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Original article

Synthesis and antitumor activities of naturally occurring oleanolic acid triterpenoid saponins and their derivatives

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ABSTRACT

Twenty-six naturally occurring oleanolic acid saponins and their derivatives, 16 of which were synthesized in this study, were preliminarily evaluated against human cancer cells. From SAR studies, the presence of α-L-rhamnosyl residue at the terminal of both C-3 and C-28 position for oleanolic acid bidesmosides was important to enhance cytotoxicity, and introducing more sugar residues at C_3–OH of compound **12** with C-28 carboxylic acid is a favorable modification to ameliorate the anticancer activity. Furthermore, α-L-rhamnosyl moiety linked to C_2–OH of the first monosaccharide (α-L-alabinose, β-D-xylose, β-D-galactose or β-D-glucose) in C_3–OH of oleanolic acid was helpful to improve the cytotoxicity. According to the predicted log *P* values, lipophilicity of the synthesized saponins was not an important factor for cytotoxicity.

1. Introduction

Triterpenoid saponins, glycosylated plant secondary metabolites [1], which exist widely in many significant foods, forage crops and herbal medicinal plants with high contents [2], act as natural chemical barriers to fungal attack because of their remarkable antifungal properties [3]. Apart from the natural protective activity, many of them are also discovered as resources for drugs at the folkloric usage, such as the saponin extracts from ginseng, licorice, senega roots and ivy leaves [4,5], or food crops such as oats and legumes [6]. However, the occurrence of triterpenoid saponins with prominent structural microheterogeneity makes separation of the homogeneous component, especially in a suitable amount, comparatively difficult, which results in the hysteretic development on elucidating the structure–activity relationships and the biological mechanisms of action of triterpenoid saponins components [7,8]. Therefore, chemical synthesis would provide a feasible access to these biologically triterpenoid components for further understanding and application of this type of natural products [7,9,10].

As we all known, the most predominant member of this family of triterpenoids is probably oleanolic acid [11,12], which has been clinically used as a hepatoprotective/antihepatitis drug in China for several decades. However, its low water solubility results in its unfavorably absolute oral bioavailability [13,14]. Therefore, compounds derived from chemical modification of oleanolic acid with prodrug strategy, or isolation of oleanolic acid saponins from natural resources for improving pharmacokinetics was researched [15,16]. In previous communications [17–20], we reported that the naturally occurring oleanolic acid saponins (**1**–**10**) with significant biological activities were synthesized via concise and efficient strategies. With the continuous interest in the oleanolic acid saponins on the biological activity and in order to search for potential new antitumor agents, we decided to investigate the effect of modification of sugar moiety of oleanolic acid saponins on the tumor cell growth inhibitory activity. Herein, we disclose the efficient synthesis of some natural (**12**, **14**–**16**) [21–25] (Fig. 1) and non-natural sugar-modified oleanolic acid saponins (**11**, **13**, **17**–**26**) (Fig. 2). Furthermore, structure–activity relationships analysis of this series of natural and non-natural oleanolic acid saponins against tumor cells including human promyelotic leukemia cancer (HL-60), non-small-cell lung cancer (A549) and human melanoma cancer (A375) is discussed. These results obtained have provided

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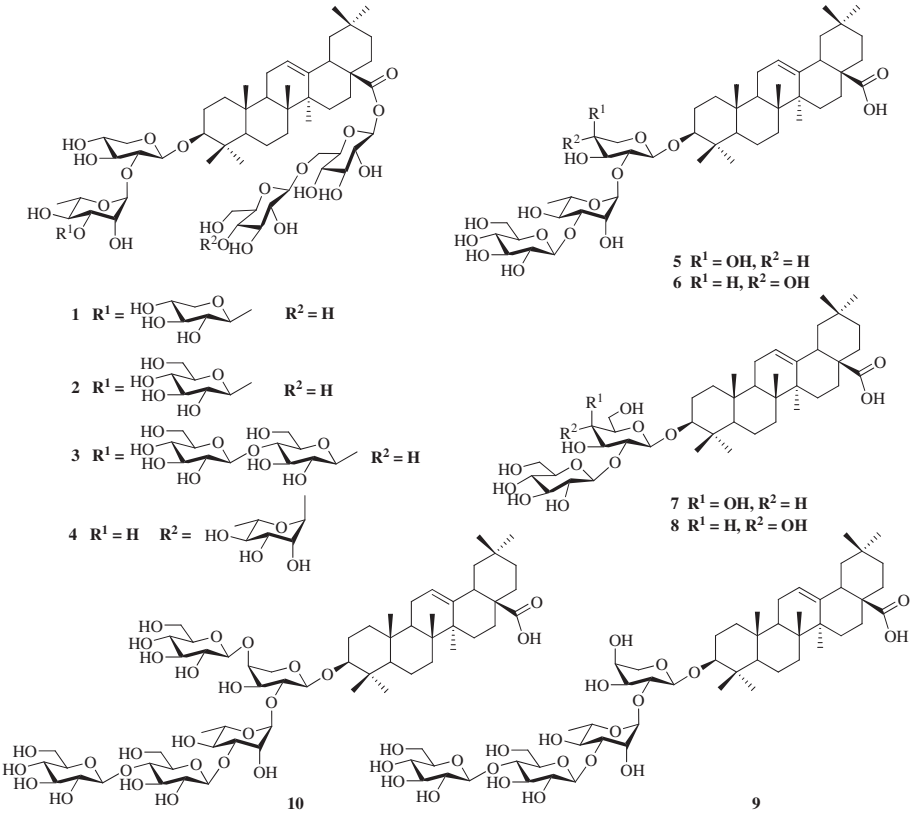


Fig. 1. Chemical structures of previous synthesized natural oleanolic acid saponins **1**–**10**.

valuable clues to the understanding of the cytotoxic profile for this type of oleanolic acid saponins.

2. Results and discussion

2.1. Chemistry

We have completed the efficient synthesis of compound **4** (flaccidoside II) previously by one-pot sequential glycosylation employing two glycosyl trichloroacetimidate donors under the promotion of TMSOTf, followed by removal of the benzoyl groups in the presence of NaOMe in MeOH–CH_2Cl_2 [19]. For the synthesis of target compound **11**, the intermediate **28** that used for synthesis of compound **4** was removed the protection of the benzoyl groups, affording the desired product **11** in 87% yield (Scheme 1).

The preparation of target compounds **12**–**15** was carried out as shown in Schemes 2–4. Glycosylation between known acceptor **29** [18,21] and donor **30a** [26,27] (or **30b**) [28] was performed through thioglycoside activation by *N*-iodosuccinimide (NIS) under the promotion of AgOTf to provide the desired product **31a** (or **31b**). The isopropylidene acetal was hydrolyzed employing *p*-TsOH in CH_2Cl_2–CH_3OH followed by 10% Pd–C promoted hydrogenolysis of the benzyl group (or deprotection of acetyl groups with NaOMe), affording the target saponins **12** and **13**.

Disaccharide trichloroacetimidate donor **33** was prepared in a straightforward manner from known *p*-tolyl β-D-xylopyranoside (**33a**) [17]. Protection of the C_4–OH with a 2-methoxypropane group and 2,3-isopropylidene formation using 2,2-dimethoxypropane and trifluoroacetic acid in *N*,*N*-dimethylformamide (DMF) simultaneously followed by removal of 2-methoxypropane group selectively with *p*-toluenesulfonic acid in CH_3OH at 0 °C gave compound **33c** in 88% yield [29]. Acetylation of compound **33c** with Ac_2O in pyridine followed by deprotection of 2,3-isopropylidene acetal with *p*-toluenesulfonic acid in CH_3OH–CH_2Cl_2 afforded compound **33e** in 92% yield for 2 steps. The resulting compound was benzoylated using BzCl in pyridine, and then regioselectively removal of acetyl group with 1% AcCl in CH_3OH afforded compound **33g**. Reaction of **33g** and **33h** in dichloromethane under the promotion of TMSOTf at −78 °C gave disaccharide **33i**, which was converted to hemiacetal **33j** by treatment with NBS in acetone and water. Finally, compound **33j** was treated with trichloroacetonitrile in the presence of DBU affording the disaccharide trichloroacetimidate donor **33**.

According to our previous strategy [16], the synthesis of target compounds **14** and **15** was carried out employing the "one-pot sequential glycosylation" with the combined use of an odorless 2-methyl-5-tert-butylphenyl (Mbp) thioglycoside and trichloroacetimidate donors. Glycosylation of Mbp thioglycoside **34** [18] and imidate **32** [17] (or **33**) was completed within 45 min with the use of catalytic amount of TMSOTf at −78 °C, affording the desired disaccharide (or trisaccharide) Mbp thioglycoside donor. Without purification, the reaction mixture was warmed to −10 °C, and then saponin acceptor **29** was added, followed by addition of NIS and TMSOTf, providing the desired saponin **35** (or **36**). The isopropylidene acetal of saponin **35** (or **36**) was hydrolyzed using *p*-TsOH in CH_2Cl_2 and CH_3OH, affording the intermediate **37** (or **38**) with the abnormal $^1C_4$ conformation of arabinopyranosyl residue. After removal of the 28-*O*-benzyl group in **37** (or **38**) by hydrogenolysis in the presence of 10% Pd–C and acetyl groups with NaOMe in MeOH and CH_2Cl_2, the expected target compound **14** (or **15**) was provided (the arabinopyranosyl moiety returned to the normal $^4C_1$ conformation), whose analytical data are identical in all respects to those reported in the literature.

