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Electronic Supplementary Information

Cytotoxic analogues of marine diterpenoid plumisclerin A by shifting the lipophilic branch on the characteristic tricyclic core

Ming Gao,[‡*] Bao-Bao Yu,[‡] Chen Jia, and Zhu-Jun Yao[*]

State Key Laboratory of Coordination Chemistry, and Jiangsu Key Laboratory of Advanced Organic Materials, School of Chemistry and Chemical Engineering, Nanjing University, 163 Xianlin Avenue, Nanjing, Jiangsu 210023, China

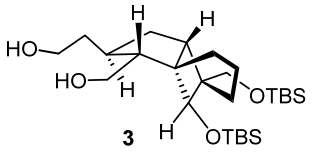
yaoz@nju.edu.cn (ZJY), *or* gaoming_0305@163.com (MG)

Table of Contents

1. General procedures

Unless otherwise noted, all reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions. Tetrahydrofuran (THF) was distilled immediately from sodium-benzophenoneketyl prior to use. Methylene chloride (CH_2Cl_2) was distilled immediately before use from calcium hydride. External bath temperatures were used to record all reaction temperatures. All other solvents were processed through the reference *Purification of Laboratory Chemicals (Seventh Edition)*. Silica gel (300~400 mesh) and petroleum ether, ethyl acetate and acetone are used for product purification by flash column chromatography. Analytical thin-layer chromatography (TLC) was performed with glass TLC plates. Visualization was accomplished with UV light, phosphomolybdic acid staining and subsequent heating. ^{1}H NMR, ^{13}C NMR and 2D NMR spectra were recorded on either 400 MHz/500 MHz/600 MHz Bruker instruments. IR spectra were recorded on Fourier Transform infrared spectrometer and listed in cm^{-1}. High-resolution mass spectral analyses (HRMS) were determined on a Q-TOF-MS spectrometer. Optical rotations were measured with a polarimeter with a sodium lamp.

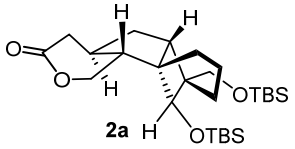
2. Experimental procedures and characterization of new compounds



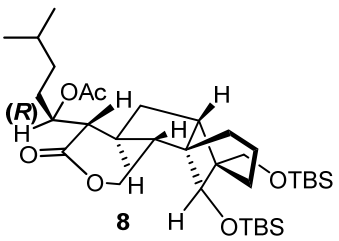
3

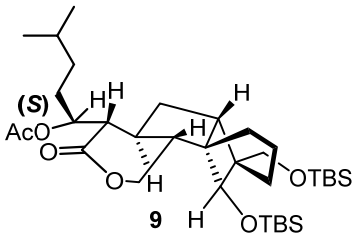
***Trans*-diol tricyclodecane 3**: To a stirred solution of *trans*-dimethyl ester **4** (537 mg, 0.99 mmol, 1 equiv) in dry THF (10 mL) was added DIBAL-H (1.5 M in toluene, 4 mL, 6 equiv.) at 29 °C. After 2 h, the reaction mixture was quenched with saturated aq. potassium sodium tartrate and stirred for 2 h. The aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate, 10:1→5:1), to give **3** (480 mg, ~100%) as a colorless oil. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 3.97 (s, 1H), 3.77 – 3.57 (m, 4H), 3.38 (s, 2H), 2.35 – 2.24 (m, 1H), 2.19 – 2.09 (m, 1H), 2.09 – 1.97 (m, 2H), 1.87 (s, 2H), 1.82 – 1.72 (m, 1H), 1.69 – 1.59 (m, 2H), 1.57 – 1.41 (m, 4H), 1.37 – 1.23 (m, 1H), 0.89 (s, 18H), 0.07 (s, 3H), 0.04 – 0.01 (m, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 67.7, 66.0, 63.6, 62.0, 57.0, 54.9, 48.6, 41.6, 41.0, 39.5, 31.2, 28.4, 27.2, 26.1, 25.9, 18.3, 18.1, 16.6, -3.9, -5.2, -5.4, -5.4. **IR** (film)

ν_{max} 3327, 2950, 2927, 2855, 1471, 1250, 1138, 1120, 1083 cm^{-1}. $[\alpha]_D^{20}$ = +9.4° (c = 0.62 in $CHCl_3$). **HRMS** (ESI, m/z): $[M + Na]^+$ calcd for $C_{26}H_{52}O_4Si_2Na^+$ 507.3296, found 507.3305. R_f = 0.41 (silica gel, petroleum ether/ethyl acetate = 3:1).



***trans*-Lactone 2a**: To a stirred solution of **3** (200 mg, 0.41 mmol, 1 equiv.) in toluene (5 mL) was add $RuCl_2(PPh_3)_3$ (475 mg, 0.49 mmol, 1.2 equiv.) at ambient temperature. The reaction was stirred in open air for 3 h. The crude product was purified by flash column chromatography on silica gel (petroleum ether/acetone 50:1→40:1), to give **2a** (171 mg, 87%) as a colorless oil. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 4.43 (dd, *J* = 10.4, 4.9 Hz, 1H), 4.20 – 4.03 (m, 2H), 3.47 – 3.31 (m, 2H), 2.87 (d, *J* = 12.7 Hz, 1H), 2.42 – 2.20 (m, 3H), 2.14 – 2.03 (m, 2H), 1.79 – 1.59 (m, 3H), 1.57 – 1.49 (m, 1H), 1.49 – 1.40 (m, 1H), 1.31 – 1.18 (m, 2H), 0.90 (s, 9H), 0.87 (s, 9H), 0.06 – 0.01 (m, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.8, 71.6, 65.6, 65.0, 54.7, 49.7, 48.4, 42.6, 41.9, 39.4, 29.4, 27.8, 26.9, 26.1, 25.8, 18.3, 18.1, 16.2, -4.2, -4.8, -5.5, -5.5. **IR** (film) ν_{max} 2952, 2928, 2855, 1737, 1471, 1251, 1118, 1089, 1031 cm^{-1}. $[\alpha]_D^{20}$ = -77.5° (c = 0.08 in $CHCl_3$). **HRMS** (ESI, m/z): $[M + Na]^+$ calcd for $C_{26}H_{48}O_4Si_2Na^+$ 503.2983, found 503.2992. R_f = 0.54 (silica gel, petroleum ether/acetone = 10:1).

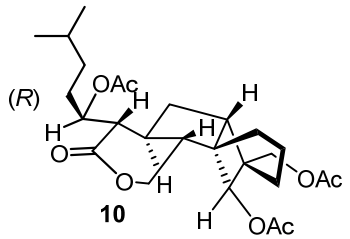




4-Methylpentyl acetates 8 and 9: To a stirred solution of **2a** (90 mg, 0.19 mmol, 1 equiv.) in THF (3 mL) was added dropwise freshly prepared LDA (0.2 M in THF, 1.2 mL, 0.25 mmol, 1.3 equiv.) at –78 °C. The reaction was stirred at –78 °C for 1 h, and 4-methylpentanal (35 μL, 0.29 mmol, 1.5 equiv.) was added dropwise. The reaction was stirred at –78 °C for 1 h until it was quenched with saturated aq. NH_4Cl. The mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was used in the next step without further purification.

To a solution of the above crude product, DMAP (5 mg, 0.038 mmol, 0.2 equiv.) and pyridine (294 μL, 3.8 mmol, 20 equiv.) in DCM (2 mL) was added Ac_2O (211 μL, 1.9 mmol, 10 equiv.) at 0 °C.

The reaction was warmed to ambient temperature for 2 h, and then quenched with saturated aq. $NaHCO_3$. The mixture was extracted with DCM. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (petroleum ether/acetone, 50:1→40:1), to give **8** (36 mg, 31%) and **9** (31 mg, 26%) as a colorless oil. **8:** ^{1}**H NMR** (400 MHz, Chloroform-*d*) δ 5.36 (dt, *J* = 9.7, 3.8 Hz, 1H), 4.36 (dd, *J* = 10.3, 4.7 Hz, 1H), 4.19 – 4.03 (m, 2H), 3.54 – 3.27 (m, 2H), 2.85 (dd, *J* = 12.0, 3.7 Hz, 1H), 2.53 (ddd, *J* = 14.3, 8.2, 2.5 Hz, 1H), 2.26 (ddd, *J* = 20.3, 11.7, 9.3 Hz, 1H), 2.05 (dt, *J* = 11.2, 3.9 Hz, 2H), 2.02 (s, 3H), 1.79 – 1.63 (m, 4H), 1.63 – 1.46 (m, 4H), 1.44 – 1.36 (m, 1H), 1.30 – 1.20 (m, 2H), 1.20 – 1.10 (m, 1H), 0.92 (s, 9H), 0.90 – 0.85 (m, 15H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H). ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 170.5, 170.0, 74.9, 71.5, 66.0, 65.0, 54.2, 53.2, 49.6, 48.6, 42.7, 42.5, 35.2, 29.6, 28.4, 27.8, 27.7, 26.6, 26.2, 25.8, 22.8, 22.7, 21.3, 18.5, 18.1, 16.2, -4.2, -4.9, -5.3, -5.4. **IR** (film) ν_{max} 2952, 2928, 2855, 1740, 1470, 1371, 1237, 1138, 1090, 1039 cm^{-1}. $[\alpha]_D^{20}$ = -48.7° (c = 0.72 in $CHCl_3$). **HRMS** (ESI, m/z): $[M + Na]^+$ calcd for $C_{34}H_{62}O_6Si_2Na^+$ 645.3977, found 645.3982. R_f = 0.40 (silica gel, petroleum ether/acetone = 10:1). **9**: ^{1}**H NMR** (400 MHz, Chloroform-*d*) δ 5.37 (ddd, *J* = 8.2, 6.6, 2.1 Hz, 1H), 4.34 (dd, *J* = 10.2, 4.5 Hz, 1H), 4.21 – 4.03 (m, 2H), 3.49 – 3.30 (m, 2H), 2.61 (dd, *J* = 11.7, 2.0 Hz, 1H), 2.58 – 2.53 (m, 1H), 2.45 – 2.32 (m, 1H), 2.08 (td, *J* = 14.1, 12.4, 4.2 Hz, 2H), 2.03 (s, 3H), 1.84 – 1.70 (m, 2H), 1.70 – 1.63 (m, 2H), 1.62 – 1.52 (m, 2H), 1.52 – 1.36 (m, 3H), 1.33 – 1.26 (m, 1H), 1.25 – 1.20 (m, 1H), 1.21 – 1.08 (m, 1H), 0.92 (s, 9H), 0.89 – 0.85 (m, 15H), 0.07 – 0.03 (m, 12H). ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 171.3, 170.2, 75.1, 71.0, 65.9, 64.7, 54.2, 53.9, 49.7, 48.9, 42.8, 42.6, 35.2, 30.1, 29.7, 28.2, 27.7, 26.6, 26.2, 25.8, 22.8, 22.6, 21.3, 18.4, 18.1, 16.2, -4.2, -5.0, -5.4, -5.4. **IR** (film) ν_{max} 2928, 2952, 2855, 1745, 1470, 1367, 1248, 1234, 1139, 1118, 1021 cm^{-1}. $[\alpha]_D^{20}$ = -13.2° (c = 0.49 in $CHCl_3$). **HRMS** (ESI, m/z): $[M + Na]^+$ calcd for $C_{34}H_{62}O_6Si_2Na^+$ 645.3977, found 645.3988. R_f = 0.30 (silica gel, petroleum ether/acetone = 10:1).

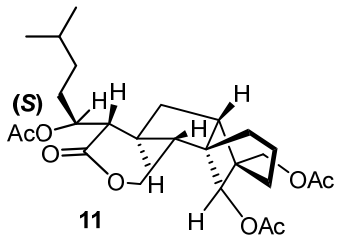


10

Triacetate 10: To a stirred solution of **8** (36 mg, 0.058 mmol, 1 equiv.) in THF (0.5 mL) was added 70% HF-pyr (0.5 mL) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 10 h, until it was quenched with saturated aq. $NaHCO_3$. The mixture was extracted with DCM. The combined organic

extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was used in the next step.

To a solution of the above crude product, DMAP (1.4 mg, 0.012 mmol, 0.2 equiv.), and pyridine (90 μL, 1.16 mmol, 20 equiv.) in DCM (0.3 mL) was added Ac_2O (64 μL, 0.58 mmol, 10 equiv.) at 0 °C. The reaction was warmed to ambient temperature and stirred for 2 h, and then quenched with saturated aq. $NaHCO_3$. The mixture was extracted with DCM. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (petroleum ether/acetone, 20:1→5:1) to give **10** (15 mg, 63 %) as a colorless oil. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 5.41 – 5.30 (m, 1H), 4.88 (s, 1H), 4.37 – 4.24 (m, 2H), 4.05 – 3.93 (m, 2H), 2.79 (dd, *J* = 11.8, 3.2 Hz, 1H), 2.45 – 2.32 (m, 1H), 2.33 – 2.24 (m, 1H), 2.20 (dd, *J* = 10.8, 2.5 Hz, 1H), 2.06 (s, 9H), 2.01 – 1.85 (m, 2H), 1.83 – 1.75 (m, 2H), 1.75 – 1.65 (m, 4H), 1.65 – 1.58 (m, 1H), 1.58 – 1.50 (m, 1H), 1.43 – 1.30 (m, 1H), 1.24 – 1.12 (m, 2H), 0.89 (d, *J* = 1.0 Hz, 3H), 0.87 (d, *J* = 1.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.0, 170.6, 170.5, 169.4, 74.6, 70.7, 67.8, 66.4, 54.5, 53.1, 48.3, 46.7, 43.5, 42.5, 35.4, 29.1, 29.1, 28.3, 27.9, 27.0, 22.7, 22.7, 21.4, 21.0, 20.9, 15.7. **IR** (film) ν_{max} 2953, 2935, 2868, 1731, 1469, 1368, 1231, 1059, 1027 cm^{-1}. $[\alpha]_D^{20}$ = -59.1° (c = 0.32 in $CHCl_3$). **HRMS** (ESI, m/z): $[M + Na]^+$ calcd for $C_{26}H_{38}O_8Na^+$ 501.2459, found 501.2459. R_f = 0.60 (silica gel, petroleum ether/acetone = 2:1).

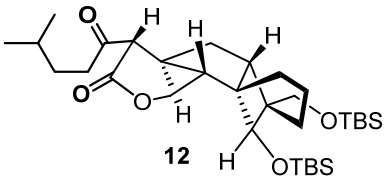


11

Triacetate 11: To a stirred solution of **9** (31 mg, 0.050 mmol, 1 equiv.) in THF (0.5 mL) was added 70% HF-pyr (0.5 mL) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 10 h, until it was quenched with saturated aq. $NaHCO_3$. The mixture was extracted with DCM. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was used in the next step.

To a solution of the above crude product, DMAP (1.2 mg, 0.010 mmol, 0.2 equiv.), and pyridine (77 μL, 1.0 mmol, 20 equiv.) in DCM (0.3 mL) was added Ac_2O (55 μL, 0.50 mmol, 10) at 0 °C. The reaction was warmed to ambient temperature and stirred for 2 h, and then quenched with saturated aq. $NaHCO_3$. The mixture was extracted with DCM. The combined organic extracts were

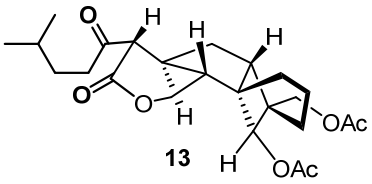
dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resdiue was purified by flash column chromatography (petroleum ether/acetone, 20:1→5:1) to give **11** (13 mg, 59 %) as a colorless oil. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 5.43 – 5.24 (m, 1H), 4.86 (s, 1H), 4.38 – 4.18 (m, 2H), 4.12 – 3.87 (m, 2H), 2.65 (dd, *J* = 11.5, 2.5 Hz, 1H), 2.53 – 2.38 (m, 1H), 2.35 – 2.18 (m, 2H), 2.08 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.01 – 1.85 (m, 2H), 1.85 – 1.75 (m, 3H), 1.75 – 1.66 (m, 3H), 1.64 – 1.48 (m, 3H), 1.36 – 1.26 (m, 1H), 1.22 – 1.10 (m, 1H), 0.89 (s, 3H), 0.88 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.9, 170.7, 170.5, 170.5, 74.7, 70.4, 68.1, 66.3, 54.2, 54.1, 48.8, 46.9, 43.3, 42.6, 35.2, 30.1, 29.5, 28.3, 28.0, 26.9, 22.7, 22.6, 21.3, 21.0, 20.9, 15.7. **IR** (film) ν_{max} 2953, 2926, 2868, 1733, 1468, 1367, 1231, 1185, 1057, 1023 cm^{-1}. $[\alpha]_D^{20}$ = -9.8° (c = 0.33 in $CHCl_3$). **HRMS** (ESI, m/z): [M + Na]$^+$ calcd for $C_{26}H_{38}O_8Na^+$ 501.2459, found 501.2469. R_f = 0.43 (silica gel, petroleum ether/acetone = 2:1).



