (1.4 g, 93%)

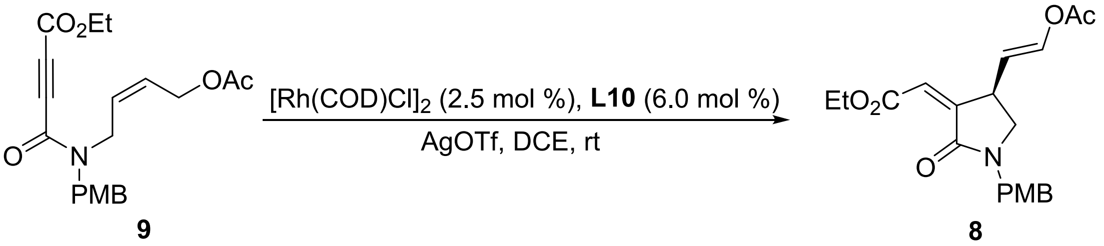
as a light yellow oil.

TLC: R$_f$ = 0.60 (petroleum ether : ethyl acetate = 2:1);

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.20 – 7.15 (m, 2H), 6.91 – 6.82 (m, 2H), 5.78 – 5.65 (m, 1H), 5.58 – 5.43 (m, 1H), 4.66 & 4.53 (s, 2H), 4.52 – 4.47 (m, 2H), 4.30 – 4.23 (m, 2H), 4.14 & 3.98 (d, *J* = 7.2 Hz, 2H), 3.80 & 3.78 (s, 3H), 2.04 & 2.03 (s, 3H), 1.33 – 1.28 (m, 3H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 170.6, 170.6, 159.6, 159.4, 152.2, 152.2, 152.1, 151.8, 129.8, 129.1, 128.3, 128.2, 127.5, 127.5, 126.9, 114.3, 114.2, 80.1, 79.9, 75.9, 75.7, 62.9, 59.7, 59.6, 55.30, 55.3, 51.6, 46.7, 44.8, 40.5, 20.9, 20.8, 13.9.

HRMS (ESI): calculated for $C_{20}H_{24}NO_6^+$ [M+H]$^+$: 374.1598, found 374.1590.



In a flame-dried Schlenk tube, [Rh(COD)Cl]$_2$ (3.3 mg, 6.7 μmol) and **L10** (15.2 mg, 16.1 μmol) were dissolved in DCE (3.0 mL), then freshly prepared enyne **9** (100 mg, 268 μmol, in 2.0 mL DCE) was added to the solution at room temperature. After stirring for 1 min, AgOTf (6.9 mg, 26.8 μmol) was added to the mixture. The reaction was stirred for 2 h for the full consumption of the starting material. The reaction mixture was directly purified by silica gel flash chromatography to afford the cyclization product **8** (95 mg, 95%, 92% ee). The ee value was determined by HPLC with an AD-H column (hexanes : isopropanol = 80:20, 0.8 mL/min).

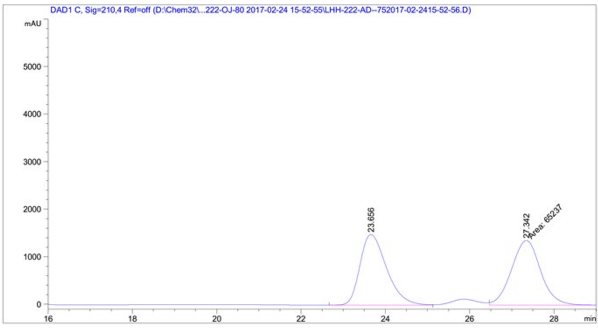
$[\alpha]_D^{25}$= -39.4 (*c* 1.0, CHCl$_3$)

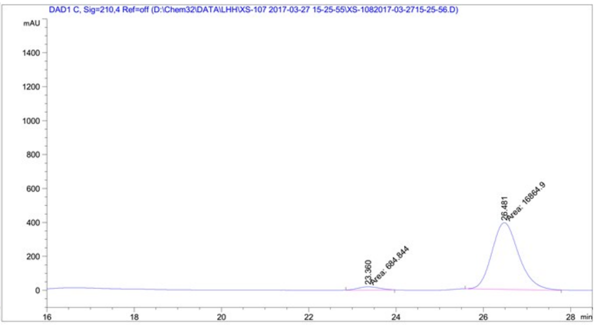
TLC: R$_f$ = 0.25 (petroleum ether : ethyl acetate = 2:1)

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.22 – 7.13 (m, 3H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.02 (d, *J* = 2.6 Hz, 1H), 5.27 (dd, *J* = 12.4, 9.2 Hz, 1H), 4.54 (d, *J* = 14.5 Hz, 1H), 4.38 – 4.27 (m, 3H), 3.78 (s, 3H), 3.51 – 3.39 (m, 2H), 3.00 (dd, *J* = 9.5, 5.5 Hz, 1H), 2.11 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$) δ 167.7, 166.6, 164.4, 159.3, 141.3, 138.4, 129.8, 127.6, 123.6, 114.2, 112.4, 61.4, 55.3, 49.8, 46.4, 36.1, 20.6, 14.1.

HRMS (ESI): calculated for $C_{20}H_{24}NO_6^+$ [M+H]$^+$: 374.1598, found 374.1588.





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Use Multiplier & Dilution Factor with ISTDs


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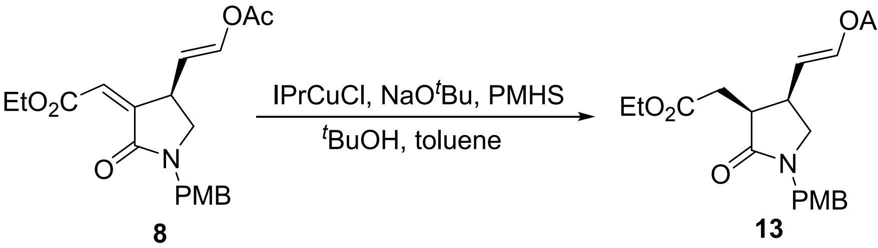


An oven-dried flask was added IPrCuCl (209 mg, 429 μmol), NaO^{t}Bu (82 mg, 853 μmol) and anhydrous toluene (80 mL). After 10 min stirring at room temperature, PMHS (0.5 mL, 8.3 mmol) was added and the resulting orange solution was further stirred for 5 min. Then additional toluene (10 mL) and PMHS (1.5 mL, 24.9 mmol) were added. A solution of **8** (3.2 g, 8.6 mmol) and ^{t}BuOH (1.6 mL, 17.5 mmol) in toluene (10 mL) was added to the freshly generated reducing system and the reaction mixture was stirred at room temperature for 40 min. The reaction mixture was directly diluted with ethyl acetate (300 mL), washed with saturated aqueous solution of NH_4Cl (2 x 80 mL), water (80 mL) and brine (80 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography to afford **13** (3.0 g, 92%) as a colorless oil.

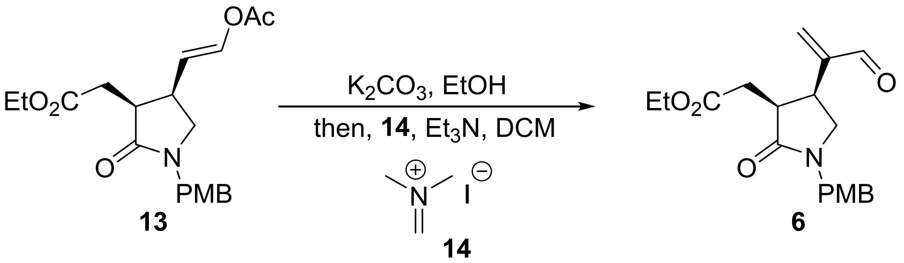
$[\alpha]_D^{25}$= -4.3 (*c* 1.0, $CHCl_3$)

TLC: R_f= 0.25 (petroleum ether : ethyl acetate = 2:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.6 Hz, 2H), 7.06 (d, *J* = 12.4 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.16 (dd, *J* = 12.4, 10.1 Hz, 1H), 4.45 – 4.32 (m, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 3.44 (dd, *J* = 10.0, 6.1 Hz, 1H), 3.13 – 3.04 (m, 2H), 2.92 (dd, *J* = 10.1, 1.6 Hz, 1H), 2.83 (dd, $J = 17.4, 3.7$ Hz, 1H), 2.35 (dd, $J = 17.3, 9.9$ Hz, 1H), 2.09 (s, 3H), 1.23 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 172.0, 167.7, 159.1, 137.6, 129.5, 128.2, 114.1, 111.7, 60.7, 55.3, 50.7, 46.2, 42.5, 34.4, 31.5, 20.6, 14.2.

HRMS (ESI): calculated for $C_{20}H_{26}NO_6^+$ [M+H]$^+$: 376.1755, found 376.1745.



K_2CO_3 (589 mg, 4.3 mmol) was added to a solution of **13** (800 mg, 2.1 mmol) in EtOH (30 mL) at 0 °C. The reaction mixture was stirred at the same temperature for 1 h. The mixture was then extracted with ethyl acetate (3 x 60 mL), and washed with water (40 mL) and brine (40 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the corresponding crude aldehyde as a colorless oil, which was used in the next step without further purification.

The obtained aldehyde was dissolved in DCM (50 mL), Et_3N (1.5 mL, 10.8 mmol) and Eschenmoser's reagent (1.2 g, 6.5 mmol) were added at 0 °C. The reaction mixture was warmed up to room temperature, and stirred for 24 h. The mixture was diluted with DCM (100 mL) and washed with saturated aqueous solution of NH_4Cl (2 x 30 mL), water (30 mL) and brine (30 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel chromatography to produce common intermediate **6** (596 mg, 81%) as a colorless oil.

$[\alpha]_D^{25}$= -21.2 (*c* 1.0, $CHCl_3$)

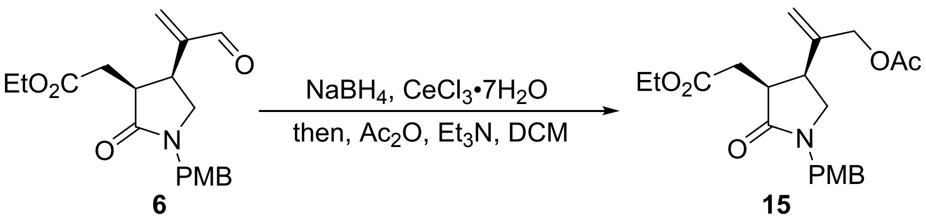
TLC: R_f= 0.20 (petroleum ether : ethyl acetate = 2:1);

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.38 (s, 1H), 7.15 (d, $J = 8.6$ Hz, 2H), 6.81 (d, $J = 8.7$ Hz, 2H), 6.01 (s, 1H), 6.00 (s, 1H), 4.45 – 4.29 (m, 2H), 4.04 (q, $J = 7.2$ Hz, 2H), 3.74 (s, 3H), 3.62 – 3.55 (m, 1H), 3.40 (dd, $J = 10.1, 7.2$ Hz, 1H), 3.23 (td, $J = 9.0, 5.0$ Hz, 1H), 3.07 (dd, $J = 10.1, 3.4$ Hz, 1H), 2.58 (dd, $J = 17.0, 5.0$ Hz, 1H), 2.13 (dd, $J = 17.0, 9.2$ Hz, 1H), 1.17 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 193.5, 173.5, 171.6, 159.2, 148.5, 135.5, 129.8, 128.0, 114.1, 60.7, 55.2, 49.6, 46.3, 42.2, 32.2, 31.6, 14.1.

HRMS (ESI): calculated for $C_{19}H_{24}NO_5^+$ [M+H]$^+$: 346.1649, found 346.1638.

2.2 Total Synthesis of (-)-Kainic Acid



To a mixture of **6** (506 mg, 1.5 mmol) and $CeCl_3 \cdot 7H_2O$ (547 mg, 1.5 mmol) in MeOH (20 mL) was slowly added $NaBH_4$ (112 mg, 2.9 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 20 min, before it was poured into saturated aqueous solution of NH_4Cl (10 mL). The resulting mixture was extracted with ethyl acetate (3 x 50 mL) and washed with water (30 mL) and brine (30 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the corresponding crude allylic alcohol as a colorless oil, which was used in the next step without further purification.

A solution of the crude allylic alcohol in DCM (20 mL) was added Ac_2O (0.3 mL, 3.2 mmol), Et_3N (0.8 mL, 5.8 mmol) and DMAP (183 mg, 1.5 mmol) at 0 °C. The reaction mixture was warmed up to room temperature and stirred for 2 h, before it was quenched by adding saturated aqueous solution of NH_4Cl (10 mL). The mixture was then extracted with ethyl acetate (3 x 50 mL) and washed with water (30 mL) and brine (30 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo.* The residue was purified by silica gel chromatography to produce **15** (533 mg, 93%) as a colorless oil.

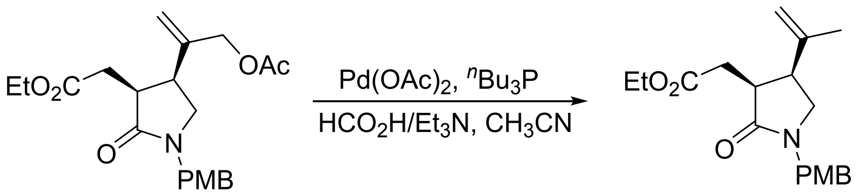
$[\alpha]_D^{25}$= -6.5 (*c* 1.0, $CHCl_3$)

TLC: R_f= 0.45 (petroleum ether : ethyl acetate = 2:1);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 5.12 (s, 1H), 4.92 (s, 1H), 4.44 (d, J = 14.4 Hz, 1H), 4.38 – 4.25 (m, 3H), 4.12 (q, J = 7.1 Hz, 2H), 3.77 (s, 3H), 3.38 (dd, J = 10.2, 6.7 Hz, 1H), 3.19 (ddd, J = 9.2, 6.8, 2.8 Hz, 1H), 3.16 – 3.09 (m, 2H), 2.81 (dd, J = 17.5, 4.2 Hz, 1H), 2.44 (dd, J = 17.5, 9.7 Hz, 1H), 2.04 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 172.3, 170.4, 159.2, 141.6, 129.8, 128.0, 116.8, 114.1, 65.53, 60.6, 55.2, 49.3, 46.3, 42.3, 39.2, 31.2, 20.8, 14.2.

HRMS (ESI): calculated for $C_{21}H_{28}NO_6^+$ $[M+H]^+$: 390.1911, found 390.1901.



15 **16**

$Pd(OAc)_2$ (59 mg, 263 μmol) and ^{n}Bu$_3$P (65 μL, 260 μmol) were dissolved in CH_3CN (25 mL) at room temperature and stirred for 5 min. A solution of allylic acetate **15** (500 mg, 1.3 mmol) and HCO_2H/Et_3N (1:2) (6.5 mL, 1.0 M/CH_3CN, 6.5 mmol) in CH_3CN (5 mL) were added. The reaction mixture was heated up to 40 ^{o}C and stirred until the apparition of black particles (approx. 1 h). The reaction was quenched with water (10 mL). The mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography to give **16** (382 mg, 90%) as a colorless oil.

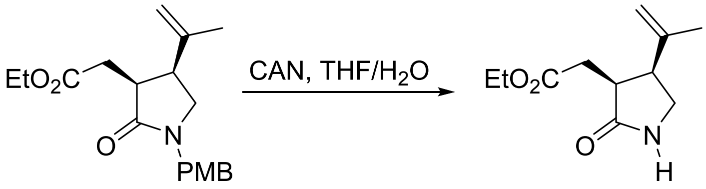
$[\alpha]_D^{25}$= -18.4 (*c* 1.0, $CHCl_3$)

TLC: R_f= 0.15 (petroleum ether : ethyl acetate = 4:1);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 4.75 (t, J = 1.6 Hz, 1H), 4.66 (s, 1H), 4.44 – 4.33 (m, 2H), 4.16 – 4.10 (m, 2H), 3.79 (s, 3H), 3.43 – 3.36 (m, 1H), 3.16 – 3.10 (m, 2H), 3.04 (dd, J = 10.2, 1.5 Hz, 1H), 2.86 – 2.79 (m, 1H), 2.31 – 2.23 (m, 1H), 1.43 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 172.4, 159.2, 143.1, 130.0, 128.1, 114.9, 114.0, 60.6, 55.3, 49.0, 46.2, 42.0, 41.6, 31.0, 19.8, 14.2.

HRMS (ESI): calculated for $C_{19}H_{26}NO_4^+$ $[M+H]^+$: 332.1856, found 332.1848.



16 **4**

Ammonium cerium(IV) nitrate (658 mg, 1.2 mmol), in three portions (one portion/3 h), was added to a solution of **16** (40 mg, 121 μmol) in THF/H_2O (4.0 mL, *v*/*v* = 3/1). The reaction mixture was stirred at room temperature until complete conversion of the starting material (monitored by TLC, approx. 20 h). The mixture was then extracted with ethyl acetate (3 x 30mL). The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (20 mL), water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel chromatography to afford **4** (18 mg, 72%) as a colorless oil.

