Synthesis of 3-Deoxypentacyclic Triterpene Derivatives as Inhibitors of Glycogen Phosphorylase

Pu Zhang,[†] Jia Hao,[†] Jun Liu,[‡] Qian Lu,[‡] Huaming Sheng,[†] Luyong Zhang,[*,‡] and Hongbin Sun[*,†]

Center for Drug Discovery, College of Pharmacy, China Pharmaceutical University, 24 Tongjia Xiang, Nanjing 210009, People's Republic of China, and Jiangsu Center for Drug Screening, China Pharmaceutical University, 1 Shennonglu, Nanjing 210038, People's Republic of China

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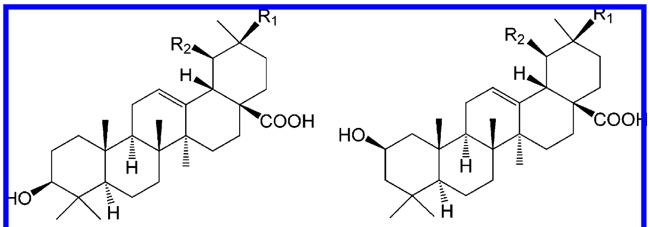
The 3-deoxy-2-keto derivatives **5** and **7** of oleanolic acid (**1**) and ursolic acid (**2**), respectively, served as precursors to the synthesis of 35 3-deoxy derivatives of pentacyclic triterpenes. The synthesized compounds were biologically assayed for their inhibitory activity against rabbit muscle glycogen phosphorylase a (GPa). Among this series of compounds, 2α-hydroxyurs-12-en-28-oic acid (**18**) (IC_{50} = 1.2 μM) exhibited the most potent activity. Preliminary structure−activity relationship analysis for the 3-deoxy triterpene derivatives as GP inhibitors is also discussed.

Oleanolic acid (**1**) and ursolic acid (**2**) (Figure 1) are two well-known members of the family of pentacyclic triterpenes and are the major effective components of many Traditional Chinese Medicines (TCM). Pentacyclic triterpenes exhibit a variety of biological activities such as anti-inflammatory, antibacterial, antiviral, antiparasitic, hepatoprotective, antitumor, wound healing, antioxidant, antipruritic, antiangiogenic, antiallergic, and immunomodulatory activities.[1−6] In previous studies, we reported that pentacyclic triterpenes represented a new class of inhibitors of glycogen phosphorylase (GP).[7] GP catalyzes the process of glycogenolysis, which is a key contributor to hepatic glucose output. Previous studies showed that lowering hepatic glucose production was effective in treatment of hyperglycemia in animals.[8] A number of synthetic GP inhibitors have been identified to evaluate their therapeutic potential for the treatment of type 2 diabetes.[9] We previously reported the synthesis of 2-isooleanolic acid (**3**) and 2-isoursolic acid (**4**) as A-ring regioisomers of **1** and **2**, respectively.[10] In structural comparison with most natural pentacyclic triterpenes that possess 3-oxygenated functions, **3** and **4** represent an interesting class of 3-deoxypentacyclic triterpenes. In continuation of our efforts in structural modifications of pentacyclic triterpenes, **3** and **4** were chosen as new lead compounds. In fact, the result of initial GP assays for **3** and **4** showed that **3** and **4** were more potent GP inhibitors than **1** and **2**, respectively. This result motivated us to carry out further structural modifications on **3** and **4**. In this paper, we present the synthesis and biological evaluation of a series of 3-deoxy-2-functionalized pentacyclic triterpene derivatives as GP inhibitors. Structure−activity relationship analysis is also discussed.

Results and Discussion

The synthesis of 3-deoxypentacyclic triterpenes **3**−**37** is summarized in Scheme 1. 2-Keto analogues **5** and **7** were readily prepared in five steps starting from **1** and **2**, respectively.[10] Hydrogenolysis of **5** and **7** over palladium/carbon afforded keto acids **6** (96%) and **8** (93%), respectively. Treatment of **5** with hydroxylamine hydrochloride in pyridine at room temperature gave oxime derivative **9** (93%), which was hydrogenolyzed over palladium/carbon to give carboxylic acid **10** (95%). In the same fashion, carboxylic acid **12** was prepared from **7**. All the oxime derivatives were mixtures of almost equal amounts of *E*, *Z* isomers that were extremely difficult to separate by common means. As described in our previous report,[10] reduction of **5** with sodium borohydride produced alcohol **13** (76%), together with a small amount of the 2α-isomer **14** (5%). Hydrogenolysis of **13** and **14** over palladium/carbon in THF furnished 2-isooleanolic acid (**3**) (92%) and its 2α-isomer **15** (93%), respectively. In the same fashion, 2-isoursolic acid (**4**) and its 2α-isomer **18** were synthesized starting from ketone **7**.[10] 2-*O*-Acyl derivatives **19**, **21**, **23**, **25**, and **27** were obtained in 78−89% yields by treatment of **13** with acyl anhydride/pyridine or acyl chloride/pyridine. 2-*O*-Acyl triterpene acids **20**, **22**, **24**, **26**, and **28** were produced in 83−98% yields via hydrogenolysis of the corresponding benzyl esters, respectively. Esterification of **3** with a bromide compound or methyl iodide in the presence of potassium carbonate in DMF yielded C-28 ester derivatives **29**−**37** in 73−95% yields.



1 R_1=CH_3, R_2=H **3** R_1=CH_3, R_2=H
2 R_1=H, R_2=CH_3 **4** R_1=H, R_2=CH_3

Figure 1. Structures of oleanolic acid (**1**), ursolic acid (**2**), 2-isooleanolic acid (**3**), and 2-isoursolic acid (**4**).

The synthesized 3-deoxypentacyclic triterpenes were biologically evaluated for their inhibitory activities against rabbit muscle glycogen phosphorylase a (RMGPa). As described previously, the activity of RMGPa was measured through detecting the released amount of phosphates from glucose-1-phosphates in the direction of glycogen synthesis.[11] The assay results are reported in Table 1. Most of the newly synthesized compounds exhibited inhibitory activity against RMGPa with IC_{50} values in the range 1.2−121.3 μM.

