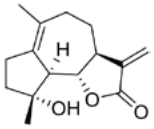
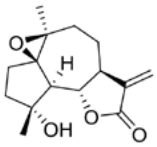
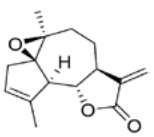
Appendix S1. Supporting information for the detailed synthesis process of PTL derivatives and their characterization data.



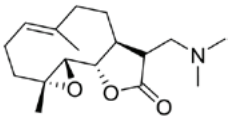
Synthesis of micheliolide (MCL). To a solution of p-toluenesulfonic acid (86 mg, 0.5 mmol) in 100 ml CH_2C_{l2} was added dropwise a solution of parthenolide (3.5 g, 14 mol) in 20 ml CH_2C_{l2} at room temperature for 20 min. The resulting reaction mixture was stirred at room temperature overnight. The reaction was quenched with 20 ml saturated $NaHCO_3$. The organic layer was washed with saturated brine (2x20 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a crude residue, which was recrystallized from acetone to yield a pale yellow crystalline solid (3.2 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (d, *J* = 3.3 Hz, 1H), 5.51 (d, *J* = 3.0 Hz, 1H), 3.82 (t, *J* = 10.3 Hz, 1H), 2.80-2.59 (m, 3H), 2.40 (dd, *J* = 16.3, 8.4 Hz, 1H), 2.30-2.14 (m, 3H), 2.14-2.04 (m, 1H), 1.84-1.74 (m, 2H), 1.69 (s, 3H), 1.40-1.28 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.71, 138.88, 131.87, 130.88, 119.39, 84.45, 80.25, 58.69, 49.62, 38.38, 34.97, 30.08, 25.81, 23.88, 22.73.



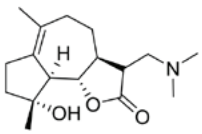
Synthesis of Compound **1**. A solution of micheliolide (1.75 g, 7 mmol) and m-CPBA (1.8 g, 10.5 mmol) in 50 ml CH_2C_{l2} was stirred at room temperature overnight. The reaction mixture was washed with Na_2SO_3 (2x30 ml), $NaHCO_3$ (2x50 ml), and saturated brine (2x30 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a crude residue, which was recrystallized from acetone to yield Compound 3 as crystalline solid (1.3 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.20 (d, *J* = 3.3 Hz, 1H), 5.48 (d, *J* = 3.0 Hz, 1H), 4.05 (t, *J* = 10.4 Hz, 1H), 2.81 (s, 1H), 2.38-2.19 (m, 4H), 2.04-1.82 (m, 4H), 1.70-1.61 (m, 1H), 1.48 (s, 3H), 1.46-1.37 (m, 1H), 1.30 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.62, 138.16, 119.55, 81.83, 79.71, 69.89, 62.19, 55.62, 49.45, 37.37, 33.41, 29.53, 23.26, 21.97.



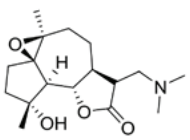
Synthesis of arglabin. To a stirred solution of Compound 1 (264 mg, 1.0 mmol) in 5 ml pyridine was added 300 μl $POCl_3$ at 0°C. The mixture was stirred for 2 h, 30 ml Et_2O was added, and the organic layer was washed successively with $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude residue. Then the residue was chromatographed on a silica gel column to afford arglabin (112 mg, yield 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (d, *J* = 3.3 Hz, 1H), 5.58 (s, 1H), 5.42 (d, *J* = 3.1 Hz, 1H), 4.01 (t, *J* = 10.2 Hz, 1H), 2.94 (d, *J* = 10.7 Hz, 1H), 2.83-2.74 (m, 1H), 2.29-2.11 (m, 3H), 2.07-2.01 (m, 1H), 1.99 (d, *J* = 7.9 Hz, 3H), 1.88-1.82 (m, 1H), 1.55-1.45 (m, 1H), 1.35 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.43, 140.57, 139.14, 124.91, 118.27, 82.89, 72.52, 62.68, 52.85, 51.05, 39.71, 33.48, 22.79, 21.45, 18.25.



Synthesis of DMAPT. Twenty milligrams of PTL was dissolved in 2 ml THF, K_2CO_3 (10 mg) and dimethylamine (40 wt.% solution in water, 0.5 ml) were added separately. The reaction mixture was stirred at room temperature overnight, 20 ml CH_2Cl_2 was added, washed with saturated brine (2x20 ml). The organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give DMAPT as yellow solid (22 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.25-5.16 (m, 1H), 3.86 (t, *J* = 9.1 Hz, 1H), 2.89-2.82 (m, 1H), 2.78-2.70 (m, 2H), 2.57 (d, *J* = 11.2 Hz, 1H), 2.39 (s, 6H), 2.33-2.02 (m, 7H), 1.74-1.62 (m, 4H), 1.30 (s, 3H), 1.26-1.20 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.21, 134.68, 125.12, 82.29, 66.38, 61.56, 57.31, 48.21, 46.15, 45.77, 41.09, 36.68, 29.81, 24.12, 17.23, 16.93. HRMS (ESI) m/z calcd for $C_{17}H_{28}NO_3^+$ $(M+H)^+$ 294.20637, found 294.20624.

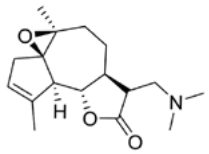


Synthesis of Compound **2**. Twenty milligrams of MCL was dissolved in 2 ml THF, K_2CO_3 (10 mg) and dimethylamine (40 wt.% solution in water, 0.5 ml) were added separately. The reaction mixture was stirred at room temperature overnight; 20 ml CH_2Cl_2 was added, washed with saturated brine (2x20 ml). The organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give Compound **2** as yellow solid (23 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (t, *J* = 10.3 Hz, 1H), 2.67 (dd, *J* = 12.9, 5.0 Hz, 1H), 2.60-2.49 (m, 2H), 2.38-2.28 (m, 2H), 2.20 (s, 6H), 2.14-2.03 (m, 4H), 1.96 (d, *J* = 11.4 Hz, 1H), 1.72 (dd, *J* = 15.1, 8.3 Hz, 2H), 1.60 (s, 3H), 1.21 (d, *J* = 17.0 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.00, 130.84, 130.34, 83.13, 79.34, 57.34, 57.11, 49.97, 44.93, 43.68, 37.43, 34.37, 29.00, 26.32, 22.75, 21.81. HRMS (ESI) m/z calcd for $C_{17}H_{28}NO_3^+$ $(M+H)^+$ 294.20637, found 294.20630.

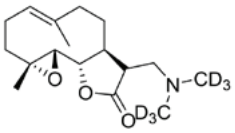


Synthesis of Compound **3**. Twenty milligrams of Compound **1** was dissolved in 2 ml THF, K_2CO_3 (10 mg) and dimethylamine (40 wt.% solution in water, 0.5 ml) were added separately. The reaction mixture was stirred at room temperature overnight, 20 ml CH_2Cl_2 was added, washed with saturated brine (2x20 ml). The organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give Compound **3** as yellow solid (22 mg, 96%). ^{1}H NMR (400 MHz, CDCl3) δ 4.00 (t, *J* = 10.4 Hz, 1H), 2.63 (dd, *J* = 13.0, 5.0 Hz, 1H), 2.51-2.44 (m, 1H), 2.31-2.24 (m, 1H), 2.17 (s, 6H), 2.09-2.03 (m, 1H), 1.88-1.81 (m, 3H), 1.80-1.70 (m, 2H), 1.66-1.53 (m, 3H), 1.39 (s, 3H), 1.34-1.27 (m, 1H), 1.21 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.94, 80.60, 78.67, 68.84, 61.23, 56.89, 54.27, 49.39, 44.93, 43.22, 36.42, 32.57,

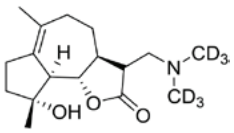
28.37, 22.20. HRMS (ESI) m/z calcd for $C_{17}H_{28}NO_4^+$ $(M+H)^+$ 310.20128, found 310.20114.



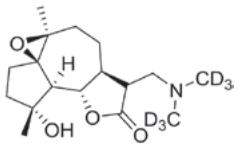
Synthesis of Compound **4**. Twenty milligrams of arglabin was dissolved in 2 ml THF, K_2CO_3 (10 mg) and dimethylamine (40 wt.% solution in water, 0.5 ml) were added separately. The reaction mixture was stirred at room temperature overnight; 20 ml CH_2Cl_2 was added, washed with saturated brine (2x20 ml). The organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give Compound **4** as a yellow solid (23 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49 (s, 1H), 3.94 (t, *J* = 10.2 Hz, 1H), 2.68 (ddd, *J* = 21.9, 17.7, 7.6 Hz, 3H), 2.49 (dd, *J* = 13.0, 6.1 Hz, 1H), 2.23 (dd, *J* = 11.8, 5.5 Hz, 1H), 2.17 (s, 6H), 2.10-2.00 (m, 2H), 1.86 (s, 4H), 1.56 (dd, *J* = 22.8, 10.8 Hz, 2H), 1.39 (d, *J* = 12.5 Hz, 1H), 1.26 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.72, 139.74, 123.71, 81.53, 71.49, 61.65, 56.99, 51.43, 50.87, 45.04, 43.55, 38.56, 32.66, 21.83, 21.70, 17.27. HRMS (ESI) m/z calcd for $C_{17}H_{26}NO_3^+$ $(M+H)^+$ 292.19072, found 292.19067.



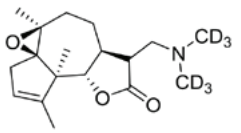
Synthesis of DMAPT-D6. Twenty milligrams of PTL was dissolved in 2 ml THF, K_2CO_3 (50 mg) and dimethyl-*d6*-amine hydrochloride (20 mg) were added separately. The reaction mixture was stirred at room temperature overnight; 20 ml CH_2Cl_2 was added, washed with saturated brine (2x20 ml). The organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give DMAPT-D6 as a yellow solid (20 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 (d, *J* = 9.9 Hz, 1H), 3.76 (t, *J* = 9.0 Hz, 1H), 2.68 (dt, *J* = 6.7, 3.9 Hz, 2H), 2.56 (dd, *J* = 13.2, 4.7 Hz, 1H), 2.35-2.27 (m, 2H), 2.25-2.16 (m, 2H), 2.12-1.96 (m, 4H), 1.62 (d, *J* = 6.1 Hz, 3H), 1.60-1.50 (m, 1H), 1.23 (s, 3H), 1.17 (dd, *J* = 13.1, 5.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.44, 133.64, 124.10, 81.10, 65.50, 60.43, 56.57, 46.92, 45.57, 40.12, 35.67, 28.98, 23.11, 16.23, 15.92. HRMS (ESI) m/z calcd for $C_{17}H_{22}D_6NO_3^+$ $(M+H)^+$ 300.24403, found 300.24438.



Synthesis of Compound **5**. Twenty milligrams of MCL was dissolved in 2 ml THF, K_2CO_3 (50 mg) and dimethyl-*d6*-amine hydrochloride (20 mg) were added separately. The reaction mixture was stirred at room temperature overnight, 20 ml CH_2Cl_2 was added, washed with saturated brine (2x20 ml). The organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give D Compound **5** as a yellow solid (23 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (t, *J* = 10.3 Hz, 1H), 2.70-2.45 (m, 4H), 2.31 (dt, *J* = 11.6, 5.3 Hz, 2H), 2.21-2.04 (m, 4H), 1.97 (dd, *J* = 22.6, 11.1 Hz, 1H), 1.78-1.67 (m, 2H), 1.61 (s, 3H), 1.23 (s, 3H), 1.21-1.15 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.06, 130.86, 130.32, 83.11, 79.33, 57.36, 57.10, 49.94, 43.76, 37.41, 34.39, 29.00, 26.36, 22.75, 21.81. HRMS (ESI) m/z calcd for $C_{17}H_{22}D_6NO_3^+$ $(M+H)^+$ 300.24403, found 300.24490.



Synthesis of Compound **6**. Twenty milligrams of Compound **1** was dissolved in 2 ml THF, K_2CO_3 (50 mg) and dimethyl-*d6*-amine hydrochloride (20 mg) were added separately. The reaction mixture was stirred at room temperature overnight, 20 ml CH_2Cl_2 was added, washed with saturated brine (2x20 ml). The organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give Compound **6** as yellow solid (21 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.00 (t, *J* = 10.4 Hz, 1H), 2.61 (dd, *J* = 13.0, 5.0 Hz, 1H), 2.47 (dd, *J* = 13.0, 6.2 Hz, 1H), 2.28-2.12 (m, 3H), 2.09-2.02 (m, 1H), 1.84 (dd, *J* = 11.6, 6.2 Hz, 3H), 1.79-1.73 (m, 1H), 1.65-1.55 (m, 2H), 1.39 (s, 3H), 1.30 (d, *J* = 11.8 Hz, 1H), 1.21 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.00, 80.56, 78.66, 68.85, 61.23, 56.84, 54.27, 49.38, 43.27, 36.42, 32.58, 28.37, 22.20. HRMS (ESI) m/z calcd for $C_{17}H_{22}D_6NO_4^+$ $(M+H)^+$ 316.23895, found 316.23895.