12

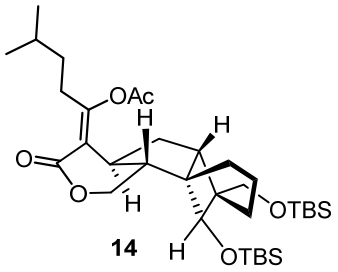
β-Keto ester 12: To a stirred solution of **2a** (100 mg, 0.21 mmol, 1 equiv.) in THF (3 mL) was added dropwise freshly prepared LDA (0.2 M in THF, 1.4 mL, 0.27 mmol, 1.3 equiv.) at –78 °C. The reaction was stirred at –78 °C for 1 h, and 4-methylpentanoyl chloride (42 μL, 0.32 mmol, 1.5 equiv.) was added dropwise. The reaction was stirred at –78 °C for 1 h until it was quenched with saturated aq. NH_4Cl. The mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (petroleum ether/acetone, 100:1→50:1) to give **12** (92 mg, 76%) as a colorless oil. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 4.41 (dd, *J* = 10.3, 4.8 Hz, 1H), 4.17 (dd, *J* = 12.2, 10.3 Hz, 1H), 4.05 (s, 1H), 3.50 – 3.21 (m, 3H), 2.84 – 2.73 (m, 1H), 2.68 – 2.49 (m, 2H), 2.33 – 2.20 (m, 1H), 2.15 – 2.01 (m, 2H), 1.77 – 1.61 (m, 4H), 1.58 – 1.43 (m, 5H), 1.23 – 1.17 (m, 1H), 0.92 – 0.89 (m, 6H), 0.88 (s, 9H), 0.87 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H), 0.02 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 205.3, 167.7, 72.0, 65.6, 65.3, 62.9, 54.6, 49.7, 47.6, 44.2, 42.5, 42.5, 32.1, 28.3, 27.7, 27.6, 26.8, 26.1, 25.8, 22.6, 22.4, 18.4, 18.1, 16.1, -4.1, -4.8, -5.5, -5.4. **IR** (film) ν_{max} 2952, 2928, 2896, 2856, 1732, 1713, 1471, 1405, 1250, 1139, 1117, 1087, 1006 cm^{-1}. $[\alpha]_D^{20}$ = -22.6° (c =

0.84 in $CHCl_3$). **HRMS** (ESI, m/z): $[M + Na]^+$ calcd for $C_{32}H_{58}O_5Si_2Na^+$ 601.3715, found 601.3720. $\mathbf{R_f}$ = 0.53 (silica gel, petroleum ether/acetone = 10:1).



Diacetate 13: To a stirred solution of **12** (42 mg, 0.073 mmol, 1 equiv.) in THF (0.5 mL) was added 70% HF-pyr (0.5 mL) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 10 h, until it was quenched with saturated aq. $NaHCO_3$. The mixture was extracted with DCM. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was used in the next step.

To a solution of the above crude product, DMAP (1.7 mg, 0.015 mmol, 0.2 equiv.), and pyridine (113 μL, 1.5 mmol, 20 equiv.) in DCM (0.3 mL) was added Ac_2O (81 μL, 0.73 mmol, 10 equiv.) at 0 °C. The reaction was warmed to ambient temperature and stirred for 2 h, and then quenched with saturated aq. $NaHCO_3$. The mixture was extracted with DCM. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether/acetone, 50:1→15:1) to give **13** (15 mg, 47%) as a colorless oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 4.92 (s, 1H), 4.50 – 4.40 (m, 1H), 4.34 (dd, *J* = 10.6, 4.9 Hz, 1H), 4.03 – 3.91 (m, 2H), 3.40 (d, *J* = 12.1 Hz, 1H), 2.94 – 2.77 (m, 2H), 2.69 – 2.48 (m, 1H), 2.22 (dd, *J* = 10.8, 2.7 Hz, 1H), 2.15 (ddd, *J* = 14.6, 8.2, 2.6 Hz, 1H), 2.07 (s, 3H), 2.06 (s, 3H), 2.01 – 1.93 (m, 1H), 1.93 – 1.84 (m, 1H), 1.78 (dq, *J* = 7.5, 5.9, 5.5 Hz, 2H), 1.75 – 1.66 (m, 3H), 1.57 – 1.46 (m, 3H), 1.36 – 1.26 (m, 1H), 0.91 (s, 3H), 0.89 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 205.0, 171.0, 170.3, 167.0, 71.5, 67.8, 66.1, 62.6, 54.7, 47.2, 46.7, 43.4, 43.2, 42.3, 32.3, 28.2, 28.2, 27.7, 27.1, 22.6, 22.4, 21.0, 20.9, 15.7. **IR** (film) $\mathbf{\nu}_{max}$ 2954, 2925, 2868, 1733, 1712, 1467, 1367, 1236, 1185, 1059, 1037 cm^{-1}. $\mathbf{[\alpha]_D^{20}}$ = -24.9° (c = 0.23 in $CHCl_3$). **HRMS** (ESI, m/z): $[M + Na]^+$ calcd for $C_{24}H_{34}O_7Na^+$ 457.2197, found 457.2203. $\mathbf{R_f}$ = 0.44 (silica gel, petroleum ether/acetone = 5:1).



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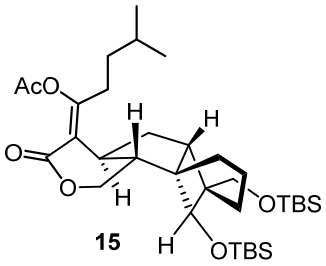
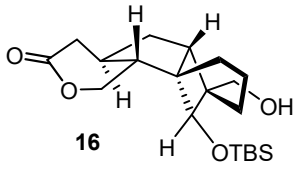


15

Enol acetates 14 and 15: To a stirred solution of NaH (60 wt.%) (7 mg, 0.17 mmol, 5 equiv.) in THF (1 mL) was added **12** (20 mg, 0.035 mmol, 1 equiv.) in dry THF (1 mL) dropwise at ambient temperature at 0 °C. The reaction was stirred at ambient temperature for 30 min, and acetyl chloride (8 μL, 0.11 mmol, 3 equiv.) was then added. After 2 h, the reaction was quenched with $NaHCO_3$, the mixture was extracted with DCM. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (petroleum ether/acetone, 100:1→50:1), to give **(*E*)-14** (2 mg, 9%) and **(*Z*)-15** (6 mg, 27%) as colorless oils. **(*E*)-14**: **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 4.33 (dd, *J* = 10.2, 4.3 Hz, 1H), 4.09 (dd, *J* = 12.0, 10.2 Hz, 1H), 3.92 (s, 1H), 3.39 (s, 2H), 3.12 – 2.94 (m, 1H), 2.86 – 2.77 (m, 1H), 2.74 – 2.61 (m, 1H), 2.29 (ddd, *J* = 14.1, 8.1, 2.4 Hz, 1H), 2.18 (s, 3H), 2.09 – 2.04 (m, 1H), 2.02 (dd, *J* = 11.0, 2.3 Hz, 1H), 1.83 – 1.70 (m, 2H), 1.70 – 1.59 (m, 4H), 1.57 – 1.47 (m, 2H), 1.46 – 1.37 (m, 1H), 1.37 – 1.30 (m, 1H), 0.90 (s, 9H), 0.90 – 0.88 (m, 6H), 0.87 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 168.3, 164.8, 164.5, 121.0, 70.1, 65.5, 65.4, 53.1, 50.3, 48.3, 46.1, 41.8, 36.1, 31.8, 28.3, 28.2, 27.8, 26.8, 26.1, 25.8, 22.6, 22.5, 21.6, 18.4, 18.1, 16.1, -4.2, -4.8, -5.3, -5.4. **IR** (film) ν_{max} 2953, 2928, 2856, 1763, 1719, 1630, 1470, 1251, 1185, 1135, 1092 cm^{-1}. $[\alpha]_D^{20}$ = -86.7° (c = 0.06 in $CHCl_3$). **HRMS** (ESI, m/z): [M + Na]$^+$ calcd for $C_{34}H_{60}O_6Si_2Na^+$ 643.3821, found 643.3827. R_f = 0.50 (silica gel, petroleum ether/acetone = 20:1). **(*Z*)-15: ^{1}H NMR** (500 MHz, Chloroform-*d*) δ 4.29 (dd, *J* = 10.1, 4.1 Hz, 1H), 4.14 – 4.00 (m, 2H), 3.55 – 3.31 (m, 2H), 3.12 – 2.84 (m, 1H), 2.59 (ddd, *J* = 13.7, 8.3, 2.4 Hz, 1H), 2.53 – 2.42 (m, 1H), 2.22 (s, 4H), 2.13 – 2.03 (m, 2H), 1.81 (td, *J* = 12.2, 4.0 Hz, 1H), 1.77 – 1.70 (m, 2H), 1.70 – 1.58 (m, 3H), 1.54 – 1.43 (m, 3H), 1.40 – 1.27 (m, 1H), 0.94 – 0.88 (m, 15H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.03 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 169.1, 163.4, 160.1, 119.7, 69.7, 65.7, 65.1, 53.0, 50.1, 49.4, 45.2, 42.4, 35.7, 32.4, 29.9, 28.4, 27.8, 26.6, 26.2, 25.8, 22.5, 21.5, 18.4, 18.1, 16.1, -4.2, -4.8, -5.4. **IR** (film) ν_{max} 2953, 2928, 2895, 2855, 1766, 1718, 1620, 1470, 1250, 1203, 1145,

1090, 1072, 1054 cm^{-1}. $[\alpha]_D^{20}$ = -42.4° (c = 0.26 in $CHCl_3$). **HRMS** (ESI, m/z): $[M + Na]^+$ calcd for $C_{34}H_{60}O_6Si_2Na^+$ 643.3821, found 643.3819. R_f = 0.32 (silica gel, petroleum ether/acetone = 20:1).

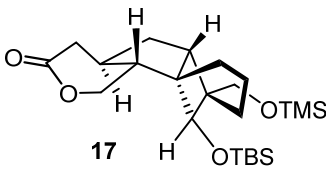


16

Primary alcohol 16: To a stirred solution of **2a** (80 mg, 0.17 mmol, 1 equiv.) in THF (1 mL) was added 70% HF-pyr (0.5 mL) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, until it was quenched with saturated aq. $NaHCO_3$. The mixture was extracted with DCM. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (petroleum ether/acetone, 50:1→10:1) to give **16** (56 mg, 92%). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 4.42 (dd, *J* = 10.4, 5.0 Hz, 1H), 4.10 (dd, *J* = 12.2, 10.4 Hz, 1H), 3.90 (s, 1H), 3.48 (s, 2H), 2.97 – 2.84 (m, 1H), 2.43 – 2.21 (m, 2H), 2.20 – 1.98 (m, 3H), 1.91 – 1.76 (m, 1H), 1.75 – 1.50 (m, 5H), 1.47 – 1.25 (m, 2H), 0.87 (s, 8H), 0.03 (s, 3H), 0.02 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.5, 71.4, 66.6, 65.6, 55.3, 49.7, 48.6, 42.0, 41.5, 39.5, 29.0, 27.5, 26.7, 25.9, 25.8, 18.1, 16.1, -4.3, -4.8. **IR** (film) ν_{max} 3447, 1950, 2927, 2855, 1728, 1470, 1405, 1249, 1198, 1139, 1112, 1071, 1029 cm^{-1}. $[\alpha]_D^{20}$ = -53.6° (c = 0.50 in $CHCl_3$). **HRMS** (ESI, m/z): $[M + Na]^+$ calcd for $C_{20}H_{34}O_4SiNa^+$ 389.2119, found 389.2125. R_f = 0.31 (silica gel, petroleum ether/acetone = 4:1).

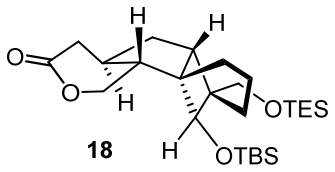
General procedures for *trans*-lactones 17-22.

To a solution of the primary alcohol **16** (1 equiv.) in DCM (1 mL) was added TEA (4 equiv.) and silane trifluoromethanesulfonate or acyl chloride (2 equiv.) dropwise at 0 °C. The reaction was stirred at 0 °C for 2 h until it was quenched with saturated aq. $NaHCO_3$ and extracted with DCM. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography.



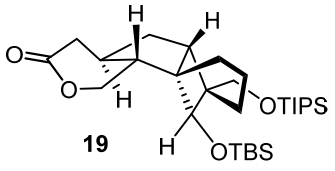
17

17: A colorless oil, 83% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 4.42 (dd, *J* = 10.4, 4.9 Hz, 1H), 4.11 (dd, *J* = 12.2, 10.4 Hz, 1H), 4.01 (s, 1H), 3.43 – 3.30 (m, 2H), 2.90 (d, *J* = 12.7 Hz, 1H), 2.37 – 2.15 (m, 3H), 2.14 – 2.00 (m, 2H), 1.81 – 1.67 (m, 2H), 1.67 – 1.57 (m, 2H), 1.57 – 1.39 (m, 2H), 1.28 (s, 1H), 0.87 (s, 9H), 0.09 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.7, 71.6, 65.6, 65.0, 54.9, 49.4, 48.6, 42.4, 41.9, 39.6, 29.1, 27.7, 26.8, 25.8, 18.1, 16.2, -0.5, -4.2, -4.9. **IR** (film) ν_{max} 2952, 2927, 2855, 1737, 1470, 1404, 1250, 1189, 1140, 1091, 1068, 1031 cm^{-1}. $[\alpha]_D^{20}$ = -42.1° (c = 0.20 in $CHCl_3$). **HRMS** (ESI, m/z): [M + Na]$^+$ calcd for $C_{23}H_{42}O_4Si_2Na^+$ 461.2514, found 461.2521. R_f = 0.52 (silica gel, petroleum ether/acetone = 5:1).



18

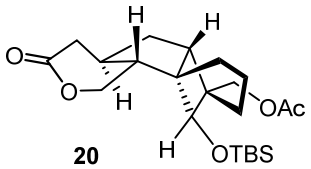
18: A colorless oil, 92% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 4.42 (dd, *J* = 10.4, 5.0 Hz, 1H), 4.10 (dd, *J* = 12.2, 10.4 Hz, 1H), 4.04 (s, 1H), 3.52 – 3.31 (m, 2H), 2.98 – 2.78 (m, 1H), 2.41 – 2.21 (m, 3H), 2.15 – 2.02 (m, 2H), 1.70 (d, *J* = 2.4 Hz, 2H), 1.58 (s, 1H), 1.57 – 1.38 (m, 3H), 1.24 – 1.14 (m, 1H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.87 (s, 9H), 0.59 (q, *J* = 7.7 Hz, 6H), 0.04 (s, 3H), 0.03 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.7, 71.6, 65.4, 54.8, 49.7, 48.5, 42.4, 41.9, 39.5, 29.3, 27.7, 26.9, 25.8, 18.1, 16.2, 7.0, 4.5, -4.2, -4.9. **IR** (film) ν_{max} 2952, 2928, 2876, 2856, 1737, 1470, 1411, 1249, 1189, 1139, 1091, 1068, 1031, 1008 cm^{-1}. $[\alpha]_D^{20}$ = -47.8° (c = 0.18 in $CHCl_3$). **HRMS** (ESI, m/z): [M + Na]$^+$ calcd for $C_{26}H_{48}O_4Si_2Na^+$ 503.2983, found 503.2993. R_f = 0.68 (silica gel, petroleum ether/acetone = 3:1).



19

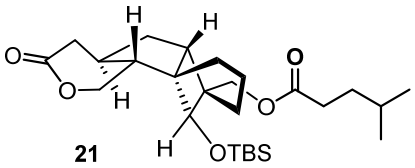
19: A colorless oil, 86% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 4.42 (dd, *J* = 10.4, 5.0 Hz, 1H), 4.10 (dd, *J* = 12.2, 10.4 Hz, 1H), 3.96 (s, 1H), 3.58 – 3.47 (m, 2H), 3.05 – 2.70 (m, 1H), 2.45 – 2.22 (m, 3H), 2.22 – 2.00 (m, 2H), 1.82 – 1.59 (m, 4H), 1.63 – 1.47 (m, 3H), 1.38 – 1.18 (m, 3H), 1.11 – 1.00 (m, 18H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.7, 71.7, 66.2, 65.9, 55.0, 50.1, 48.6, 42.2, 42.0, 39.5, 29.3, 27.7, 26.9, 25.8, 18.3, 16.2, 12.2, -4.1, -4.7. **IR** (film) ν_{max} 2945, 2927, 2894, 2863, 1736, 1463, 1405, 1388, 1250, 1189, 1140, 1092, 1066, 1031 cm^{-1}.

$[\alpha]_D^{20}$ = -47.7° (c = 0.19 in $CHCl_3$). **HRMS** (ESI, m/z): $[M + Na]^+$ calcd for $C_{29}H_{54}O_4Si_2Na^+$ 545.3453, found 545.3458. R_f = 0.57 (silica gel, petroleum ether/acetone = 5:1).