As shown in Table 1, migration of the 3-OH group to C-2 significantly improves the potency (**3** vs **1**; **15** vs **1**; **4** vs **2**; **18** vs **2**). As for the compounds with a 28-*O*-benzyl ester group, the compounds with 2α-OH groups are less potent than those with 2β-OH groups (e.g., **14** vs **13**; **17** vs **16**). However, the potency trend of the compounds with a 28-carboxyl group is not clear. For the 2-keto derivatives, the 28-*O*-benzyl esters are more potent than the corresponding carboxylic acids (e.g., **5** vs **6**; **7** vs **8**). On the other hand, there is a reverse trend among 2-oxime derivatives (e.g., **9** vs **10**; **11** vs **12**). The introduction of 2-keto and 2-oxime groups in the oleanane skeleton enhanced GP inhibitory activity compared with the parent compound **1** (e.g., **5**, **6** vs **1**; **9**, **10** vs **1**), while in the ursane skeleton, the potency was slightly reduced compared with the parent compound **2** (e.g., **7**, **8** vs **2**; **11** vs **2**). Among the

* To whom correspondence should be addressed. Tel: +86-25-85327950. Fax: +86-25-83271335. E-mail: hbsun2000@yahoo.com; drugscreen@126.com.
[†] Center for Drug Discovery.
[‡] Jiangsu Center for Drug Screening.

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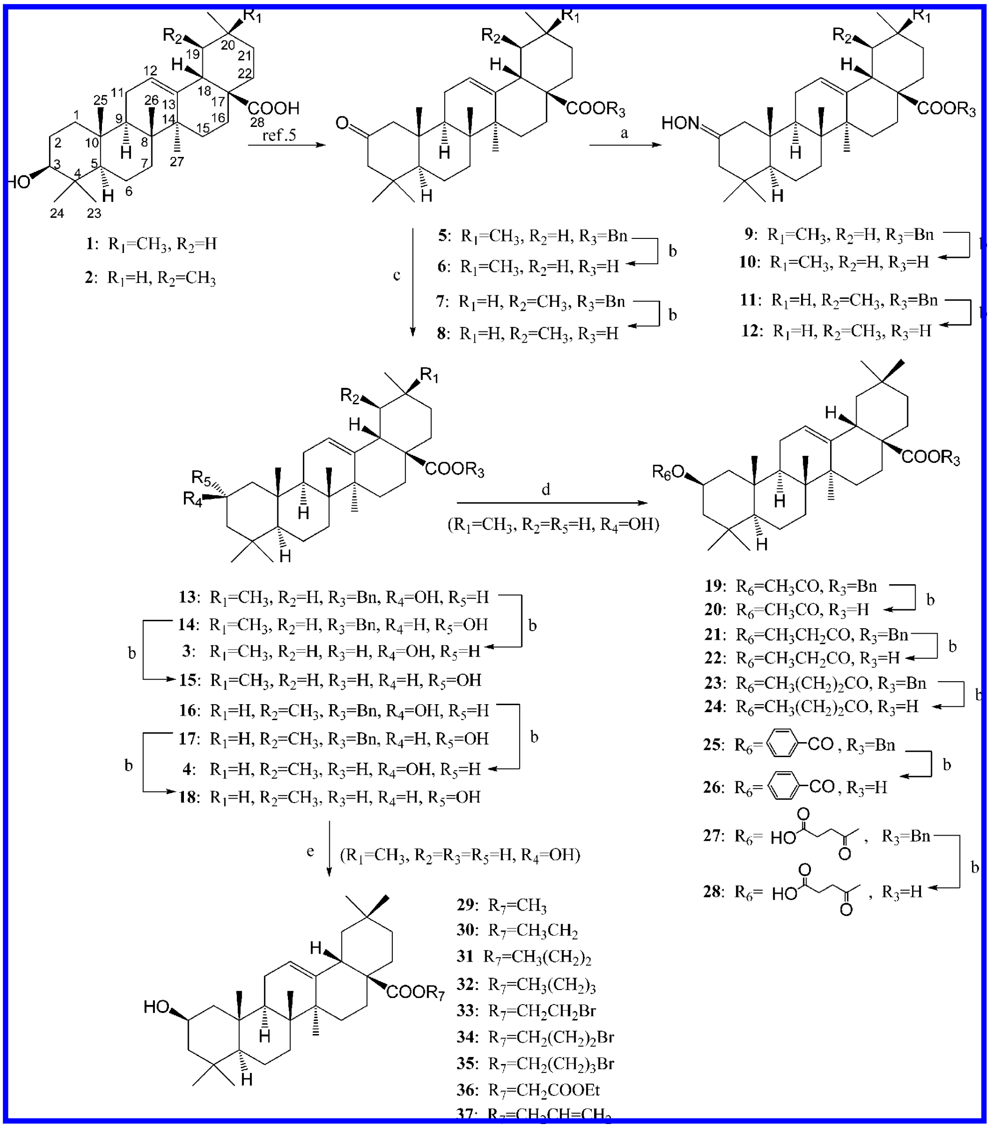
Scheme 1. Synthesis of 3-Deoxypentacyclic Triterpenes **3**−**37**[a]



[a] (a) $HONH_2 \cdot HCl$, pyridine, rt; (b) 10% Pd−C, H_2, THF, rt; (c) $NaBH_4$, THF, EtOH, rt; (d) acyl chloride or anhydride, pyridine, rt; (e) a bromide compound or methyl iodide, K_2CO_3, DMF, rt.

Table 1. Inhibition of RMGPa by Triterpenes **1**−**37**

compound	RMGPa IC_{50}[a] (μM)	compound	RMGPa IC_{50}[a] (μM)
1	22.1 ± 1.9	**20**	42.4 ± 3.7
2	15.3 ± 0.8	**21**	121.3 ± 10.5
3	3.5 ± 0.3	**22**	80.2 ± 7.8
4	5.5 ± 0.4	**23**	107.9 ± 8.5
5	3.2 ± 0.5	**24**	75.6 ± 5.1
6	14.9 ± 0.9	**25**	48.4 ± 4.6
7	24.2 ± 2.2	**26**	40.7 ± 2.3
8	28.9 ± 2.7	**27**	80.9 ± 6.3
9	16.3 ± 1.2	**28**	NI[b]
10	13.1 ± 1.4	**29**	28.1 ± 2.5
11	20.2 ± 2.0	**30**	15.3 ± 1.3
12	14.7 ± 1.1	**31**	27.3 ± 2.5
13	4.2 ± 0.3	**32**	13.8 ± 0.9
14	5.6 ± 0.4	**33**	25.4 ± 2.6
15	8.5 ± 0.6	**34**	37.2 ± 3.5
16	22.3 ± 1.8	**35**	48.7 ± 3.9
17	55.8 ± 4.5	**36**	22.5 ± 2.0
18	1.2 ± 0.1	**37**	23.1 ± 1.9
19	NI[b]	caffeine[c]	75.3 ± 6.6

[a] Values are means of three experiments. [b] NI means no inhibition. [c] Caffeine was used as a positive control.

