Electronic Supplementary Material (ESI) for ChemComm.

Supplementary Information

Asymmetric Total Synthesis of Prostaglandin C_2 TBS Ether

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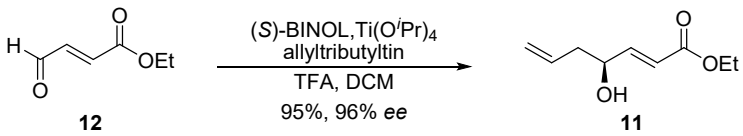
1. General Information

All commercially available reagents were used without further purification. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl and Dichloromethane (DCM) was distilled from calcium hydride. Chromatography was conducted by using 200−300 mesh silica gel. All new compounds gave satisfactory spectroscopic analyses (IR, ^{1}H NMR, ^{13}C NMR, HRMS). NMR spectra were recorded on a 400 or 600 MHz NMR. Reference values for residual solvents were taken as δ = 7.26 (Chloroform-*d*) ppm for ^{1}H NMR and δ = 77.16 (Chloroform-*d*) ppm for ^{13}C NMR. Coupling constants (*J*) are given in Hz and are uncorrected and multiplicities for coupled signals were denoted as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad, apt. = apparent and dd = double doublet etc. Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum Two FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on a Bruker TOF Premier, by the ESI method. Optical rotation was obtained from Rudolph Research Analytical Autopol VI automatic polarimeter. Chiral HPLC was performed using a Daicel Chiralcel OD column (4.6 × 250 mm) analytical column. Unless otherwise noted, all products are isolated yields.

2. Experimental Procedures

Synthesis of 11

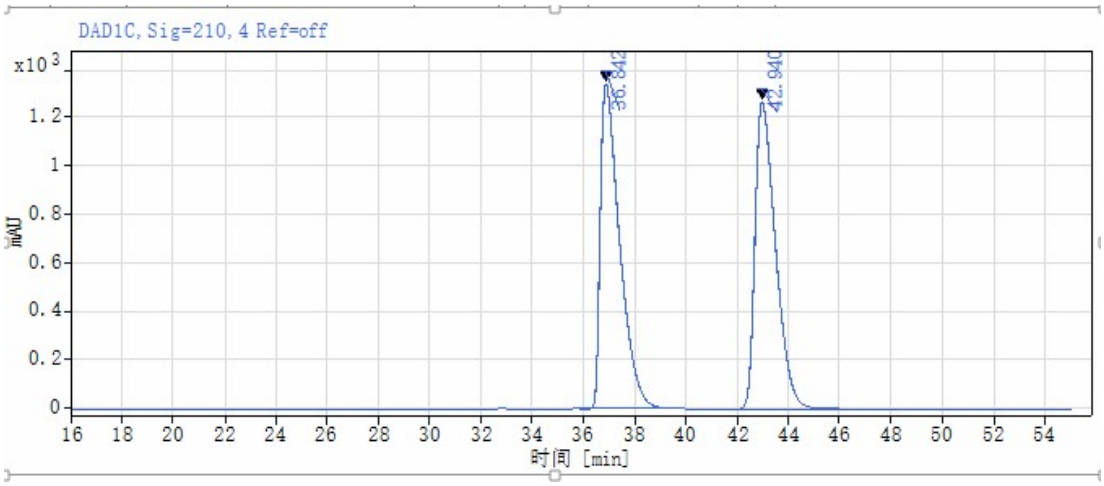


To a suspension of molecular sieve (9.39 g), (*S*)-BINOL (1.34 g, 4.68 mmol, 0.2 equiv.) in dry DCM (80 mL) was added a solution of 1.0 M Ti($O^{i}Pr$)$_4$ (2.30 mL, 2.34 mmol, 0.1 equiv.) in DCM via syringe, and a freshly prepared solution of 0.5 M TFA (328.0 μL, 0.16 mmol, 0.007 equiv.) in DCM under an atmosphere of Ar. The reaction mixture was stirred at reflux for 1 h and cooled to room temperature. Commercially available aldehyde **12** (3.00 g, 23.41 mmol, 1.0 equiv.) was added and stirred at room temperature for 0.5 h, then cooled to –78 °C. Allyltributyltin (11.63 g, 35.12 mmol, 1.5 equiv.) was added to the stirring mixture and stirred for additional 10 min, the reaction mixture was warmed to –20 °C. After 12 h, the reaction mixture was filtered over a pad of Celite and washed with DCM, saturated aqueous $NaHCO_3$ solution was added and stirred for 1 h, then the layers were separated. The aqueous layer was extracted with DCM, combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, filtered, concentrated under vacuum and isolated by using silica flash column chromatography (only petroleum) to afford **11** as colorless oil (3.79 g, 95%): Rf = 0.3 (petroleum ether/acetone = 20:3). $[\alpha]_D^{20}$ = –12.77 (*c* = 1.0, $CHCl_3$). **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 6.92 (dd, *J* = 15.6, 3.6 Hz, 1H), 6.03 (d, *J* = 15.6 Hz, 1H), 5.80 – 5.74 (m, 1H), 5.15 (d, *J* = 13.8 Hz, 2H), 4.34 (d, *J* = 6.0 Hz, 1H), 4.17 (q, *J* =

6.6 Hz, 2H), 2.40 – 2.37 (m, 1H), 2.32 – 2.27 (m, 1H), 1.26 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (151 MHz, Chloroform-*d*)** δ 166.65, 149.36, 133.27, 120.61, 119.26, 119.23, 69.98, 60.59, 41.15, 14.29. **IR (KBr)**: 3451, 3078, 2982, 1715, 1657, 1369, 1308, 1179, 1042, 986, 920, 719 cm^{-1}. **HRMS (ESI) *m/z*** calcd for $C_9H_{15}O_3$ [M + H]$^+$: 171.1016, found: 171.1019. The enantiomeric excess (*ee*) was 96% *ee*, determined by HPLC on Chiralpak OD-H column, *n*–hexane:isopropanol = 98:2; flow rate = 0.5 mL/min; UV detection at 210 nm; t_{R1} = 37.008 min (major), t_{R2} = 43.671 min (minor).

The data is consistent with data reported in the literature.[1]

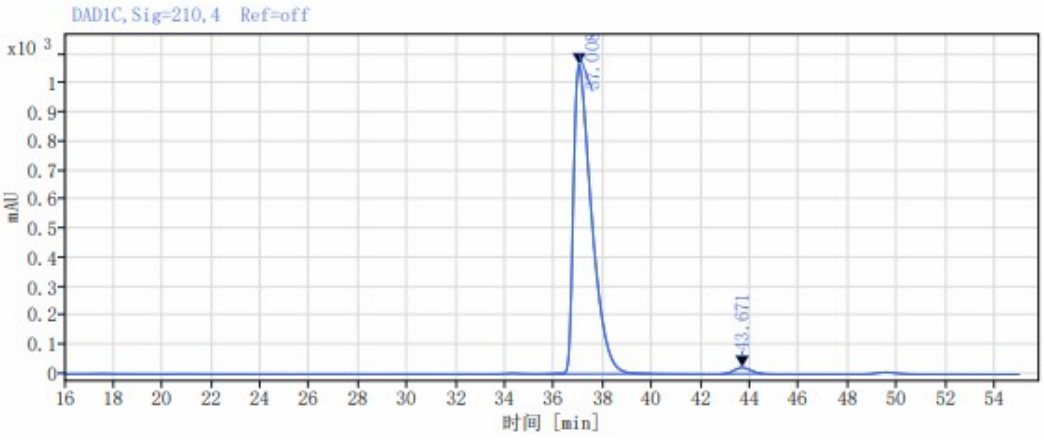
HPLC analysis rac-11



Ret Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area%
36.842	MMm	0.77	70253.30	1342.81	49.79
42.940	MMm	0.85	70837.50	1270.31	50.21

Chiral HPLC conditions: Daicel Chiralcel OD-H column, 98:2 *n*–hexane/*i*–PrOH, 0.5 mL/min, UV detector at 210 nm. t_{R1} = 36.842 min, t_{R2} = 42.940 min.

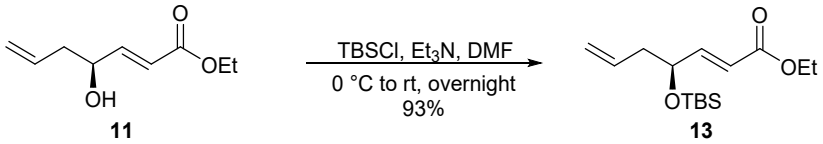
Enantioenriched 11



Ret Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area%
37.008	MM m	0.76	54735.76	1063.60	98.20
43.671	MM m	0.66	1005.29	21.30	1.80

Chiral HPLC conditions: Daicel Chiralcel OD-H column, 98:2 *n*–hexane/*i*–PrOH, 0.5 mL/min, UV detector at 210 nm. t_{R1} = 37.008 min, t_{R2} = 43.671 min.

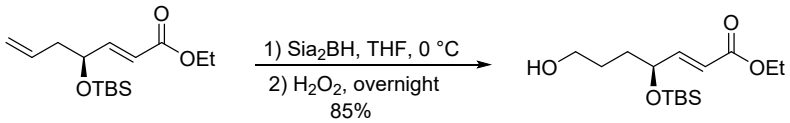
Synthesis of 13



11 **13**

To a solution of **11** (33.26 g, 0.20 mol, 1.0 equiv.) in DMF (750 mL) was added triethylamine (163.00 mL, 1.17 mol, 6.0 equiv.) and TBSCl (35.40 g, 0.24 mol, 1.2 equiv.). The reaction mixture was stirred at room temperature overnight. TLC analysis indicated complete consumption of starting material. The resulting mixture was quenched by water and then extracted with 10% ethyl acetate/hexane, combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, filtered, concentrated under vacuum and isolated by using silica flash column chromatography (petroleum ether/ethyl acetate = 30:1) to afford **13** as yellow oil (52.91 g, 93%): Rf = 0.7 (petroleum ether/ethyl acetate = 10:3). $[\alpha]_D^{20}$ = +11.70 (*c* = 1.02, $CHCl_3$). **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 6.92 (dd, *J* = 15.6, 4.8 Hz, 1H), 5.97 (dd, *J* = 15.6, 1.8 Hz, 1H), 5.79 – 5.72 (m, 1H), 5.08 – 5.05 (m, 2H), 4.34 – 4.31 (m, 1H), 4.22 – 4.14 (m, 2H), 2.31 – 2.29 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.90 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H). **^{13}C NMR (151 MHz, Chloroform-*d*)** δ 166.78, 150.36, 133.81, 120.20, 117.98, 71.52, 60.45, 42.11, 25.93, 18.33, 14.37, –4.52, –4.73. **IR (KBr)**: 3842, 3676, 2932, 1722, 1543, 1472, 1366, 1258, 1165, 980, 837, 777 cm^{-1}. **HRMS (ESI) *m/z*** calcd for $C_{15}H_{28}O_3SiNa$ [M + Na]$^+$: 307.1700, found: 307.1697.

Synthesis of 14

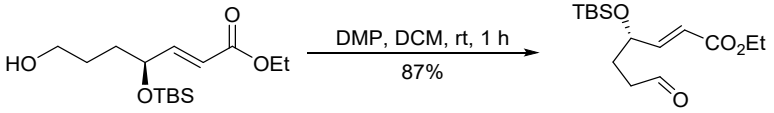


13 **14**

To a solution of 2-methyl-2-butene (6.26 g, 89.22 mmol, 3.0 equiv.) in dry THF (96 mL) was added 10.0 M BH_3-DMS (4.46 mL, 44.61 mmol, 1.5 equiv.) slowly at 0 °C under an atmosphere of Ar. The reaction mixture was stirred at room temperature for 4 h and then cooled to 0 °C. A solution of **13** (8.45 g, 29.74 mmol, 1.0 equiv.) in THF (35 mL) was added to the mixture and stirred for 6 h at room temperature. 3 N NaOH (12 mL) and 30% H_2O_2 (18 mL) were added dropwise respectively at 0 °C and stirred at room temperature overnight. The resulting mixture was quenched by saturated aqueous $Na_2S_2O_3$ solution and then extracted with ethyl acetate, combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, filtered, concentrated under vacuum

and isolated by using silica flash column chromatography (petroleum ether/ethyl acetate = 15:1) to afford **14** as colorless oil (7.64 g, 85%): Rf = 0.3 (petroleum ether/ethyl acetate = 10:3). $[\alpha]_D^{20}$ = –7.33 (*c* = 1.01, $CHCl_3$). **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 6.89 (dd, *J* = 15.6, 4.8 Hz, 1H), 5.95 (d, *J* = 15.6 Hz, 1H), 4.39 – 4.36 (m, 1H), 4.20 – 4.14 (m, 2H), 3.61 (t, *J* = 6.0 Hz, 2H), 1.90 (s, 1H), 1.65 – 1.58 (m, 4H), 1.27 (t, *J* = 7.2 Hz, 3H), 0.90 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H). **^{13}C NMR (151 MHz, Chloroform-*d*)** δ 166.73, 150.60, 120.22, 71.38, 62.66, 60.43, 33.71, 27.87, 25.86, 18.22, 14.27, –4.59, –4.90. **IR (KBr)**: 3482, 2932, 2859, 1722, 1657, 1470, 1368, 1260, 1167, 1042, 8377, 777 cm^{-1}. **HRMS (ESI) *m/z*** calcd for $C_{15}H_{30}O_4SiNa$ $[M + Na]^+$: 325.1806, found: 325.1809.

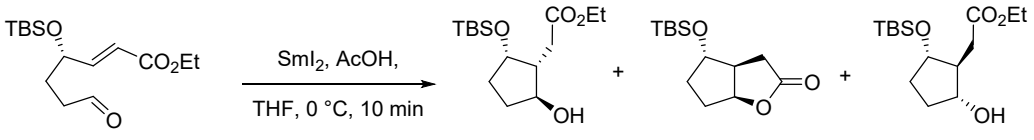
Synthesis of 10



14 **10**

To a solution of **14** (17.50 g, 57.90 mmol, 1.0 equiv.) in DCM (950 mL) was added Dess-Martin Periodinane (DMP) (31.90 g, 75.29 mmol, 1.3 equiv.) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched by saturated aqueous $NaHCO_3$ solution and saturated aqueous $Na_2S_2O_3$ solution and then extracted with DCM, combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, filtered, concentrated under vacuum and isolated by using silica flash column chromatography (petroleum ether/ethyl acetate = 15:1) to afford **10** as light yellow oil (15.12 g, 87%): Rf = 0.6 (petroleum ether/ethyl acetate = 10:3). $[\alpha]_D^{20}$ = –6.27 (*c* = 1.00, $CHCl_3$). **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 9.75 (s, 1H), 6.83 (dd, *J* = 15.6, 3.6 Hz, 1H), 5.96 (d, *J* = 15.6 Hz, 1H), 4.43 – 4.40 (m, 1H), 4.18 – 4.16 (m, 2H), 2.54 – 2.48 (m, 1H), 2.45 – 2.39 (m, 1H), 1.97 – 1.91 (m, 1H), 1.84 – 1.78 (m, 1H), 1.28 – 1.26 (m, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H). **^{13}C NMR (151 MHz, Chloroform-*d*)** δ 201.83, 166.45, 149.71, 120.99, 70.27, 60.53, 38.80, 29.28, 25.88, 18.22, 14.32, –4.57, –4.90. **IR (KBr)**: 2932, 2722, 2367, 1724, 1468, 1368, 1261, 1080, 1038, 984, 837, 779 cm^{-1}. **HRMS (ESI) *m/z*** calcd for $C_{15}H_{28}O_4SiNa$ $[M + Na]^+$: 323.1649, found: 323.1649.

Synthesis of 9



10 **9** (58%) **15** (11%) **16** (<5%)

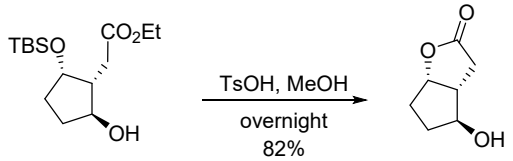
To a degassed solution of AcOH (762.0 µL, 13.33 mmol, 4.0 equiv.) in THF (10 mL) under Ar atmosphere was added a solution of **10** (1.00 g, 3.33 mmol, 1.0 equiv.) in THF (12 mL) at 0 °C. To the mixture reaction was added SmI_2 in THF (0.1 M, about 90 mL) slowly until the mixture turns purple. TLC analysis indicated complete consumption of starting material. The reaction mixture was quenched by saturated ammonium chloride solution

and then extracted with ethyl acetate, combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, filtered, concentrated under vacuum and isolated by using silica flash column chromatography (petroleum ether/acetone = 20:1) to afford **9** as colorless oil (584 mg, 58%): Rf = 0.3 (petroleum ether/acetone = 5:1). $[\alpha]_D^{20}$ = +32.59 (*c* = 1.07, $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 4.23 – 4.20 (m, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 4.04 (q, *J* = 7.2 Hz, 1H), 3.08 (s, 1H), 2.57 – 2.43 (m, 2H), 2.21 – 2.12 (m, 1H), 2.04 – 1.90 (m, 2H), 1.58 – 1.49 (m, 2H), 1.24 (t, *J* = 7.2 Hz, 3H), 0.83 (s, 9H), –0.01 (s, 3H), –0.02 (s, 3H). **^{13}C NMR (101 MHz, Chloroform-*d*)** δ 174.97, 77.02, 74.90, 60.69, 50.19, 33.29, 33.02, 31.79, 25.84, 18.05, 14.27, –4.54, –5.09. **IR (KBr)**: 3480, 2932, 2365, 1734, 1466, 1370, 1254, 1180, 1055, 989, 835, 775 cm^{-1}. **HRMS (ESI) *m/z*** calcd for $C_{15}H_{30}O_4SiNa$ $[M + Na]^+$: 325.1806, found: 325.1806.

The residue was isolated again by using silica flash column chromatography (only DCM) to afford **15** as yellow oil (94 mg, 11%): Rf = 0.4 (petroleum/acetone = 5:1). $[\alpha]_D^{20}$ = +20.19 (*c* = 1.03, $CHCl_3$). **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 4.90 (t, *J* = 7.2 Hz, 1H), 4.17 (q, 6.0 Hz, 1H), 2.82 – 2.79 (m, 2H), 2.48 – 2.43 (m, 1H), 2.04 – 2.00 (m, 1H), 1.89 – 1.83 (m, 1H), 1.74 – 1.65 (m, 2H), 0.87 (s, 9H), 0.05 (s, 6H). **^{13}C NMR (151 MHz, Chloroform-*d*)** δ 177.92, 84.37, 73.42, 43.02, 32.49, 29.90, 28.80, 25.81, 18.11, –4.58, –4.97. **IR (KBr)**: 2957, 2857, 2362, 1773, 1472, 1259, 1183, 1061, 1028, 956, 838, 738 cm^{-1}. **HRMS (ESI) *m/z*** calcd for $C_{13}H_{25}O_3Si$ $[M + H]^+$: 257.1567, found: 257.1570.

