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Supplemental Information

A Glucose-Triptolide Conjugate Selectively Targets Cancer Cells under Hypoxia

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Supplemental Information

Supplemental data

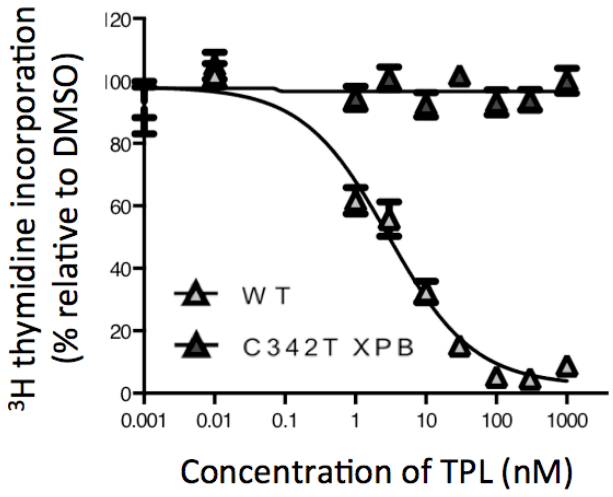


Figure S1 (related to Figure 1). XPB C342T mutation leads to resistance to triptolide. Expression of mutant XPB C342T in the knock-in cell line T7115 (dark gray triangle) leads to triptolide resistance but not in the isogenic cell line expressing wild type XPB (gray triangle). Proliferation was measured by ^{3}H thymidine incorporation and plotted using GraphPad prism. Data represents mean ± SEM relative to DMSO (*n* = 3).

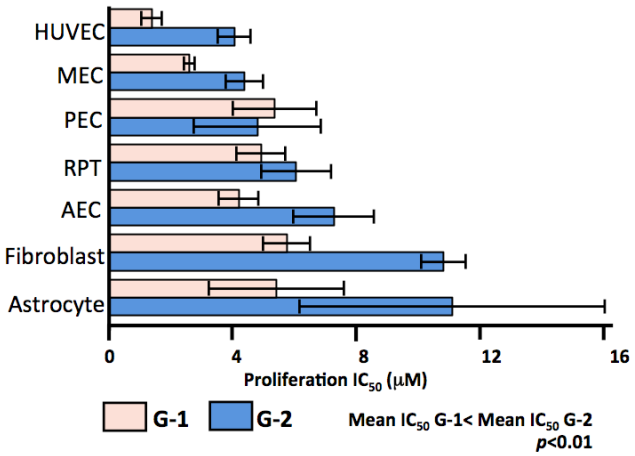


Figure S2 (related to Figure 2). G-2 is less toxic than G-1 in primary cells. Primary cells show increased sensitivity to G-1 in comparison to G-2 as measured by XTT viability assay. Mean IC_{50} for G-1 is significantly lower than mean IC_{50} for G-2, $p < 0.01$. HUVEC = Human Umbilical Vascular Endothelial Cell, MEC = Mammary Epithelial Cell, PEC = Prostate Epithelial Cell, RPT = Renal Proximal Tubule, AEC = Airway Epithelial Cell. Data represents mean ± SEM viability relative to DMSO (n = 3-7).

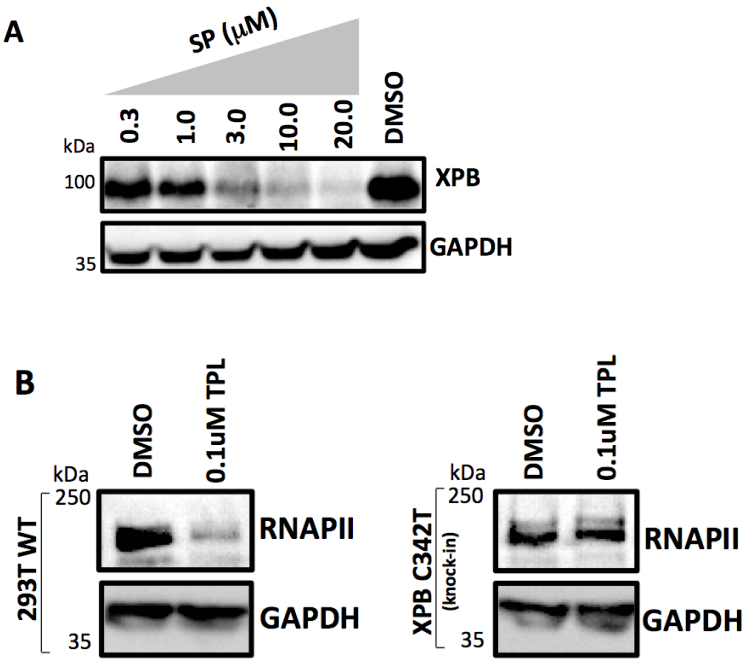


Figure S3 (related to Figure 3). Spironolactone degrades XPB while triptolide requires wild type XPB for the degradation of Rpb1. (**A**) Whole cell lysates of cells treated with increasing concentrations of spironolactone (SP) were subjected to western blot analysis using antibodies specific for XPB shows that spironolactone induces the degradation of endogenous XPB in cells in a dose dependent manner. (**B**) Isogenic cells with wild type (293T WT) or triptolide resistant mutant (XPB C342T) XPB were treated with 0.1 mM triptolide then lysed for western blot analysis using anti-Rpb1 specific antibodies. Treatment with triptolide leads to the degradation of the Rpb1 subunit of RNAPII degradation in WT XPB cells in contrast to triptolide exposed cells with XPB C342T mutation where Rpb1 levels resemble DMSO control. GAPDH was used a loading control.

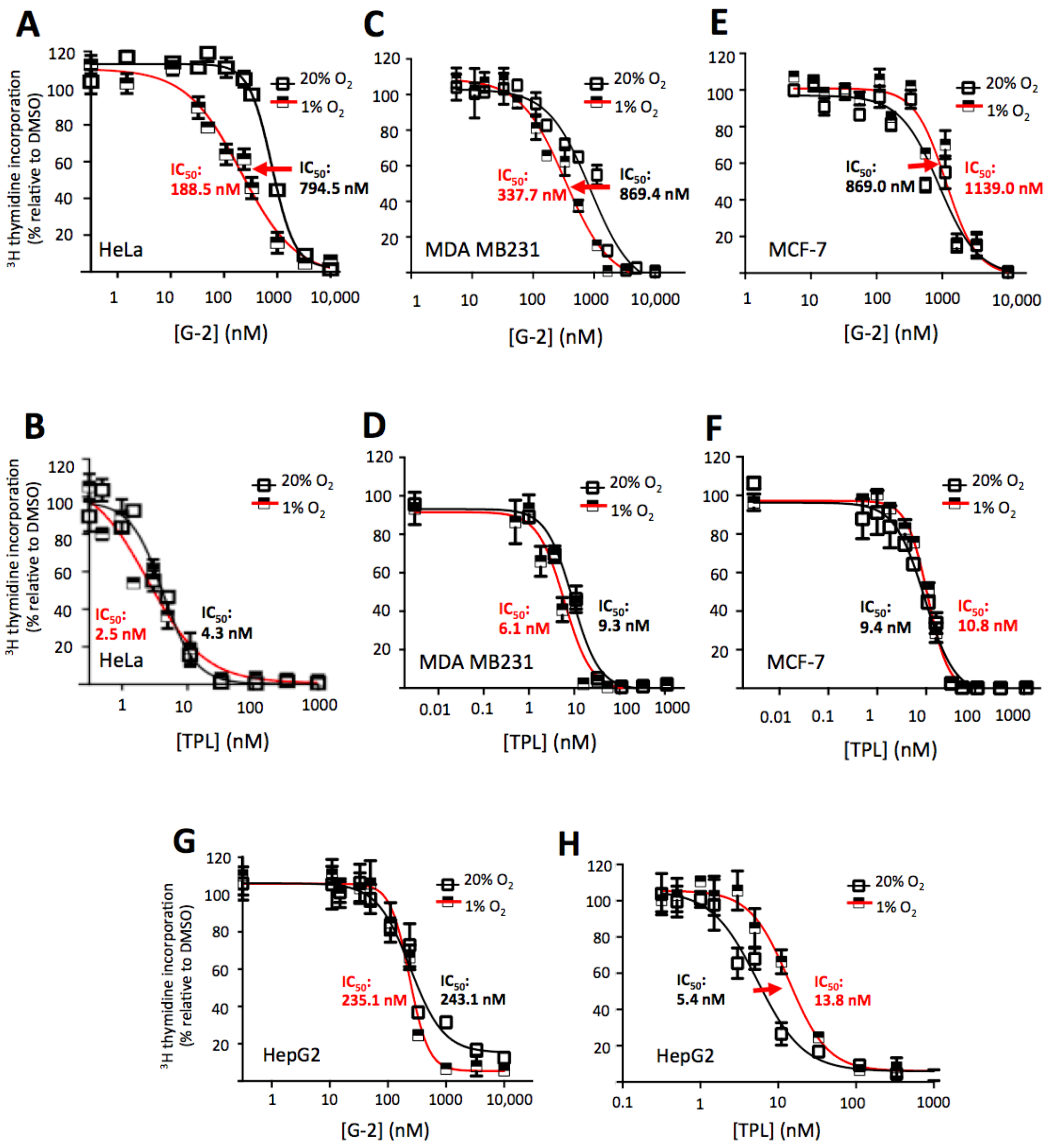
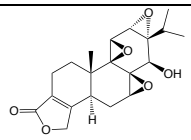
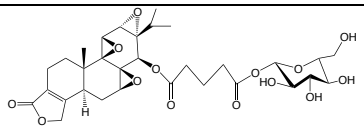
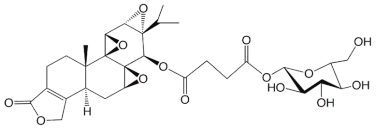
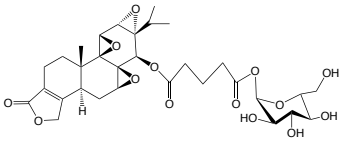
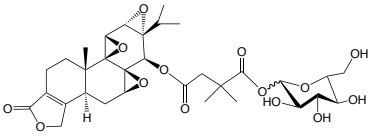
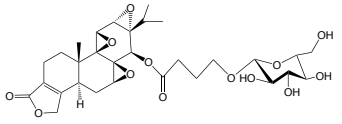
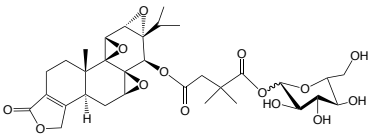
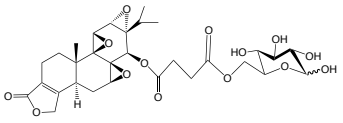
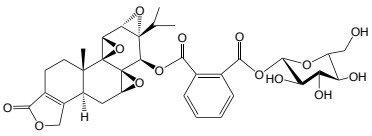
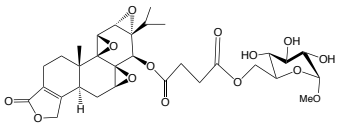
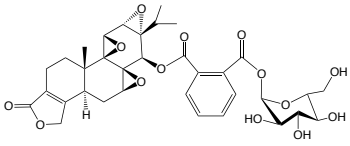


Figure S4 (related to Figure 5). Hypoxia affects sensitivity of cancer cells to glutriptolide-2. Exposure of HeLa (**A**) and MDA MB231 cells (**B**) to a hypoxic environment enhances the anti-proliferative effect of glutriptolide-2 (G-2) at 48 h post treatment as measured by ^{3}H thymidine incorporation in contrast to MCF-7 (**E**) or HepG2 (**G**) where modest enhancement or resistance is observed during hypoxia. Triptolide (*TPL*) shows modest anti-proliferative effect in all cells tested except HepG2 that showed resistance upon hypoxia. Proliferation was measured by ^{3}H thymidine incorporation and plotted using GraphPad prism. Data represents mean ± SEM relative to DMSO (n = 3).

Table S1 (related to Figure 1). Chemical structures of glucose-conjugated triptolides and their antiproliferative activities against HEK 293T cells.

Entry	Structure	IC50 ±SEM(nM)	Entry	Structure	IC50 ±SEM(nM)
TPL		5.6 (±0.415)	G2-5		1134 (±0.1.15)
G1		279 (±0.611)	G2-6		735 (±0.1.11)
G2-1		3305 (±0.980)	G2-7		71 (±0.1.07)
G2-2		999 (±0.2.17)	G2-8		244 (±0.810)
G2-3		5888 (±0.1.19)	G2-9		395 (±0.523)
G2-4		6667 (±0.2.03)			

Note: Data represents mean ± SEM relative to DMSO (*n* = 3).

Table S2 (related to Figure 2). Bioactivities of G-1 and G-2 in cancer and primary cells.

Cancer cell line		G2 IC_{50} (μM)	G9 IC_{50} (μM)
Prostate Cancer	PC3	0.50±0.10	0.61±0.18
	LNCaP	0.56±0.09	0.45±0.33
	DU-145	0.40±0.13	0.44±0.19
Breast Cancer	MDA-MB-231	0.28±0.01	0.26±0.10
	MDA-MB-453	0.53±0.20	0.53±0.28
	SK-BR-3	1.30±1.84	2.16±1.59
Head and Neck Cancer	A253	0.71±0.47	0.54±0.40
	Detroit 562	1.42±0.83	1.24±0.61
	SCC-25	1.26±0.99	1.63±0.78
Melanoma	SK-Mel-3	0.42±0.34	0.44±0.25
	SK-Mel-1	1.29±0.47	3.44±2.36
	RPMI-7951	2.67±1.34	5.95±2.45
Pancreatic Cancer	CfPAC-1	0.51±0.35	0.47±0.32
	BxPC3	4.15±0.18	5.00±2.83
	SW1990	1.52±0.33	6.48±2.79
Lung Cancer	A549	1.70±0.79	2.72±1.41
	NCI-H1299	6.40±2.43	11.49±5.51
	NCI-H1437	N/A	N/A
Liver Cancer	SNU-475	3.85±3.26	4.60±4.55
	SK-HEP-1	3.38±0.71	5.90±0.28
	SNU-387	15.51±9.28	24.43±8.90

Primary cells		G2 IC_{50} (μM)	G9 IC_{50} (μM)
Normal Cells	Astrocyte	5.31±4.29	10.88±9.66
	Fibroblast	5.64±1.28	10.61±1.22
	Airway Epithelial cell	4.12±1.39	7.13±2.84
	Renal Proximal Tubule	4.83±1.54	5.94±2.21
	Prostate Epithelial cell	5.27±2.29	4.72±3.48
	Mammary Epithelial cell	2.56±0.29	4.31±1.03
	HUVEC	1.37±0.73	3.98±1.15

Cell type	Average IC_{50} (μM)	
	G2	G9
Cancer cell lines (n = 21)	2.42±2.00	3.94±3.26
- Sensitive lines (n = 8)	0.49±0.07	0.47±0.06
- Less sensitive lines (n = 13)	3.70±2.33	6.25±3.68
Non-malignant cells	4.16±0.93	6.80±1.67

Sample comparison T-test[a]	P value[b]
Cancer cells G2 vs G9 (ALL)	0.373
- Sensitive lines	0.513
- Less sensitive lines	0.007
Primary cells G2 vs G9	0.009

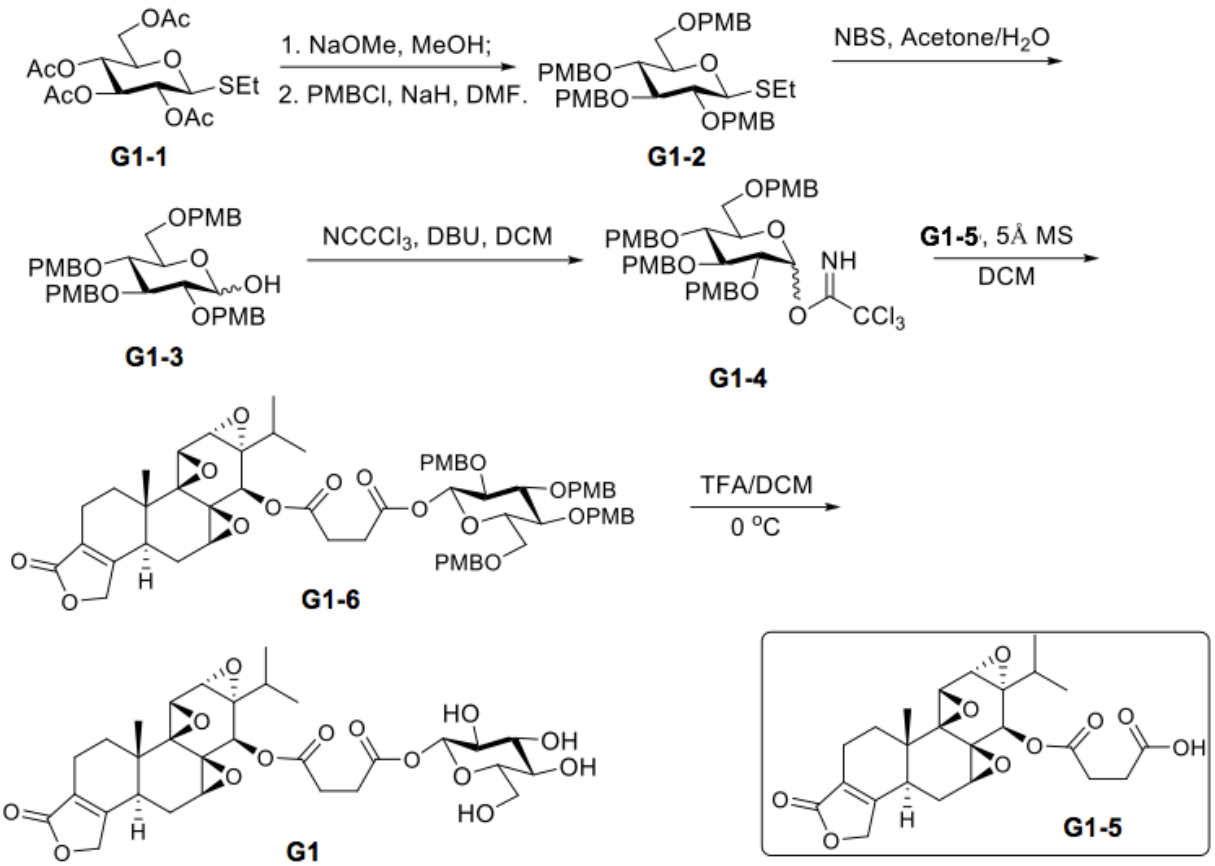
Note: Sensitive cell lines (black) have IC50 < 1 μM while less sensitive cancer cell lines (red) have IC50 > 1 μM. Mean IC50 values and their standard deviation from three independent experiments are shown. N/A indicates not applicable due to absence of sigmoidal response in dose curve. Data represents mean ± SEM relative to DMSO (*n* = 3).

[a] Student T-test done with unequal variance.

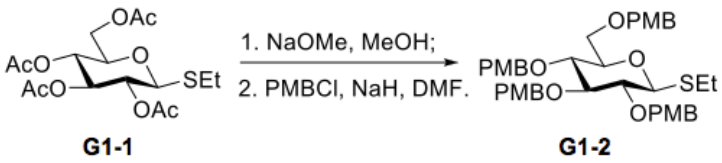
[b] P values of IC50s for G-1 versus G-2.

Supplemental Schemes

Scheme S1. Reagents and conditions for synthesis of glutriptolide G1, Related to Figure 1.



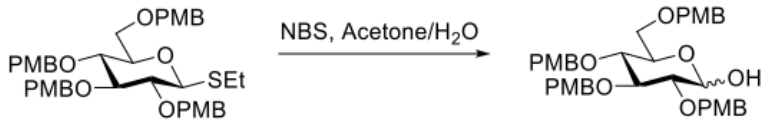
Procedures for synthesis of glutriptolide G1, Related to Figure 1.



To a solution of Compound **G1-1**[1] (2.1 g, 5.3 mmol) in methanol (20 mL), was added NaOMe (29 mg, 0.5 mmol). Stirring was continued until complete conversion of the starting material

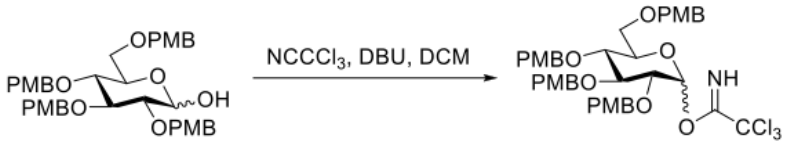
(monitored by TLC, about 2 hours). The mixture was neutralized with acidic resin, filtered and concentrated. Then the mixture was coevaporated with toluene three times and dried *in vacuo*.

The mixture was dissolved in dry DMF (27 mL), and cooled to 0 °C. NaH (1.28 g, 60% suspension, 32.1 mmol) was added slowly over 5 min. After 10 min, PMBCl (5.8 mL, 42.8 mmol) was added and the reaction stirred for another 10 min, at which time the temperature was raised to room temperature for 4 h. The reaction was re-cooled to 0 °C and water was added to quench the reaction. The organic layer was diluted with ethyl acetate, and washed twice with water, once with brine, dried over Na_2SO_4. Then, the mixture was filtered and concentrated. Column chromatography (Petroleum ether/Ethyl acetate = 4/1) afforded the product **G1-2** as a white solid (3.4 g, 4.8 mmol, 91% for two steps); ESI-MS *m/z* calcd for $C_{40}H_{48}O_9Na$ $[M+Na]^+$ 727.2911, found 727.2919.



G1-2 **G1-3**

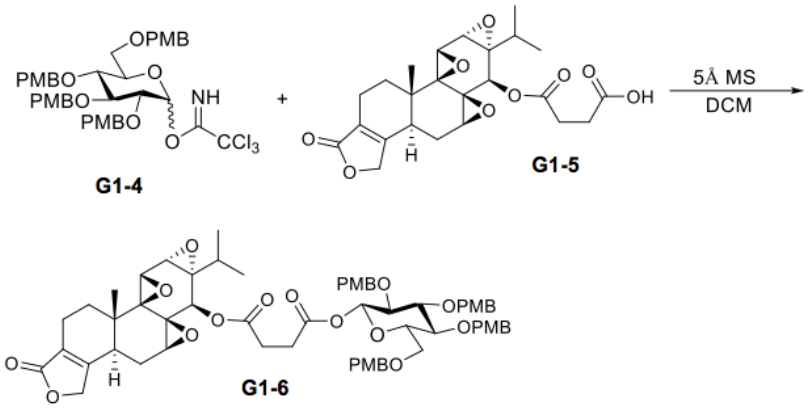
The thioglycoside **G1-2** (3.0 g, 4.25 mmol) was dissolved in acetone (50 mL) and water (5 mL), and cooled to 0 °C. N-bromosuccinimide (1.9 g, 10.7 mmol) was added which produced a bright orange color. Stirring was continued at 0 °C until TLC indicated disappearance of the starting material (about 1 h). The reaction was concentrated, then dissolved in ethyl acetate and washed with water and brine. The organic layers were dried over Na_2SO_4. Then, the mixture was filtered and concentrated. Column chromatography (Petroleum ether/Ethyl acetate = 2/1 to 1/1) afforded the product **G1-3** as a white solid (1.95 g, 3.0 mmol, 71%). ESI-MS (*m/z*): 683.6 $[M+Na]^+$.