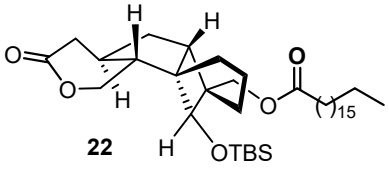
20

20: A colorless oil, 89% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 4.42 (dd, *J* = 10.4, 4.9 Hz, 1H), 4.10 (dd, *J* = 12.2, 10.5 Hz, 1H), 3.97 (d, *J* = 11.6 Hz, 1H), 3.91 (s, 1H), 3.85 (d, *J* = 11.6 Hz, 1H), 3.09 – 2.80 (m, 1H), 2.42 – 2.22 (m, 2H), 2.14 (dd, *J* = 10.9, 2.6 Hz, 1H), 2.12 – 2.06 (m, 1H), 2.05 (s, 3H), 1.96 – 1.83 (m, 1H), 1.78 – 1.66 (m, 2H), 1.66 – 1.54 (m, 4H), 1.43 – 1.27 (m, 1H), 0.88 (s, 9H), 0.03 (s, 3H), 0.03 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.1, 170.3, 71.3, 66.9, 66.8, 55.5, 48.6, 47.7, 42.0, 41.9, 39.5, 29.9, 29.1, 27.7, 26.6, 25.8, 21.1, 18.1, 16.0, -4.3, -4.8. **IR** (film) ν_{max} 2952, 2928, 2856, 1736, 1470, 1383, 1236, 1191, 1143, 1031 cm^{-1}. $[\alpha]_D^{20}$ = -84.4° (c = 0.09 in CHCl3). HRMS (ESI, m/z): $[M + Na]^+$ calcd for $C_{22}H_{36}O_5SiNa^+$ 431.2224, found 431.2239. R*f* = 0.54 (silica gel, petroleum ether/acetone = 5:1).



21

21: A colorless oil, 92% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 4.42 (dd, *J* = 10.4, 5.0 Hz, 1H), 4.10 (dd, *J* = 12.2, 10.4 Hz, 1H), 3.98 (d, *J* = 11.6 Hz, 1H), 3.92 (s, 1H), 3.84 (d, *J* = 11.6 Hz, 1H), 3.00 – 2.83 (m, 1H), 2.40 – 2.22 (m, 4H), 2.14 (dd, *J* = 10.8, 2.5 Hz, 1H), 2.11 – 2.02 (m, 2H), 1.92 – 1.82 (m, 1H), 1.78 – 1.65 (m, 2H), 1.65 – 1.60 (m, 2H), 1.60 – 1.55 (m, 2H), 1.55 – 1.48 (m, 2H), 1.40 – 1.28 (m, 1H), 0.91 (s, 3H), 0.89 (s, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.0, 170.3, 71.3, 66.7, 66.6, 55.4, 48.5, 47.8, 42.0, 41.9, 39.4, 34.0, 32.5, 29.2, 27.8, 26.6, 25.8, 22.4, 18.1, 16.0, -4.3, -4.8. **IR** (film) $\boldsymbol{\nu}_{max}$ 2953, 2928, 2857, 1735, 1470, 1326, 1250, 1188, 1144, 1119, 1071, 1031 cm^{-1}. $[\alpha]_D^{20}$ = -58.7° (c = 0.17 in $CHCl_3$). **HRMS** (ESI, m/z): $[M + Na]^+$ calcd for $C_{26}H_{44}O_5SiNa^+$ 487.2850, found 487.2855. $\mathbf{R_f}$ = 0.47 (silica gel, petroleum ether/acetone = 3:1).



22

22: A colorless oil, 71% yield. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 4.40 (dd, *J* = 10.4, 5.0 Hz, 1H), 4.08 (dd, *J* = 12.2, 10.4 Hz, 1H), 3.96 (d, *J* = 11.6 Hz, 1H), 3.90 (s, 1H), 3.82 (d, *J* = 11.6 Hz, 1H), 2.99 – 2.78 (m, 1H), 2.39 – 2.23 (m, 5H), 2.19 – 1.99 (m, 3H), 1.93 – 1.78 (m, 1H), 1.77 – 1.64 (m, 2H), 1.64 – 1.51 (m, 5H), 1.23 (s, 28H), 0.86 (s, 12H), 0.01 (s, 3H), 0.00 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.9, 170.3, 71.3, 66.7, 66.5, 55.4, 48.6, 47.8, 42.0, 41.9, 39.4, 34.5, 33.9, 32.1, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 27.8, 26.6, 25.8, 25.2, 24.9, 22.8, 18.1, 16.0, 14.3, -4.3, -4.8. **IR** (film) ν_{max} 2921, 2851, 1736, 1465, 1250, 1188, 1143, 1118, 1071, 1031 cm^{-1}. $[\alpha]_D^{20}$ = -22.4° (c = 0.25 in $CHCl_3$). **HRMS** (ESI, m/z): $[M + Na]^+$ calcd for $C_{38}H_{68}O_5SiNa^+$ 655.4728, found 655.4741. R_f = 0.67 (silica gel, petroleum ether/acetone = 3:1).

3. The cytotoxicity test

Cell Lines and Culture Methods. A549 and HepG2 cell lines were cultured in RPMI-1640 (KeyGen BioTECH, KGM31800H-500) medium supplemented with 10% (v/v) fetal bovine serum (FBS, CELLMAX, SA311.02) and 1% (v/v) penicillin−streptomycin. MDA-MB-231 and L-02 cells were cultured in DMEM (KeyGen BioTECH, KGM12800-500) supplemented with 10% (v/v) FBS and 1% (v/v) penicillin−streptomycin. All cells were grown in a humidified incubator at 37 °C and 5% CO_2.

Cell Growth Inhibition Assays. Cells were grown at 37 °C, under 95% air and 5% CO_2 until about reaching 70% confluency, and subcultured at least twice before the experiment. Cells were seeded in 96-well plates at the individual density in 100 µL of culture medium for 24 h. The cell seeding numbers for individual cell lines were as follows: A549 (2500/well), HepG2 (1500/well), MDA-MB-231 (2800/well) and L-02 (800/well). Compounds were prepared as a 10 mM stock solution in 100% DMSO, and each compound of final gradient concentrations from 1 uM to 84 µM was added to each well. After 72 h, cell viability was assessed by 3-(4,5-dimethythiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay. Briefly, 40 µL MTT (2.5 mg/mL in PBS, KeyGen BioTECH) was added to each well and incubated for 3~4 h, then the medium was discarded and replaced with 150 µL dimethyl sulfoxide (DMSO, Sigma–Aldrich). The plates were shaken for 10 min for mixing and the absorbance was read at 490 nm via the microplate reader (ALLSHENG). The readings were normalized to the DMSO-treated cells, and the IC_{50} was calculated by nonlinear regression analysis using GraphPad Prism 8 software.

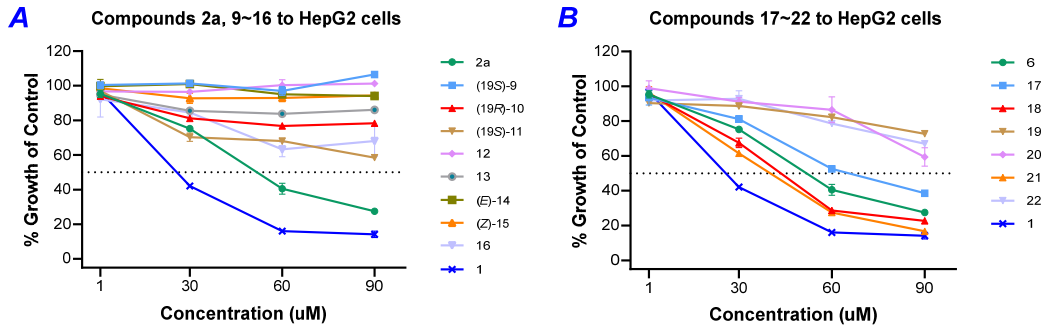


Figure 1. Cytotoxicity assessment of PA derivatives 2a, 9~16 (*A*) and 17~22 (*B*). HepG2 Cells were treated with indicated doses for 3 days. Cell viability was determined by the MTT assay.

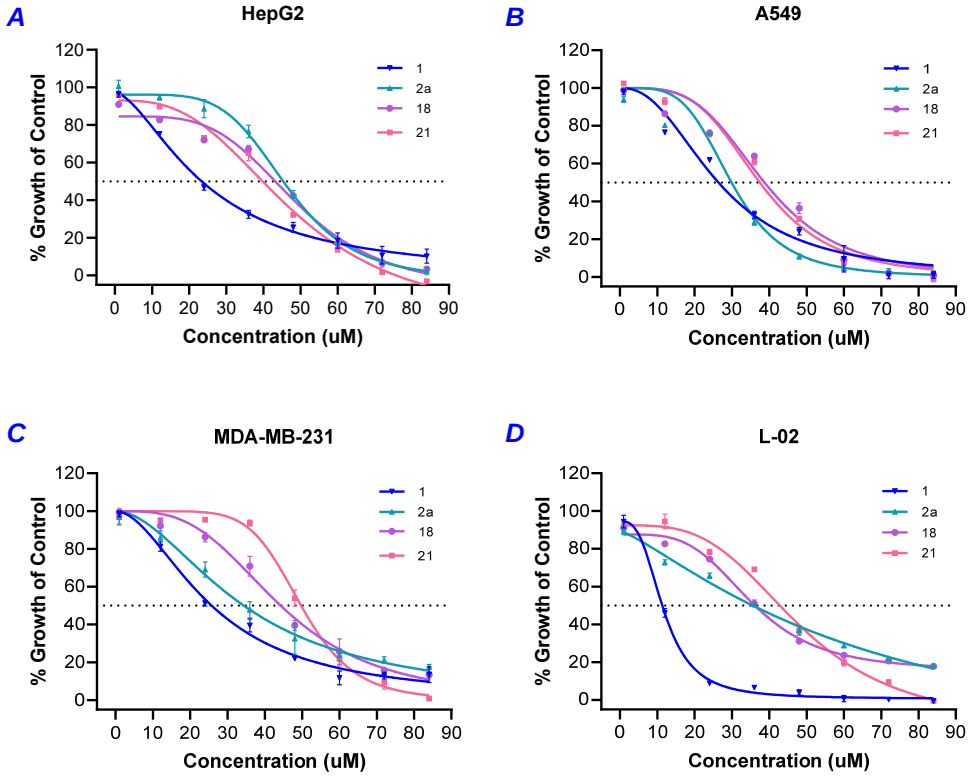
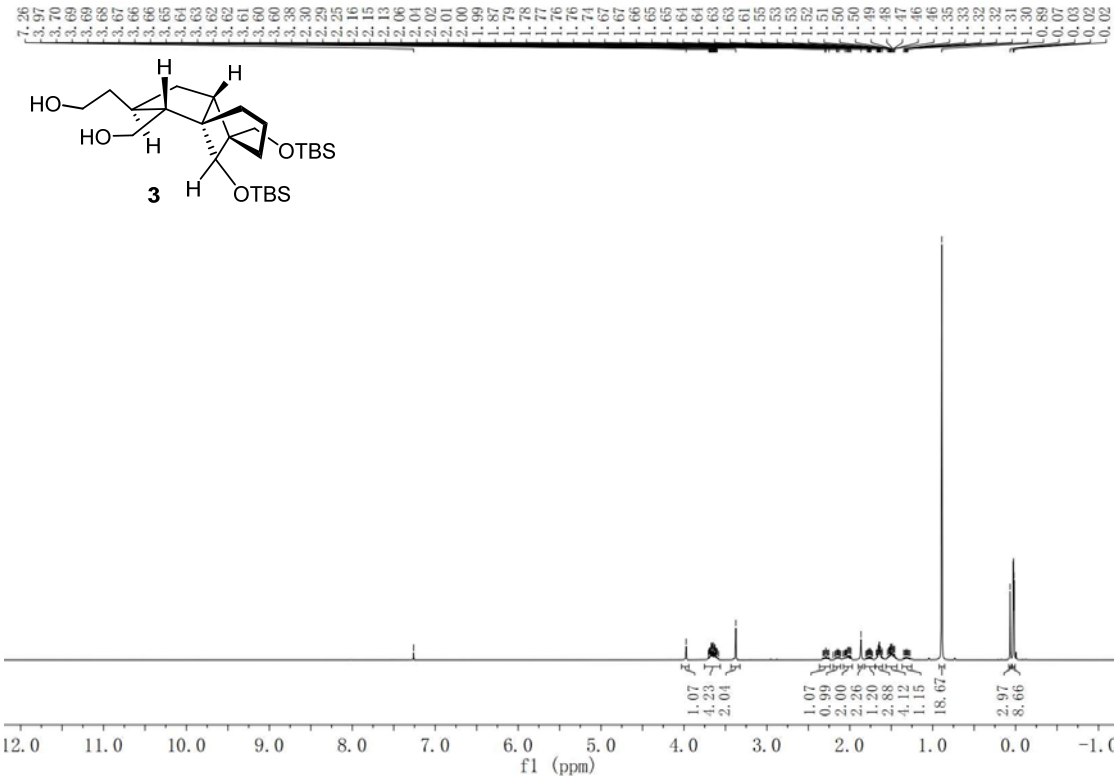


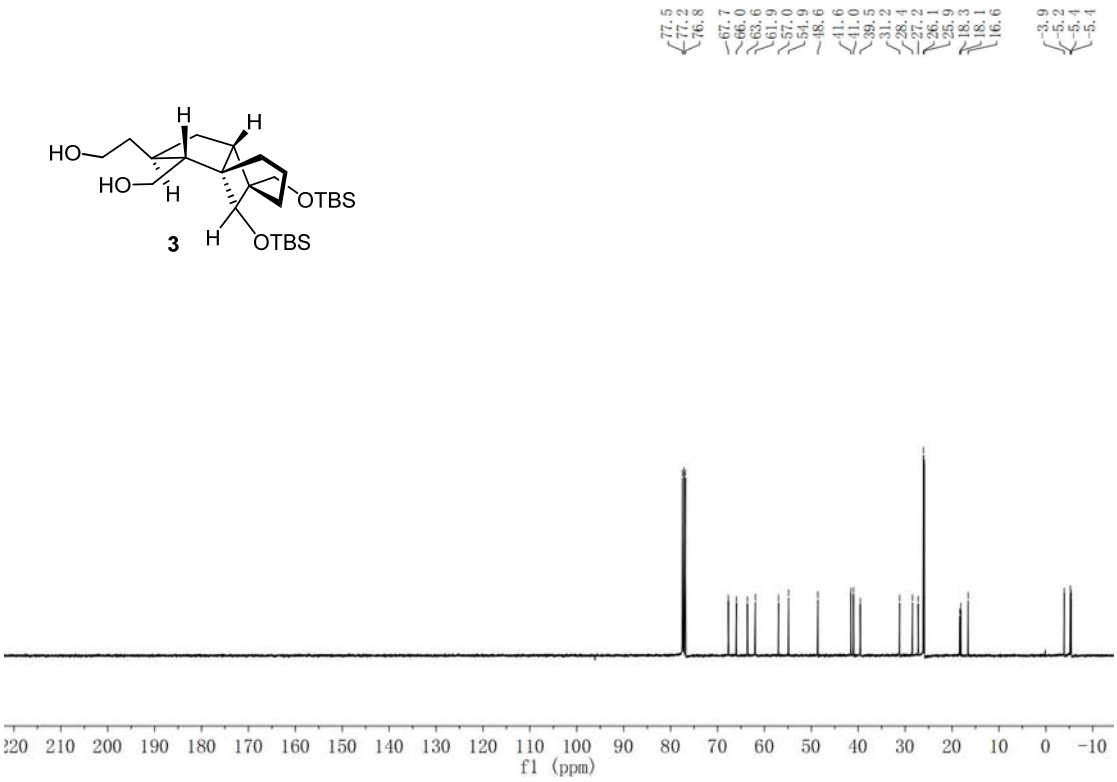
Figure 2. HepG2 (*A*), A549 (*B*), MDA-MB-231 (*C*) cancer Cells, and L-02 (*D*) normal cells were incubated with increasing concentrations of PA derivatives, and growth over 72 h was assessed by the MTT assay.