And silica flash column chromatography (DCM/MeOH = 60:1) to afford **16** as yellow oil (50 mg, about 5%): Rf = 0.4 (petroleum/acetone = 5:1). $[\alpha]_D^{20}$ = +29.64 (*c* = 0.56, $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 4.13 (q, *J* = 6.8 Hz, 2H), 3.87 – 3.83 (m, 1H), 3.75 (q, *J* = 6.4. Hz, 1H), 3.55 (s, 1H), 2.50 (dd, *J* = 16.4, 5.2 Hz, 1H), 2.19 (dd, *J* = 16.0, 10.00 Hz, 1H), 2.12 – 2.06 (m, 1H), 1.96 – 1.70 (m, 4H), 1.25 (t, *J* = 6.8 Hz, 3H), 0.86 (s, 9H), 0.03 – 0.02 (m, 6H). **^{13}C NMR (101 MHz, Chloroform-*d*)** δ 174.02, 77.16, 76.32, 60.93, 52.42, 35.93, 32.21, 31.06, 25.86, 18.01, 14.25, –4.46, –4.78. **IR (KBr)**: 3446, 2956, 2857, 2362, 1733, 1472, 1373, 1257, 1121, 837, 777, 739 cm^{-1}. **HRMS (ESI) *m/z*** calcd for $C_{15}H_{30}O_4SiNa$ $[M + Na]^+$: 325.1806, found: 325.1806.

Synthesis of 17

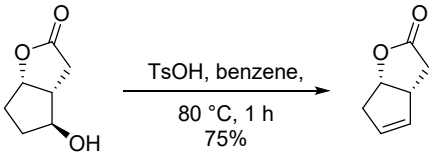


9 **17**

To a solution of **9** (597 mg, 1.98 mmol, 1.0 equiv.) in MeOH (10 mL) was added TsOH (341 mg, 1.98 mmol, 1.0 equiv.) at 0 °C and stirred at room temperature for 12 h. The reaction mixture was concentrated under vacuum and dissolved by saturated aqueous $Na_2S_2O_3$ solution and then extracted with ethyl acetate, combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, filtered, concentrated under vacuum and isolated by using silica flash column chromatography (petroleum ether/ethyl acetate = 1:1) to afford **17** as light yellow oil (230 mg, 82%): Rf = 0.4 (petroleum ether/ethyl acetate = 1:1). $[\alpha]_D^{20}$ = –17.20 (*c* = 0.25, $CHCl_3$). **^{1}H**

NMR (400 MHz, Chloroform-*d*) δ 5.12 (t, *J* = 6.0 Hz, 1H), 4.14 – 4.13 (m, 1H), 2.88 – 2.81 (m, 2H), 2.35 – 2.27 (m, 1H), 2.22 – 2.12 (m, 1H), 2.05 – 1.99 (m, 1H), 1.90 – 1.80 (m, 2H), 1.78 – 1.72 (m, 1H). **^{13}C NMR (101 MHz, Chloroform-*d*)** δ 176.06, 84.53, 78.04, 46.25, 32.02, 31.10, 29.54. **IR (KBr)**: 3744, 3426, 2967, 2367, 1753, 1647, 1543, 1456, 1358, 1261, 1188, 1003 cm^{-1}. **HRMS (ESI) *m/z*** calcd for $C_7H_{11}O_3$ [M + H]$^+$: 143.0703, found: 143.0703.

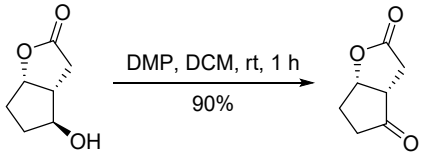
Synthesis of 18



17 **18**

To a solution of **17** (120 mg, 0.84 mmol, 1.0 equiv.) in benzene (5 mL), was added TsOH (16 mg, 0.84 mmol, 1.00 equiv.) and stirred at 80 °C for 1 h. The reaction mixture was concentrated under vacuum and isolated by using silica flash column chromatography (petroleum ether/ethyl acetate = 10:1) to afford **18** as colorless oil (79 mg, 75%): Rf = 0.6 (petroleum ether/ethyl acetate = 2:1). $[\alpha]_D^{20}$ = –107.00 (*c* = 0.96, MeOH) {lit.[2] $[\alpha]_D^{20}$ = –103.00 (*c* = 0.8, MeOH)}. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 5.72 – 5.71 (m, 1H), 5.52 – 5.52 (m, *J* = 6.0, 3.0 Hz, 1H), 5.06 (t, *J* = 6.0 Hz, 1H), 3.47 – 3.44 (m, 1H), 2.73 – 2.59 (m, 3H), 2.38 – 2.34 (m, 1H). **^{13}C NMR (151 MHz, Chloroform-*d*)** δ 176.72, 131.28, 131.27, 129.59, 83.01, 76.94, 45.51, 39.44, 33.20. **IR (KBr)**: 3522, 2932, 2342, 1773, 1539, 1422, 1346, 1256, 1173, 1015, 920, 725 cm^{-1}. **HRMS (ESI) *m/z*** calcd for $C_7H_8O_2Na$ [M + Na]$^+$: 147.0417, found: 147.0414.

Synthesis of 8

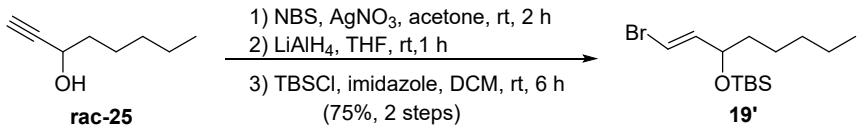


17 **8**

To a solution of **17** (638 mg, 4.49 mmol, 1.0 equiv.) in DCM (130 mL) was added DMP (2.85 g, 6.73 mmol, 1.5 equiv.) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched by saturated aqueous $Na_2S_2O_3$ solution and then extracted with DCM, combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, filtered, concentrated under vacuum and isolated by using silica flash column chromatography (petroleum ether/ethyl acetate = 3:1) to afford **8** as colorless oil (566 mg, 90%): Rf = 0.4 (petroleum ether/ethyl acetate = 2:1). $[\alpha]_D^{20}$ = +170.0 (*c* = 0.31, $CHCl_3$) {lit.[3] $[\alpha]_D^{20}$ = +142.0 (*c* = 4.15, $CHCl_3$) (92% *ee*)}. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 5.22 (t, *J* = 5.2 Hz, 1H), 2.97 – 2.93 (m, 1H), 2.89 – 2.71 (m, 2H), 2.55 – 2.42 (m, 3H), 2.30 – 2.20 (m, 1H). **^{13}C NMR (101 MHz, Chloroform-*d*)** δ 216.57, 175.01, 82.31, 47.70, 34.70, 32.47, 27.02. **IR (KBr)**: 2957, 2369, 1776, 1744, 1416, 1344, 1271, 1169, 1032, 976, 889,

797 cm^{-1}. **HRMS (ESI)** ***m/z*** calcd for $C_7H_8O_3Na$ $[M + Na]^+$: 163.0366,found: 163.0363.

Synthesis of 19



To a solution of **rac-25** (10.00 g, 79.24 mmol, 1.0 equiv.) in acetone (200 mL), was added NBS (16.93 g, 95.09 mmol, 1.2 equiv.) and $AgNO_3$ (1.35 g, 7.93 mmol, 0.1 equiv.), The reaction mixture was stirred for 2 h and quenched with water and then extracted with ethyl acetate, combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, filtered, concentrated under vacuum to afford crude product.

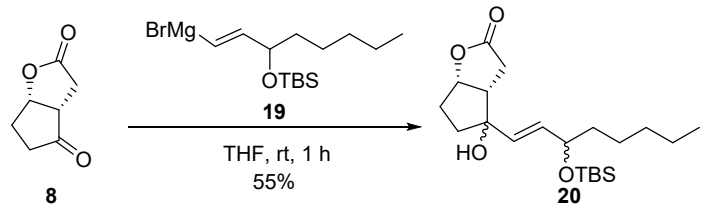
To a suspension of $LiAlH_4$ (6.02 g, 158.48 mmol, 2.0 equiv.) in dry THF (60 mL) was added a solution of crude product in dry THF (10 mL) at 0 °C. The mixture was stirred at room temperature for 1 h. The resulting mixture was quenched by saturated ammonium chloride solution at 0 °C and extracted by ether. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was directly used in the next step without further purification.

To a solution of the residue in dry DCM (180 mL) was added imidazole (10.62 g, 158.48 mmol, 2.0 equiv.) and TBSCl (16.72 g, 110.94 mmol, 1.4 equiv.). The mixture was stirred at room temperature for 6 h. The resulting mixture was quenched by adding saturated ammonium chloride solution and then extracted with DCM, the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, filtered, concentrated under vacuum and isolated by using silica flash column chromatography (only petroleum) to afford **19'** as colorless oil (19.10 g, 75% for three steps): Rf = 0.8 (only petroleum).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.18 (d, *J* = 3.8 Hz, 2H), 4.12 – 4.08 (m, 1H), 1.54 – 1.43 (m, 2H), 1.33 – 1.24 (m, 6H), 0.89 (s, 12H), 0.05 (s, 3H), 0.04 (s, 3H). **^{13}C NMR (101 MHz, Chloroform-*d*)** δ 141.22, 105.60, 73.25, 37.92, 31.88, 25.97, 24.70, 22.74, 18.33, 14.17, –4.35, –4.71. **HRMS (ESI)** ***m/z*** calcd for $C_{14}H_{29}BrOSi$ $[M + H]^+$: 321.1244, found: 321.1244.

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

Synthesis of 20

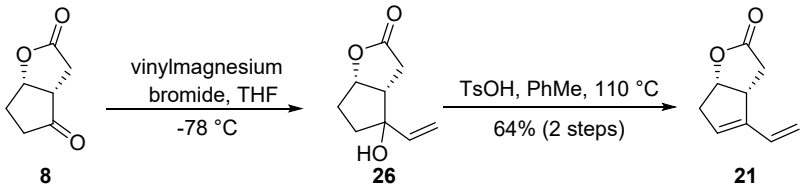


To a solution of **19'** (412 mg, 1.28 mmol, 1.5 equiv.) in dry THF was added dropwise to magnesium turnings (38 mg, 1.54 mmol, 1.8 equiv.) to prepare Grignard reagent **19**. Then was added to the solution of **8** (120 mg, 0.86 mmol, 1.0 equiv.) in THF. The mixture was stirred at room temperature for 1 h and quenched by saturated ammonium chloride solution and then extracted with ethyl acetate, combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, filtered, concentrated under vacuum. The residue was isolated by using silica flash column chromatography (petroleum ether/ethyl acetate = 5:1) to afford **20** as colorless oil (180 mg, 55%): Rf = 0.5 (petroleum ether/ethyl acetate = 1:2).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.78 – 5.63 (m, 2H), 4.37 (q, *J* = 6.8 Hz, 1H), 4.15 – 4.10 (m, 1H), 2.89 (d, *J* = 18.0 Hz, 1H), 2.66 – 2.48 (m, 2H), 2.23 – 2.17 (m, 1H), 2.04 – 2.00 (m, 1H), 1.85 – 1.60 (m, 2H), 1.47 – 1.40

(m, 2H), 1.32 – 1.26 (m, 6H), 0.89 (s, 12H), 0.04 (s, 3H), 0.01 (s, 3H). **^{13}C NMR (101 MHz, Chloroform-*d*)** δ 177.21, 177.21, 132.97, 132.85, 130.12, 130.05, 94.28, 94.18, 72.94, 72.94, 72.51, 72.48, 48.31, 48.27, 38.25, 38.22, 35.54, 35.39, 33.46, 33.42, 31.90 (2), 28.38, 28.36, 26.03 (6), 24.99, 24.95, 22.74 (2), 18.41 (2), 14.17 (2), –4.15 (2), –4.60 (2). **HRMS (ESI) *m/z*** calcd for $C_{21}H_{38}NaBrO_4Si$ [M + Na]$^+$: 405.2432, found: 405.2432.

Synthesis of 21

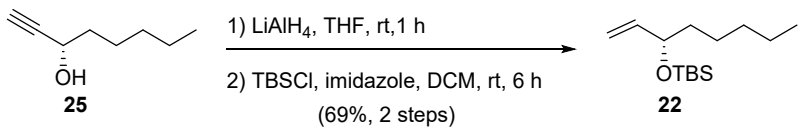


8 **26** **21**

To a solution of **8** (4.00 g, 28.54 mmol, 1.0 equiv.) in dry THF (126 mL), was added 1.0 M vinylmagnesium bromide in THF (31.4 mL, 31.40 mmol, 1.1 equiv.) at –78 °C under Ar atmosphere. TLC analysis indicated complete consumption of starting material. The reaction mixture was quenched by saturated ammonium chloride solution and then extracted with ethyl acetate, combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, filtered, concentrated under vacuum. The residue was directly used in the next step without further purification. An analytic sample (**26**) was obtained by column chromatography. Rf = 0.4 (petroleum ether/ethyl acetate = 2:1). $[\alpha]_D^{20}$ = +56.47 (*c* = 0.34, $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 5.89 (dd, *J* = 17.2, 10.8 Hz, 1H), 5.30 (d, *J* = 17.2 Hz, 1H), 5.12 (d, *J* = 10.8 Hz, 1H), 4.36 (q, *J* = 6.8 Hz, 1H), 2.90 – 2.86 (m, 1H), 2.65 – 2.50 (m, 2H), 2.26 – 2.15 (m, 1H), 2.04 – 1.97 (m, 1H), 1.89 – 1.73 (m, 2H). **^{13}C NMR (101 MHz, Chloroform-*d*)** δ 177.57, 139.07, 113.51, 94.67, 72.87, 48.07, 35.14, 33.30, 28.34. **IR (KBr)**: 3674, 3445, 2965, 2371, 1753, 1643, 1416, 1192, 1074, 978, 908, 671 cm^{-1}. **HRMS (ESI) *m/z*** calcd for $C_9H_{12}O_3Na$ [M + Na]$^+$: 191.0679, found: 191.0679.

To a solution of the above crude product (**26**) in PhMe (118 mL), was added TsOH (4.91 g, 28.54 mmol, 1.0 equiv.) and refluxed at 110 °C for 1 h. The reaction mixture was concentrated under vacuum and isolated by using silica flash column chromatography (petroleum ether/ethyl acetate = 5:1) to afford **21** as light yellow oil (2.74 g, 64% for 2 steps): Rf = 0.4 (petroleum ether/ethyl acetate = 2:1). $[\alpha]_D^{20}$ = +126.76 (*c* = 0.37, $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 6.46 – 6.41 (m, 1H), 5.67 (s, 1H), 5.17 – 5.14 (m, 2H), 5.02 – 4.99 (m, 1H), 3.63 – 3.60 (m, 1H), 2.83 – 2.71 (m, 3H), 2.60 – 2.57 (m, 1H). **^{13}C NMR (101 MHz, Chloroform-*d*)** δ 176.86, 142.20, 131.29, 128.41, 115.62, 83.08, 44.01, 39.60, 32.38. **IR (KBr)**: 3464, 2920, 2851, 2365, 1773, 1645, 1416, 1261, 800, 739 cm^{-1}. **HRMS (ESI) *m/z*** calcd for $C_9H_{11}O_2$ [M + H]$^+$: 151.0754, found: 151.0755.

Synthesis of 22

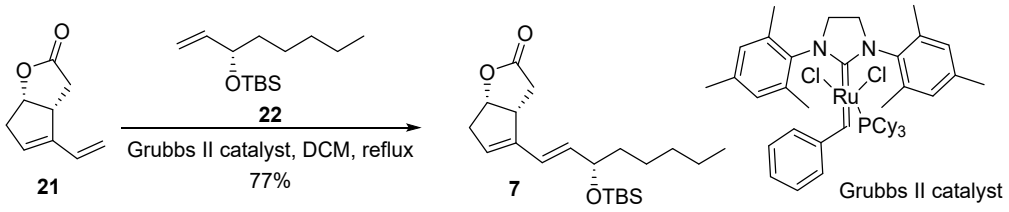


25 **22**

To a suspension of $LiAlH_4$ (1.50 g, 39.60 mmol, 2.0 equiv.) in dry THF (60 mL) was added a solution of **25** (2.50 g, 19.80 mmol, 1.0 equiv.) in dry THF (10 mL) at 0 °C. The mixture was stirred at room temperature for 1 h. The resulting mixture was quenched by saturated ammonium chloride solution at 0 °C and extracted by ether. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was directly used in the next step without further purification.

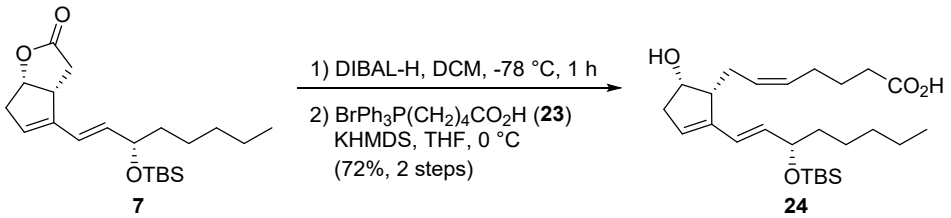
To a solution of the above crude product in DCM (70 mL), was added imidazole (2.70 g, 39.60 mmol, 2.0 equiv.) and TBSCl (3.58 g, 23.76 mmol, 1.2 equiv.). The mixture was stirred at room temperature for 6 h. The resulting mixture was quenched by adding saturated ammonium chloride solution and then extracted with DCM, the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, filtered, concentrated under vacuum and isolated by using silica flash column chromatography (only petroleum) to afford **22** as colorless oil (3.31 g, 69% for two steps): Rf = 0.8 (only petroleum). $[\alpha]_D^{20}$ = +10.61 (*c* = 0.44, $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 5.84 – 5.76 (m, 1H), 5.16 – 5.11 (m, 1H), 5.03 – 4.99 (m, 1H), 4.11 – 4.05 (m, 1H), 1.52 – 1.43 (m, 2H), 1.34 – 1.27 (m, 6H), 0.91 – 0.87 (m, 12H), 0.06 (s, 3H), 0.04 (s, 3H). **^{13}C NMR (101 MHz, Chloroform-*d*)** δ 142.14, 113.50, 74.08, 38.27, 32.03, 26.06, 25.05, 22.82, 18.44, 14.21, –4.21, –4.67. **IR (KBr)**: 1645, 1466, 1364, 1254, 1082, 1032, 922, 862, 835, 775, 677, 584 cm^{-1}. **HRMS (ESI) *m/z*** calcd for $C_{14}H_{31}OSi$ $[M + H]^+$: 243.2139, found: 243.2139.