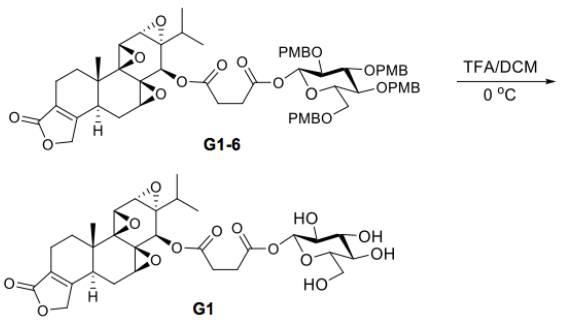
G1-3 **G1-4**

The lactol **G1-3** (380 mg, 0.58) was dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C. Trichloroacetonitrile (0.3 mL, 2.88 mmol) and DBU (cat.) were added successively. After stirring at room temperature for about 2 h, the reaction mixture was concentrated *in vacuo*. The residue was chromatographed over silica gel (Petroleum ether/EtOAc = 4:1, containing 1% Et_3N) to

yield imidate **G1-4** (400 mg, 86 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.42 – 6.69 (m, 16H), 6.47 (d, J = 3.4 Hz, 1H), 4.87 (d, J = 10.6 Hz, 1H), 4.79 – 4.71 (m, 2H), 4.66 (d, J = 11.3 Hz, 1H), 4.60 (d, J = 11.3 Hz, 1H), 4.56 (d, J = 11.7 Hz, 1H), 4.40 (d, J = 2.9 Hz, 1H), 4.37 (d, J = 4.4 Hz, 1H), 4.03 – 3.89 (m, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H), 3.75 – 3.66 (m, 3H), 3.60 (dd, J = 10.8, 2.1 Hz, 1H).

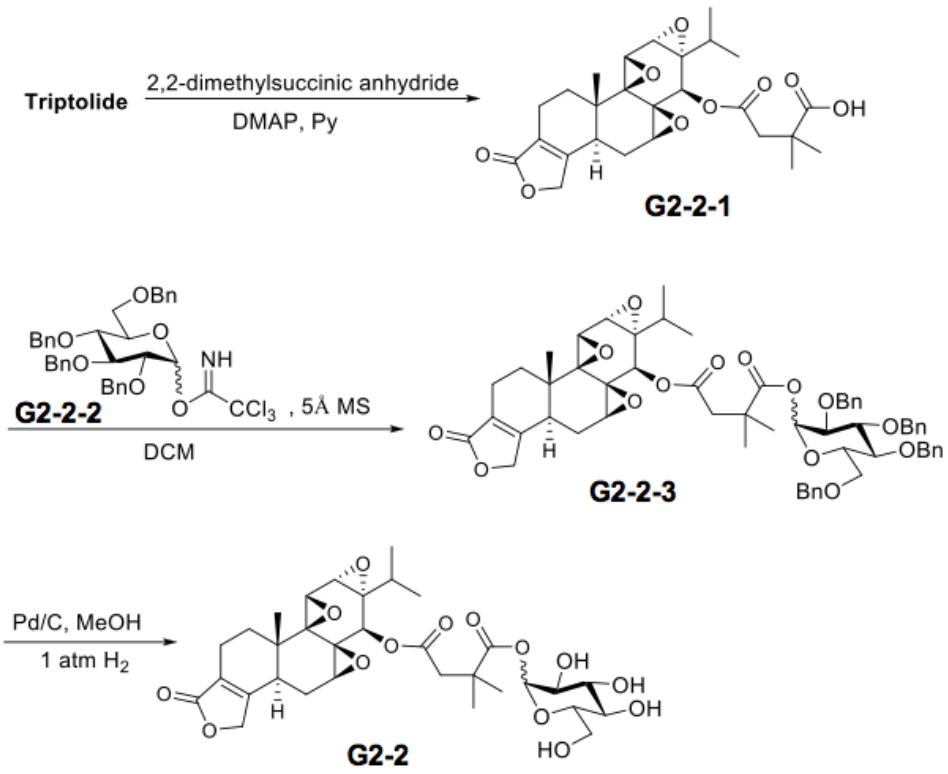


Trichloroacetimidate donor **G1-4** (2.7 g, 3.35 mmol) and acid **G1-5** (1.03g, 2.24 mmol) were dissolved in CH_2Cl_2 (100 mL) under nitrogen. Powdered freshly activated 5Å molecular sieves (200 mg) were added. Stirring was continued until TLC indicated the disappearance of the donor (about 8 h). The mixture was filtered through Celite, and the filtrated was concentrated in vacuum. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 1:1) to give compound **G1-6** (2.43 g, 2.2 mmol, 98%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 6.71 (m, 16H), 5.58 (d, J = 8.0 Hz, 1H), 5.08 (s, 1H), 4.93 – 4.50 (m, 9H), 4.46 – 4.26 (m, 2H), 3.74 – 3.26 (m, 10H), 2.72 (m, 6H), 1.04 (s, 3H), 0.95 (d, J = 7.0 Hz, 3H), 0.83 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.43, 171.55, 170.70, 160.18, 159.36, 159.29, 130.72, 130.37, 130.27, 130.03, 129.81, 129.67, 129.62, 129.56, 125.66, 113.90, 113.86, 94.49, 84.57, 80.68, 75.60, 75.44, 74.70, 73.17, 71.44, 70.11, 67.65, 63.61, 63.41, 61.28, 59.72, 55.45, 55.37, 55.32, 55.08, 40.44, 35.74, 29.90, 29.22, 28.95, 28.00, 23.50, 17.58, 17.13, 16.79, 13.85; ESI-MS m/z calcd for $C_{62}H_{70}O_{18}Na$ $[M+Na]^+$ 1125.4454, found 1125.4471.



Compound **G1-6** (2.0 g, 1.81 mmol) was dissolved in DCM (36.0 mL), and cooled to 0 °C. Then TFA (3.6 mL) was added. After stirring at this temperature for about 10 min, the reaction mixture was concentrated *in vacuo*. The residue was chromatographed over silica gel (DCM/Methanol = 10:1) to yield the product **G1** (1.1 g, 1.77 mmol, 98%) as a white solid. ^{1}H NMR (500 MHz, CD_3OD) δ 5.54 – 5.43 (d, J = 8.0, 1H), 5.08 (s, 1H), 3.97 (d, J = 3.1 Hz, 1H), 3.90 – 3.77 (m, 1H), 3.68 (dd, J = 12.0, 4.4 Hz, 1H), 3.64 (d, J = 2.7 Hz, 1H), 3.48 (d, J = 5.7 Hz, 1H), 3.46 – 3.35 (m, 4H), 2.85 – 2.67 (m, 4H), 2.39 – 2.18 (m, 2H), 2.07 (m, 1H), 1.91 (m, 2H), 1.50 (dd, J = 12.4, 4.9 Hz, 1H), 1.34 (td, J = 12.1, 5.8 Hz, 1H), 1.03 (s, 3H), 0.93 (d, J = 7.0 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H);); ^{13}C NMR (125 MHz, CD_3CN) δ 174.53, 172.51, 172.04, 162.45, 125.25, 94.96, 76.48, 73.09, 72.68, 71.29, 64.56, 63.91, 62.65, 62.33, 60.67, 56.37, 55.70, 41.05, 36.46, 30.50, 29.67, 29.48, 28.78, 23.75, 17.88, 17.72, 17.11, 14.29; ESI-MS *m/z* calcd for $C_{30}H_{38}O_{14}Na$ $[M+Na]^+$ 645.2154, found 645.2166.

Scheme S2. Synthetic route of Glutriptolide G2-2 and G2-3, Related to Figure 1.



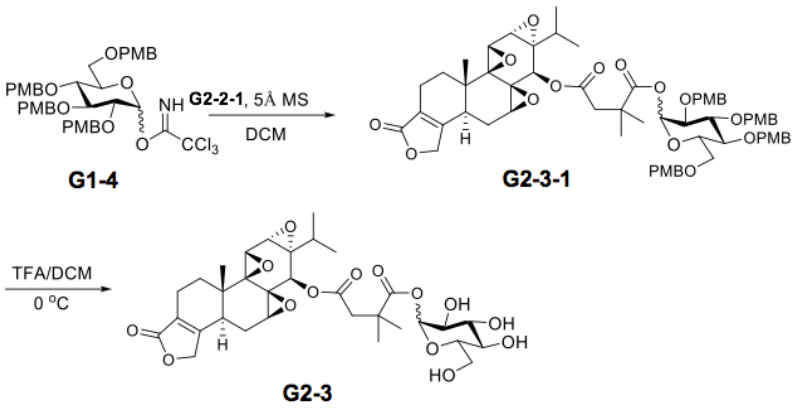
Synthetic procedures for Glutriptolide G2-2 and G2-3, Related to Figure 1.

To a solution of Triptolide (200 mg, 0.56 mmol) in pyridine (4 mL) were added 2,2-dimethylsuccinic anhydride (285 mg, 2.22 mmol) and DMAP (14 mg, 0.11 mmol). After stirring overnight, the mixture was diluted with ethyl acetate, then washed with saturated copper sulfate, water and brine, respectively. The organic layers were dried over Na_2SO_4 and filtered. The filtrate was concentrated using a rotary evaporator to give a residue. The residue was purified by silica gel column chromatography (CH_2Cl_2/CH_3OH, 15:1) to give compound **G2-2-1** (215 mg, 0.44 mmol, 80%) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (s, 1H), 4.68 (s, 2H), 3.81 (d, J = 3.1 Hz, 1H), 3.53 (d, J = 2.7 Hz, 1H), 3.45 (d, J = 5.6 Hz, 1H), 2.71 (dd, J = 23.2, 7.1 Hz, 4H), 2.32 (d, J = 16.4 Hz, 1H), 2.15 (ddd, J = 25.7, 15.9, 10.0 Hz, 2H), 2.00 – 1.81 (m, 2H), 1.37 (s, 3H), 1.35 (s, 3H), 1.23 (dt, J = 11.6, 7.9 Hz, 3H), 1.05 (s, 3H), 0.94 (d, J = 6.9 Hz, 3H), 0.82 (d, J = 6.9 Hz, 3H); ESI-MS (*m/z*): 511.3 $[M+Na]^+$.

Trichloroacetimidate donor **G2-2-2** (100 mg, 0.15 mmol) and acid **G2-2-1** (49 mg, 0.1 mmol) were dissolved in CH_2Cl_2 (2 mL) under nitrogen. Powdered freshly activated 5Å molecular sieves (200 mg) were added. Stirring was continued until TLC indicated the disappearance of the donor (about 8 h). The mixture was filtered through Celite, and the filtrated was concentrated in vacuum. The residue was purified by silica gel column chromatography

(petroleum ether/EtOAc, 2:1 to 1:1) to give the product **G2-2-3** (48 mg, 0.047 mmol, α/β = 1.1: 1.0, 47%) as a white solid.

Palladium on charcoal (10%, 10 mg) was added to a solution of compound **G2-2-3** (22 mg, 0.022 mmol) in CH_3OH. The mixture was placed under an atmosphere of hydrogen for about 4 h. The mixture was filtered and concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2/CH_3OH, 15:1) to give the product **G2-2** (10 mg, 0.015 mmol, α/β = 1.0: 1.0, 71%) as a white solid; ^{1}H NMR (400 MHz, CD_3OD) δ 6.11 (d, J = 3.7 Hz, 0.5H), 5.45 (d, J = 7.7 Hz, 0.5H), 5.07 (d, J = 4.3 Hz, 1H), 4.80 (dd, J = 19.6, 10.1 Hz, 2H), 3.96 (d, J = 3.0 Hz, 1H), 3.84 (d, J = 11.2 Hz, 1H), 3.80 – 3.59 (m, 4H), 3.56 (dd, J = 9.8, 3.7 Hz, 1H), 3.51 – 3.33 (m, 4H), 2.76 (p, J = 15.9 Hz, 3H), 2.33 – 2.16 (m, 2H), 2.02 (d, J = 47.8 Hz, 1H), 1.90 (ddt, J = 11.6, 9.3, 7.6 Hz, 2H), 1.50 (dd, J = 12.5, 4.6 Hz, 1H), 1.35 (d, J = 5.8 Hz, 6H), 1.03 (s, 3H), 0.94 (dd, J = 7.0, 2.0 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H) ; ESI-MS *m/z* calcd for $C_{32}H_{42}O_{14}Na$ $[M+Na]^+$ 673.2467, found 673.2466.

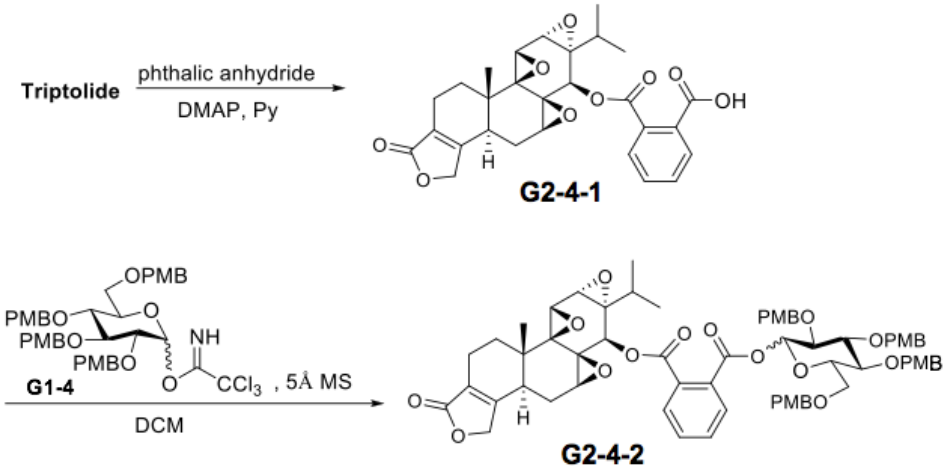


Trichloroacetimidate donor **G1-4** (371 mg, 0.46 mmol) and acid **G2-2-1** (150 mg, 0.31 mmol) were dissolved in CH_2Cl_2 (6 mL) under nitrogen. Powdered freshly activated 5Å molecular sieves (600 mg) were added. Stirring was continued until TLC indicated the disappearance of the donor (about 8 h). The mixture was filtered through Celite, and the filtrated was concentrated in vacuum. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 2:1 to 1:1) to give the product **G2-3-1** (180 mg, 0.16 mmol, α/β = 6.6: 1.0, 52%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, J = 5.7, 2.8 Hz, 6H), 7.03 (d, J = 8.6 Hz, 3H), 6.89 – 6.70 (m, 10H), 6.37 (d, J = 3.5 Hz, 1H), 5.02 (d, J = 0.9 Hz, 1H), 4.86 (d, J = 10.6 Hz, 1H), 4.73 (dd, J = 10.3, 7.6 Hz, 2H), 4.66 – 4.43 (m, 6H), 4.39 (dd, J = 11.1, 4.5 Hz, 2H), 3.83 – 3.72 (m, 18H), 3.71 – 3.62 (m, 4H), 3.62 – 3.52 (m, 2H), 3.51 – 3.39 (m, 1H), 3.30 (d, J = 5.5 Hz, 1H), 1.35 (d, J = 5.1 Hz, 7H), 1.00 (s, 3H), 0.92 (d, J = 6.9 Hz, 4H), 0.79 (d, J = 6.9 Hz, 4H); ESI-MS *m/z* calcd for $C_{64}H_{74}O_{18}Na$ $[M+Na]^+$ 1153.4767, found 1153.4781.

Compound **G2-3-1**(148 mg, 0.13 mmol) was dissolved in DCM (5 mL), and cooled to 0 °C. Then TFA (0.5 mL) was added. After stirring at this temperature for about 10 min, the reaction

mixture was concentrated *in vacuo*. The residue was chromatographed over silica gel (DCM/Methanol = 10:1) to yield the product **G2-3** (77 mg, 0.12 mmol, α/β = 5.2: 1.0, 91%) as a white solid. ^{1}H NMR (500 MHz, CD_3OD) δ 6.08 (d, *J* = 3.6 Hz, 1H), 5.42 (d, *J* = 7.9 Hz, 0H), 5.02 (d, *J* = 4.6 Hz, 1H), 4.86 – 4.68 (m, 2H), 4.01 – 3.85 (m, 1H), 3.79 – 3.51 (m, 5H), 3.43 (dd, *J* = 12.2, 7.4 Hz, 2H), 2.89 – 2.64 (m, 3H), 2.21 (tt, *J* = 16.9, 4.6 Hz, 2H), 2.03 (t, *J* = 13.4 Hz, 1H), 1.93 – 1.76 (m, 2H), 1.45 (dd, *J* = 12.7, 5.3 Hz, 1H), 1.32 (d, *J* = 5.4 Hz, 7H), 0.99 (s, 3H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 177.13, 176.06, 172.35, 163.93, 125.43, 93.92, 75.92, 74.90, 72.96, 72.51, 71.99, 70.80, 64.83, 64.10, 62.82, 62.05, 61.04, 56.68, 56.14, 49.85, 44.78, 42.35, 41.38, 36.75, 30.71, 29.31, 25.63, 25.26, 24.12, 17.91, 17.85, 17.14, 14.16; ESI-MS (*m/z*): 673.6 $[M+Na]^+$; ESI-MS *m/z* calcd for $C_{32}H_{42}O_{14}Na$ $[M+Na]^+$ 673.2467, found 673.2466.

Scheme S3. Synthetic route of Glutriptolide G2-4 and G2-5, Related to Figure 1.



Synthetic procedures for Glutriptolide G2-4 and G2-5, Related to Figure 1.

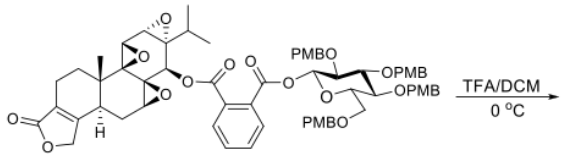
To a solution of Triptolide (200 mg, 0.56 mmol) in pyridine (4 mL) were added phthalic anhydride (285 mg, 2.22 mmol) and DMAP (14 mg, 0.11 mmol). After stirring overnight, the mixture was diluted with ethyl acetate, then washed with saturated copper sulfate, water and brine, respectively. The organic layers were dried over Na_2SO_4 and filtered. The filtrate was concentrated using a rotary evaporator to give a residue. The residue was purified by silica gel column chromatography (CH_2Cl_2/CH_3OH, 15:1) to give compound **G2-4-1** (260 mg, 0.51 mmol, 91%) as a white solid; ^{1}H NMR (400 MHz, CD_3Cl) δ 5.07 (s, 1H), 4.68 (s, 2H), 3.81 (d, J = 3.1 Hz, 1H), 3.53 (d, J = 2.7 Hz, 1H), 3.45 (d, J = 5.6 Hz, 1H), 2.71 (dd, J = 23.2, 7.1 Hz, 4H), 2.32 (d, J = 16.4 Hz, 1H), 2.15 (ddd, J = 25.7, 15.9, 10.0 Hz, 2H), 2.00 – 1.81 (m, 2H), 1.37 (s, 3H), 1.35 (s, 3H), 1.23 (dt, J = 11.6, 7.9 Hz, 3H), 1.05 (s, 3H), 0.94 (d, J = 6.9 Hz, 3H), 0.82 (d, J = 6.9 Hz, 3H); ESI-MS (*m/z*): 511.3 $[M+Na]^+$.

Trichloroacetimidate donor **G1-4** (618 mg, 0.77 mmol) and acid **G2-4-1** (260 mg, 0.51 mmol) were dissolved in CH_2Cl_2 (10 mL) under nitrogen. Powdered freshly activated 5Å molecular sieves (900 mg) were added. Stirring was continued until TLC indicated the disappearance of the donor (about 8 h). The mixture was filtered through Celite, and the filtrated was concentrated in vacuum. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 2:1 to 1:1) to give the products **G2-4-2α** (75 mg, 0.065 mmol, 13%) and **G2-4-2β** (225 mg, 0.195 mmol, 39%) as a white solid.

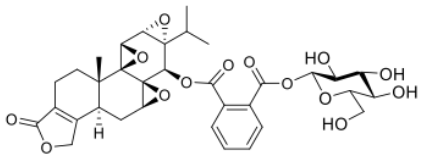
G2-4-2α: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, J = 7.5, 1.4 Hz, 1H), 7.69 (dd, J = 7.6, 1.4 Hz, 1H), 7.62 – 7.50 (m, 2H), 7.35 – 7.23 (m, 6H), 7.06 – 7.00 (m, 2H), 6.91 – 6.77 (m, 8H), 6.53 (d, J = 3.5 Hz, 1H), 5.28 (s, 1H), 4.86 (d, J = 10.6 Hz, 1H), 4.78 – 4.54 (m, 9H), 4.40 (dd, J = 11.0, 8.4 Hz, 2H), 3.97 – 3.86 (m, 2H), 3.83 – 3.67 (m, 21H), 3.61 (dd, J = 10.8, 2.0 Hz, 1H), 3.54 (d, J = 3.1 Hz, 1H), 3.46 (d, J = 5.6 Hz, 1H), 2.68 (d, J = 12.9 Hz, 1H), 2.31 (d, J = 17.6 Hz,

1H), 2.19 (ddd, *J* = 24.9, 12.5, 6.3 Hz, 4H), 1.90 – 1.79 (m, 1H), 1.54 (dd, *J* = 12.1, 5.4 Hz, 1H), 1.06 (s, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.81 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 173.37, 166.23, 165.61, 160.19, 159.44, 159.40, 159.28, 131.78, 131.64, 131.47, 131.03, 130.42, 130.11, 130.02, 129.79, 129.74, 129.72, 129.67, 129.19, 125.63, 113.92, 113.90, 113.87, 91.22, 81.48, 78.70, 77.36, 76.60, 75.38, 75.03, 73.25, 72.72, 72.27, 70.08, 67.60, 63.70, 61.21, 60.50, 60.06, 55.60, 55.38, 55.34, 55.02, 40.47, 35.76, 29.97, 27.36, 23.53, 21.17, 17.58, 17.16, 16.76, 14.31, 13.88; ESI-MS *m/z* calcd for $C_{66}H_{70}O_{18}Na$ $[M+Na]^+$ 1173.4454, found 1173.4466.