4. NMR spectral copies

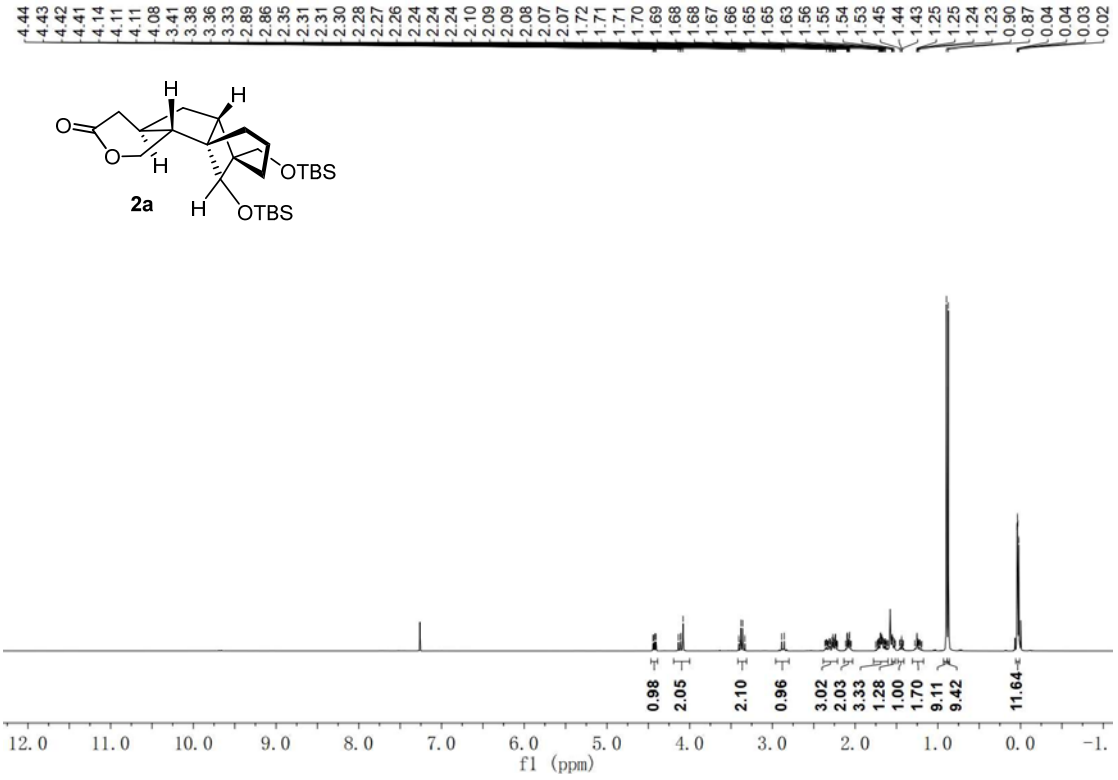
^{1}H NMR Spectrum of 3 (400 MHz, $CDCl_3$)



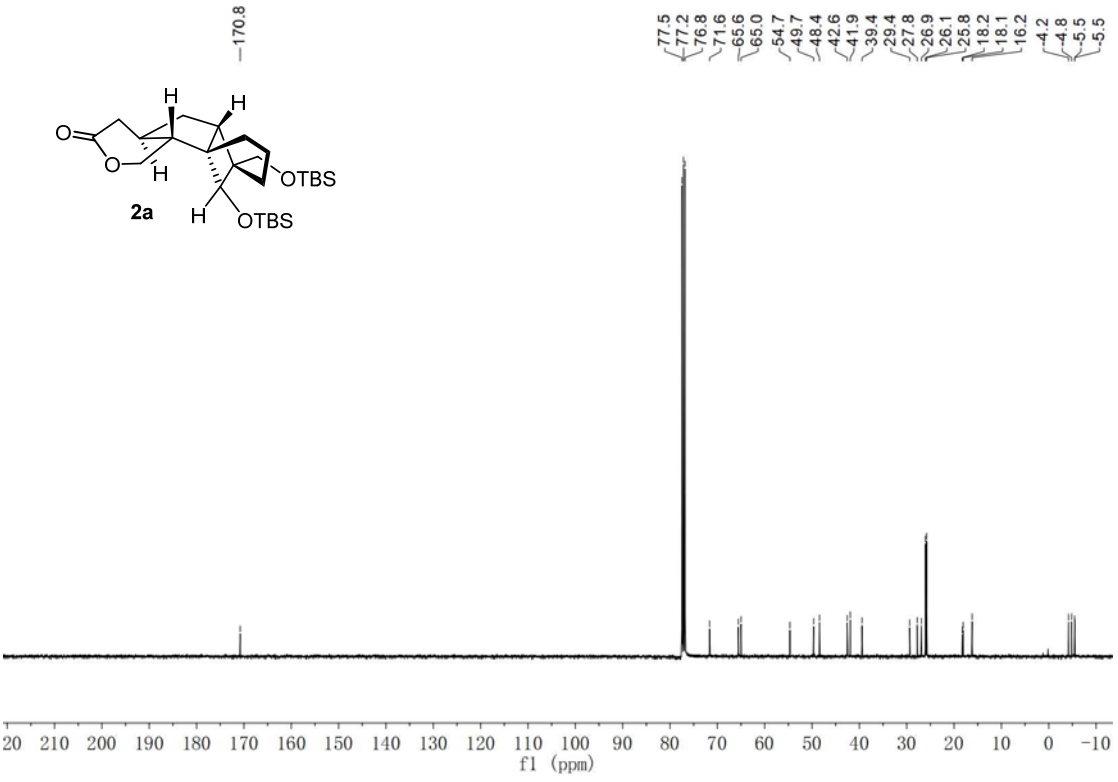
^{13}C NMR Spectrum of 3 (101 MHz, $CDCl_3$)



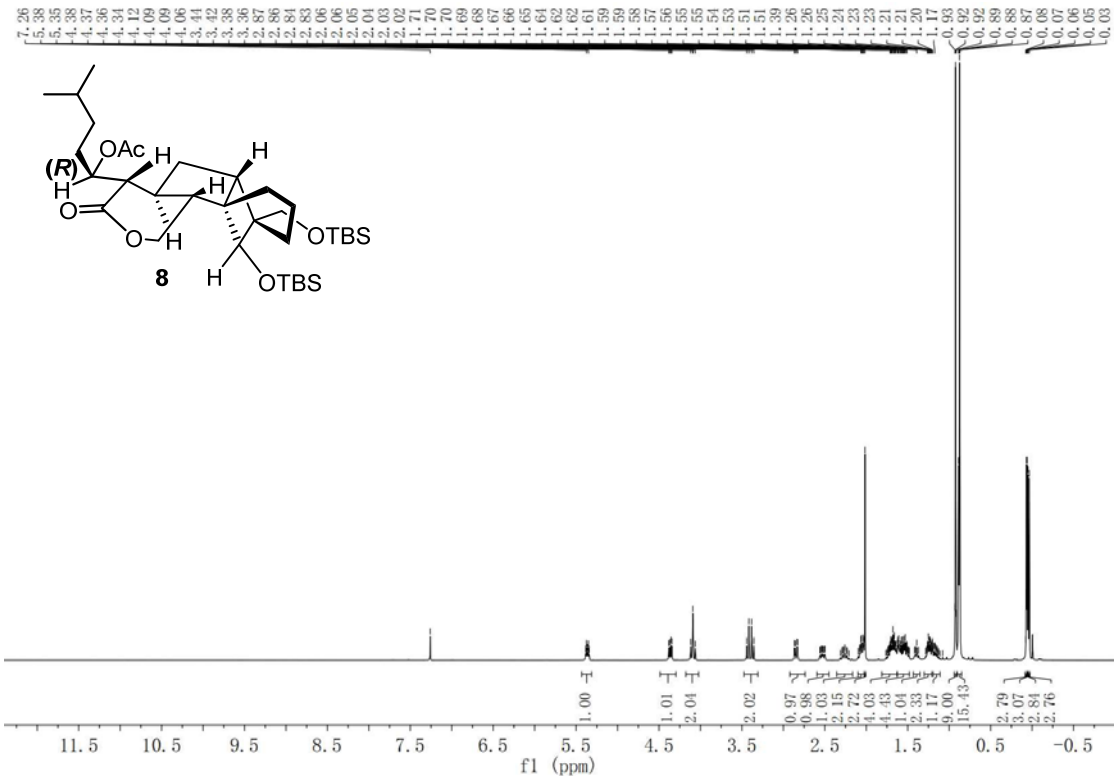
^{1}H NMR Spectrum of 2a (400 MHz, $CDCl_3$)



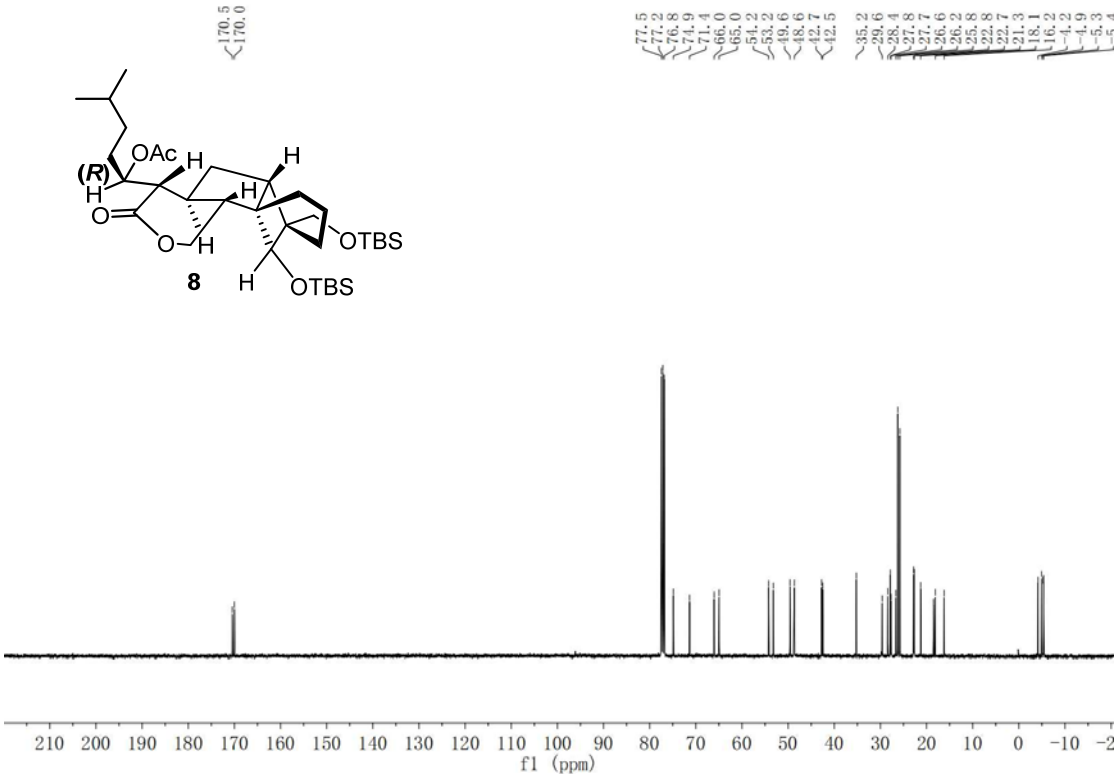
^{13}C NMR Spectrum of 2a (101 MHz, $CDCl_3$)



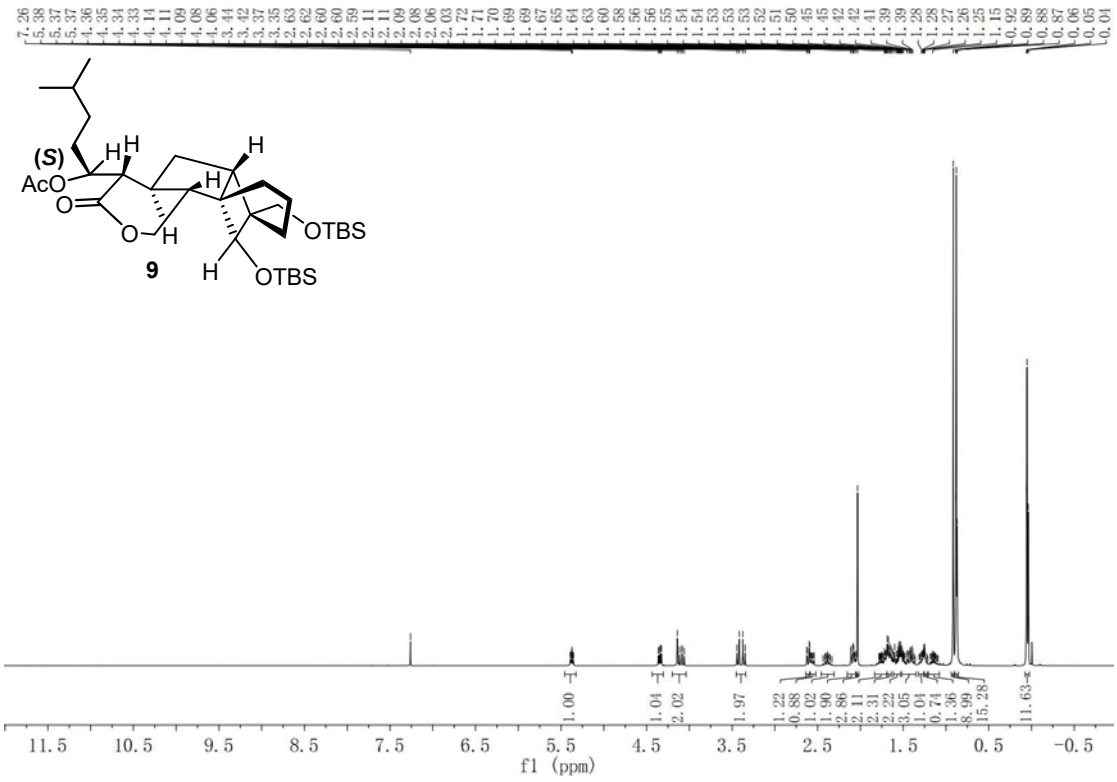
^{1}H NMR Spectrum of 8 (400 MHz, $CDCl_3$)



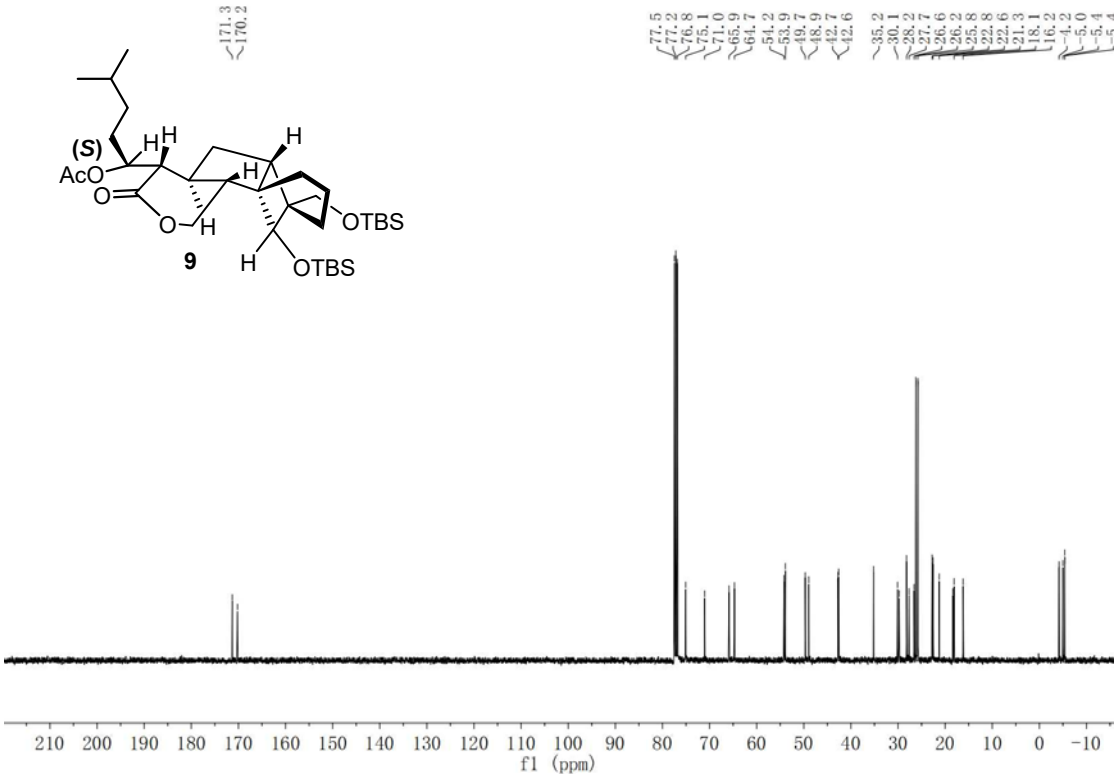
^{13}C NMR Spectrum of 8 (101 MHz, $CDCl_3$)



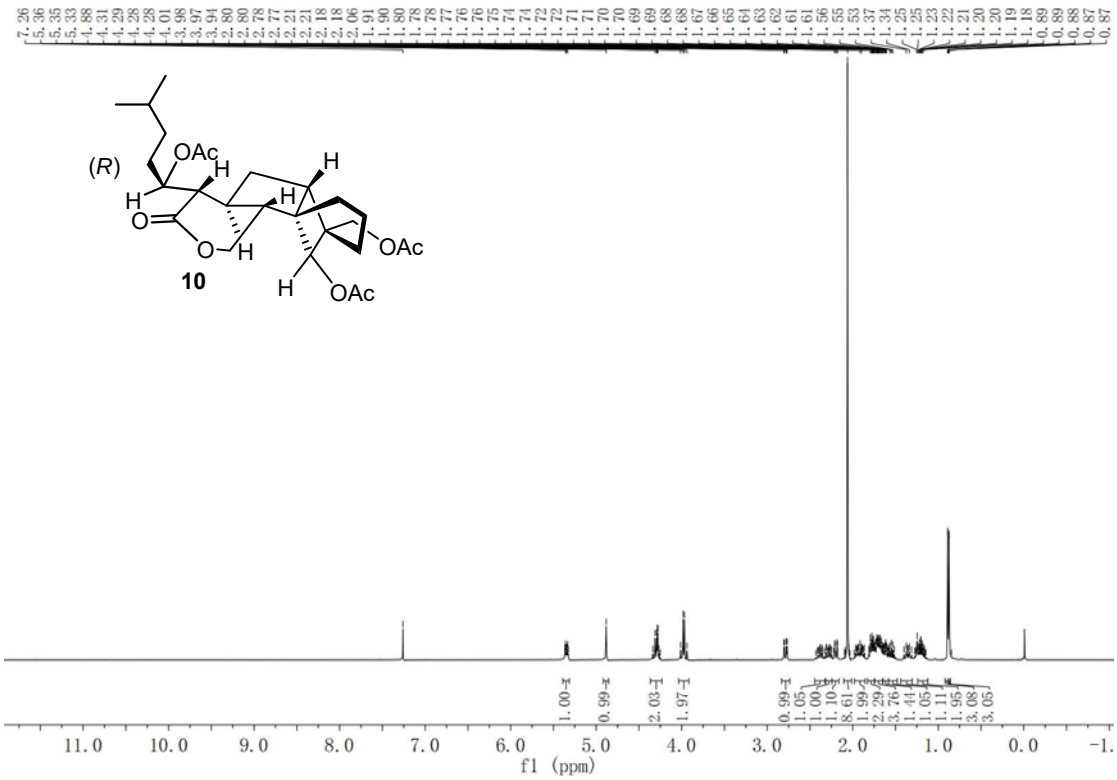
^{1}H NMR Spectrum of 9 (400 MHz, $CDCl_3$)