Synthesis of 7



To a solution of **21** (730 mg, 4.86 mmol, 1.0 equiv.) in dry DCM (10 mL), was added Grubbs II catalyst (416 mg, 0.49 mmol, 0.1 equiv.) in DCM (10 mL) and **22** (11.80 g, 48.60 mmol, 10.0 equiv.) in dry DCM (50 mL), and the mixture was stirred at reflux for 2 h. TLC analysis indicated complete consumption of starting material. The reaction mixture was concentrated under vacuum and isolated by using silica flash column chromatography (petroleum ether/ethyl acetate = 15:1) to afford **7** as light yellow oil (1.36 g, 77%): Rf = 0.7 (petroleum ether/ethyl acetate = 4:1). $[\alpha]_D^{20}$ = +46.83 (*c* = 0.20, $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 6.22 (d, *J* = 16.0 Hz, 1H), 5.60 (d, *J* = 2.4 Hz, 1H), 5.46 (dd, *J* = 16.0, 6.4 Hz, 1H), 5.18 (t, *J* = 6.8 Hz, 1H), 4.13 (q, *J* = 6.4 Hz, 1H), 3.58 (t, *J* = 8.4 Hz, 1H), 2.86 – 2.69 (m, 3H), 2.56 – 2.50 (m, 1H), 2.51 – 1.38 (m, 2H), 1.28 – 1.23 (m, 6H), 0.88 (s, 12H), 0.04 (s, 3H), 0.01 (s, 3H). **^{13}C NMR (101 MHz, Chloroform-*d*)** δ 176.92, 141.46, 135.74, 127.21, 123.28, 83.20, 73.33, 44.42, 39.67, 38.52, 32.62, 31.87, 25.95, 25.00, 22.68, 18.33, 14.12, –4.22, –4.68. **IR (KBr)**: 3753, 3443, 2930, 2372, 1778, 1647, 1466, 1358, 1254, 1175, 1053, 835 cm^{-1}. **HRMS (ESI) *m/z*** calcd for $C_{21}H_{36}O_3SiNa$ $[M + Na]^+$: 387.2326, found: 387.2328.

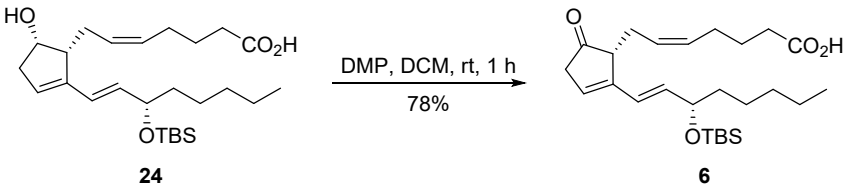
Synthesis of 24



To a solution of **7** (285 mg, 0.78 mmol, 1.0 equiv.) in DCM (30 mL) was slowly added 1.5 M DIBAL-H in THF (1.0 mL, 1.56 mmol, 2.0 equiv.) at –78 °C. The reaction mixture was stirred for 1 h at this temperature, the reaction was quenched with MeOH (0.5 mL) and saturated ammonium chloride solution (0.1 mL). The mixture was stirred for 10 min and the residue was filtrated through a pad of celite and washed with DCM. The mixture was concentrated under reduced pressure to give light yellow oil as crude product, which was directly used in next step without further purification.

To a suspension of (4-Carboxybutyl) (triphenyl) phosphonium bromide (**23**) (2.08 g, 4.68 mmol, 6.0 equiv.) in THF was added 1.0 M KHMDS (9.36 mL, 9.36 mmol, 12.0 equiv.) by syringe and the resulting orange mixture stirred at 0 °C for 40 min. To the reaction mixture was added a solution of crude product in THF (10 mL). The mixture was stirred for 2 h at this temperature. The reaction was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The combined organic phase was dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure and purified by using silica flash column chromatography (DCM/MeOH) = 30:1 to give **24** as light yellow oil (254 mg, 72% for two steps): Rf = 0.4 (DCM/MeOH = 10:1). $[\alpha]_D^{20}$ = –1.46 (*c* = 0.41, $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 6.13 (d, *J* = 15.6 Hz, 1H), 5.64 – 5.55 (m, 3H), 5.42 – 5.35 (m, 1H), 4.56 (q, *J* = 7.6 Hz, 1H), 4.11 (q, *J* = 6.4 Hz, 1H), 2.86 (q, *J* = 6.8 Hz, 1H), 2.65 – 2.56 (m, 1H), 2.37 – 2.30 (m, 5H), 2.16 (q, *J* = 7.2 Hz, 2H), 1.75 – 1.68 (m, 2H), 1.54 – 1.41 (m, 2H), 1.33 – 1.26 (m, 6H), 0.89 (s, 12H), 0.06 (s, 3H), 0.03 (s, 3H). **^{13}C NMR (101 MHz, Chloroform-*d*)** δ178.18, 143.58, 134.01, 130.03, 129.59, 126.70, 125.37, 75.04, 74.11, 47.19, 39.88, 38.50, 31.95, 29.85, 26.76, 26.05, 25.15, 24.83, 24.68, 22.77, 18.46, 14.19, –4.19, –4.59. **IR (KBr)**: 3735, 2928, 2855, 2346, 1709, 1461, 1251, 1074, 965, 835, 775, 547 cm^{-1}. **HRMS (ESI) *m/z*** calcd for $C_{26}H_{46}O_4SiNa$ $[M + Na]^+$: 473.3058, found: 473.3057.

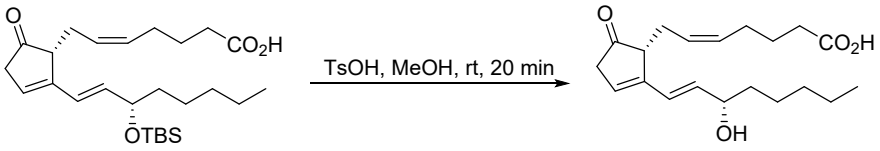
Synthesis of 6



To a solution of **24** (130 mg, 288.40 mmol, 1.0 equiv.) in DCM (10 mL) was added DMP (183 mg, 432.60 mmol, 1.5 equiv.) at 0 °C. The reaction mixture was stirred at room temperature for 1 h, the reaction mixture was concentrated under vacuum and isolated by using silica flash column chromatography (DCM/MeOH = 30:1) to

afford **6** as sticky oil (101 mg, 78%): Rf = 0.5 (DCM/MeOH = 10:1). $[\alpha]_D^{20}$ = +5.58 (*c* = 0.55, $CHCl_3$). **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 6.23 (d, *J* = 16.0 Hz, 1H), 5.99 (t, *J* = 2.8 Hz, 1H), 5.69 (dd, *J* = 16.4, 6.4 Hz, 1H), 5.40 – 5.32 (m, 2H), 4.17 (q, *J* = 6.4 Hz, 1H), 3.10 – 3.01 (m, 1H), 2.89 – 2.87 (m, 1H), 2.38 – 2.31 (m, 4H), 2.22 (t, *J* = 7.6 Hz, 1H), 2.07 – 2.00 (m, 2H), 1.67 – 1.62 (m, 2H), 1.55 – 1.45 (m, 2H), 1.33 – 1.27 (m, 6H), 0.92 – 0.88 (m, 12H), 0.07 (s, 3H), 0.04 (s, 3H). **^{13}C NMR (101 MHz, Chloroform-*d*)** δ 218.61, 178.67, 142.17, 135.38, 131.29, 125.56, 125.33, 124.82, 73.63, 51.95, 43.43, 38.46, 31.93, 29.84, 27.26, 26.62, 26.02, 25.10, 24.68, 22.75, 18.43, 14.17, –4.24, –4.61. **IR (KBr)**: 2930, 2359, 1437, 1252, 1165, 1119, 1090, 835, 721, 694, 542 cm^{-1}. **HRMS (ESI) *m/z*** calcd for $C_{26}H_{45}O_4Si$ $[M + H]^+$: 449.3082, found: 449.3082.

Synthesis of PGC_2 (2)



6 PGC_2 (**2**)

To a solution of **6** (30 mg, 0.067 mmol, 1.0 equiv.) in MeOH (1 mL) was added TsOH (3 mg, 0.0134 mmol, 0.2 equiv.). The reaction mixture was stirred at room temperature for 20 min, then concentrated under vacuum and isolated by using silica flash column chromatography to afford PGC_2 (**2**).

Sincerely, we have endeavored to make a great deal of experiments for preparing PGC_2 (**2**) for months (Table 1). Despite we cannot obtain pure product of PGC_2 (**2**), probably because it is extremely unstable and sensitive in both weak acidic and alkaline environments, we could unambiguously find PGC_2 (**2**) in rough **NMR** and **HRMS**.

HRMS (ESI) *m/z* calcd for $C_{20}H_{30}O_4Na$ $[M + Na]^+$: 357.2036, found: 357.2036.

HRMS (ESI) *m/z* calcd for $C_{20}H_{29}O_4$ $[M – H]^-$: 333.2071, found: 333.2068.

{See the **HRMS** and rough **NMR** of PGC_2 (**2**)}.

Table 1 Exploration and optimization studies for desilylation

entry	conditions	results
1	TBAF/THF	the complicated product containing trace PGC_2, but difficult to isolate
2	AcOH/TBAF/THF	the complicated product containing trace PGC_2, but difficult to isolate
3	1% HCl/THF	the complicated product containing trace PGC_2, but difficult to isolate
4	1% HCl/MeCN	the complicated product containing trace PGC_2, but difficult to isolate
5	AcOH/H_2O	the complicated product containing trace PGC_2, but difficult to isolate
6	$BiBr_3$/MeCN/H_2O	the complicated product containing no PGC_2
7	$SbCl_3$/MeCN	the complicated product containing no PGC_2
8	HF-pyridine/THF	no reaction
9	HF-Et_3N/THF	no reaction
10	H_2SiF_4/MeCN	the complicated product containing no PGC_2
11	HBF_4/MeCN	the complicated product containing no PGC_2
12	PPTS/MeOH	no reaction
13	TsOH/MeOH	the crude product dominantly containing PGC_2, which could be identified by rough NMR and HRMS

3. Supplemental References

1 G. E. Keck, D. S. Welch and P. K. Vivian, *Org. Lett.*, 2006, **8**, 3667.

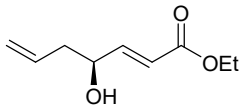
2 E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf and R. K. Varma, *J. Am. Chem. Soc.*, 1971, **93**, 14913.

3 Konigsberger and H. Griengl, *Bioorg. Med. Chem.*, 1994, **2**, 595.

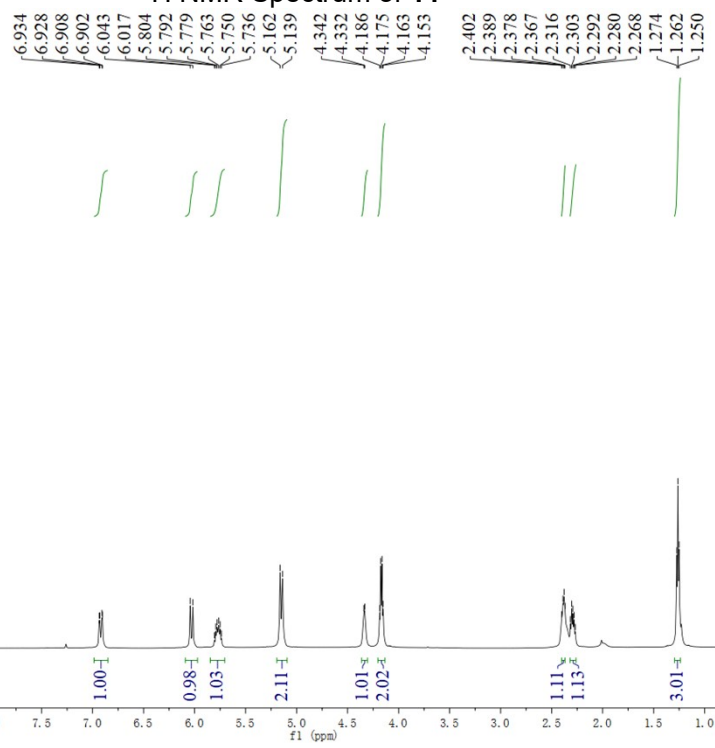
4 C. Jing and V. K. Aggarwal, *Org. Lett.,* 2020, **22**, 6505.