The synthesis of target compounds **16**–**18** was done by the similar route as that for compounds **14**–**15** described. As depicted

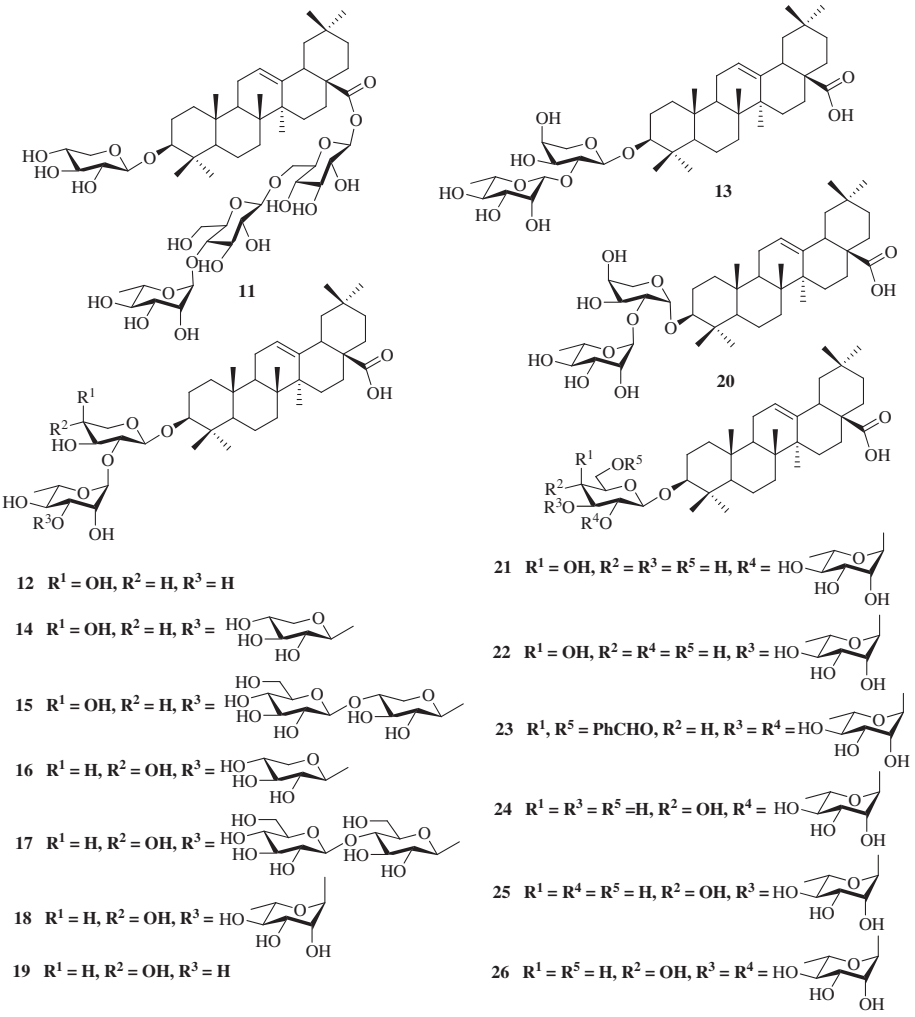
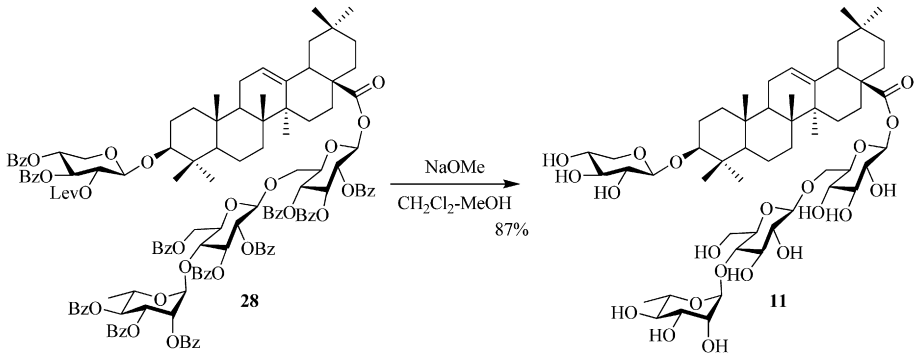


Fig. 2. Chemical structures of synthesized natural and non-natural oleanolic acid saponins **11**–**26**.

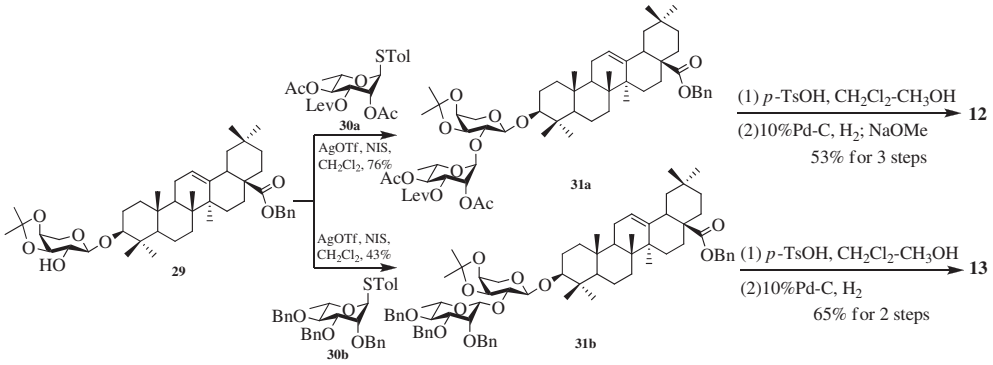
in Scheme 5, with the glycosyl trichloroacetimidate donor **32** (or **39**–**40**) [17,30], 2-methyl-5-tert-butylphenyl (Mbp) thioglycoside **34** and acceptor **41** in hand, their coupling reaction was performed under the promotion of TMSOTf and NIS to obtain **42** (or **43**–**44**), which was subjected to the benzyl cleavage with 10% Pd–C and acetyl deprotection with NaOMe in CH_2Cl_2–MeOH to provide the target compound **16** (or **17**–**18**) efficiently.

The preparation of target compound **19** was performed as outlined in Scheme 6. Glycosylation between acceptor **41** [20] and donor **40** was achieved in the presence of TMSOTf to afford the desired saponin **45** in 91% yield, which was subjected to benzyl cleavage with 10% Pd–C, followed by removal of acetyl groups with NaOMe in CH_2Cl_2–MeOH, providing the target saponin **19**.

As depicted in Scheme 7, the synthesis of target saponin **20** was commenced with known *p*-tolyl 3,4-*O*-isopropylidene-1-thio-α-L-arabinopyranoside **40**, which was coupled with donor **46** [31] under the promotion of TMSOTf in CH_2Cl_2 at low temperature (−78 °C) to provide the desired disaccharide **47**, followed by



Scheme 1. Synthesis of non-natural oleanolic acid saponin **11**.



Scheme 2. Synthesis of oleanolic acid saponins **12** and **13**.

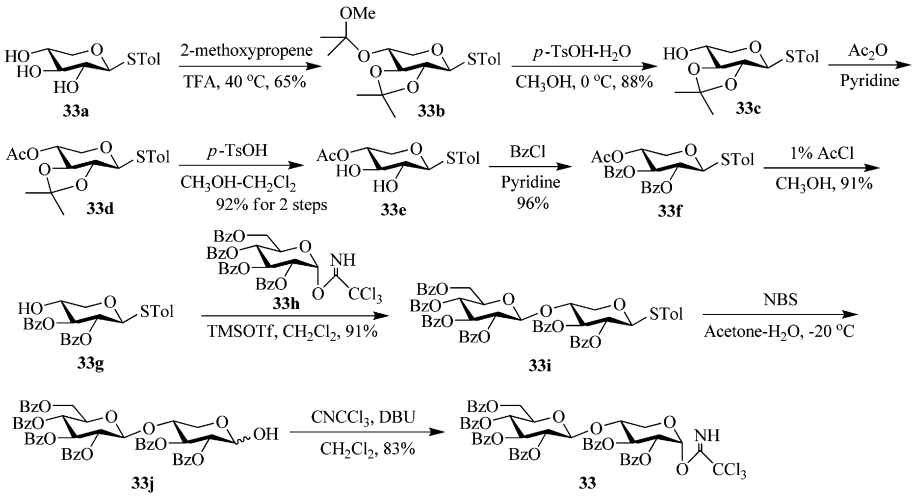
glycosylation with the acceptor **48** [32,33] in the presence of NIS and AgOTf stereoselectively affording the fully protected intermediate **49** in 35% yield. The diisopropylidene was achieved by treatment of compound **49** with *p*-TsOH in CH_2Cl_2–MeOH solution to obtain **50**. Subsequent deprotection of the benzyl ether with 10% Pd–C and the benzoyl ester with NaOMe in CH_2Cl_2–MeOH was achieved to afford the target compound **20**.