2-*O*-acyl triterpenes with a 28-*O*-benzyl group, the inhibitory potency increased as the bulk of 2-*O*-substituents increased (e.g., **19** < **21** < **23**).

In summary, 35 3-deoxypentacyclic triterpene derivatives, including 28 new compounds, have been synthesized and biologically evaluated as inhibitors of rabbit muscle GPa. Within this series of compounds, **18** (IC_{50} = 1.2 μM) exhibited 13-fold more potent GP inhibitory activity than the parent compound **2** (IC_{50} = 15.3 μM). SAR analysis shows that migration of the 3-OH group to C-2 of pentacyclic triterpenes may enhance GP inhibition. On the other hand, introduction of hydrophobic groups at C-2 and C-28 might not be suitable for potency improvement regarding GP inhibition.

Experimental Section

General Experimental Procedures. All commercially available solvents and reagents were used without further purification. Melting points are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Chemical shifts are reported as values from an internal tetramethylsilane standard. Low- and high-resolution mass spectra (LRMS and HRMS) were recorded with electron impact mode.

2-Oxoolean-12-en-28-oic acid (6). Ketone **5**[10] (100 mg, 0.184 mmol) was dissolved in THF (4 mL) and treated with 10% Pd/C (10 mg).

The mixture was stirred at room temperature under H_2 atmospheric pressure for 5 h. The reaction mixture was filtered through Celite, and the insoluble substance was washed with THF. The filtrate was concentrated *in vacuo* to give **6** as a white solid (80 mg, 96%): ^{1}H NMR (pyridine-d_5) δ 0.82 (s, 3H), 0.86 (s, 3H), 0.96 (s, 3H), 1.01 (s, 3H), 1.25 (s, 3H), 1.26 (s, 3H), 1.29 (s, 3H), 3.30 (d, J = 12.6 Hz, 1H), 5.46 (s, 1H); ^{13}C NMR (pyridine-d_5) δ 16.5, 17.0, 19.3, 22.9, 23.4, 23.7, 26.1, 28.3, 29.6, 30.0, 31.0, 32.1, 32.8, 33.2, 33.3, 34.3, 39.1, 40.1, 42.0, 43.0, 46.5, 46.7, 47.5, 55.4, 55.6, 56.5, 122.1, 144.9, 180.1, 210.3; ESIMS m/z 453.3 [M − H]$^-$; HRMS for $C_{30}H_{46}O_3$ calcd 454.3447, found 454.3449.

2-Oxours-12-en-28-oic acid (8). Following the procedure described for preparation of **6**, compound **8** was prepared from **7**[10] as a white solid (93%): ^{1}H NMR (pyridine-d_5) δ 0.81 (s, 3H), 0.84 (s, 3H), 0.96 (s, 9H), 1.22 (s, 6H), 2.62 (d, J = 10.7 Hz, 1H), 5.44 (s, 1H); ^{13}C NMR (pyridine-d_5) δ 16.7, 17.1, 17.5, 19.3, 21.4, 23.4, 23.6, 23.9, 24.9, 28.7, 31.1, 33.1, 33.3, 37.4, 39.0, 39.4, 39.6, 40.4, 42.7, 42.9, 47.4, 48.1, 53.6, 55.5, 55.9, 56.5, 125.2, 139.4, 179.8, 210.4; ESIMS m/z 453.5 [M − H]$^-$; HRMS for $C_{30}H_{46}O_3$+H calcd 455.35197, found 455.35311.

Benzyl 2-hydroxyiminoolean-12-en-28-oate (9). To a solution of **5** (100 mg, 0.18 mmol) in pyridine (0.6 mL) was added hydroxylamine hydrochloride (25 mg, 0.36 mmol). The reaction mixture was allowed to stir at room temperature for 3 h, and the solution was acidified with 2 N HCl and extracted with EtOAc. The EtOAc layer was washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by column chromatography on silica gel, eluted with an mixture of petroleum ether/EtOAc (6:1 v:v), to give **9** as a white solid (95 mg, 93%): ^{1}H NMR ($CDCl_3$) δ 0.59 (s, 6H), 0.83 (s, 3H), 0.84 (s, 6H), 0.86 (s, 3H), 0.90 (s, 6H), 0.92 (s, 6H), 1.00 (s, 3H), 1.03 (s, 3H), 1.15 (s, 6H), 2.92 (dd, J = 4.1 Hz, 13.4 Hz, 2H), 3.14 (d, J = 13.6 Hz, 1H), 3.29 (d, J = 12.7 Hz, 1H), 5.01−5.13 (m, 4H), 5.30 (s, 1H), 5.31 (s, 1H), 7.28−7.35 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 15.5, 15.9, 16.6, 16.7, 18.7, 18.8, 22.3, 22.8, 23.1, 23.4, 23.56, 23.64, 25.8, 27.6, 30.7, 32.38, 32.45, 32.50, 32.8, 33.1, 33.9, 36.8, 38.7, 39.4, 39.6, 39.7, 40.7, 40.8, 41.42, 41.45, 41.80, 41.82, 45.9, 46.2, 46.8, 47.0, 47.2, 56.25, 56.36, 65.95, 66.00, 122.30, 122.32, 127.9, 128.0, 128.4, 136.4, 143.65, 143.70, 159.4, 159.5, 177.39, 177.41; ESIMS m/z 560.4 [M + H]$^+$; HRMS for $C_{37}H_{53}NO_3$+H calcd 560.40982, found 560.41122.