Synthesis of Compound **7**. Twenty milligrams of arglabin was dissolved in 2 ml THF, K_2CO_3 (50 mg) and dimethyl-*d6*-amine hydrochloride (20 mg) were added separately. The reaction mixture was stirred at room temperature overnight, 20 ml CH_2Cl_2 was added, washed with saturated brine (2x20 ml). The organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give Compound **7** as yellow solid (23 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (s, 1H), 4.01 (t, *J* = 10.2 Hz, 1H), 2.86-2.67 (m, 3H), 2.57 (dd, *J* = 13.1, 6.0 Hz, 1H), 2.33-2.00 (m, 5H), 1.93 (s, 3H), 1.46 (dd, *J* = 18.6, 6.3 Hz, 2H), 1.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.74, 140.75, 124.75, 82.58, 72.51, 62.68, 57.78, 52.46, 51.84, 44.57, 39.58, 33.67, 29.71, 29.33, 27.23, 22.86, 22.73, 18.29, 14.11. HRMS (ESI) m/z calcd for $C_{17}H_{20}D_6NO_3^+$ $(M+H)^+$ 298.22838, found 298.22818.

Figure S1. [1]H-NMR spectrum for MCL. MCL, micheliolide.

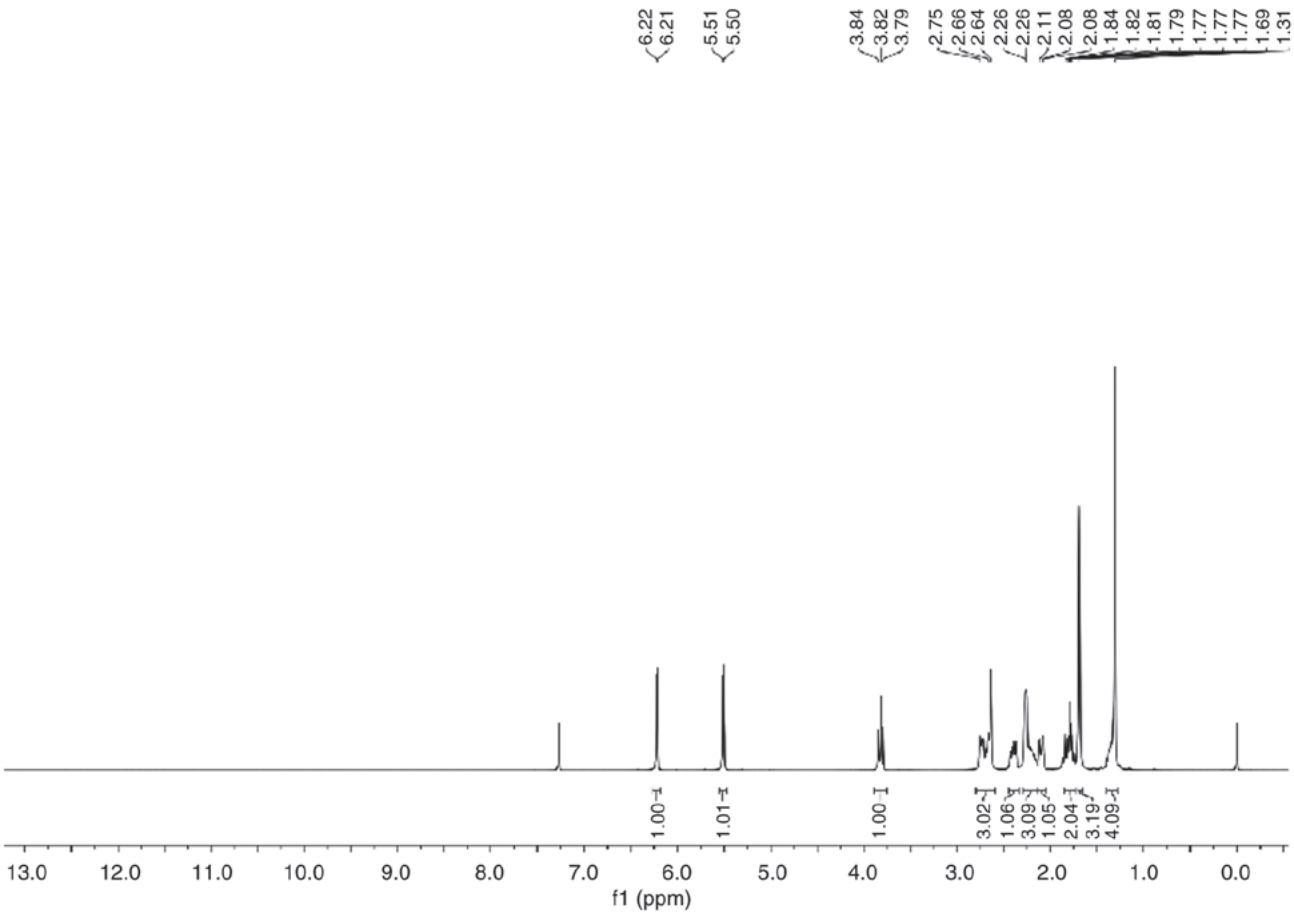


Figure S2. ^{13}C-NMR spectrum for MCL. MCL, micheliolide.

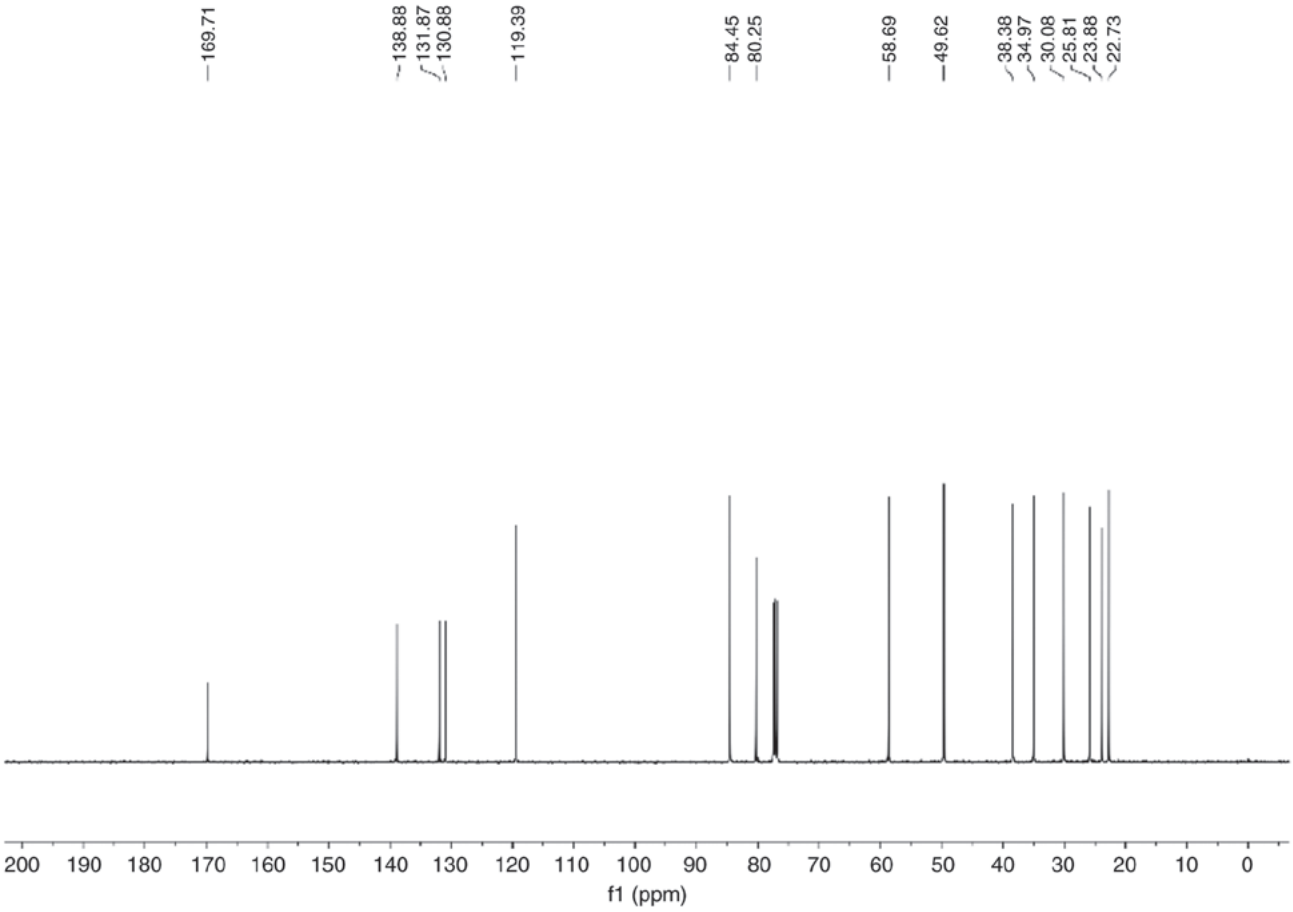


Figure S3. ^{1}H-NMR spectrum for Compound 1.

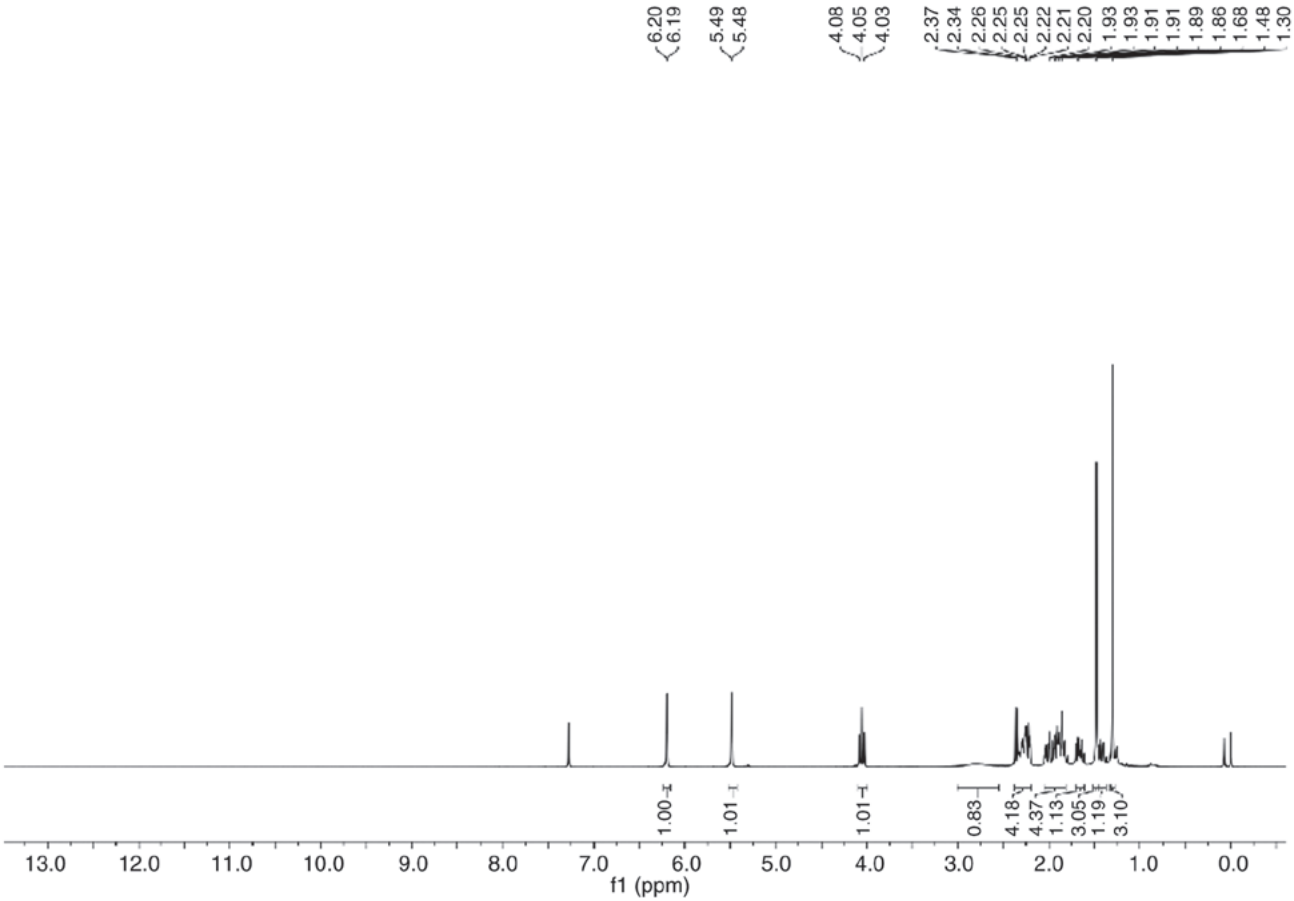


Figure S4. ^{13}C-NMR spectrum for Compound 1.