The synthesis of non-natural saponins **21**–**26** was achieved in a straight-forward manner. As shown in Scheme 8, the oleanolic acid saponin acceptor **51** (or **53**) was condensed with the known donor **40** in the presence of TMSOTf to obtain the intermediates **52a**–**c** (or **54a**–**c**). Subsequent removal of benzyl and acetyl groups provided the desired saponins **21**–**23** (or **24**–**26**).

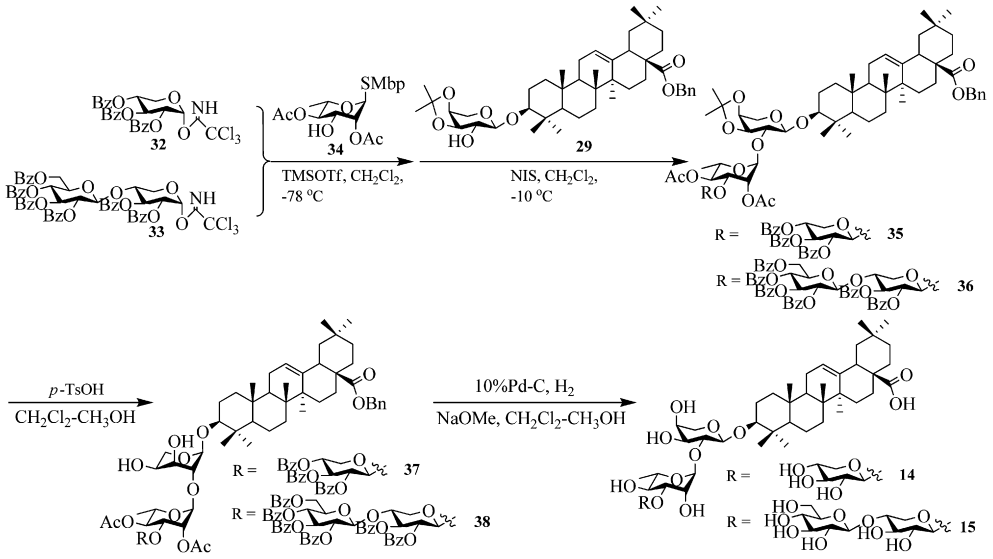
2.2. Cytotoxic activity

To examine the potential ability of the natural and non-natural oleanolic acid saponins **1**–**26**, the *in vitro* cytotoxic activity against human promyelotic leukemia cancer (HL-60), non-small-cell lung cancer (A549) and human melanoma cancer (A375) was assessed using methyl-thiazol-tetrazolium (MTT) reduction test and sulforhodamine B (SRB) staining methods for protein. The cytotoxicity results presented in Table 1 are shown as the IC_{50} values. They are subdivided into two groups: Oleanolic acid bidesmosides (**1**–**4**, **11**), and Oleanolic acid monodesmosides (**5**–**10**, **12**–**26**). In the first group, saponin **4** exhibited the most cytotoxic activity against the three tumor cells (with IC_{50} ranging from 3.2 to 10.5 μM) followed by saponin **11** (IC_{50} 4.7–10.3 μM). In contrast, saponins **1**–**3** did not show any cytotoxic activity ($IC_{50} > 20$ μM) against HL-60, A549 and A375 cell lines. These results proved that the presence of α-L-rhamnosyl residue at the terminal of both C-3 and C-28 position was critical to enhance cytotoxicity.

In the second group, most of compounds except **20**, **22**–**23** and **25**–**26** exerted better anticancer activity. When compared compounds **6**, **16**–**17** with **1**–**3**, the influence of free C-28 carboxylic acid on enhancing the cytotoxicity was clear. As for compound **12**, we anticipated that changing the spatial configuration of L-alabinosyl moiety at the C-3 position of oleanolic acid should improve anticancer activity. Actually, the changed compound **20** exhibited no cytotoxicity against all tested cell lines ($IC_{50} > 20$ μM). However, when α-L-rhamnosyl residue of compound **12** was converted to β-L-rhamnosyl residue, the derived compound **13** exerted good cytotoxicity, especially enhanced the cytotoxicity about 2-fold against HL-60 cell line (IC_{50} 4.2 μM). Meanwhile, compounds **5** (IC_{50} 6.1 μM), **9** (IC_{50} 3.5 μM), **10** (IC_{50} 3.1 μM), **14** (IC_{50} 3.4 μM), and **15** (IC_{50} 4.2 μM), were 1.5- to 3-fold more potent against HL-60 cell line comparing with compound **12** (IC_{50} 9.2 μM), which suggested that introducing more sugar residues at C_3–OH of compound **12** is a favorable modification to ameliorating the anticancer activity. Replacement of α-L-alabinose by β-D-xylose, β-D-galactose or β-D-glucose at the C_3–OH of **12** afforded compound **19**, **21** or **24**, which has no significant increase in cytotoxicity. However, adding α-L-rhamnosyl moiety at the C_2–OH and C_3–OH (or C_3–OH solely) of β-D-galactose or β-D-glucose respectively, obtained compounds



Scheme 3. Synthesis of disaccharide donor **33**.



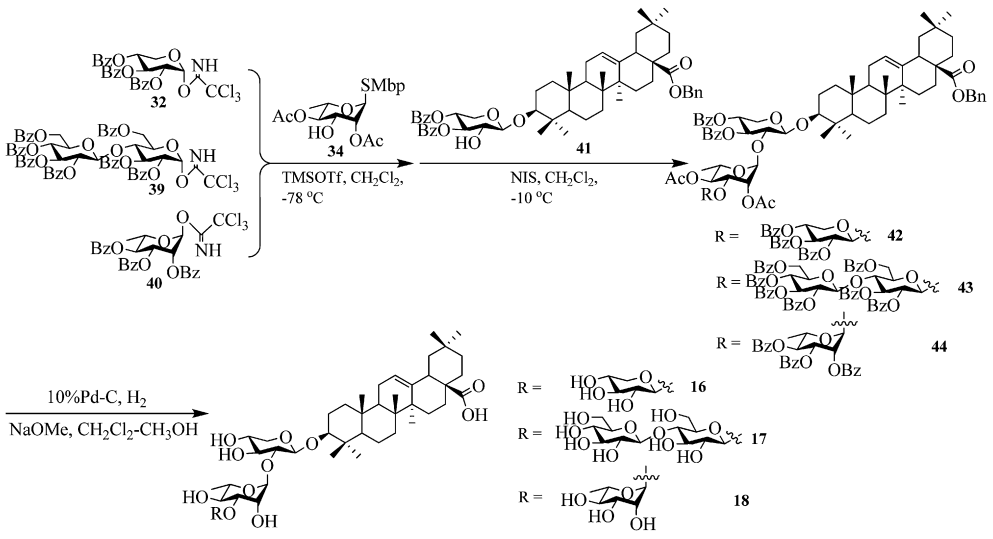
Scheme 4. Synthesis of target compounds **14**–**15**.

22–**23** or **25**–**26**, which did not exhibit desirable antitumor activity. These results demonstrated that the type of the first monosaccharide linked to C_3–OH of oleanolic acid has no obvious influence on improving the cytotoxicity, and α-L-rhamnose moiety linked to C_2–OH with free C_3–OH of the first monosaccharide (α-L-alabinose by β-D-xylose, β-D-galactose or β-D-glucose) favored the cytotoxic activity.

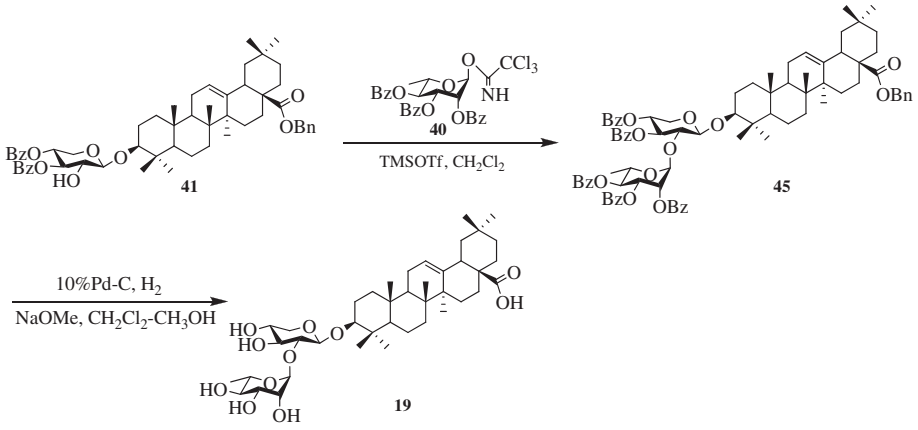
The logarithm of a partition coefficient (log *P*) is a parameter which reflects a drug equilibrium partition ratio between polar (water) and non-polar (octanol) phases, and it has been proved to determine the absorption, the distribution, the biological availability, and pharmacological activity of drugs. In this study, we have employed the ACD lab program to predict the values of log *P* for each oleanolic acid saponin **1**–**26**. The results are arranged in Table 2, comparing the log *P* values of all synthesized compounds, we found that the order of antitumor activity was not consistent with the order of lipophilicity, which indicated that lipophilicity of the compounds had no important effect on cytotoxicity.