G2-4-2β: ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.77 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.63 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.52 (td, *J* = 7.6, 1.3 Hz, 1H), 7.42 (td, *J* = 7.6, 1.3 Hz, 1H), 7.21 – 7.11 (m, 5H), 7.11 – 7.04 (m, 2H), 7.03 – 6.96 (m, 2H), 6.80 – 6.63 (m, 9H), 5.77 – 5.70 (m, 1H), 5.22 (s, 1H), 4.77 – 4.45 (m, 9H), 4.37 (dd, *J* = 12.9, 11.0 Hz, 2H), 3.73 (d, *J* = 3.2 Hz, 1H), 3.71 (s, 3H), 3.69 (s, 3H), 3.67 (s, 3H), 3.65 (s, 3H), 3.63 (q, *J* = 5.4, 4.2 Hz, 5H), 3.55 – 3.48 (m, 1H), 3.46 (d, *J* = 3.0 Hz, 1H), 3.40 (d, *J* = 5.5 Hz, 1H), 2.56 (d, *J* = 12.7 Hz, 1H), 2.20 (d, *J* = 17.8 Hz, 1H), 2.15 – 1.91 (m, 3H), 1.77 (t, *J* = 14.0 Hz, 1H), 1.45 (dd, *J* = 12.4, 5.3 Hz, 1H), 1.10 (td, *J* = 12.3, 5.8 Hz, 1H), 0.97 (s, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.73 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.30, 166.56, 164.77, 160.22, 159.30, 159.22, 132.90, 132.04, 130.97, 130.66, 130.30, 130.26, 130.20, 130.18, 129.76, 129.73, 129.66, 129.56, 129.51, 129.45, 129.24, 125.43, 113.80, 113.77, 94.88, 84.68, 80.50, 77.01, 75.81, 75.24, 74.59, 74.51, 73.15, 72.16, 70.02, 67.75, 63.61, 63.57, 61.29, 60.02, 55.56, 55.29, 55.24, 55.21, 54.89, 40.33, 35.65, 29.85, 27.33, 23.36, 17.54, 17.06, 16.81, 13.80; ESI-MS *m/z* calcd for $C_{66}H_{70}O_{18}Na$ $[M+Na]^+$ 1173.4454, found 1173.4466.



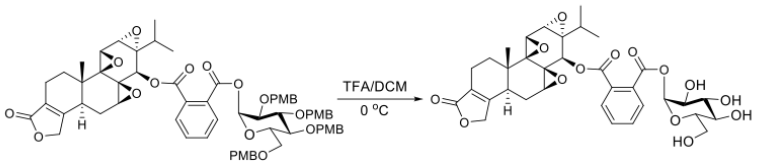
G2-4-2



G2-4

Compound **G2-4-2β** (118 mg, 0.10 mmol) was dissolved in DCM (5 mL), and cooled to 0 °C. Then TFA (0.5 mL) was added. After stirring at this temperature for about 10 min, the reaction mixture was concentrated *in vacuo*. The residue was chromatographed over silica gel (DCM/Methanol = 10:1) to yield the product **G2-4** (55 mg, 80%) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) *δ* 8.05 – 7.57 (m, 4H), 5.72 (d, *J* = 7.7 Hz, 1H), 5.29 (d, *J* = 1.0 Hz, 1H), 4.85 – 4.69 (m, 2H), 4.01 (d, *J* = 3.2 Hz, 1H), 3.88 (dd, *J* = 12.2, 2.2 Hz, 1H), 3.76 – 3.67 (m, 2H), 3.58

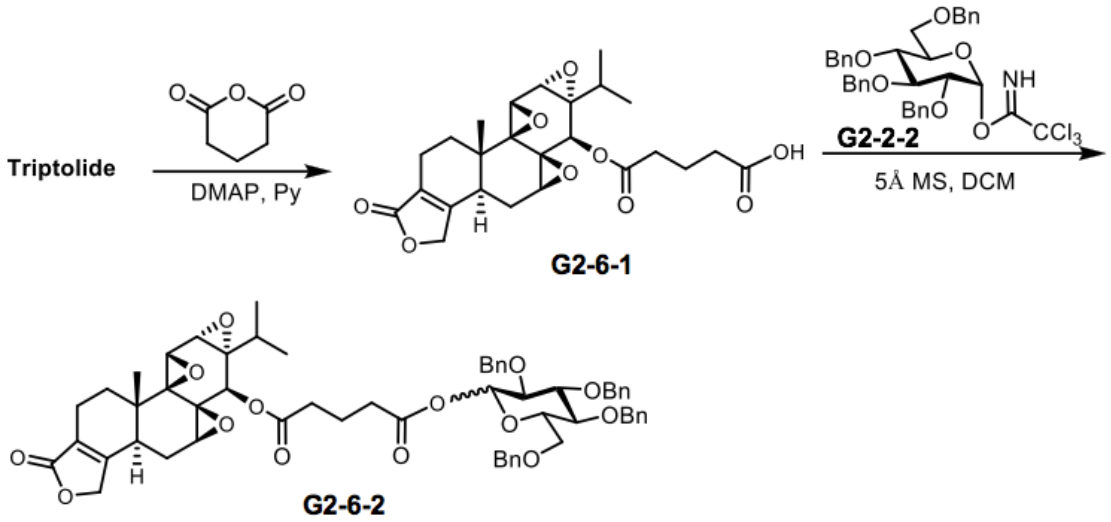
(d, J = 5.6 Hz, 1H), 3.54 – 3.37 (m, 4H), 2.87 – 2.71 (m, 1H), 2.36 – 1.98 (m, 4H), 1.57 – 1.43 (m, 1H), 1.33 (ddd, J = 17.0, 11.4, 4.9 Hz, 1H), 1.06 (s, 3H), 1.03 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 184.70, 176.86, 175.66, 172.48, 142.00, 141.68, 141.49, 141.09, 139.42, 139.36, 134.12, 105.44, 87.66, 86.46, 83.20, 82.88, 80.62, 79.63, 73.61, 72.96, 71.45, 71.02, 70.16, 65.58, 64.91, 50.00, 45.41, 39.42, 37.60, 32.78, 26.61, 26.49, 25.84, 22.88; ESI-MS m/z calcd for $C_{34}H_{38}O_{14}Na$ $[M+Na]^+$ 693.2154, found 693.2143.



G2-4-2 **G2-5**

Compound **G2-4-2α** (50mg, 0.043 mmol) was dissolved in DCM (2 mL), and cooled to 0 °C. Then TFA (0.2 mL) was added. After stirring at this temperature for about 10 min, the reaction mixture was concentrated *in vacuo*. The residue was chromatographed over silica gel (DCM/Methanol = 10:1) to yield the product **G2-5** (24 mg, 83%) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.14 – 7.51 (m, 4H), 6.38 (d, J = 3.7 Hz, 1H), 5.27 (d, J = 0.9 Hz, 1H), 4.86 – 4.70 (m, 2H), 4.00 (d, J = 3.1 Hz, 1H), 3.93 – 3.71 (m, 3H), 3.71 – 3.67 (m, 1H), 3.66 (d, J = 3.7 Hz, 1H), 3.58 (d, J = 5.6 Hz, 1H), 3.48 (s, 1H), 2.78 (d, J = 12.3 Hz, 1H), 2.33 – 2.18 (m, 2H), 2.10 (q, J = 6.9 Hz, 1H), 1.99 – 1.87 (m, 1H), 1.56 – 1.46 (m, 1H), 1.39 – 1.27 (m, 2H), 1.04 (s, 3H), 1.00 (d, J = 6.9 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 176.08, 167.95, 167.72, 163.89, 133.99, 133.20, 132.53, 132.10, 130.94, 130.25, 125.48, 94.92, 76.28, 74.86, 74.50, 72.61, 71.99, 70.83, 64.95, 64.33, 62.89, 62.11, 61.52, 56.89, 56.28, 41.41, 36.79, 30.80, 29.13, 24.15, 17.98, 17.89, 17.23, 14.23; ESI-MS m/z calcd for $C_{34}H_{38}O_{14}Na$ $[M+Na]^+$ 693.2154, found 693.2143.

Scheme S4. Synthetic route of Glutriptolide G2-6 and G2-7, Related to Figure 1.



Synthetic procedures for Glutriptolide G2-6 and G2-7, Related to Figure 1.

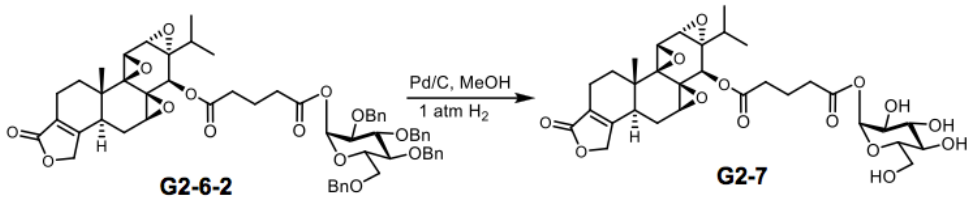
To a solution of Triptolide (50 mg, 0.14 mmol) in pyridine (2 mL) were added glutaric anhydride (63 mg, 4 mmol) and DMAP (24 mg, 0.556 mmol). After stirring overnight, the mixture was diluted with ethyl acetate, then washed with saturated copper sulfate, water and brine, respectively. The organic layers were dried over Na_2SO_4 and filtered. The filtrate was concentrated using a rotary evaporator. The residue was purified by silica gel column chromatography (CH_2Cl_2/CH_3OH, 15:1) to give the product **G2-6-1** (48 mg, 0.10 mmol, 73%) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.08 (s, 1H), 4.67 (s, 2H), 3.83 (d, J = 3.1 Hz, 1H), 3.53 (d, J = 2.7 Hz, 1H), 3.47 (d, J = 5.6 Hz, 1H), 2.68 (d, J = 13.1 Hz, 1H), 2.61 – 1.81 (m, 14H), 1.04 (s, 3H), 0.95 (d, J = 7.0 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H); ESI-MS (*m/z*): 497.3 $[M+Na]^+$.

Trichloroacetimidate donor **G2-2-2** (103 mg, 0.15 mmol) and acid **G2-6-1** (48 mg, 0.1 mmol)were dissolved in CH_2Cl_2 (2 mL) under nitrogen. Powdered freshly activated 5Å molecular sieves (200 mg) were added. Stirring was continued until TLC indicated the disappearance of the donor (about 8 h). The mixture was filtered through Celite, and the filtrated was concentrated in vacuum. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 1:1) to give the products **G2-6-2α** (12 mg, 0.012 mmol, 12%) and **G2-6-2β** (15 mg, 0.015 mmol, 15%) as a white solid.

G2-6-2α: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.00 (m, 21H), 6.39 (d, J = 3.4 Hz, 1H), 5.08 (s, 1H), 4.96 (d, J = 10.9 Hz, 1H), 4.82 (t, J = 10.2 Hz, 2H), 4.76 – 4.41 (m, 7H), 4.02 – 3.81 (m, 2H), 3.81 – 3.56 (m, 5H), 3.45 (dd, J = 14.9, 4.1 Hz, 2H), 2.63 (d, J = 13.1 Hz, 1H), 2.52 (dt,

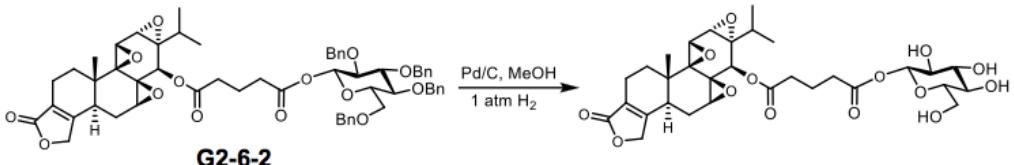
J = 17.8, 7.2 Hz, 4H), 2.33 – 2.17 (m, 1H), 2.17 – 1.92 (m, 4H), 1.92 – 1.73 (m, 2H), 1.67 – 1.44 (m, 2H), 1.34 – 1.05 (m, 3H), 1.00 (s, 3H), 0.94 (d, J = 7.0 Hz, 3H), 0.81 (d, J = 6.9 Hz, 3H); ESI-MS m/z calcd for $C_{59}H_{64}O_{14}Na$ $[M+Na]^+$ 1019.4188, found 1019.4183.

G2-6-2β: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.04 (m, 21H), 5.61 (d, J = 8.1 Hz, 1H), 5.08 (s, 1H), 4.79 (d, J = 24.9 Hz, 5H), 4.63 (d, J = 12.1 Hz, 5H), 3.73 (s, 5H), 3.67 – 3.52 (m, 2H), 3.48 (d, J = 3.0 Hz, 1H), 3.44 (d, J = 5.5 Hz, 1H), 2.65 (d, J = 13.3 Hz, 1H), 2.59 – 2.22 (m, 5H), 2.04 (s, 7H), 1.66 – 1.47 (m, 2H), 1.33 – 1.12 (m, 3H), 1.01 (s, 3H), 0.94 (d, J = 7.0 Hz, 3H), 0.82 (d, J = 6.9 Hz, 3H); ESI-MS m/z calcd for $C_{59}H_{64}O_{14}Na$ $[M+Na]^+$ 1019.4188, found 1019.4183.



G2-6-2 G2-7

Palladium on charcoal (10%, 5 mg) was added to a solution of compound **G2-6-2α** (10 mg, 0.01 mmol) in CH_3OH. The mixture was placed under an atmosphere of hydrogen for about 4 h. The mixture was filtered and concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2/CH_3OH, 15:1) to give the product **G2-7** (5 mg, 0.008 mmol, 82%) as a white solid; ^{1}H NMR (400 MHz, CD_3OD) δ 6.04 (d, J = 3.7 Hz, 1H), 4.99 (s, 1H), 4.73 – 4.68 (m, 2H), 3.86 (d, J = 3.1 Hz, 1H), 3.70 – 3.63 (m, 1H), 3.62 – 3.51 (m, 4H), 3.45 (dd, J = 9.7, 3.8 Hz, 1H), 3.38 (d, J = 5.6 Hz, 1H), 3.33 – 3.24 (m, 2H), 2.76 – 2.29 (m, 6H), 2.22 – 2.09 (m, 2H), 2.06 – 1.72 (m, 6H), 1.46 – 1.38 (m, 1H), 0.95 (s, 3H), 0.85 (d, J = 7.0 Hz, 3H), 0.75 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 176.11, 173.91, 173.68, 163.89, 125.54, 93.47, 75.99, 74.81, 72.77, 72.30, 71.99, 70.98, 64.92, 64.15, 62.84, 62.27, 61.15, 56.79, 56.24, 41.45, 36.83, 34.17, 33.87, 30.79, 29.62, 24.17, 21.28, 17.95, 17.11, 14.25; ESI-MS (m/z): 659.5 $[M+Na]^+$.

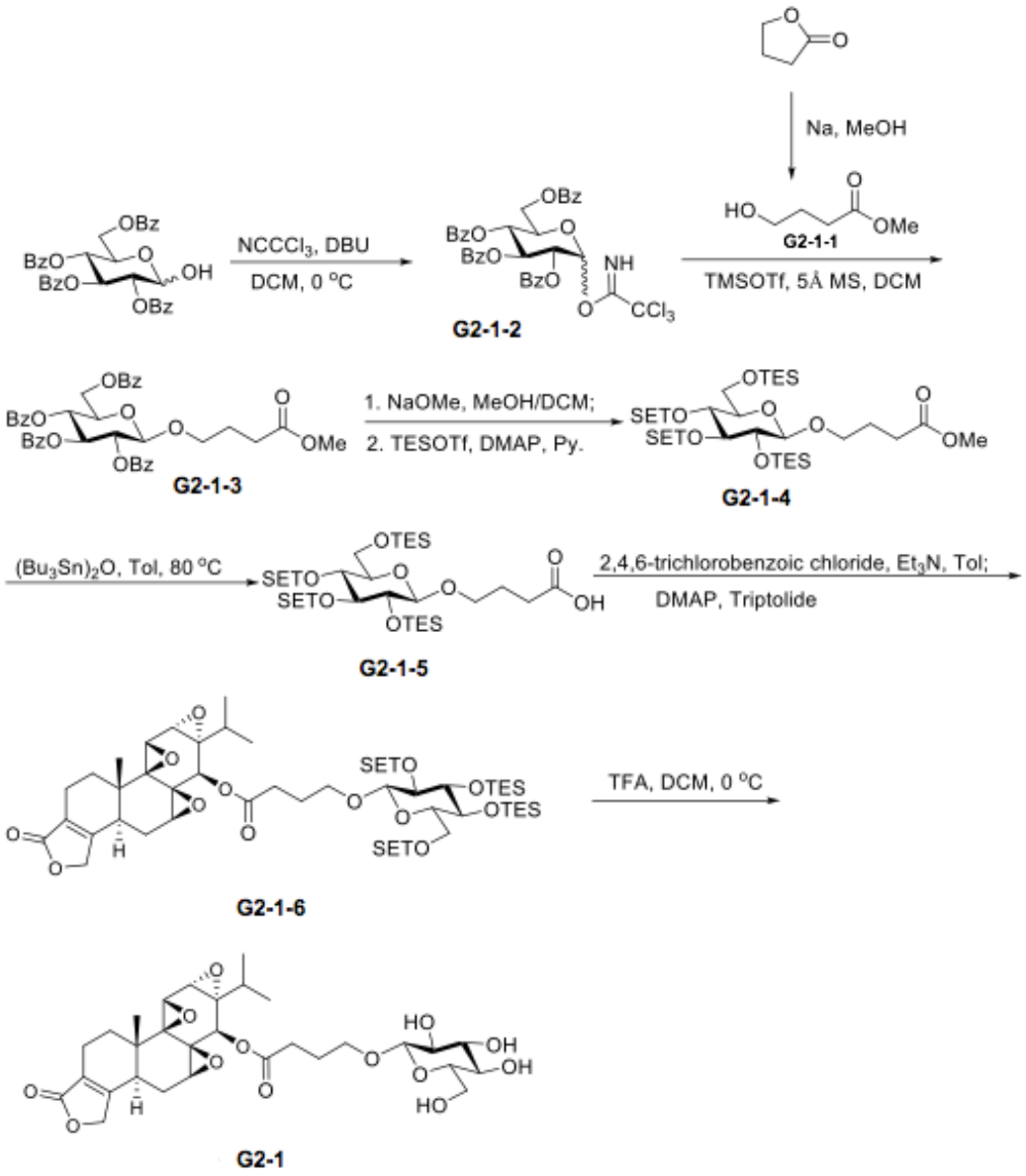


G2-6-2 G2-6

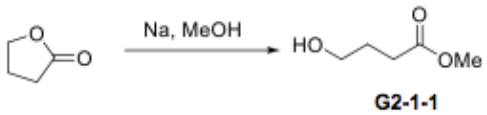
Palladium on charcoal (10%, 5 mg) was added to a solution of compound **G2-6-2β** (10 mg, 0.010 mmol) in CH_3OH. The mixture was placed under an atmosphere of hydrogen for about 4 h. The mixture was filtered and concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2/CH_3OH, 15:1) to give compound **G2-6** (5 mg, 0.008 mmol, 82%) as a white solid; ^{1}H NMR (400 MHz, CD_3OD) δ 5.49 (d, J = 8.1 Hz, 1H), 5.09 (s, 1H), 4.83 – 4.78 (m, 1H), 3.96 (d, J = 3.2 Hz, 1H), 3.83 (dd, J = 12.1, 1.7 Hz, 1H), 3.70 – 3.57 (m, 2H), 3.48 (d, J

= 5.6 Hz, 1H), 3.45 – 3.35 (m, 3H), 2.78 (d, *J* = 15.3 Hz, 1H), 2.60 – 2.42 (m, 4H), 2.27 (dt, *J* = 15.0, 5.9 Hz, 2H), 2.15 – 1.81 (m, 5H), 1.51 (dd, *J* = 12.7, 4.5 Hz, 1H), 1.39 – 1.19 (m, 3H), 1.04 (s, 2H), 0.95 (d, *J* = 7.0 Hz, 2H), 0.85 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 176.11, 173.91, 173.68, 163.89, 125.54, 93.47, 75.99, 74.81, 72.77, 72.30, 71.99, 70.98, 64.92, 64.15, 62.84, 62.27, 61.15, 56.79, 56.24, 41.45, 36.83, 34.17, 33.87, 30.79, 29.62, 24.17, 21.28, 17.95, 17.11, 14.25; ESI-MS (m/z): 659.5 $[M+Na]^+$.

Scheme S5. Synthetic route 1 for Glutriptolide G2-1, Related to Figure 1.

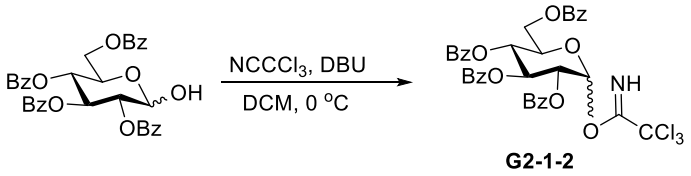


Synthetic procedures for Glutriptolide G2-1, Related to Figure 1.



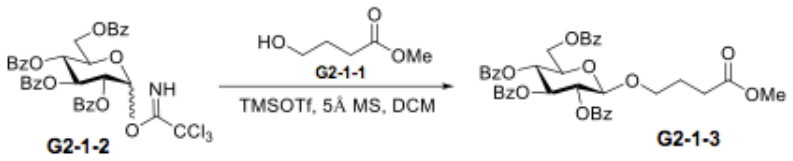
To a solution of gamma-Butyrolactone (4.3 mL, 56.5 mmol) in methanol (150 mL) at 0 °C, was added Na (1.3 g, 56.5 mmol). Stirring was continued until complete conversion of the

starting material (monitored by TLC, about 24 hours). The reaction was quenched with saturated ammonium chloride (300 mL), extracted with ethyl acetate (150 mL × 4), the organic layer was combined, washed with brine (100 mL × 4), dried over Na_2SO_4. The mixture was filtered and concentrated. Column chromatography (Petroleum ether/Ethyl acetate = 2/1) afforded the product **G2-1-1** as a colorless liquid (4.5 g, 38.1 mmol, 67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.68 – 3.59 (m, 5H), 2.41 (t, J = 7.2 Hz, 2H), 1.85 (ddd, J = 7.2, 6.1, 1.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.54, 61.94, 51.76, 30.82, 27.75



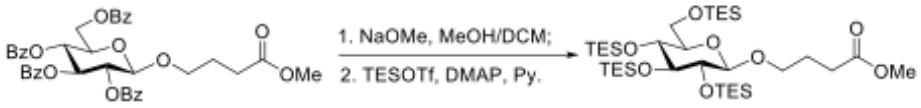
G2-1-2

The lactol (4.4 g, 7.4 mmol) was dissolved in CH_2Cl_2 (50 mL) and cooled to 0 °C. Trichloroacetonitrile (3.7 mL, 36.9 mmol) and DBU (52 µL, 0.4 mmol) were added successively. After stirring at room temperature for about 2 h, the reaction mixture was concentrated *in vacuo*. The residue was chromatographed over silica gel (Petroleum ether/EtOAc = 4:1, containing 1% Et_3N) to yield imidate **G2-1-2** (4.9 g, 6.6 mmol, 90 %) as a colorless oil.