Benzyl 2-hydroxyiminours-12-en-28-oate (11). Following the procedure described for preparation of **9**, compound **11** was prepared from **7** as a white solid (92%): ^{1}H NMR ($CDCl_3$) δ 0.63 (s, 6H), 0.81 (s, 3H), 0.83 (s, 3H), 0.85 (s, 6H), 0.86 (s, 6H), 0.95 (s, 6H), 1.01 (s, 3H), 1.04 (s, 3H), 1.10 (s, 6H), 3.15 (dd, J = 1.9 Hz, 13.5 Hz, 1H), 3.32 (d, J = 13.0 Hz, 1H), 4.95−5.14 (m, 4H), 5.23−5.27 (m, 2H), 7.25−7.36 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 15.6, 16.1, 16.7, 16.8, 16.9, 18.7, 18.8, 21.1, 22.3, 22.9, 23.3, 23.4, 23.5, 24.3, 28.0, 30.7, 32.73, 32.76, 32.82, 32.87, 36.6, 36.93, 36.96, 38.8, 39.0, 39.1, 39.5, 39.86, 39.95, 40.8, 41.0, 42.1, 42.2, 46.1, 46.6, 47.0, 47.1, 48.1, 52.9, 56.2, 56.3, 66.0, 125.4, 127.9, 128.2, 128.4, 136.3, 138.1, 138.2, 160.3, 177.1; ESIMS m/z 560.4 [M + H]$^+$; HRMS for $C_{37}H_{53}NO_3$+H calcd 560.40982, found 560.41147.

2-Hydroxyiminoolean-12-en-28-oic acid (10). Following the procedure described for preparation of **6**, compound **10** was prepared from **9** as a white solid (95%): ^{1}H NMR (DMSO-d_6) δ 0.71 (s, 3H), 0.72 (s, 3H), 0.76 (s, 6H), 0.81 (s, 3H), 0.88 (s,12H), 0.95 (s, 3H), 0.97 (s, 3H), 1.13 (s, 6H), 1.24 (s, 3H), 2.75 (d, J = 10.4 Hz, 2H), 2.99 (d, J = 13.0 Hz, 1H), 3.15 (d, J = 12.3 Hz, 1H), 5.20 (s, 2H), 10.15 (s, 1H), 10.17 (s, 1H), 12.05 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 15.0, 15.5, 16.4, 16.5, 18.1, 18.2, 21.9, 22.6, 22.7, 22.9, 23.2, 25.4, 27.1, 28.8, 30.2, 32.0, 32.3, 32.4, 32.7, 33.2, 35.9, 36.0, 37.8, 38.7, 38.8, 38.9, 39.1, 40.3, 40.7, 41.3, 45.4, 45.5, 45.6, 46.0, 46.3, 46.5, 55.36, 55.40, 121.2, 121.3, 143.6, 143.7, 155.3, 178.3; ESIMS m/z 468.3 [M − H]$^-$; HRMS for $C_{30}H_{47}NO_3$+H calcd 470.36287, found 470.36391.

2-Hydroxyiminours-12-en-28-oic acid (12). Following the procedure described for preparation of **6**, compound **12** was prepared from **11** as a white solid (95%): ^{1}H NMR (DMSO-d_6) δ 0.75 (s, 12H), 0.82 (s, 12H), 0.92 (s, 6H), 0.95 (s, 3H), 0.96 (s, 3H), 1.08 (s, 6H), 2.99 (d, J = 12.0 Hz, 1H), 3.17 (d, J = 12.3 Hz, 1H), 5.15 (s, 2H), 10.13 (s, 2H), 11.93 (brs, 2H); ^{13}C NMR (DMSO-d_6) δ 15.4, 15.8, 16.6, 16.7, 17.1, 18.3, 18.4, 21.1, 22.2, 22.8, 22.9, 23.0, 23.3, 23.9, 27.6, 30.3, 32.46, 32.53, 32.6, 36.1, 36.4, 38.1, 38.6, 38.9, 39.0, 39.5, 40.1, 40.5, 41.8, 45.8, 46.1, 46.4, 46.6, 46.9, 52.5, 55.5, 55.6, 124.5, 138.2, 138.3, 155.5, 178.2; ESIMS m/z 468.3 [M − H]$^-$; HRMS for $C_{30}H_{47}NO_3$+H calcd 470.36287, found 470.36389.

Compounds 3, 4, 13, 14, and 16 were prepared following the literature procedues.[10] **2α-Hydroxyolean-12-en-28-oic acid (15).** Following the procedure described for preparation of **6**, compound **15** was prepared from **14**[5] as a white solid (93%): ^{1}H NMR (pyridine-d_5) δ 0.87 (s, 3H), 0.94 (s, 3H), 0.95 (s, 3H), 0.96 (s, 3H), 1.01 (s, 6H), 1.02 (s, 3H), 1.27 (s, 3H), 3.30 (dd, J = 4.0 Hz, 13.7 Hz, 1H), 4.12−4.21 (m, 1H), 5.48 (t, J = 3.2 Hz, 1H); ^{13}C NMR (pyridine-d_5) δ 16.7, 17.6, 18.8, 22.8, 22.9, 23.7, 23.8, 24.0, 26.2, 28.3, 31.0, 33.2, 33.3, 33.8, 34.3, 34.9, 39.2, 40.0, 42.1, 42.3, 46.5, 46.7, 48.3, 50.4, 52.2, 56.1, 63.9, 122.6, 144.9, 180.1; ESIMS m/z 479.4 [M + Na]$^+$; *anal.* calcd for $C_{30}H_{48}O_3 \cdot 0.4CH_3COOH$ C 76.95, H 10.40, found C 77.07, H 9.91.

Benzyl 2α-Hydroxyurs-12-en-28-oate (17). Following the literature procedures,[5] compound **17** was prepared from **7** as a white solid (10%): ^{1}H NMR ($CDCl_3$) δ 0.64 (s, 3H), 0.86 (s, 3H), 0.87 (s, 3H), 0.94 (s, 6H), 0.95 (s, 3H), 1.08 (s, 3H), 2.27 (d, J = 11.6 Hz, 1H), 3.89 (m, 1H), 4.98 (d, J = 12.5 Hz, 1H), 5.10 (d, J = 12.5 Hz, 1H), 5.25 (t, J = 3.6 Hz, 1H), 7.26−7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 16.6, 17.0, 17.2, 18.4, 21.1, 22.7, 23.4, 23.6, 24.3, 28.0, 30.7, 33.0, 33.6, 34.9, 36.7, 38.9, 39.0, 39.2, 39.8, 42.2, 47.7, 48.2, 49.8, 51.3, 53.0, 55.7, 65.2, 66.0, 125.8, 127.9, 128.2, 128.4, 136.5, 138.3, 177.2; ESIMS m/z 569.4 [M + Na]$^+$; HRMS for $C_{37}H_{54}O_3$+H calcd 547.41457, found 547.41603.