3. Conclusions

A series of natural and non-natural sugar-modified oleanolic acid saponins was synthesized in a concise and practical way and their cytotoxicity was evaluated *in vitro*. In terms of structure–activity relationships, we can conclude that: (i) with regard to oleanolic acid bidesmosides, the presence of α-L-rhamnosyl residue at the terminal of both C-3 and C-28 position was critical to enhance cytotoxicity; (ii) for oleanolic acid monodesmosides, free C-28 carboxylic acid favors the cytotoxicity; (iii) changing the spatial configuration of L-alabinosyl moiety at the C-3 position of oleanolic acid disfavor anticancer activity; (iv) introducing more sugar residues at C_3–OH of compound **12** is a favorable modification to ameliorate the anticancer activity; (v) the type of the first monosaccharide linked to C_3–OH of oleanolic acid has no obvious influence on improving the cytotoxicity; (vi) α-L-rhamnose moiety linked to C_2–OH with free C_3–OH of the first monosaccharide (α-L-alabinose by β-D-xylose, β-D-galactose or β-D-glucose) was helpful



Scheme 5. Synthesis of target compounds **16**–**18**.



Scheme 6. Synthesis of target compound **19**.

to improve the cytotoxic activity. Meanwhile, lipophilicity of the compounds was not an important factor for cytotoxicity.

4. Experimental section

4.1. Chemistry

Thin-layer chromatography (TLC) was performed on precoated E. Merck Silica Gel 60 F254 plates. Flash column chromatography was performed on silica gel (200–300 mesh, Qingdao, China). Optical rotations were determined with a Perkin–Elmer Model 241 MC polarimeter. ^{1}H NMR and ^{13}C NMR spectra were taken on a JEOL JNM-ECP 600 spectrometer with tetramethylsilane as the internal standard, and chemical shifts are recorded in δ values. Mass spectra were recorded on a Q-TOF Global mass spectrometer.

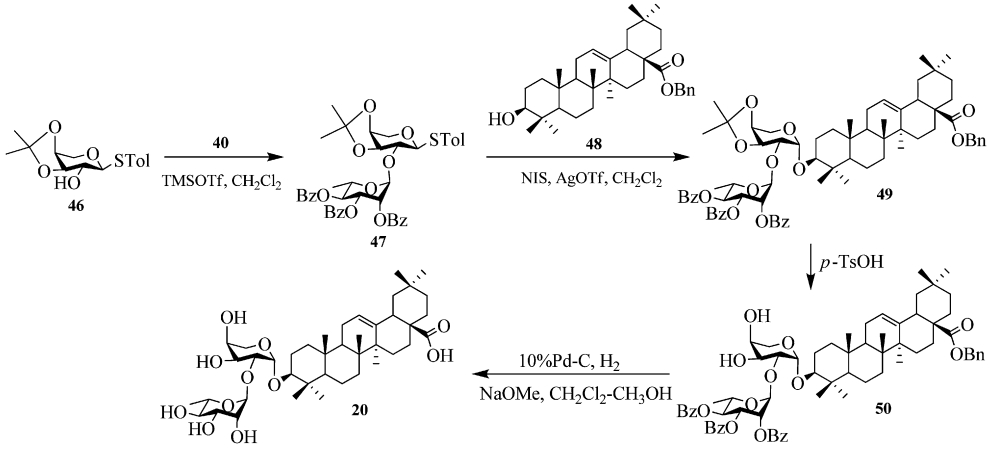
Commercial reagents were all analytically or chemically pure and used without further purification unless specified. All anhydrous solvents were dried and redistilled prior to use in the usual way.

4.1.1. 28-O-α-L-Rhamnopyranosyl-(1 → 4)-O-β-D-glucopyranosyl-(1 → 6)-O-β-D-glucopyranosyl oleanate 3-O-β-D-xylopyranoside (**11**)

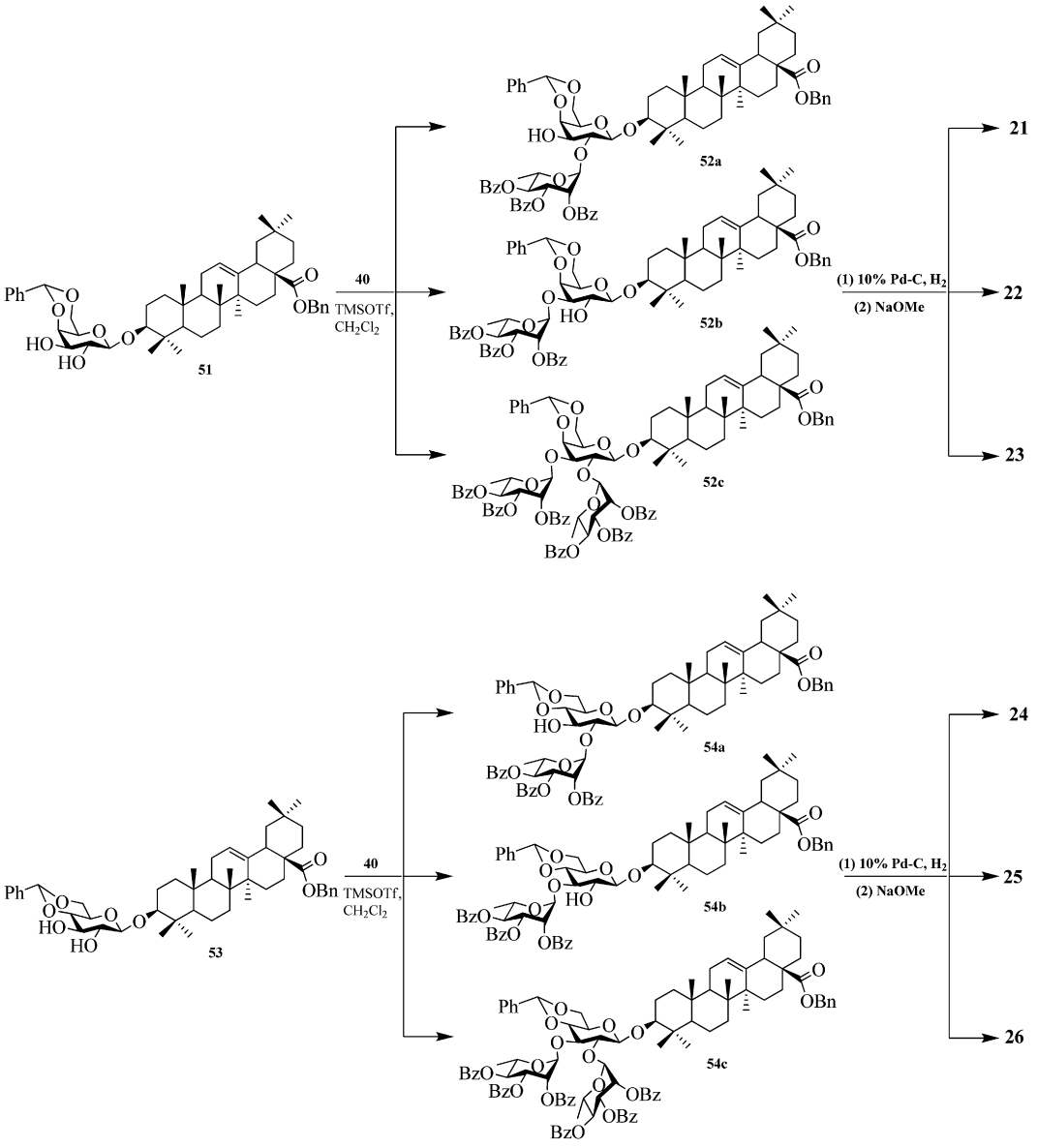
To a solution of compound **28** (100 mg) in dry CH_2Cl_2–MeOH (1:2, 12 mL) was added a newly prepared NaOMe in MeOH solution (1.0 mol/L, 0.20 mL). The mixture was stirred at room temperature for 5 h and neutralized with Dowex H^+ resin to pH 7 and then filtered. The filtrate was concentrated and the resulting residue was subjected to a silica gel column chromatography (MeOH–$CHCl_3$–H_2O, 1:25:0.1) to give **11** (40 mg, 87%) as a white amorphous solid. $[\alpha]_D^{25}$ −13.3 (*c* 0.25, CH_3OH); IR (KBr) ν_{max} 3499, 2938, 1731, 1645, 1453, 1073 cm^{-1}; ^{1}H NMR (500 MHz, C_5D_5N) δ: 6.23 (d, J = 8.1 Hz, 1H, H-1″), 5.85 (br s, 1H, H-1‴), 5.39 (t, J = 3.6 Hz, 1H, H-12), 4.98 (d, J = 7.8 Hz, 1H, H-1′), 4.96 (qd, J = 9.1, 6.0 Hz, 1H, H-5‴), 4.82 (d, J = 7.5 Hz, 1H, H-1⁗), 4.68 (dd, J = 3.2, 1.7 Hz, 1H, H-2‴), 4.65 (m, 1H, H-4′), 4.54 (dd, J = 9.3, 3.2 Hz, 1H, H-3‴), 4.41 (t, J = 9.6 Hz, 1H, H-3″), 4.31–4.37 (m, H-3⁗, H-4‴, H-5⁗-1, H-6′-1), 4.09–4.23 (m, 8H, H-2″, H-3′, H-4″, H-4⁗, H-5′, H-5″, H-6″-1, H-6′-2), 4.02 (t-like, J = 8.8, 7.9 Hz, 1H, H-2⁗), 3.93 (t-like, J = 8.7, 8.3 Hz, 1H, H-2′), 3.78 (t, J = 11.0 Hz, 1H, H-5⁗-2), 3.64 (m, 1H, H-6″-2), 3.33 (dd, J = 11.7, 4.3 Hz, 1H, H-3), 3.15 (dd, J = 13.7, 3.7 Hz, 1H, H-18), 1.69 (d, J = 6.0 Hz, 3H, H-6‴), 1.29, 1.24, 1.09, 0.99, 0.89, 0.89, 0.89 (s each, 3H each, CH_3 ×7). ^{13}C NMR (125 MHz, C_5D_5N) δ: 176.5 (C-28), 144.0 (C-13), 122.9 (C-12), 107.6 (C-1⁗), 104.9 (C-1″), 102.8 (C-1‴), 95.6 (C-1′), 88.7 (C-3), 78.8, 78.6, 78.4, 78.1, 77.2, 76.6, 75.5, 75.4, 74.0, 73.9, 72.8, 72.6, 71.3, 71.0, 70.3, 69.3, 67.1, 62.0, 56.0, 49.7, 48.2, 47.1, 46.3, 42.2, 41.8, 40.0, 39.6, 38.9, 37.1, 34.1, 33.2, 32.6, 30.8, 28.4, 28.3, 26.8, 26.1, 23.9, 23.8, 23.4, 18.5, 17.6, 17.0, 15.7. HR-MS (ESI): m/z calcd for $C_{53}H_{86}O_{21}Na$ $[M + Na]^+$ 1081.5554, found 1081.5579.