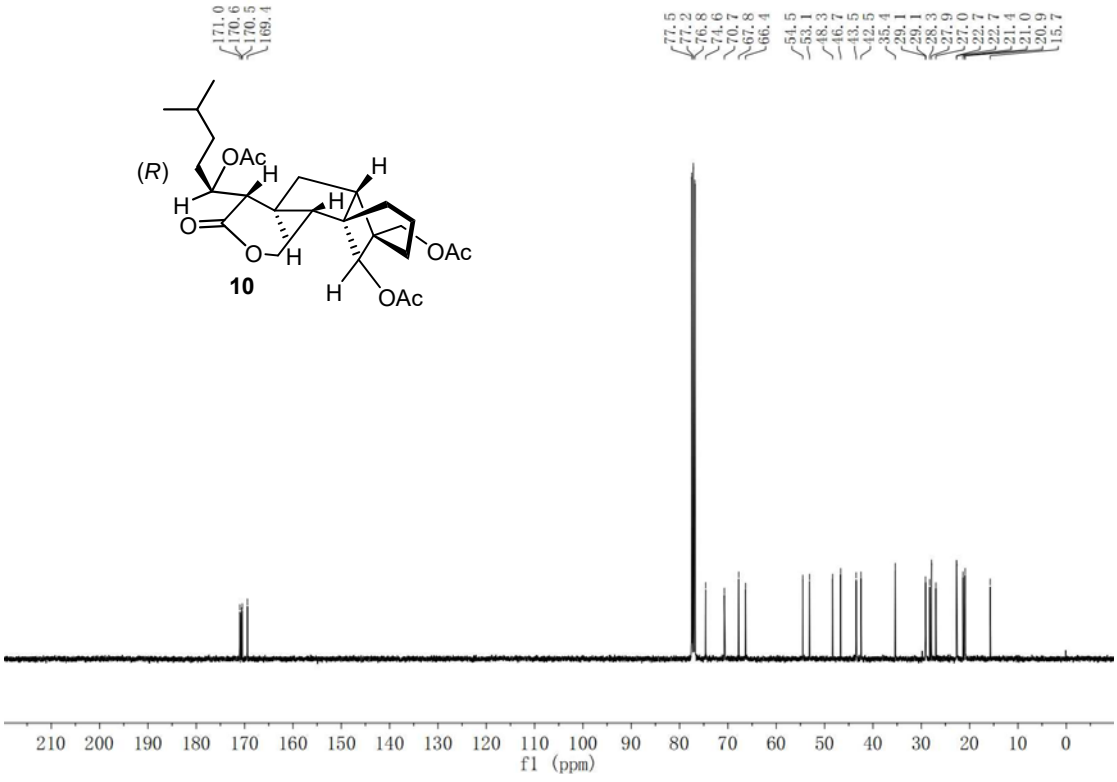
^{13}C NMR Spectrum of 9 (101 MHz, $CDCl_3$)



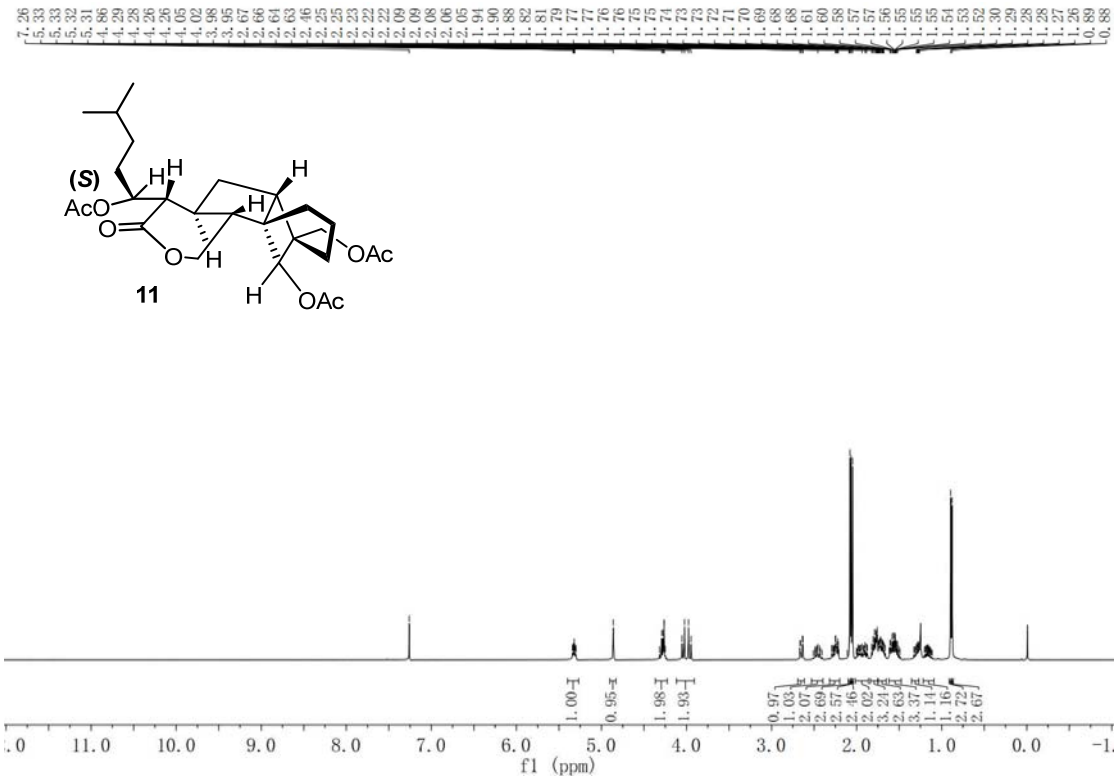
^{1}H NMR Spectrum of 10 (400 MHz, $CDCl_3$)



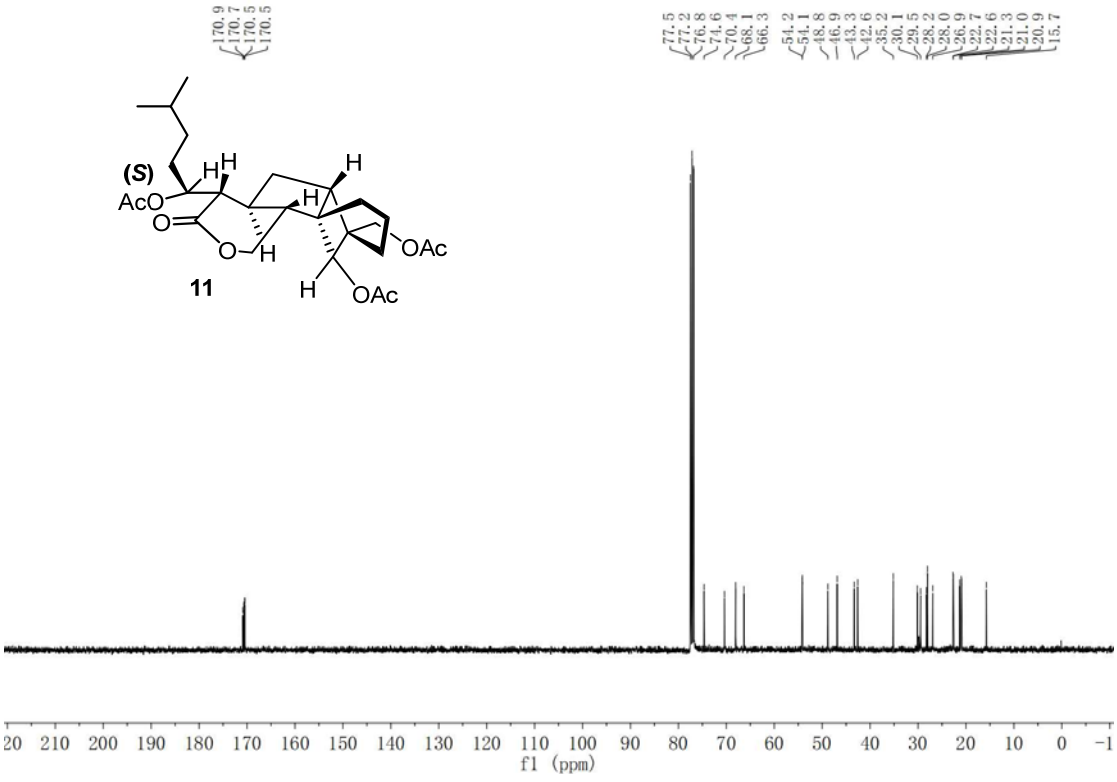
^{13}C NMR Spectrum of 10 (101 MHz, $CDCl_3$)



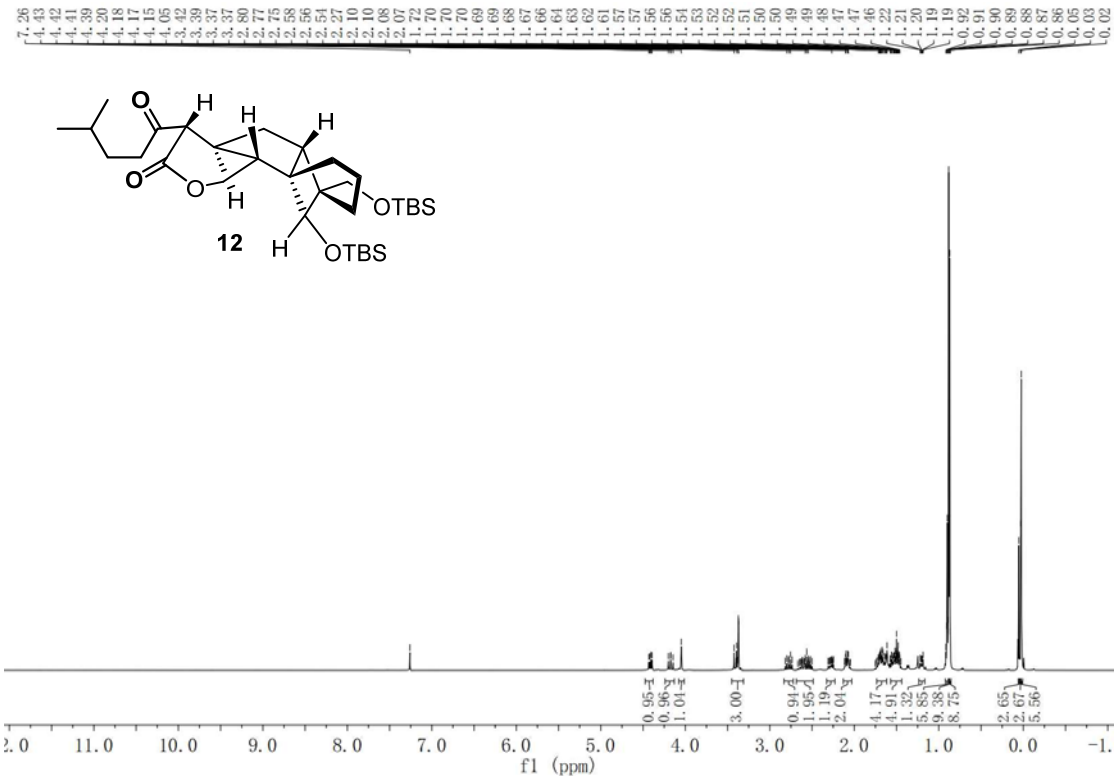
^{1}H NMR Spectrum of 11 (400 MHz, $CDCl_3$)



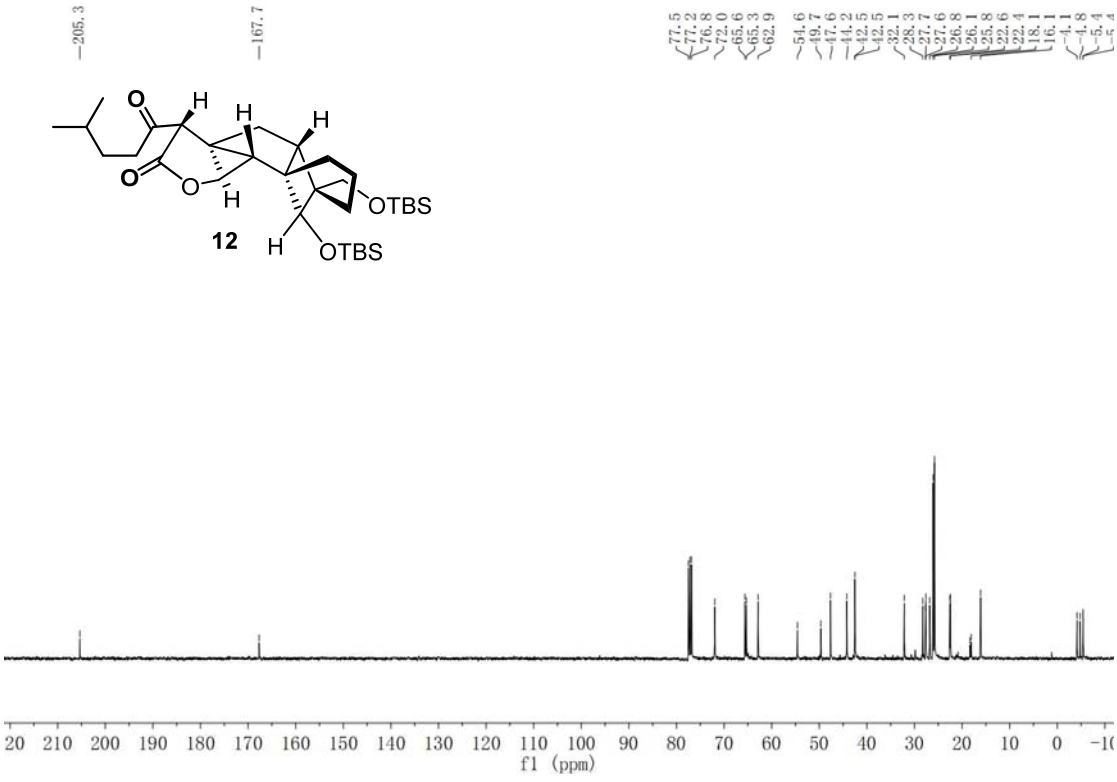
^{13}C NMR Spectrum of 11 (101 MHz, $CDCl_3$)



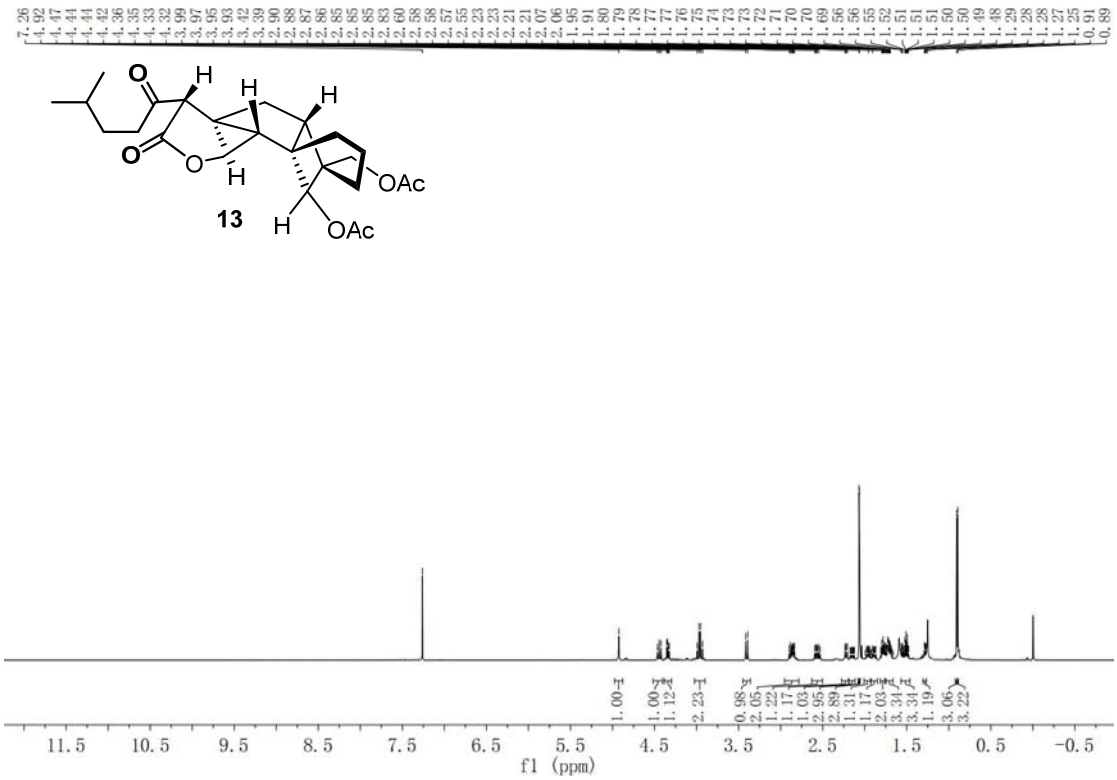
^{1}H NMR Spectrum of 12 (400 MHz, $CDCl_3$)