G2-1-2 **G2-1-3**

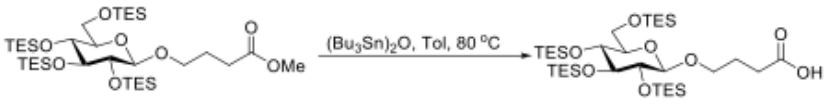
Trichloroacetimidate donor **G2-1-2** (1.8 g, 2.4 mmol) and **G2-1-1** (260 mg, 2.2 mmol) were dissolved in CH_2Cl_2 (25 mL) under nitrogen at 0 °C. Powdered freshly activated 5Å molecular sieves (2 g) were added. After 15 min, TMSOTf (40 µL, 0.22 mmol) was added and stirring was continued at 0 °C until TLC indicated the disappearance of the donor (about 8 h). The mixture was filtered through Celite, and the filtrated was concentrated in vacuum. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 2:1) to give compound **G2-1-3** (1.23 g, 1.77 mmol, 80%) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 8.00 (m, 2H), 8.00 – 7.93 (m, 2H), 7.93 – 7.87 (m, 2H), 7.88 – 7.81 (m, 2H), 7.61 – 7.28 (m, 13H), 5.90 (t, J = 9.6 Hz, 1H), 5.67 (t, J = 9.7 Hz, 1H), 5.51 (dd, J = 9.8, 7.8 Hz, 1H), 4.84 (d, J = 7.9 Hz, 1H), 4.64 (dd, J = 12.1, 3.3 Hz, 1H), 4.50 (dd, J = 12.1, 5.2 Hz, 1H), 4.20 – 4.14 (m, 1H), 3.95 (dt, J = 9.8, 5.9 Hz, 1H), 3.62 (ddd, J = 9.8, 7.0, 5.6 Hz, 1H), 3.52 (s, 3H), 2.29 (t, J = 7.3 Hz, 2H), 1.95 – 1.76 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.72, 166.25, 165.92, 165.28, 165.20, 133.54, 133.35, 133.32, 133.25, 130.00, 129.91, 129.87, 129.86, 129.84, 129.82, 129.63, 129.31, 128.84, 128.82, 128.50, 128.47, 128.46, 128.39, 101.30, 72.97, 72.27, 71.94, 69.80, 68.94, 63.21, 51.51, 30.04, 24.79. ESI-MS *m/z* calcd for $C_{39}H_{36}O_{12}Na$ $[M+Na]^+$ 719.2099, found 719.2102.



G2-1-3 **G2-1-4**

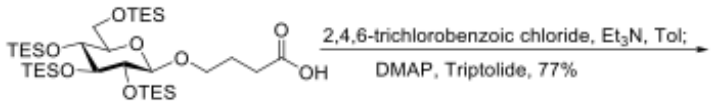
To a solution of Compound **G2-1-3** (2.9 g, 4.4 mmol) in methanol (20 mL), was added NaOMe (120 mg, 2.2 mmol). Stirring was continued until complete conversion of the starting material (monitored by TLC, about 8 hours). The mixture was neutralized with acidic resin, filtered and concentrated. Then the mixture was coevaporated with toluene three times and dried *in vacuo*.

The mixture was dissolved in dry pyridine (20 mL), and cooled to 0 °C. DMAP (108 mg, 0.9 mmol) and TESOTf (6.0 mL, 26.4 mmol) was added slowly over 5 min. Stirring was continued at 0 °C until complete conversion of the starting material (monitored by TLC, about 8 hours). The reaction was concentrated, then diluted with ethyl acetate, and washed twice with 2% HCl, once with saturated and brine, dried over Na_2SO_4. Then, the mixture was filtered and concentrated. Column chromatography (Petroleum ether/Ethyl acetate = 30/1) afforded the product **G2-1-4** as a colorless liquid (2.4 g, 3.3 mmol, 75% for two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (d, J = 6.9 Hz, 1H), 3.92 – 3.81 (m, 1H), 3.77 (dd, J = 10.4, 5.4 Hz, 1H), 3.72 – 3.63 (m, 5H), 3.60 (dd, J = 5.9, 4.6 Hz, 1H), 3.53 – 3.37 (m, 3H), 2.41 (d, J = 19.8 Hz, 2H), 1.94 (t, J = 7.0 Hz, 2H), 0.98 – 0.92 (m, 36H), 0.62 (dd, J = 15.4, 7.6 Hz, 24H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.01, 102.48, 79.79, 79.27, 77.23, 71.27, 67.95, 63.28, 51.66, 30.98, 25.25, 7.17, 7.10, 6.89, 5.28, 5.20, 5.13, 4.56; ESI-MS *m/z* calcd for $C_{35}H_{76}O_8Si_4Na$ $[M+Na]^+$ 759.4509, found 759.4515.

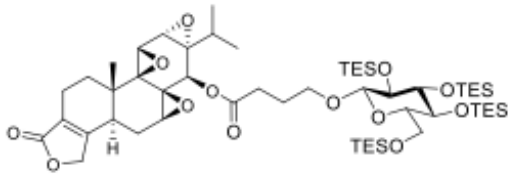


G2-1-4 **G2-1-5**

To a solution of Compound **G2-1-4** (850 mg, 1.2 mmol) in toluene (12 mL), was added bis(tributyltin) oxide (4.7 mL, 9.2 mmol). The reaction was heated to 80 °C overnight. The mixture was concentrated. Then the mixture was coevaporated with toluene three times. Column chromatography (Petroleum ether/Ethyl acetate = 20/1 to 10/1) afforded the product as a colorless liquid **G2-1-5** (450 mg, 0.62 mmol, 54%), recovered starting material (250 mg, 0.34 mmol, 29%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40 (d, J = 6.9 Hz, 1H), 3.86 (d, J = 9.5 Hz, 1H), 3.76 (d, J = 5.2 Hz, 1H), 3.75 – 3.64 (m, 2H), 3.60 (t, J = 5.2 Hz, 1H), 3.55 – 3.40 (m, 3H), 2.52 - 2.45 (m, 2H), 1.96 (q, J = 7.0 Hz, 2H), 0.98 - 0.92 (m, 36H), 0.74 – 0.48 (m, 24H); ESI-MS *m/z* calcd for $C_{34}H_{74}O_8Si_4Na$ $[M+Na]^+$ 745.4353, found 745.4358.

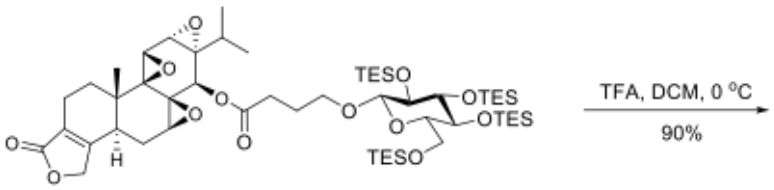


G2-1-5

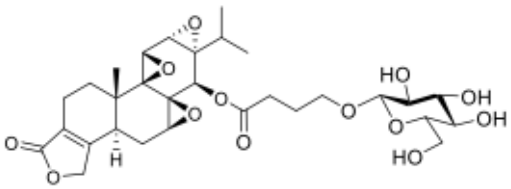


G2-1-6

To a solution of **G2-1-5** (475 mg, 0.53 mmol) in toluene (9 mL) was added NEt_3 (0.29 mL, 2.1 mmol) and 2,4,6-trichlorobenzoyl chloride (0.25 mL, 1.6 mmol) at 0 °C and was stirred at room temperature for 0.5h. After the formation of mixed anhydride (TLC), the solution was cooled to 0°C and 4-(dimethylamino)pyridine (428 mg, 3.5 mmol) and triptolide (126 mg, 0.35 mmol) was introduced dropwise in to the reaction mixture. The reaction mixture was warmed to room temperature and was stirred for additional 5h. After the completion of the reaction (TLC), it was quenched by addition of saturated $NaHCO_3$ solution (10 mL) and the aqueous layer was washed with DCM (3×10 mL). The combined organic layer was washed with brine (5 mL), dried over Na_2SO_4. The mixture was filtered and concentrated. Purification by silica gel column chromatography (PE/EtOAc, 2:1) afforded ester **G2-1-6** (339 mg, 0.32 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02 (d, J = 1.0 Hz, 1H), 4.60 (s, 2H), 4.34 (d, J = 6.9 Hz, 1H), 3.88 – 3.77 (m, 1H), 3.76 – 3.67 (m, 2H), 3.68 – 3.58 (m, 2H), 3.54 (dd, J = 5.8, 4.5 Hz, 1H), 3.50 – 3.32 (m, 6H), 2.60 (s, 1H), 2.55 – 2.35 (m, 2H), 2.31 – 2.19 (m, 1H), 2.14 – 2.01 (m, 2H), 1.98 – 1.89 (m, 3H), 1.84 – 1.77 (m, 2H), 0.93 – 0.86 (m, 36H), 0.64 – 0.47 (m, 24H); ESI-MS *m/z* calcd for $C_{54}H_{96}O_{13}Si_4Na$ $[M+Na]^+$ 1087.5820, found 1087.5801.



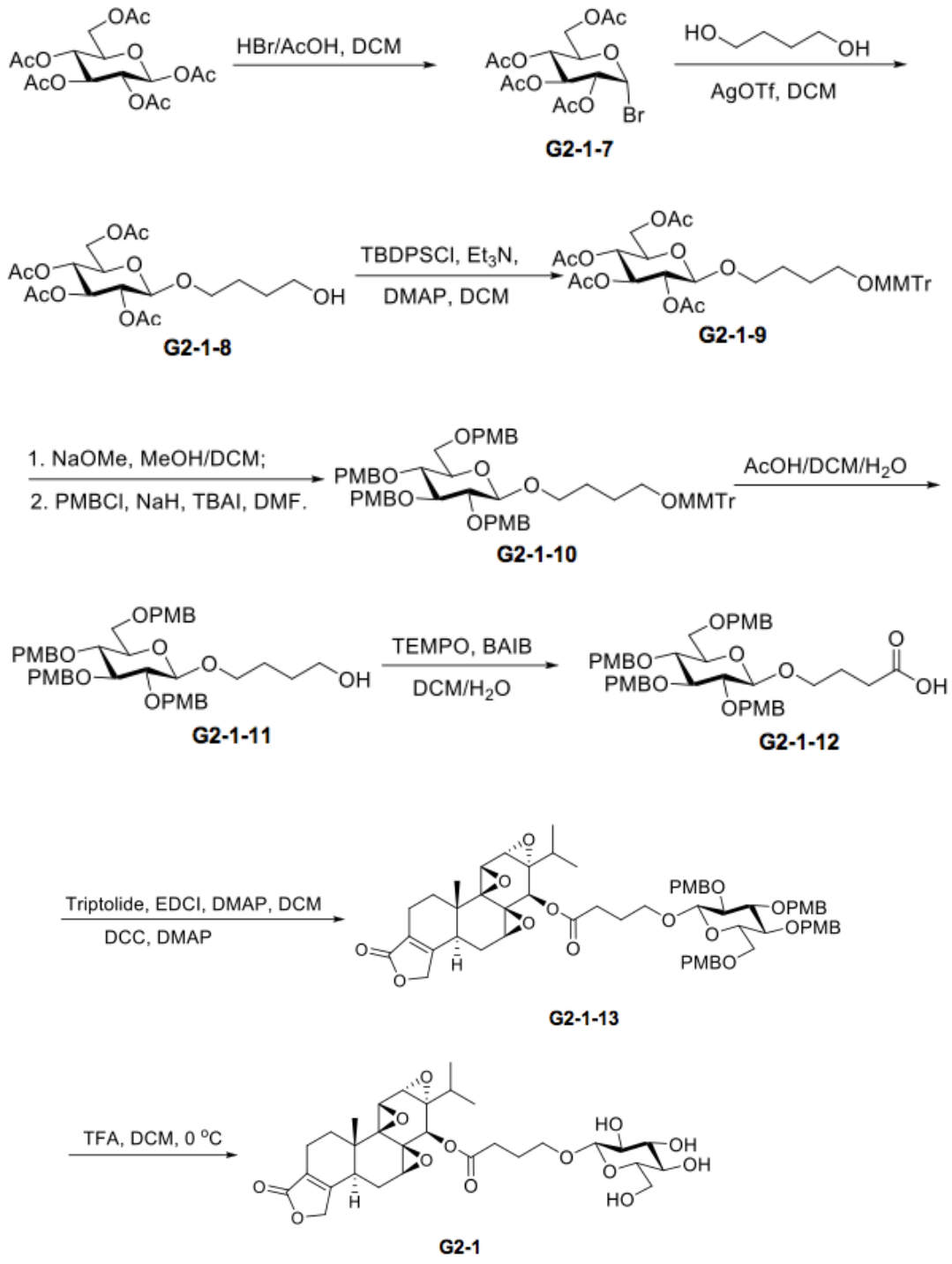
G2-1-6



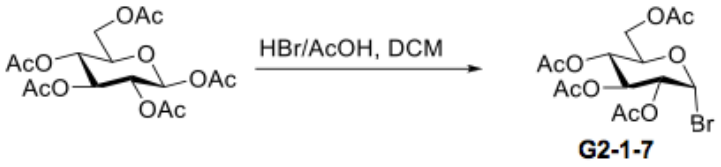
G2-1

Compound **G2-1-6** (570 mg, 0.54 mmol) was dissolved in DCM (10 mL), and cooled to 0 ^{o}C. Then TFA (1.0 mL) was added. After stirring at this temperature for about 15 min, the reaction mixture was concentrated *in vacuo*. The residue was chromatographed over silica gel (DCM/Methanol = 15:1) to yield **G2-1** (300 mg, 0.49 mml, 91%) as a white solid. ^{1}H NMR (500 MHz, CD_3OD) δ 5.09 (d, J = 1.0 Hz, 1H), 4.83 – 4.72 (m, 2H), 4.26 (d, J = 7.8 Hz, 1H), 4.03 – 3.92 (m, 2H), 3.86 (dd, J = 11.9, 2.1 Hz, 1H), 3.72 – 3.59 (m, 3H), 3.47 (d, J = 5.7 Hz, 1H), 3.18 (dd, J = 9.1, 7.8 Hz, 1H), 2.78 (d, J = 13.1 Hz, 1H), 2.69 – 2.46 (m, 2H), 2.32 – 2.19 (m, 2H), 2.08 (t, J = 13.8 Hz, 1H), 2.03 – 1.77 (m, 4H), 1.51 (dd, J = 12.4, 5.0 Hz, 1H), 1.37-1.27 (m, 1H), 1.04 (s, 3H), 0.95 (d, J = 7.0 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 176.07, 174.57, 163.87, 125.51, 104.49, 78.00, 77.90, 75.08, 72.66, 71.98, 71.61, 69.68, 64.88, 64.21, 62.76, 61.10, 56.74, 56.21, 41.44, 36.81, 31.85, 30.82, 29.48, 26.35, 24.17, 17.94, 17.91, 17.13, 14.23; ESI-MS *m/z* calcd for $C_{30}H_{40}O_{13}Na$ $[M+Na]^+$ 631.2361, found 631.2368.

Scheme S6. Synthetic route 2 for Glutriptolide G2-1, Related to Figure 1.

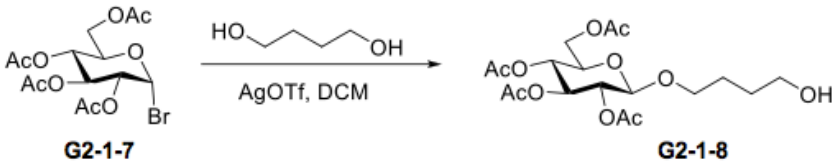


Synthetic procedure (route 2) for Glutriptolide G2-1, Related to Figure 1.



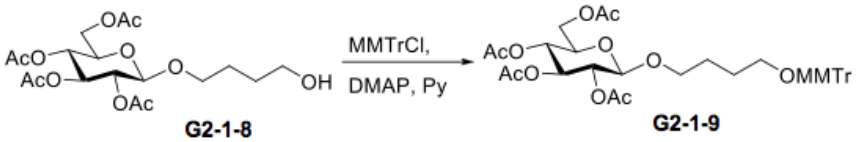
G2-1-7

To a solution of β-D-glucose pentaacetate (5.0 g, 12.8 mmol) in DCM (30 mL) at 0 °C, was added hydrobromic acid solution in acetic acid (8 mL). Stirring was continued at 0 °C until complete conversion of starting material (about 3 h). The reaction mixture was quenched with ice water (200 mL), and extracted with DCM (3×80 mL). The organic layer was combined and washed with ice water (3×80 mL), saturated $NaHCO_3$, and brine, dried over Na_2SO_4. The mixture was filtered and concentrated to provide 2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl bromide **G2-1-7** (4.85 g, 11.8 mmol, 92%) as a white solid.



G2-1-7 **G2-1-8**

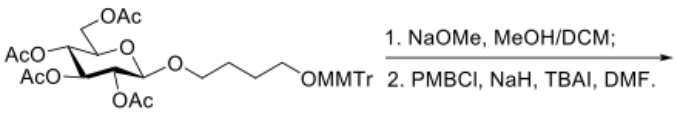
2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl bromide **G2-1-7** (8.0 g, 2.4 mmol) and 1,4-Butylene glycol (260 mg, 2.2 mmol) were dissolved in CH_2Cl_2 (25 mL) under nitrogen. AgOTf (5.5 g, 21.5 mmol) were added. Stirring was continued until TLC indicated the disappearance of the donor (about 2 h). The mixture was quenched with saturated $NaHCO_3$, and filtered through Celite. The filtration was diluted with DCM, and washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4. The mixture was filtered and concentrated in vacuum. The residue was coevaporated with toluene twice.



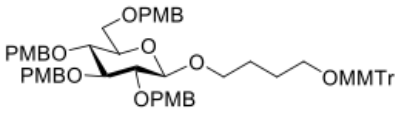
G2-1-8 **G2-1-9**

To a solution of **G2-1-8** in pyridine (40 mL) at 0 °C, DMAP (500 mg, 3.9 mmol) and MMTrCl (12.0 g, 39.0 mmol) was added. Stirring was continued at room temperature until complete consume of starting material. The mixture was concentrated, then diluted with ethyl acetate. The organic layer was was washed with saturated $CuSO_4$ (2×100 mL), and brine, dried over Na_2SO_4. The mixture was filtered and concentrated. Purification by silica gel column

chromatography (PE/EtOAc, 3:1) afforded ester **G2-1-9** (6.8 g, 9.5 mmol, 50% for two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.31 (m, 4H), 7.29 – 7.11 (m, 8H), 6.76 (d, J = 8.9 Hz, 2H), 5.12 (t, J = 9.5 Hz, 1H), 5.01 (t, J = 9.7 Hz, 1H), 4.90 (dd, J = 9.6, 8.0 Hz, 1H), 4.36 (d, J = 7.9 Hz, 1H), 4.19 (dd, J = 12.3, 4.6 Hz, 1H), 4.10 – 3.98 (m, 1H), 3.80 (dt, J = 10.7, 5.6 Hz, 1H), 3.73 (s, 3H), 3.59 (ddd, J = 9.8, 4.6, 2.4 Hz, 1H), 3.45 – 3.32 (m, 1H), 3.03 – 2.93 (m, 2H), 2.00 (s, 3H), 1.96 (s, 3H), 1.94 (s, 6H), 1.61 – 1.56 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.89, 170.49, 169.56, 158.80, 147.19, 144.93, 139.32, 130.41, 129.35, 128.51, 128.03, 127.96, 127.86, 127.32, 126.89, 113.33, 113.11, 100.95, 100.91, 81.86, 77.36, 72.92, 71.92, 71.42, 70.15, 68.51, 62.52, 62.02, 55.40, 29.48, 25.99, 20.93, 20.85, 20.80, 20.78; ESI-MS *m/z* calcd for $C_{38}H_{44}O_{12}Na$ $[M+Na]^+$ 715.2725, found 715.2722.



G2-1-9

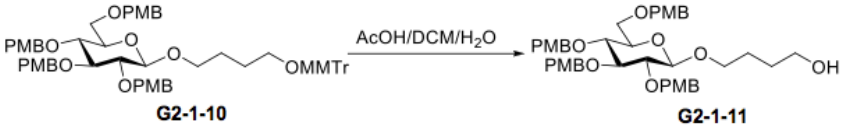


G2-1-10

To a solution of Compound **G2-1-9** (8.0 g, 11.6 mmol) in methanol (60 mL) and DCM (15 mL), was added NaOMe (312 mg, 5.8 mmol). Stirring was continued until complete conversion of the starting material (monitored by TLC, about 6 hours). The mixture was neutralized with acid resin, filtered and concentrated. Then the mixture was coevaporated with toluene three times and dried *in vacuo*.