4.1.2. General procedure for synthesizing compounds ***31a*–*31b***

A mixture of compound **29** (0.139 mmol), powdered 4 Å molecular sieves and compound **30a** or **30b** (0.209 mmol) in dry CH_2Cl_2 (5 mL) was stirred at room temperature for 30 min then cooled to 0 °C. NIS (0.221 mmol) and AgOTf (0.016 mmol) was



Scheme 7. Synthesis of target compound **20**.



Scheme 8. Synthesis of target compounds **21**–**26**.

added, and the reaction mixture was stirred for 30 min and then warmed to room temperature. The product was detected on TLC (2:1, petroleum ether–EtOAc). After completion of the reaction, the reaction mixture was quenched by addition of Et_3N, and then filtered. The filtrate was concentrated and purified by a silica gel column chromatography to afford the products.

*4.1.2.1. Benzyl oleanolate 2,4-di-O-acetyl-3-O-levulinoyl-α-L-rhamnopyranosyl-(1 → 2)-3,4-O-isopropylid-ene-α-L-arabinopyranoside (**31a**).* Yield: 76%; $[\alpha]_D^{25}$ +21.3 (*c* 0.8, $CHCl_3$); IR (KBr) ν_{max} 2929, 1731, 1447, 1356, 1123, 1023, 707, 673 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.07–7.35 (m, 5H, Ph–H), 5.34 (s, 1H, H-1″), 5.29–5.32 (m, 3H, H-3′, H-4′, H-12), 5.03–5.11 (m, 3H, H-2″, PhCH_2), 4.34 (d, *J* = 7.7 Hz, 1H, H-1′), 4.10–4.21 (m, 4H, H-3″, H-4″, H-5″, H-5′-1), 3.73–3.78 (m, 2H, H-2′, H-5′-2), 3.08 (dd, *J* = 11.8, 4.4 Hz, 1H, H-3), 2.90 (dd, *J* = 13.9, 4.0 Hz, 1H, H-18), 2.72–2.76 (m, 1H, Lev–C*H*H), 2.61–2.66 (m, 1H, Lev–C*H*H), 2.50–2.55 (m, 1H, Lev–CH*H*), 2.39–2.44 (m, 1H, Lev–CH*H*), 2.16, 2.15, 2.05 (s each, 3H each, Ac ×2, Lev–CH_3), 1.53, 1.33 (s each, 3H each, O–$(CH_3)_2$C–O), 1.20 (d, *J* = 6.2 Hz, 3H, H-6″), 1.12, 1.04, 0.92, 0.89, 0.88, 0.81, 0.60 (s each, 3H each, CH_3 ×7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 206.2, 177.5 (C-28), 171.4, 170.2, 143.7 (C-13), 136.4, 128.4, 128.0, 127.9, 122.5 (C-12), 110.4 ($(CH_3)_2C$), 103.1 (C-1′), 95.2 (C-1″), 89.0 (C-3), 79.1, 75.1, 73.3, 70.9, 70.5, 69.7, 69.6, 69.3, 66.2, 65.9, 62.6, 55.8, 47.6, 46.7, 45.9, 41.7, 41.4, 39.3, 39.0, 37.8, 37.7, 37.6, 36.7, 33.9, 33.1, 32.7, 32.4, 30.9, 30.7, 29.7, 28.0, 27.8, 27.6, 26.1, 25.9, 23.7, 23.4, 23.0, 21.0, 20.8, 18.2, 17.3, 16.9, 16.4, 15.4, 15.3. HR-MS (ESI): *m/z* calcd for $C_{60}H_{86}O_{15}Na$ $[M + Na]^+$ 1069.5859, found 1069.5883.

*4.1.2.2. Benzyl oleanolate 2,3,4-tri-O-benzyl-β-L-rhamnopyranosyl-(1 → 2)-3,4-O-isopropylidene-α-L-arabin-opyranoside (**31b**).* Yield: 43%; $[\alpha]_D^{23}$ +5.92 (*c* 1.18, $CHCl_3$); IR (KBr) ν_{max} 2939, 1733, 1454, 1368, 1116, 1023, 738, 685 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.27–7.34 (m, 20H, Ph–H), 5.33 (d, *J* = 1.1 Hz, 1H, H-1″), 5.29 (t, *J* = 3.6 Hz, 1H, H-12), 5.11 (d, *J* = 12.7 Hz, 1H, PhC*H*H), 5.05 (d, *J* = 12.7 Hz, 1H, PhCH*H*), 5.01 (d, *J* = 15.4 Hz, 1H, PhC*H*H), 4.95 (d, *J* = 13.5 Hz, 1H, PhCH*H*), 4.76 (d, *J* = 12.7 Hz, 1H, PhC*H*H), 4.67 (d, *J* = 11.0 Hz, 1H, PhCH*H*), 4.64 (d, *J* = 10.4 Hz, 1H, PhC*H*H), 4.56

Table 1
In vitro cytotoxicity of oleanolic acid bidesmosides (**1**–**4**, **11**), and oleanolic acid monodesmosides (**5**–**10**, **12**–**26**) against cancer cell lines.

Group[a]	Compound	IC_{50} (μmol/L)[b]		
		HL-60	A549	A375
I	**1**	>20	>20	>20
	2	>20	>20	>20
	3	>20	>20	>20
	4	3.2 ± 1.0	10.5 ± 2.3	7.3 ± 1.4
	11	5.7 ± 1.3	11.9 ± 4.1	13.5 ± 1.7
II	**5**	6.1 ± 2.3	16.7 ± 1.5	12.1 ± 1.1
	6	4.6 ± 2.9	14.7 ± 1.6	5.5 ± 1.7
	7	10.1 ± 3.7	17.9 ± 4.2	9.7 ± 2.3
	8	12.5 ± 2.6	15.3 ± 3.2	10.3 ± 3.1
	9	3.5 ± 1.3	7.9 ± 1.3	5.9 ± 0.9
	10	3.1 ± 1.8	6.2 ± 1.1	3.5 ± 0.4
	12	9.2 ± 2.9	15.8 ± 4.3	8.4 ± 1.8
	13	4.2 ± 1.5	17.5 ± 3.4	7.7 ± 3.8
	14	3.4 ± 1.2	15.4 ± 1.3	8.9 ± 2.4
	15	4.2 ± 0.3	>20	22.1 ± 6.1
	16	4.5 ± 1.5	11.5 ± 3.1	6.3 ± 2.9
	17	2.5 ± 0.9	7.8 ± 4.4	6.1 ± 1.3
	18	9.3 ± 0.8	16.2 ± 3.4	8.4 ± 3.3
	19	3.6 ± 0.1	10.7 ± 4.2	5.0 ± 1.8
	20	>20	>20	>20
	21	2.5 ± 1.1	12.4 ± 5.5	5.1 ± 1.2
	22	>20	15.2 ± 0.7	15.4 ± 0.9
	23	>20	>20	>20
	24	12.9 ± 2.7	23.5 ± 2.7	11.6 ± 1.8
	25	>20	>20	>20
	26	>20	>20	>20
	ADM[c]	0.90 ± 0.3	0.56 ± 0.2	0.75 ± 0.1
	HCPT[d]	0.25 ± 0.1	0.30 ± 0.1	0.15 ± 0.1

[a] (I) oleanolic acid bidesmosides; (II) oleanolic acid monodesmosides.
[b] Data represent mean values ± standard deviation for three independent experiments made in triplicate.
[c] Adriamycin, positive control.
[d] Hydroxycamptothecin, positive control.