4. NMR Spectra

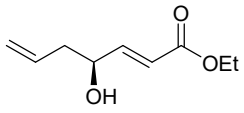
^{1}H NMR Spectrum of **11**



11

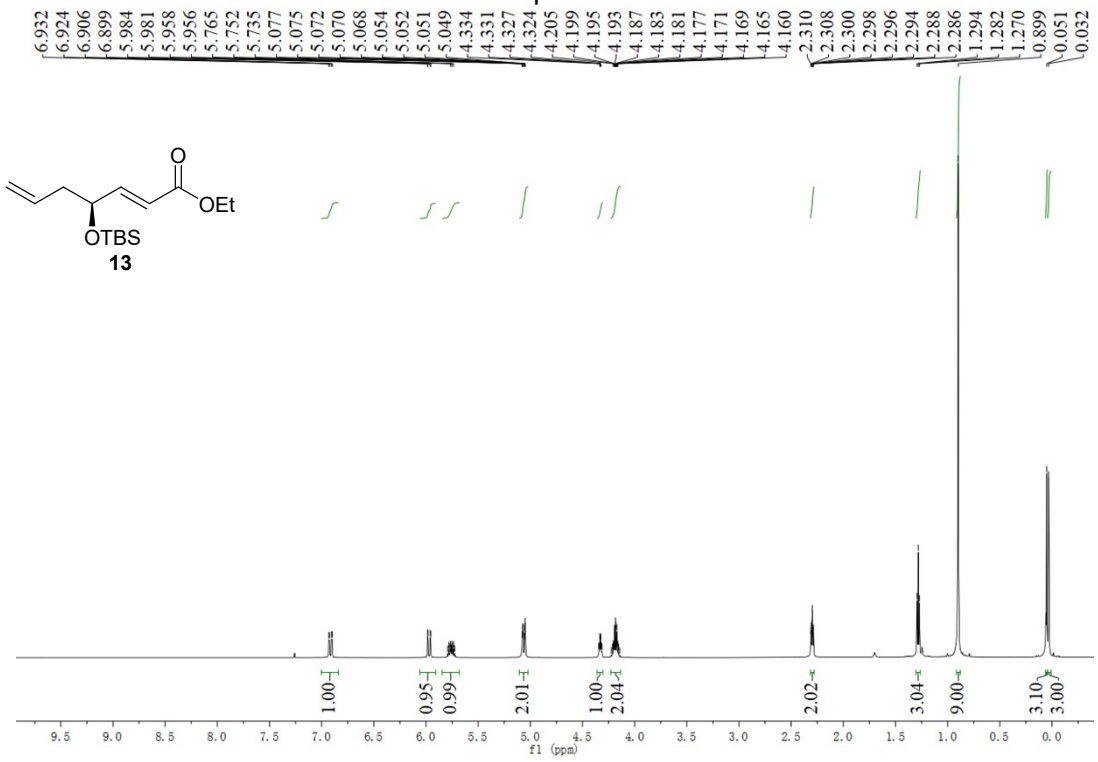


^{13}C NMR Spectrum of **11**

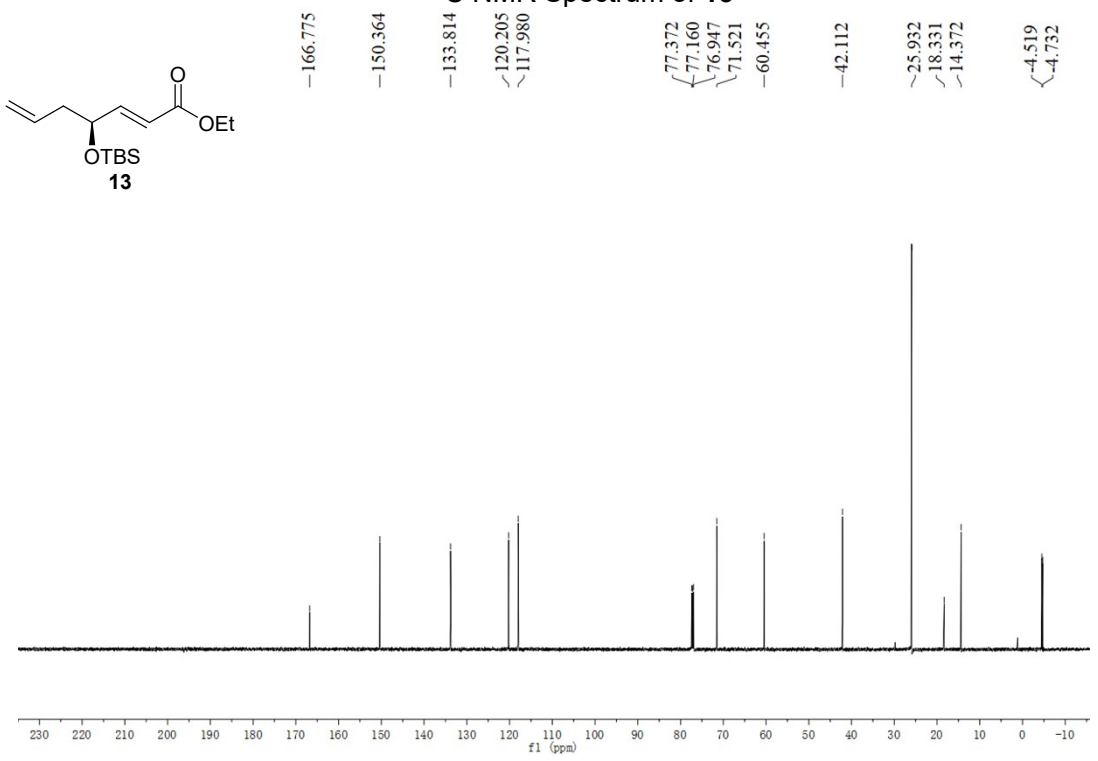


11

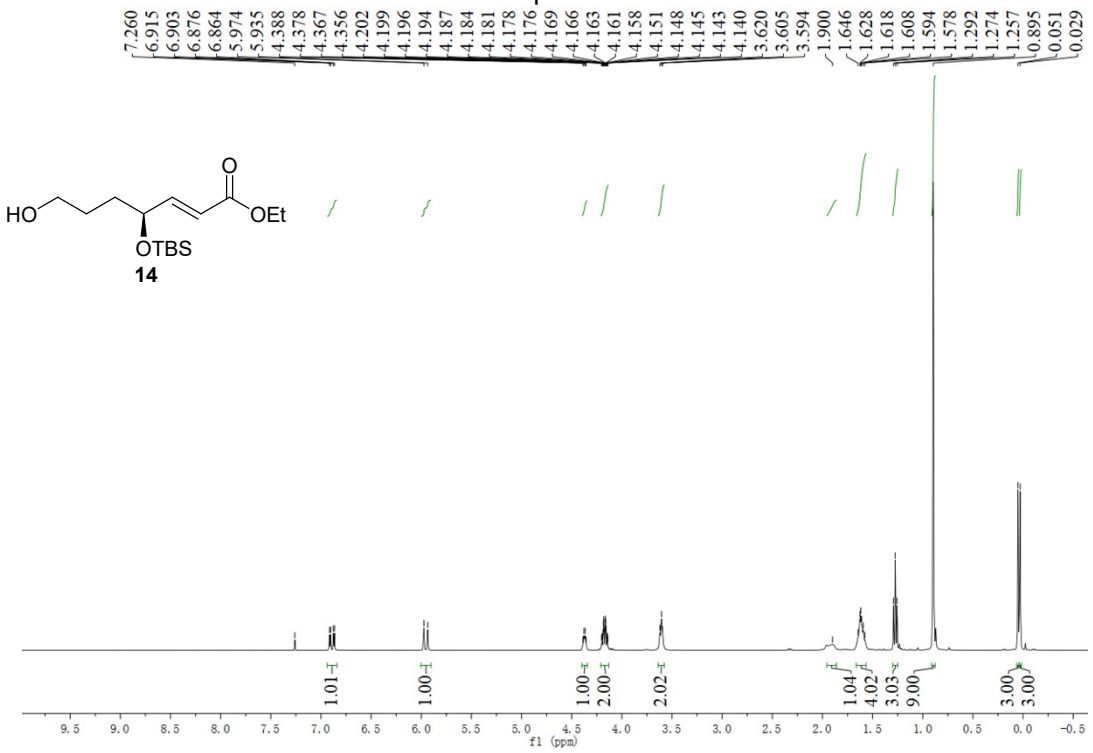
^{1}H NMR Spectrum of **13**



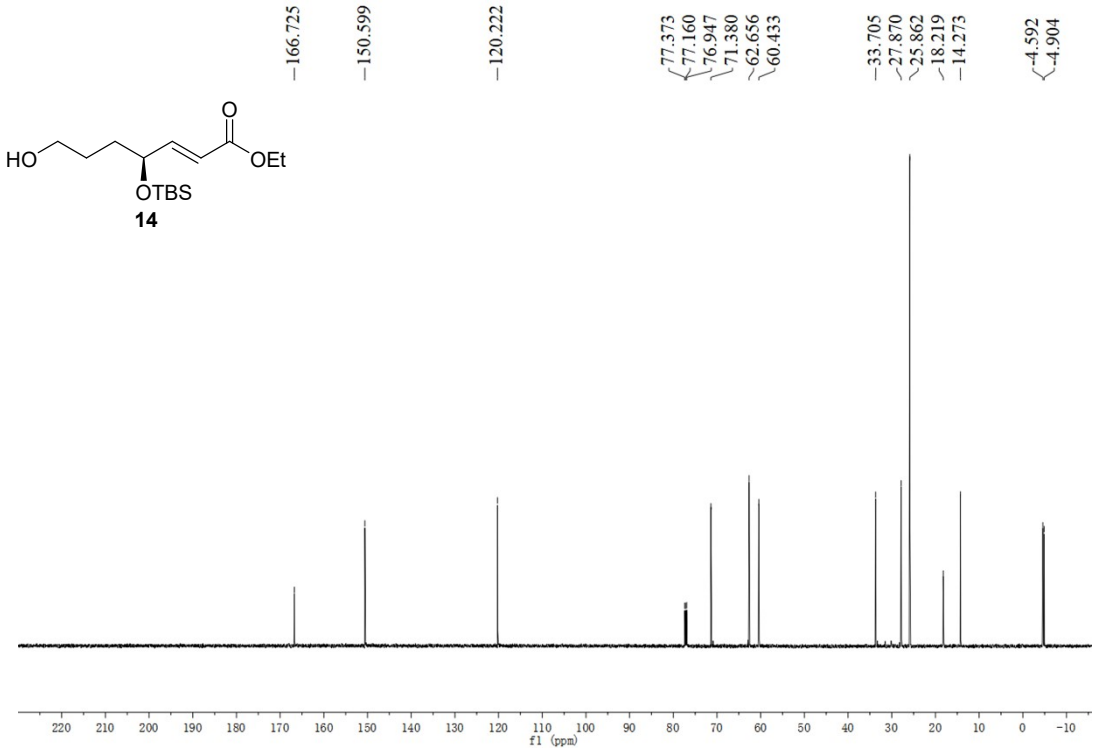
^{13}C NMR Spectrum of **13**



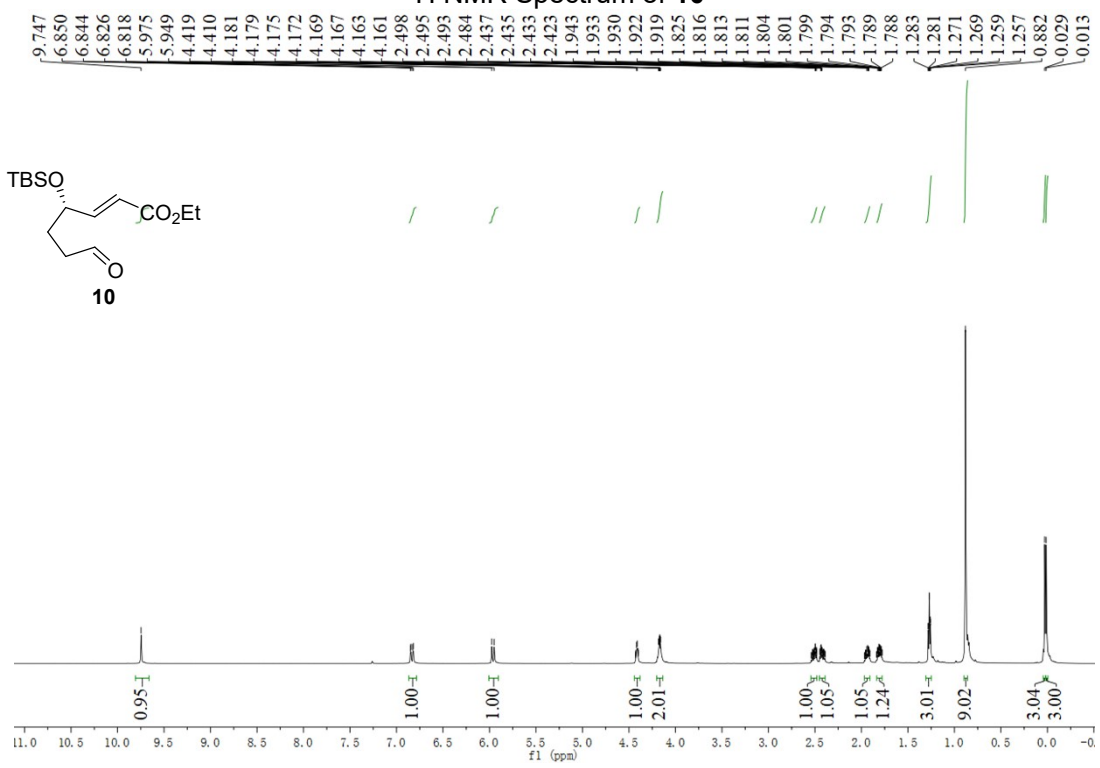
^{1}H NMR Spectrum of **14**



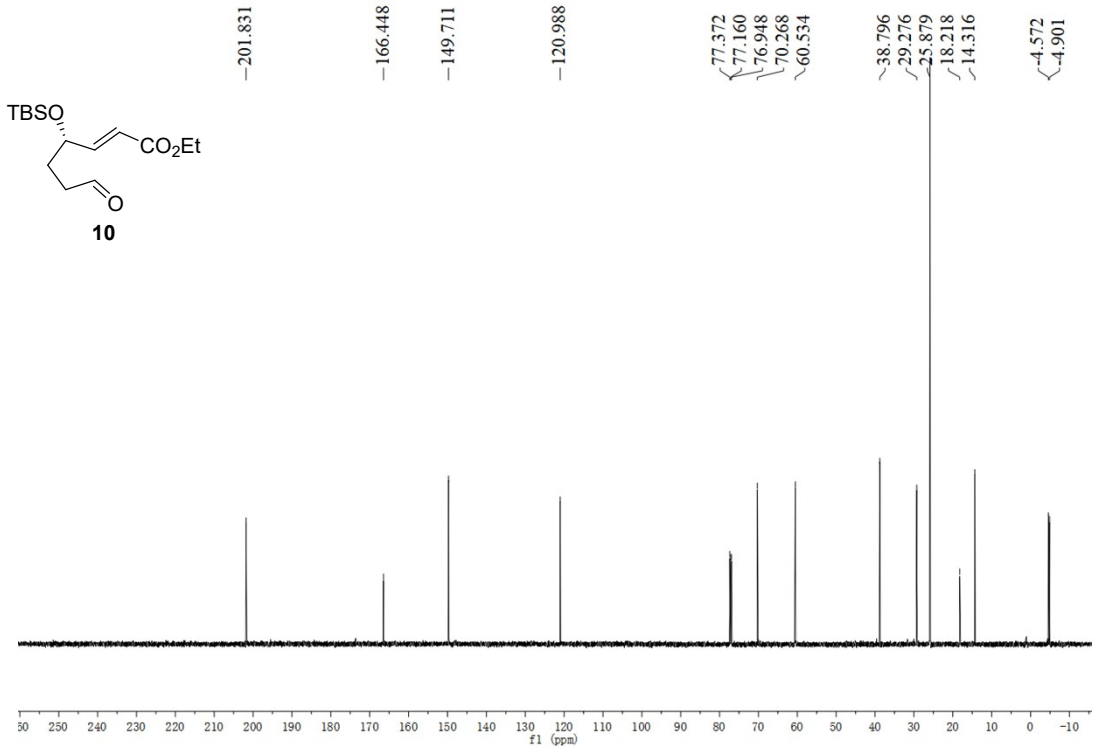
^{13}C NMR Spectrum of **14**



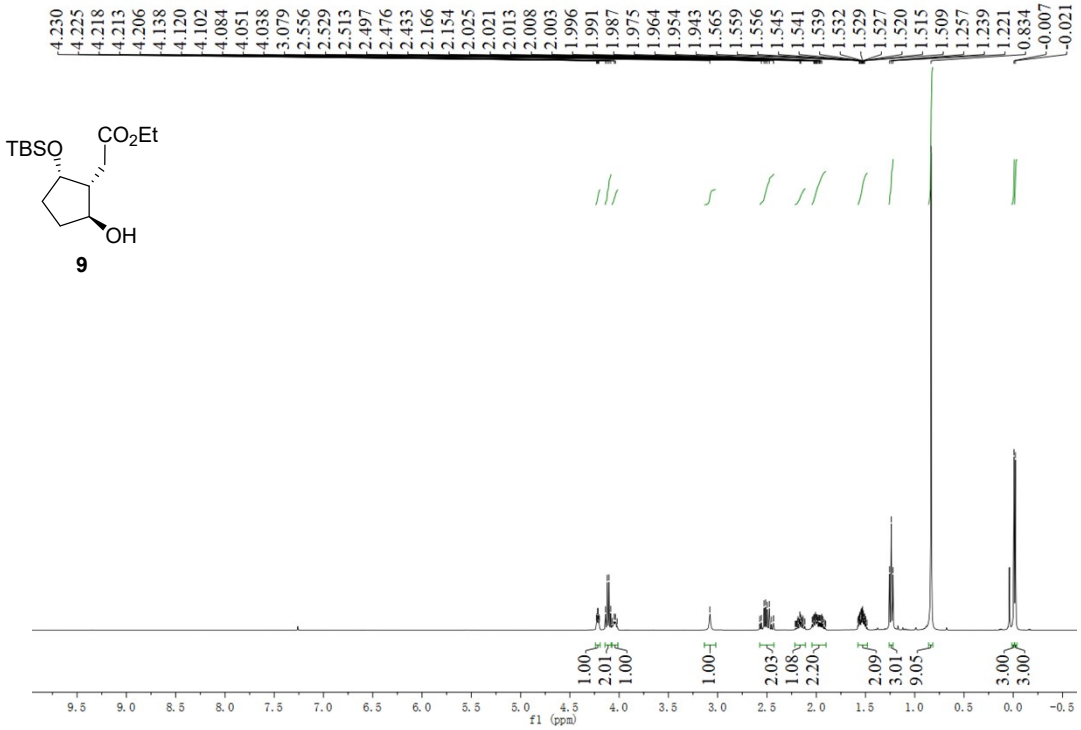
^{1}H NMR Spectrum of **10**



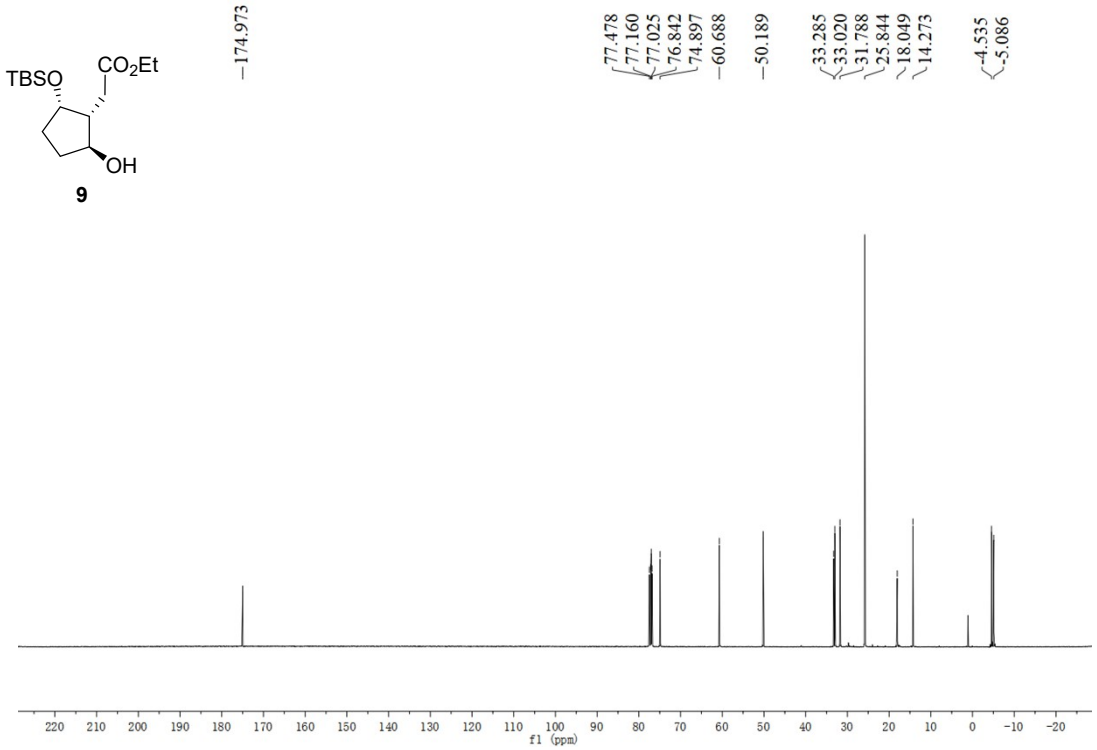
^{13}C NMR Spectrum of **10**

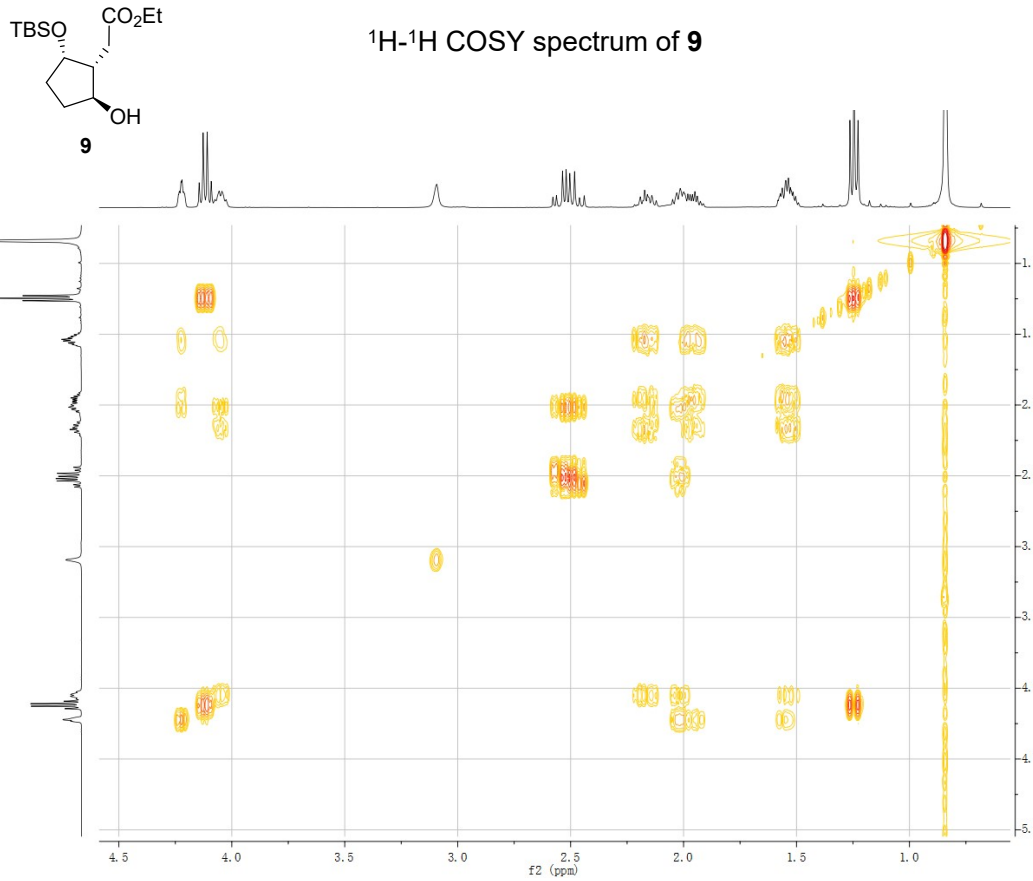


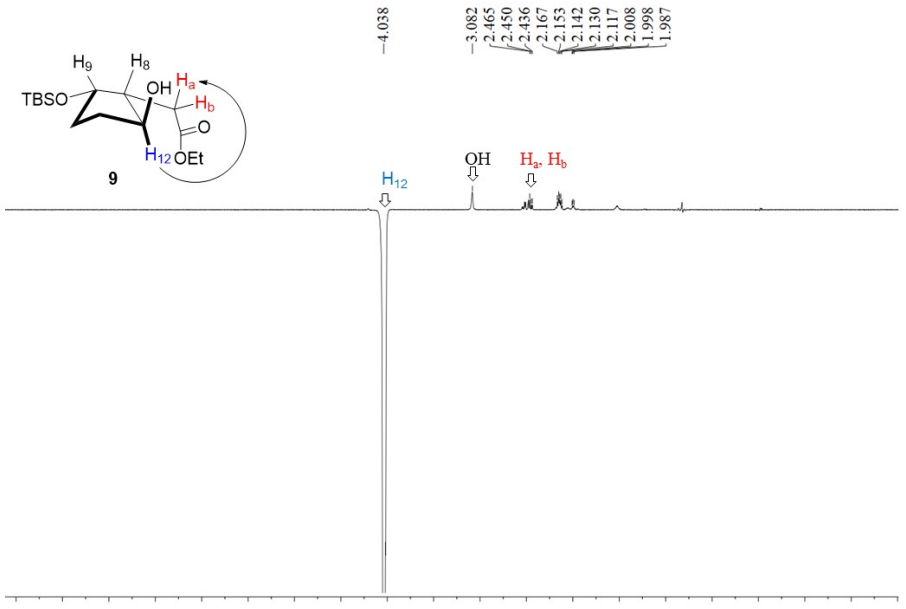
^{1}H NMR Spectrum of **9**



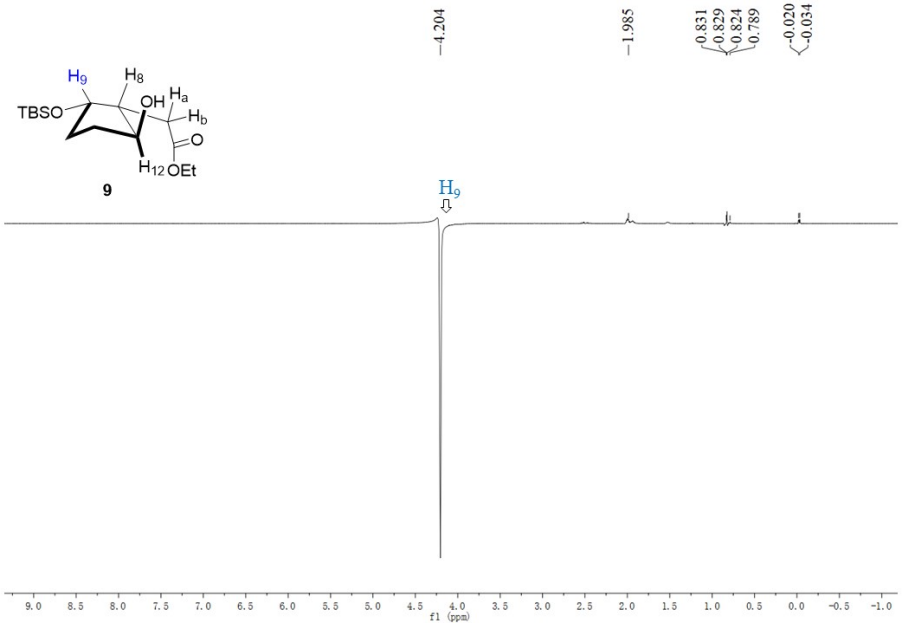
^{13}C NMR Spectrum of **9**



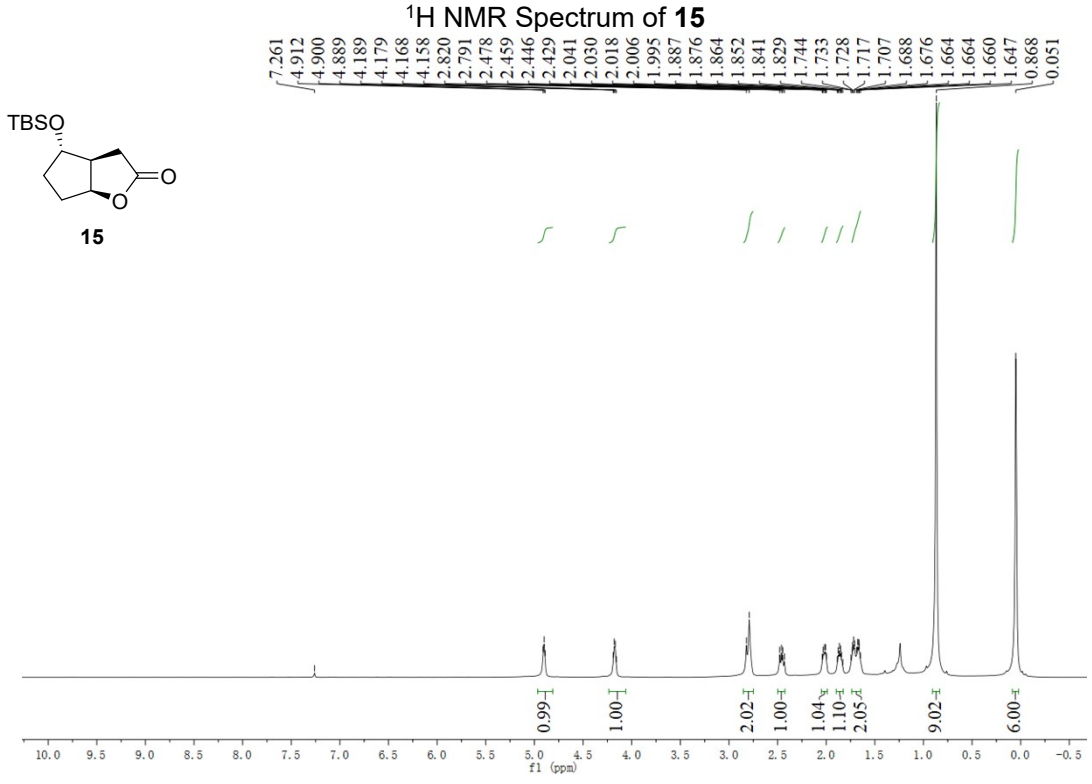

TBSO
CO2Et
OH
9
1H-1H COSY spectrum of 9
f2 (ppm)
f1 (ppm)


NOEds spectrum of 9
TBSO
H9
H8
OH
Ha
Hb
O
H12 OEt
9
4.038
3.082
2.465
2.450
2.436
2.167
2.153
2.142
2.130
2.117
2.008
1.998
1.987
H12
OH
Ha, Hb