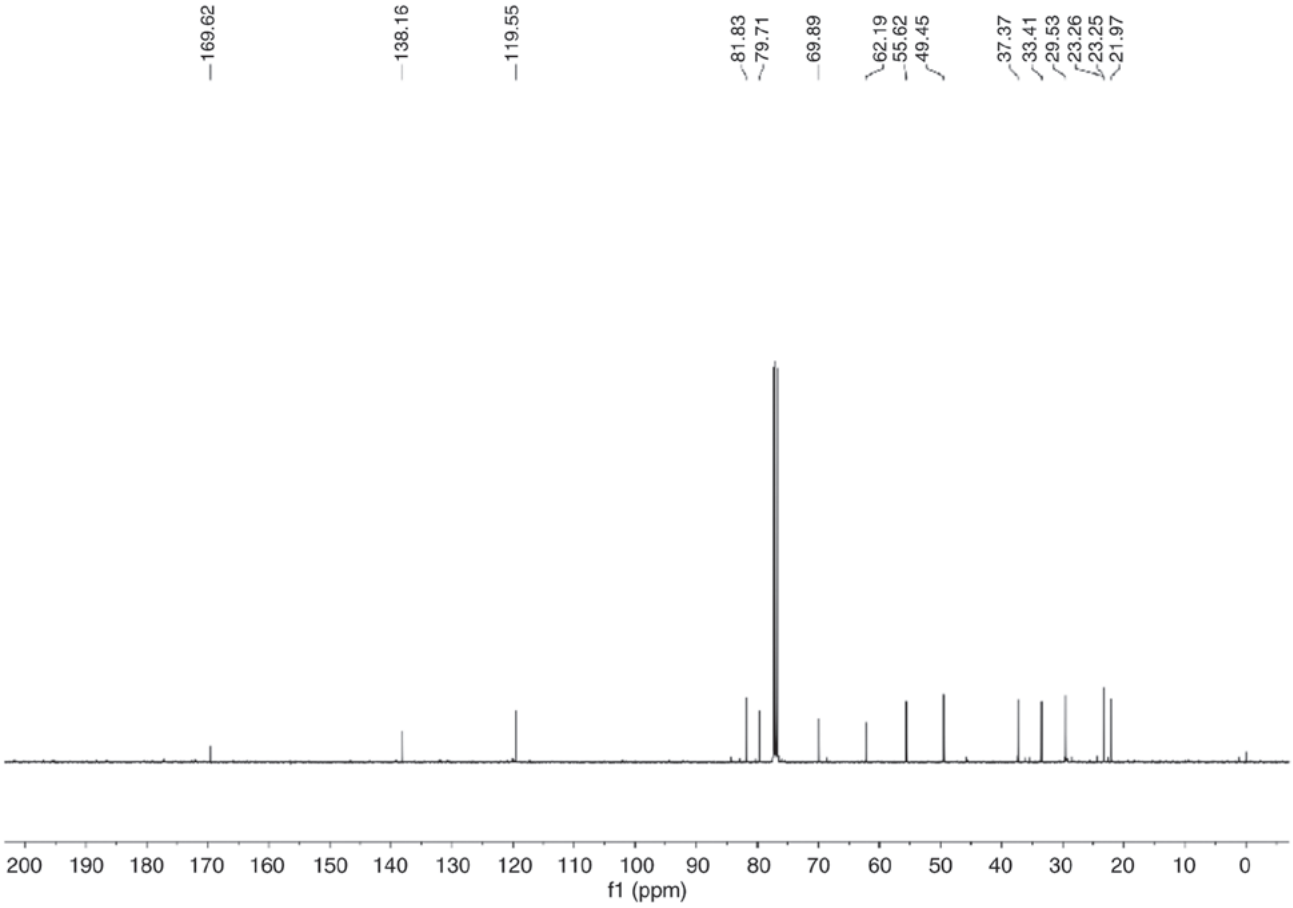


Figure S5. [1]H-NMR spectrum for arglabin.

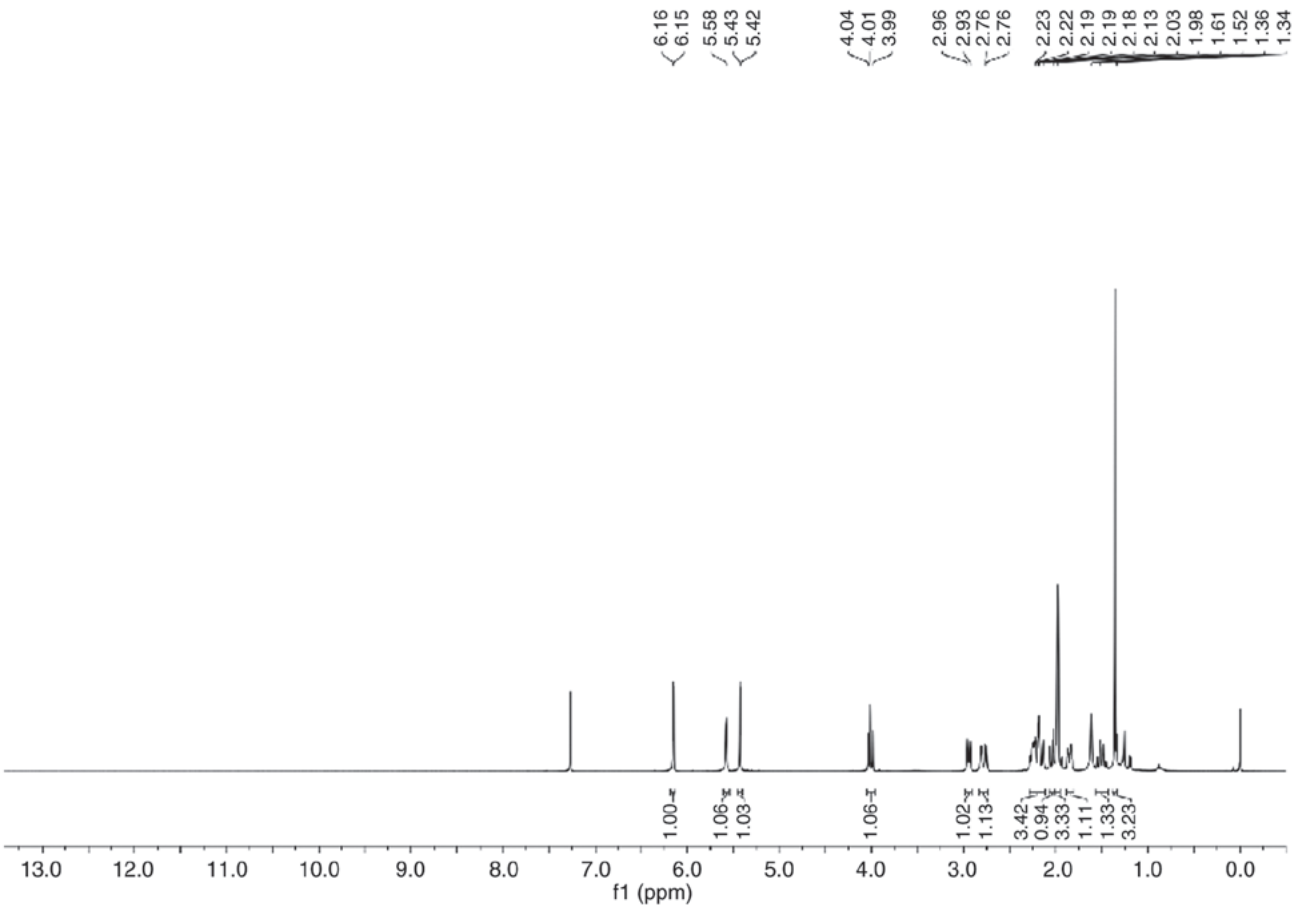


Figure S6. ^{13}C-NMR spectrum for arglabin.

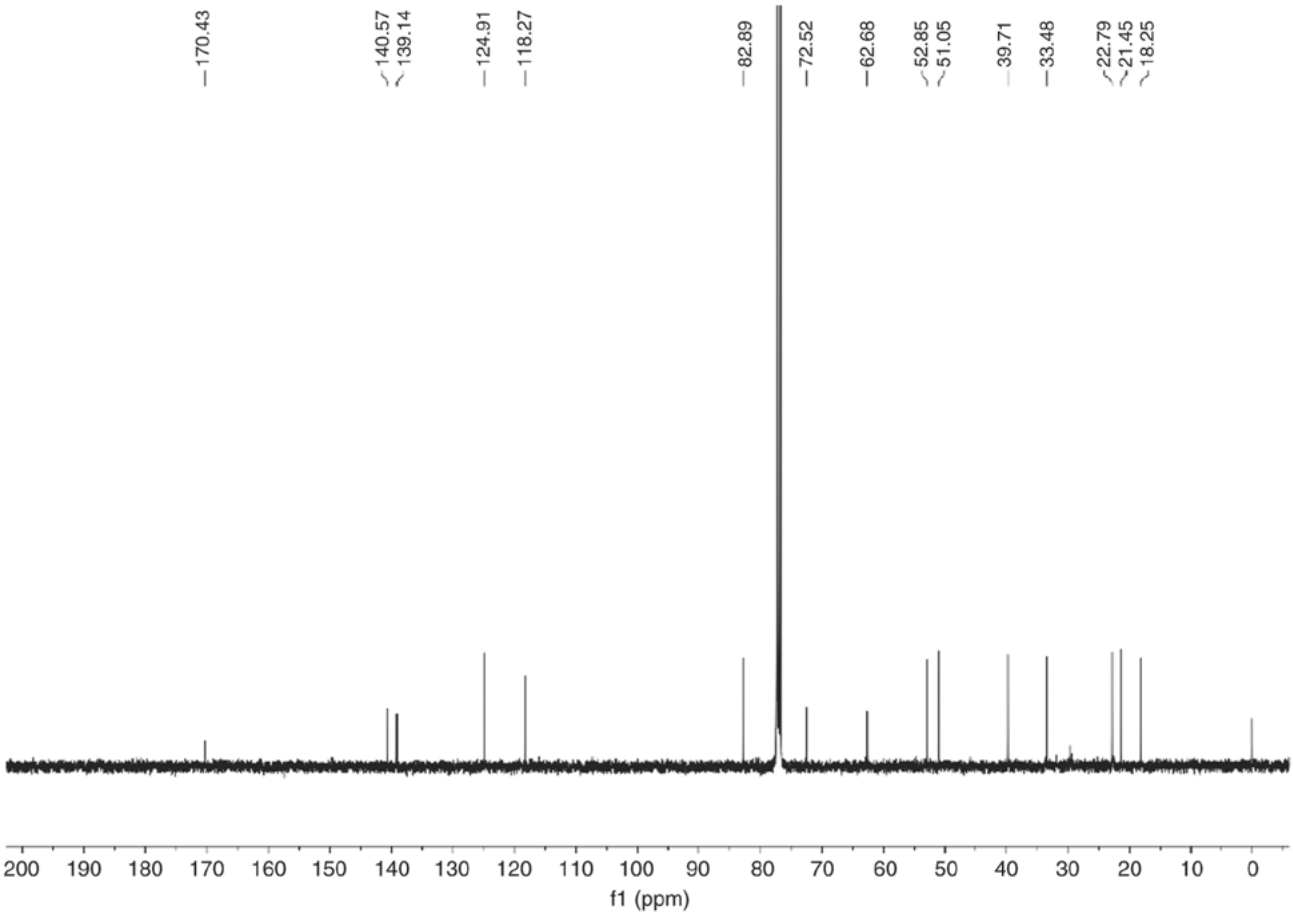


Figure S7. ^{1}H-NMR spectrum for DMAPT. DMAPT, dimethylaminoparthenolide.