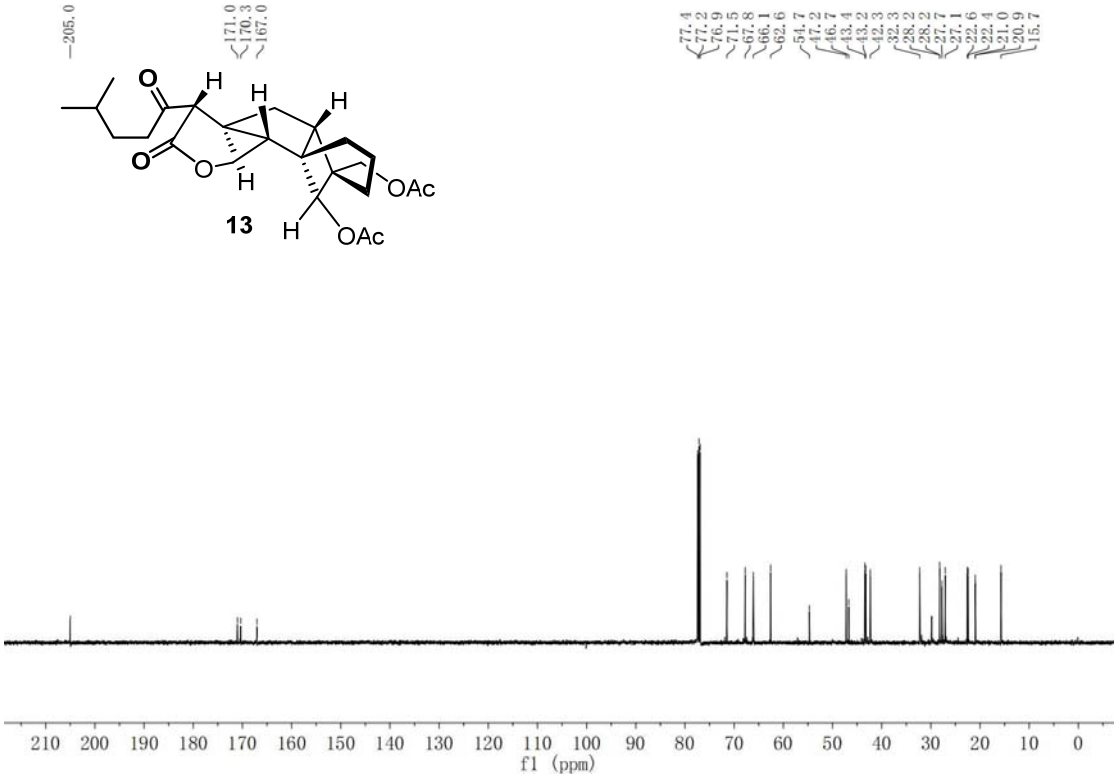
^{13}C NMR Spectrum of 12 (101 MHz, $CDCl_3$)



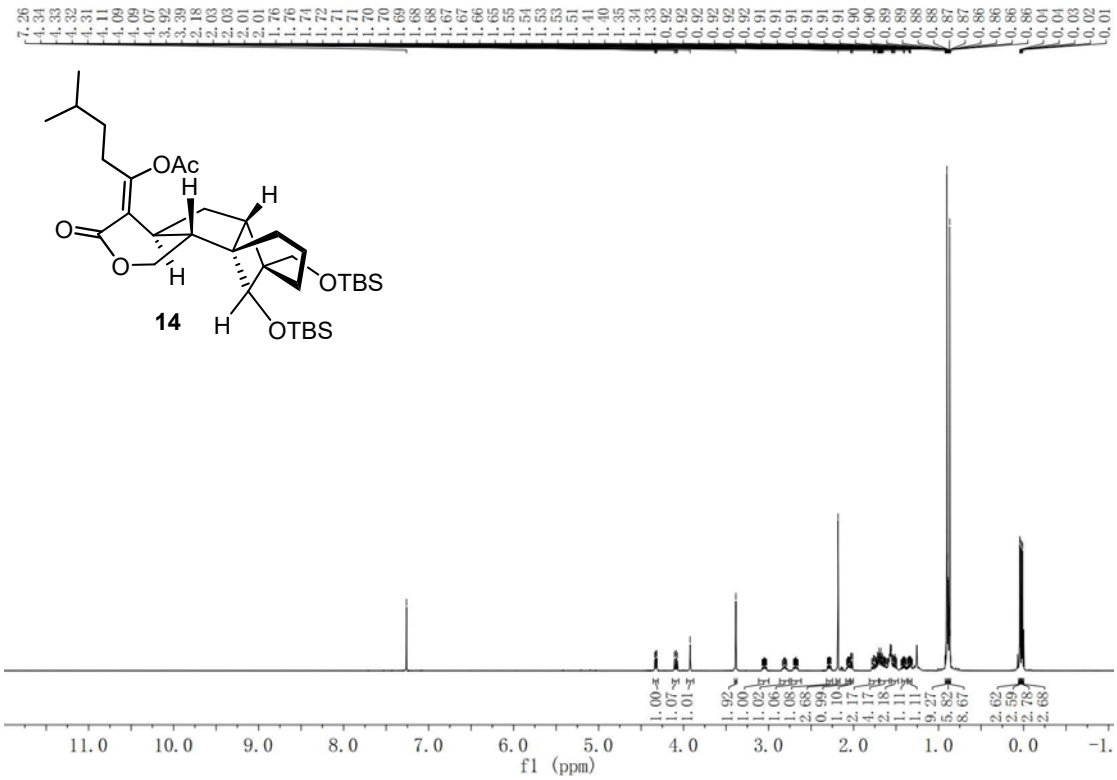
^{1}H NMR Spectrum of 13 (500 MHz, $CDCl_3$)



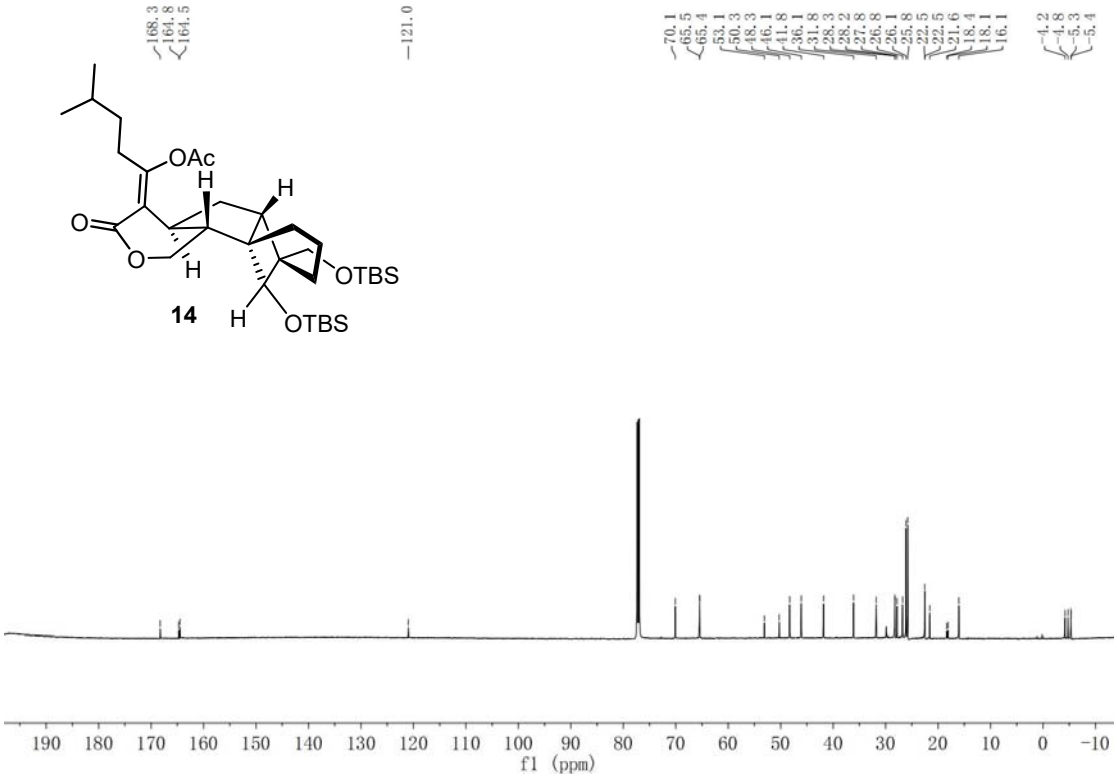
^{13}C NMR Spectrum of 13 (126 MHz, $CDCl_3$)



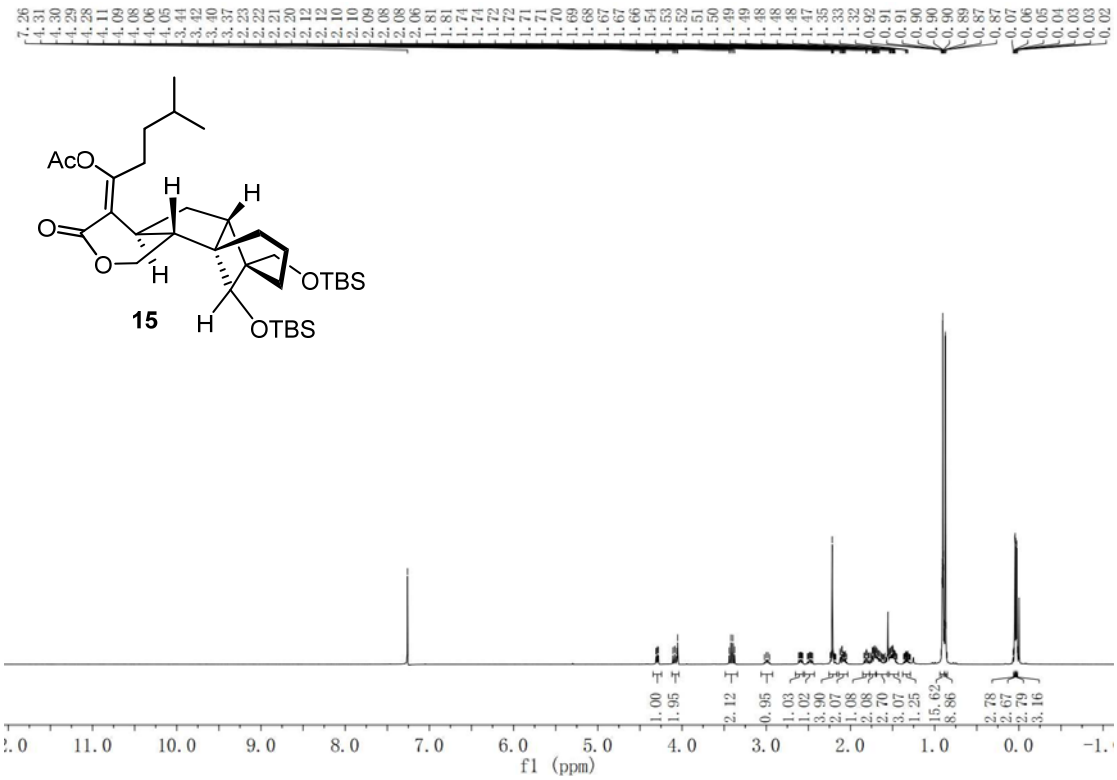
^{1}H NMR Spectrum of 14 (600 MHz, $CDCl_3$)



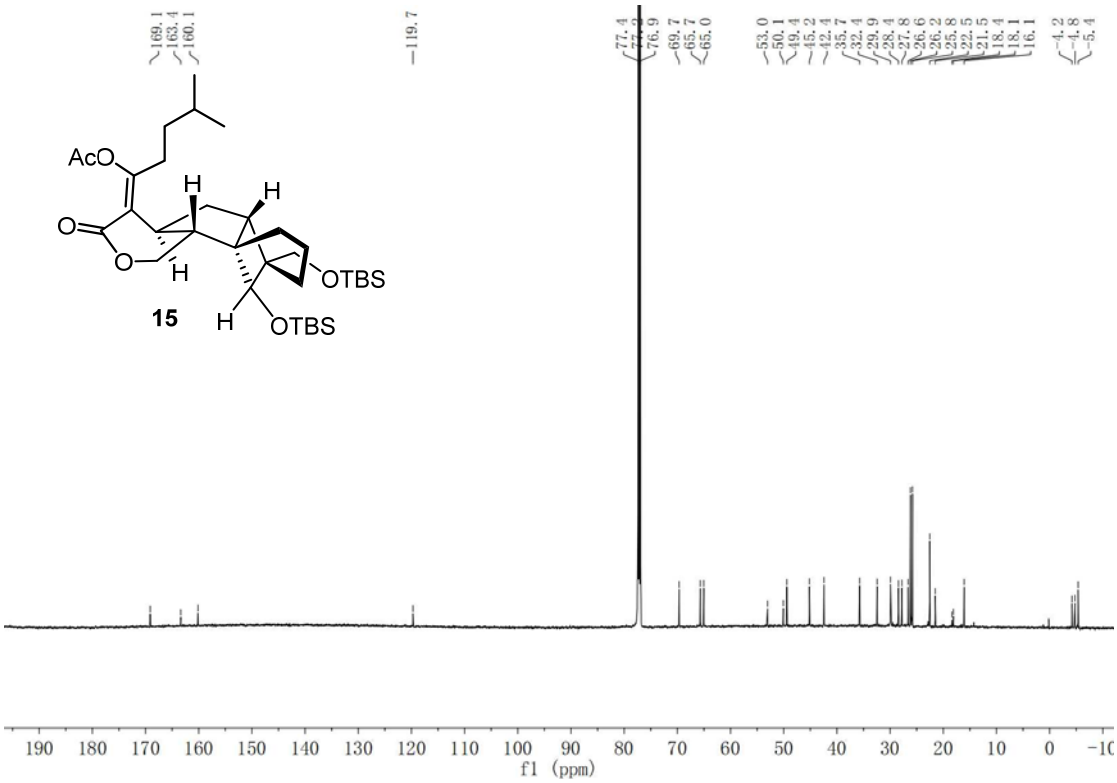
^{13}C NMR Spectrum of 14 (151 MHz, $CDCl_3$)



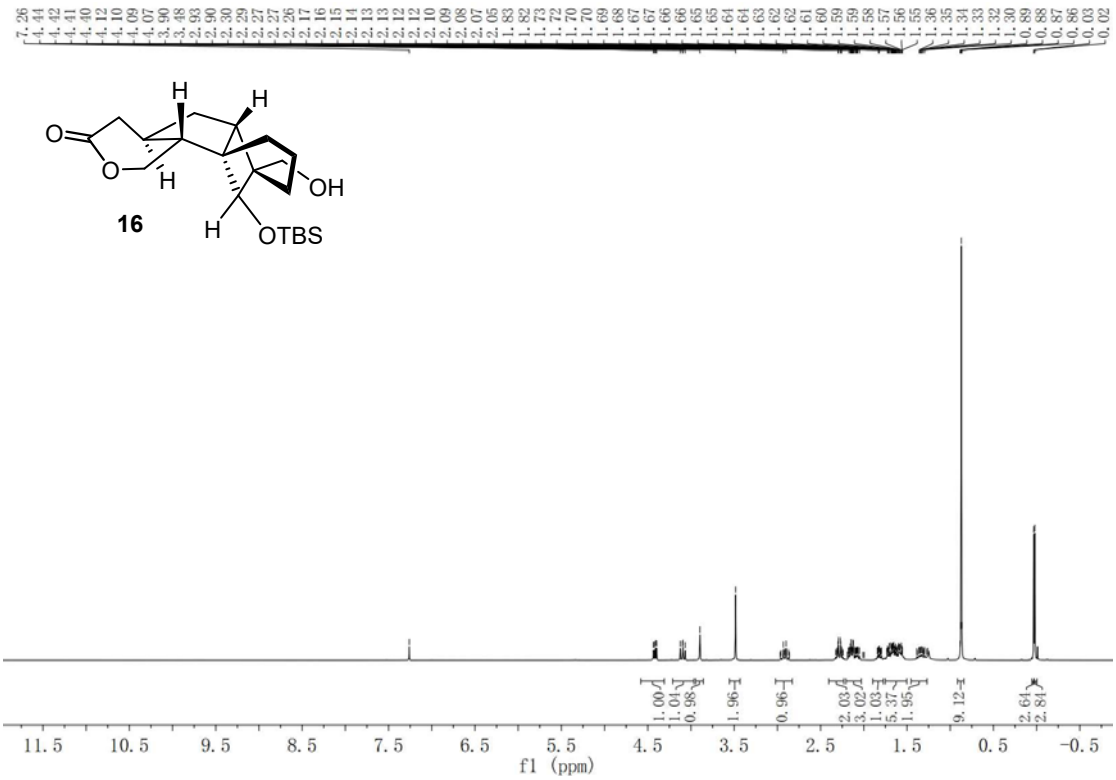
^{1}H NMR Spectrum of 15 (500 MHz, $CDCl_3$)