2α-Hydroxyurs-12-en-28-oic acid (18). Following the procedure described for preparation of **6**, compound **18** was prepared from **17** as a white solid (98%): ^{1}H NMR (pyridine-d_5) δ 0.85 (s, 3H), 0.91 (s, 3H), 0.94 (s, 9H), 0.97 (s, 3H), 1.15 (s, 3H), 2.43 (d, J = 11.4 Hz, 1H), 3.99−4.03 (m, 1H), 5.37 (s, 1H); ^{13}C NMR (pyridine-d_5) δ 15.4, 16.0, 17.4, 20.1, 21.5, 22.3, 22.5, 23.4, 27.1, 29.7, 32.0, 32.5, 33.5, 35.9, 37.7, 37.9, 38.1, 38.7, 41.2, 46.6, 46.7, 48.8, 50.3, 52.0, 54.7, 62.7, 124.2, 137.7, 178.8; HRMS for $C_{30}H_{48}O_3$+H calcd 457.36762, found 457.36954.

General Procedure for the Acylation of 13. Compound **13** was dissolved in pyridine and treated with an excess of anhydride or acyl chloride. The reaction mixture was stirred at room temperature until the substrate was consumed. Then, the solution was acidified with 2 N HCl and extracted with EtOAc. The EtOAc layer was washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by column chromatography on silica gel.

Benzyl 2β-acetoxyolean-12-en-28-oate (19). Following the general procedure, compound **19** was prepared from **13** as a white solid (78%): ^{1}H NMR ($CDCl_3$) δ 0.65 (s, 3H), 0.92 (s, 3H), 0.94 (s, 6H), 1.01 (s, 3H), 1.13 (s, 3H), 1.15 (s, 3H), 2.04 (s, 3H), 2.93 (dd, J = 4.1 Hz, 13.7 Hz, 1H), 5.04−5.15 (m, 3H), 5.31 (t, J = 3.5 Hz, 1H), 7.32−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 17.0, 17.1, 18.7, 21.5, 23.2, 23.5, 23.7, 23.8, 26.0, 27.7, 30.8, 32.5, 32.7, 33.1, 33.4, 34.1, 37.4, 39.7, 41.6, 42.1, 43.5, 46.0, 46.9, 48.2, 54.6, 66.0, 70.7, 122.7, 127.9, 128.1, 128.4, 136.6, 143.8, 170.4, 177.4; ESIMS m/z 611.5 [M + Na]$^+$; HRMS for $C_{39}H_{56}O_4$+H calcd 589.42514, found 589.42701.

Benzyl 2β-(1-oxopropoxy)olean-12-en-28-oate (21). Following the general procedure, compound **21** was prepared from **13** as a white solid in a yield of 82%: ^{1}H NMR ($CDCl_3$) δ 0.63 (s, 3H), 0.90 (s, 3H), 0.92 (s, 6H), 0.99 (s, 3H), 1.11 (s, 3H), 1.12 (s, 3H), 1.13 (s, 3H), 2.26 (d, J = 7.6 Hz, 1H), 2.31 (d, J = 7.6 Hz, 1H), 2.91 (dd, J = 3.3 Hz, 13.5 Hz, 1H), 5.01−5.12 (m, 3H), 5.29 (t, J = 3.1 Hz, 1H), 7.27−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 9.1, 17.1, 18.7, 23.2, 23.5, 23.7, 26.0, 27.7, 28.3, 30.7, 32.5, 32.7, 33.1, 33.5, 34.0, 37.3, 39.7, 41.6, 42.1, 43.5, 43.6, 46.0, 46.9, 48.2, 54.7, 66.0, 70.5, 122.7, 127.9, 128.0, 128.4, 143.8; ESIMS m/z 625.5 [M + Na]$^+$; HRMS for $C_{40}H_{58}O_4$+Na calcd 625.42273, found 625.42398.

Benzyl 2β-(1-oxobutoxy)olean-12-en-28-oate (23). Following the general procedure, compound **23** was prepared from **13** as a white solid (87%): ^{1}H NMR ($CDCl_3$) δ 0.66 (s, 3H), 0.93 (s, 3H), 0.95 (s, 6H), 0.97 (s, 3H), 1.01 (s, 3H), 1.14 (s, 3H), 1.15 (s, 3H), 2.27 (t, J = 7.5 Hz, 2H), 2.93 (dd, J = 3.9 Hz, 13.8 Hz, 1H), 5.05−5.15 (m, 3H), 5.32 (t, J = 3.5 Hz, 1H), 7.30−7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.7, 17.0, 17.1, 18.4, 18.7, 23.2, 23.5, 23.67, 23.75, 25.9, 27.6, 30.7, 32.5, 32.7, 33.1, 33.5, 34.0, 37.0, 37.3, 39.7, 41.6, 42.1, 43.56, 43.62, 46.0, 46.9, 48.2, 54.6, 66.0, 70.4, 122.7, 127.9, 128.0, 128.4, 136.6, 143.8, 173.0, 177.4; ESIMS m/z 639.4 [M + Na]$^+$; HRMS for $C_{41}H_{60}O_4$+Na calcd 639.43838, found 639.44026.

Benzyl 2β-benzoyloxyolean-12-en-28-oate (25). Following the general procedure, compound **25** was prepared from **13** as a white solid (79%): ^{1}H NMR (CDCl$_3$) δ 0.64 (s, 3H), 0.90 (s, 3H), 0.92 (s, 3H), 0.96 (s, 3H), 1.09 (s, 3H), 1.15(s, 3H), 1.21 (s, 3H), 2.91 (d, J = 11.0 Hz, 1H), 5.04 (d, J = 12.6 Hz, 1H), 5.11 (d, J = 12.7 Hz, 1H), 5.30 (s, 1H), 5.37 (t, J = 4.0 Hz, 1H), 7.26−7.35 (m, 5H), 7.41−7.46 (m, 2H), 7.52−7.57 (m, 1H), 8.00−8.03 (m, 2H); ^{13}C NMR (CDCl$_3$) δ 17.0, 17.1, 18.7, 23.2, 23.5, 23.7, 23.8, 26.0, 27.6, 30.7, 32.5, 32.7, 33.1, 33.6, 34.0, 37.2, 39.7, 41.5, 42.0, 43.5, 43.8, 46.0, 46.9, 48.2, 54.9, 66.0, 71.5, 122.7, 127.9, 128.0, 128.34, 128.42, 129.5, 131.1, 132.7, 136.6, 143.8, 166.2, 177.4; HRMS for $C_{44}H_{58}O_4$+Na calcd 673.42273, found 673.42546.