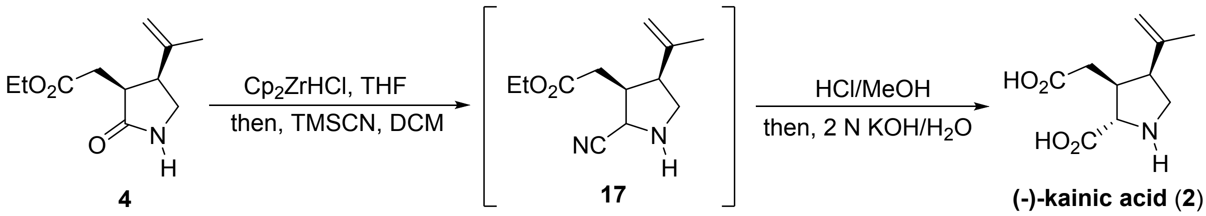
[α]$_D$^{25}= -2.1 (*c* 1.0, $CHCl_3$)

TLC: R_f= 0.30 (petroleum ether : ethyl acetate = 1:1);

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94 (brs, 1H), 4.86 (t, *J* = 1.6 Hz, 1H), 4.77 (s, 1H), 4.19 – 4.10 (m, 2H), 3.61 – 3.53 (m, 1H), 3.32 – 3.24 (m, 2H), 3.07 (ddd, *J* = 10.0, 8.2, 4.3 Hz, 1H), 2.78 (dd, *J* = 17.4, 4.3 Hz, 1H), 2.28 (dd, *J* = 17.5, 10.0 Hz, 1H), 1.66 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 178.1, 172.6, 143.2, 115.3, 60.9, 44.9, 44.9, 40.6, 30.9, 20.5, 14.5.

HRMS (ESI): calculated for $C_{11}H_{18}NO_3^+$ $[M+H]^+$: 212.1281, found 212.1276.



To a suspension of Cp_2ZrHCl (67 mg, 260 μmol) in freshly distilled THF (1.0 mL) at -30 °C was added a solution of **4** (11 mg, 52 μmol) in THF (1.0 mL). After 10 min the reaction mixture was gradually warmed up to 5 °C for 5 h. The reaction mixture was then transferred via syringe to a cold and dry solution of hexanes (10 mL) with vigorous stirring. The heterogeneous mixture was filtered under vacuum, and the filtrate was concentrated *in vacuo* to afford the corresponding imine. TMSCN (33 μL, 264 μmol) was added to a solution of the crude imine in DCM (2.0 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 3 h. The mixture was concentrated *in vacuo* to give crude intermediate **17**, which was used in the next step without further purification

To a solution of crude intermediate **17** in MeOH (2.0 mL) at 0 °C was bubbled with freshly prepared HCl (g) for 2 min. The reaction mixture was then warmed up to room temperature and stirred for 24 h. Then, KOH (8.0 mL, 16.0 mmol, 2 N in H_2O) was slowly added to the mixture at 0 °C. The mixture was stirred for another 20 h before it was diluted with water (30 mL) and washed with ethyl ether (10 mL). The aqueous layer was acidified with freshly conditioned Dowex-50WX8 (100-200 mesh, H^+ form). The heterogeneous mixture was poured onto a column of Dowex-50WX8 (100-200 mesh, H^+ form). The resin was washed with water (40 mL) and the product was eluted with 2% ammonium hydroxide solution.

Concentration of the collected fractions *in vacuo* afforded (-)-kainic acid (**2**) (6.6 mg, 60%).

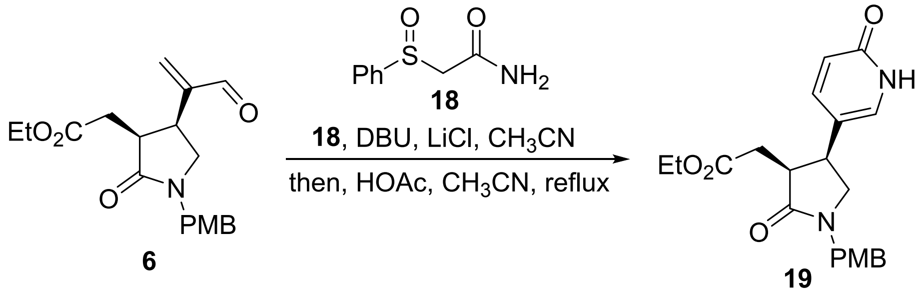
[α]$_D$^{20}= -14.2 (*c* 0.2, H_2O) ;[lit.[2] [α]$_D$^{20} = -14.6 (*c* 0.49, H_2O)]

^{1}H NMR (500 MHz, D_2O) *δ* 4.97 (s, 1H), 4.68 (s, 1H), 4.00 (d, *J* = 3.2 Hz, 1H), 3.56 (dd, *J* = 11.9, 7.4 Hz, 1H), 3.38 (dd, *J* = 11.9, 10.6 Hz, 1H), 3.02 – 2.88 (m, 2H), 2.22 (dd, *J* = 15.6, 6.5 Hz, 1H), 2.10 (dd, *J* = 15.5, 8.3 Hz, 1H), 1.72 (s, 3H).

^{13}C NMR (125 MHz, D_2O) *δ* 179.5, 173.6, 140.1, 112.8, 65.8, 46.2, 45.7, 41.7, 35.9, 22.1.

HRMS (ESI): calculated for $C_{10}H_{16}NO_4^+$ $[M+H]^+$: 214.1074, found 214.1067.

2.3 Total Synthesis of (+)-Acromelic Acid C



DBU (0.5 mL, 3.4 mmol) was slowly added to a stirred suspension of common intermediate **6** (580 mg, 1.7 mmol), 2-(phenylsulfinyl)acetamide **18**[3] (615 mg, 3.4 mmol) and LiCl (212 mg, 5.0 mmol) in CH_3CN (45 mL) at 0 °C. The mixture was gradually warmed up to room temperature and stirred for 1 h before quenched with saturated aqueous solution of NH_4Cl (10 mL). The mixture was extracted with ethyl acetate (3 x 70 mL), washed with water (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting crude 1,4-addition product was directly used without further purification.

To a stirred solution of the crude product in CH_3CN (125 mL) was added HOAc (1.0 mL, 17.5 mmol) at room temperature. The mixture was refluxed for 24 h before cooled to room temperature. The solvent was removed *in vacuo*, and the residue was purified by silica gel chromatography to afford **19** (374 mg, 58%) as a white foam.

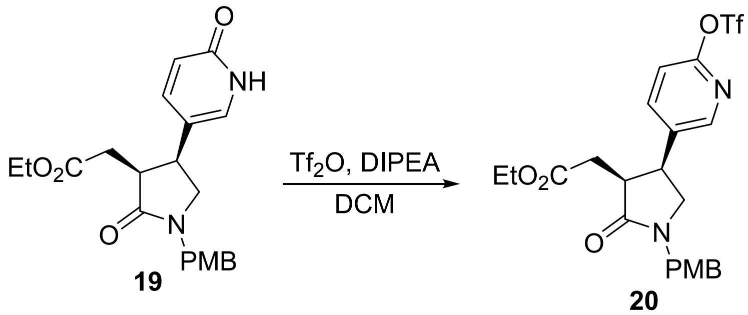
[α]$_D$^{25}= -49.9 (*c* 1.0, $CHCl_3$)

TLC: R_f= 0.75 (ethyl acetate : methanol = 10:1);

^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.23 (d, *J* = 8.6 Hz, 2H), 7.03 (dd, *J* = 9.4, 2.6 Hz, 1H), 7.00 (d, *J* = 2.5 Hz, 1H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.44 (d, *J* = 9.3 Hz, 1H), 4.58 – 4.38 (m, 2H), 4.09 (q, *J* = 6.9 Hz, 2H), 3.82 (s, 3H), 3.66 (dd, *J* = 10.4, 7.0 Hz, 1H), 3.50 (dd, *J* = 7.4 Hz, 1H), 3.26 (ddd, *J* = 12.0, 8.7, 3.9 Hz, 1H), 3.17 (d, *J* = 10.5 Hz, 1H), 2.85 (dd, *J* = 17.7, 3.9 Hz, 1H), 2.00 (dd, *J* = 17.8, 11.0 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) *δ* 173.3, 172.0, 164.6, 159.4, 141.3, 133.0, 129.9, 127.7, 120.6, 119.1, 114.2, 60.8, 55.3, 51.0, 46.4, 43.2, 36.8, 31.4, 14.1.

HRMS (ESI): calculated for $C_{21}H_{25}N_2O_5^+$ $[M+H]^+$: 385.1758, found 385.1746.



To a stirred solution of **19** (395 mg, 1.0 mmol) in DCM (20 mL) at 0 °C was added DIPEA (1.0 mL, 6.1 mmol) and Tf_2O (0.5 mL, 3.0 mmol). The reaction mixture was warmed up to room temperature and stirred for 3 h. Then the reaction was quenched with saturated aqueous solution of NH_4Cl (5 mL). The mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel chromatography to produce **20** (467 mg, 88%) as a colorless oil.

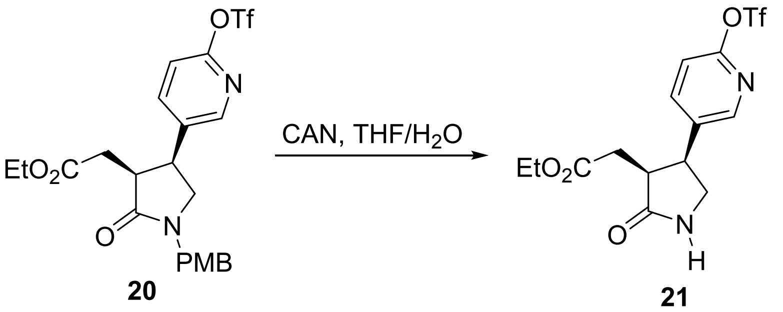
$[\alpha]_D^{25}$= -17.8 (*c* 1.0, $CHCl_3$)

TLC: R_f= 0.20 (petroleum ether : ethyl acetate = 2:1);

^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.98 (d, *J* = 2.6 Hz, 1H), 7.37 (dd, *J* = 8.5, 2.6 Hz, 1H), 7.20 (d, *J* = 8.6 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.55 (d, *J* = 14.2 Hz, 1H), 4.37 (d, *J* = 14.3 Hz, 1H), 3.99 (q, *J* = 7.1 Hz, 2H), 3.80 – 3.69 (m, 5H), 3.34 (ddd, *J* = 11.0, 8.6, 4.1 Hz, 1H), 3.25 (dd, *J* = 10.5, 1.5 Hz, 1H), 2.77 (dd, *J* = 17.7, 4.1 Hz, 1H), 1.78 (dd, *J* = 17.7, 11.1 Hz, 1H), 1.12 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) *δ* 172.8, 171.6, 159.4, 154.9, 148.1, 139.7, 137.2, 130.0, 127.6, 118.5 (q, *J* = 320.5 Hz), 115.1, 114.2, 60.8, 55.2, 51.1, 46.4, 43.3, 37.3, 31.4, 13.9.

HRMS (ESI): calculated for $C_{22}H_{24}F_3N_2O_7S^+$ $[M+H]^+$: 517.1251, found 517.1234.



CAN (1.2 g, 2.2 mmol), in three portions (one portion/3 h), was added to a solution of **20** (109 mg, 211 μmol) in THF/H_2O (8.0 mL, *v*/*v* = 3:1). The reaction mixture was stirred at room temperature until the full conversion of the starting material (monitored by TLC, approx. 20 h). The mixture was then extracted with ethyl acetate (3 x 30mL). The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (20 mL), water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel chromatography to afford **21** (60 mg, 71%) as a colorless oil.

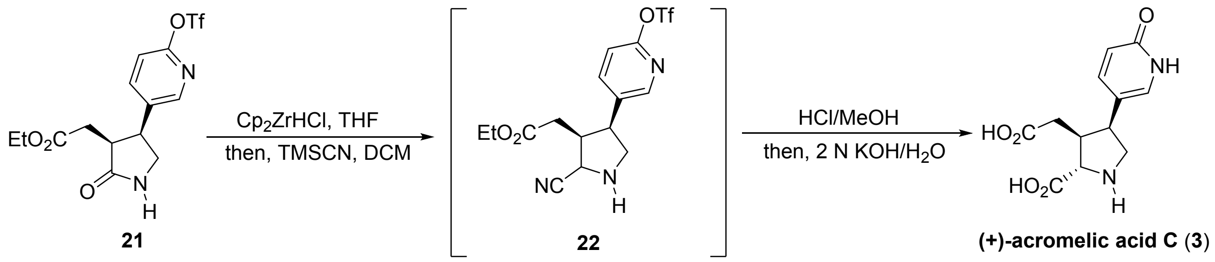
$[\alpha]_D^{25}$= +48.9 (*c* 1.0, $CHCl_3$)

TLC: R_f= 0.20 (petroleum ether : ethyl acetate = 1:1);

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 2.5 Hz, 1H), 7.78 (dd, *J* = 8.4, 2.6 Hz, 1H), 7.15 (d, *J* = 8.5 Hz, 1H), 7.02 (brs, 1H), 4.05 (q, *J* = 7.2 Hz, 2H), 3.99 – 3.88 (m, 2H), 3.50 (d, *J* = 10.2 Hz, 1H), 3.32 (ddd, *J* = 10.9, 8.5, 4.0 Hz, 1H), 2.76 (dd, *J* = 17.8, 4.0 Hz, 1H), 1.82 (dd, *J* = 17.8, 11.1 Hz, 1H), 1.17 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 169.2, 152.6, 145.6, 137.4, 134.4, 116.0 (q, *J* = 320.5 Hz), 112.8, 58.5, 44.6, 39.7, 37.4, 28.4, 11.5.

HRMS (ESI): calculated for $C_{14}H_{16}F_3N_2O_6S^+$ $[M+H]^+$: 397.0676, found 397.0664.



To a suspension of Cp_2ZrHCl (65 mg, 252 μmol) in freshly distilled THF (1.0 mL) at -30 °C was added a solution of **21** (20 mg, 51 μmol) in THF (1.0 mL). After 10 min the reaction mixture was gradually warmed up to 5 °C for 5 h. The reaction mixture was then transferred by syringe to a cold and dry solution of hexanes (10 mL) with vigorous stirring. The heterogeneous mixture was filtered under vacuum, and the filtrate was concentrated *in vacuo* to afford the corresponding imine. TMSCN (31 μL, 250 μmol) was then added to a solution of the crude imine in DCM (2.0 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 3 h. The mixture was concentrated *in vacuo* to give crude intermediate **22**, which was used without further purification.

To a solution of crude intermediate **22** in MeOH (2.0 mL) at 0 °C was bubbled with freshly prepared HCl (g) for 2 min. The reaction mixture was then warmed up to room temperature and stirred for 24 h. Then, KOH (8.0 mL, 16 mmol, 2 N in H_2O) was slowly added to the mixture at 0 °C. The mixture was stirred for another 20 h before it was diluted with water (30 mL) and washed with ethyl ether (10 mL). The aqueous layer was acidified with freshly conditioned Dowex-50WX8 (100-200 mesh, H^+ form). The resin was washed with water (40 mL) and the product was eluted with 3% ammonium hydroxide solution. The collected fractions were concentrated *in vacuo.* The resulting ammonium salt was charged onto a column containing Amberlite-CG-50 (H^+ form). After elution with H_2O, the collected fractions were concentrated *in vacuo* to afforded (+)-acromelic acid C (**3**) (7.0 mg, 52%).

$[\alpha]_D^{20}$= +30.3 (*c* 0.15, H_2O) ;[lit.[4] $[\alpha]_D$ = +31.9 (c 0.23, H_2O)]

^{1}H NMR (500 MHz, D_2O) δ 7.39 (dd, *J* = 9.5, 2.6 Hz, 1H), 7.15 (d, *J* = 2.6 Hz, 1H), 6.42 (d, *J* = 9.5 Hz, 1H), 3.76 (d, *J* = 6.0 Hz, 1H), 3.62 (dd, *J* = 12.0, 7.9 Hz, 1H), 3.48 – 3.41 (m, 1H), 3.30 (dd, *J* = 12.0, 9.5 Hz, 1H), 2.89 – 2.79 (m, 1H), 2.13 (dd, *J* = 16.1, 5.9 Hz, 1H), 1.83 (dd, *J* = 16.1, 9.2 Hz, 1H).

^{13}C NMR (125 MHz, D_2O) δ 176.8, 172.7, 163.8, 143.9, 133.6, 118.9, 116.5, 65.2, 46.8, 42.8, 41.0, 35.1.

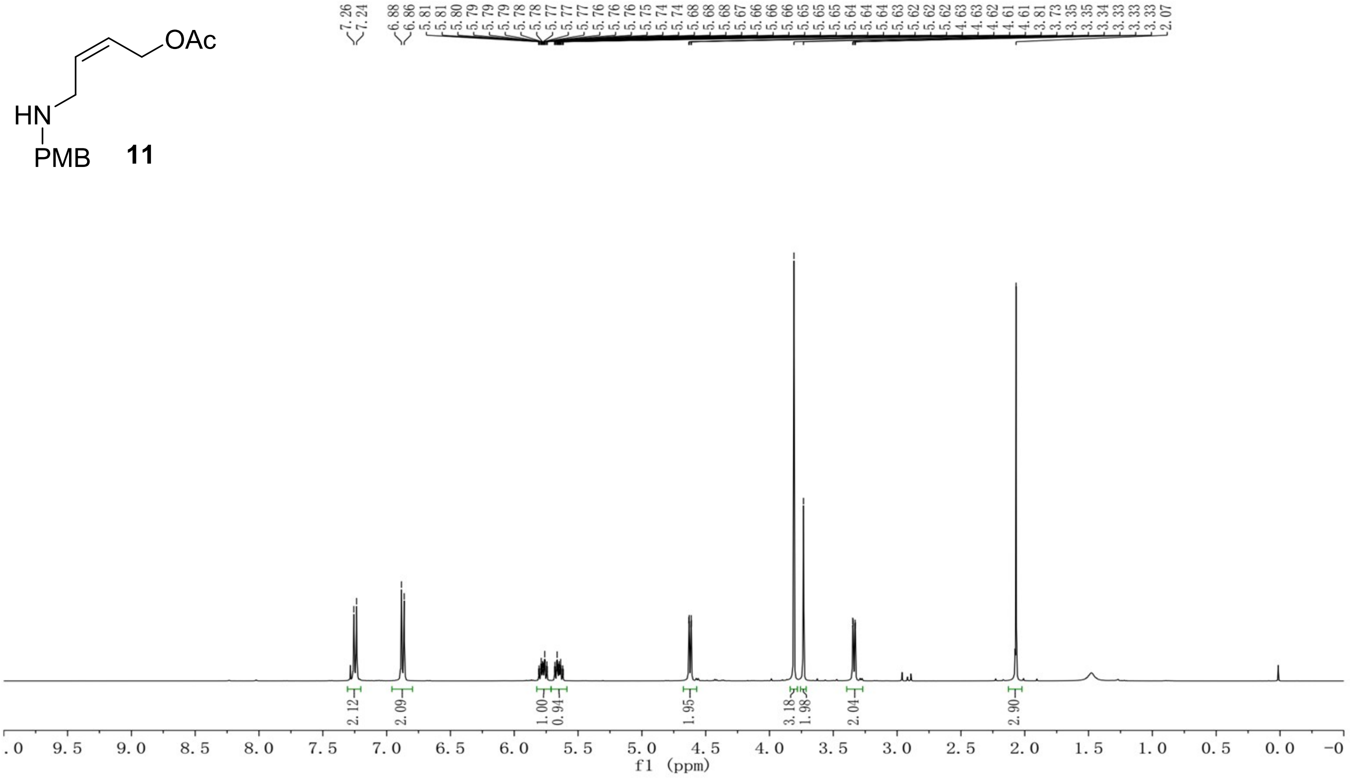
HRMS (ESI): calculated for $C_{12}H_{15}N_2O_5^+$ $[M+H]^+$: 267.0975, found 267.0966.