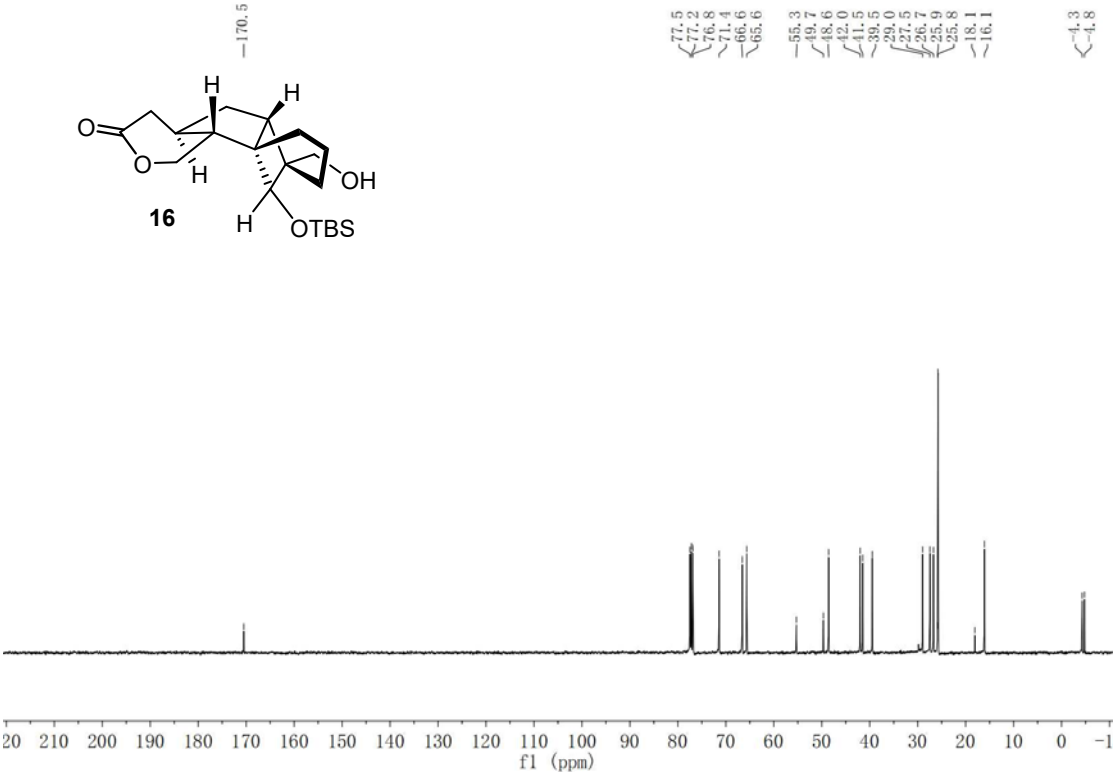
^{13}C NMR Spectrum of 15 (151 MHz, $CDCl_3$)



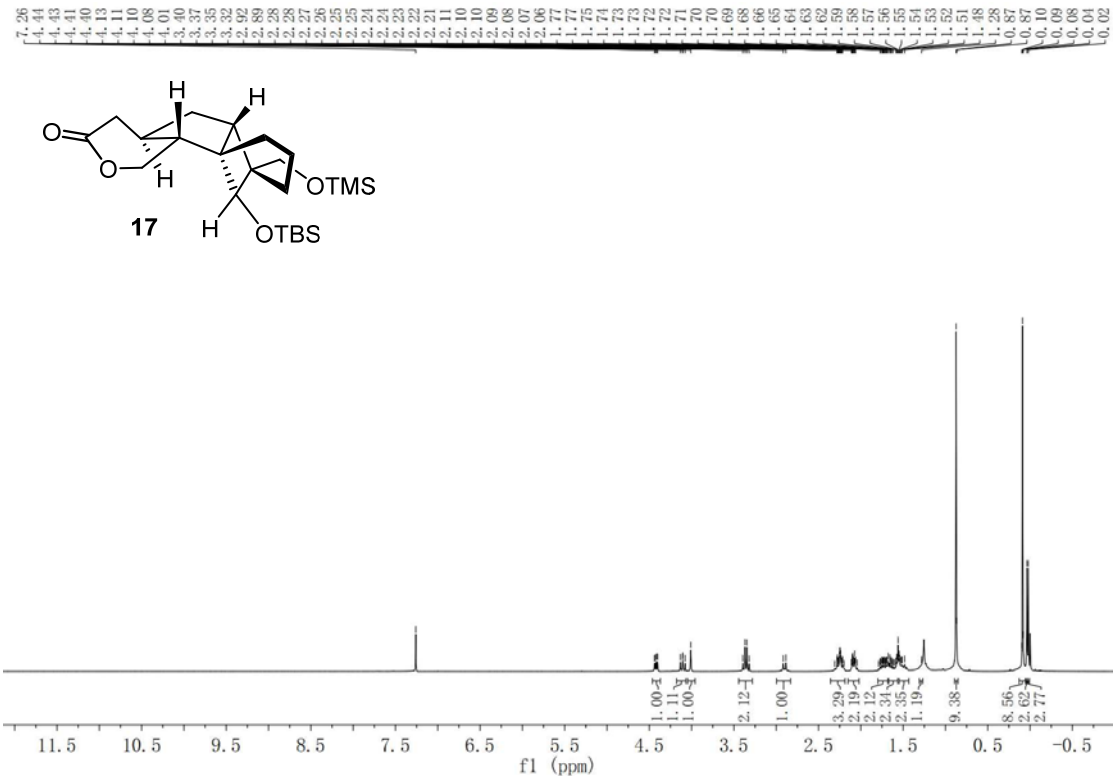
^{1}H NMR Spectrum of 16 (400 MHz, $CDCl_3$)



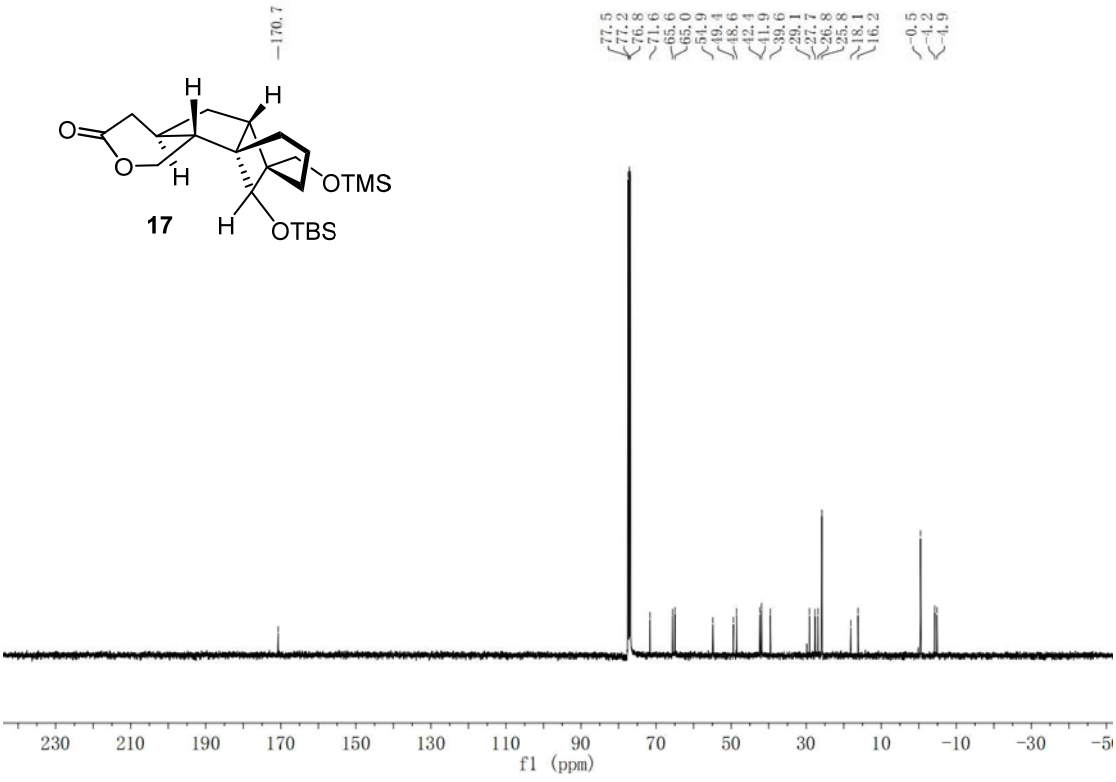
^{13}C NMR Spectrum of 16 (101 MHz, $CDCl_3$)



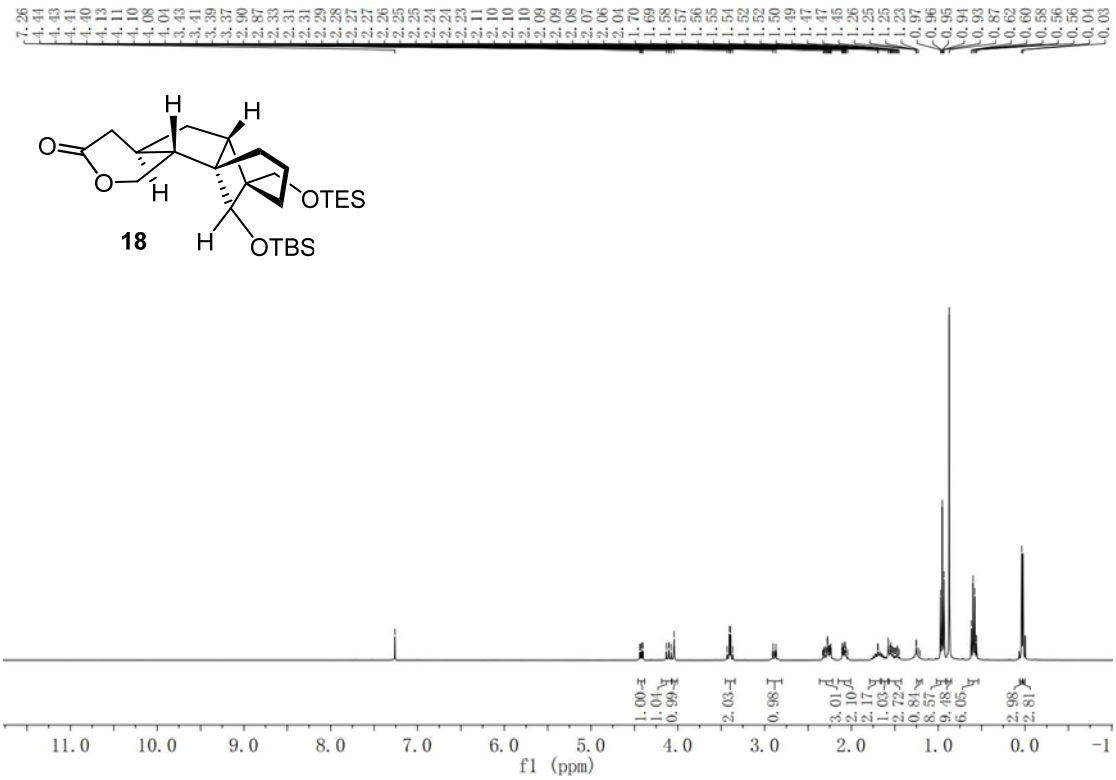
^{1}H NMR Spectrum of 17 (400 MHz, $CDCl_3$)



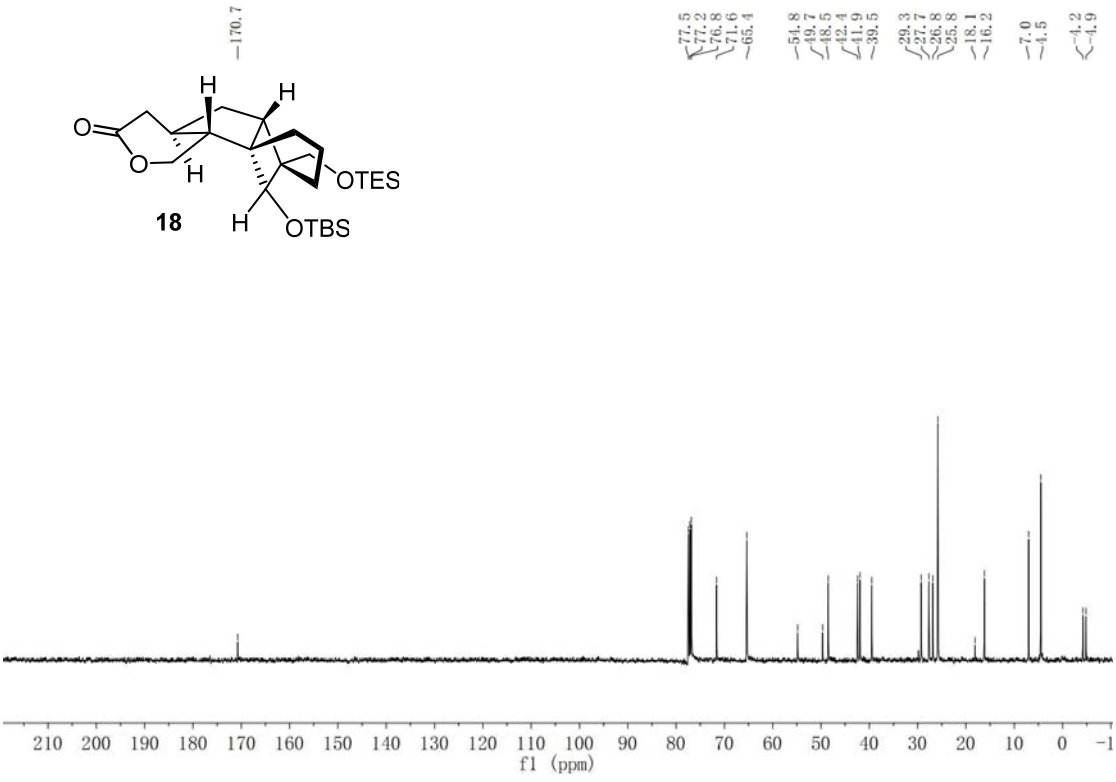
^{13}C NMR Spectrum of 17 (101 MHz, $CDCl_3$)



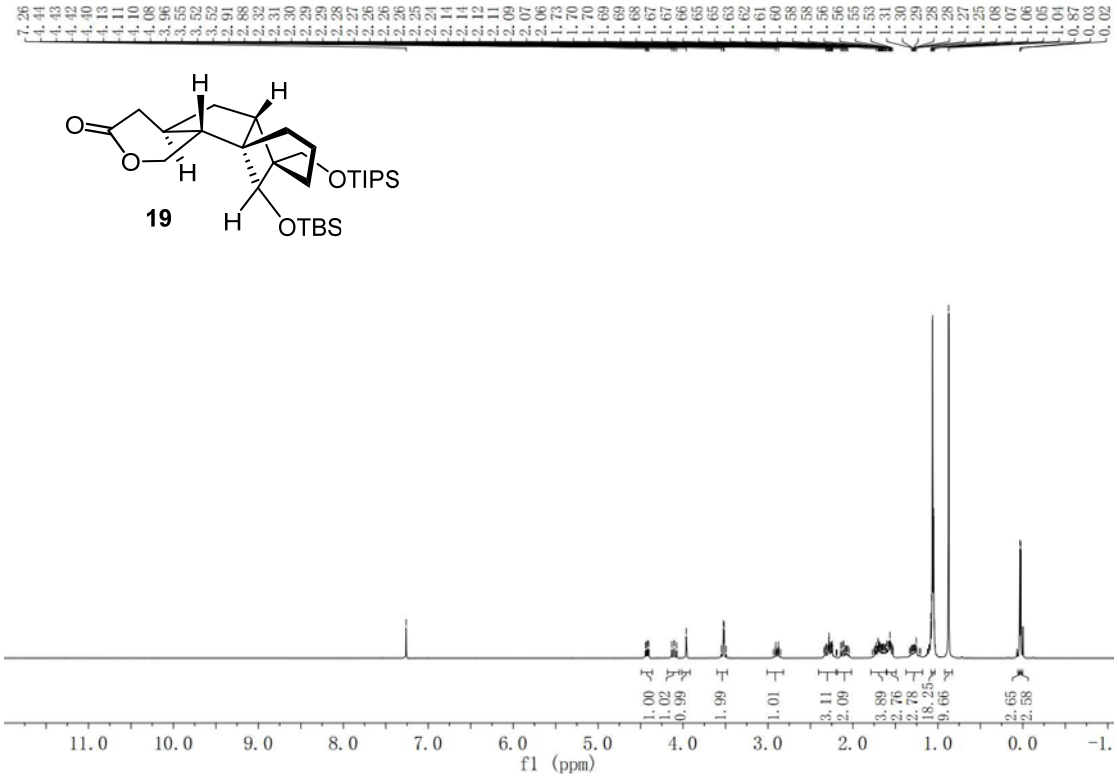
^{1}H NMR Spectrum of 18 (400 MHz, $CDCl_3$)