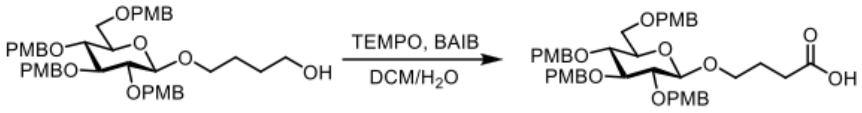
The mixture and TBAI (854 mg, 2.3 mmol) was dissolved in dry DMF (100 mL), and cooled to 0 °C. NaH (2.8 g, 60% suspension, 69.4 mmol) was added slowly over 5 min. After 20 min, PMBCl (9.4 mL, 69.4 mmol) was added and the reaction stirred for another 10 min, at which time the temperature was raised to room temperature for 4 h. The reaction was re-cooled to 0 °C and water was added to quench the reaction. The organic layer was diluted with ethyl acetate, and washed twice with water, once with brine, dried over Na_2SO_4. Then, the mixture was filtered and concentrated. Column chromatography (Petroleum ether/Ethyl acetate = 3/1) afforded the product **G2-1-10** as a white solid (11.0 g, 10.9 mmol, 94% for two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.43 (m, 4H), 7.37 – 7.20 (m, 14H), 7.11 – 7.04 (m, 2H), 6.94 – 6.78 (m, 10H), 4.88 (dd, J = 10.6, 4.7 Hz, 2H), 4.74 (d, J = 10.3 Hz, 2H), 4.69 – 4.61 (m, 1H), 4.57 (d, J = 11.8 Hz, 1H), 4.49 (d, J = 11.8 Hz, 1H), 4.43 (d, J = 10.4 Hz, 1H), 4.36 (d, J = 7.8 Hz, 1H), 3.99 (dd, J = 9.8, 5.1 Hz, 1H), 3.87 – 3.75 (m, 15H), 3.72 – 3.48 (m, 5H), 3.46 – 3.36 (m, 2H), 3.13 (d, J = 5.6 Hz, 2H), 1.79 (t, J = 5.4 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.34,

159.28, 159.27, 159.23, 158.48, 144.98, 136.22, 131.03, 130.75, 130.39, 130.34, 129.96, 129.74, 129.60, 128.74, 128.52, 127.82, 126.81, 114.03, 113.89, 113.87, 113.86, 113.84, 113.08, 103.74, 86.10, 84.52, 82.08, 77.76, 75.44, 74.94, 74.73, 74.61, 73.18, 70.01, 68.64, 63.28, 55.37, 55.34, 55.28, 26.97, 26.91; ESI-MS *m/z* calcd for $C_{62}H_{68}O_{12}Na$ $[M+Na]^+$ 1027.4603, found 1027.4600.



G2-1-10 **G2-1-11**

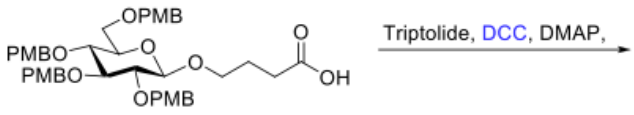
After a solution of **G2-1-10** (11.0 g, 10.9 mmol) in $AcOH/CH_2Cl_2/H_2O$ (15:4:1, 120 mL) was stirred at room temperature for 2.0 h, it was diluted with CH_2Cl_2 and poured into cold water. The organic layer was washed with water (4×80 mL), saturated aqueous $NaHCO_3$ and brine, then dried over Na_2SO_4. After concentration in vacuum, the residue was purified by silica gel column chromatography (Petroleum ether/Ethyl acetate = 1/1) to give **G2-1-11** (7.2 g, 9.8 mmol, 90%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.13 (m, 6H), 7.07 – 6.86 (m, 2H), 6.86 – 6.55 (m, 8H), 4.77 (dd, J = 10.6, 2.6 Hz, 2H), 4.64 (dd, J = 10.5, 2.0 Hz, 2H), 4.59 (d, J = 10.6 Hz, 1H), 4.47 (d, J = 11.8 Hz, 1H), 4.40 (d, J = 11.8 Hz, 1H), 4.33 (d, J = 10.4 Hz, 1H), 4.29 (d, J = 7.8 Hz, 1H), 3.96 – 3.87 (m, 1H), 3.79 – 3.68 (m, 12H), 3.66 – 3.47 (m, 6H), 3.42 (t, J = 9.2 Hz, 1H), 3.37 – 3.27 (m, 2H), 1.64 (dt, J = 18.4, 6.1 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.32, 159.28, 159.26, 159.21, 130.95, 130.73, 130.32, 130.24, 129.83, 129.73, 129.60, 129.55, 113.86, 113.84, 113.82, 103.68, 84.53, 82.05, 77.72, 75.40, 74.88, 74.71, 74.59, 73.14, 70.02, 68.59, 62.62, 55.35, 55.32, 29.67, 26.38; ESI-MS *m/z* calcd for $C_{42}H_{52}O_{11}Na$ $[M+Na]^+$ 755.3402, found 755.3409.



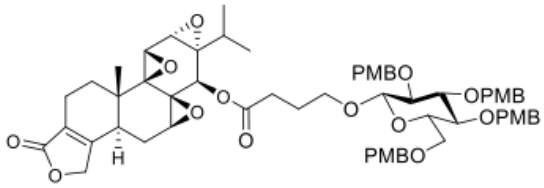
G2-1-11 **G2-1-12**

To a solution of **G2-1-11** (1.8 g, 2.4 mmol) in DCM (12 mL) and water (6 mL), TEMPO (75 mg, 0.48 mmol) and BAIB (2.3 g, 7.2 mmol) was added. Stirring was continued until complete conversion of starting material (about 3 hours). The mixture was quenched with saturated $NaHSO_3$, and extracted with DCM three times. The organic layer was combined and washed with brine, dried over Na_2SO_4. After concentration in vacuum, the residue was purified by silica gel column chromatography (Petroleum ether/Ethyl acetate = 1/4) to give **G2-1-12** (1.3 g, 1.7 mmol, 73%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.11 (m, 6H), 6.96 (d, J = 8.2 Hz, 2H), 6.88 – 6.63 (m, 8H), 4.75 (dd, J = 10.6, 3.0 Hz, 2H), 4.61 (dd, J = 23.8, 10.7 Hz, 3H), 4.51 – 4.28 (m, 3H), 4.27 (d, J = 7.7 Hz, 1H), 3.96 – 3.81 (m, 1H), 3.72 – 3.71 (m, 12H),

3.65 – 3.23 (m, 8H), 2.43 (t, J = 7.4 Hz, 2H), 2.06 – 1.90 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.66, 159.35, 159.31, 159.24, 130.96, 130.66, 130.36, 130.22, 129.93, 129.75, 129.65, 129.59, 113.92, 113.87, 103.63, 84.52, 82.04, 77.68, 75.44, 74.90, 74.73, 73.18, 68.74, 68.52, 55.38, 30.77, 25.03; ESI-MS *m/z* calcd for $C_{42}H_{50}O_{12}Na$ $[M+Na]^+$ 769.3194, found 769.3196.

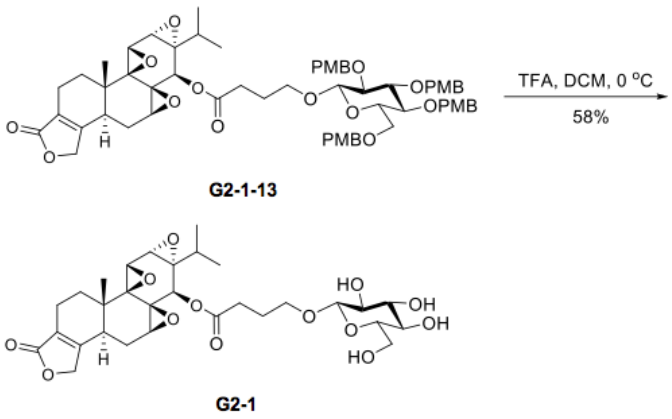


G2-1-12



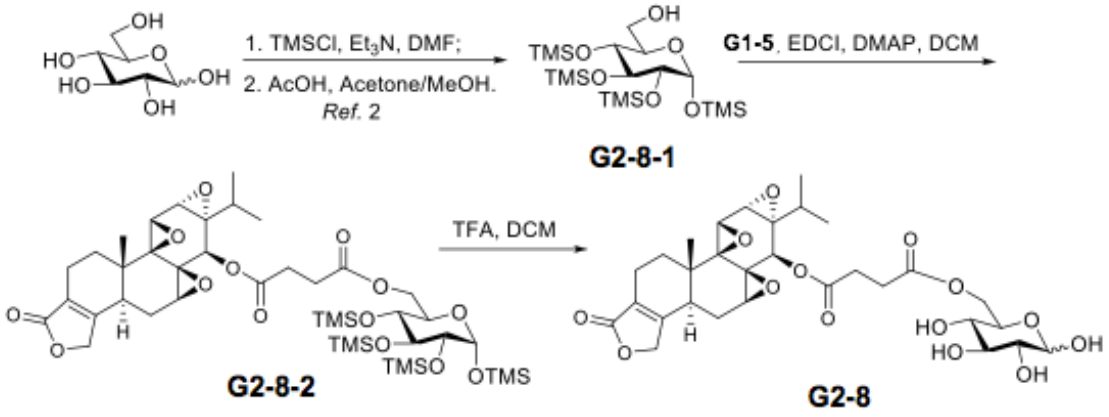
G2-1-13

A solution of compound **G2-1-12** (1.3 g, 1.7 mmol), Triptolide (523 mg, 1.45 mmol), DMAP (36 mg, 0.3 mmol), and DCC (462 mg, 2.2 mmol) in CH_2Cl_2 (30 mL) was stirred for 8 h at RT. The resulting mixture was concentrated and diluted with ethyl acetate, then filtrated. The filtrate was concentrated in vacuum. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 1:1) to give compounds **G2-1-13** (1.3 g, 1.2 mmol, 82%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.12 (m, 6H), 6.96 (d, J = 8.6 Hz, 2H), 6.85 – 6.66 (m, 8H), 5.06 – 4.97 (m, 1H), 4.77 (t, J = 11.0 Hz, 2H), 4.69 – 4.54 (m, 5H), 4.48 (d, J = 11.8 Hz, 1H), 4.39 (d, J = 11.9 Hz, 1H), 4.32 (d, J = 10.4 Hz, 1H), 4.28 (d, J = 7.8 Hz, 1H), 4.11 – 4.03 (m, 1H), 3.79 – 3.70 (m, 13H), 3.60 – 3.30 (m, 10H), 2.67 – 2.42 (m, 4H), 0.95 (s, 3H), 0.87 (d, J = 6.9 Hz, 3H), 0.73 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.38, 172.76, 160.16, 159.33, 159.27, 159.21, 130.97, 130.77, 130.36, 130.28, 130.00, 129.72, 129.61, 129.56, 125.64, 113.88, 113.85, 103.75, 84.49, 82.01, 77.66, 75.42, 74.92, 74.73, 74.64, 73.18, 70.94, 70.09, 68.78, 68.55, 63.61, 63.40, 61.25, 59.83, 55.37, 55.34, 55.09, 49.20, 40.43, 35.75, 34.04, 31.18, 29.89, 28.15, 25.72, 25.37, 25.05, 23.52, 17.66, 17.14, 16.80, 13.83. ESI-MS *m/z* calcd for $C_{62}H_{72}O_{17}Na$ $[M+Na]^+$ 1111.4662, found 1111.4649.



Compound **G2-1-13** (1.0 g, 1.45 mmol) was dissolved in DCM (30 mL), and cooled to 0 °C. Then TFA (3.0 mL) was added. After stirring at this temperature for about 15 min, the reaction mixture was concentrated *in vacuo*. The residue was chromatographed over silica gel (DCM/Methanol = 15:1) to yield **G2-1** (510 mg, 0.84 mmol, 58%) as a white solid. ^{1}H NMR (500 MHz, CD_3OD) δ 5.09 (d, J = 1.0 Hz, 1H), 4.83 – 4.72 (m, 2H), 4.26 (d, J = 7.8 Hz, 1H), 4.03 – 3.92 (m, 2H), 3.86 (dd, J = 11.9, 2.1 Hz, 1H), 3.72 – 3.59 (m, 3H), 3.47 (d, J = 5.7 Hz, 1H), 3.18 (dd, J = 9.1, 7.8 Hz, 1H), 2.78 (d, J = 13.1 Hz, 1H), 2.69 – 2.46 (m, 2H), 2.32 – 2.19 (m, 2H), 2.08 (t, J = 13.8 Hz, 1H), 2.03 – 1.77 (m, 4H), 1.51 (dd, J = 12.4, 5.0 Hz, 1H), 1.37-1.27 (m, 1H), 1.04 (s, 3H), 0.95 (d, J = 7.0 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 176.07, 174.57, 163.87, 125.51, 104.49, 78.00, 77.90, 75.08, 72.66, 71.98, 71.61, 69.68, 64.88, 64.21, 62.76, 61.10, 56.74, 56.21, 41.44, 36.81, 31.85, 30.82, 29.48, 26.35, 24.17, 17.94, 17.91, 17.13, 14.23; ESI-MS *m/z* calcd for $C_{30}H_{40}O_{13}Na$ $[M+Na]^+$ 631.2361, found 631.2368.

Scheme S7. Synthetic route of Glutriptolide G2-8, Related to Figure 1.



Synthetic procedures for Glutriptolide G2-8, Related to Figure 1.

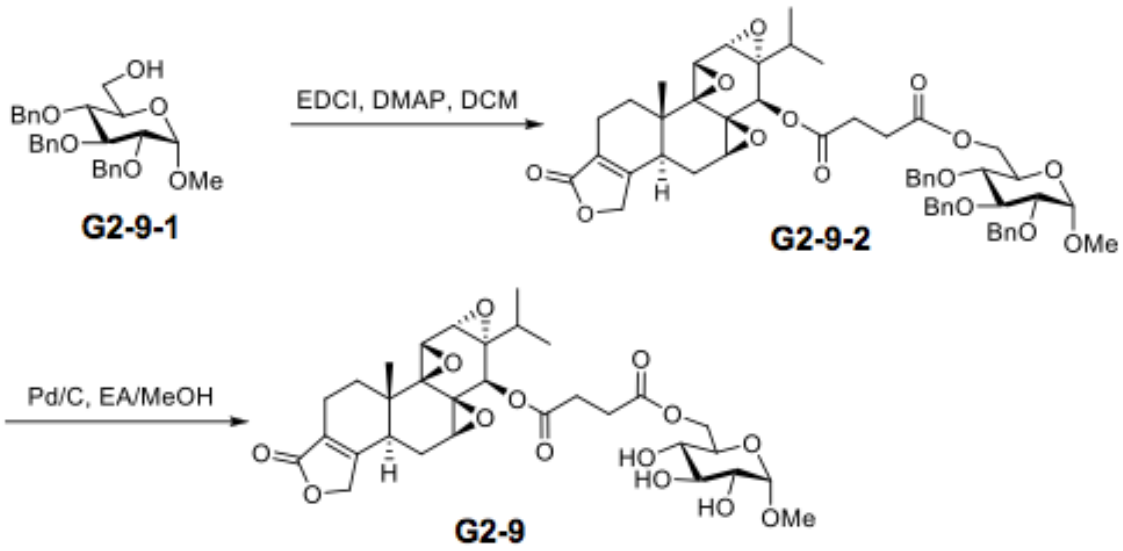
A solution of Acid **G1-5** (60 mg, 0.13 mmol), compound **G2-8-1** (92 mg, 0.20 mmol), DMAP (cat.), and EDCI (50 mg, 0.26 mmol) in CH_2Cl_2 (4 mL) was stirred for 8 h at RT. The resulting mixture was diluted with CH_2Cl_2, then washed with water and brine, respectively. The organic layers were dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 3:2) to give compounds **G2-8-2** (97 mg, 0.11 mmol, 82%) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.04 (d, J = 0.9 Hz, 1H), 4.96 (d, J = 3.0 Hz, 1H), 4.63 (s, 2H), 4.32 (dd, J = 11.8, 2.3 Hz, 1H), 4.01 (dd, J = 11.8, 5.4 Hz, 1H), 3.86 (ddd, J = 9.8, 5.3, 2.2 Hz, 1H), 3.78 (d, J = 3.2 Hz, 1H), 3.74 (t, J = 8.8 Hz, 1H), 3.49 (dd, J = 3.1, 0.9 Hz, 1H), 3.41 (d, J = 5.8 Hz, 1H), 3.40 – 3.36 (m, 1H), 3.32 (dd, J = 9.1, 3.0 Hz, 1H), 2.80 – 2.60 (m, 5H), 2.31 – 2.02 (m, 4H), 1.93 – 1.81 (m, 2H), 1.52 (dd, J = 11.9, 5.8 Hz, 1H), 1.01 (s, 3H), 0.90 (d, J = 6.9 Hz, 3H), 0.79 (d, J = 6.9 Hz, 3H) , 0.11 (s, 3H) , 0.11 (s, 3H) , 0.10 (s, 3H) , 0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.25, 172.00, 171.70, 160.11, 125.54, 93.91, 73.93, 73.84, 72.38, 71.23, 70.02, 69.91, 64.16, 63.52, 63.35, 61.19, 59.70, 55.36, 55.02, 40.38, 35.69, 29.86, 29.14, 29.00, 27.99, 23.46, 17.53, 17.09, 16.74, 13.79, 1.27, 0.96, 0.48, 0.17; ESI-MS *m/z* calcd for $C_{42}H_{70}O_{14}NaSi$ $[M+Na]^+$ 933.3735, found 933.3740.

Compound **G2-8-2** (25 mg, 0.027 mmol) was dissolved in DCM (1.5 mL), and cooled to 0 ^{o}C. Then TFA (0.15 mL) was added. After stirring at this temperature for about 45 min, the reaction mixture was concentrated *in vacuo*. The residue was chromatographed over silica gel (DCM/Methanol = 10:1) to yield the product **G2-8** (15 mg, 0.024 mmol, 89%) as a white solid. ^{1}H NMR (500 MHz, CD_3OD) δ 5.51 (s, 0.37H), 5.11 (d, J = 3.7 Hz, 0.66H), 5.09 (d, J = 1.1 Hz, 1H), 4.86 – 4.76 (m, 2H), 4.50 (d, J = 7.8 Hz, 0.33H), 4.49 – 4.43 (m, 0.32H), 4.39 (dd, J = 11.7, 2.2 Hz, 0.63H), 4.29 – 4.17 (m, 1H), 4.03 – 3.98 (m, 0.57H), 3.98 (dd, J = 3.3, 1.2 Hz, 1H), 3.69 (t, J = 9.3 Hz, 0.62H), 3.65 (td, J = 3.5, 1.0 Hz, 1H), 3.52 (ddd, J = 9.5, 6.1, 2.1 Hz, 0.35H), 3.48

(d, J = 5.7 Hz, 1H), 3.37 (s, 1H), 3.31 – 3.26 (m, 1.45H), 3.16 (dd, J = 9.0, 7.8 Hz, 032H), 2.84 – 2.76 (m, 1H), 2.76 – 2.65 (m, 4H), 2.27 (ddt, J = 17.0, 11.0, 5.7 Hz, 2H), 2.16 – 2.04 (m, 1H), 1.99 – 1.85 (m, 2H), 1.53 (ddd, J = 12.5, 5.6, 1.5 Hz, 1H), 1.34 (ddd, J = 21.7, 10.8, 5.2 Hz, 2H), 1.26 (t, J = 7.1 Hz, 0H), 1.06 (s, 3H), 0.96 (d, J = 7.0 Hz, 3H), 0.85 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 176.10, 173.92, 173.85, 173.35, 173.31, 163.91, 125.50, 98.22, 93.96, 77.93, 76.16, 75.31, 74.73, 73.73, 73.06, 73.05, 72.00, 71.96, 71.71, 70.60, 65.35, 65.27, 64.87, 64.27, 62.70, 61.00, 56.74, 56.18, 41.45, 36.79, 30.82, 30.06, 29.84, 29.82, 29.11, 24.16, 17.91, 17.87, 17.08, 14.21, 14.19; ESI-MS *m/z* calcd for $C_{30}H_{38}O_{14}Na$ $[M+Na]^+$ 645.2154, found 645.2159.

Reference: [2]Fan, W.; Wu, Y.; Li, X.; Yao, N.; Yu, Y.; Hai, L. *Eur. J. Med. Chem.,* **2011**, *46*, 3651–3661; Cui, Y.; Cheng, Z.; Mao, J.; Yu, Y. *Tetrahedron Lett.*, **2013**, *54*, 3831–3833.

Scheme S8. Synthetic route of Glutriptolide G2-9, Related to Figure 1.



Synthetic procedures for Glutriptolide G2-9, Related to Figure 1.

A solution of Acid **G1-5** (25 mg, 0.054 mmol), compound **G2-9-1**[3] (50 mg, 0.11 mmol), DMAP (2 mg, 0.011mmol), and DCC (22 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) was stirred for 8 h at RT. The resulting mixture was diluted with CH_2Cl_2, then washed with water and brine, respectively. The organic layers were dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 3:2) to give the product **G2-9-2** (41 mg, 0.045 mmol, 83%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.13 (m, 13H), 5.04 (s, 1H), 4.99 (d, J = 10.8 Hz, 1H), 4.86 (d, J = 10.8 Hz, 1H), 4.82 (d, J = 10.8 Hz, 1H), 4.78 (d, J = 12.1 Hz, 1H), 4.70 – 4.53 (m, 5H), 4.35 (dd, J = 11.9, 4.5 Hz, 1H), 4.26 (dd, J = 11.9, 2.1 Hz, 1H), 3.99 (t, J = 9.2 Hz, 1H), 3.84 – 3.75 (m, 2H), 3.54 (dd, J = 9.6, 3.6 Hz, 1H), 3.51 – 3.45 (m, 2H), 3.39 (d, J = 5.6 Hz, 1H), 3.36 (s, 3H), 2.30 (d, J = 15.1 Hz, 1H), 1.54 (dd, J = 12.5, 4.7 Hz, 1H), 1.02 (s, 3H), 0.90 (d, J = 7.0 Hz, 3H), 0.80 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.32, 171.95, 171.77, 160.05, 138.75, 138.16, 128.61, 128.55, 128.24, 128.18, 128.12, 128.10, 127.98, 127.80, 125.70, 98.19, 82.16, 80.03, 77.47, 75.95, 75.19, 73.52, 71.34, 70.06, 68.70, 63.62, 63.42, 63.35, 61.30, 59.76, 55.47, 55.38, 55.10, 40.46, 35.77, 29.96, 29.16, 29.03, 28.16, 23.51, 17.58, 17.18, 16.81, 13.88; ESI-MS (*m/z*): 930.4 $[M+Na]^+$.

Palladium on charcoal (10%, 10 mg) was added to a solution of compound **G2-9-2** (17 mg, 0.019 mmol) in CH_3OH. The mixture was placed under an atmosphere of hydrogen for about 14 h. The mixture was filtered and concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2/CH_3OH, 15:1) to give compound **G2-9** (7 mg, 0.011 mmol, 60%) as a

white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 5.07 (s, 1H), 4.87 – 4.72 (m, 2H), 4.65 (d, J = 3.7 Hz, 1H), 4.41 (dd, J = 11.7, 2.0 Hz, 1H), 4.26 – 4.14 (m, 1H), 3.96 (d, J = 3.2 Hz, 1H), 3.80 – 3.69 (m, 1H), 3.63 (d, J = 3.0 Hz, 1H), 3.60 (d, J = 9.2 Hz, 1H), 3.46 (d, J = 5.6 Hz, 1H), 3.45 – 3.38 (m, 4H), 2.71 (t, J = 3.6 Hz, 6H), 2.37 – 1.83 (m, 5H), 1.04 (s, 3H), 0.94 (d, J = 7.0 Hz, 3H), 0.83 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 176.08, 173.82, 173.27, 163.89, 125.51, 101.25, 75.04, 73.45, 73.07, 71.98, 71.89, 71.02, 65.23, 64.87, 64.27, 62.69, 61.00, 56.73, 56.19, 55.63, 41.46, 36.80, 30.83, 30.09, 29.86, 29.10, 24.17, 17.92, 17.87, 17.08, 14.19; ESI-MS (*m/z*): 659.6 $[M+Na]^+$.