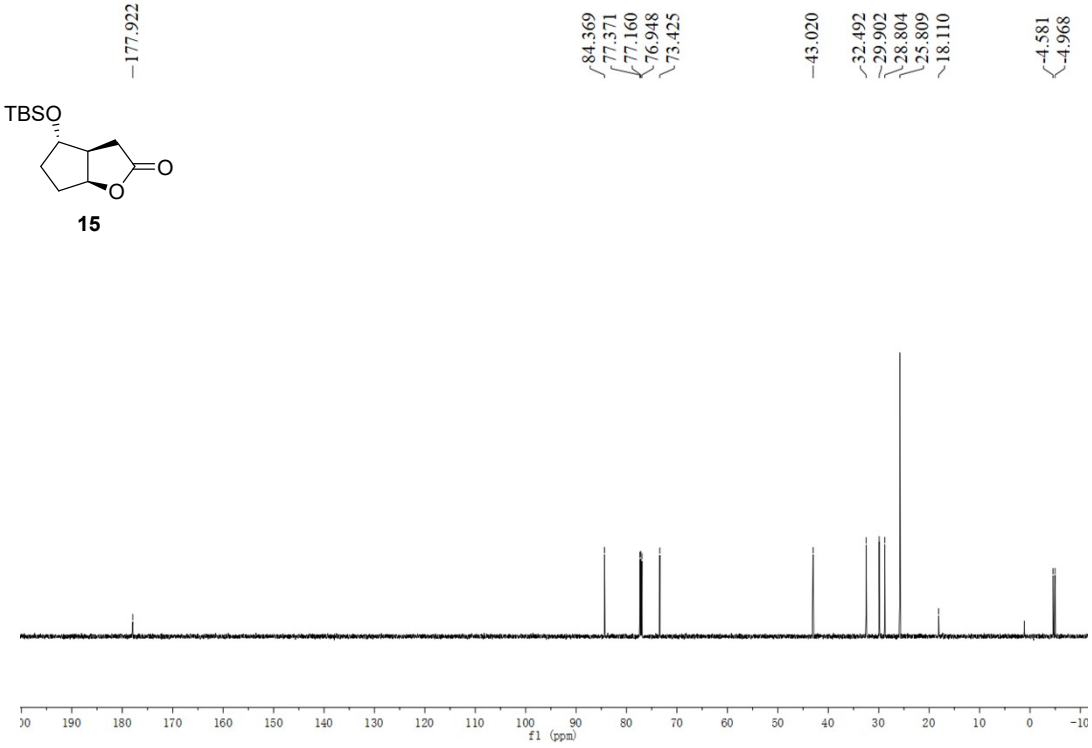
NOEds spectrum of **9**



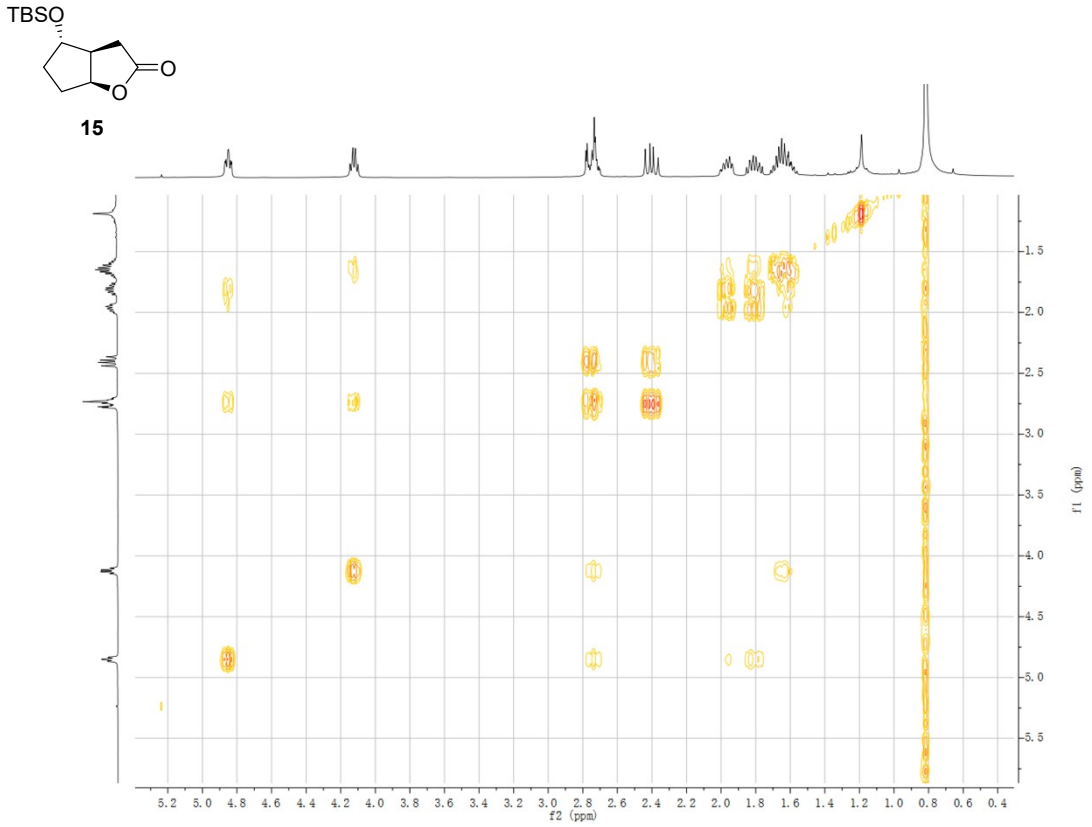
^{1}H NMR Spectrum of **15**



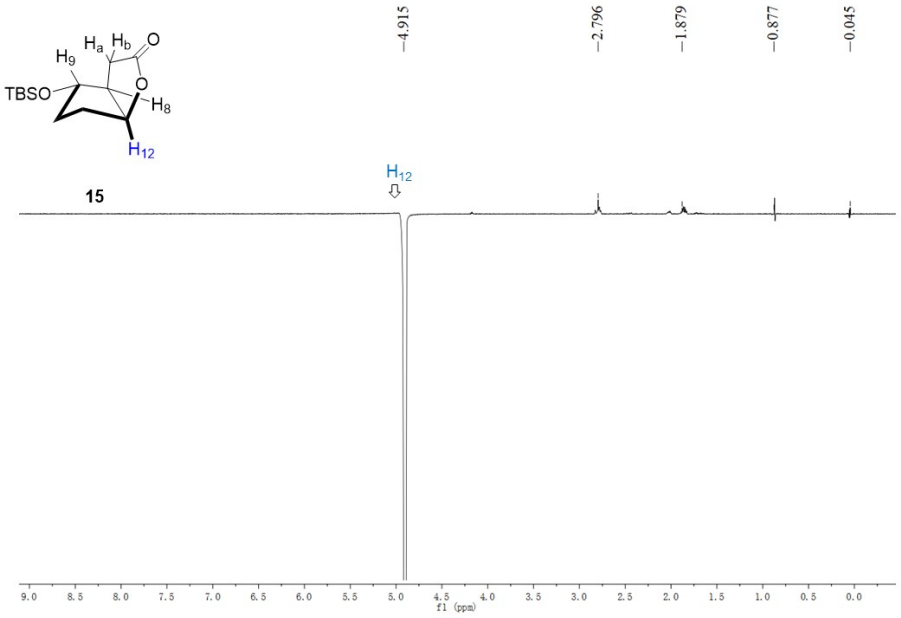
^{13}C NMR Spectrum of **15**



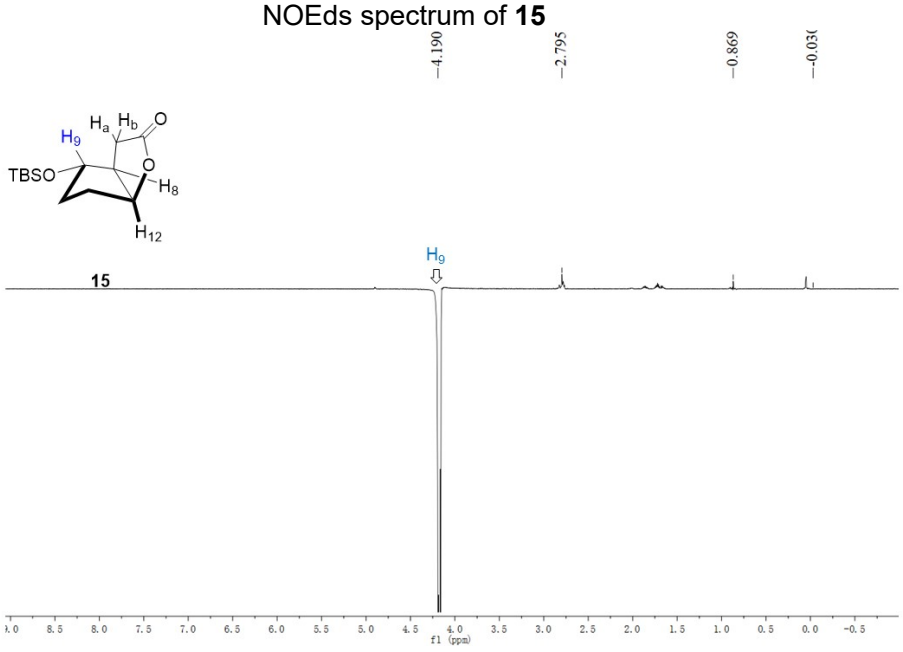
^{1}H-^{1}H COSY spectrum of **15**



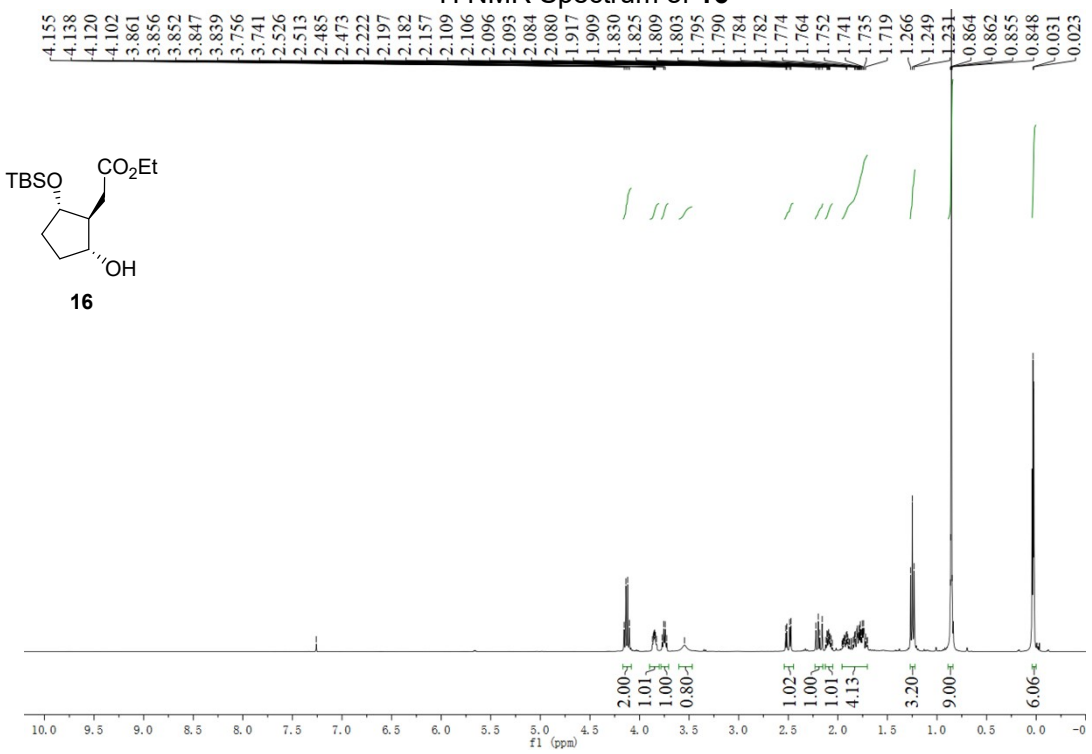
NOEds spectrum of **15**



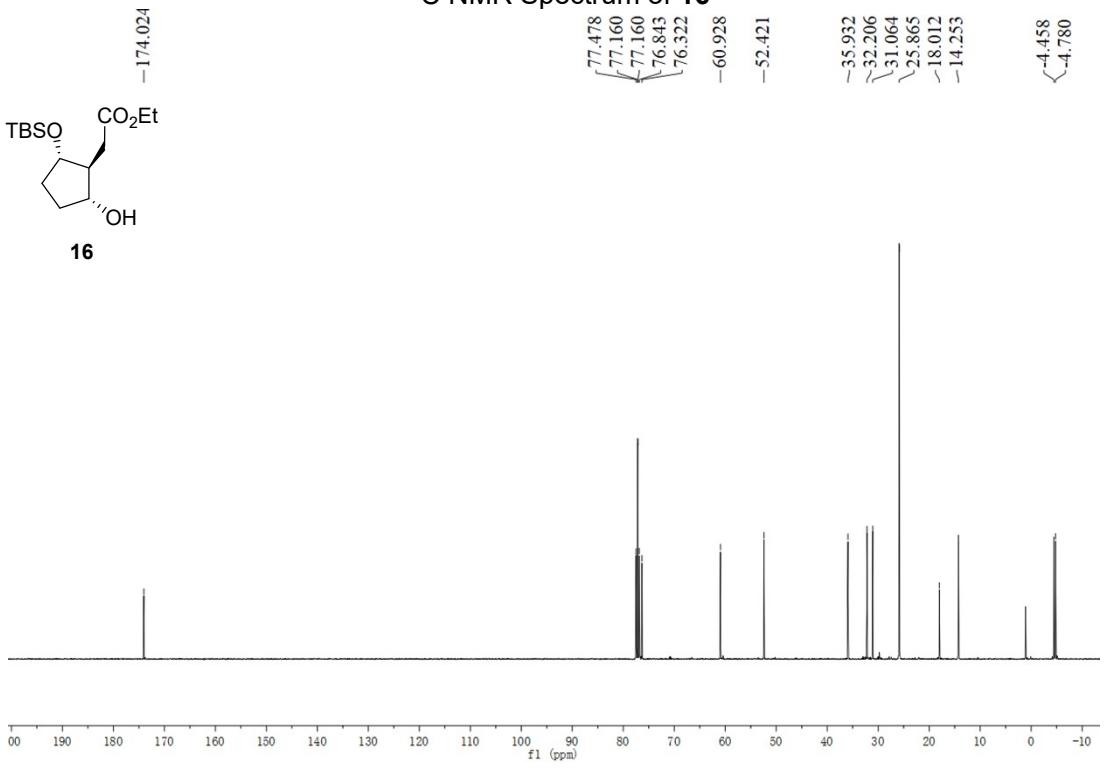
NOEds spectrum of **15**

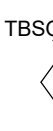


^{1}H NMR Spectrum of **16**



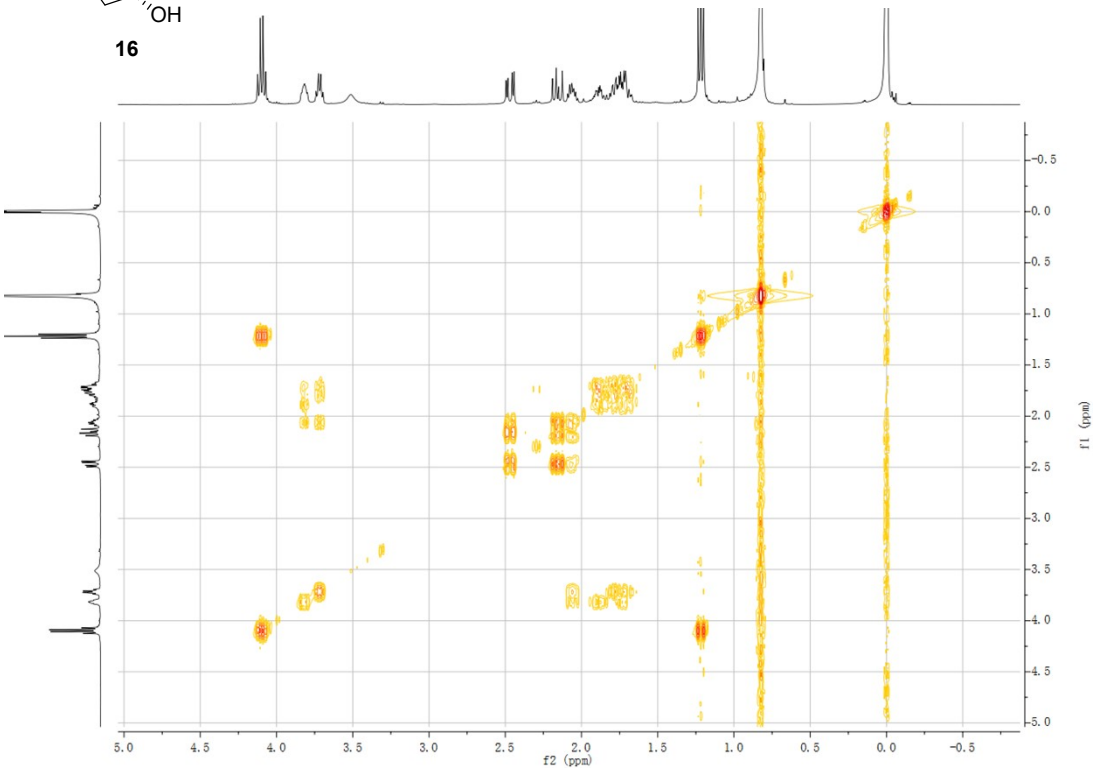
^{13}C NMR Spectrum of **16**

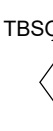




16

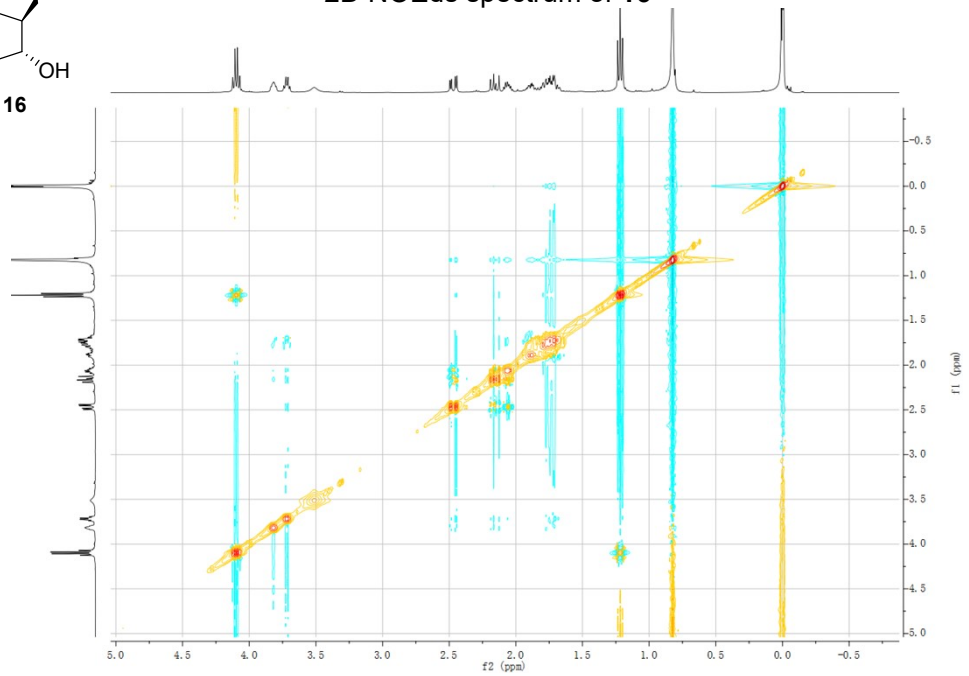
^{1}H-^{1}H COSY spectrum of **16**



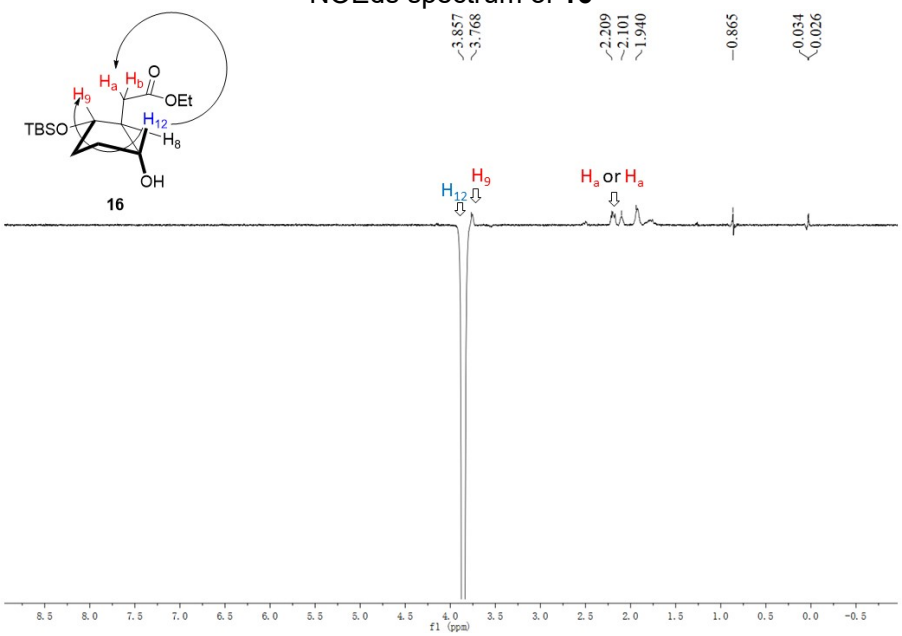


16

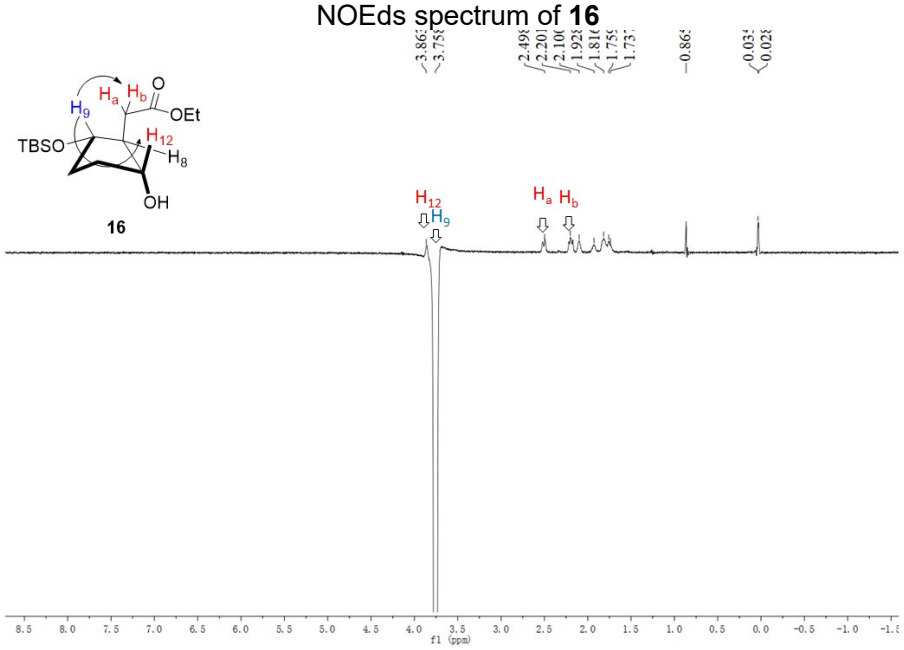
2D NOEds spectrum of **16**



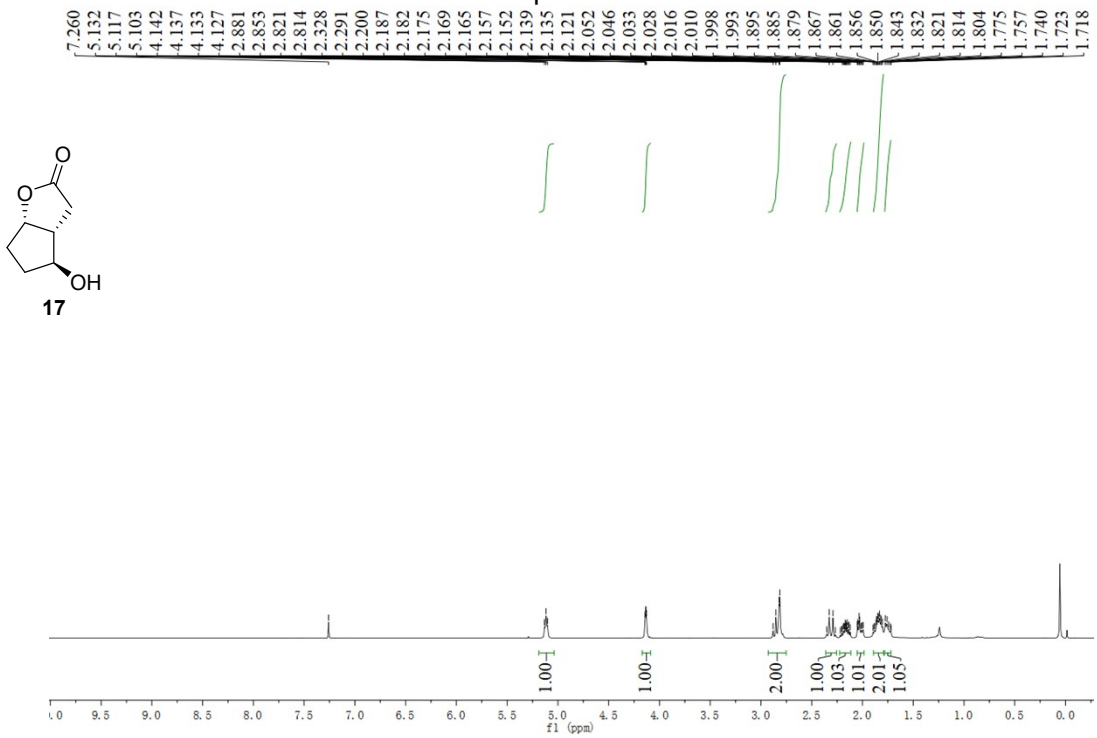
NOEds spectrum of **16**



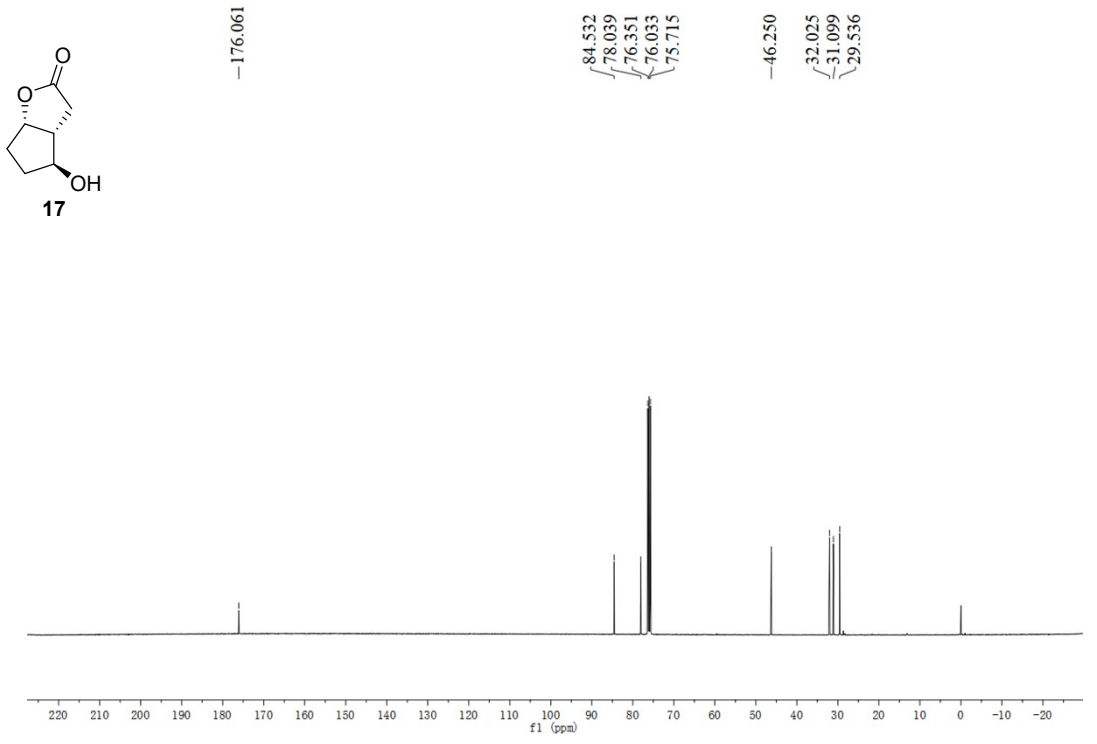
NOEds spectrum of **16**



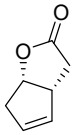
^{1}H NMR Spectrum of **17**



^{13}C NMR Spectrum of **17**

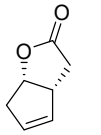


^{1}H NMR Spectrum of **18**



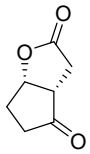
18

^{13}C NMR Spectrum of **18**



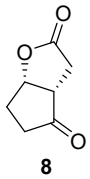
18

^{1}H NMR Spectrum of **8**



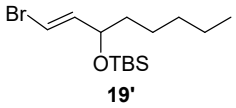
8

^{13}C NMR Spectrum of **8**



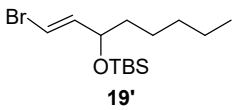
8

^{1}H NMR Spectrum of **19'**

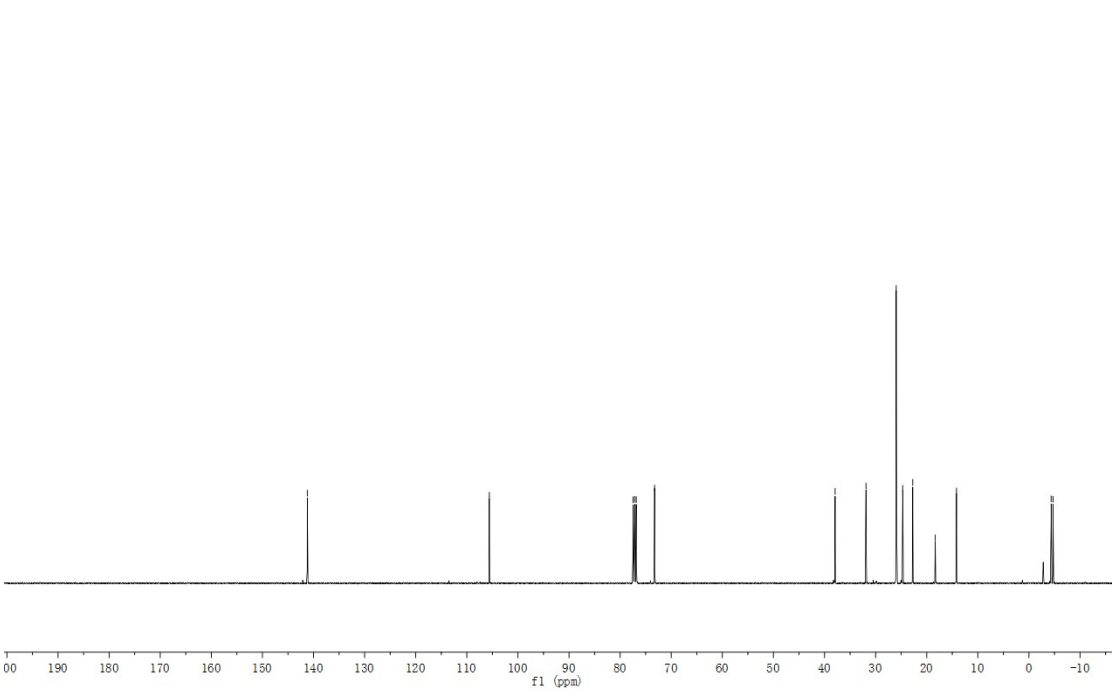


19'