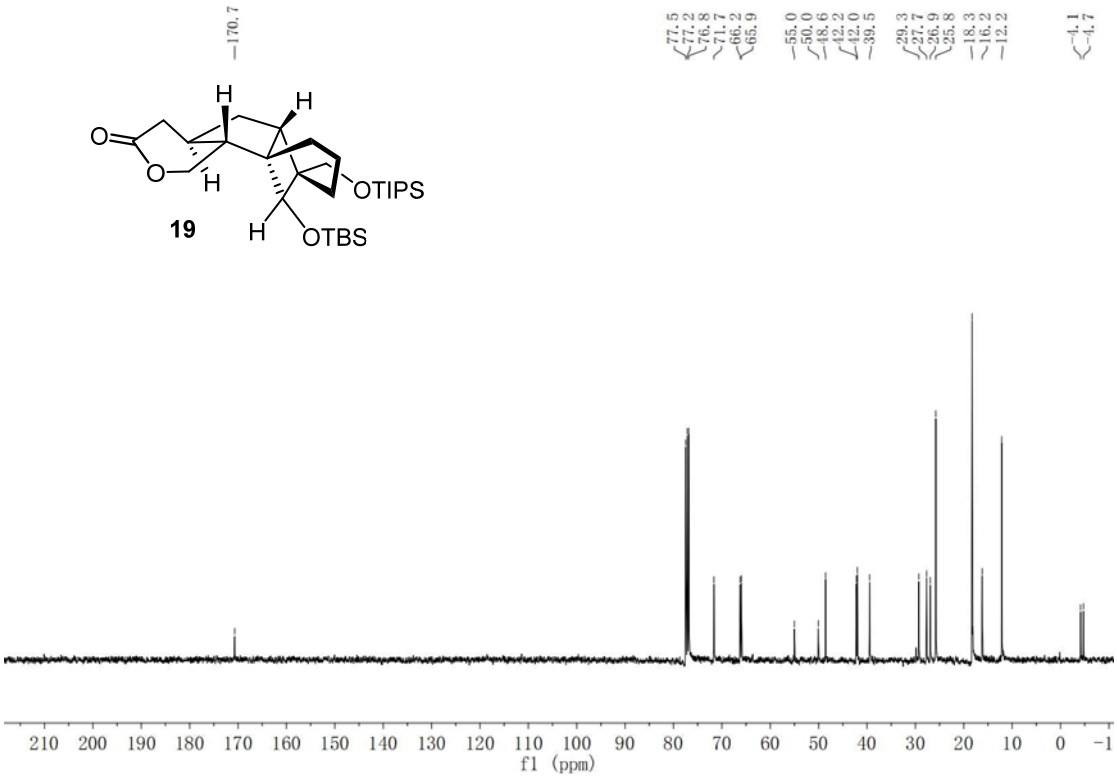
^{13}C NMR Spectrum of 18 (101 MHz, $CDCl_3$)



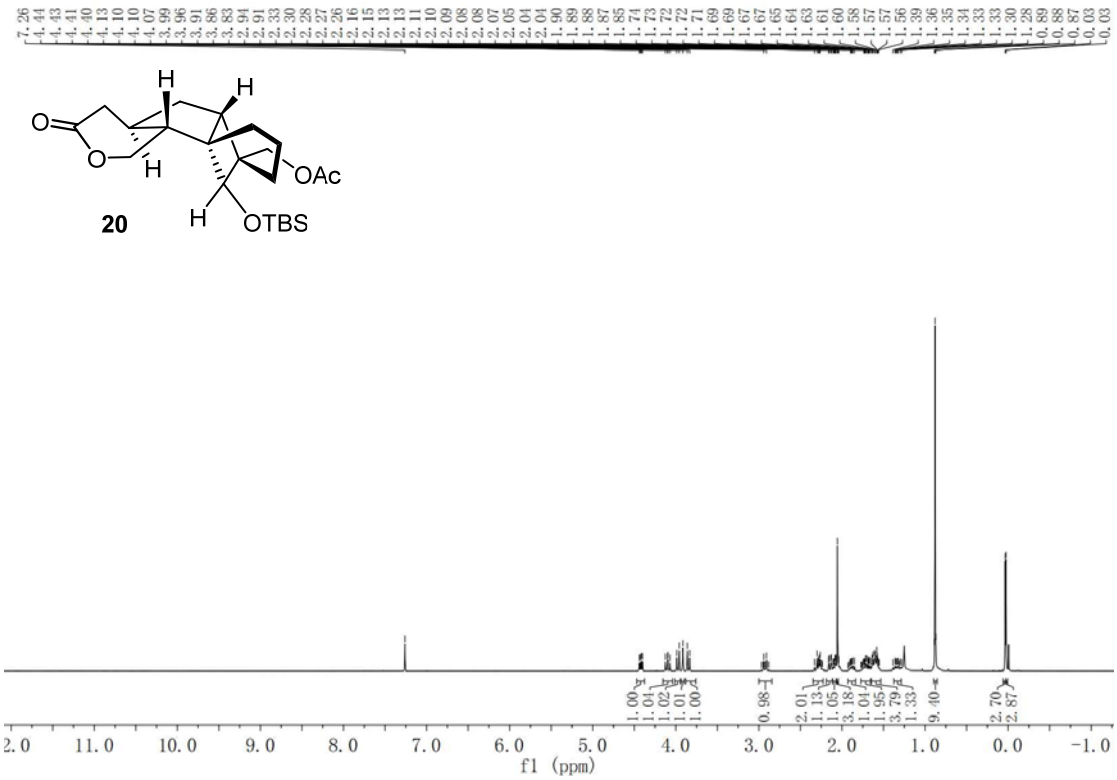
^{1}H NMR Spectrum of 19 (400 MHz, $CDCl_3$)



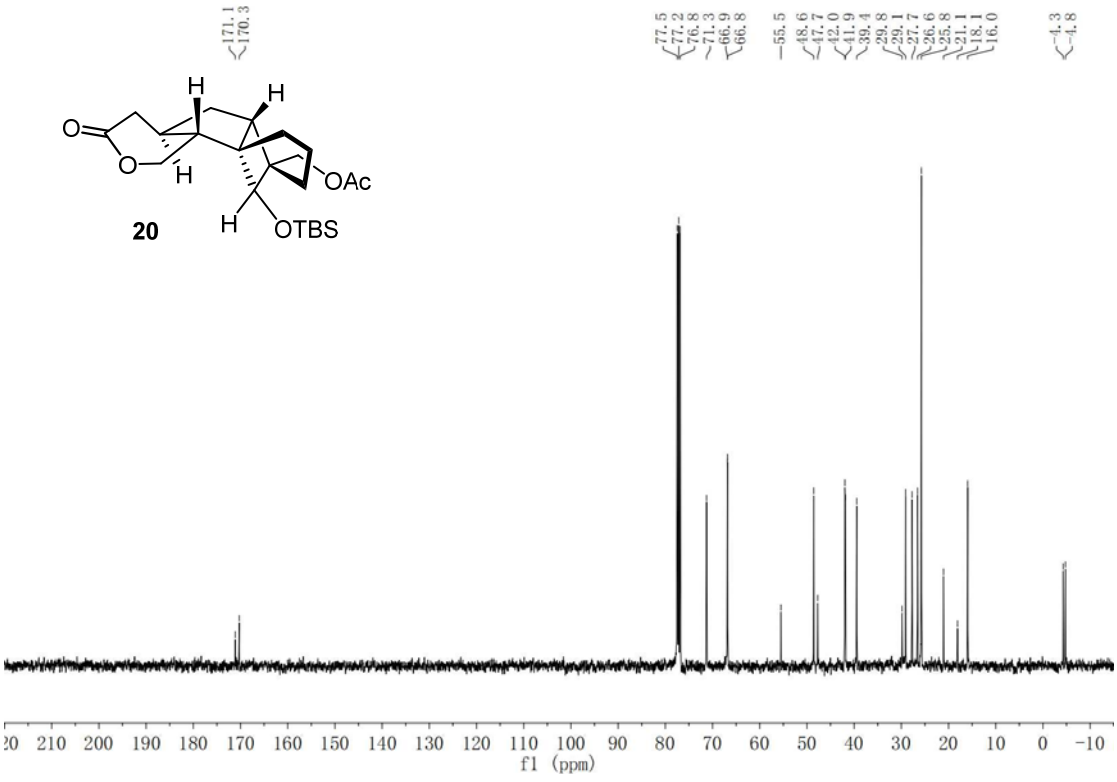
^{13}C NMR Spectrum of 19 (101 MHz, $CDCl_3$)



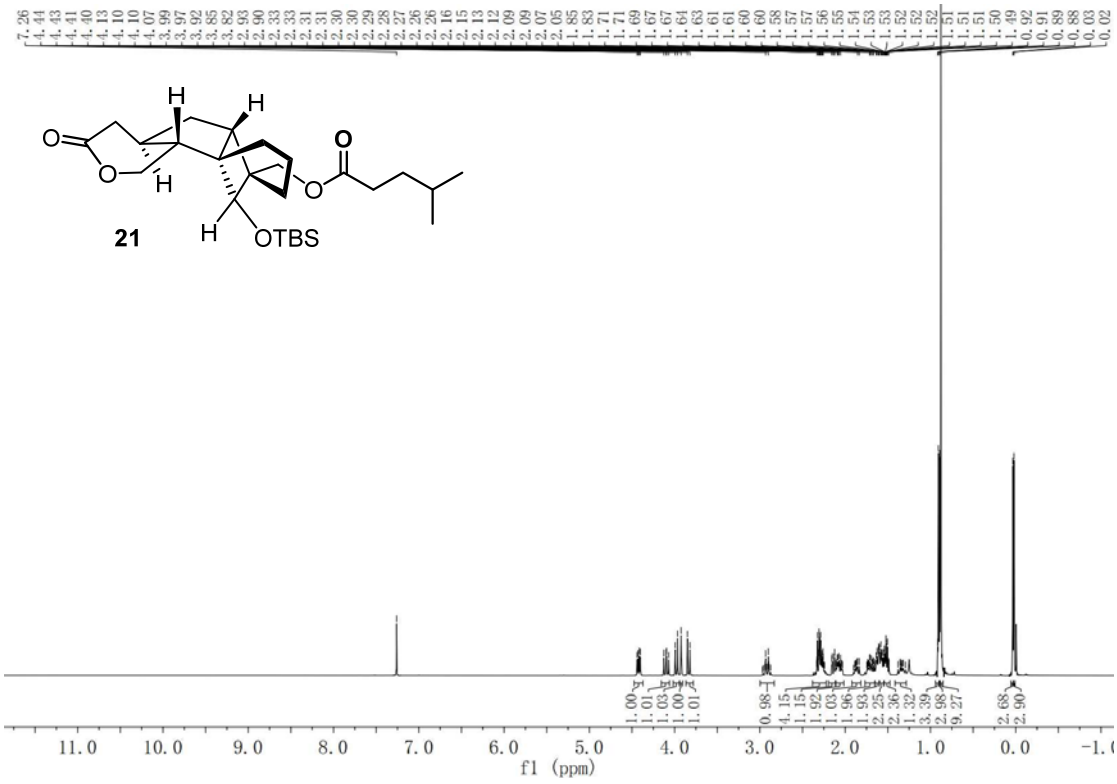
^{1}H NMR Spectrum of 20 (400 MHz, $CDCl_3$)



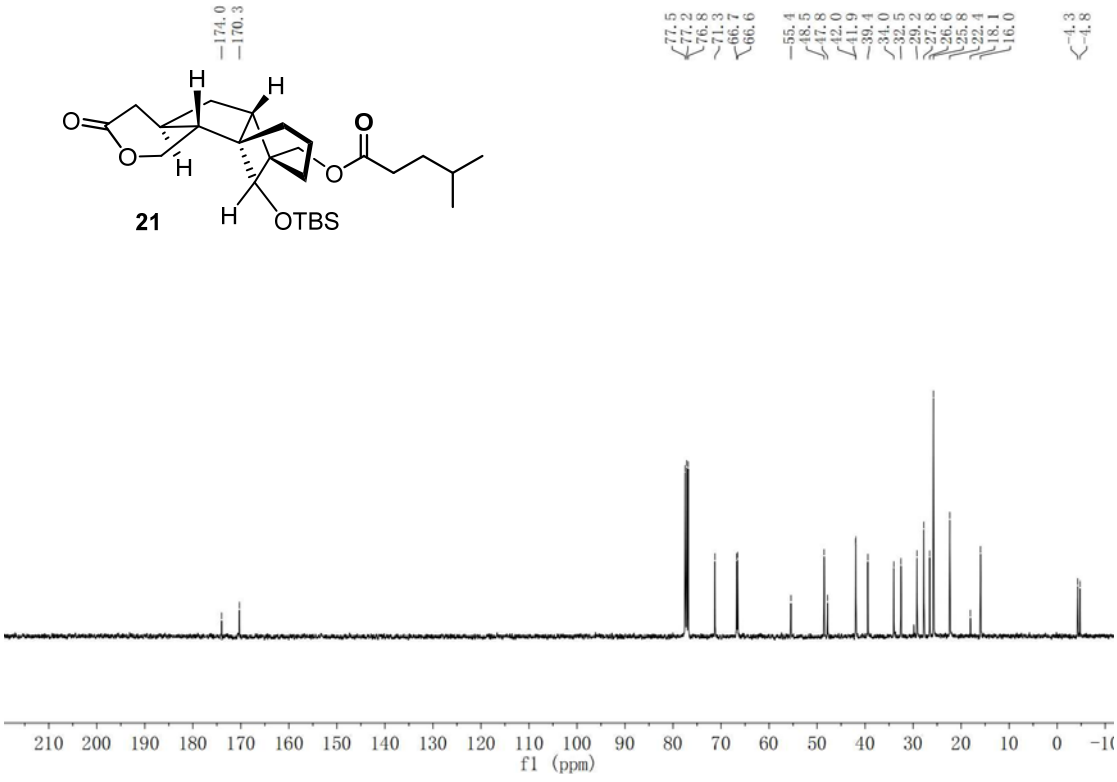
^{13}C NMR Spectrum of 20 (101 MHz, $CDCl_3$)



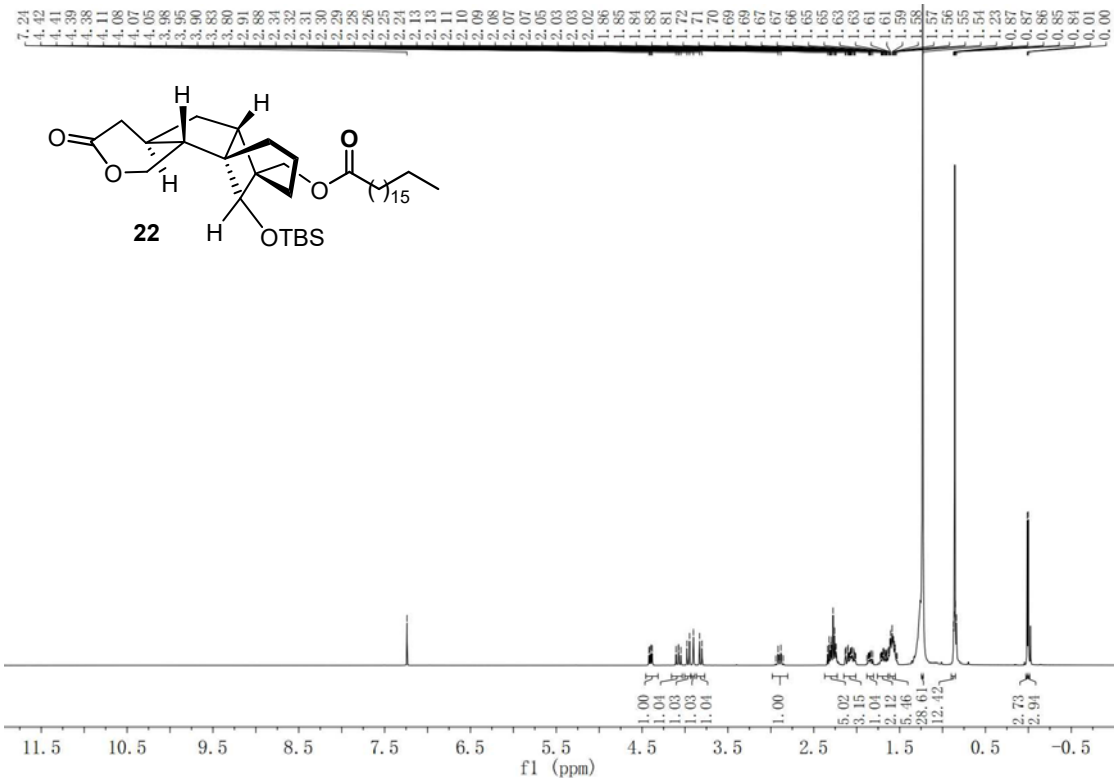
^{1}H NMR Spectrum of 21 (400 MHz, $CDCl_3$)



^{13}C NMR Spectrum of 21 (101 MHz, $CDCl_3$)



^{1}H NMR Spectrum of 22 (400 MHz, $CDCl_3$)



^{13}C NMR Spectrum of 22 (101 MHz, $CDCl_3$)