(d, J = 12.7 Hz, 1H, PhCH*H*), 4.31 (d, J = 7.2 Hz, 1H, H-1′), 4.21 (dd, J = 10.4, 4.4 Hz, 1H, H-5′-1), 3.99–4.02 (m, 2H, H-4′, H-4″), 3.95 (dq, J = 9.1, 6.6 Hz, 1H, H-5″), 3.88 (dd, J = 9.4, 2.8 Hz, 1H, H-5′-2), 3.69–3.72 (m, 2H, H-2′, H-3″), 3.61 (dd, J = 9.6, 3.8 Hz, 1H, H-3′), 3.01 (dd, J = 12.1, 4.9 Hz, 1H, H-3), 2.91 (dd, J = 13.7, 3.8 Hz, 1H, H-18), 1.48, 1.33 (s each, 3H each, O–$(CH_3)_2$C–O), 1.28 (d, J = 6.6 Hz, 3H, H-6″), 1.11, 0.92, 0.91, 0.89, 0.88, 0.81, 0.61 (s each, 3H each, CH_3 ×7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 177.7 (C-28), 143.9 (C-13), 138.9, 138.6, 136.6, 128.6, 128.4, 128.3, 128.2, 122.8 (C-12), 110.4 ($(CH_3)_2$C), 103.3 (C-1′), 96.7 (C-1″), 88.9 (C-3), 80.1, 80.0, 79.3, 75.3, 74.9, 73.5, 72.3, 68.7, 68.5, 66.1, 55.9, 47.8, 46.9, 46.2, 41.7, 41.5, 40.0, 39.3, 38.2, 36.9, 33.6, 33.3, 30.9, 28.0, 26.3, 23.9, 23.6, 18.1, 17.1, 15.9, 15.6; HRMALDIMS: calcd for [M + Na^+] $C_{72}H_{94}O_{11}Na$ 1157.6686, found 1157.6688.

Table 2
Lipophilicity (log P) of oleanolic acid saponins **1**–**26**.

Compound	Log P[a]	Compound	Log P[a]
1	6.26	**14**	10.02
2	4.06	**15**	7.38
3	3.86	**16**	10.02
4	6.11	**17**	7.42
5	7.49	**18**	10.51
6	7.49	**19**	9.96
7	6.80	**20**	9.96
8	6.80	**21**	10.06
9	7.42	**22**	9.87
10	4.78	**23**	10.34
11	5.83	**24**	10.06
12	9.96	**25**	9.87
13	9.96	**26**	10.34

[a] Predicted octanol/water partition coefficient.

*4.1.2.3. 1-(4-Tolyl)thio-2,3-O-isopropylidene-4-O-(1-methoxy-1-methylethyl)-β-D-xylopyranoside (**33b**).* Compound **33a** (1.60 g, 6.24 mmol) was dissolved in DMF (2 mL) and heated to 40 °C. Trifluoroacetic acid (100 μL, 1% TFA in DMF) was added followed by 2-methoxypropene (2 mL, 21.22 mmol). The reaction mixture was stirred for 12 h at this temperature. TLC (10:1 petroleum ether–EtOAc) indicated that the reaction was complete. The reaction was quenched with Et_3N (20 μL), and the mixture was diluted with CH_2Cl_2 and sequentially washed with saturated $NaHCO_3$, saturated NaCl, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (10:1 petroleum ether–EtOAc) affording compound **33b** (1.50 g, 65%) as a white solid; R_f = 0.35 (petroleum ether–EtOAc, 10:1); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.47 (d, J = 8.2 Hz, 2H, Ph–H), 7.13 (d, J = 7.8 Hz, 2H, Ph–H), 4.69 (d, J = 9.1 Hz, 1H, H-1), 4.09 (dd, J = 11.5, 5.0 Hz, 1H, H-5-1), 4.00 (ddd, J = 9.6, 9.2, 5.0 Hz, 1H, H-4), 3.53 (t, J = 9.1 Hz, 1H, H-3), 3.22 (s, 3H, OCH_3), 3.18–3.21 (m, 2H, H-2, H-5-2), 2.35 (s, 3H, $SPhCH_3$), 1.46, 1.41, 1.37, 1.33 (s each, 3H each, CH_3 ×4); HRESIMS: calcd for [M + Na^+] $C_{19}H_{28}O_5SNa$ 391.1550, found 391.1576.

*4.1.2.4. 1-(4-Tolyl)thio-2,3-O-isopropylidene-β-D-xylopyranoside (**33c**).* Compound **33b** (1.40 g, 3.80 mmol) was dissolved in MeOH (15 mL) and cooled to 0 °C. A solution of *p*-toluenesulfonic acid in MeOH (1 mg/mL, 200 μL) was added. The reaction mixture was stirred and monitored by. TLC (6:1 petroleum ether–EtOAc) When the starting material was disappeared, the reaction was quenched with strongly basic ion exchange resin (OH^- form). The solution was filtrated, and the filtrate was concentrated. The residue was purified by column chromatography (6:1 petroleum ether–EtOAc) affording compound **33c** as a white solid (1.00 g, 88%): R_f = 0.31 (petroleum ether–EtOAc, 6:1); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.47 (d, J = 7.8 Hz, 2H, Ph–H), 7.13 (d, J = 7.8 Hz, 2H, Ph–H), 4.73 (d, J = 9.6 Hz, 1H, H-1), 4.12 (dd, J = 11.5, 5.0 Hz, 1H, H-5-1), 3.94–3.99 (m, 1H, H-4), 3.52 (t, J = 9.2 Hz, 1H, H-3), 3.20–3.24 (m, 2H, H-2, H-5-2), 2.35 (s, 3H, $SPhCH_3$), 1.49, 1.44 (s each, 3H each, CH_3 ×2); ESI-MS (m/z): 297.1 (M + H^+); 615.2 (2M + Na^+); HRESIMS: calcd for [M + Na^+] $C_{15}H_{20}O_4SNa$ 319.0975, found 319.0997.

*4.1.2.5. 1-(4-Tolyl)thio-4-O-acetyl-β-D-xylopyranoside (**33e**).* To a solution of compound **33c** (140 mg, 0.472 mmol) in pyridine–CH_2Cl_2 (2 mL, 1:1), Ac_2O (120 μL) and DMAP (5 mg) was added. The mixture was stirred for 2 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with CH_3OH, concentrated under reduced pressure. The residue was diluted with EtOAc and sequentially washed with saturated 1 mol/L HCl, saturated $NaHCO_3$, saturated NaCl, dried over Na_2SO_4, filtered and concentrated. The crude product **33d** was dissolved in CH_3OH–CH_2Cl_2 (5 mL, 1:1), and then *p*-toluenesulfonic acid (24 mg) was added. The mixture was stirred for 2 h. The reaction mixture was concentrated and purified by column chromatography (petroleum ether–EtOAc, 2:1) to afford **33e** as a white solid (130 mg, 92% for two steps); R_f = 0.31 (petroleum ether–EtOAc, 2:1); $[\alpha]_D^{23}$ −54.2 (c 1.70, $CHCl_3$); IR (KBr) ν_{max} 3403, 3337, 2972, 2913, 2860, 1713, 1487, 1242, 1070, 950, 824, 804, 592 cm^{-1}; ^{1}H NMR (DMSO-d_6, 600 MHz): δ 7.35 (d, J = 8.2 Hz, 2H, Ph–H), 7.15 (d, J = 8.2 Hz, 2H, Ph–H), 5.51 (d, J = 5.9 Hz, 1H, C_3–OH), 5.41 (d, J = 5.5 Hz, 1H, C_2–OH), 4.61 (d, J = 9.2 Hz, 1H, H-1), 4.50 (ddd, J = 10.1, 5.5 Hz, 1H, H-4), 3.84 (dd, J = 11.0, 5.0 Hz, 1H, H-5-1), 3.43 (ddd, J = 9.2, 5.0 Hz, 1H, H-2), 3.26 (dd, J = 11.0, 10.1 Hz, 1H, H-5-2), 3.09 (ddd, J = 9.2, 5.9 Hz, 1H, H-3), 2.28 (s, 3H, $SPhCH_3$), 2.01 (s, 3H, Ac–CH_3); ^{13}C NMR (DMSO-d_6, 150 MHz): δ 170.7, 137.5, 133.2, 130.1, 129.6, 88.2 (C-1), 74.5, 72.5, 71.6, 65.7, 21.2, 21.0; ESI-MS (m/z): 321.1 (M + Na^+); ESIHRMS: m/z calcd for $C_{14}H_{18}O_5NaS$ [M + Na^+] 321.0773; found: 321.0780.