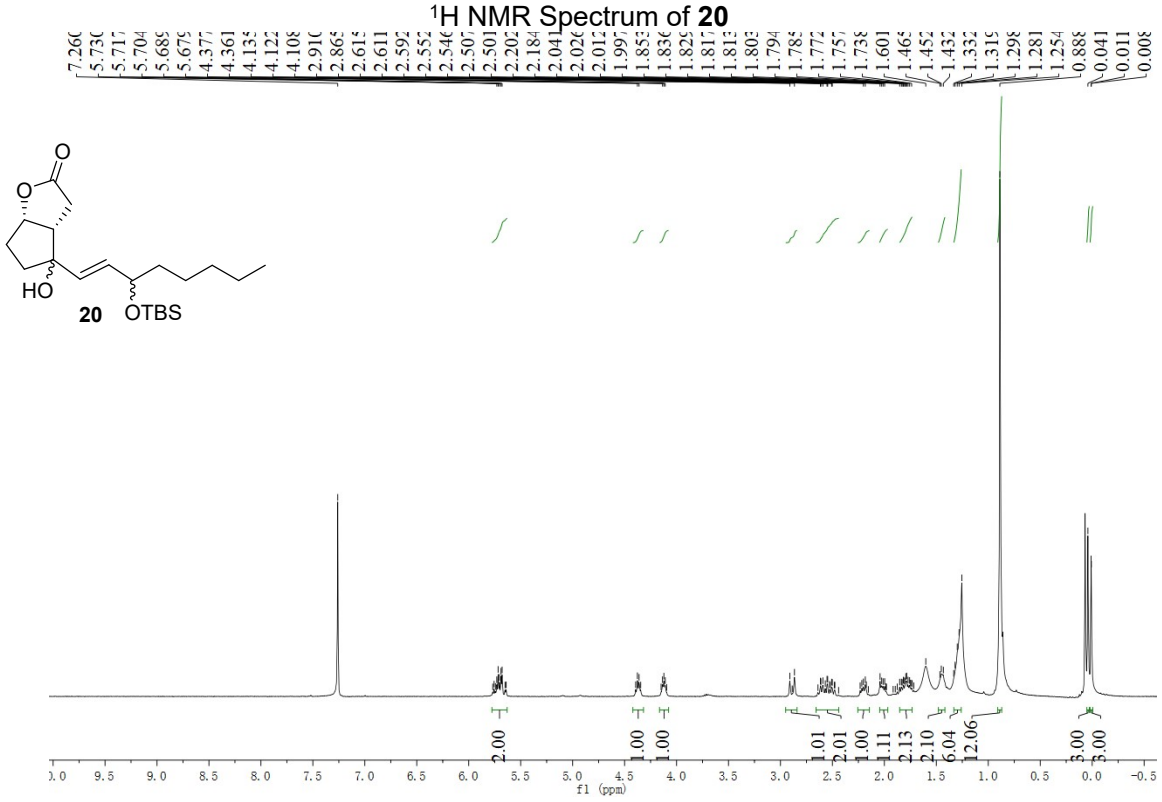
^{13}C NMR Spectrum of **19'**



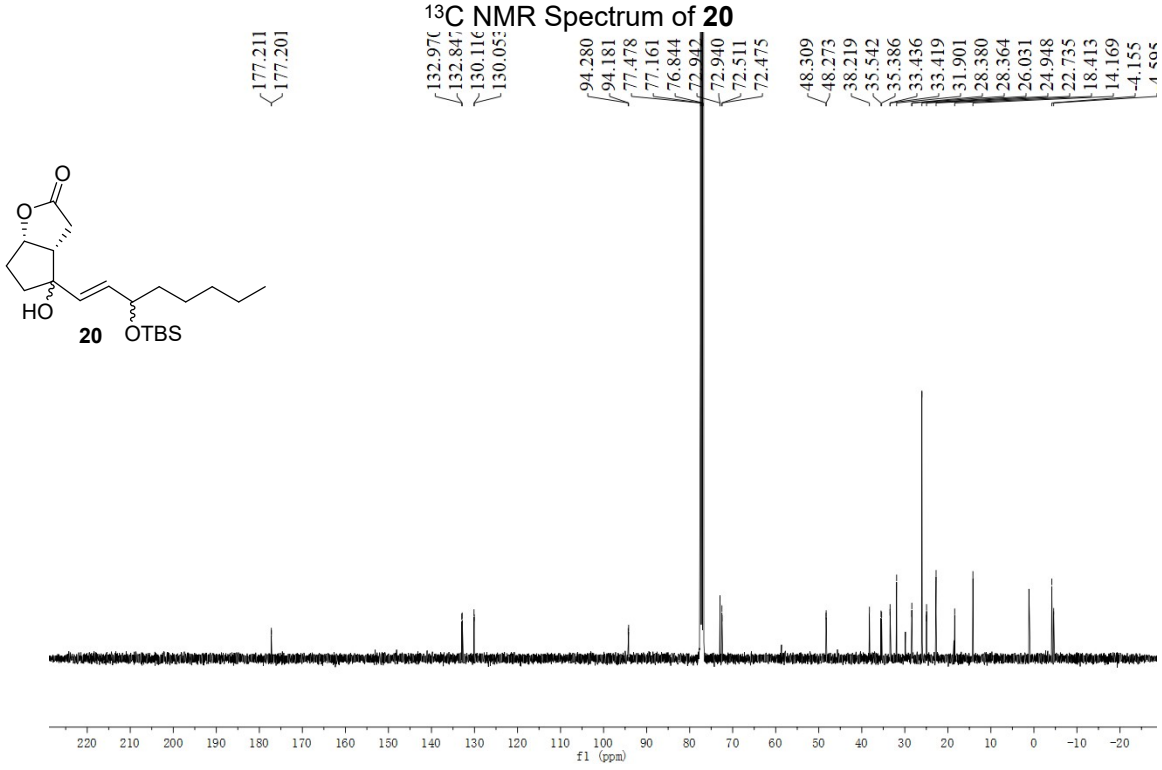
19'