3. References

(1) Mitchell, M.; Qaio, L.; Wong, C.-H. *Adv. Synth. Catal.* **2001**, *343*, 596-599.
(2) Evans, P. A.; Inglesby, P. A. *J. Am. Chem. Soc.* **2012**, *134*, 3635-3638.
(3) Fujii, M.; Nishimura, T.; Koshiba, T.; Yokoshima, S.; Fukuyama, T. *Org. Lett*. **2013**, *15*, 232-234.
(4) Fushiya, S.; Sato, S.; Kanazawa, T.; Kusano, G.; Nozoe, S. *Tetrahedron Lett.* **1990**, *31*, 3901-3904.

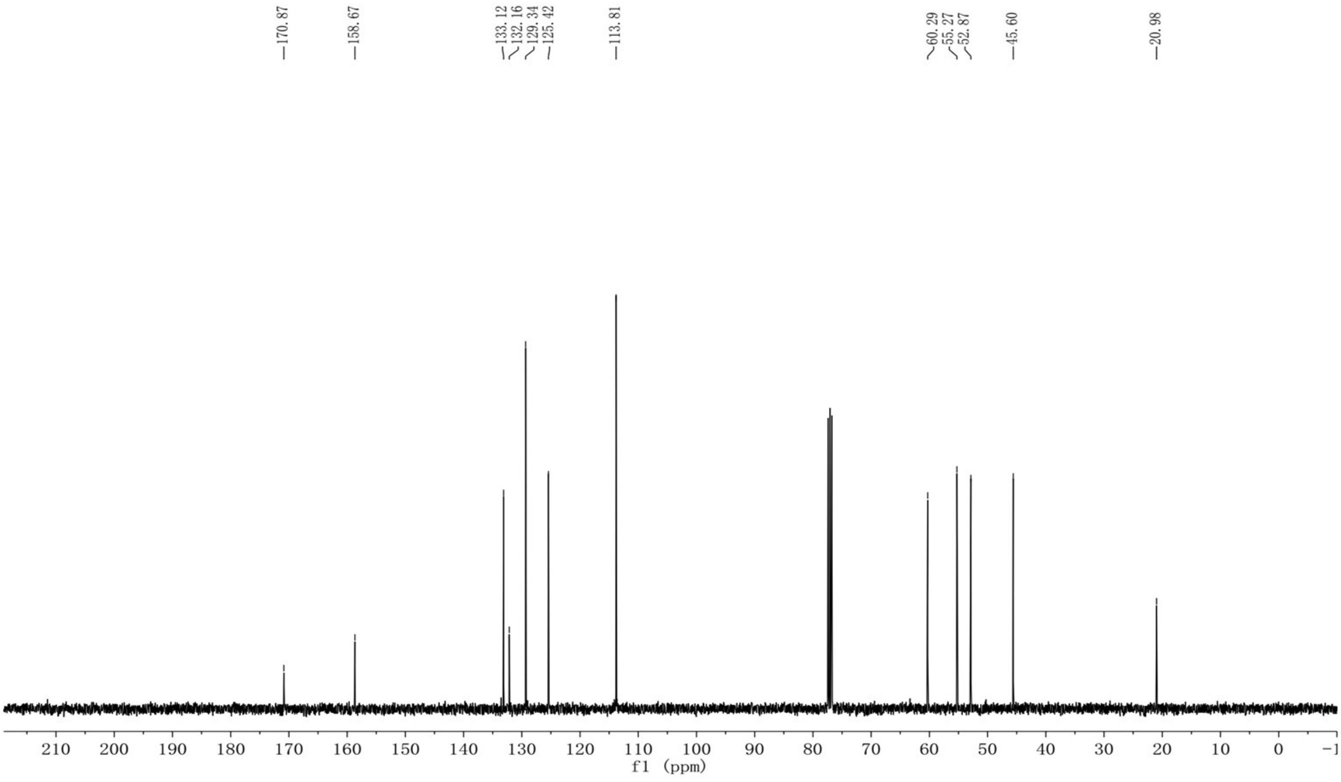
4. Spectra

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

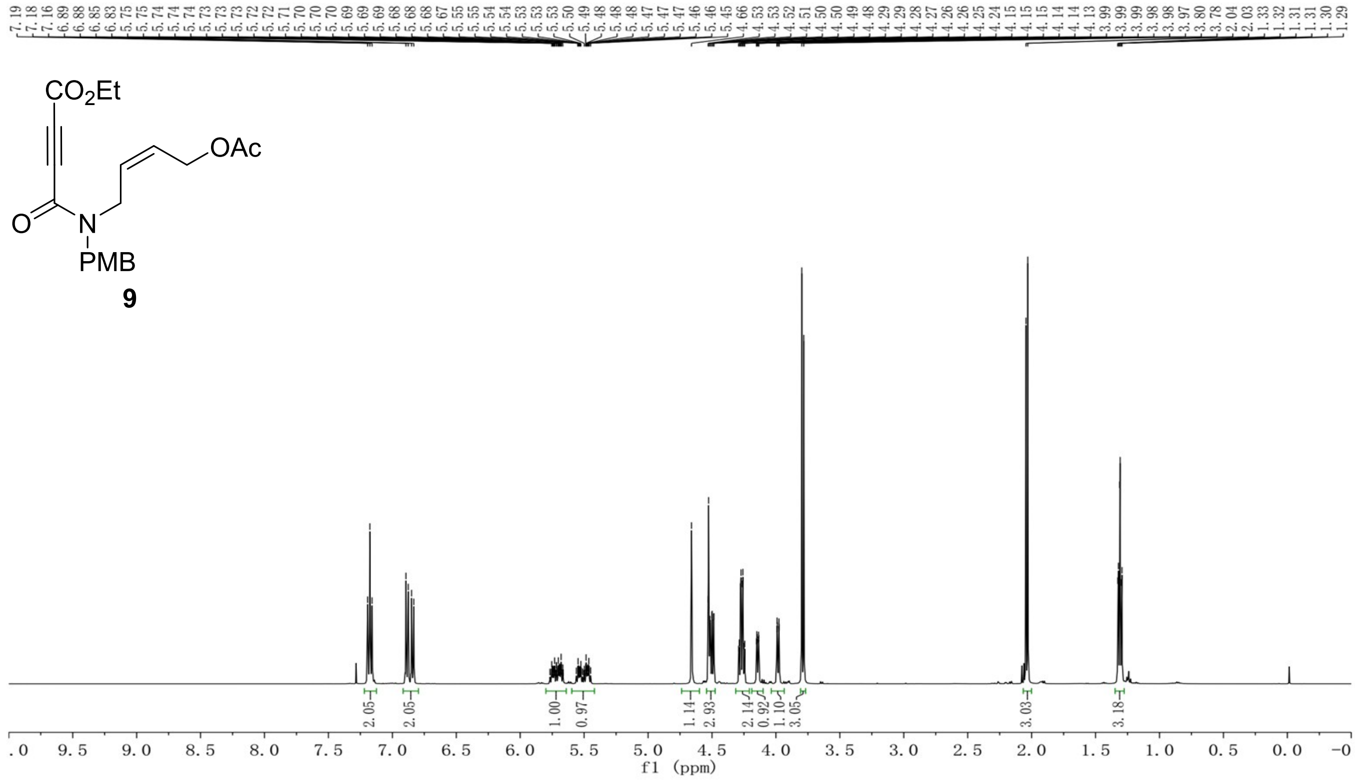


11

^{13}C NMR (100 MHz, $CDCl_3$)

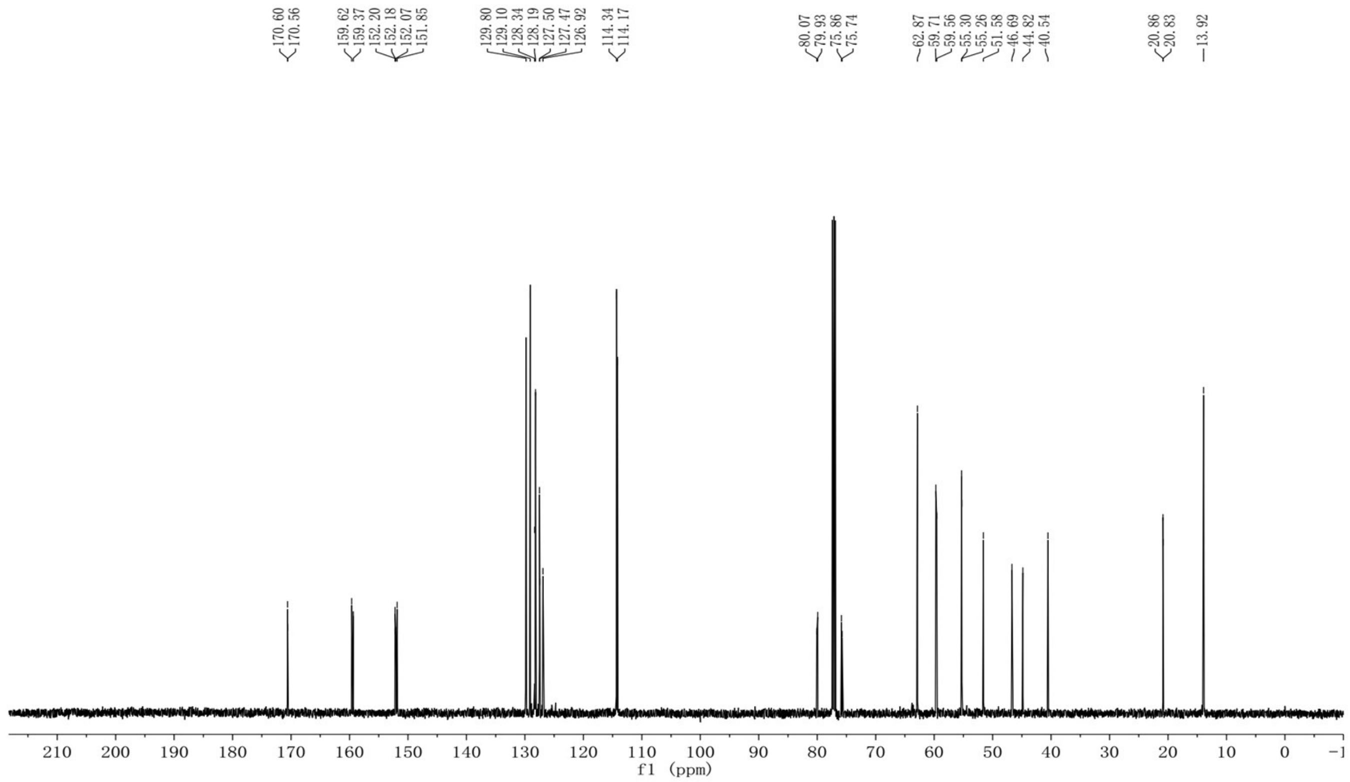


^{1}H NMR (500 MHz, $CDCl_3$)

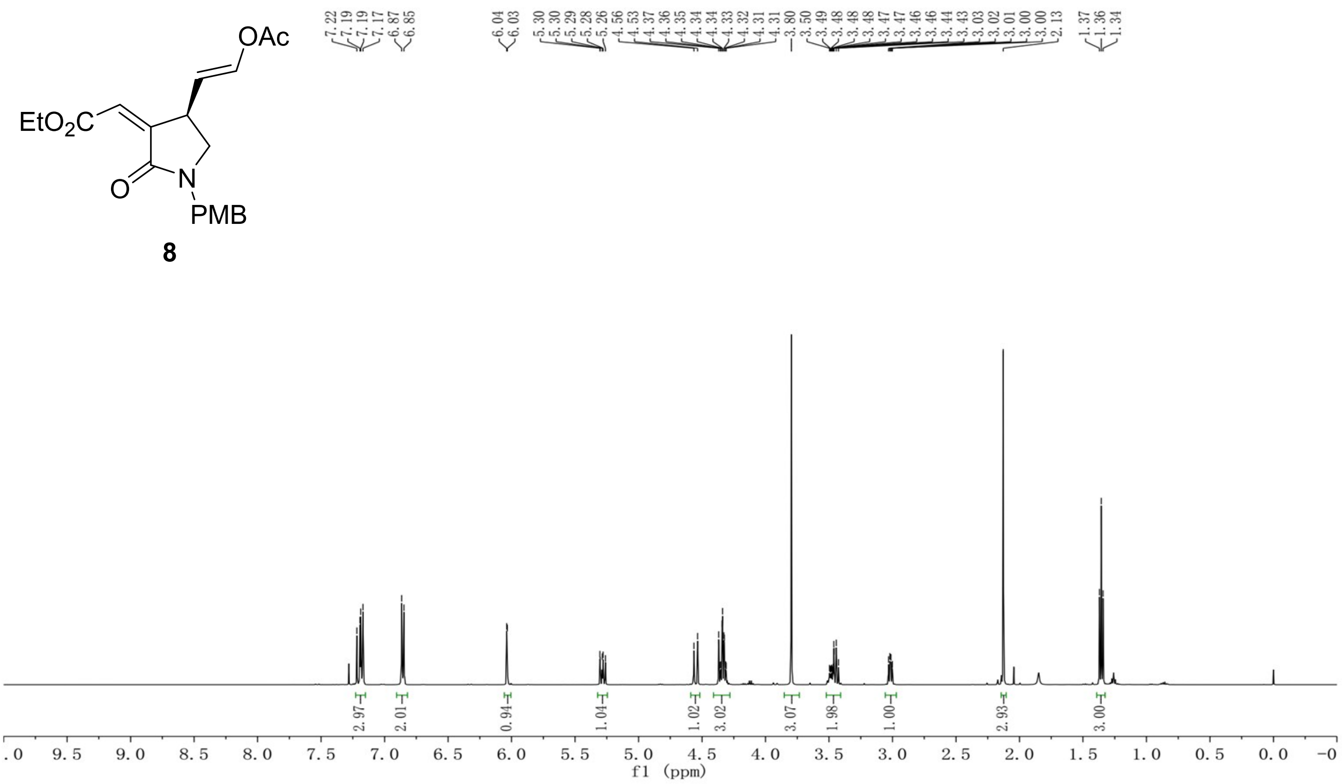


9

^{13}C NMR (125 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)