Benzyl 2β-(3-carboxy-1-oxopropoxy)olean-12-en-28-oate (27). Following the general procedure, compound **27** was prepared from **13** as a white solid (89%): ^{1}H NMR (CDCl$_3$) δ 0.63 (s, 3H), 0.90 (s, 3H), 0.92 (s, 6H), 0.98 (s, 3H), 1.10 (s, 3H), 1.12 (s, 3H), 2.57−2.71 (m, 4H), 2.88−2.92 (m, 1H), 5.02−5.14 (m, 3H), 5.29 (t, J = 3.4 Hz, 1H), 7.28−7.36 (m, 5H); ^{13}C NMR (CDCl$_3$) δ 17.0, 17.2, 18.7, 23.2, 23.5, 23.7, 23.8, 25.9, 27.6, 28.6, 29.6, 30.7, 32.5, 32.7, 33.1, 33.4, 34.0, 37.3, 39.7, 41.6, 42.0, 43.4, 46.0, 46.9, 48.2, 54.5, 66.0, 71.4, 122.7, 127.9, 128.0, 128.4, 136.6, 143.8, 171.5, 177.4; ESIMS m/z 645.3 [M − H]$^-$; HRMS for $C_{41}H_{58}O_6$+H calcd 647.43062, found 647.43359.

2β-Acetoxyolean-12-en-28-oic acid (20). Following the procedure described for preparation of **6**, compound **20** was prepared from **19** as a white solid (97%): ^{1}H NMR (CDCl$_3$) δ 0.77 (s, 3H), 0.91 (s, 3H), 0.92 (s, 3H), 0.93 (s, 3H), 0.98 (s, 3H), 1.13 (s, 3H), 1.14 (s, 3H), 2.00 (s, 3H), 2.83 (dd, J = 4.4 Hz, 13.6 Hz, 1H), 5.06−5.10 (m, 1H), 5.29 (t, J = 3.3 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 17.2, 18.7, 21.5, 23.1, 23.5, 23.6, 23.7, 26.0, 27.7, 30.7, 32.5, 32.6, 33.1, 33.4, 33.9, 37.4, 39.7, 41.3, 42.0, 43.5, 46.0, 46.6, 48.2, 54.6, 70.7, 122.9, 143.6, 170.4, 182.2; ESIMS m/z 497.4 [M − H]$^-$; HRMS for $C_{32}H_{50}O_4$+H calcd 499.37819, found 499.37929.

2β-(1-Oxopropoxy)olean-12-en-28-oic acid (22). Following the procedure described for preparation of **6**, compound **22** was prepared from **21** as a white solid (94%): ^{1}H NMR (CDCl$_3$) δ 0.78 (s, 3H), 0.93 (s, 3H), 0.94 (s, 3H), 0.95 (s, 3H), 1.00 (s, 3H), 1.15 (s, 6H), 1.17 (s, 3H), 2.31 (q, J = 7.58 Hz, 2H), 2.85 (d, J = 10.1 Hz, 1H), 5.14 (s, 1H), 5.31 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 9.1, 17.0, 17.2, 18.7, 23.0, 23.5, 23.6, 26.0, 27.7, 28.3, 30.7, 32.5, 32.6, 33.1, 33.5, 33.9, 37.4, 39.7, 41.2, 41.9, 43.4, 43.6, 45.9, 46.7, 48.2, 54.7, 70.5, 122.8, 143.6, 173.8, 183.5; ESIMS m/z 511.5 [M − H]$^-$; HRMS for $C_{33}H_{52}O_4$+Na calcd 535.37578, found 535.37770.

2β-(1-Oxobutoxy)olean-12-en-28-oic acid (24). Following the procedure described for preparation of **6**, compound **24** was prepared from **23** as a white solid (98%): ^{1}H NMR (CDCl$_3$) δ 0.75 (s, 3H), 0.90 (s, 3H), 0.91 (s, 3H), 0.92 (s, 3H), 0.93 (s, 3H), 0.99 (s, 3H), 1.12 (s, 3H), 1.14 (s, 3H), 2.23 (t, J = 7.5 Hz, 2H), 2.82 (d, J = 9.6 Hz, 1H), 5.11 (t, J = 4.1 Hz, 1H), 5.28 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 13.7, 17.1, 17.2, 18.4, 18.6, 23.0, 23.5, 23.6, 23.7, 26.0, 27.7, 30.7, 32.4, 32.6, 33.1, 33.5, 33.9, 37.0, 37.3, 39.6, 41.2, 41.9, 43.4, 43.6, 45.9, 46.6, 48.1, 54.6, 70.4, 122.8, 143.6, 173.0, 183.3; ESIMS m/z 525.5 [M − H]$^-$; HRMS for $C_{34}H_{54}O_4$+H calcd 527.40949, found 527.41081.

2β-Benzoyloxyolean-12-en-28-oic acid (26). Following the procedure described for preparation of **6**, compound **26** was prepared from **25** as a white solid (95%): ^{1}H NMR (CDCl$_3$) δ 0.78 (s, 3H), 0.91 (s, 3H), 0.93 (s, 3H), 0.97 (s, 3H), 1.08 (s, 3H), 1.15 (s, 3H), 1.24 (s, 3H), 2.81−2.85 (m, 1H), 5.29 (s, 1H), 5.38 (t, J = 3.7 Hz, 1H), 7.40−7.45 (m, 2H), 7.52−7.57 (m, 1H), 7.99−8.02 (m, 2H); ^{13}C NMR (CDCl$_3$) δ 17.1, 17.2, 18.7, 23.1, 23.5, 23.6, 23.8, 26.0, 27.7, 30.7, 32.5, 32.6, 32.7, 33.0, 33.6, 34.0, 37.3, 39.7, 41.3, 42.0, 43.5, 43.8, 46.0, 46.6, 48.2, 54.9, 71.5, 122.9, 128.4, 129.5, 131.1, 132.6, 143.6, 166.2, 182.0; ESIMS m/z 583.3 [M + Na]$^+$; HRMS for $C_{37}H_{52}O_4$+Na calcd 583.37578.40949, found 583.37677.