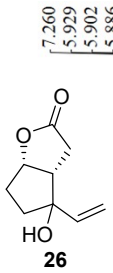
^{1}H NMR Spectrum of **20**



^{13}C NMR Spectrum of **20**

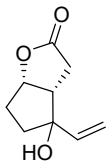


^{1}H NMR Spectrum of **26**



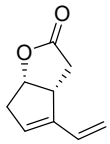
26

^{13}C NMR Spectrum of **26**

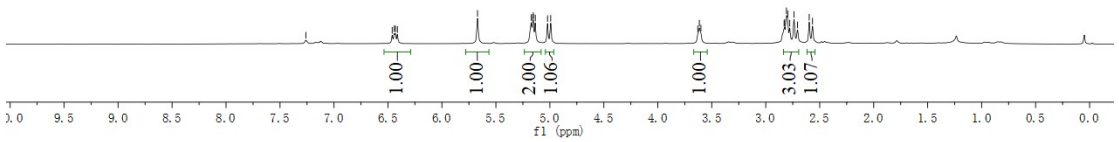


26

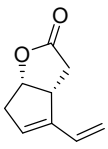
^{1}H NMR Spectrum of **21**



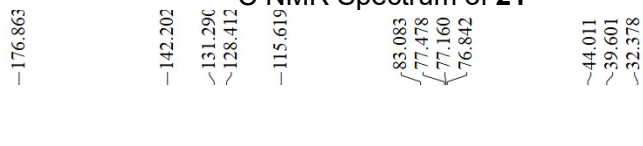
21

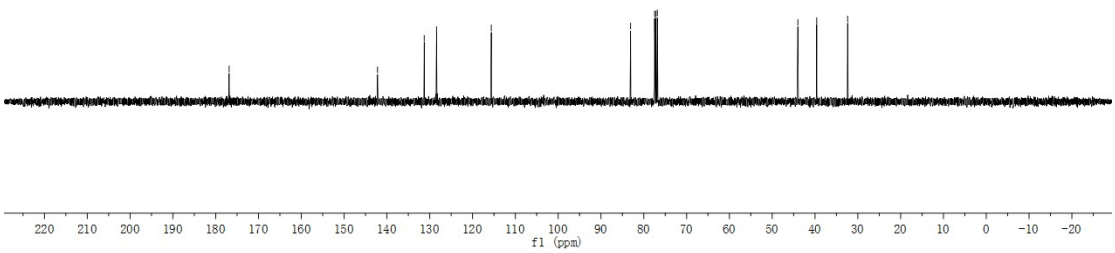


^{13}C NMR Spectrum of **21**

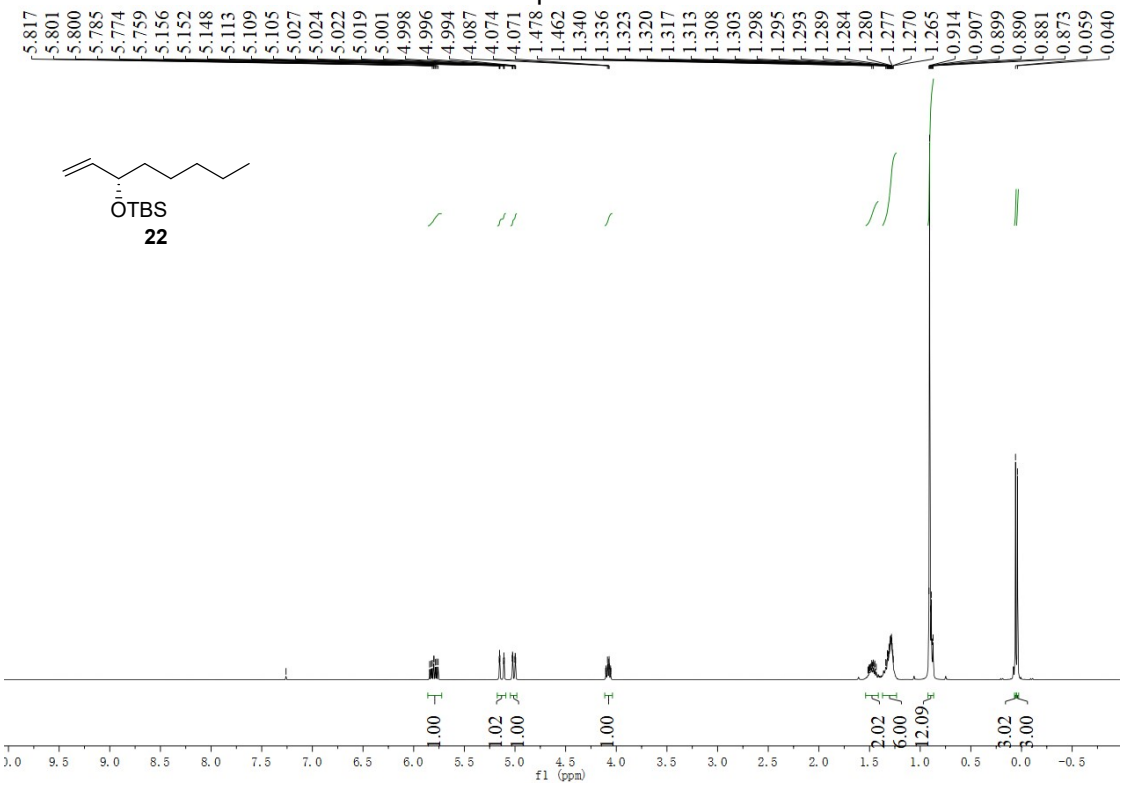


21

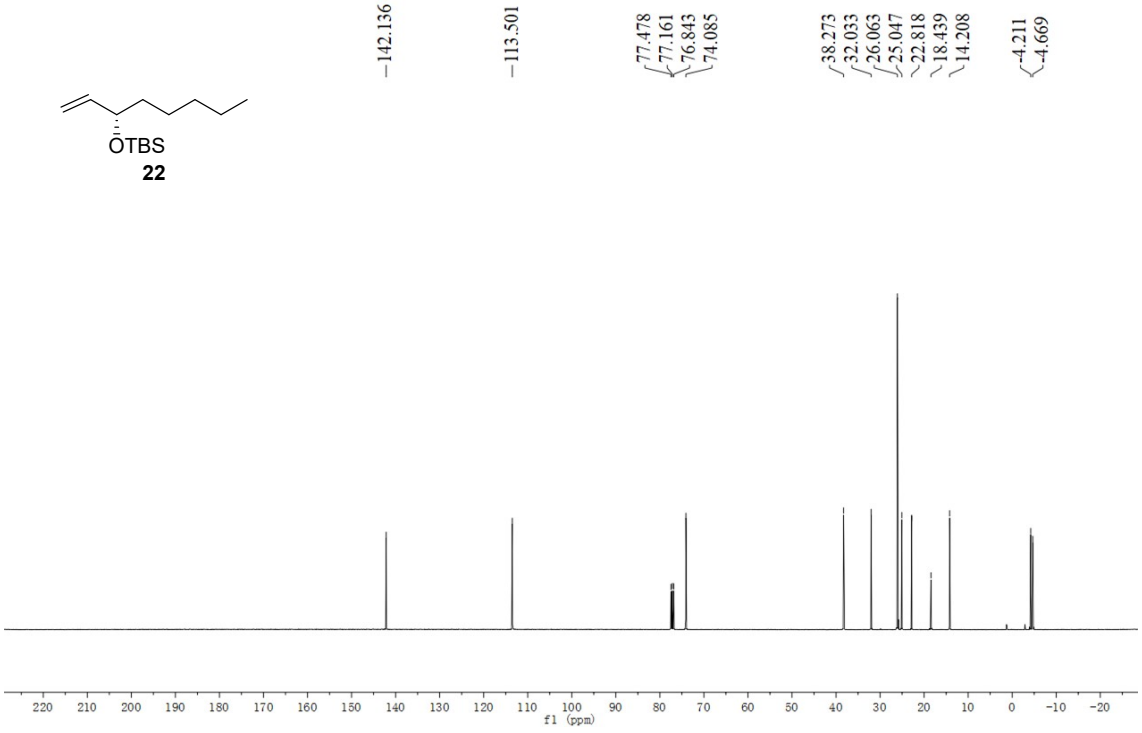




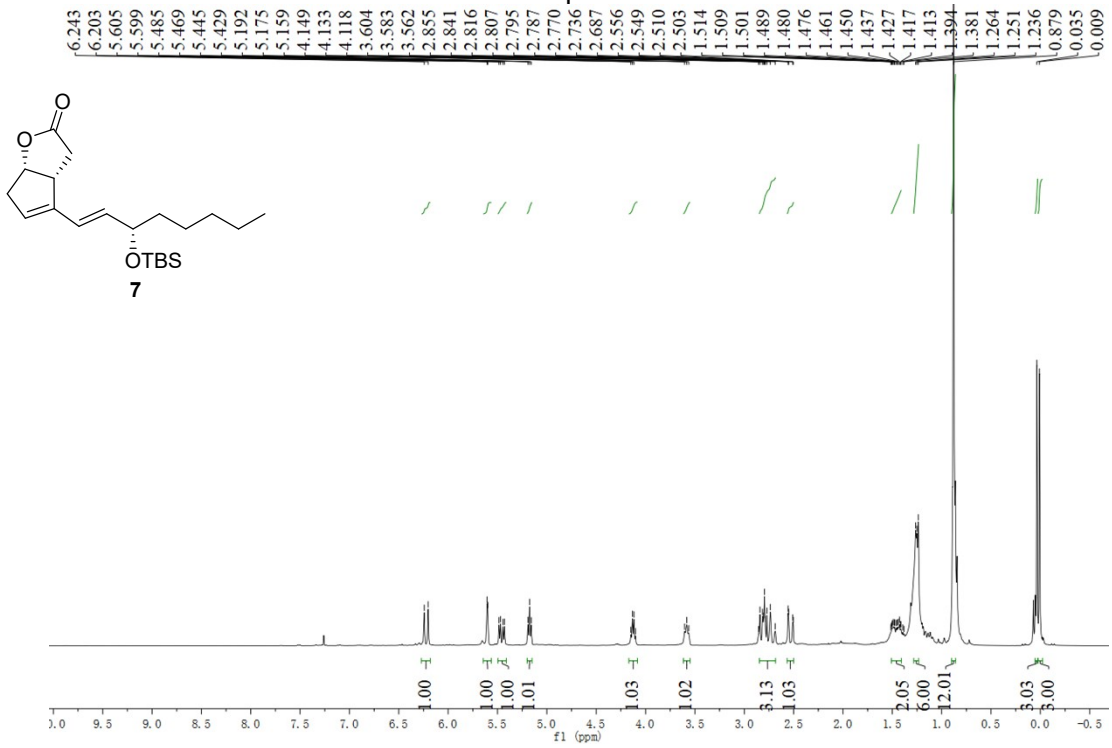
^{1}H NMR Spectrum of **22**



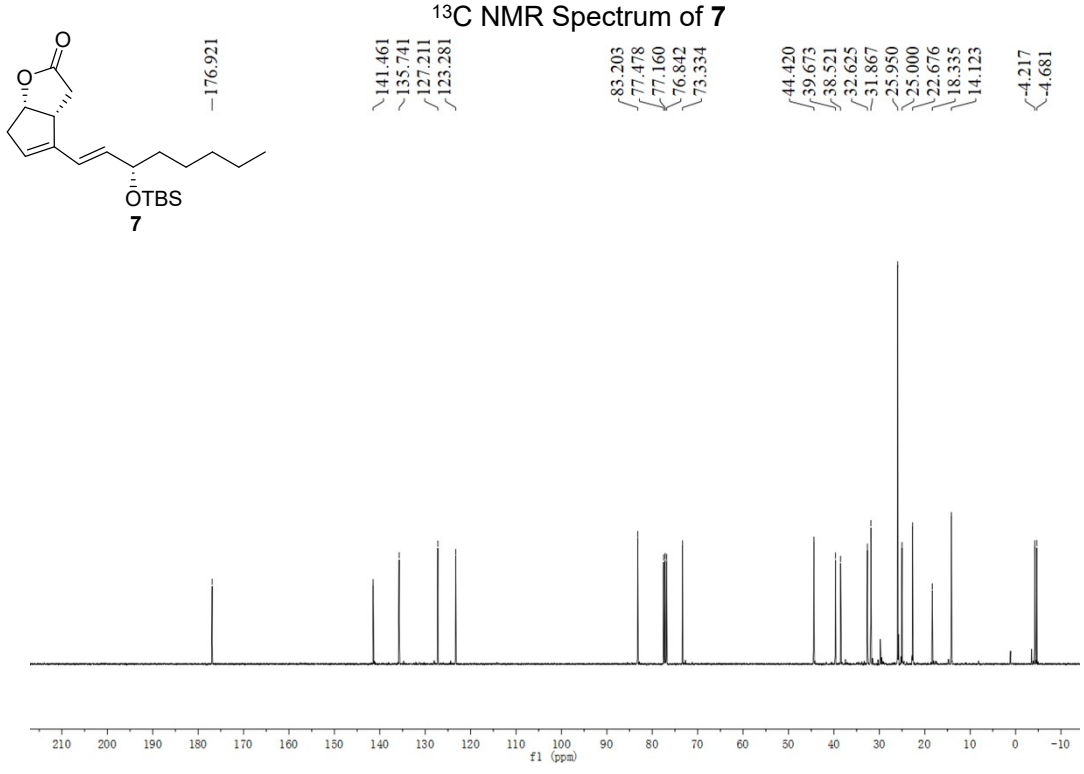
^{13}C NMR Spectrum of **22**



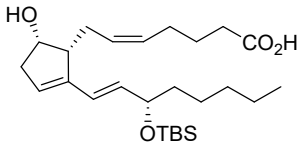
^{1}H NMR Spectrum of **7**



^{13}C NMR Spectrum of **7**

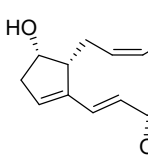


^{1}H NMR Spectrum of **24**



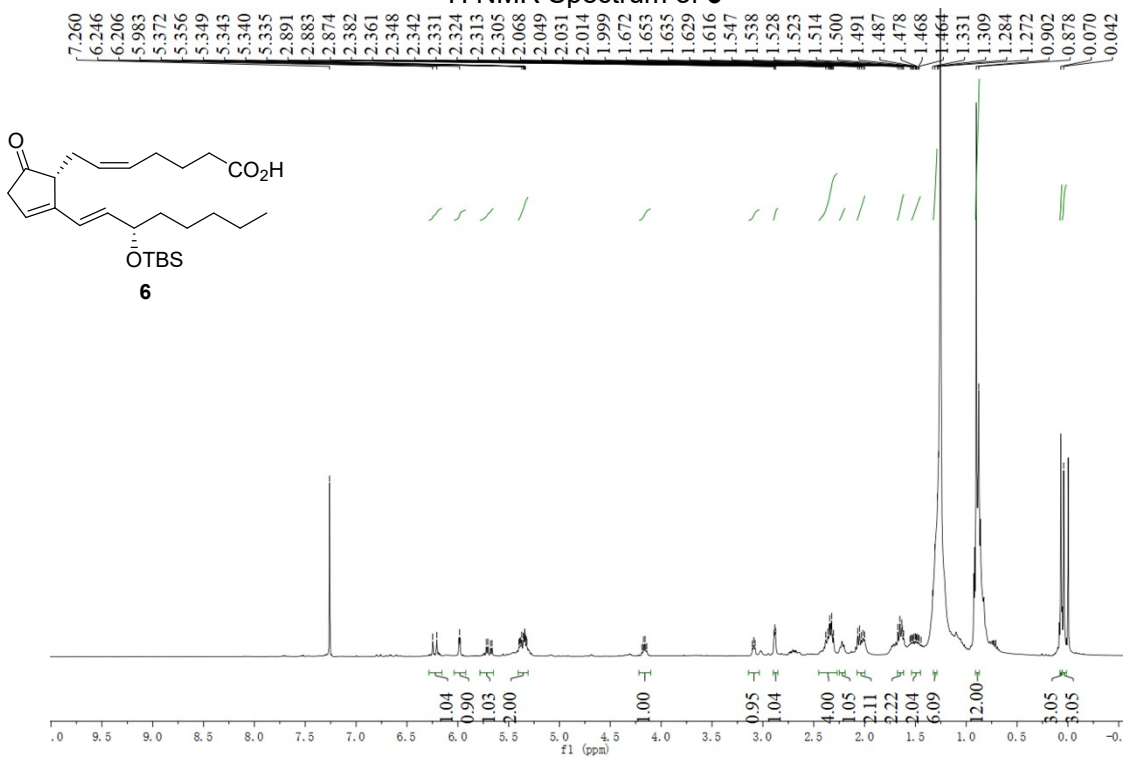