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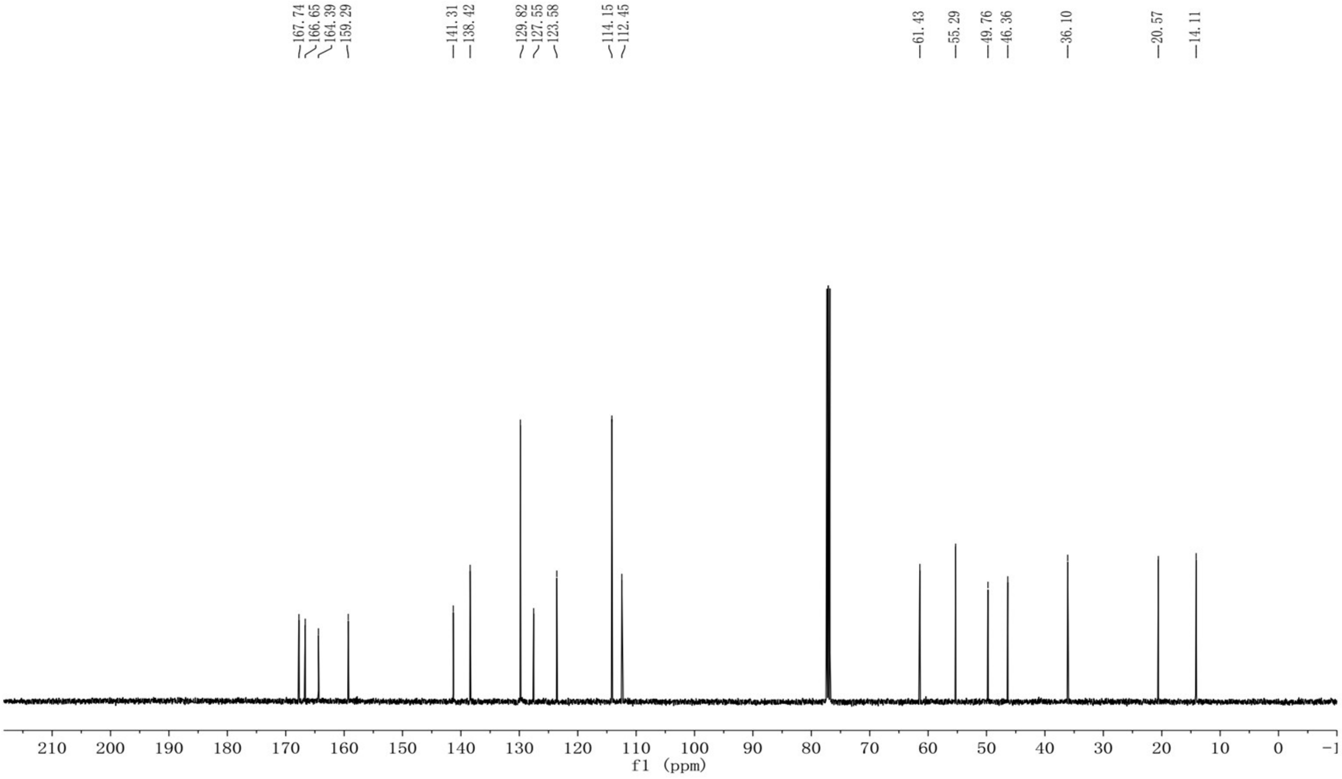
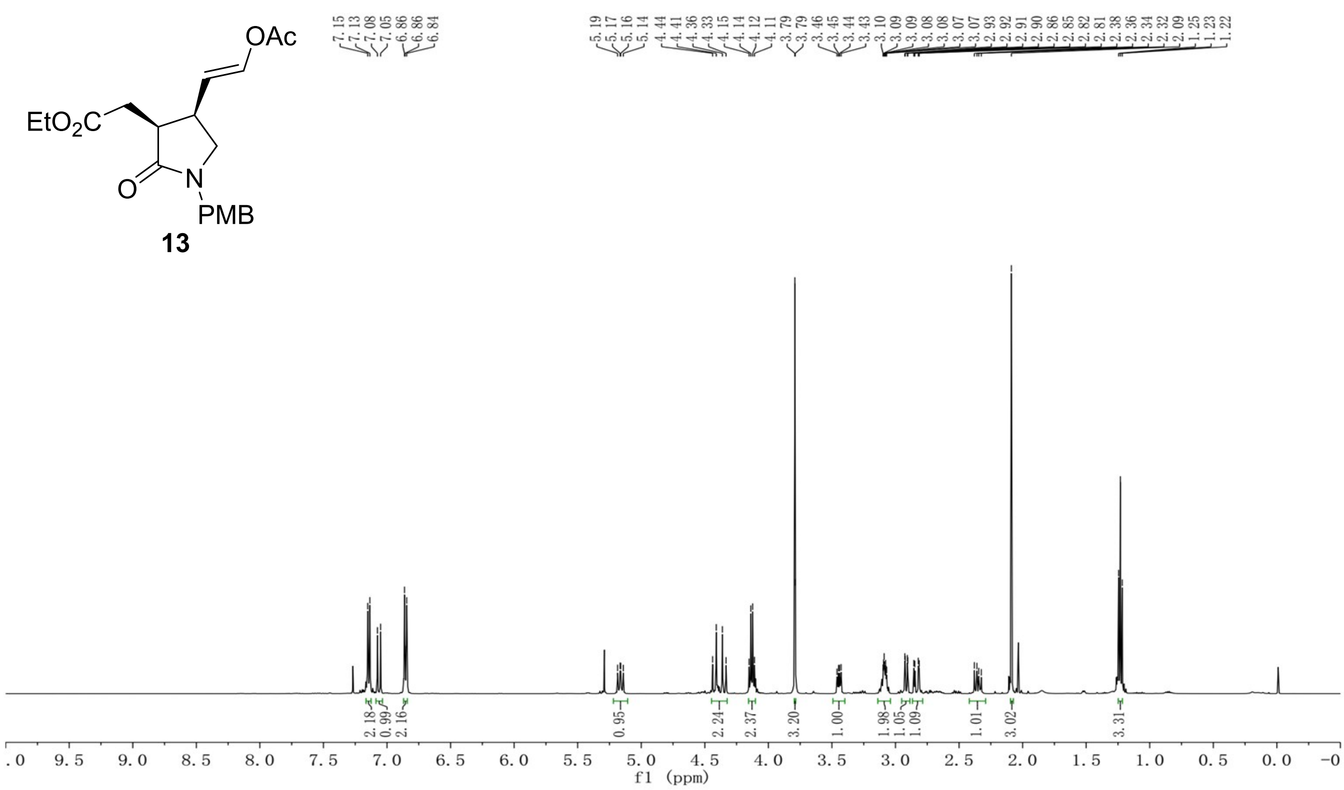
^{13}C NMR (125 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, $CDCl_3$)



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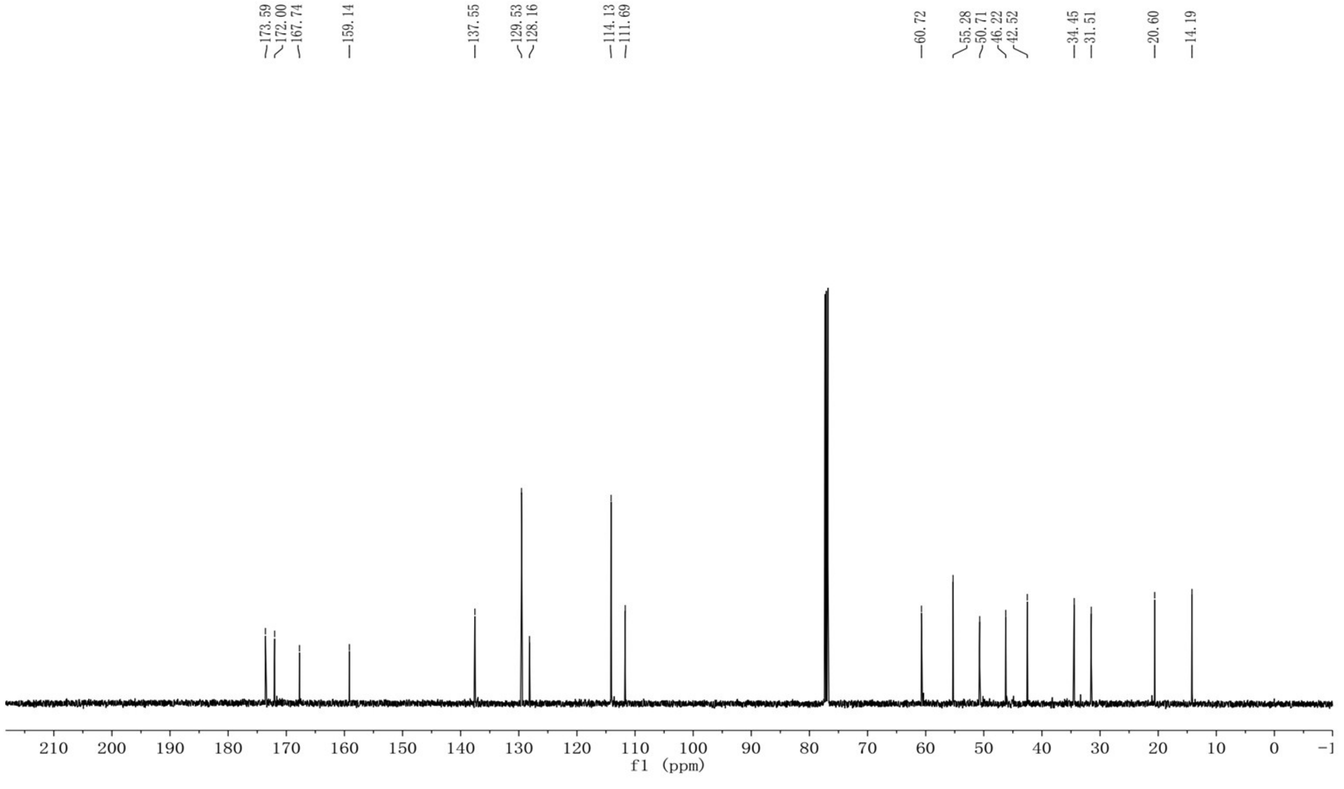
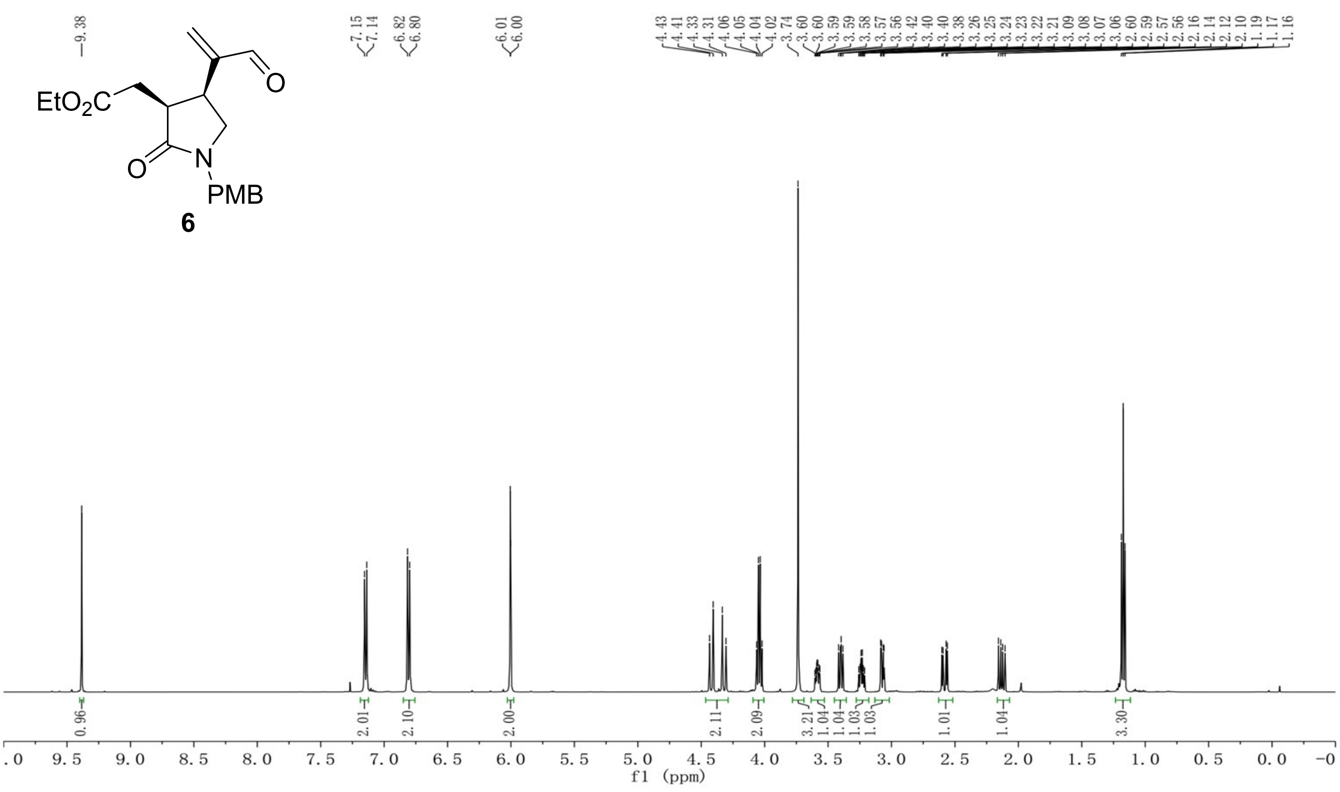


^{1}H NMR (500 MHz, CDCl$_3$)



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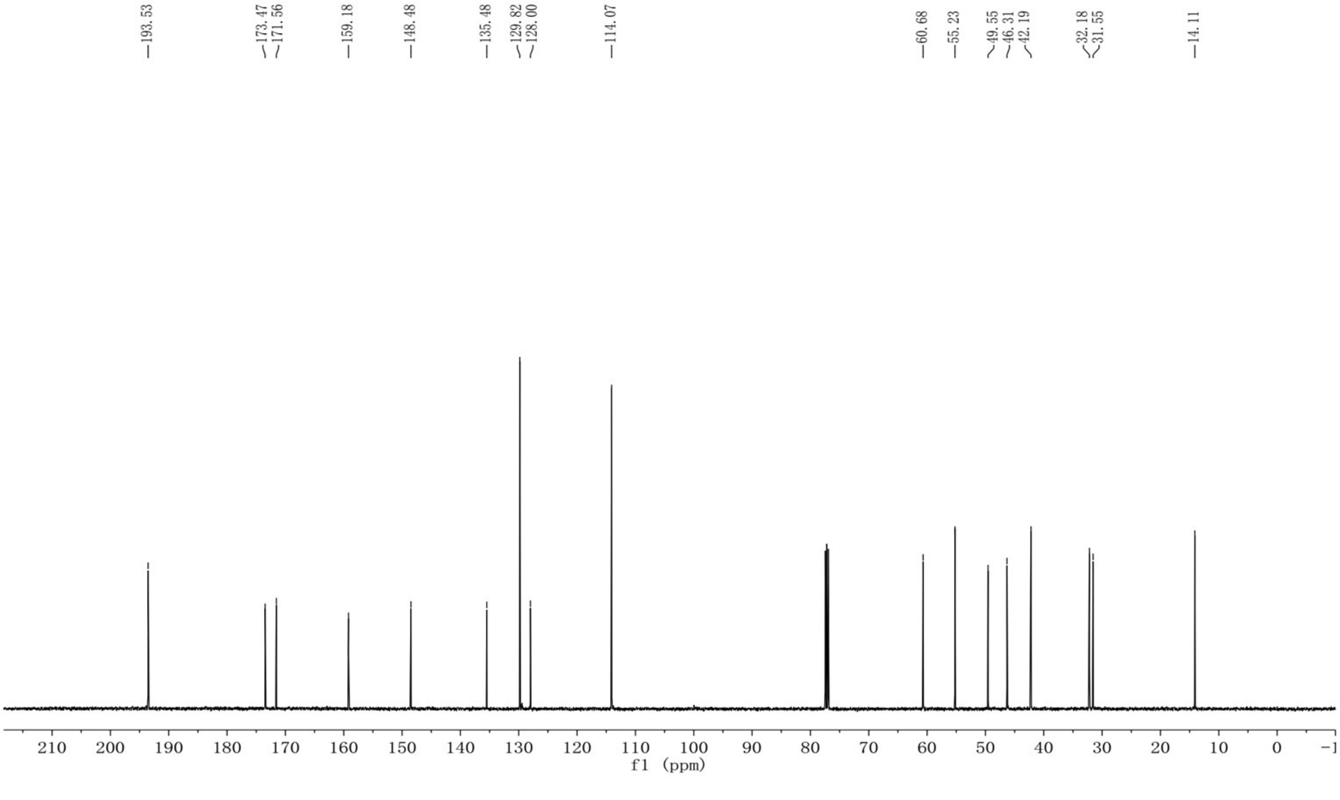
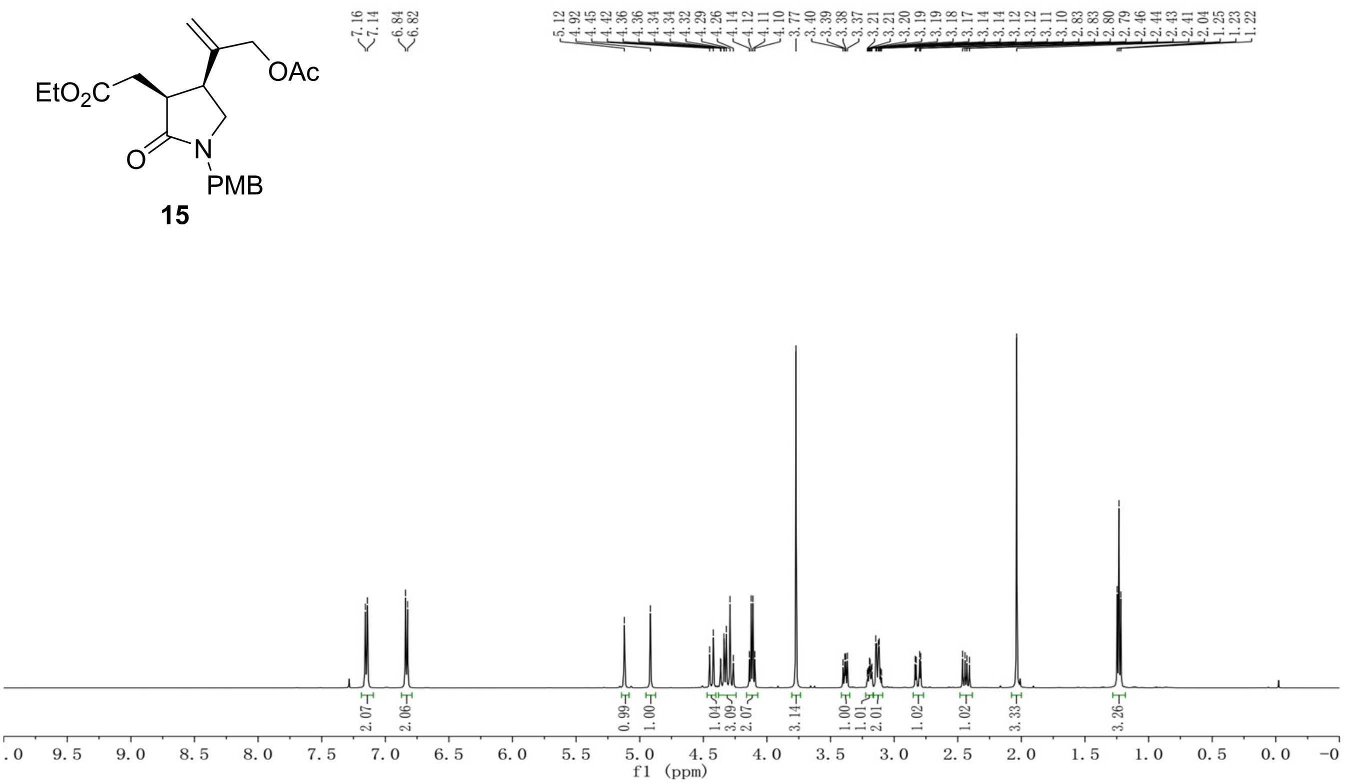
^{13}C NMR (125 MHz, CDCl$_3$)