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Biological samples		
Human serum	Sigma	Cat#H4522-20mL
Anti-Rpb1	Santa Cruz Biotechnology	Cat#SC-17798
Anti-XPB	Biotechne	Cat#AF6349-SP
Anti-Actin	Developmental Studies Hybridoma Bank	Cat#JLA20
Anti-GAPDH	Santa Cruz Biotechnology	Cat#SC-20357
Anti-cytochrome C	Santa Cruz Biotechnology	Cat#SC-7159
Anti-PARP1	Santa Cruz Biotechnology	Cat#SC-7150
Anti-cleaved caspase 3	Cell Signaling Technology	Cat#9661
Anti-VDAC	ProteinTech	Cat#10866-1-AP
Anti-HIF 1a	BD Sciences	Cat#610958
Anti-GLUT1	Santa Cruz Biotechnology	Cat#SC-377228
Anti-mouse IgG HRP	GE	Cat#NXA931-1mL
Anti-rabbit IgG HRP	GE	Cat#NXA934-1mL
Anti-mouse Alexa Fluor 488	Invitrogen	Cat#A28175
Chemicals, Peptides, and Recombinant Proteins		
Triptolide	Sigma	Cat#T3652
Glutriptolides	He et al., 2016	N/A
Purified TFIIH complex	Titov et al. 2011	N/A
Spironolactone	Acros Organics/Fisher Scientific	Cat#AC207460010
Doxorubicin	APExBio	Cat#A1832
1% O_2	Airgas	Cat#X03NI94C2000650
[^{3}H] Thymidine	Perkin Elmer	Cat# NET027W001MC
[γ-^{32}P] ATP	Perkin Elmer	Cat#BLU002A250UC
DAPI	ThermoFisher	Cat#D1306
Hoechst 33258	Sigma	Cat#861405

2-NBDG	ThermoFisher	Cat#N13195
Critical Commercial Assays		
TACS XTT Cell Proliferation/Viability Assay	R&D Systems	Cat#4891-025-K
Experimental Models: Animal		
Male NOD/SCID/IL2Rγnull Mouse	JHU Animal Resources Core	N/A
Experimental Models: Cell lines		
PC3/ML/fluc	Bhatnagar et al. 2014	N/A
Primary astrocytes	Lonza	Cat#CC-2565
Fibroblast	ATCC	Cat#PCS-201-012
Airway epithelial cell	ATCC	Cat#PCS-301-010
Renal proximal tubule cell	ATCC	Cat#PCS-400-010
Prostate Epithelial cell	Lonza	Cat#CC-2555
Mammary Epithelial cell	Lonza	Cat#CC-2551
PC3	ATCC	Cat#CRL-1435
LNCap	ATCC	Cat#CRL-1740
DU-145	ATCC	Cat#HTB-81
MDA-MB-231	ATCC	Cat#HTB-26
MDA-MB-453	ATCC	Cat#HTB-131
SK-BR-3	ATCC	Cat#HTB-30
A253	ATCC	Cat#HTB-41
Detroit 562	ATCC	Cat#CCL-138
SCC-25	ATCC	Cat#CRL-1625
SK-Mel-3	ATCC	Cat#HTB-69
SK-Mel-1	ATCC	Cat#HTB-67
RPMI-7951	ATCC	Cat#HTB-66
CFPAC-1	ATCC	Cat#CRL-1918
BxPC3	ATCC	Cat#CRL-1687

SW1990	ATCC	Cat#CRL-2172
A549	ATCC	Cat#CCL-185
NCI-H1299	ATCC	Cat#CRL-5803
NCI-H1437	ATCC	Cat#CRL-5872
SNU-475	ATCC	Cat#CRL-2236
SK-HEP-1	ATCC	Cat#HTB-52
SNU-387	ATCC	Cat#CRL-2237
HeLa	ATCC	Cat#CCL-2
HEK 293T WT	ATCC	Cat#CRL-3216
HEK 293T 7115 (C342T XPB)	He et al. 2016	N/A
HUVEC	Lonza	Cat#C2517A
MCF-7	ATCC	Cat#HTB-22
HepG2	ATCC	Cat#HB-8065
Recombinant DNA		
RNA Polymerase II promoter positive control DNA	Promega	Cat#E3621
Software and Algorithms		
ImageJ	NIH	http:// imagej.nih.gov/ij/index.html
GraphPad Prism	GraphPAd Software Inc	http://www.graphpad.com/scientific- software/prism/
Other		
Hypoxia chamber	Billups-Rothenberg	Cat#MIC-101
PEI cellulose plates	Sigma	Cat#Z122882-25EA
Typhoon FLA 9500 Variable Imager system	GE Healthcare Life Sciences	Cat# 28996943
Nikon Eclipse TE200 Inverted microscope	Nikon Instruments Inc./Johns Hopkins School of Medicine, Department of Pharmacology and Molecular Sciences	N/A
IVIS Spectrum Imaging System	Caliper Life Sciences	Cat#124262

Transparent Methods

Cells and culture conditions

Primary astrocytes (Lonza, Walkersville, MD; ABMÔ Basal Media with AGMTM SingleQuotsTM Supplement Pack), fibroblast (ATCC; Fibroblast Basal Medium (ATCC® PCS-201-030TM) with Fibroblast Growth Kit-Serum-free (ATCC® PCS-201- 040TM)), airway epithelial cell (ATCC; Airway Epithelial Cell Basal Medium (ATCC® PCS- 300-030TM) with Bronchial Epithelial Cell Growth Kit (ATCC® PCS-300-040TM)), renal proximal tubule (ATCC; Renal Epithelial Cell Basal Medium (ATCC® PCS-400-030TM) with Renal Epithelial Cell Growth Kit (ATCC® PCS-400-040TM)), prostate epithelial cell (Lonza; PrEGMTM BulletKitTM) and mammary epithelial cell (Lonza; MEBMTM BulletKitTM) were kept in a humidified incubator at 37 °C adjusted to 5% CO2. Prostate (PC3, LNCaP, DU-145), breast (MDA-MB-231, MDA-MB-453, SK-BR-3), head and neck (A253, Detroit 562, SCC-25), melanoma (SK-Mel-3, SK-Mel-1, RPMI-7951), pancreatic (CfPAC-1, BxPC3, SW1990), lung (A549, NCI-H1299, NCI-H1437) and liver (SNU-475, SK-HEP-1, SNU-387) cancer cell lines were obtained from ATCC and cultured in their respective media (prostate cells: RPMI-1640, MDA-MB-231: RPMI-1640, MDA-MB-453: Leibovitz's L-15, SK-BR-3: McCoy's 5a, A253: McCoy's 5a, Detroit 562: EMEM, SCC-25: DMEM, SK-Mel-3: McCoy's 5a, SK-Mel-1: EMEM, RPMI-7951: EMEM), CfPAC-1: IMDM, BxPC3: RPMI-1640, SW1990: Leibovitz's L-15), A549: F-12K, NCI-H1299: RPMI-1640, NCI-H1437: RPMI-1640, SNU-475: RPMI-1640, SK-HEP-1: EMEM, SNU-387: RPMI-1640. All media were supplemented with 10% (vol/vol) filtered fetal bovine serum (FBS, Invitrogen, Carlsbad, CA), 1% penicillin/streptomycin (Invitrogen) and maintained in a humidified incubator at 37 °C with 5% CO2 except for MDA-MB-453 and SW1990 grown at 37 °C without CO2 control. Wild type (ATCC) and C342T XPB knock-in cells (named T7115) of Human Embryonic Kidney 293T (HEK293T), HeLa (ATCC), DLD-1 parental and GLUT1 KO (provided by Dr. Bert Vogelstein at Johns Hopkins University School of Medicine) were cultured in DMEM (GIBCO) with 10% (vol/vol) filtered fetal bovine serum (FBS, Invitrogen, Carlsbad, CA), 1% penicillin/streptomycin (Invitrogen).

In vivo tumor xenograft assay

Animal experiments were performed following the protocols approved by the Johns Hopkins University Animal Care and Use Committee. The experimental murine model of human prostate cancer metastasis used in this study was generated based on a published procedure (Bhatnagar et al., 2014). Briefly, four-to-six-week-old, male NOD/SCID/IL2Rgnull (NSG, purchased from Animal Resources Core, JHU) were injected with a million PC3/ML/fluc cells via tail vein. Tumor formation was confirmed by bioluminescence imaging (BLI) using the IVIS Spectrum Imaging System (Caliper Life Sciences, Hopkinton, MA) three weeks after injection and the mice were given indicated doses of drug once daily (intraperitoneal injection) for 30 days. Tumor progression was then monitored weekly by BLI and survival monitored concurrently.

Reagents

Triptolide and WZB117 were purchased from Sigma while spironolactone was obtained from Acros Organics. Doxorubicin was from APExBio. Glutriptolides were synthesized following procedures detailed in the Supplemental Information.

Proliferation and viability assays

[3H]-thymidine incorporation. HEK293T cells (10,000 cells/well) were seeded into 96-well plates then cultured in DMEM plus 10% FBS and 1% penicillin/streptomycin at 37°C with 5% CO2 overnight. Drugs were added at indicated concentrations and incubation was continued for an additional 24 h. For hypoxia, PC3 (5,000 cells/well) were exposed to 1% O2 (Airgas) in a humidified hypoxia chamber (Billups-Rothenberg) in 37°C for 48 h prior to drug exposure for 48 h. Treated cells were then pulsed using an aliquot of 1 μCi of [^{3}H]-thymidine (Perkin Elmer) per well for an additional 6 h. Radiolabelled cells were harvested onto a printed Filtermat A glass fiber filter (Perkin Elmer) using a Tomtec Harvester 96 Mach III M. Betaplate Scint (Perkin Elmer) scintillation fluid was added to radiolabelled filters followed by scintillation counting on Microbeta2 LumiJET Microplate Counter (Perkin Elmer).

XTT assay. Five thousand cells/well were plated on flat-bottom, transparent 96-well plate in a full growth media and incubated at appropriate culture conditions. Twenty four hours after seeding, cells were treated with indicated drugs and incubated for 47 hrs. Cell viability was measured using the R&D SystemsTM TACS XTT Cell Proliferation/Viability Assay (R&D Systems, Minneapolis, MN).

ATPase activity assay

The TFIIH complex was purified and its DNA-dependent ATPase assay was performed based on a published protocol (Titov et al., 2011). Briefly, a 10-µl reaction mixture contained 20 mM Tris (pH 7.9), 4 mM $MgCl_2$, 1 µM of ATP, 0.1 μCi [γ-^{32}P]ATP (3000 Ci/mmol), 100 μg/ml BSA, 100 nM RNA Polymerase II promoter positive control DNA , 1 nM TFIIH and indicated concentrations of triptolide or its analogs. The reactions were started by either addition of TFIIH for 2 hr and stopped by addition of 2 μl of 0.5 M EDTA. An aliquot of 1 μl reaction mixture was spotted on PEI-cellulose (sigma) and the chromatogram was developed with 0.5 M LiCl and 1 M HCOOH. The percent of ATP hydrolysis was quantified using a Typhoon FLA 9500 Variable Imager (GE Healthcare).

Stability of glutriptolides in human serum

Human serum (Sigma,10% in DMEM media) was treated with 10 μM drug (triptolide or glutriptolides) at room temperature for various time points. The incubation was stopped by placing samples on dry ice followed by overnight storage in -80 °C. Frozen samples were then lyophilized and reconstituted in DMSO at room temperature for an hour. Samples were centrifuged at 12,000 RPM for 10 minutes and supernatants loaded into an HPLC-MS with the following conditions: (Varian pursuit XR5 Diphenyl 150x 4.6 mm; A phase: Millipore water with 0.1% HCOOH; B phase: Acetonitrile with 0.1% HCOOH; 0 - 6 min: 95% B; 6 - 24 min: 5% B-100% B; 24 - 28 min: 100% B; 28 - 29 min: 100% B-5% B; 29 -30 min: 5% B).

Western blot analysis

Whole cell lysates were prepared by adding lysis buffer [4% SDS, 20% glycerol, 10% 2-mercaptoethanol, 0.004% bromophenol blue, 0.125 M Tris-HCl (pH 6.8)] to the cell pellets for 30 minutes in ice followed by centrifugation at 12,000 x g for 10 minutes then boiling for 5 minutes. For isolation of cytosolic and mitochondrial fractions of cytochrome C, cell pellets were resuspended in CLAMI buffer (250 mM sucrose, 70 mM KCl, 50 mg/ml digitonin in 1X PBS, protease inhibitor cocktail (1 tablet/ 10 ml CLAMI buffer)) then incubated on ice for 5 minutes. After centrifugation at 12,000 x g for 5 minutes at 4°C, supernatant (cytoplasmic fraction) was collected and the pellet resuspended in lysis buffer as described above. Proteins were then separated by SDS-PAGE and transferred to nitrocellulose membranes (Bio-Rad). After blocking at room temperature for 1 h, membranes were incubated at 4°C overnight with the primary antibodies including anti-Rpb1 (Santa Cruz Biotechnology), anti–XPB (Biotechne), anti-Actin (Developmental Studies Hybridoma Bank), anti-GAPDH (Santa Cruz Biotechnology), anti-cytochrome C (Santa Cruz Biotechnology), anti-PARP1 (Santa Cruz Biotechnology), anti-cleaved caspase 3 (Cell Signaling Technology), anti-VDAC (ProteinTech), anti-HIF-1 (BD sciences), and anti-GLUT1 (Santa Cruz Biotechnology) antibodies followed by incubation with horseradish peroxidase–conjugated anti-mouse or anti-rabbit IgG (GE Healthcare) at room temperature for 2 hours. Antibody–protein complexes were detected using enhanced chemiluminescence (ECL) immunoblotting detection reagent (EMD Millipore).

Immunocytochemistry and cytochemistry

HeLa or PC3 cells (2 × 105) were seeded on a MatTek glass bottom culture dish (Fisher Scientific, Pittsburgh, PA, USA) and allowed to adhere for 24 h. Cells were then treated with either DMSO or drugs for 6 or 24 h then fixed with 4% paraformaldehyde, permeabilized using 1X PBS with 0.5% triton X 100 then probed for endogenous RNA Polymerase II catalytic subunit Rpb1 or HIF-1a using anti-RNAPII (Santa Cruz Biotechnology) and anti-HIF-1a (BD sciences) antibodies, respectively. Detection was then done using anti-mouse Alexa Fluor 488 (Invitrogen). For nuclear staining, fixed and permeabilized cells were incubated in DAPI (ThermoFisher) or Hoechst 33258 (Sigma) for 30 minutes prior to imaging. Glucose uptake was monitored by incubating cells in 200 μM 2-NBDG (ThermoFisher) for 6 hours prior to fixation. Fluorescence was observed under the Nikon Eclipse TE200 Inverted microscope (Nikon Instruments Inc., Melville, NY, USA). ImageJ software (NIH, Bethesda, MD, USA; http:// imagej.nih.gov/ij/index.html) was used to measure intracellular protein levels in immuno-cytochemistry samples (Li et al., 2015). Rpb1 levels were measured using the MEASURE feature of ImageJ where all the background signals were subtracted from the intergrated density of nuclear Rpb1.

Statistical analysis

Data fitting for dose curves was performed using GraphPad Prism for Mac, GraphPad

Software (www.graphpad.com). Statistical values were reported in the Figures (Figures 3A and S2) and Tables (Table 2). Results are presented as mean with SEM unless otherwise specified and statistical significance was determined using two-tailed Student's *t-test* (unequal variance). Survival curves were estimated using Kaplan-Meier method and chi-square testing was used to determine significant differences among groups (Sullivan, 2017) through GraphPad Software. Effect size between conditions were estimated using Cohen's d ($d = M_1 – M_2 / s$; $M_1 - M_2$ is the difference between the group means and s is the standard deviation of either group) (Sullivan and Feinn, 2012).

NMR of glutriptolides

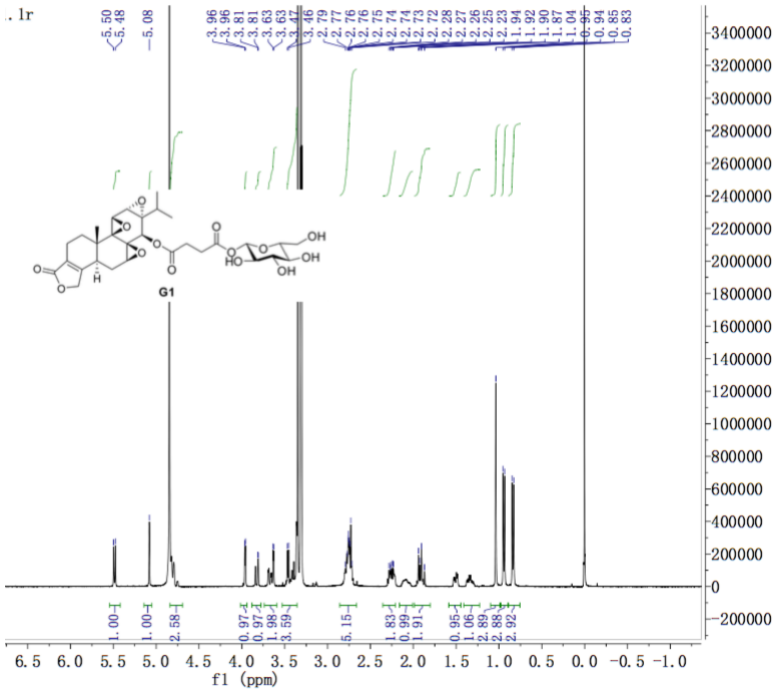


Figure S5. ^{1}H (500 MHz) – NMR of **G1** in CD_3OD, Related to Figure 1.

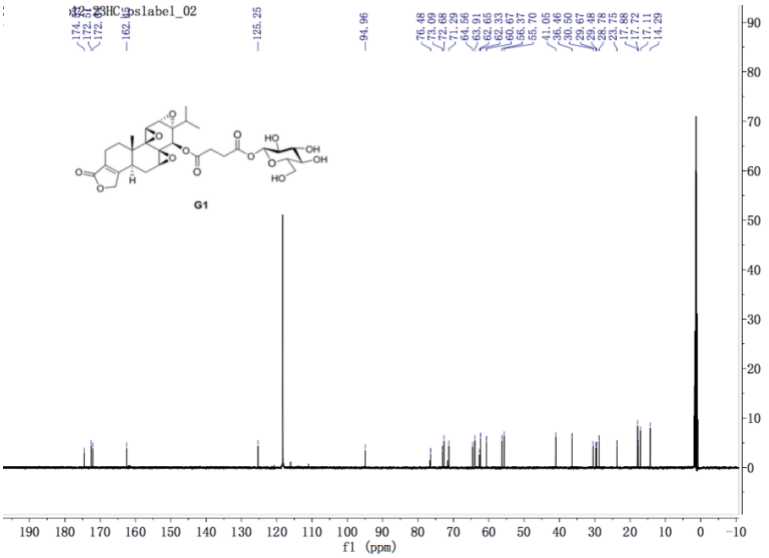


Figure S6. ^{13}C (125 MHz) – NMR of **G1** in CD_3CN, Related to Figure 1.

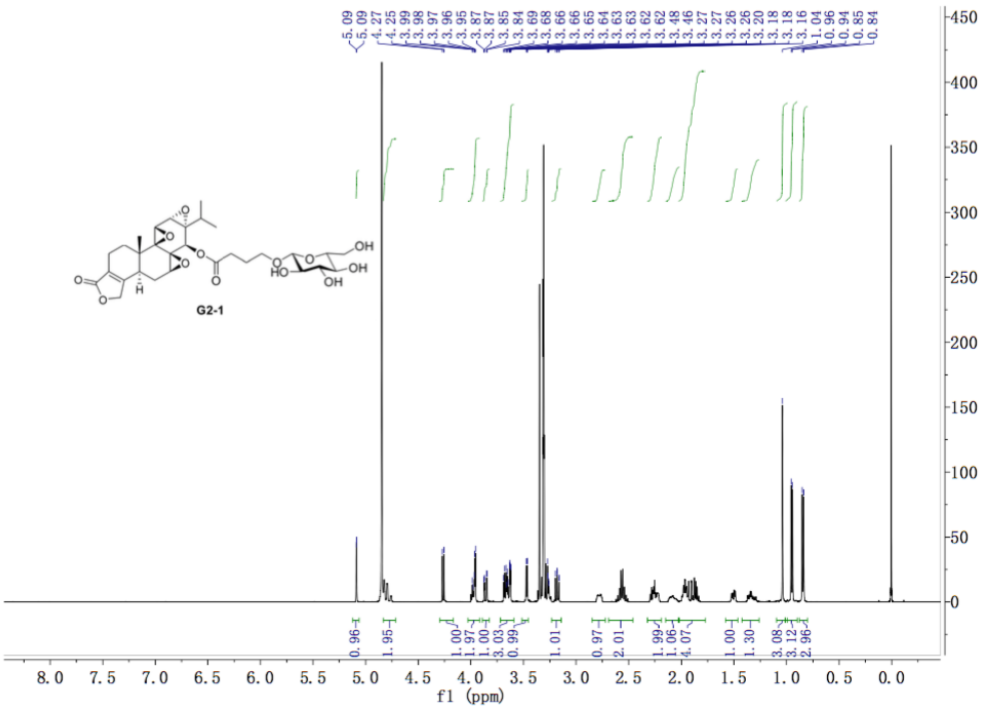


Figure S7. ^{1}H (500 MHz) – NMR of **G2-1** in CD_3OD, Related to Figure 1.