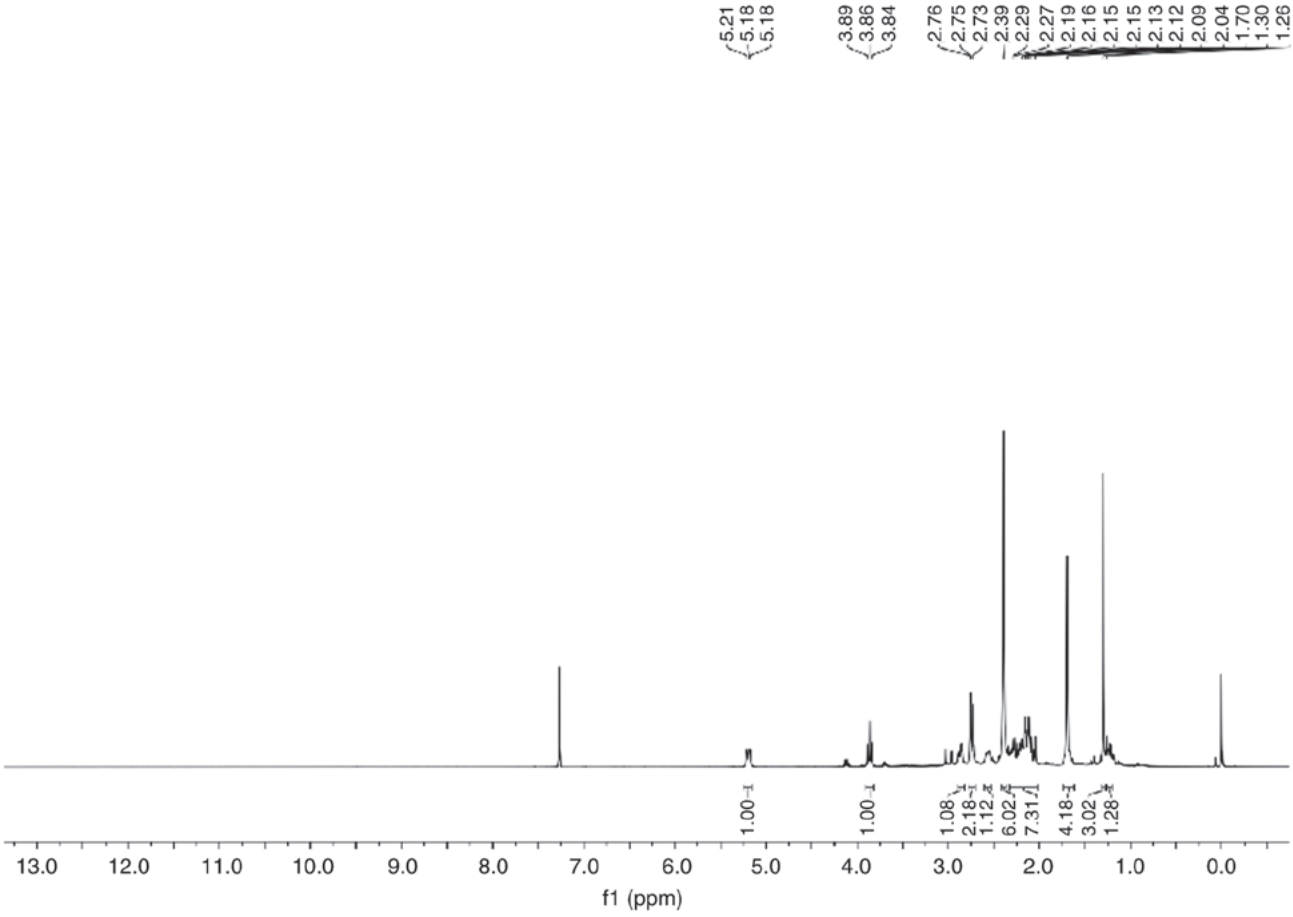


Figure S8. ^{13}C-NMR spectrum for DMAPT. DMAPT, dimethylaminoparthenolide.

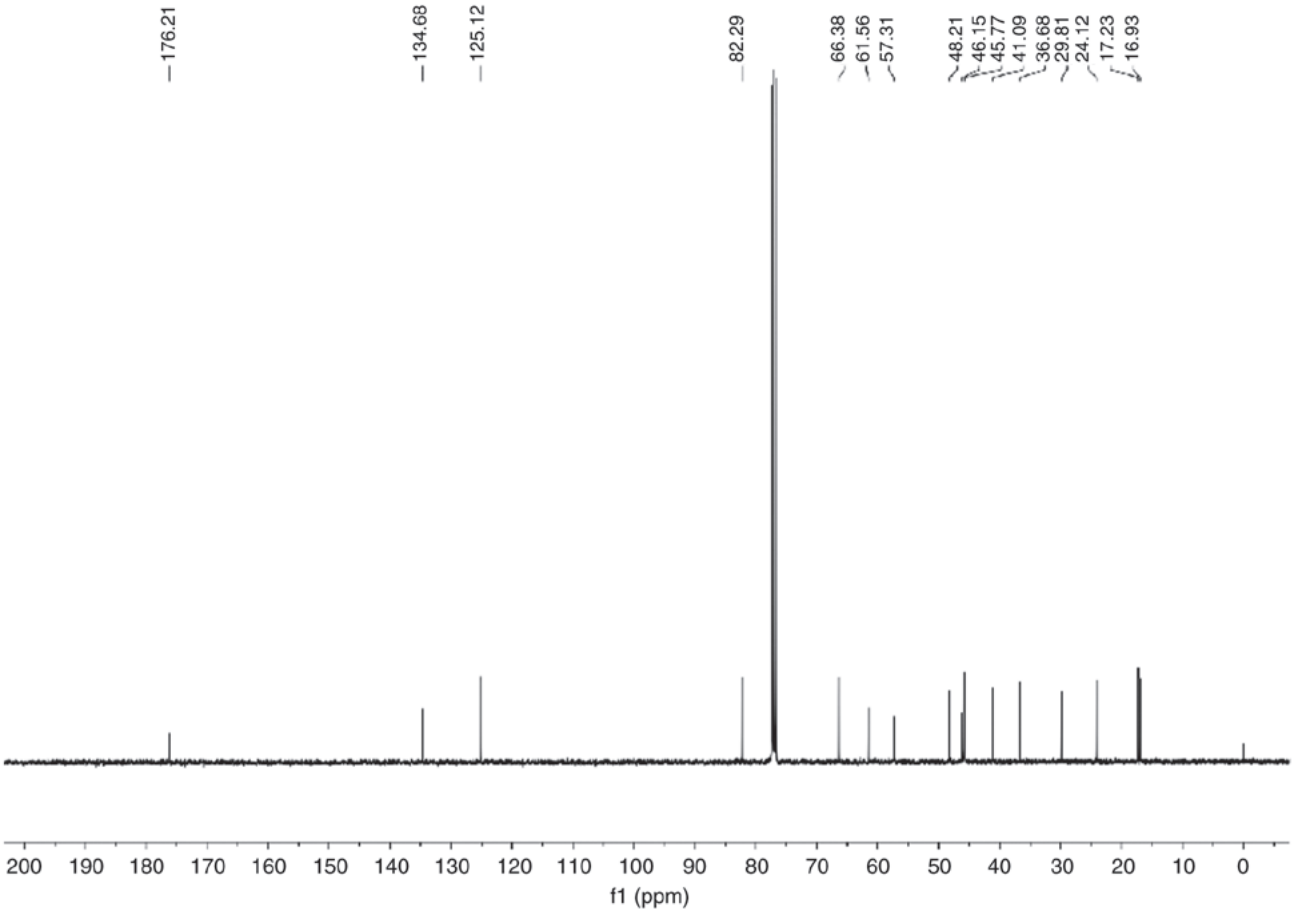


Figure S9. [1]H-NMR spectrum for Compound 2.

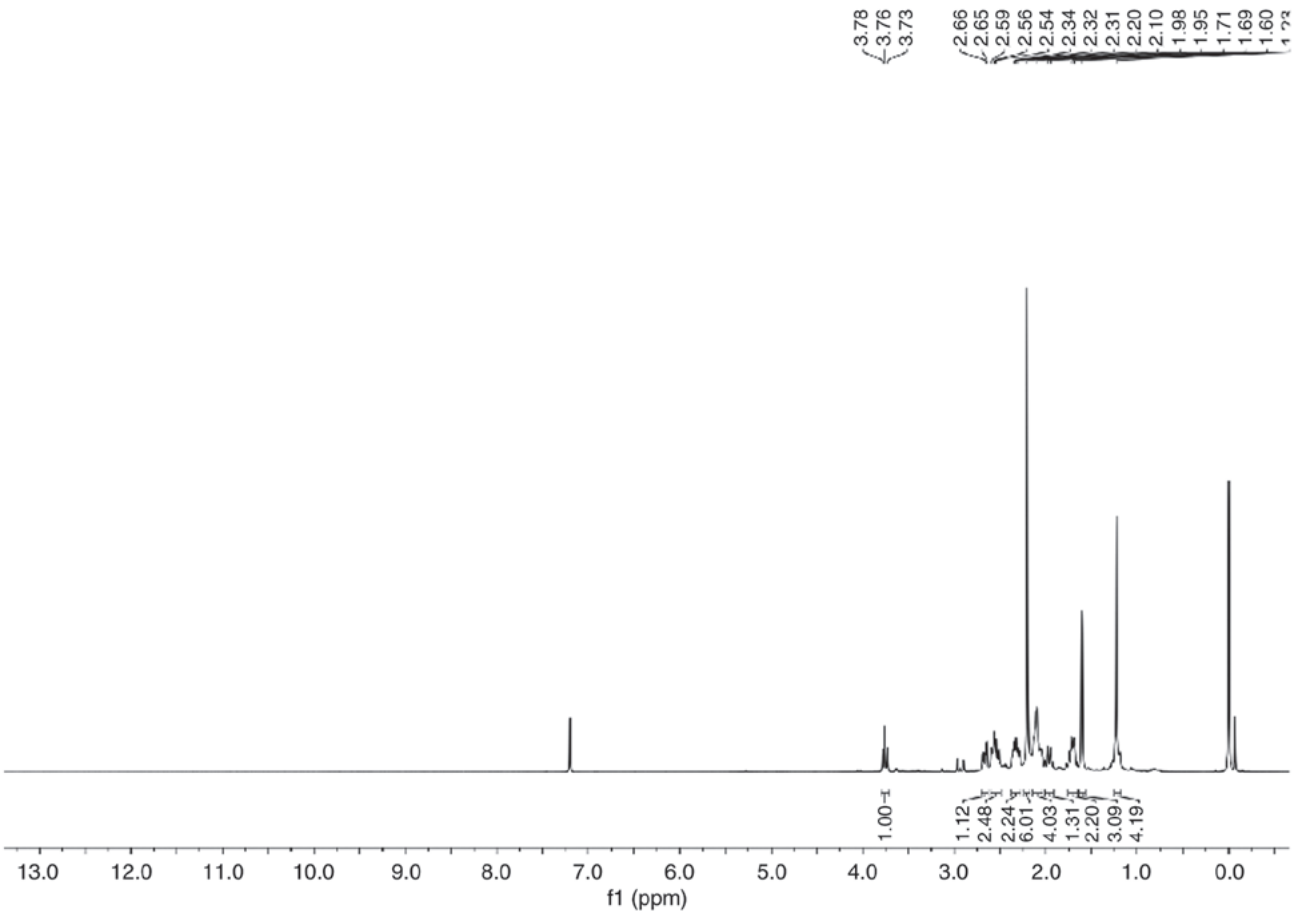


Figure S10. ^{13}C-NMR spectrum for Compound 2.