24

^{13}C NMR Spectrum of **24**

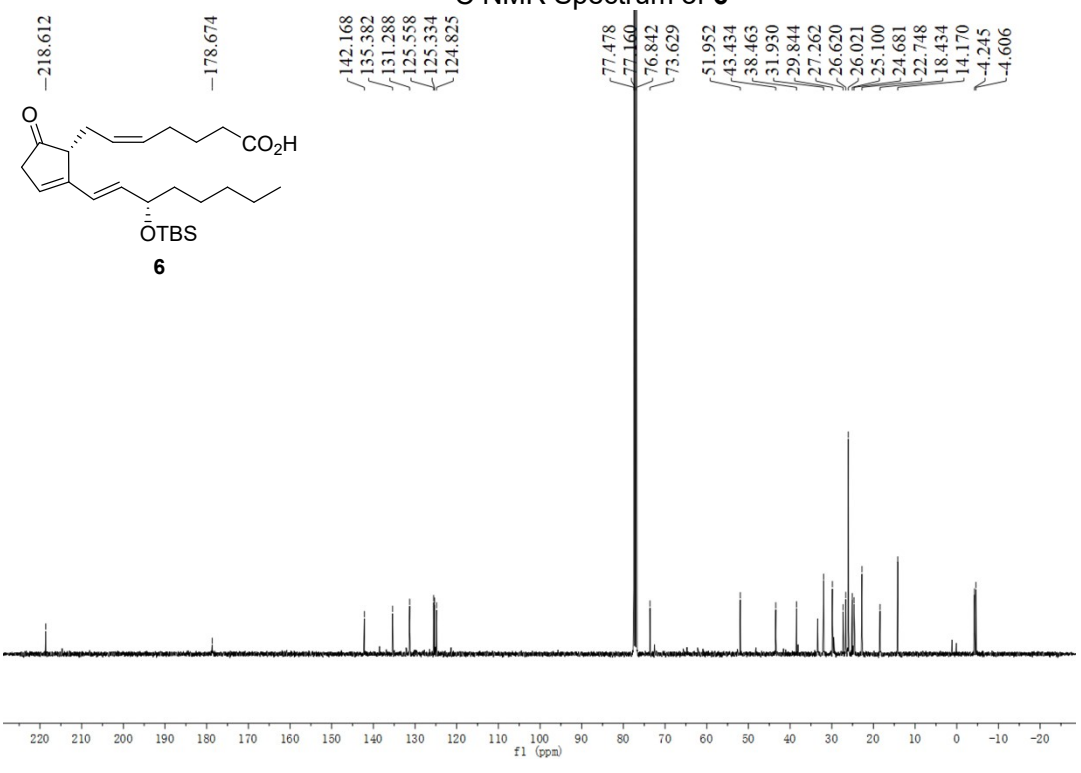


24

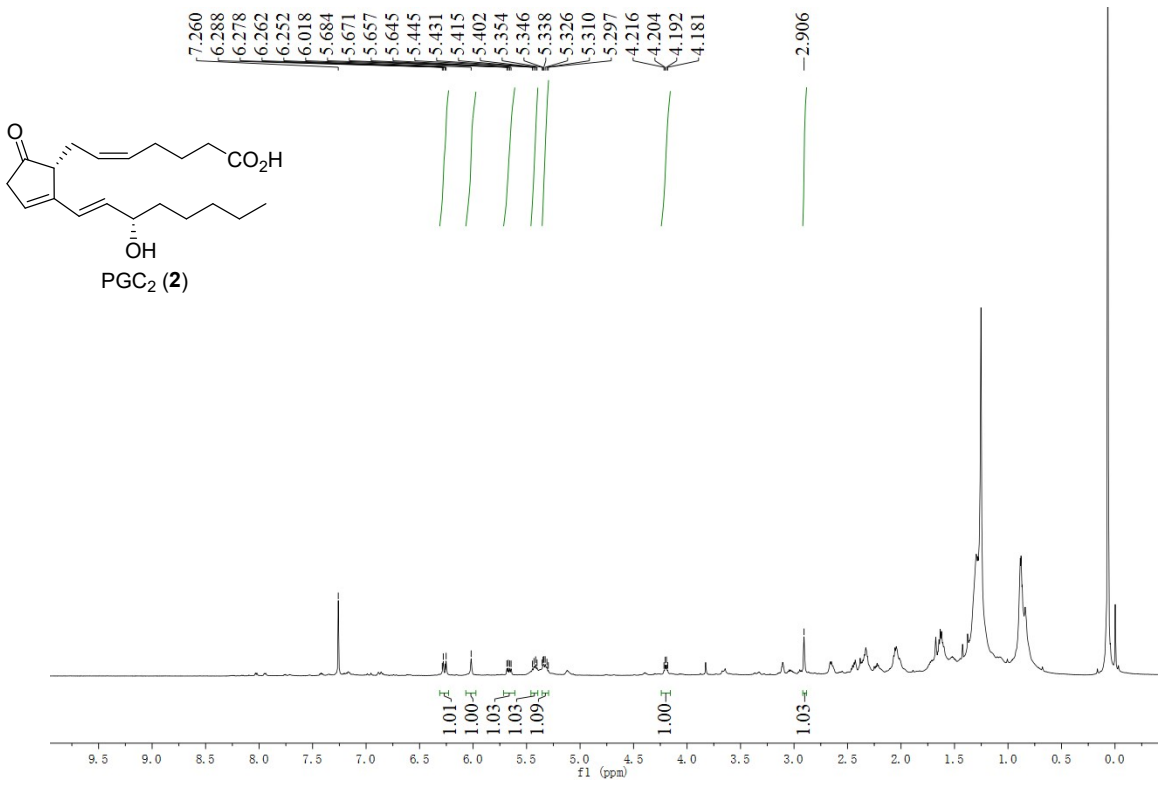
^{1}H NMR Spectrum of **6**



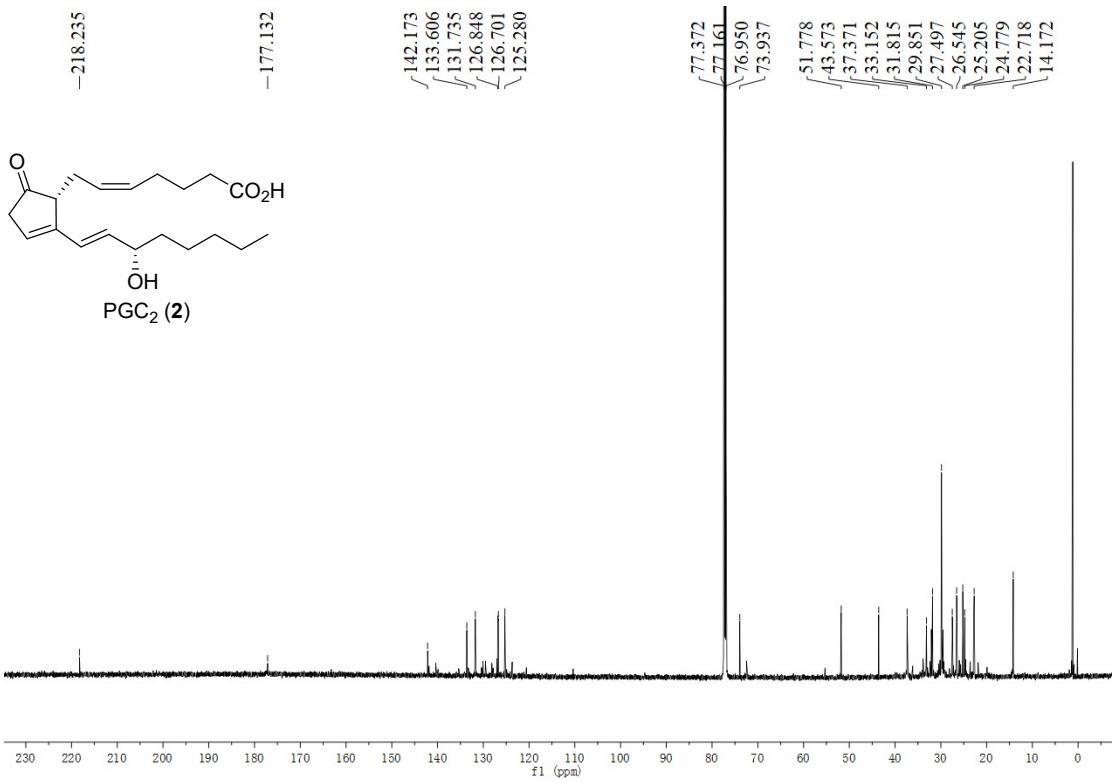
^{13}C NMR Spectrum of **6**



Rough ^{1}H NMR Spectrum of PGC_2 **(2)**



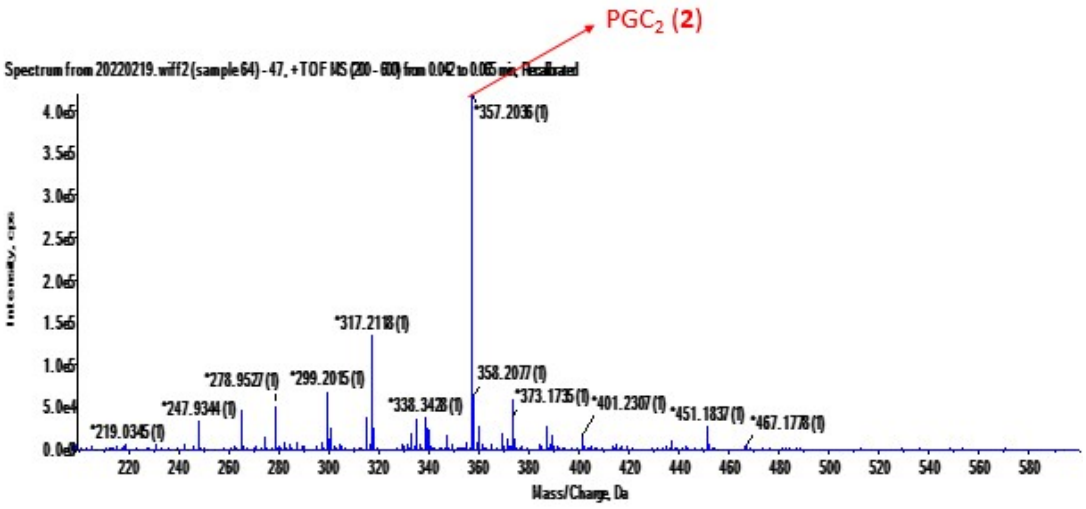
Rough ^{13}C NMR Spectrum of PGC_2 (**2**)

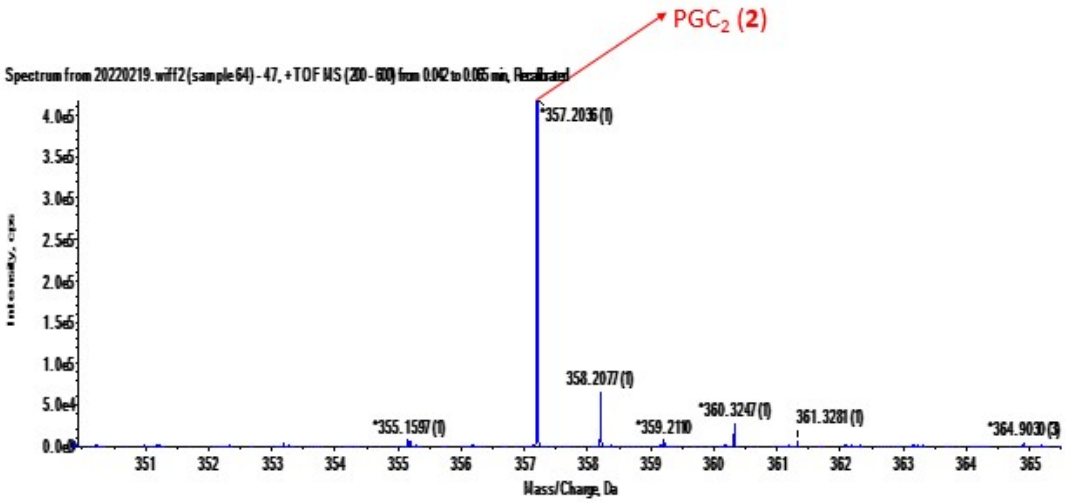


5. HRMS of PGC_2 (2)

ESI+ HRMS of PGC_2 (**2**)

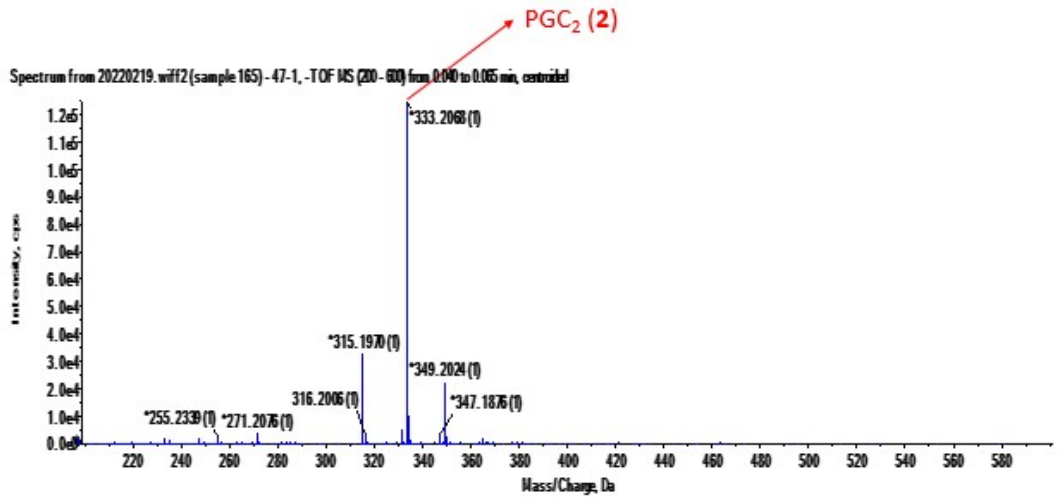
{HRMS (ESI) *m/z* calcd for $C_{20}H_{30}O_4Na$ $[M + Na]^+$: 357.2036, found: 357.2036. }

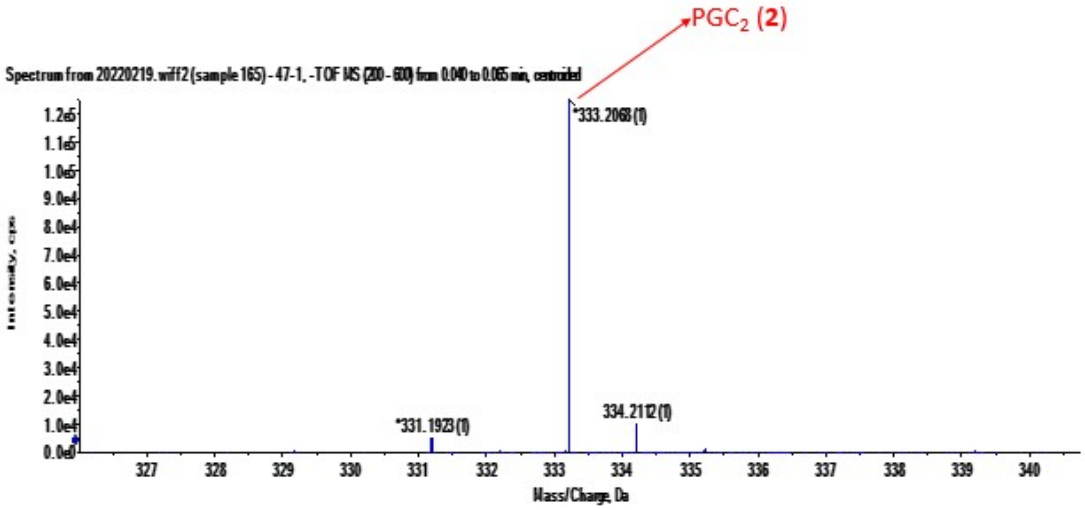




ESI- HRMS of PGC_2 (**2**)

{HRMS (ESI) *m/z* calcd for $C_{20}H_{29}O_4$ [M - H]$^-$: 333.2071, found: 333.2068.}




PGC2 (2)
Spectrum from 20220219.wiff2 (sample 165) - 47-1, -TOF MS (200 - 600) from 0.040 to 0.085 min, centroided
*333.2068 (1)
*331.1923 (1)
334.2112 (1)
Intensity, cps
Mass/Charge, Da