*4.1.2.6. 1-(4-Tolyl)thio-2,3-di-O-benzoyl-4-O-acetyl-β-D-xylopyranoside (**33f**).* To a solution of **33e** (100 mg, 0.335 mmol) and 4-dimethylamino-pyridine (5 mg, 0.034 mmol) in pyridine (5 mL) and CH_2Cl_2 (10 mL) was added benzoyl chloride (156 μL, 1.01 mmol) dropwise at 0 °C. The reaction mixture was stirred for 3 h, and then quenched with CH_3OH. The solvents were evaporated *in vacuo*. The resulting residue was diluted with EtOAc and sequentially washed with 1 N HCl, saturated $NaHCO_3$, and saturated NaCl, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (petroleum ether–EtOAc, 6:1) to afford **33f** as a white solid (163 mg, 94%); R_f = 0.41 (petroleum ether–EtOAc, 5:1); $[\alpha]_D^{23}$ +21.2 (*c* 1.30, $CHCl_3$); IR (KBr) ν_{max} 2946, 2873, 1739, 1229, 1123, 1056, 804, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.11–8.02 (m, 14H, Ph–H), 5.56 (t, *J* = 7.1 Hz, 1H, H-3), 5.36 (t, *J* = 7.1 Hz, 1H, H-2), 5.12 (td, *J* = 7.7, 4.4 Hz, 1H, H-4), 5.06 (d, *J* = 7.1 Hz, 1H, H-1), 4.48 (dd, *J* = 12.1, 4.4 Hz, 1H, H-5-1), 3.64 (dd, *J* = 12.1, 7.1 Hz, 1H, H-5-2), 2.34 (s, 3H, SPhCH$_3$), 2.01 (s, 3H, Ac–CH$_3$); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 170.1, 165.5, 165.2, 138.8, 133.7, 133.6, 130.1, 130.0, 128.9, 128.7, 128.6, 86.8 (C-1), 71.6, 70.2, 68.4, 64.4, 21.4, 21.0; ESI-MS (*m*/*z*): 529.1 (M + Na^+); ESIHRMS: *m*/*z* calcd for $C_{28}H_{26}O_7NaS$ [M + Na^+] 529.1297; found: 529.1302.

*4.1.2.7. 1-(4-Tolyl)thio-2,3-di-O-benzoyl-4-β-D-xylopyranoside (**33g**).* To a solution of **33f** (120 mg, 0.237 mmol) in CH_3OH (10 mL) was added acetyl chloride (120 μL) dropwise at 0 °C. The reaction mixture was stirred for 5 h, and then quenched with Et_3N. The solvent was evaporated *in vacuo*. The resulting residue was purified by column chromatography (petroleum ether–EtOAc, 4:1) to afford **33g** as a white solid (100 mg, 90%); R_f = 0.32 (petroleum ether–EtOAc, 3:1); $[\alpha]_D^{23}$ +47.1 (*c* 0.88, $CHCl_3$); IR (KBr) ν_{max} 3456, 3059, 2846, 1726, 1487, 1269, 1063, 804, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.12–8.04 (m, 14H, Ph–H), 5.40 (t-like, *J* = 7.8, 7.3 Hz, 1H, H-3), 5.32 (t-like, *J* = 7.8, 7.3 Hz, 1H, H-2), 5.01 (d, *J* = 7.3 Hz, 1H, H-1), 4.42 (dd, *J* = 11.9, 4.6 Hz, 1H, H-5-1), 3.98 (td, *J* = 7.7, 4.6 Hz, 1H, H-4), 3.57 (dd, *J* = 11.9, 7.8 Hz, 1H, H-5-2), 2.34 (s, 3H, SPhCH$_3$); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 167.2, 165.3, 138.7, 133.9, 133.7, 133.5, 130.3, 129.0, 128.7, 87.1 (C-1), 76.3, 70.3, 68.6, 67.8, 21.4; ESI-MS (*m*/*z*): 487.1 (M + Na^+); ESIHRMS: *m*/*z* calcd for $C_{26}H_{24}O_6NaS$ [M + Na^+] 487.1191; found: 487.1174.

*4.1.2.8. 2,3,4,6-Tetra-O-benzoyl-β-D-glucopyranosyl–(1 → 4)-1-(4-tolyl)thio-2,3-di-O-benzoyl-β-D-xylopyranoside (**33i**).* A mixture of compound **33g** (100 mg, 0.22 mmol), powdered 4 Å molecular sieves and compound **33h** (239 mg, 0.32 mmol) in dry CH_2Cl_2 (3 mL) was stirred at r.t. for 30 min then cooled to −78 °C. TMSOTf (10 μL, 0.02 mmol) was added dropwise and the reaction mixture was stirred for 30 min and then warmed to r.t. The product was detected on TLC (2:1, petroleum ether–EtOAc). After completion of the reaction, the reaction mixture was quenched with Et_3N (0.05 mL) and filtered. The filtrate was concentrated and purified by a silica gel column chromatography (3:1, petroleum ether–EtOAc) to afford **33i** (204 mg, 91%); $[\alpha]_D^{23}$ −11.8 (*c* 0.92, $CHCl_3$); IR (KBr) ν_{max} 3456, 3059, 2846, 1726, 1487, 1269, 1063, 804, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.08–8.03 (m, 34H, Ph–H), 5.81 (t, *J* = 9.6 Hz, 1H, H-3′), 5.68 (t, *J* = 7.4 Hz, 1H, H-3), 5.44 (dd, *J* = 9.7, 7.8 Hz, 1H, H-2′), 5.36 (t, *J* = 9.6 Hz, 1H, H-4′), 5.31 (t-like, *J* = 8.7, 7.0 Hz, 1H, H-4), 5.30 (d, *J* = 7.3 Hz, 1H, H-1), 4.99 (t, *J* = 7.8, 6.4 Hz, 1H, H-2), 4.97 (d, *J* = 7.8 Hz, 1H, H-1′), 4.25 (dd, *J* = 12.4, 4.6 Hz, 1H, H-6′-1), 4.17 (dd, *J* = 11.9, 3.2 Hz, 1H, H-5-1), 4.03 (m, 1H, H-5′), 3.98 (dd, *J* = 11.9, 5.5 Hz, 1H, H-5-2), 3.45 (dd, *J* = 12.4, 7.7 Hz, 1H, H-6′-2), 2.31 (s, 3H, SPhCH$_3$); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 171.4, 166.1, 165.9, 165.3, 165.1, 165.0, 138.5, 133.6, 133.4, 133.2, 130.0, 129.9, 129.8, 129.6, 128.6, 128.5, 128.4, 101.9 (C-1), 86.8 (C-1′), 73.0, 72.8, 72.1, 70.5, 69.6, 65.2, 63.1, 60.6, 29.9, 22.9, 21.4, 21.3, 14.4; ESI-MS (*m*/*z*): 1065.6 (M + Na^+); ESIHRMS: *m*/*z* calcd for $C_{60}H_{50}O_{15}NaS$ [M + Na^+] 1065.2768; found: 1065.2798.

*4.1.2.9. 2,3,4,6-Tetra-O-benzoyl-β-D-glucopyranosyl–(1 → 4)-2,3-di-O-benzoyl-β-D-xylopyranoside trichloroacetimidate (**33**).* To a solution of compound **33i** (150 mg, 0.144 mmol) in 10 mL of acetone-H_2O (9/1), NBS (67 mg, 0.374 mmol) were added at −20 °C. The mixture was stirred for 5 min, quenched with satd aq $NaHCO_3$. The reaction mixture was concentrated, and the residue was diluted with EtOAc, washed with satd aq $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (3:1 to 1:1, petroleum ether–EtOAc) to give **33j** (115 mg, 85%) as a white solid. A solution of **33j** (100 mg, 0.107 mmol), $CNCCl_3$ (0.08 mL, 0.859 mmol) and DBU (0.02 mL, 0.054 mmol) in dry CH_2Cl_2 (2 mL) was stirred for 3 h at room temperature, then the solvent was evaporated *in vacuo* to give a residue, which was purified by silica-gel flash column chromatography (petroleum ether–EtOAc, 3:1) to afford **33** (97 mg, 83%) as a white solid; R_f = 0.36 (petroleum ether–EtOAc, 1:1); ^1H NMR ($CDCl_3$): δ 8.52 (s, 1H, N-H), 7.21–8.18 (m, 30H, Ph–H), 6.57 (d, *J* = 3.7 Hz, 1H, H-1), 5.98 (t, *J* = 9.6 Hz, 1H, H-3), 5.83 (t, *J* = 9.6 Hz, 1H, H-3′), 5.52 (t, *J* = 9.6 Hz, 1H, H-4′), 5.45 (dd, *J* = 9.6, 7.7 Hz, 1H, H-2′), 5.35 (dd, *J* = 10.1, 3.7 Hz, 1H, H-2), 4.97 (d, *J* = 8.2 Hz, 1H, H-1′), 4.26 (m, 1H, H-4), 4.09 (m, 2H, H-6′-1, H-6′-2), 3.97 (m, 1H, H-5′), 3.89 (dd, *J* = 11.5, 5.5 Hz, 1H, H-5-1), 3.77 (t, *J* = 11.0 Hz, 1H, H-5-2); ESI-MS: *m*/*z* 1080.3 (M + H^+); HRESIMS: calcd for $C_{55}H_{45}O_{16}NCl_3$ [M + H^+]: *m*/*z* 1080.1804; found: *m*/*z* 1080.1849.

*4.1.3. General procedure for synthesizing compounds **35**–**36***

A solution of Mbp thioglycoside **34** (40 mg, 0.112 mmol) and 4 Å MS (80 mg) in CH_2Cl_2 (5 mL) was stirred at room temperature under argon for 30 min, and then cooled to −78 °C. At this temperature, a solution of TMSOTf (0.2 equiv.) in dry CH_2Cl_2 was injected and after 10 min a trichloroacetimidate **32** or **33** (2.1 equiv.) in dry CH_2Cl_2 was added. The mixture was stirred for additional 30 min and then warmed up to −10 °C. To the above mixture was added a solution of saponin acceptor **29** (79 mg, 0.112 mmol, 1.0 equiv.) in CH_2Cl_2 (2 mL) followed by NIS (50 mg, 0.112 mmol, 2.0 equiv.). After being stirred for 1 h, the reaction mixture was quenched with Et_3N, and then filtered through a pad of Celite. The filtrate was concentrated. The residue was purified silica gel column chromatography (2.5:1, petroleum ether–EtOAc) to give the fully protected saponin. The amounts of the reactants and the yields of the saponin products were calculated based on saponin accepter **29**.