^{1}H NMR (500 MHz, CDCl$_3$)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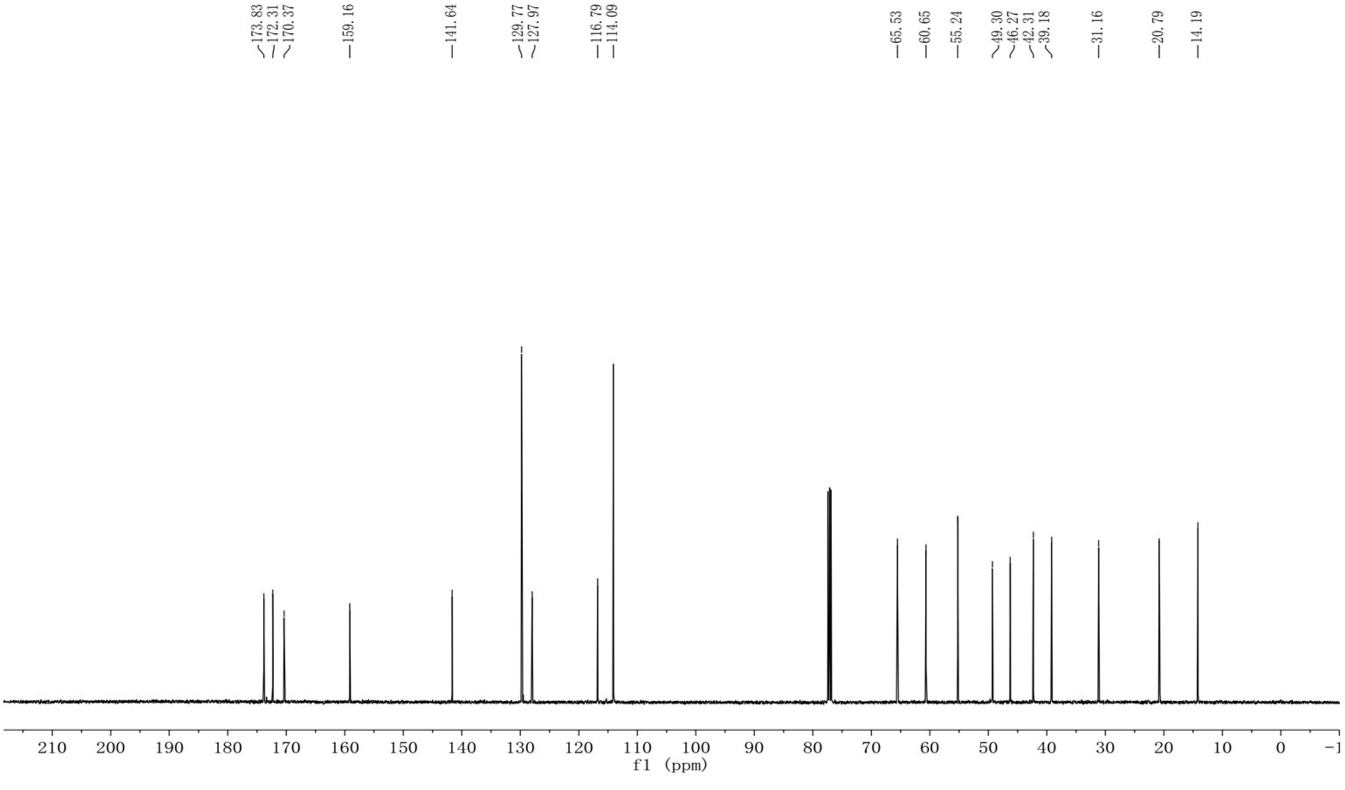
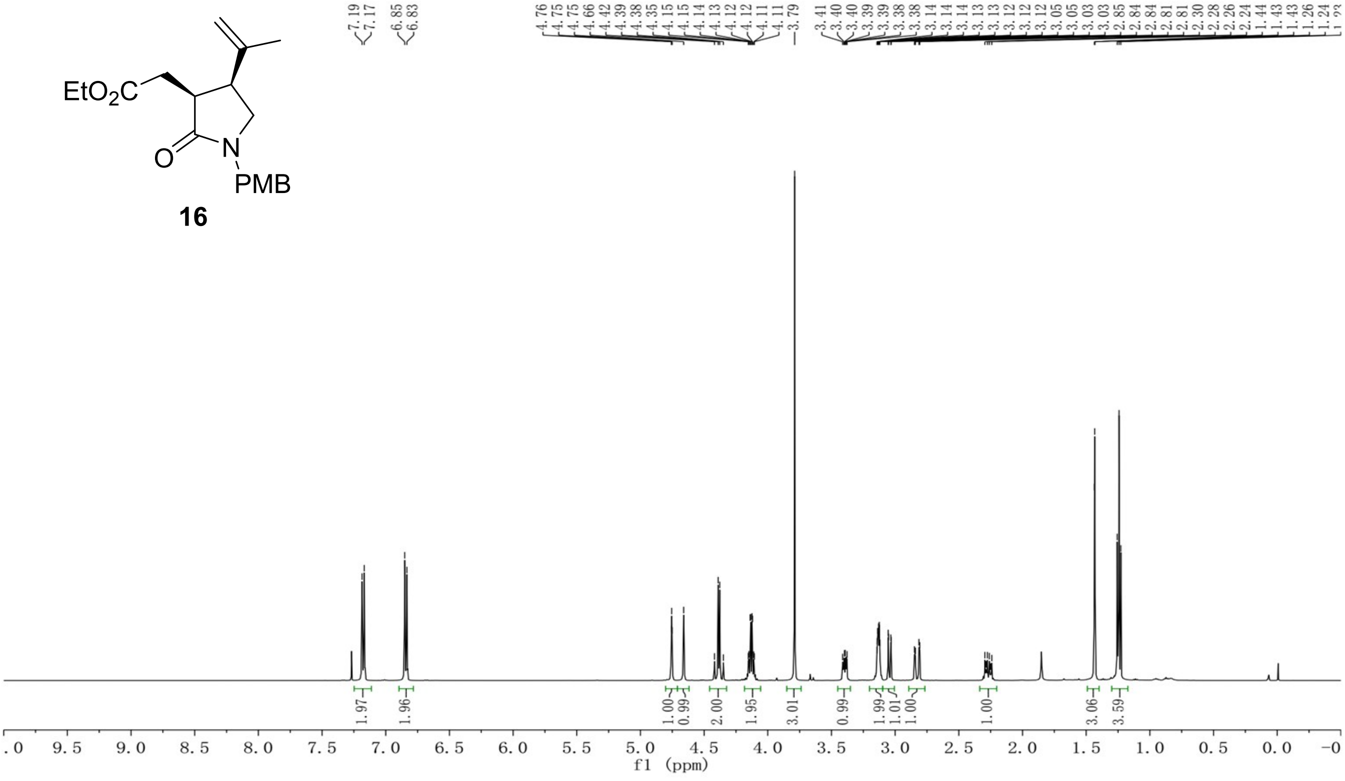
^{13}C NMR (125 MHz, CDCl$_3$)



^{1}H NMR (500 MHz, CDCl$_3$)



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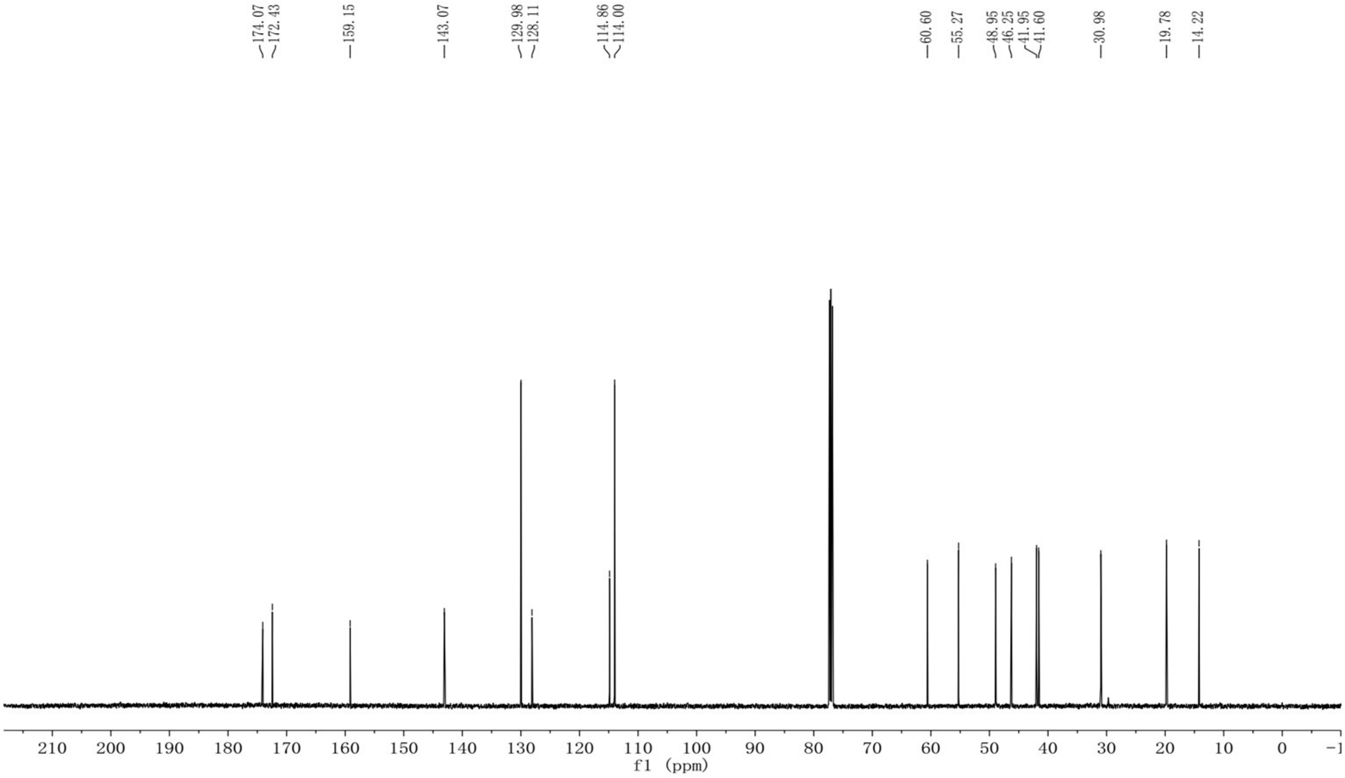
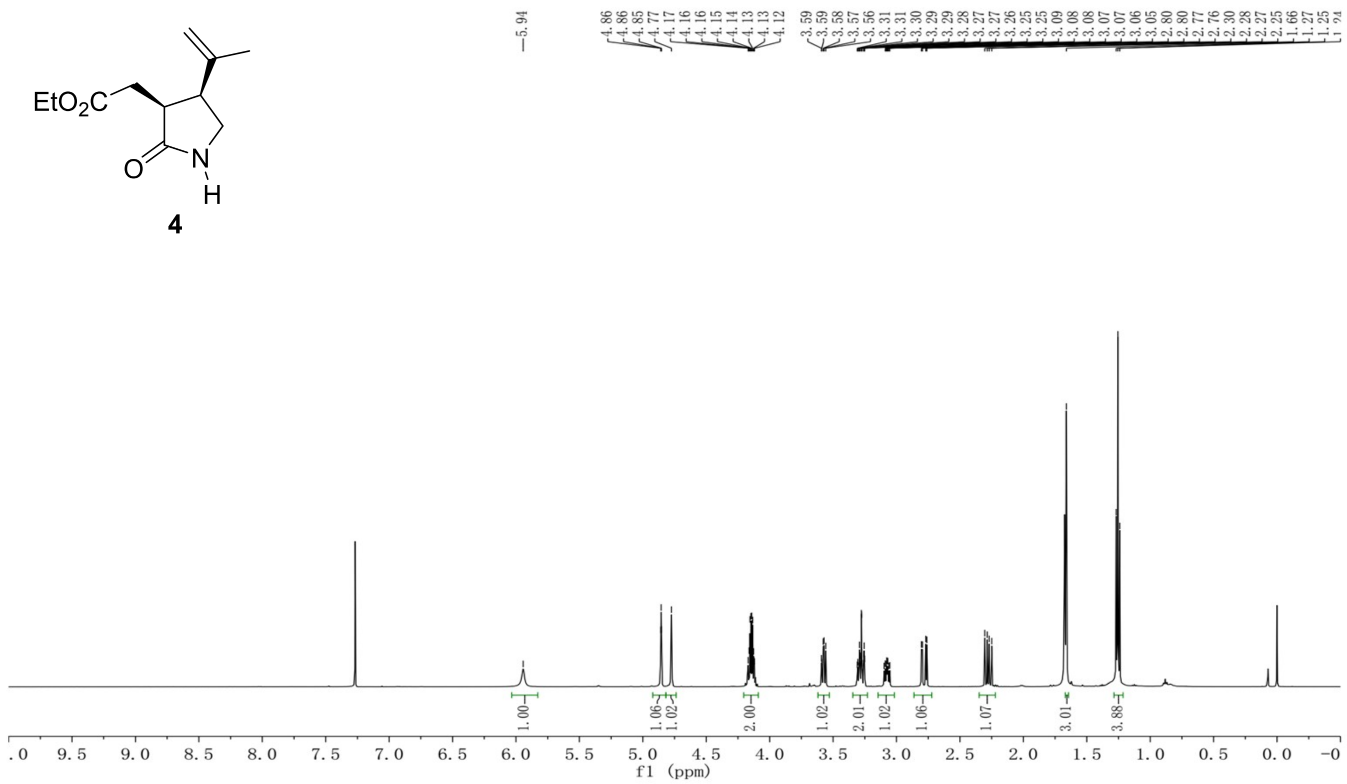
^{13}C NMR (125 MHz, CDCl$_3$)

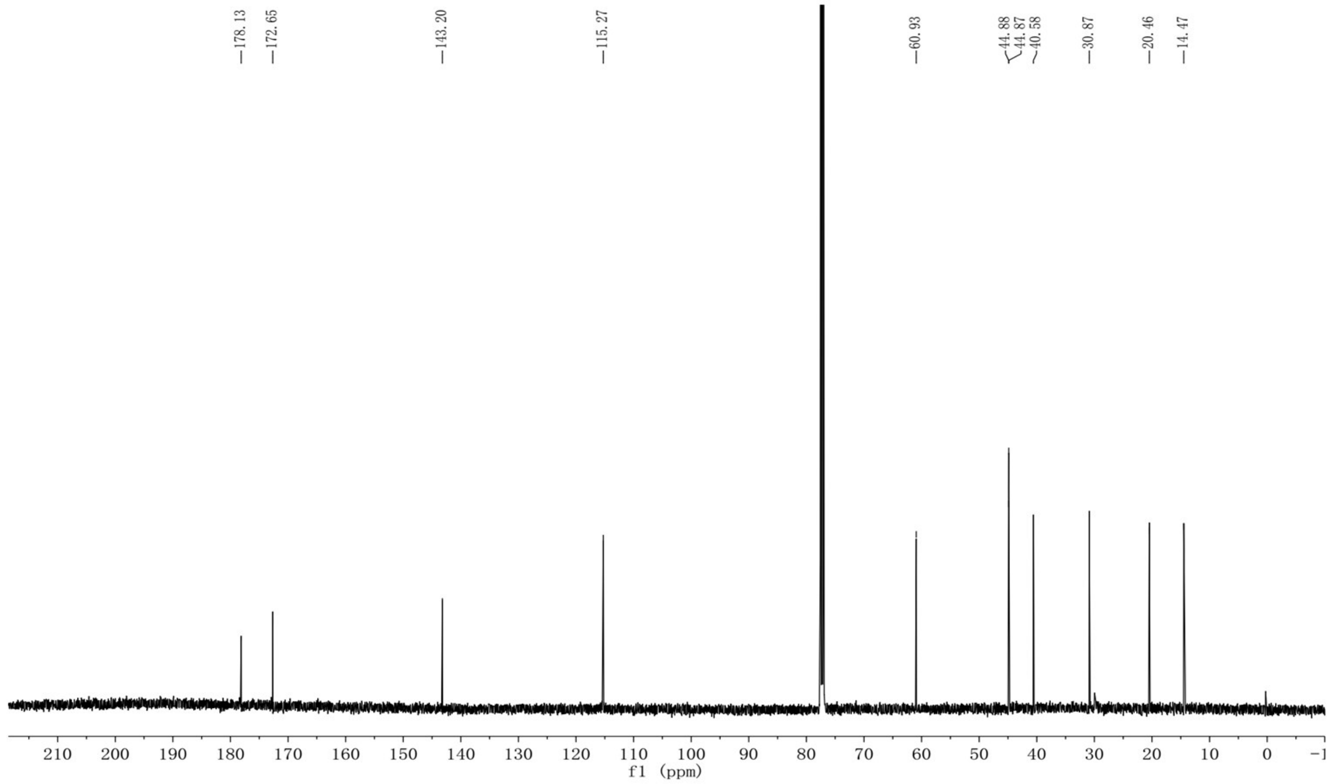


^{1}H NMR (500 MHz, CDCl$_3$)