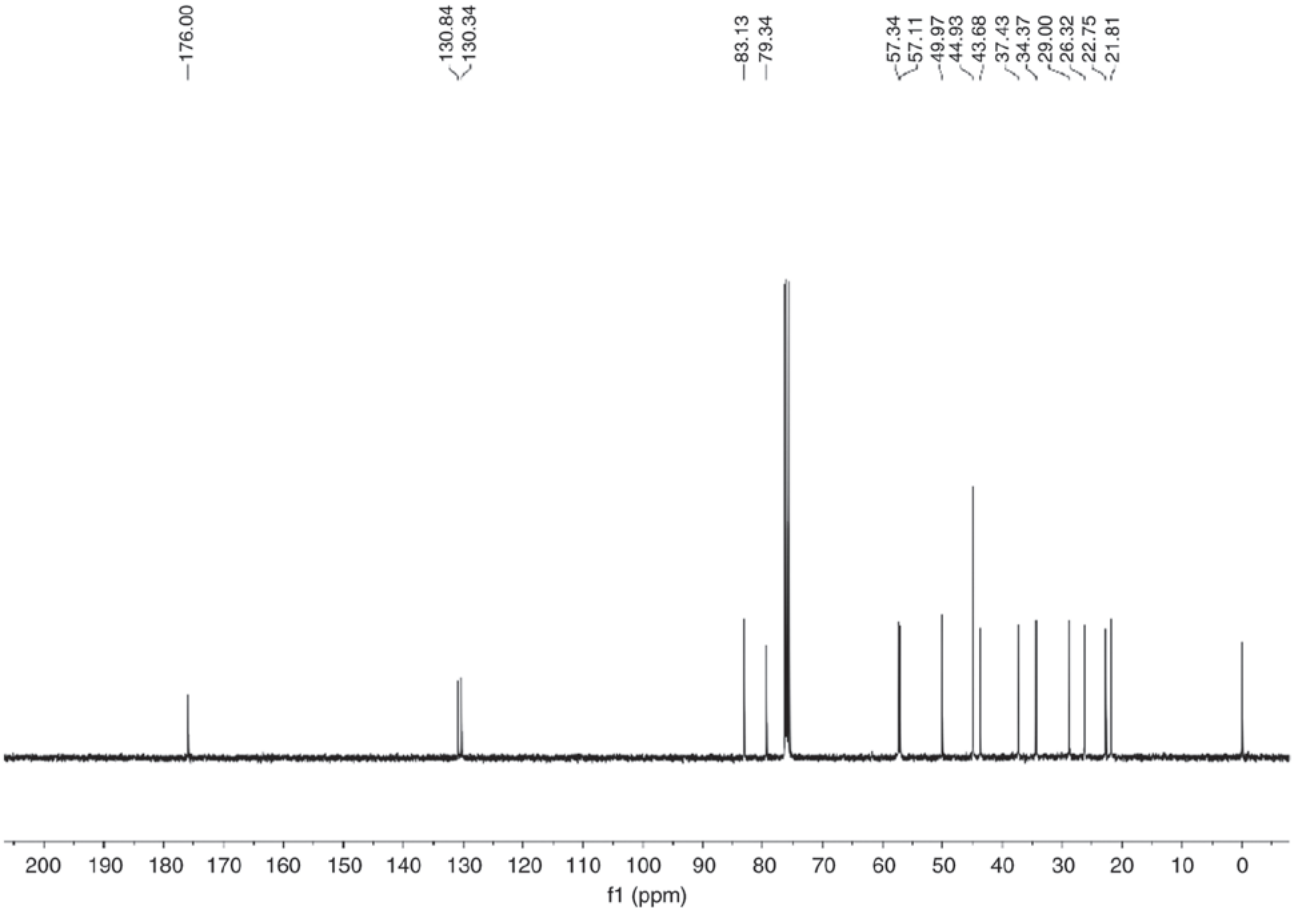


Figure S11. ^{1}H-NMR spectrum for Compound 3.

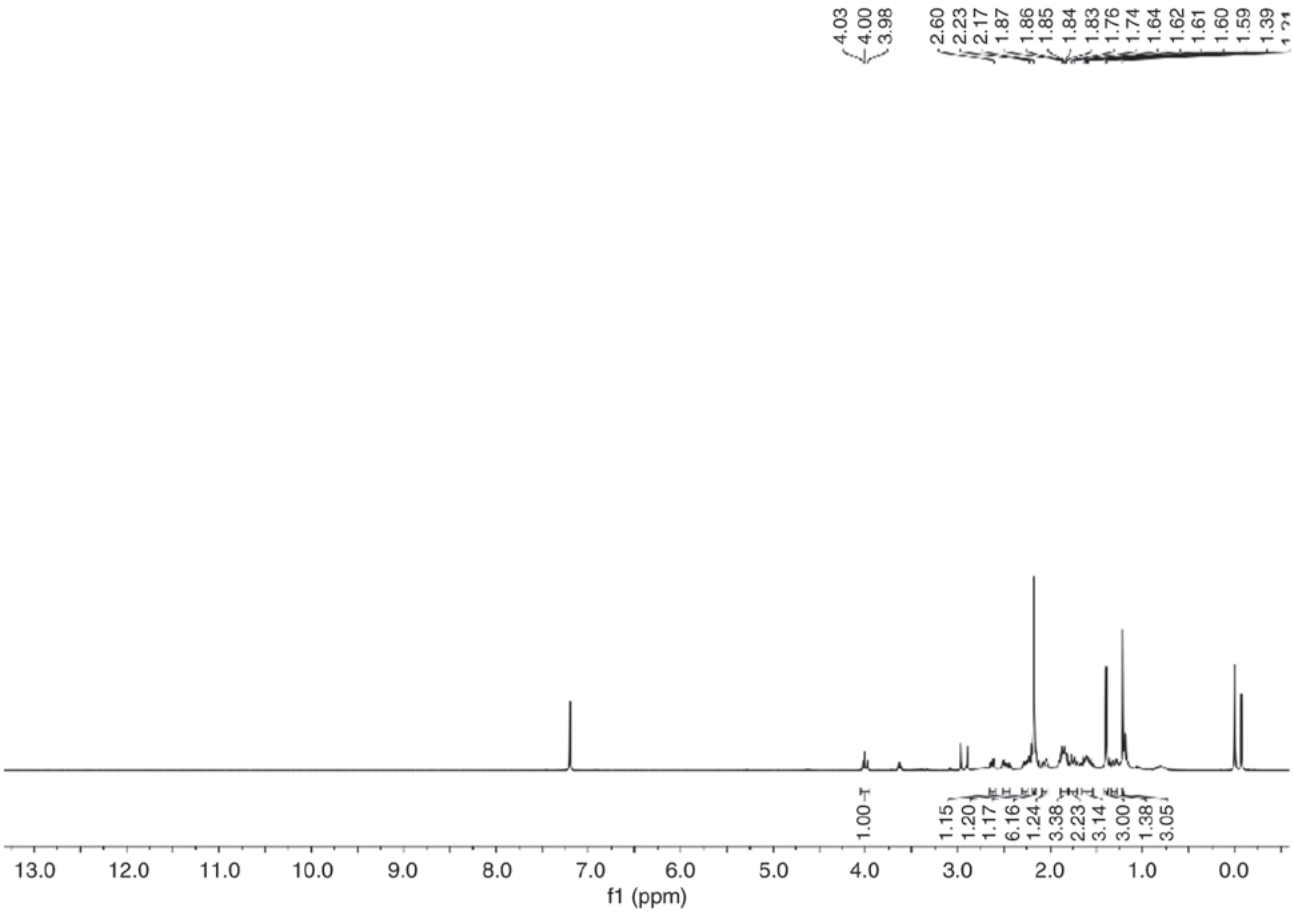


Figure S12. ^{13}C-NMR spectrum for Compound 3.