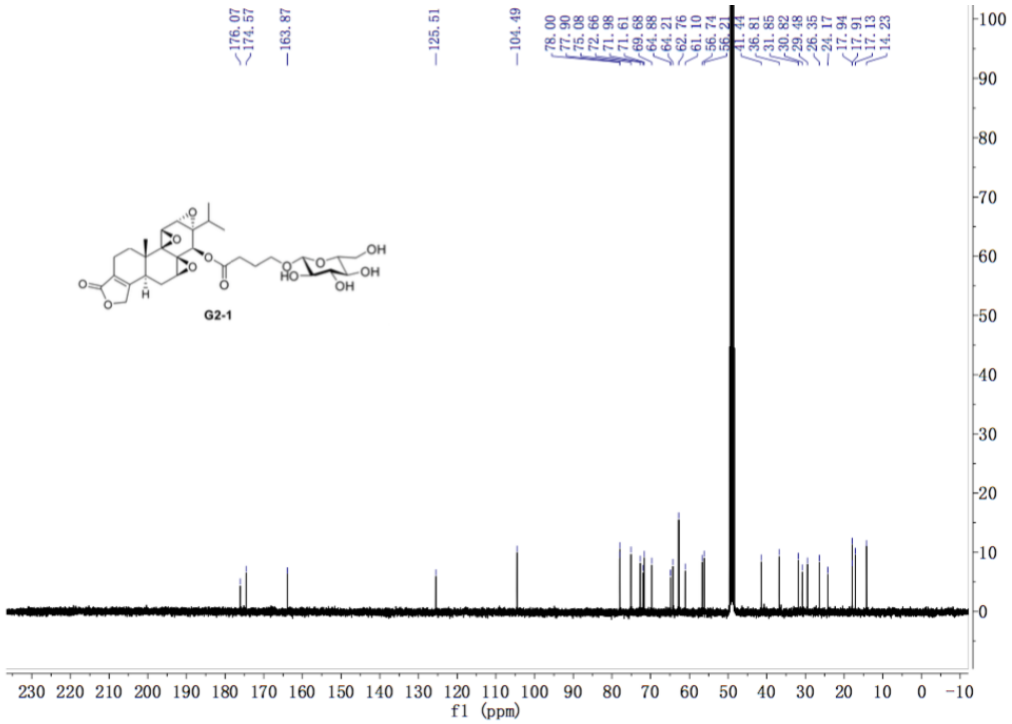


Figure S8. ^{13}C (100 MHz) – NMR of **G2-1** in CD_3OD, Related to Figure 1.

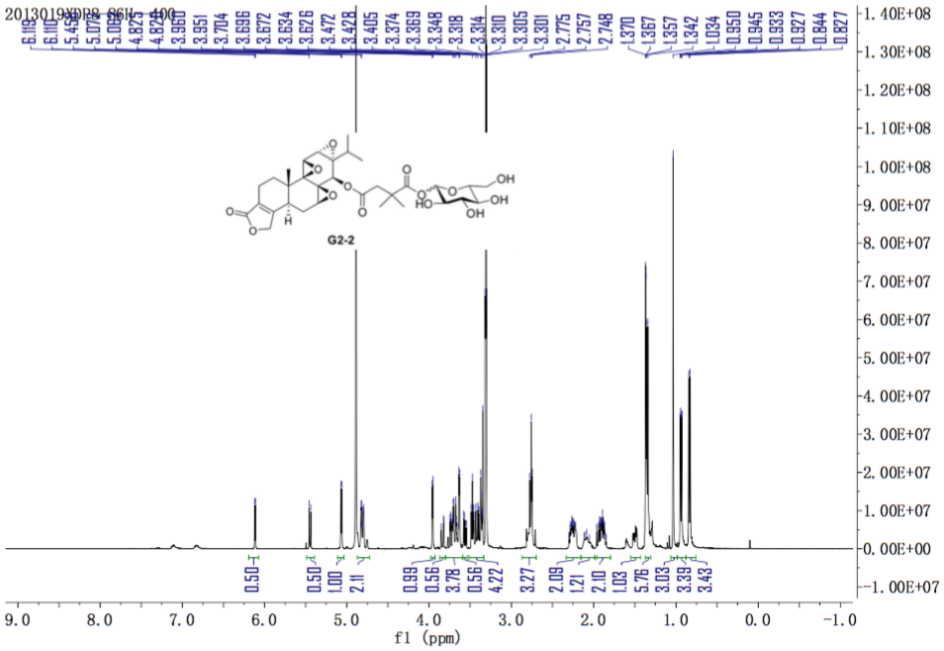


Figure S9.[1]H (400 MHz) – NMR of **G2-2** in CD_3OD, Related to Figure 1.

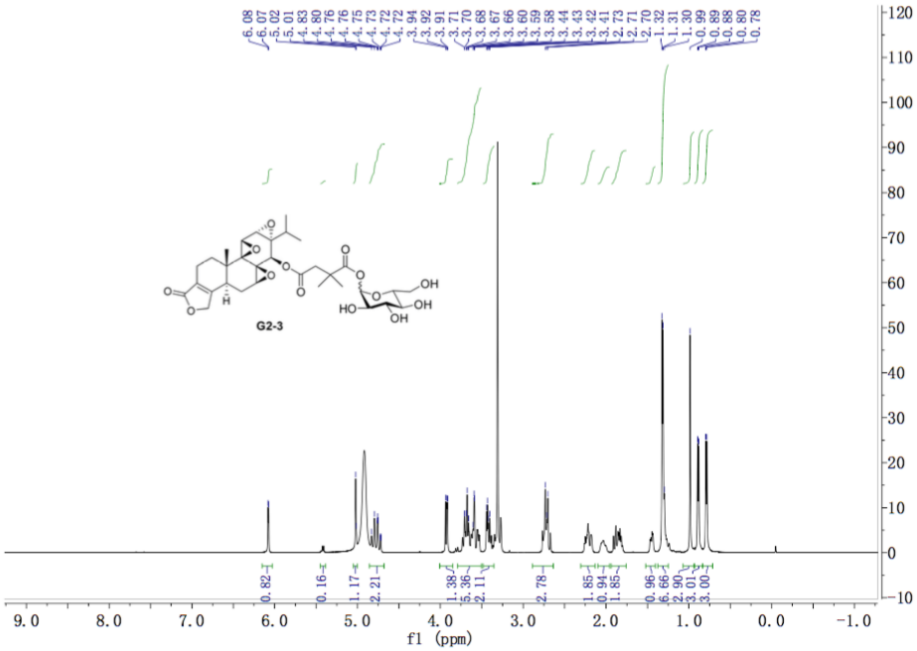


Figure S10. ^{1}H (500 MHz) – NMR of **G2-3** in CD_3OD, Related to Figure 1.

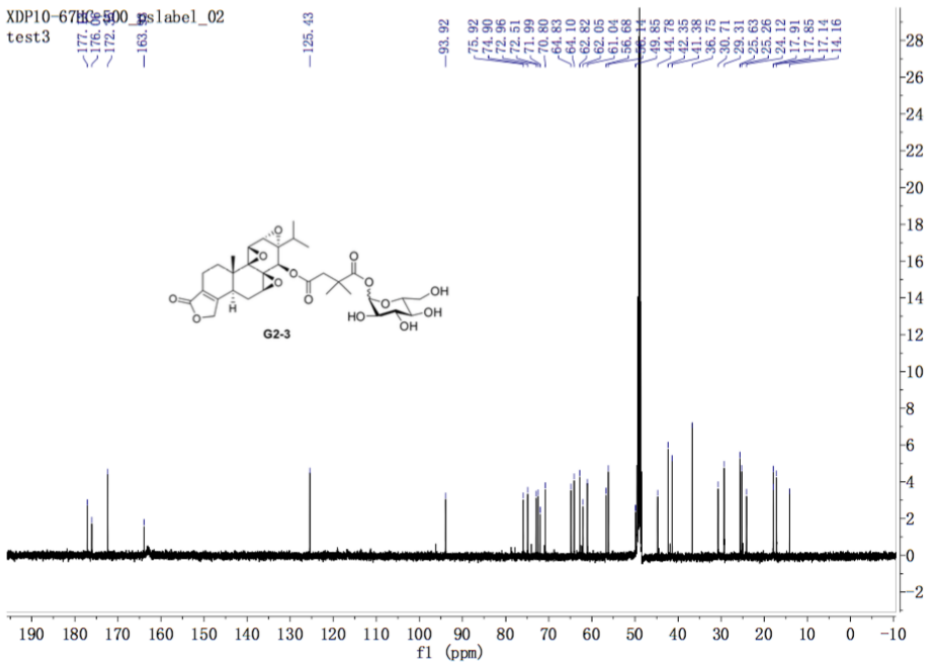


Figure S11.^{13}C (126 MHz) – NMR of **G3-3** in CD_3OD, Related to Figure 1.

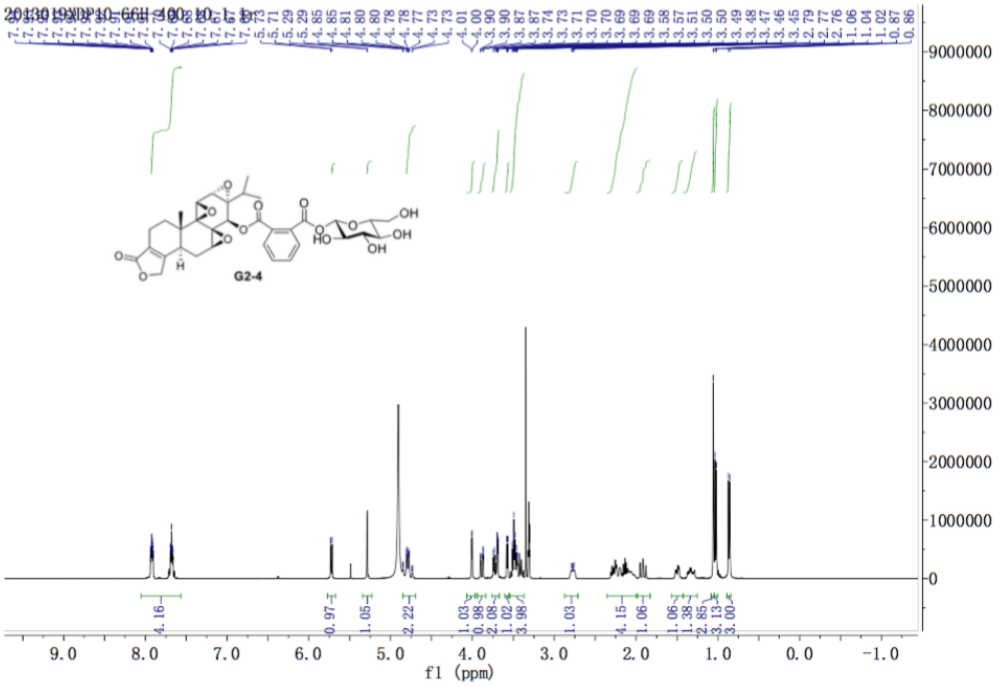


Figure S12. ^{1}H (400 MHz) – NMR of **G2-4** in CD_3OD, Related to Figure 1.

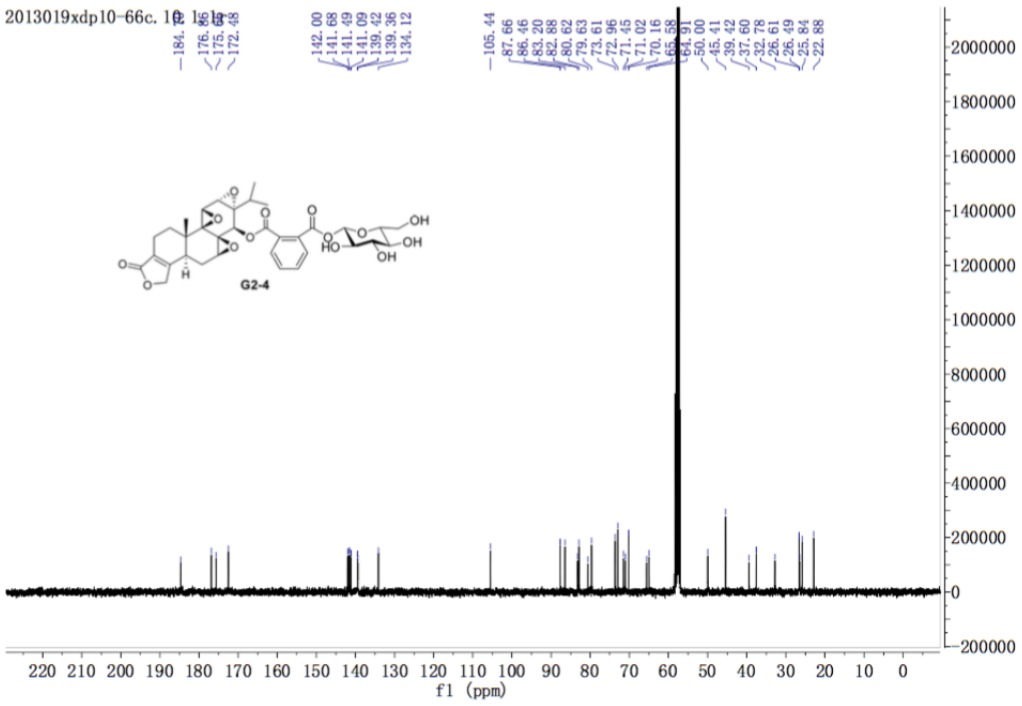


Figure S13. ^{13}C (100 MHz) – NMR of **G2-4** in CD_3OD, Related to Figure 1.

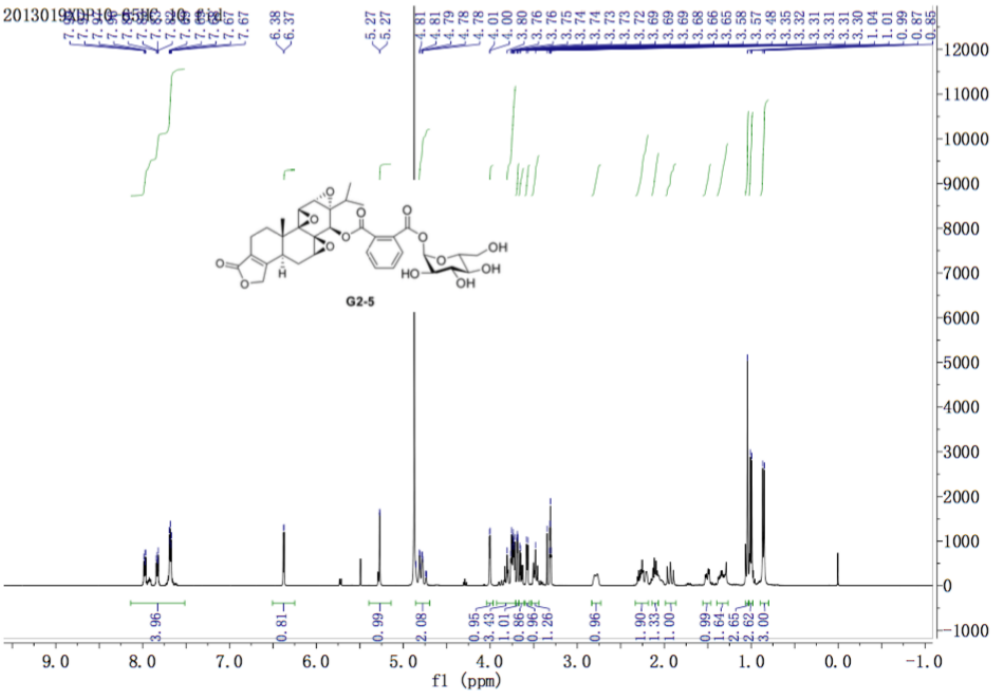


Figure S14. ^{1}H (400 MHz) – NMR of **G2-5** in CD_3OD, Related to Figure 1.

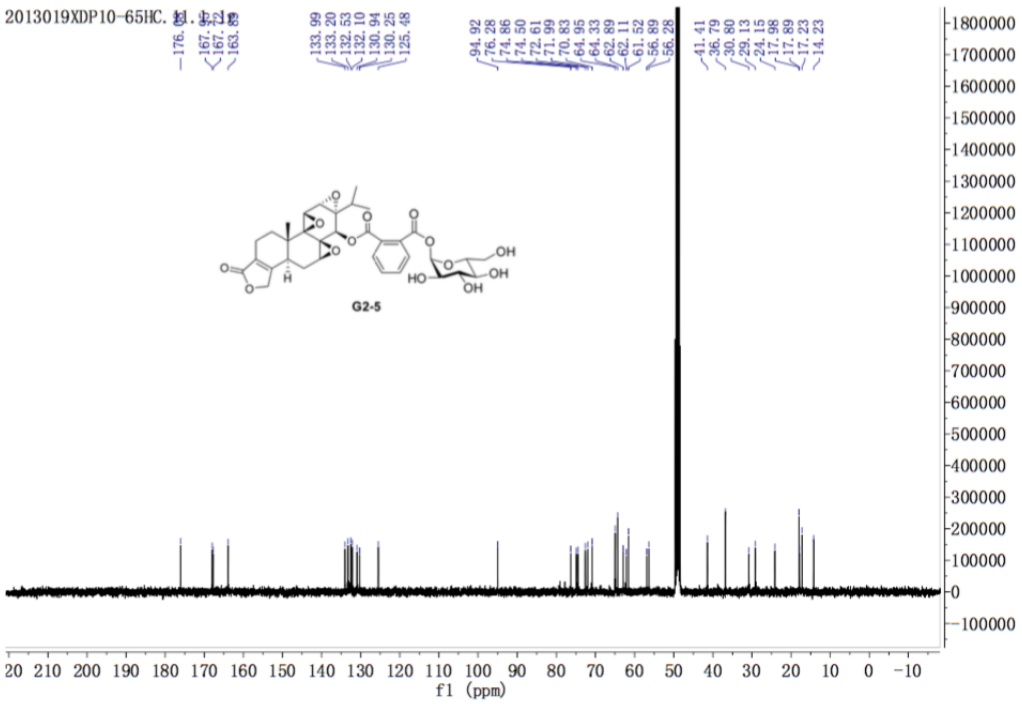


Figure S15. ^{13}C (100 MHz) – NMR of **G2-5** in CD_3OD, Related to Figure 1.

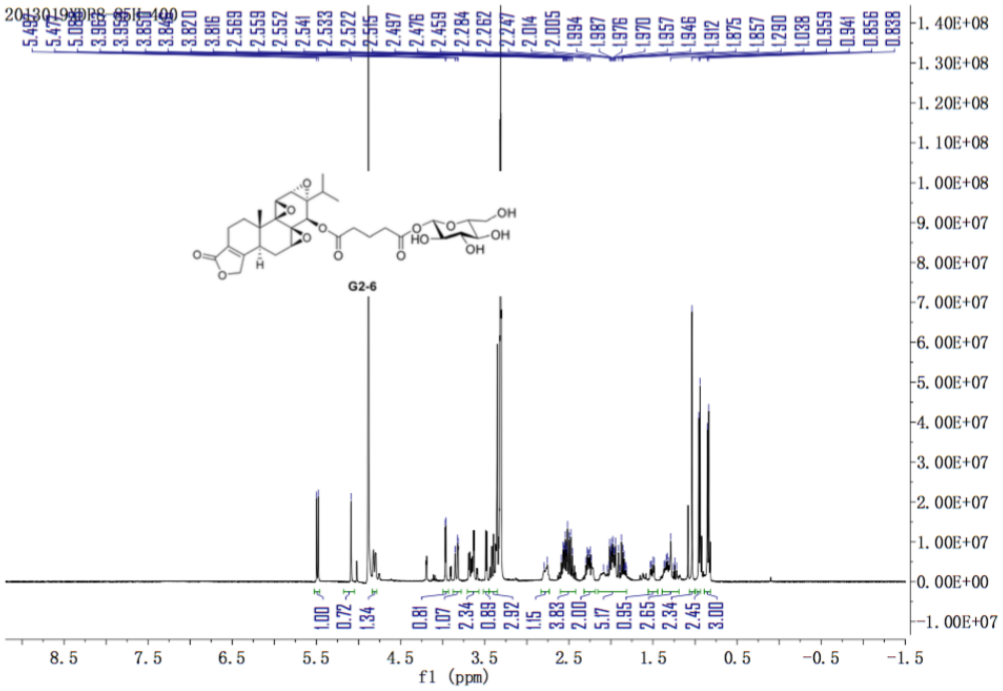


Figure S16. ^{1}H (400 MHz) – NMR of **G2-6** in CD_3OD, Related to Figure 1.

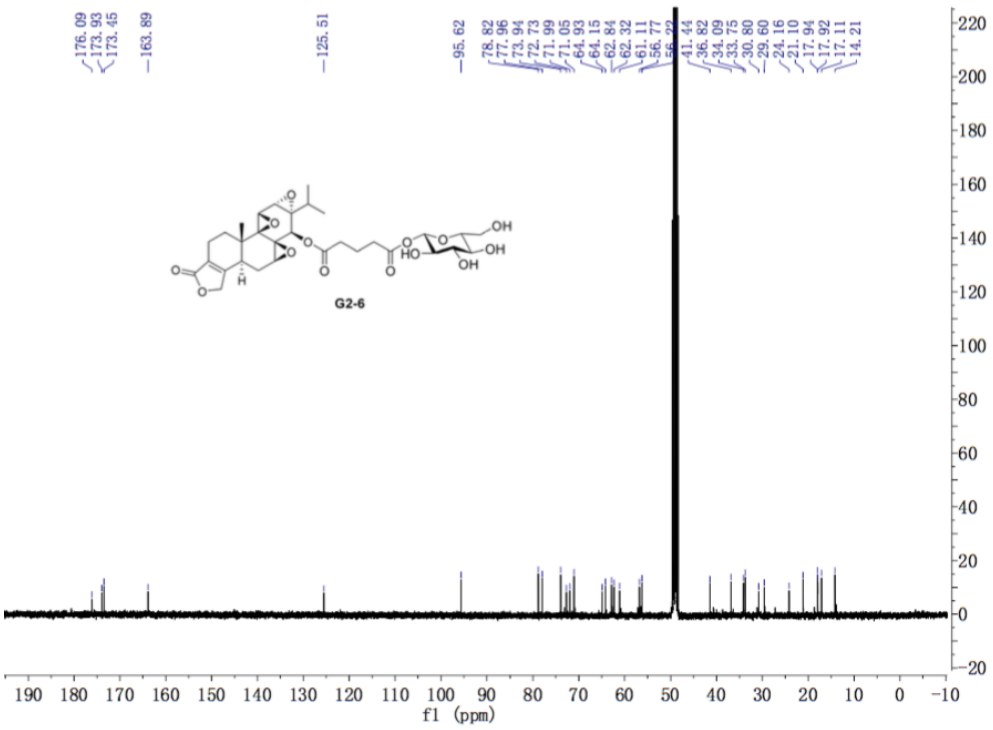


Figure S17. ^{13}C (100 MHz) – NMR of **G2-6** in CD_3OD, Related to Figure 1.