2β-(3-Carboxy-1-oxopropoxy)olean-12-en-28-oic acid (28). Following the procedure described for preparation of **6**, compound **28** was prepared from **27** as a white solid (83%): ^{1}H NMR (C_5D_5N) δ 0.85 (s, 3H), 0.93 (s, 3H), 0.98 (s, 3H), 0.99 (s, 3H), 1.01 (s, 3H), 1.15 (s, 3H), 1.23 (s, 3H), 2.81−2.90 (m, 4H), 3.27 (d, J = 10.4 Hz, 1H), 5.29 (s, 1H), 5.46 (s, 1H); ^{13}C NMR (C_5D_5N) δ 17.4, 18.9, 23.8, 24.0, 26.2, 28.2, 29.9, 30.5, 30.9, 32.5, 33.0, 33.2, 33.4, 34.3, 37.5, 40.0, 42.1, 42.4, 43.6, 46.5, 46.7, 48.5, 54.7, 70.9, 122.5, 144.9, 172.0, 174.7, 180.0; ESIMS m/z 579.3 [M + Na]$^+$; HRMS for $C_{34}H_{52}O_6$+Na calcd 579.36561, found 579.36777.

General Procedure for the Esterification of 3. Compound **3**[5] was dissolved in DMF and treated with 1.2 equiv of a bromide compound or methyl iodide. The reaction mixture was stirred at room temperature until the substrate was consumed. Then, the mixture was filtered and extracted with EtOAc. The EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by column chromatography on silica gel.

Methyl 2β-hydroxyolean-12-en-28-oate (29). Following the general procedure, compound **29** was prepared from **3** as a white solid (95%): ^{1}H NMR (CDCl$_3$) δ 0.73 (s, 3H), 0.89 (s, 3H), 0.92 (s, 6H), 1.00 (s, 3H), 1.12 (s, 3H), 1.18 (s, 3H), 2.85 (dd, J = 3.4 Hz, 14.0 Hz, 1H), 3.62 (s, 3H), 4.08 (t, J = 4.8 Hz, 1H), 5.30 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 16.8, 18.5, 19.0, 23.1, 23.4, 23.6, 24.6, 25.9, 27.6, 30.7, 32.4, 32.5, 32.7, 33.08, 33.10, 33.9, 37.8, 39.6, 41.4, 41.9, 45.8, 46.6, 46.8, 47.2, 48.0, 51.5, 53.5, 67.7, 122.6, 143.7, 178.3; ESIMS m/z 493.4 [M + Na]$^+$; HRMS for $C_{31}H_{50}O_3$+Na calcd 493.36522, found 493.36640.

Ethyl 2β-hydroxyolean-12-en-28-oate (30). Following the general procedure, compound **30** was prepared from **3** as a white solid (94%): ^{1}H NMR (CDCl$_3$) δ 0.75 (s, 3H), 0.89 (s, 3H), 0.92 (s, 6H), 1.00 (s, 3H), 1.13 (s, 3H), 1.18 (s, 3H), 1.25 (s, 3H), 2.86 (dd, J = 3.7 Hz, 13.8 Hz, 1H), 4.03−4.13 (m, 3H), 5.31 (t, J = 3.3 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 14.3, 16.9, 18.5, 19.0, 23.0, 23.5, 23.6, 24.7, 25.9, 27.6, 29.7, 30.7, 32.4, 32.6, 32.7, 33.07, 33.12, 34.0, 37.8, 39.7, 41.4, 41.9, 45.9, 46.6, 47.3, 48.0, 53.5, 60.1, 67.7, 122.6, 143.8, 177.7; ESIMS m/z 507.5 [M + Na]$^+$; HRMS for $C_{32}H_{52}O_3$+H calcd 485.39892, found 485.39981.

***n*-Propyl 2β-hydroxyolean-12-en-28-oate (31).** Following the general procedure, compound **31** was prepared from **3** as a white solid (92%): ^{1}H NMR (CDCl$_3$) δ 0.75 (s, 3H), 0.89 (s, 3H), 0.93 (s, 6H), 0.94 (s, 3H), 1.01 (s, 3H), 1.13 (s, 3H), 1.18 (s, 3H), 2.88 (dd, J = 4.2 Hz, 13.7 Hz, 1H), 3.92−4.01 (m, 2H), 4.06−4.10 (m, 1H), 5.31 (t, J = 3.5 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 10.6, 16.9, 18.5, 19.0, 22.0, 23.1, 23.5, 23.6, 24.7, 25.9, 27.6, 30.7, 32.5, 32.6, 32.7, 33.0, 33.1, 34.0, 37.8, 39.7, 41.5, 42.0, 45.9, 46.6, 46.8, 47.3, 48.0, 53.5, 65.8, 67.7, 122.6, 143.8, 177.7; ESIMS m/z 521.4 [M + Na]$^+$; HRMS for $C_{33}H_{54}O_3$+H calcd 499.41457, found 499.41483.

***n*-Butyl 2β-hydroxyolean-12-en-28-oate (32).** Following the general procedure, compound **32** was prepared from **3** as a white solid (86%): ^{1}H NMR (CDCl$_3$) δ 0.75 (s, 3H), 0.90 (s, 3H), 0.92 (s, 9H), 1.01 (s, 3H), 1.13 (s, 3H), 1.18 (s, 3H), 2.87 (d, J = 12.8 Hz, 1H), 4.01−4.08 (m, 3H), 5.30 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 13.7, 16.9, 18.5, 19.0, 19.2, 23.0, 23.5, 23.6, 24.6, 25.9, 27.5, 29.7, 30.7, 32.5, 32.6, 32.7, 33.0, 33.1, 33.9, 37.8, 39.6, 41.4, 41.9, 45.9, 46.6, 46.7, 47.3, 48.0, 53.4, 63.9, 67.7, 122.6, 143.8, 177.7; ESIMS m/z 535.4 [M + Na]$^+$; HRMS for $C_{34}H_{56}O_3$+H calcd 513.43022, found 513.43176.

(2-Bromoethyl) 2β-hydroxyolean-12-en-28-oate (33). Following the general procedure, compound **33** was prepared from **3** as a white solid (91%): ^{1}H NMR (CDCl$_3$) δ 0.75 (s, 3H), 0.90 (s, 3H), 0.93 (s, 6H), 1.01 (s, 3H), 1.14 (s, 3H), 1.18 (s, 3H), 2.88 (dd, J = 3.5 Hz, 13.6 Hz, 1H), 3.50 (t, J = 6.0 Hz, 2H), 4.06−4.10 (m, 1H), 4.28−4.39 (m, 2H), 5.33 (t, J = 3.1 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 17.0, 18.5, 19.0, 23.0, 23.5, 23.6, 24.6, 25.9, 27.6, 29.0, 29.7, 30.7, 32.47, 32.55, 32.7, 33.1, 33.9, 37.8, 39.7, 41.4, 41.9, 45.8, 46.6, 46.9, 47.3, 48.0, 53.5, 63.6, 67.7, 122.9, 143.4, 177.3; ESIMS m/z 601.3 [M + K]$^+$; HRMS for $C_{32}H_{51}BrO_3$+Na calcd 585.29138, found 585.29301.