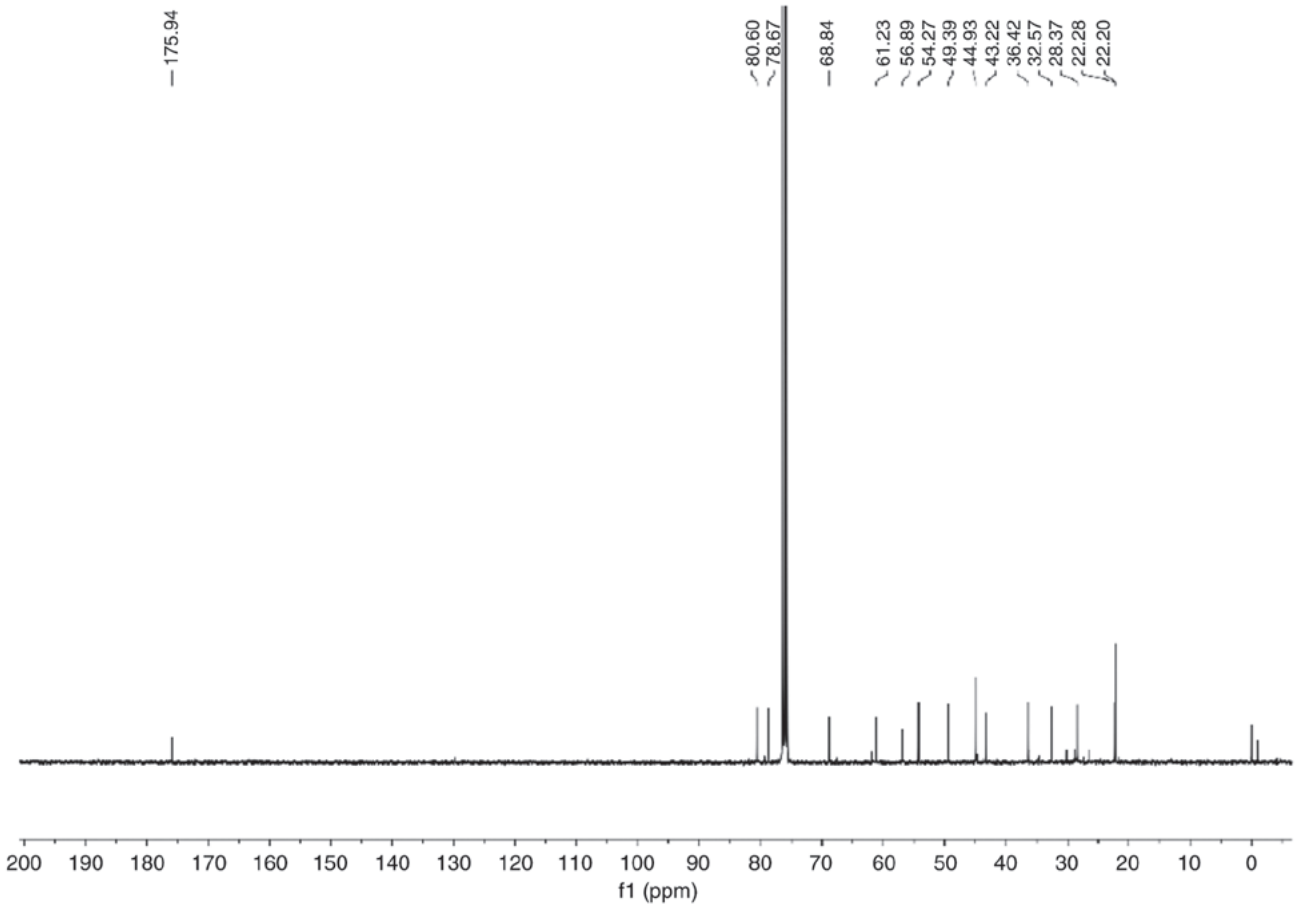


Figure S13. ^{1}H-NMR spectrum for Compound 4

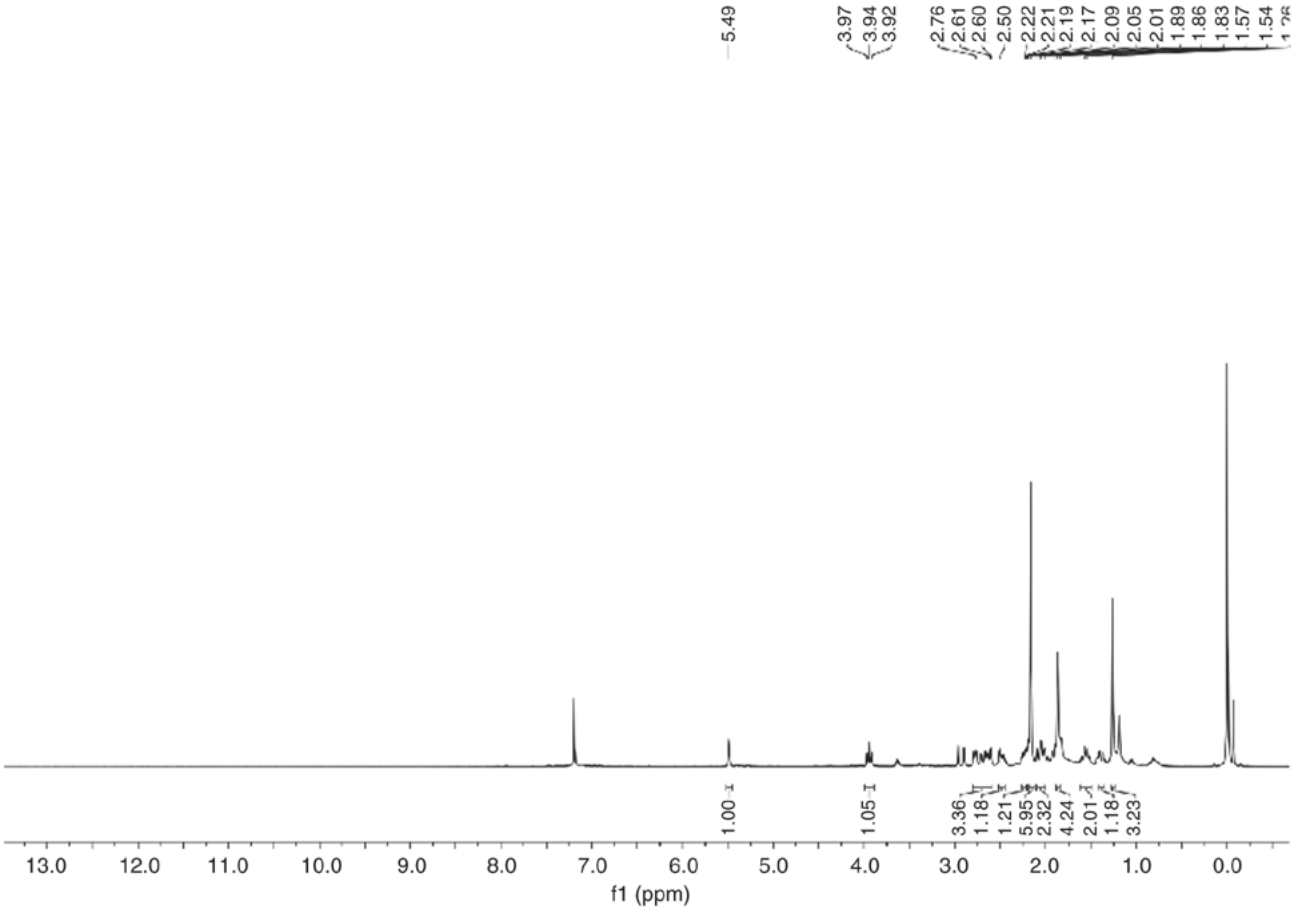


Figure S14. ^{13}C-NMR spectrum for Compound 4.

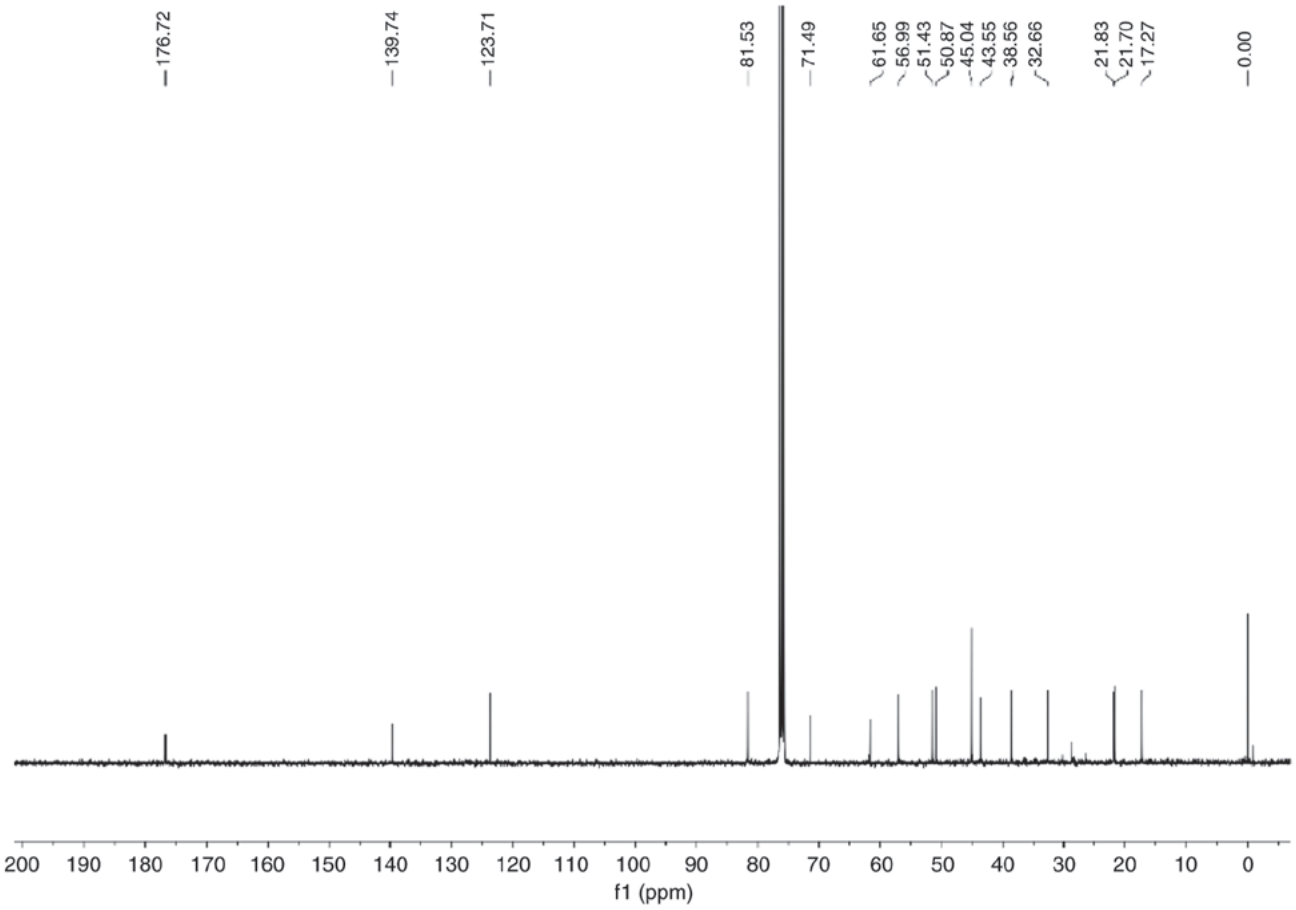


Figure S15. ^{1}H-NMR spectrum for DMAPT-D6. DMAPT, dimethylaminoparthenolide.

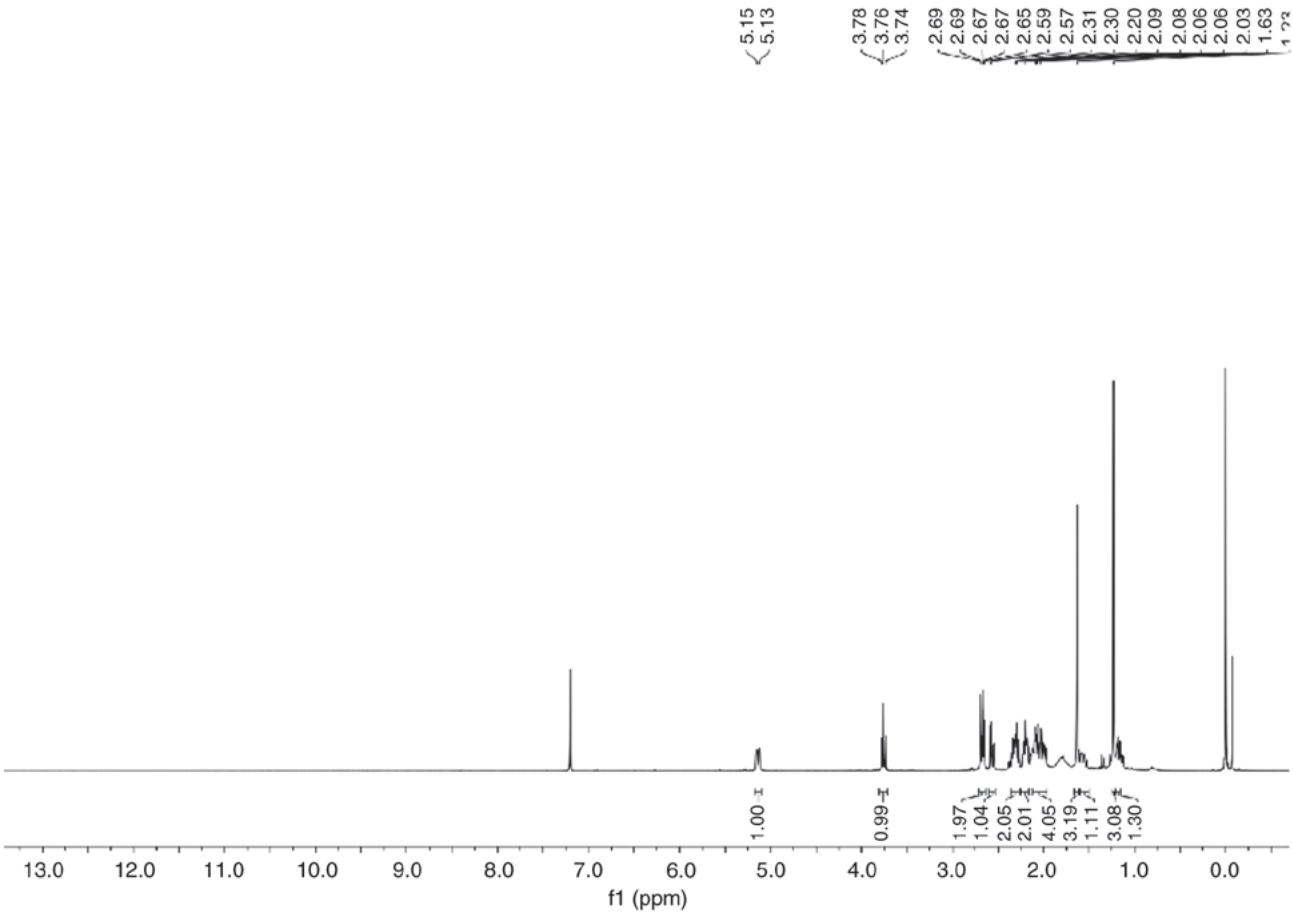


Figure S16. ^{13}C-NMR spectrum for DMAPT-D6. DMAPT, dimethylaminoparthenolide.

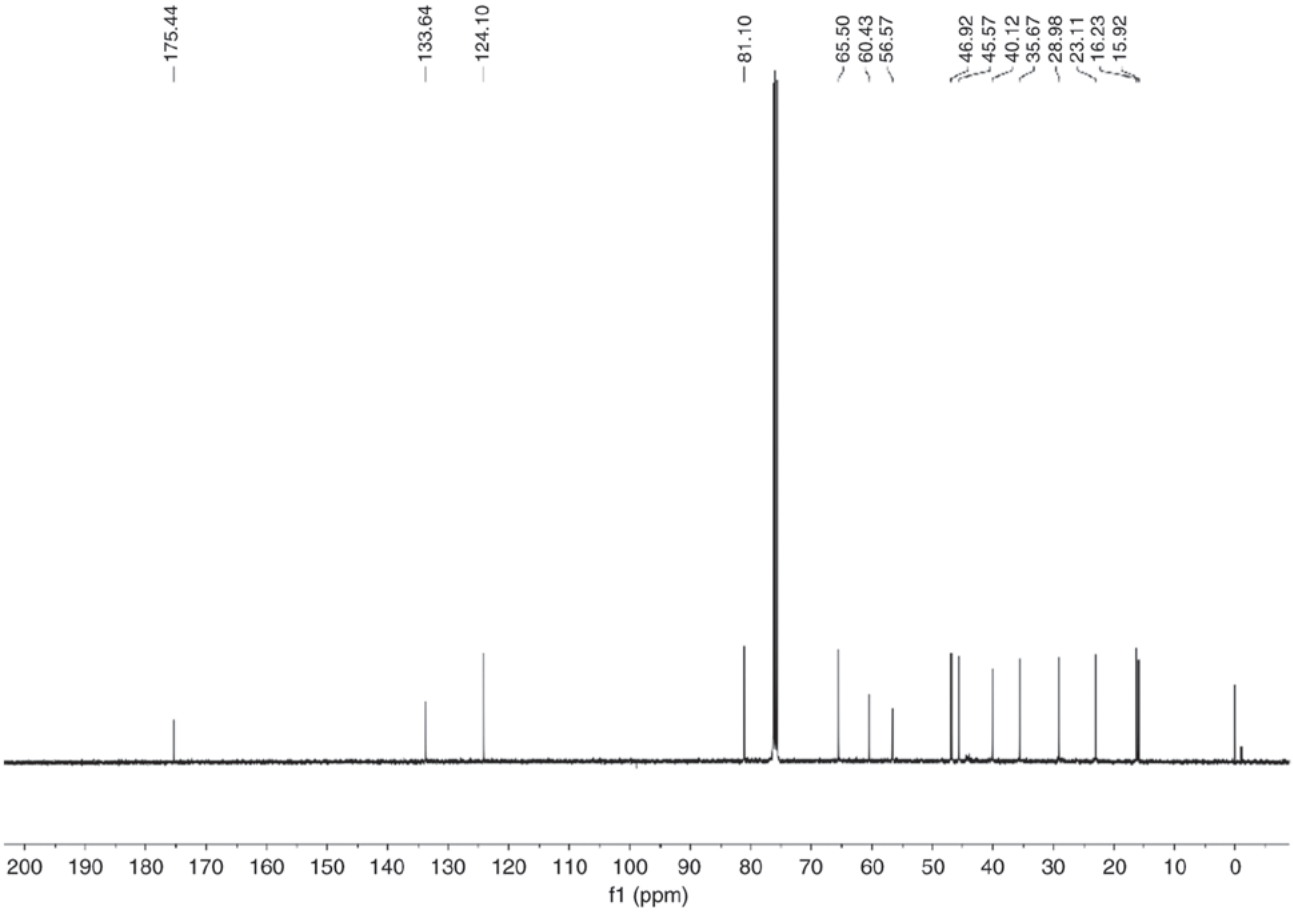


Figure S17. ^{1}H-NMR spectrum for Compound 5.