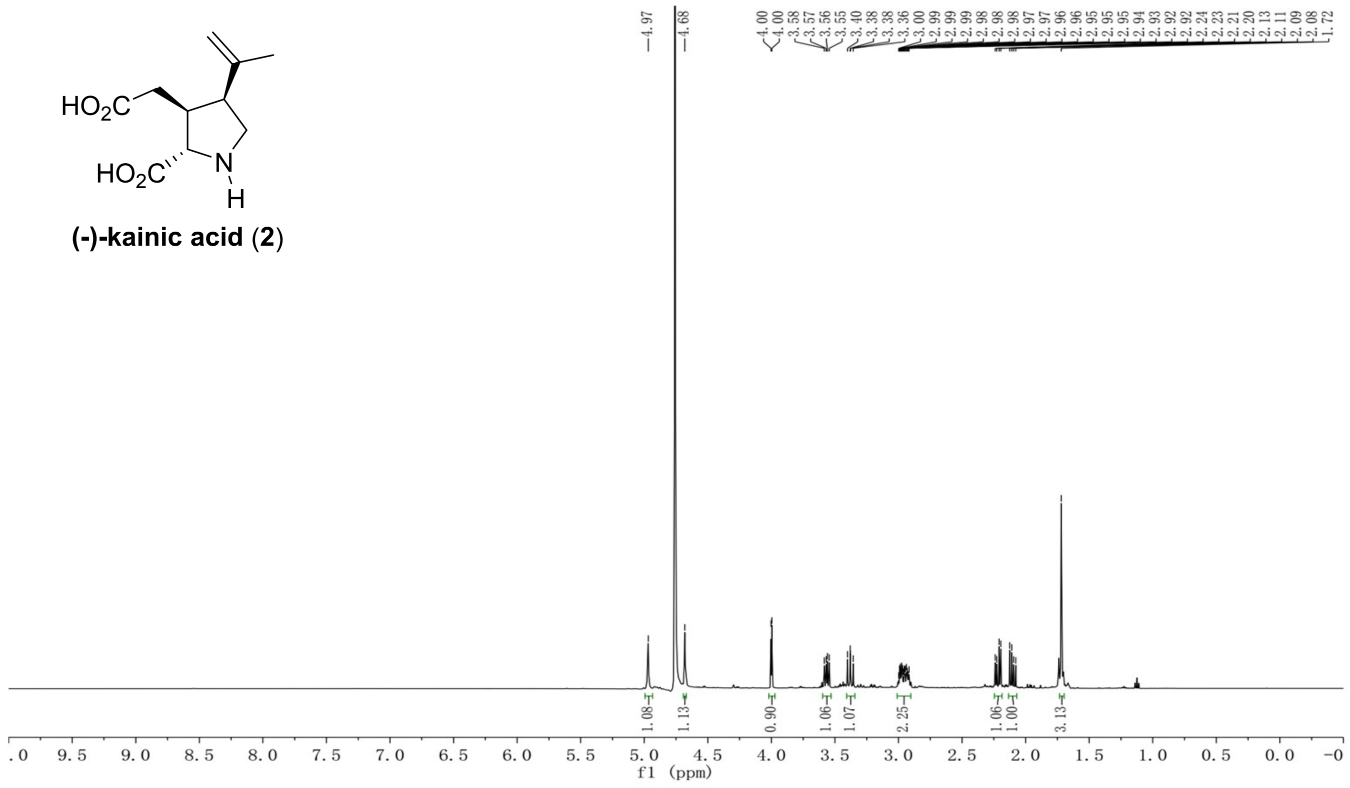


4

^{13}C NMR (125 MHz, CDCl$_3$)

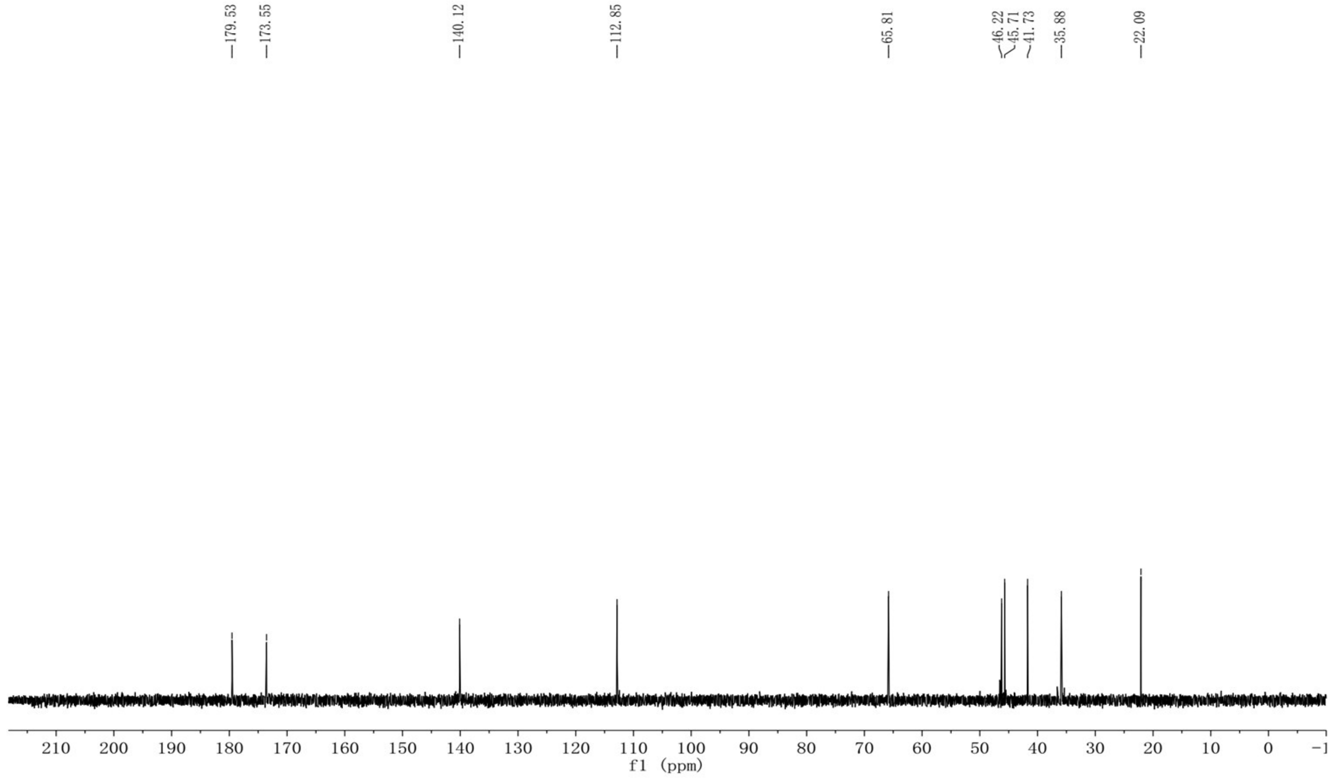


^{1}H NMR (500 MHz, D$_2$O)

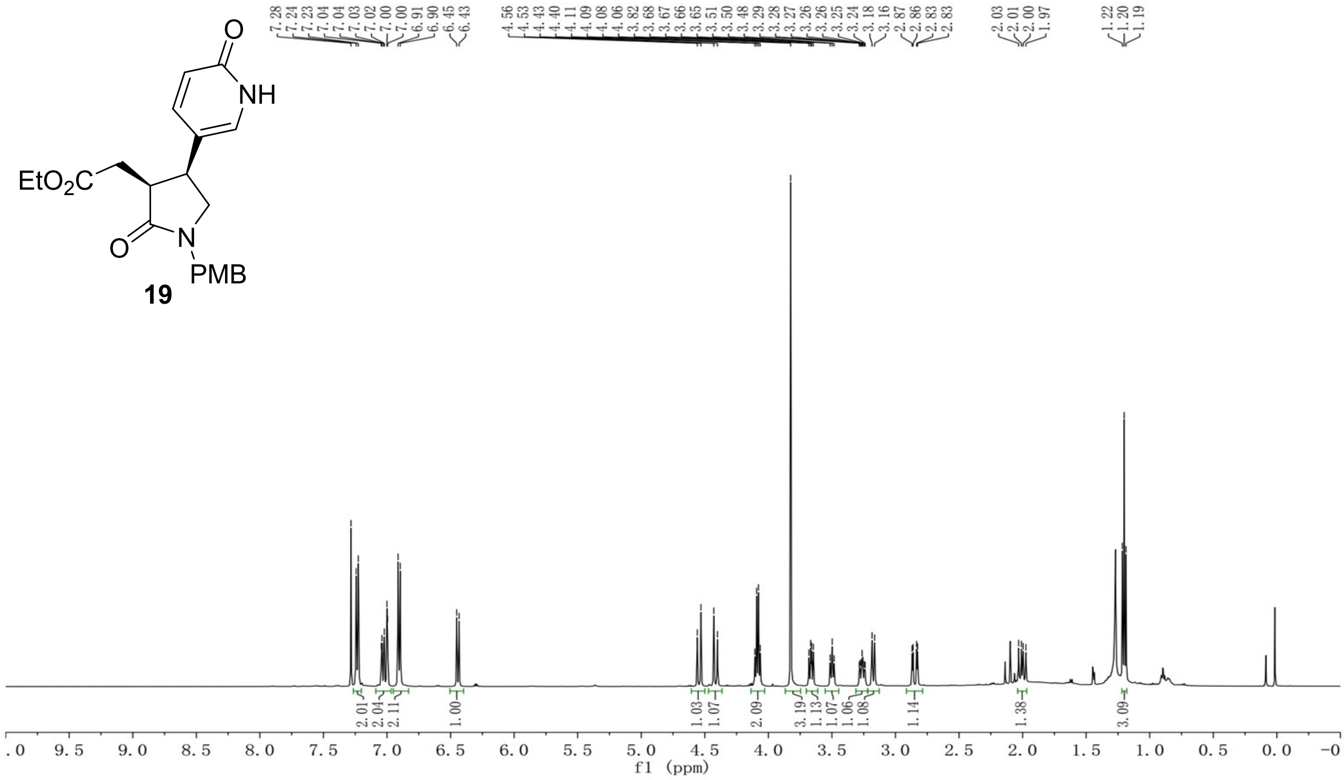


(-)-kainic acid (**2**)

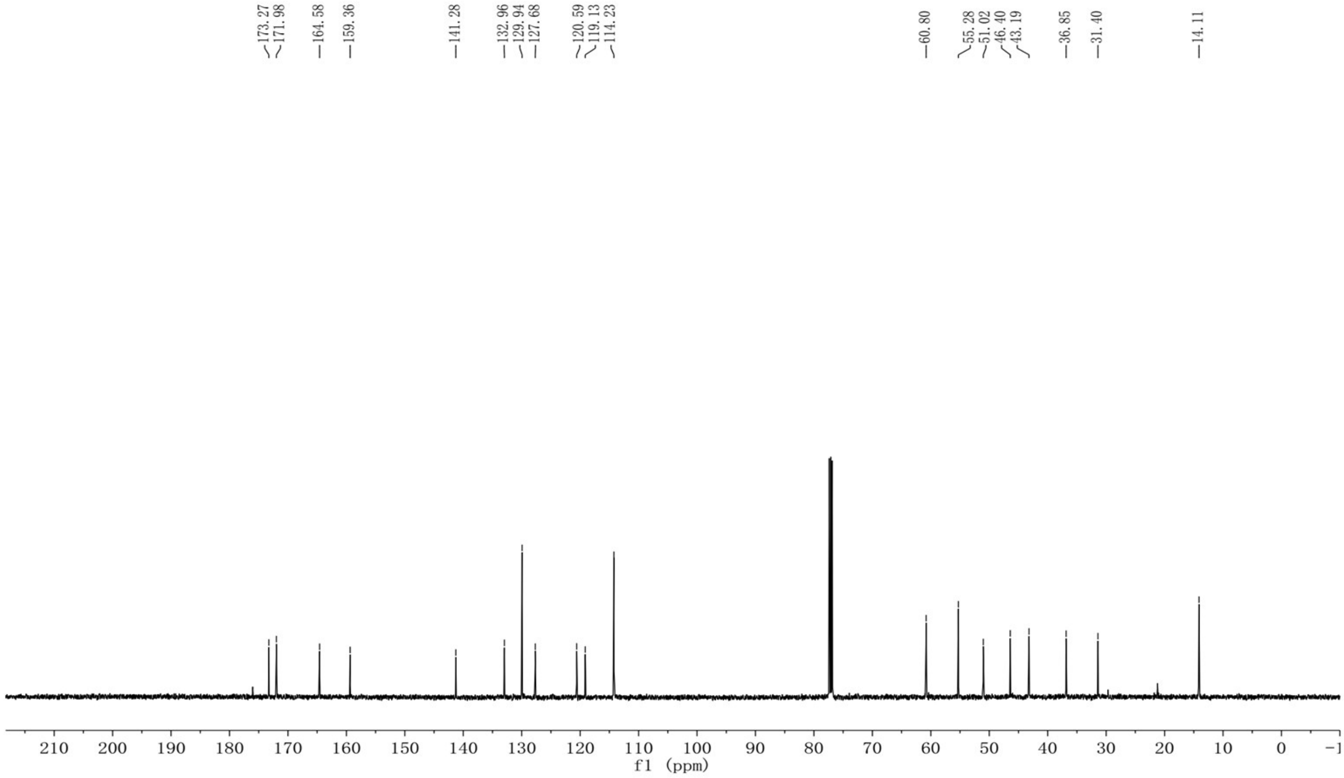
^{13}C NMR (125 MHz, D$_2$O)



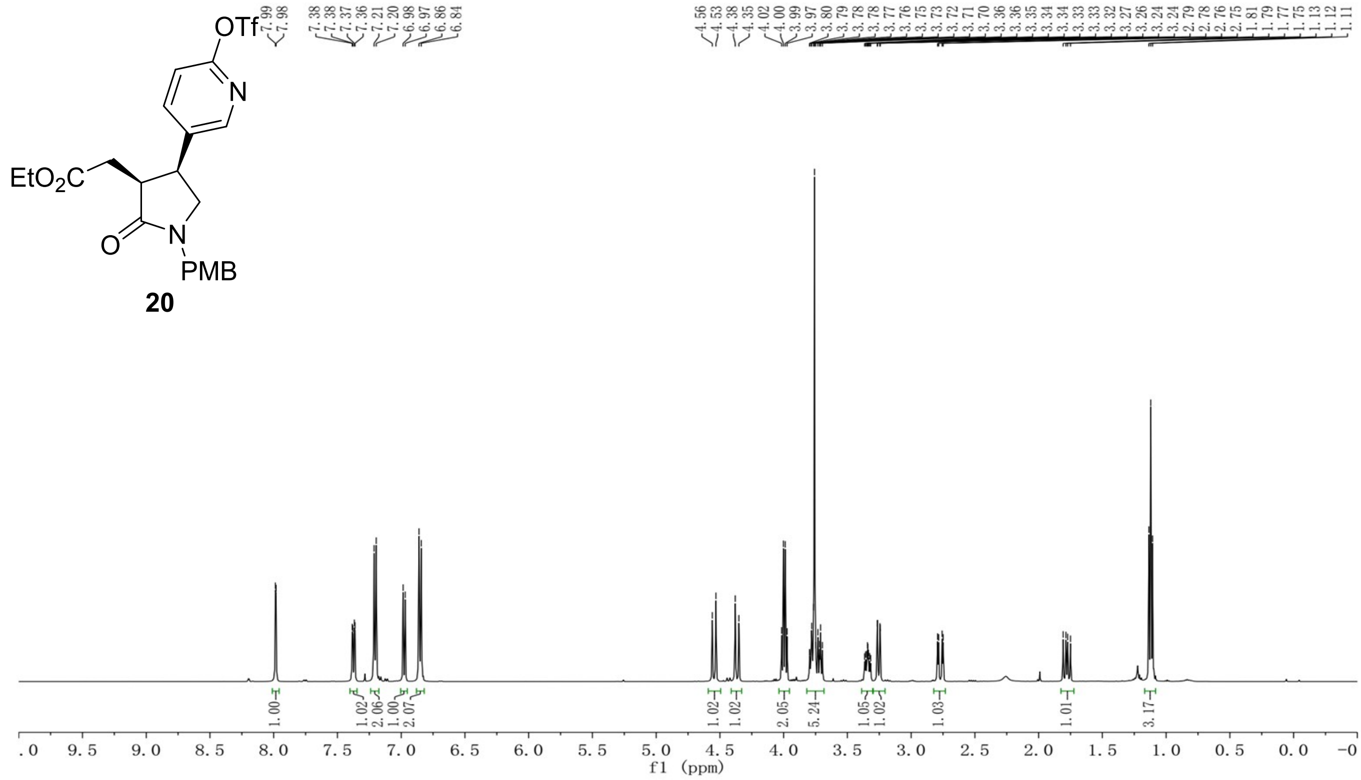
^{1}H NMR (500 MHz, $CDCl_3$)