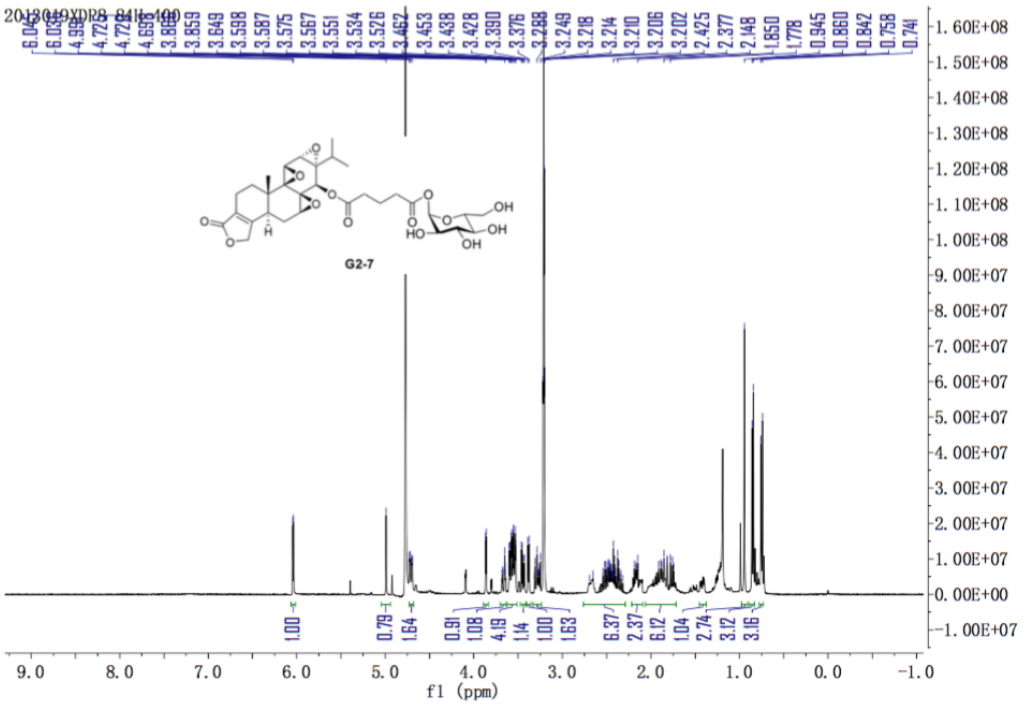


Figure S18. ^{1}H (400 MHz) – NMR of **G2-7** in CD_3OD, Related to Figure 1.

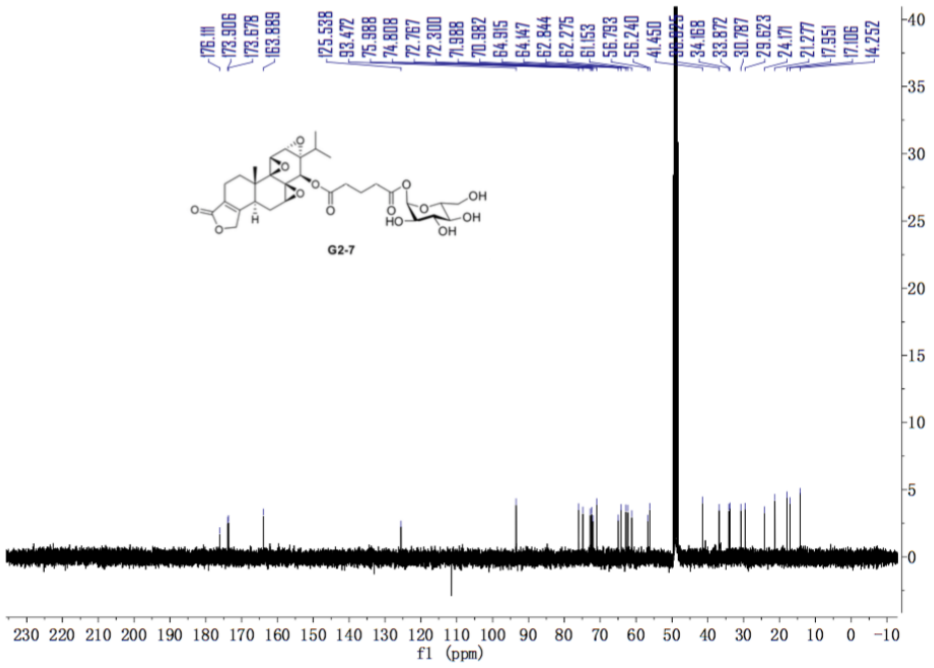


Figure S19. ^{13}C (100 MHz) – NMR of **G2-7** in CD_3OD, Related to Figure 1.

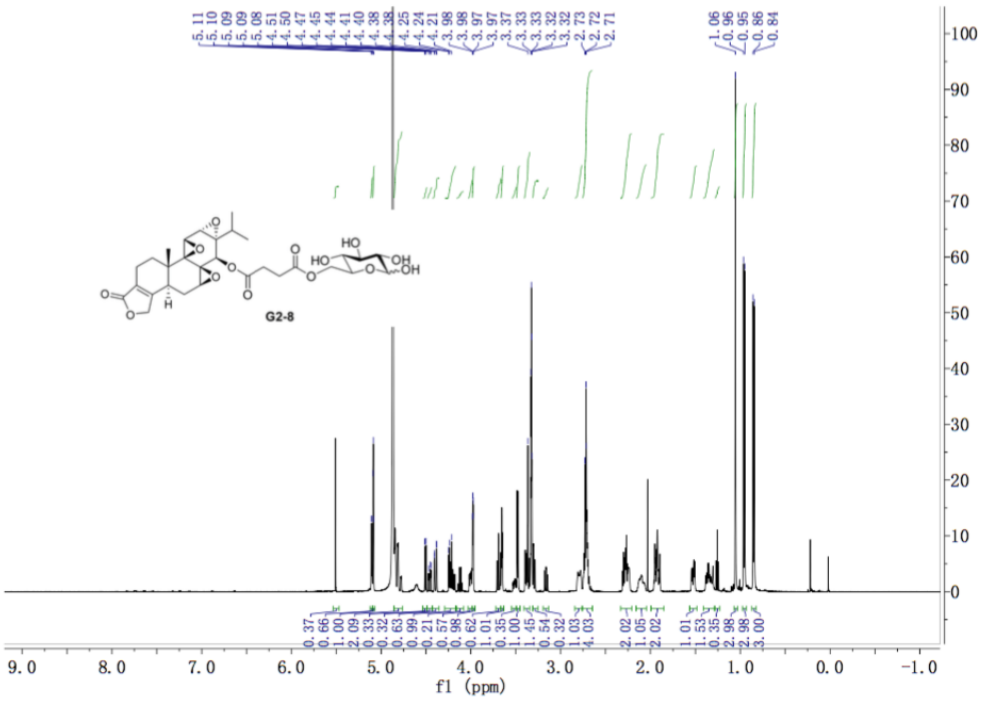


Figure S20. ^{1}H (500 MHz) – NMR of **G2-8** in CD_3OD, Related to Figure 1.

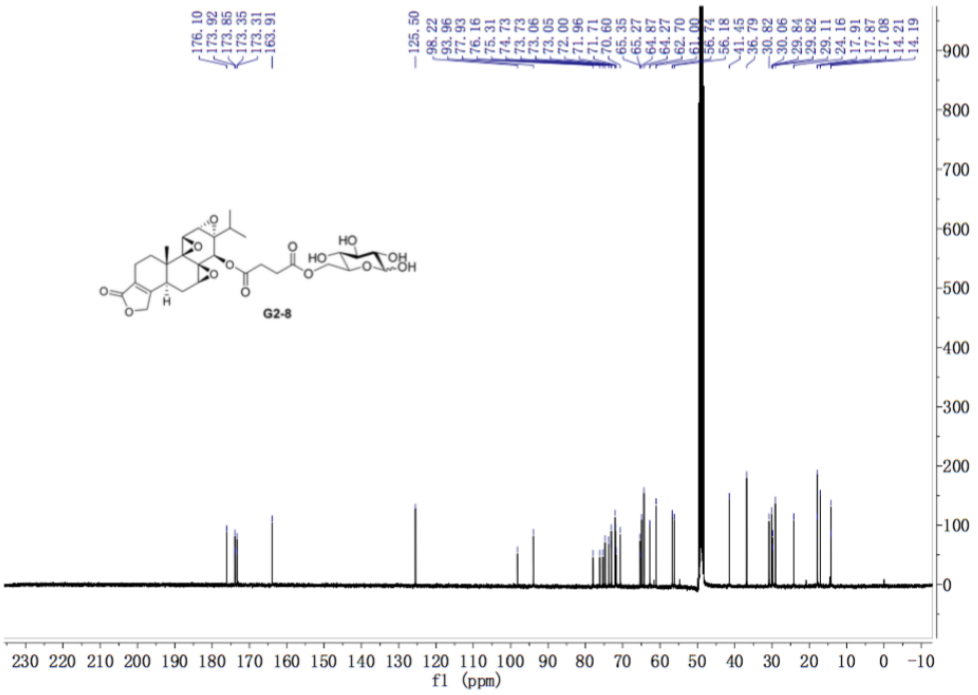


Figure S21. ^{13}C (100 MHz) – NMR of **G2-8** in CD_3OD, Related to Figure 1.

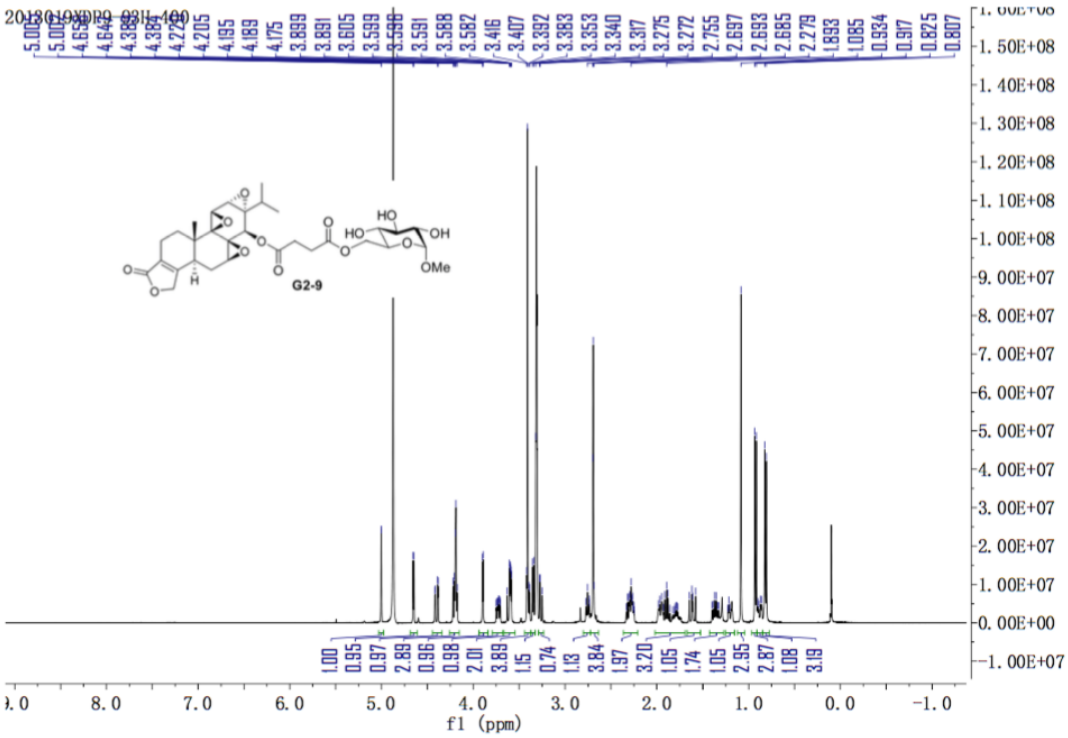


Figure S22. ^{1}H (400 MHz) – NMR of **G2-9** in CD_3OD, Related to Figure 1.

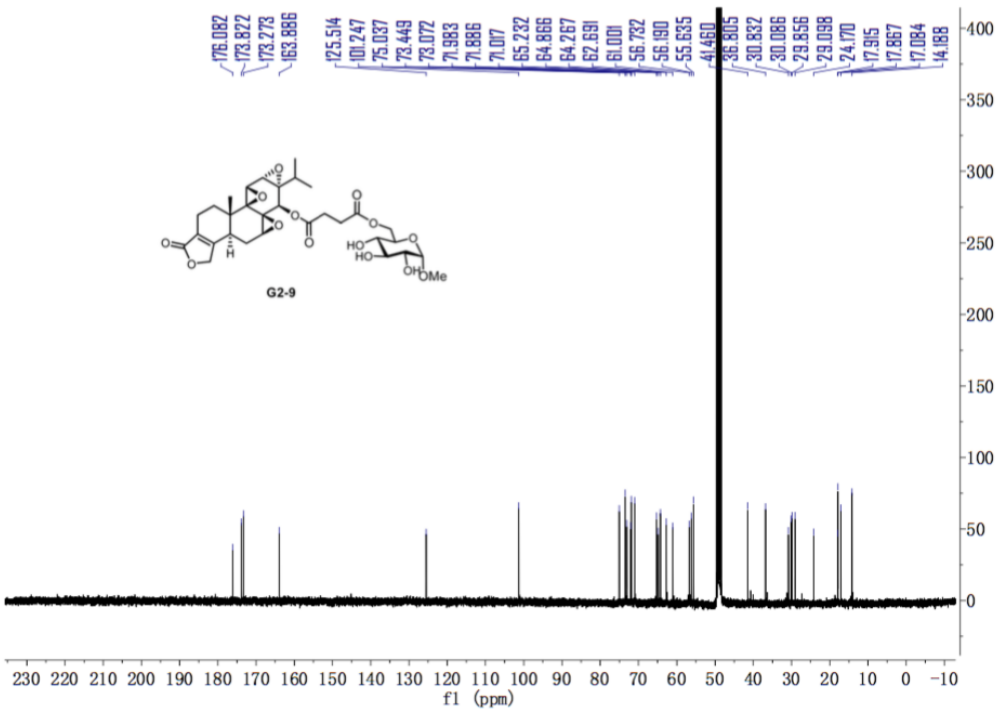


Figure S23. ^{13}C (100 MHz) – NMR of **G2-9** in CD_3OD, Related to Figure 1.

HPLC of Glutriptolides

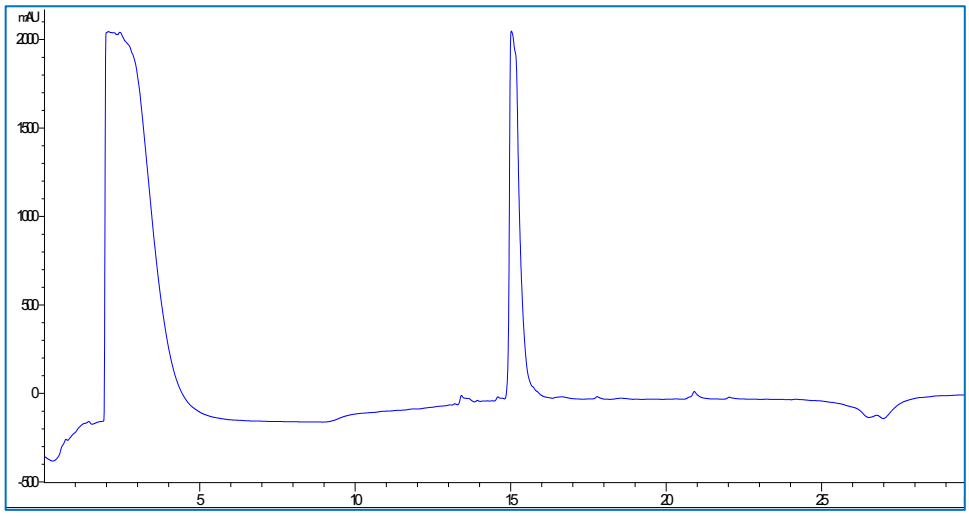


Figure S24. HPLC spectrum of **G2-3**, Related to Figure 1.

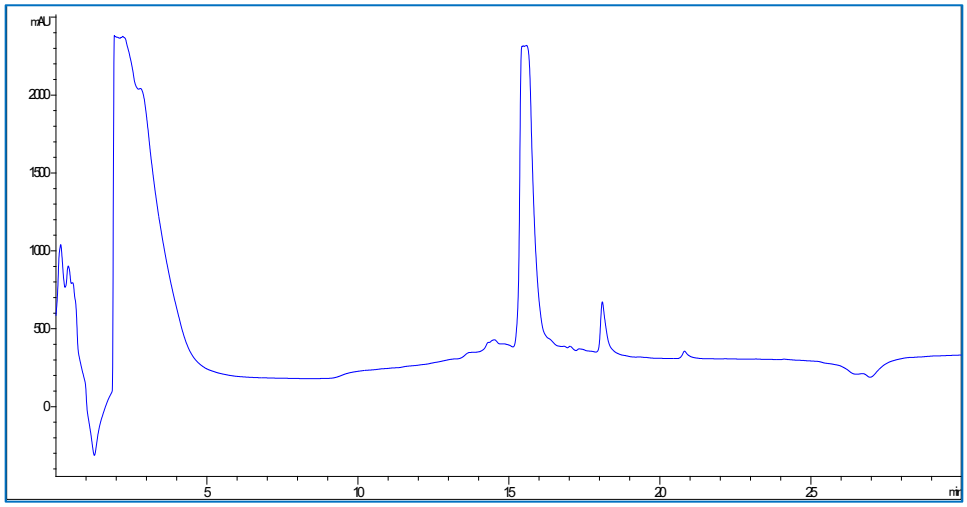


Figure S25. HPLC spectrum of **G2-4**, Related to Figure 1.

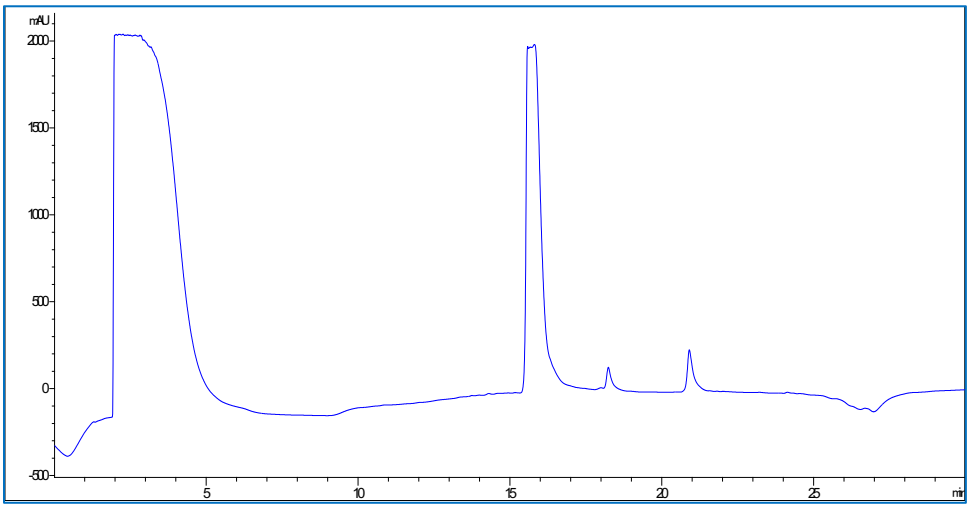


Figure S26. HPLC spectrum of **G2-5**, Related to Figure 1.

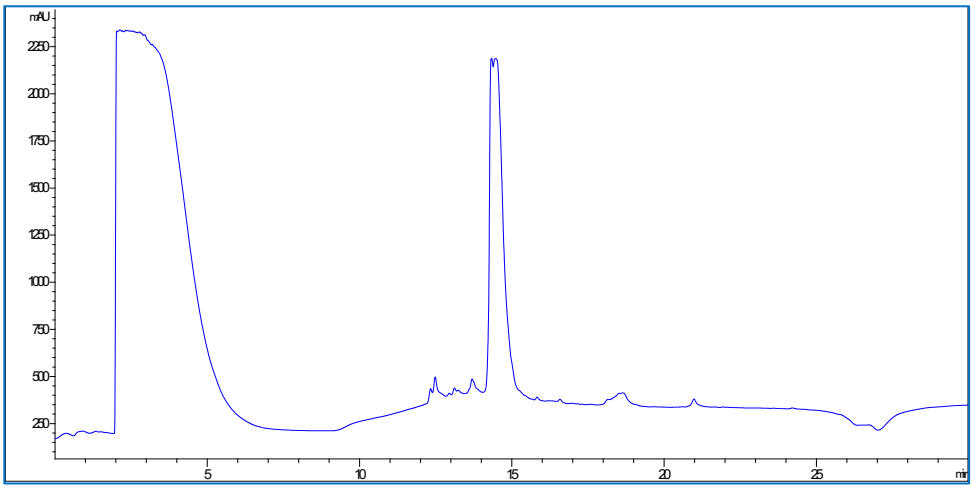


Figure S27. HPLC spectrum of **G2-8**, Related to Figure 1.

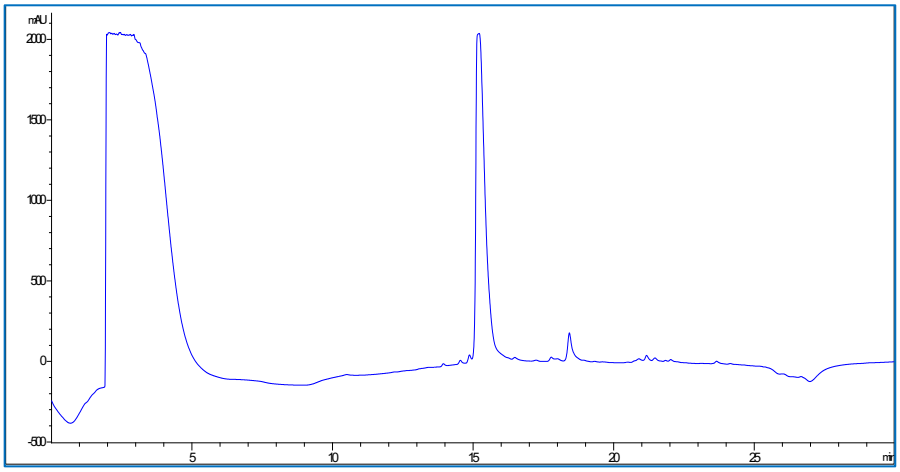


Figure S28. HPLC spectrum of **G2-9**, Related to Figure 1.

Supplemental References

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