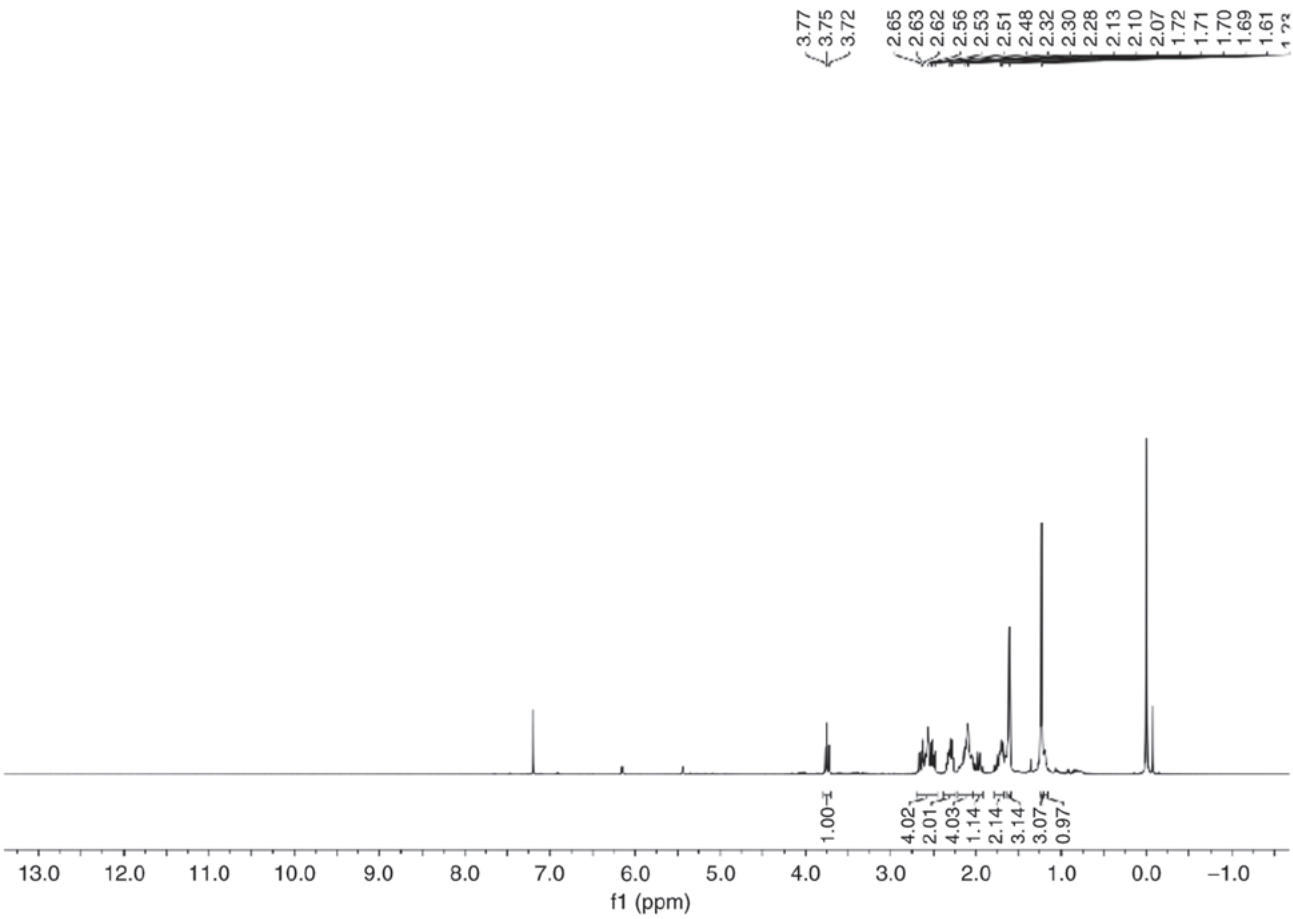


Figure S18. ^{13}C-NMR spectrum for Compound 5.

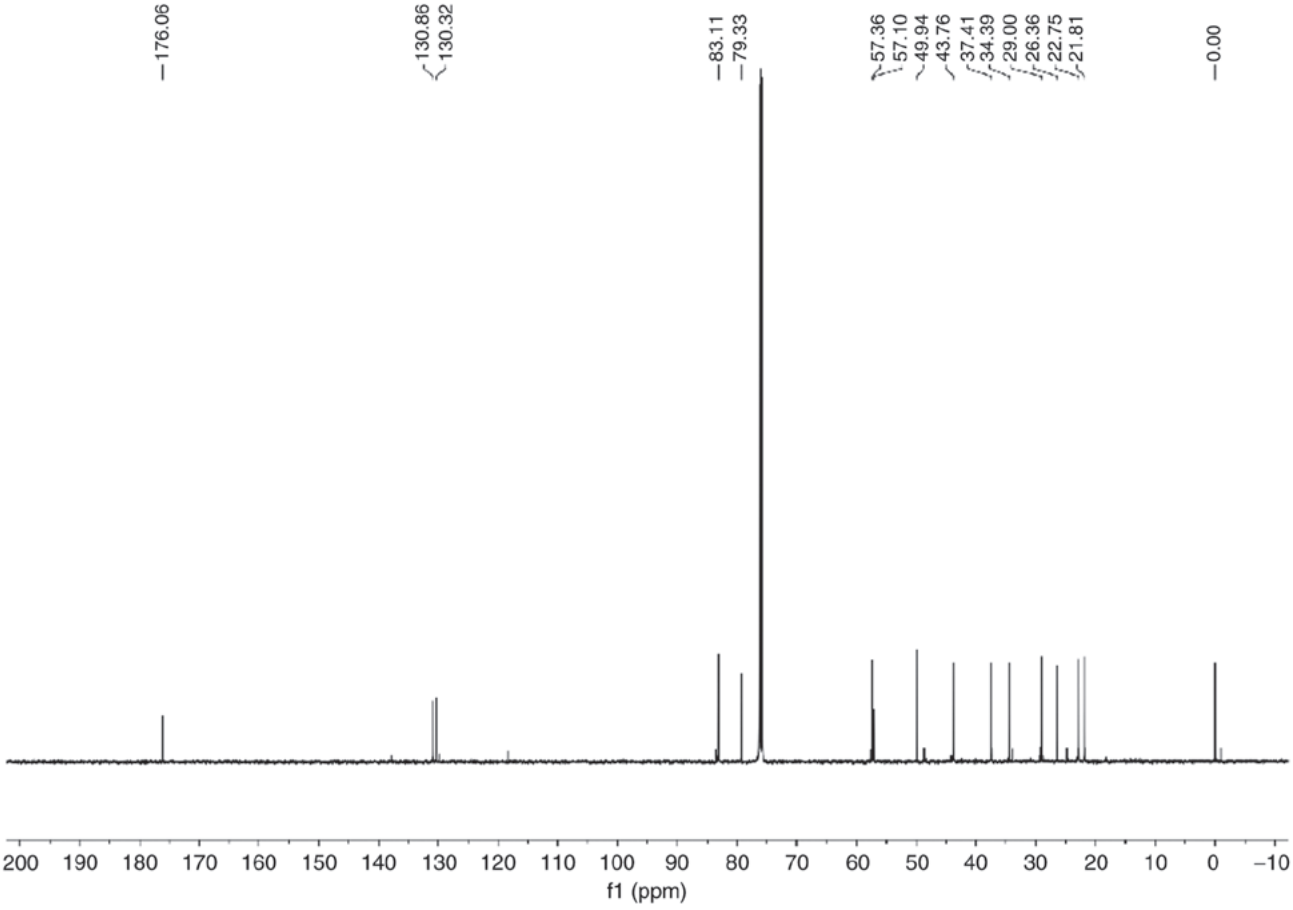


Figure S19. ^{1}H-NMR spectrum for Compound 6.

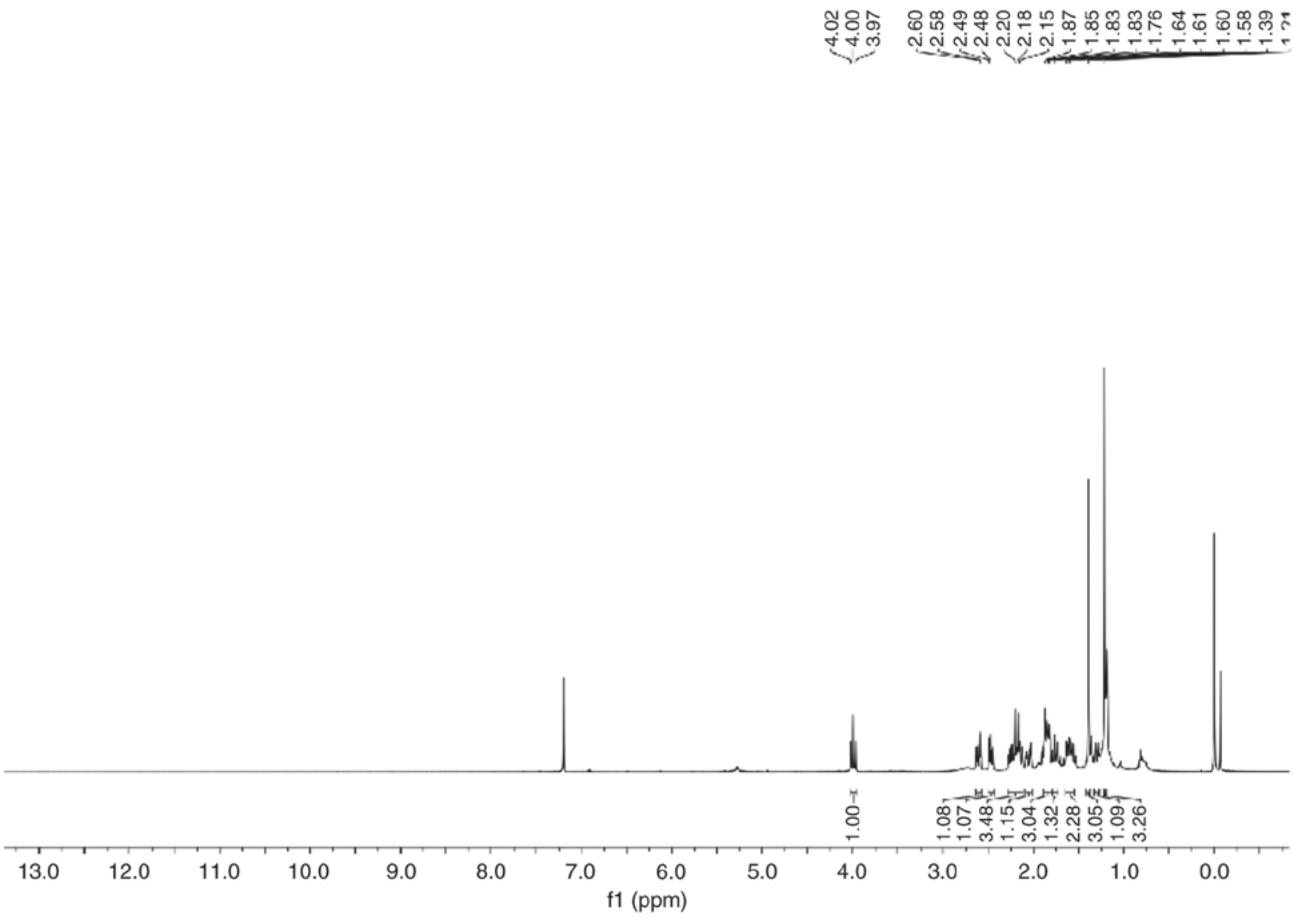


Figure S20. ^{13}C-NMR spectrum for Compound 6.