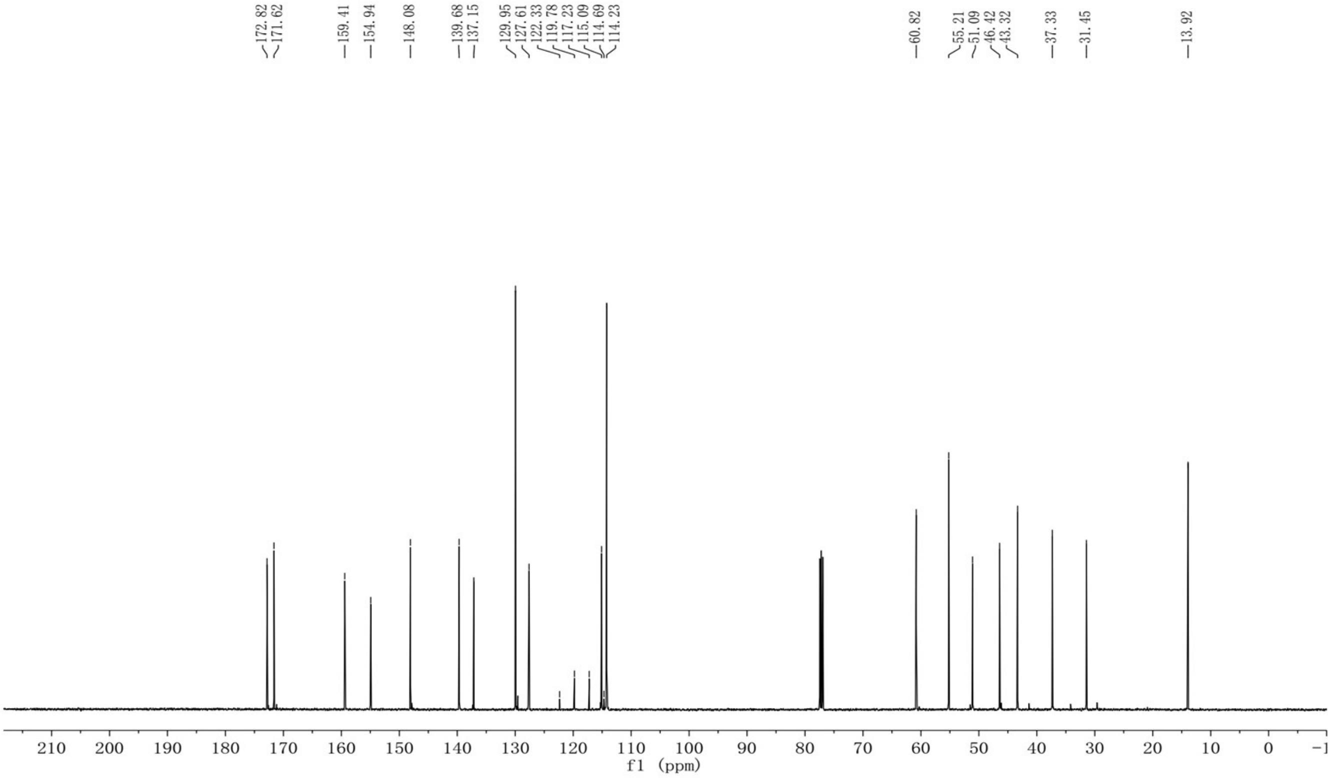
^{13}C NMR (125 MHz, $CDCl_3$)



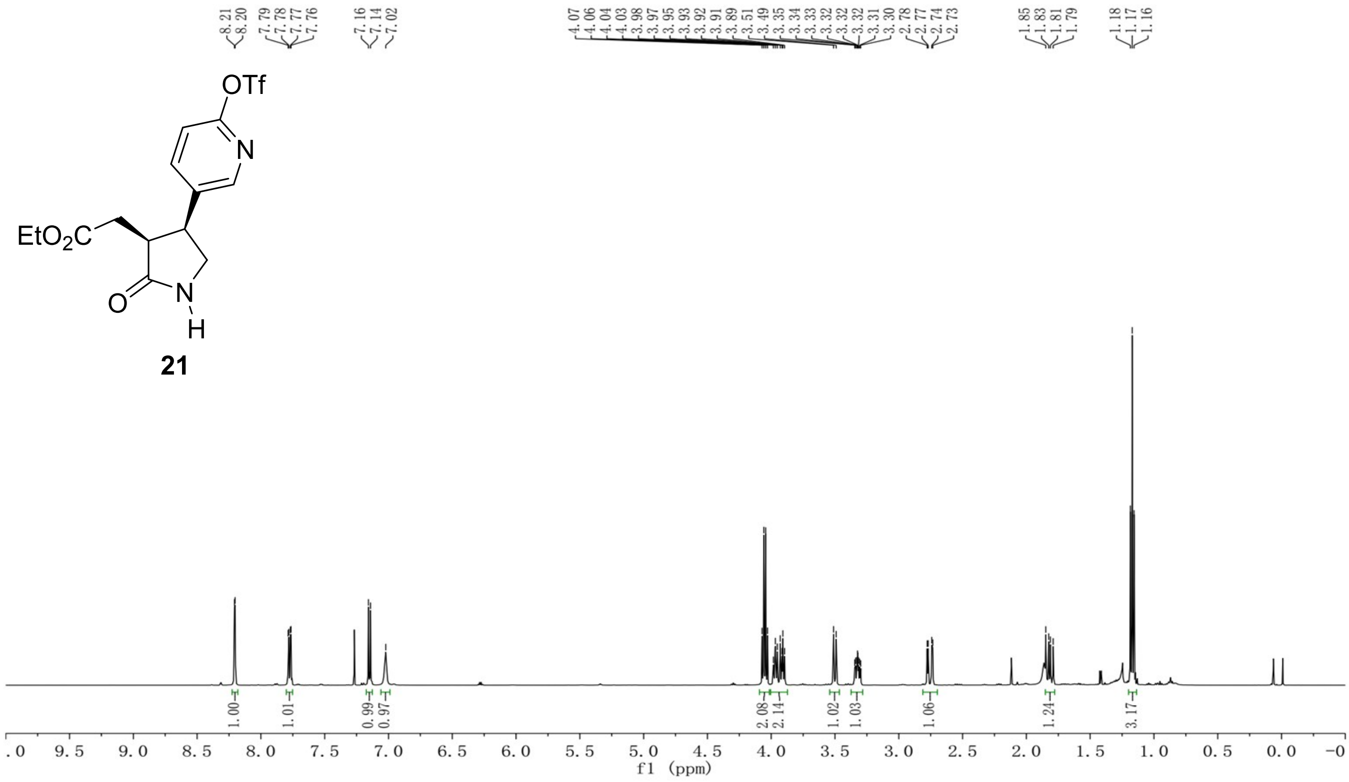
^{1}H NMR (500 MHz, CDCl$_3$)


20

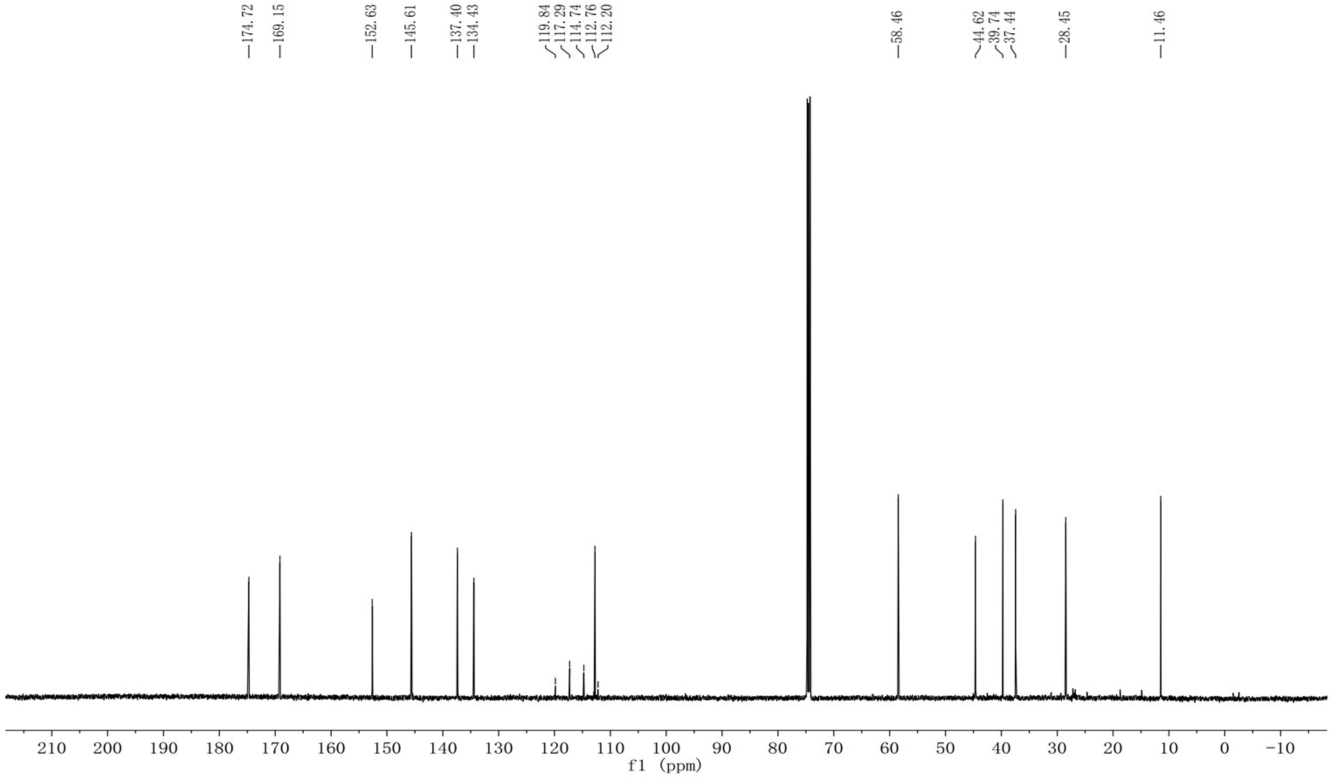
^{13}C NMR (125 MHz, CDCl$_3$)



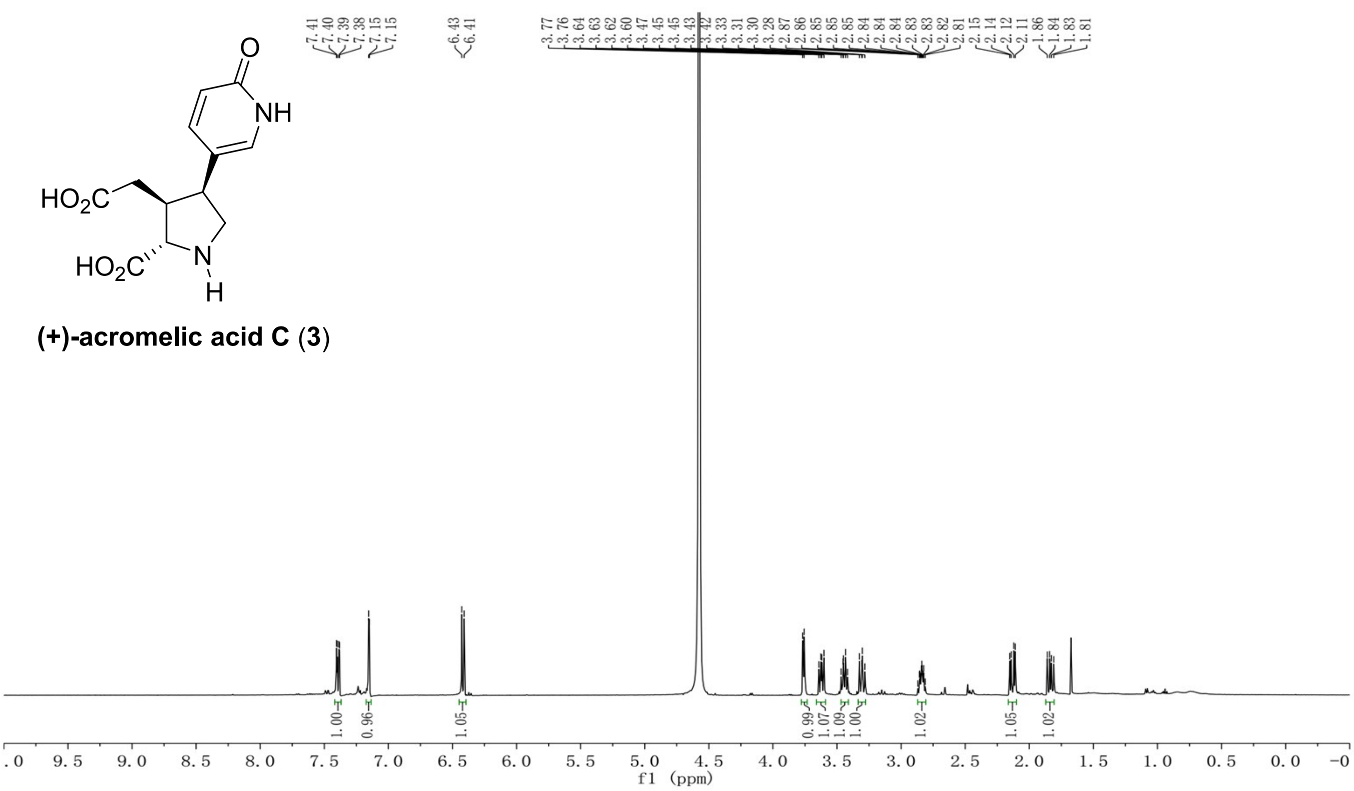
^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)

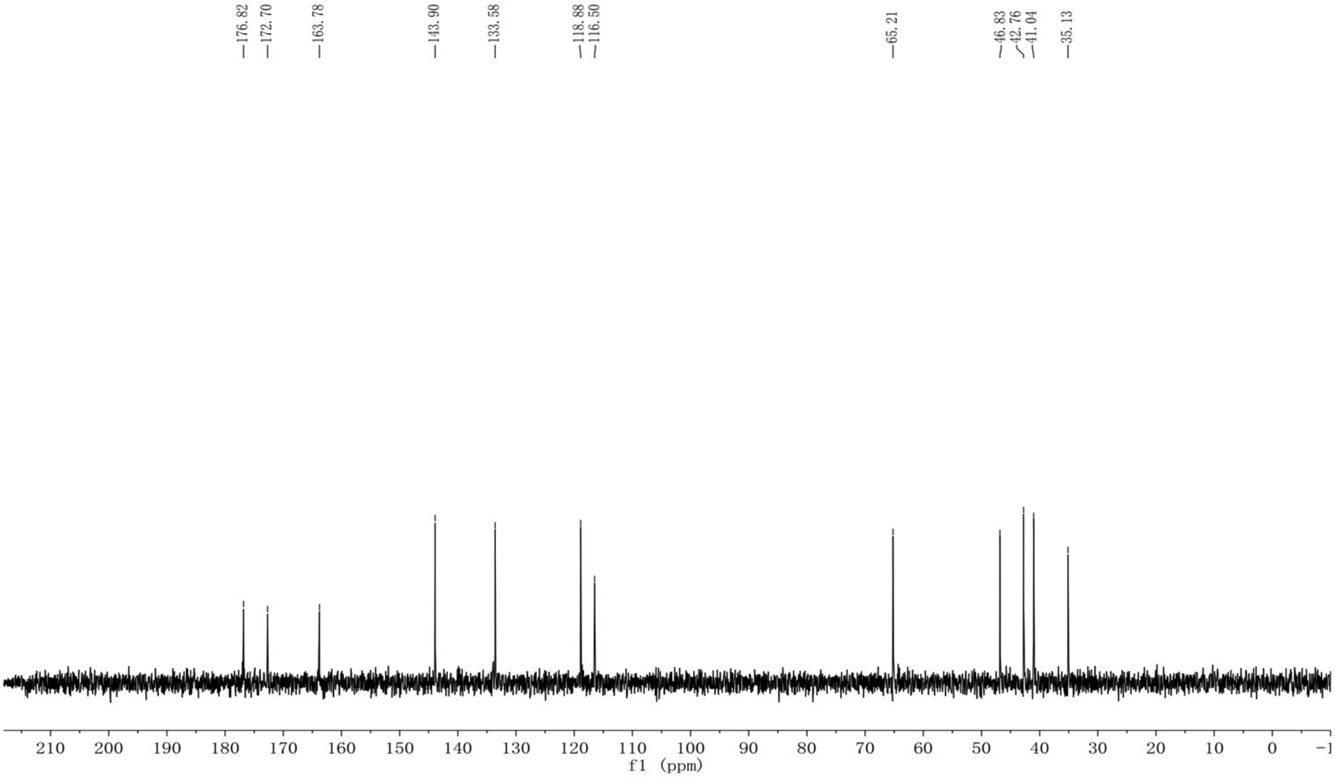


^{1}H NMR (500 MHz, D_2O)

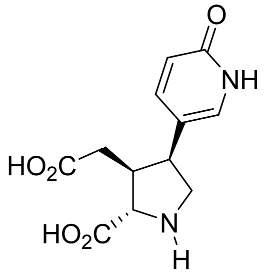


(+)-acromelic acid C (3)

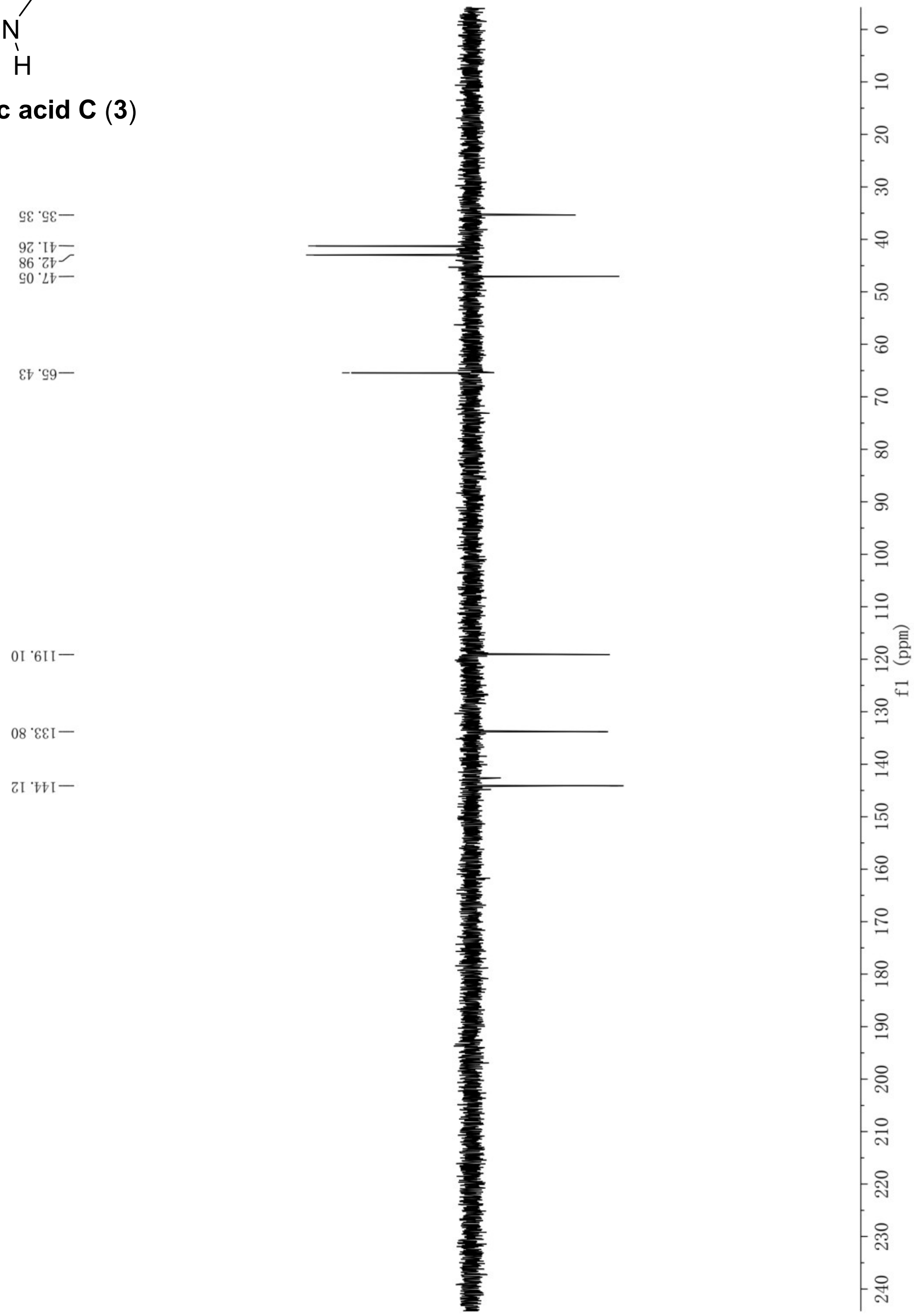
^{13}C NMR (125 MHz, D_2O)