(3-Bromopropyl) 2β-hydroxyolean-12-en-28-oate (34). Following the general procedure, compound **34** was prepared from **3** as a white solid (82%): ^{1}H NMR (CDCl$_3$) δ 0.75 (s, 3H), 0.90 (s, 3H), 0.92 (s, 6H), 1.00 (s, 3H), 1.13 (s, 3H), 1.18 (s, 3H), 2.11−2.20 (m, 2H), 2.85 (d, J = 10.0 Hz, 1H), 3.46 (t, J = 6.6 Hz, 2H), 4.09−4.17 (m, 3H), 5.30 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 17.1, 18.5, 19.0, 23.1, 23.5, 23.6, 24.6, 25.9, 27.5, 29.5, 29.7, 30.7, 31.8, 32.51, 32.56, 32.7, 33.1, 33.9, 37.8, 39.7, 41.5, 42.0, 45.8, 46.6, 46.9, 47.3, 48.0, 53.5, 61.8, 67.6, 122.8, 143.7, 177.5; ESIMS m/z 615.3 [M + K]$^+$; HRMS for $C_{33}H_{53}BrO_3$+Na calcd 599.30703, found 599.30758.

(4-Bromobutyl) 2β-hydroxyolean-12-en-28-oate (35). Following the general procedure, compound **35** was prepared from **3** as a white solid (85%): ^{1}H NMR (CDCl$_3$) δ 0.74 (s, 3H), 0.90 (s, 3H), 0.93 (s, 6H), 1.01 (s, 3H), 1.13 (s, 3H), 1.18 (s, 3H), 2.86 (dd, J = 3.9 Hz, 13.5 Hz, 1H), 3.43 (t, J = 6.7 Hz, 2H), 4.03−4.10 (m, 3H), 5.31 (t, J = 3.5 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 17.0, 18.5, 19.0, 23.1, 23.5, 23.6, 24.6, 25.9, 27.4, 27.6, 29.6, 29.7, 30.7, 32.5, 32.6, 32.7, 33.0, 33.1, 33.9, 37.8, 39.7, 41.5, 42.0, 45.9, 46.6, 46.8, 47.3, 48.0, 53.5, 63.2, 67.7, 122.7, 143.7, 177.7; ESIMS m/z 613.4 [M + Na]$^+$; HRMS for $C_{34}H_{55}BrO_3$+H calcd 591.34073, found 591.34282.

(2-Ethoxy-2-oxoethyl) 2β-hydroxyolean-12-en-28-oate (36). Following the general procedure, compound **36** was prepared from **3** as a white solid (84%): ^{1}H NMR ($CDCl_3$) δ 0.74 (s, 3H), 0.90 (s, 3H), 0.92 (s, 3H), 0.93 (s, 3H), 1.01 (s, 3H), 1.14 (s, 3H), 1.18 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H), 2.88 (dd, J = 4.0 Hz, 13.6 Hz, 1H), 4.08 (brs, 1H), 4.20 (q, J = 7.1 Hz, 2H), 4.49 (d, J = 15.7 Hz, 1H), 4.61 (d, J = 15.7 Hz, 1H), 5.32 (t, J = 3.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 16.8, 18.5, 19.0, 23.2, 23.5, 23.6, 24.7, 25.8, 27.6, 29.7, 30.7, 32.2, 32.5, 32.7, 33.1, 33.9, 37.8, 39.7, 41.4, 42.0, 46.0, 46.6, 46.8, 47.3, 48.1, 53.5, 60.5, 61.2, 67.7, 122.8, 143.5, 168.1, 177.0; ESIMS *m/z* 565.3 $[M + Na]^+$; HRMS for $C_{34}H_{54}O_5$+Na calcd 565.38635, found 565.38817.

Allyl 2*β*-hydroxyolean-12-en-28-oate (37). Following the general procedure, compound **37** was prepared from **3** as a white solid (73%): ^{1}H NMR ($CDCl_3$) δ 0.74 (s, 3H), 0.90 (s, 3H), 0.93 (s, 6H), 1.01 (s, 3H), 1.13 (s, 3H), 1.18 (s, 3H), 2.89 (dd, J = 4.1 Hz, 13.8 Hz, 1H), 4.05−4.10 (m, 1H), 4.48−4.54 (m, 2H), 5.18−5.22 (m, 1H), 5.28−5.35 (m, 1H), 5.85−5.94 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 16.9, 18.5, 19.0, 23.1, 23.5, 23.6, 24.6, 25.9, 27.6, 29.6, 30.7, 32.5, 32.6, 32.7, 33.1, 33.9, 37.8, 39.7, 41.5, 41.9, 45.9, 46.6, 46.8, 47.3, 48.0, 53.5, 64.8, 67.7, 117.7, 122.7, 132.6, 143.7, 177.3; ESIMS *m/z* 519.5 $[M + Na]^+$; HRMS for $C_{33}H_{52}O_3$+H calcd 497.39892, found 497.40056.

Enzyme Assay. The inhibitory activity of the compounds against rabbit muscle GPa was monitored using a microplate reader (BIO-RAD) based on the published method.[7] In brief, GPa activity was measured in the direction of glycogen synthesis by the release of phosphate from glucose-1-phosphate. Each test compound was dissolved in DMSO and diluted at different concentrations for IC_{50} determination. The enzyme was added into 100 μL of buffer containing 50 mM Hepes (pH 7.2), 100 mM KCl, 2.5 mM $MgCl_2$, 0.5 mM glucose-1-phosphate, 1 mg/mL glycogen, and the test compound in 96-well microplates (Costar). After the addition of 150 μL of 1 M HCl containing 10 mg/mL ammonium molybdate and 0.38 mg/mL malachite green, reactions were run at 22 °C for 25 min, and then the phosphate absorbance was measured at 655 nm. The IC_{50} values were estimated by fitting the inhibition data to a dose-dependent curve using a logistic derivative equation.

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Supporting Information Available: This material is available free of charge via the Internet at http://pubs.acs.org.

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