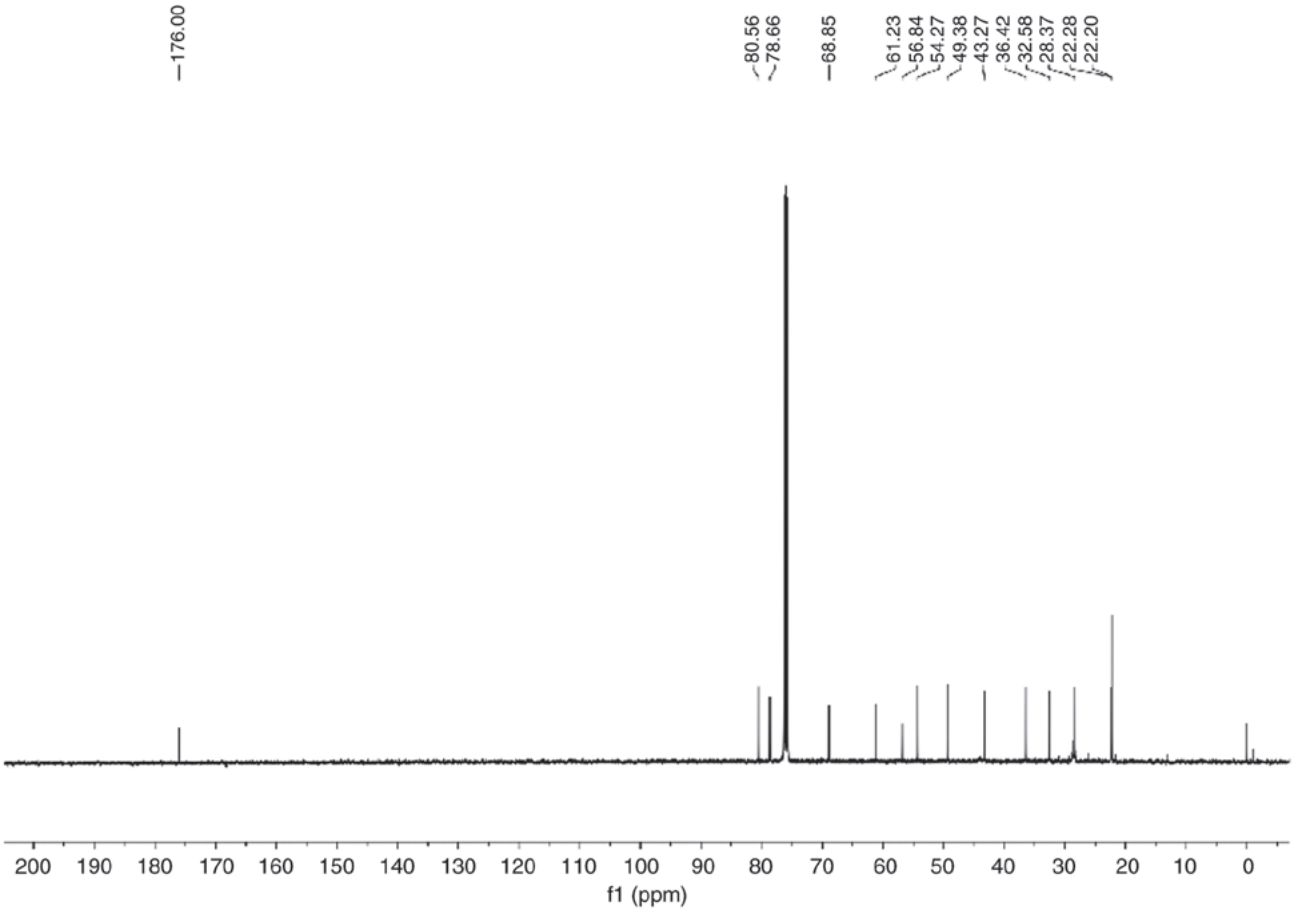


Figure S21. ^{1}H-NMR spectrum for Compound 7.

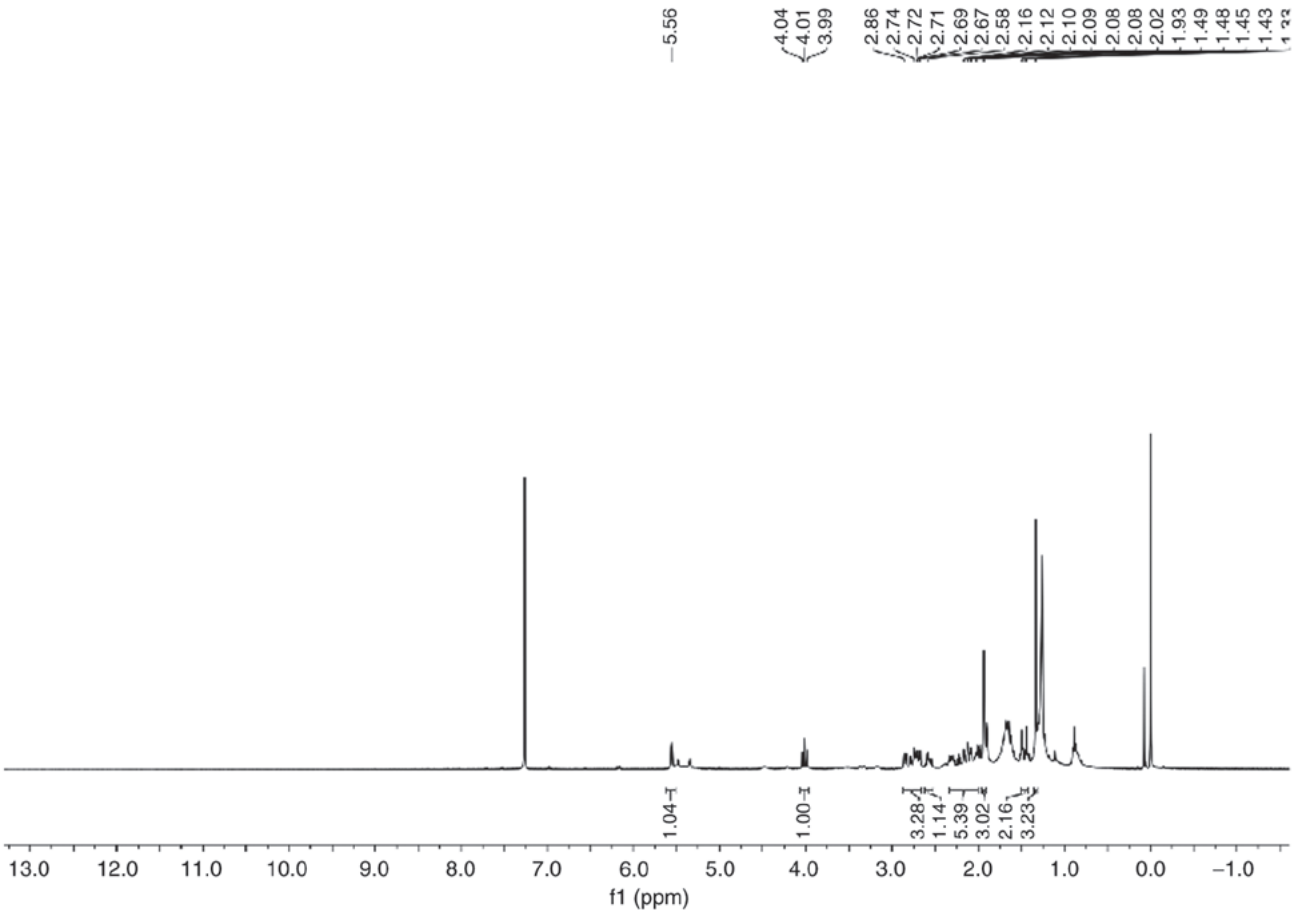


Figure S22. ^{13}C-NMR spectrum for Compound 7.

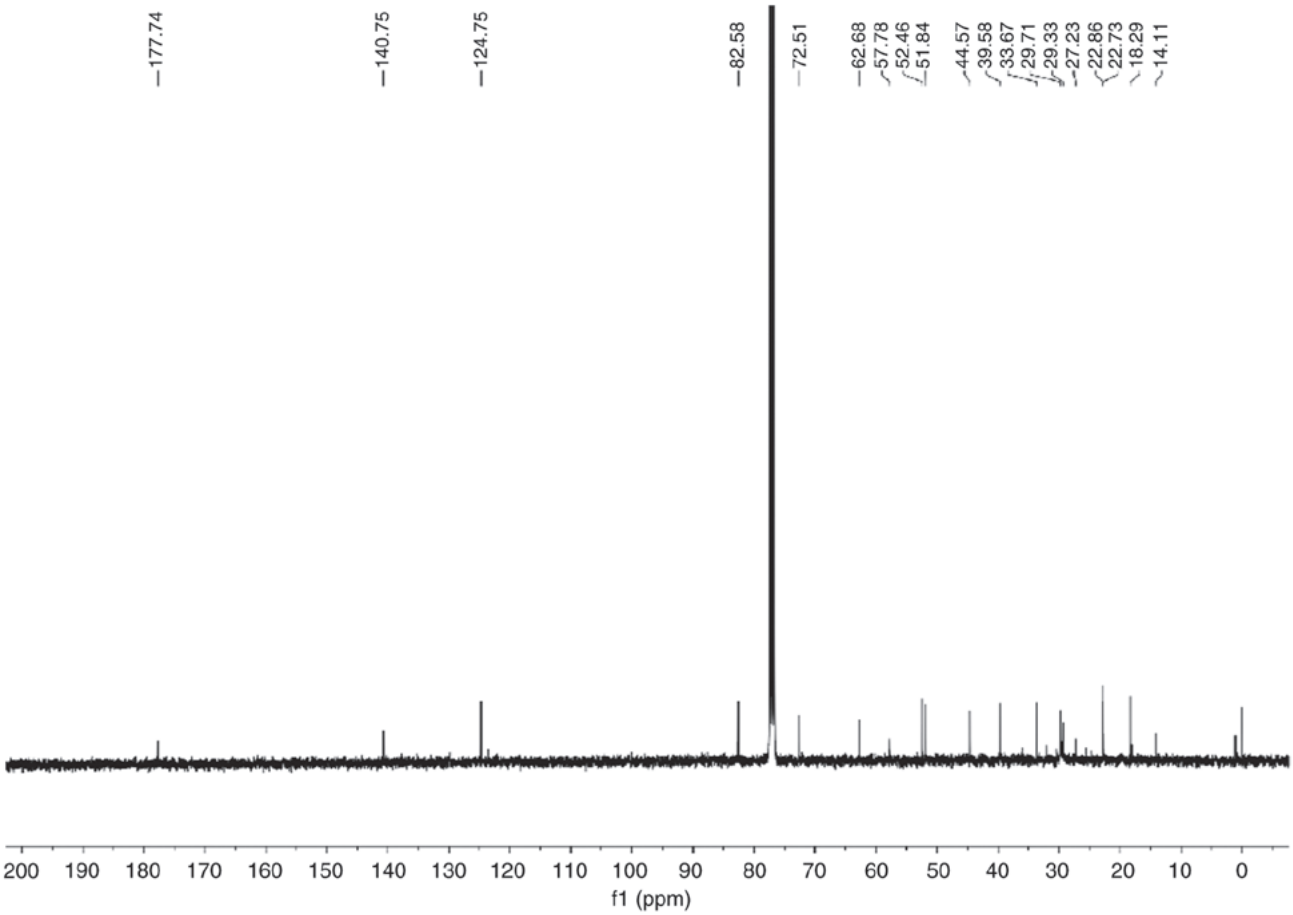


Table SI. IC_{50} value of PTL derivatives was measured after 48 h treatment in U87 cells.

Compounds	U87-IC_{50} (μM)	Compounds	U87-IC_{50} (μM)	Compounds	U87-IC_{50} (μM)
PTL	11.11	DMAPT	14.22	DMAPT-D6	15.50
MCL	11.69	Compound 2	11.44	Compound 5	25.17
Compound 1	29.87	Compound 3	32.79	Compound 6	59.16
Arglabin	22.96	Compound 4	15.57	Compound 7	18.02

IC_{50}, half maximal inhibitory concentration; PTL, parthenolide; MCL, micheliolide; DMAPT, dimethylaminoparthenolide.