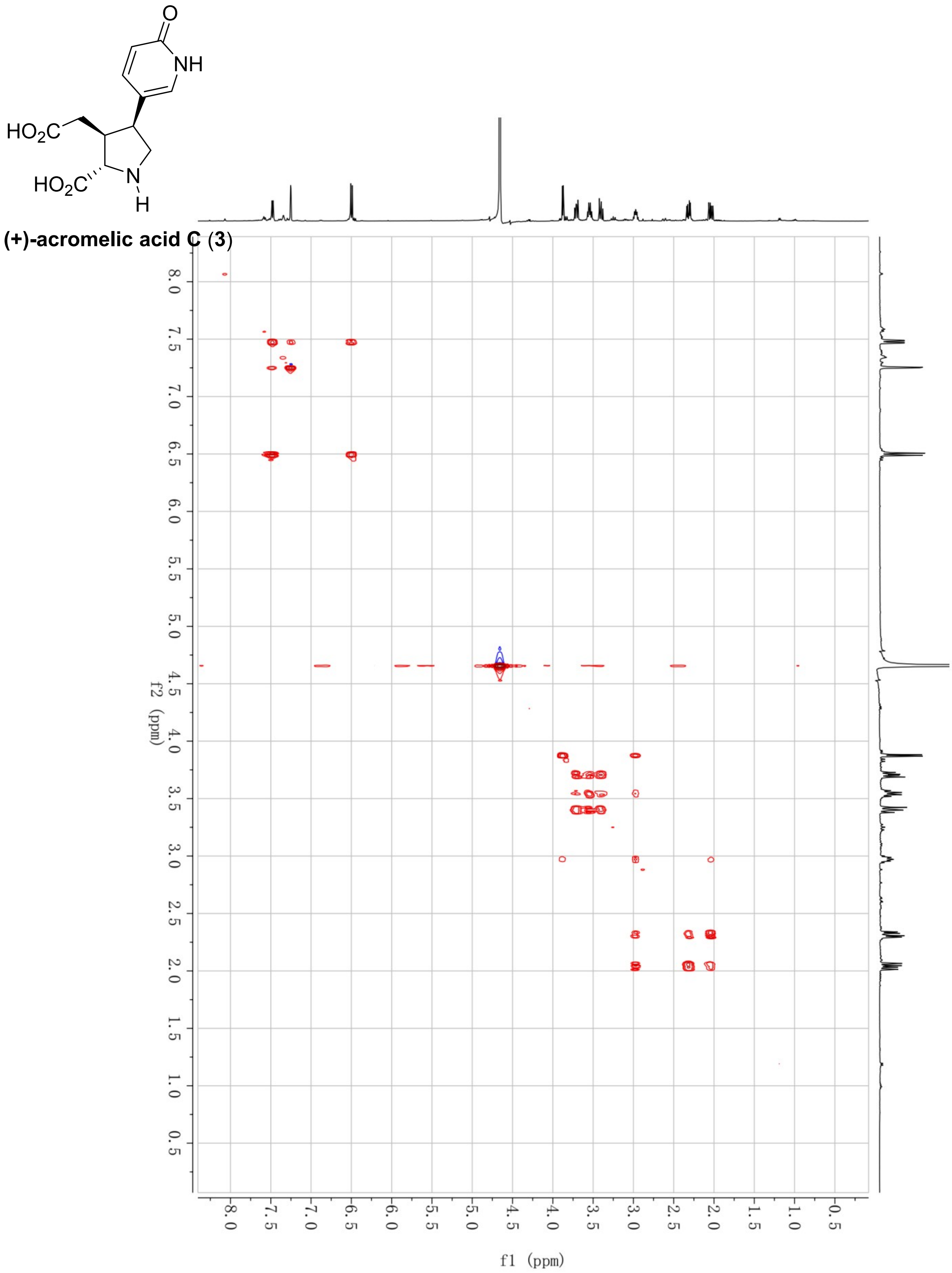
Dept 135 (500 MHz, D_2O)



(+)-acromelic acid C (**3**)

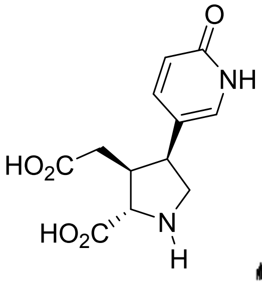


COSY (500 MHz, D_2O)

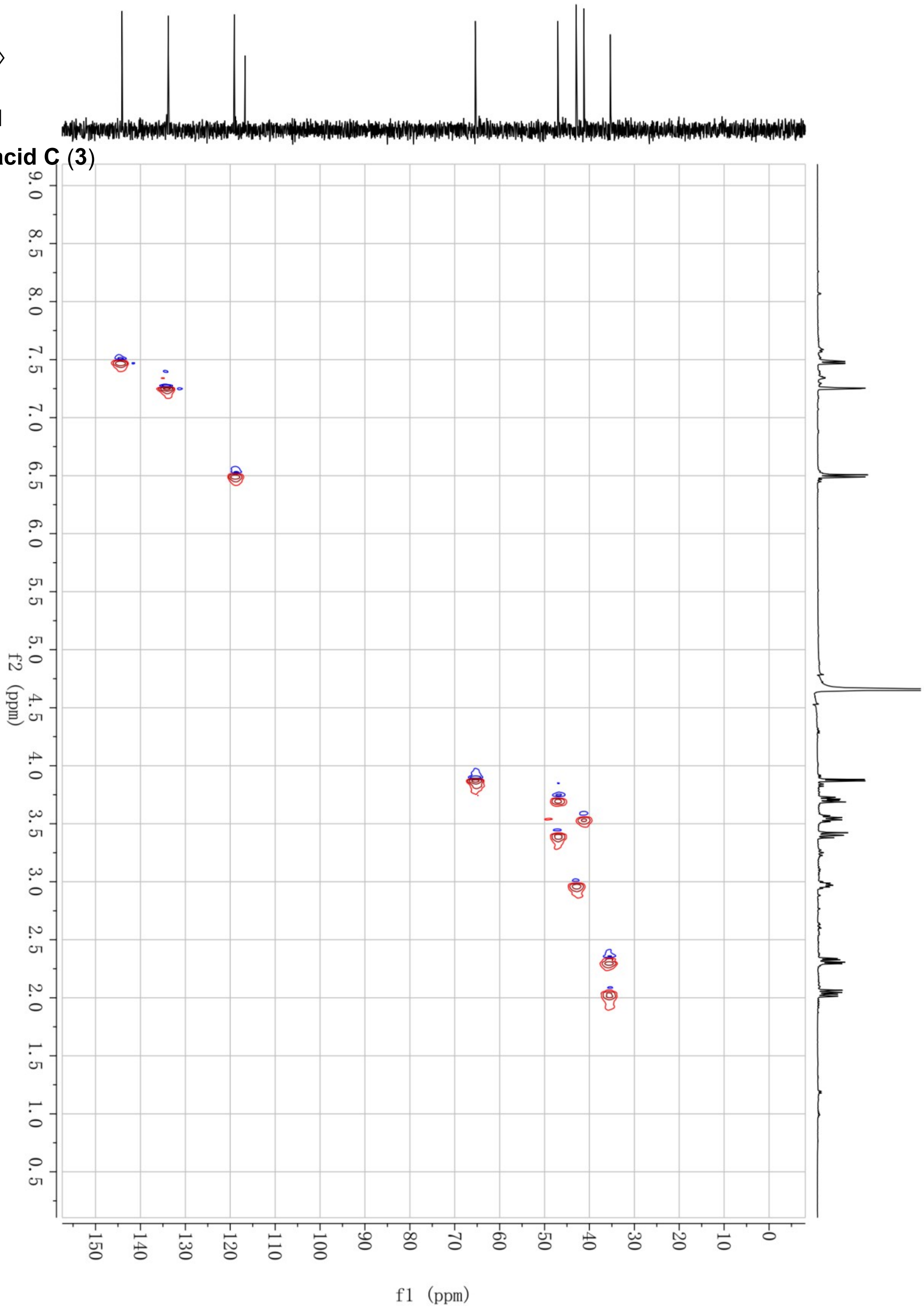


(+)-acromelic acid C (3)

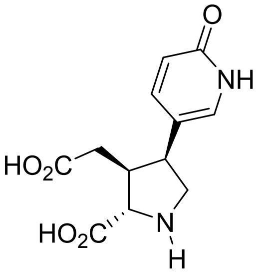
HSQC (500 MHz, D_2O)



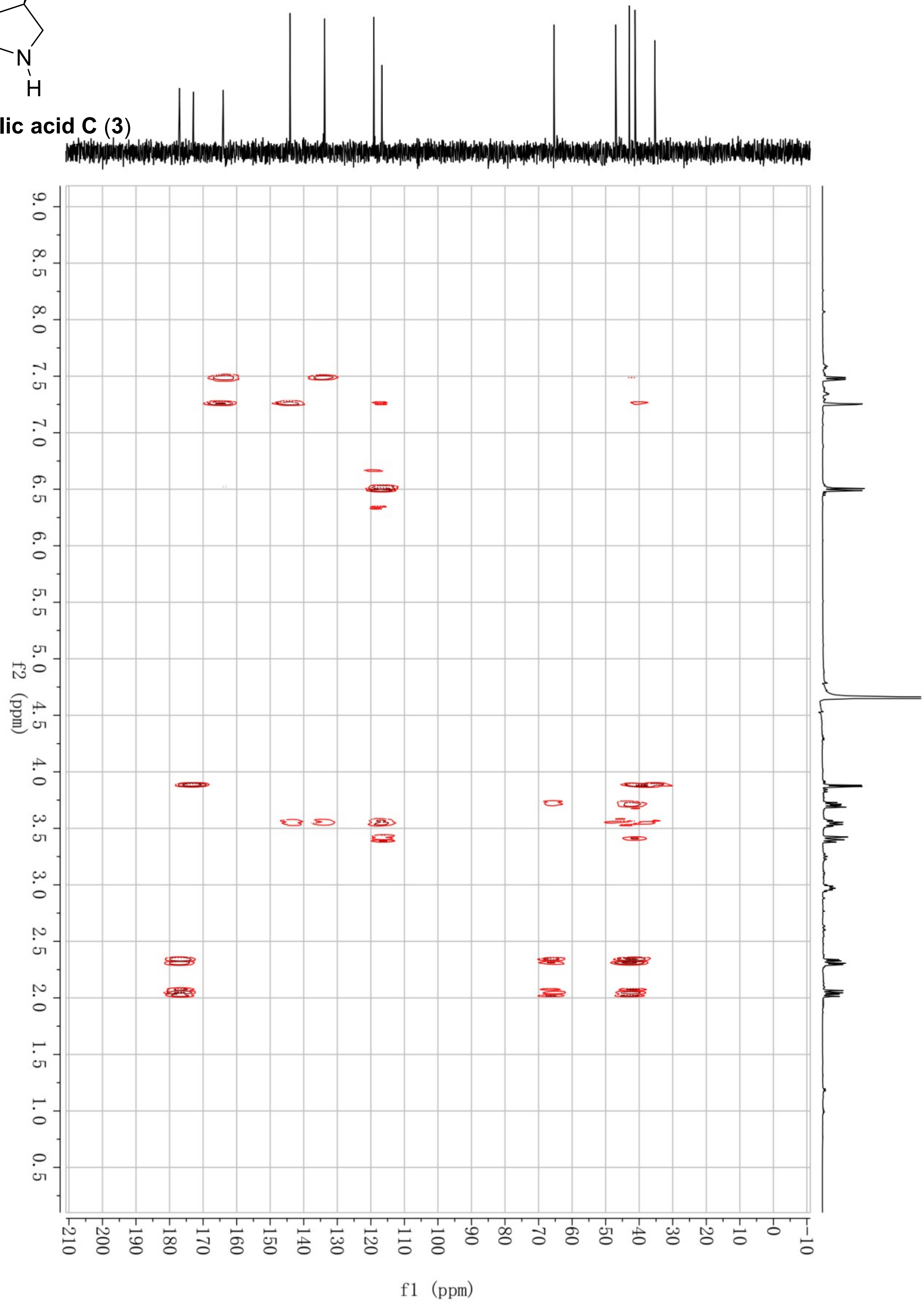
(+)-acromelic acid C (3)



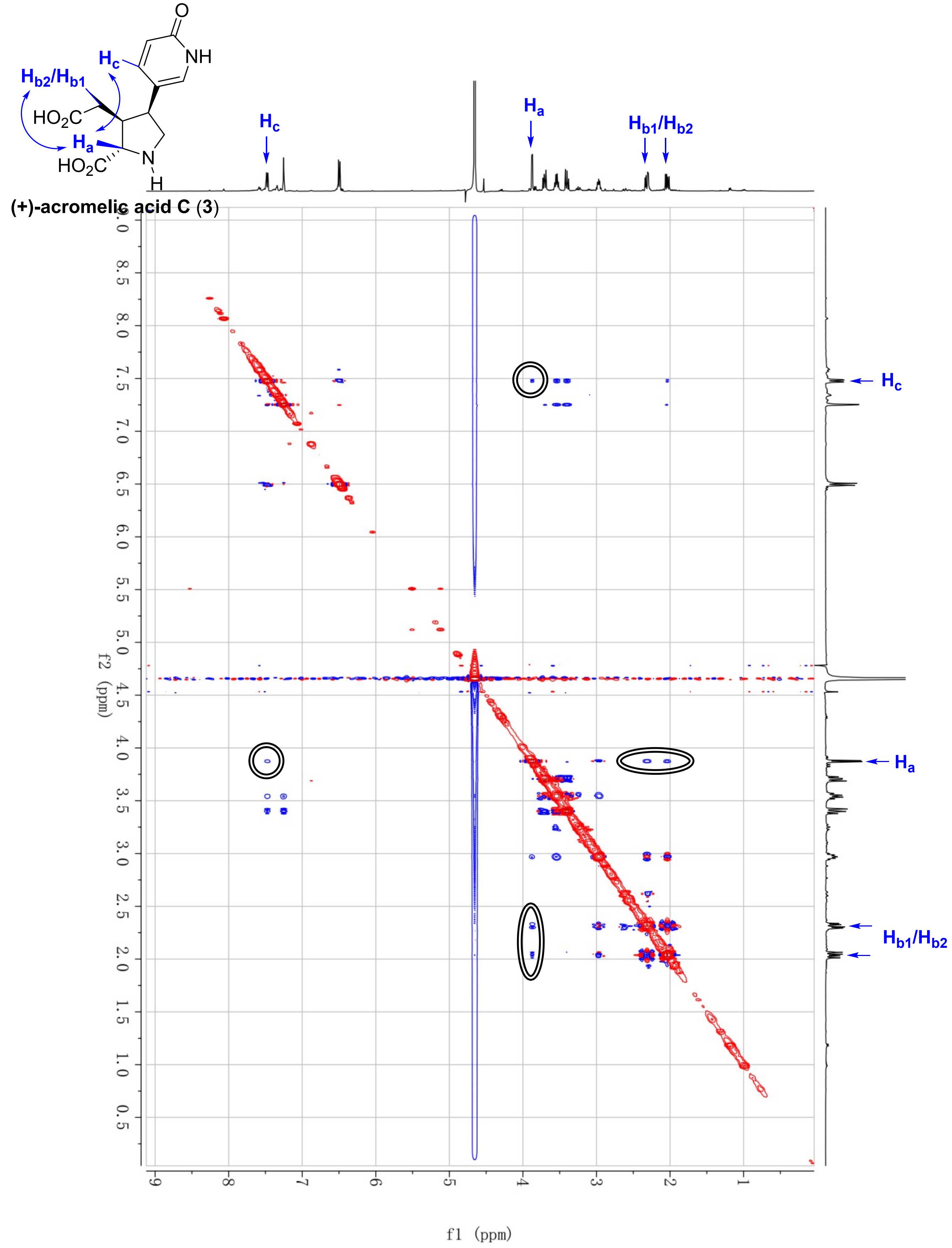
HMBC (500 MHz, D_2O)



(+)-acromelic acid C (**3**)



NOESY (500 MHz, D_2O)



(+)-acromelic acid C (3)