*4.1.3.1. Benzyl oleanolate 2,3,4-tri-O-benzoyl-β-D-xylopyranosyl-(1 → 3)-2,4-di-O-acetyl-α-L-rhamnopyranosyl-(1 → 2)-3,4-O-isopropylidene-α-L-arabinopyranoside (**35**).* Yield: 73% for two steps; $[\alpha]_D^{22}$ +3.68 (*c* 2.88, $CHCl_3$); Mp: 137–139 °C; IR (KBr) ν_{max} 2939, 1719, 1448, 1255, 1096, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.25–8.03 (m, 20H, Ph–H), 5.72 (t-like, *J* = 7.3, 6.9 Hz, 1H, H-3′), 5.35 (dd, *J* = 3.2, 1.9 Hz, 1H, H-2″), 5.31 (d, *J* = 1.9 Hz, 1H, H-1″), 5.26–5.29 (m, 3H, H-12, H-2′, H-4′), 5.11 (d, *J* = 12.9 Hz, 1H, PhCHH), 5.08 (d, *J* = 12.7 Hz, 1H, PhCHH), 5.07 (t, *J* = 10.1 Hz, 1H, H-4″), 4.86 (d, *J* = 5.0 Hz, 1H, H-1′), 4.36 (dd, *J* = 12.4, 4.1 Hz, 1H, H-5′-1), 4.31 (d, *J* = 7.3 Hz, 1H, H-1‴), 4.21 (dd, *J* = 10.1, 3.7 Hz, 1H, H-3″), 4.15–4.19 (m, 2H, H-4‴, H-5‴-1), 4.10–4.14 (m, 2H, H-3‴, H-5‴-2), 4.01 (dq, *J* = 9.2, 6.0 Hz, 1H, H-5″), 3.72 (m, 1H, H-2‴), 3.65 (dd, *J* = 12.4, 6.4 Hz, 1H, H-5′-2), 3.05 (dd, *J* = 11.9, 4.6 Hz, 1H, H-3), 2.91 (dd, *J* = 13.4, 4.1 Hz, 1H, H-18), 2.09, 2.04 (s each, 3H each, Ac ×2), 1.57, 1.31 (s each, 3H each, O–$(CH_3)_2$–O), 1.12 (d, *J* = 6.4 Hz, 3H, H-6″), 1.09, 0.99, 0.92, 0.89, 0.88, 0.80, 0.60 (s each, 3H each, CH_3 ×7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 177.5 (C-28), 170.5, 169.7, 165.6, 165.5, 143.7 (C-13), 136.5, 133.5, 130.0, 128.5, 122.6 (C-12), 110.4 ((CH_3)$_2$C),

103.5 (C-1‴), 101.6 (C-1′), 94.9 (C-1″), 89.1 (C-3), 76.1, 75.8, 73.4, 71.7, 70.5, 66.0, 62.8, 61.3, 60.9, 55.9, 47.7, 46.8, 46.3, 41.8, 39.4, 36.8, 30.8, 28.2, 27.8, 26.2, 23.7, 20.6, 17.5, 16.5, 15.5, 13.8; HRMALDIMS: calcd for [M + Na^+] $C_{81}H_{100}O_{20}Na$: 1415.6721; found: *m*/*z* 1415.6700.

*4.1.3.2. Benzyl oleanolate 2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl-(1 → 4)-2,3-di-O-benzoyl-β-D-xylopyr-anosyl-(1 → 3)-2,4-di-O-acetyl-α-L-rhamnopyranosyl-(1 → 2)-3,4-O-isopropylidene-α-L-arabinopyranoside (**36**).* Yield: 73% for two steps; $[\alpha]_D^{22}$ +12.0° (*c* 1.10, $CHCl_3$); IR (KBr) ν_{max} 2934, 1731, 1455, 1369, 1260, 1097, 1058, 1027, 707 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.27–7.98 (m, 35H, Ph–H), 5.82 (t, *J* = 9.9 Hz, 1H, H-3‴′), 5.63 (t, *J* = 7.1 Hz, 1H, H-3′), 5.47 (dd, *J* = 9.9, 7.7 Hz, 1H, H-2‴′), 5.41 (t, *J* = 9.9 Hz, 1H, H-4‴′), 5.29 (t, *J* = 3.6 Hz, 1H, H-12), 5.27 (dd, *J* = 3.3, 1.7 Hz, 1H, H-2″), 5.25 (d, *J* = 1.7 Hz, 1H, H-1″), 5.13 (dd, *J* = 7.1, 5.5 Hz, 1H, H-2′), 5.11 (d, *J* = 12.1 Hz, 1H, PhC*H*H), 5.07 (d, *J* = 12.1 Hz, 1H, PhCH*H*), 5.02 (t, *J* = 9.9 Hz, 1H, H-4″), 4.97 (d, *J* = 7.7 Hz, 1H, H-1‴′), 4.67 (d, *J* = 5.5 Hz, 1H, H-1′), 4.27 (d, *J* = 7.7 Hz, 1H, H-1‴), 4.20 (dd, *J* = 12.1, 2.8 Hz, 1H, H-5‴-1), 4.17 (m, 1H, H-4‴), 4.09–4.13 (m, 2H, H-3‴, H-6‴′-1), 4.08 (dd, *J* = 9.9, 3.3 Hz, 1H, H-6″), 4.02–4.06 (m, 2H, H-4′, H-5‴′), 3.96–4.01 (m, 3H, H-5′-1, H-5″, H-6‴′-2), 3.68–3.72 (m, 2H, H-2‴, H-5′-2), 3.36 (dd, *J* = 12.7, 7.1 Hz, 1H, H-5‴-2), 3.02 (dd, *J* = 12.1, 4.4 Hz, 1H, H-3), 2.89 (dd, *J* = 13.7, 4.4 Hz, 1H, H-18), 2.04, 2.01 (s each, 3H each, Ac ×2), 1.49, 1.29 (s each, 3H each, O–$(CH_3)_2$–O), 1.10 (d, *J* = 6.0 Hz, 3H, H-6″), 1.13, 0.92, 0.90, 0.87, 0.86, 0.75, 0.60 (s each, 3H each, CH_3 ×7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 177.7 (C-28), 170.6, 166.1, 165.9, 165.5, 165.3, 165.1, 143.9 (C-13), 136.6, 133.6, 133.5, 133.4, 133.3, 129.9, 129.8, 129.7, 128.6, 128.5, 128.2, 123.2 (C-12), 110.5 ($(CH_3)_2\underline{C}$), 103.5 (C-1‴), 102.0 (C-1′), 101.8 (C-1‴′), 95.0 (C-1″), 89.1 (C-3), 79.0, 73.1, 72.1, 71.1, 69.4, 66.6, 66.1, 63.1, 60.6, 56.0, 47.8, 47.0, 46.1, 42.0, 41.6, 39.3, 38.9, 36.9, 35.6, 33.3, 32.8, 32.5, 30.9, 29.9, 28.2, 27.9, 26.3, 26.1, 23.9, 23.3, 21.3, 20.6, 18.4, 17.6, 17.1, 16.6, 15.6, 14.4; HRMALDIMS: calcd for [M + Na^+] $C_{108}H_{122}O_{28}Na$: 1889.8059; found: *m*/*z* 1889.8015.

*4.1.4. General procedure for synthesizing compounds **37**–**38***

To a solution of compound **35** or **36** (0.054 mmol) in CH_2Cl_2–MeOH (*V*:*V*/1:2, 5 mL) was added *p*-TsOH (0.054 mmol) was stirred at room temperature. When TLC (3:2, petroleum ether–EtOAc) showed that deprotection had completed, Et_3N (0.1 mL) was added and the mixture was concentrated and purified through a silica gel column chromatography (petroleum ether–EtOAc), affording the product **37** or **38**.

*4.1.4.1. Benzyl oleanolate 2,3,4-tri-O-benzoyl-β-D-xylopyranosyl-(1 → 3)-2,4-di-O-acetyl-α-L-rhamnopyranosyl-(1 → 2)-α-L-arabinopyranoside (**37**).* Yield: 95%; $[\alpha]_D^{23}$ −17.6° (*c* 3.65, $CHCl_3$); Mp: 141–143 °C; IR (KBr) ν_{max} 2945, 1731, 1451, 1373, 1260, 1097, 707 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.27–8.04 (m, 20H, Ph–H), 5.70 (t-like, *J* = 7.1, 6.6 Hz, 1H, H-3‴), 5.27–5.30 (m, 4H, H-12, H-3″, H-2‴, H-4‴), 5.10 (d, *J* = 12.1 Hz, 1H, PhC*H*H), 5.08 (s, 1H, H-2″), 5.06 (d, *J* = 12.7 Hz, 1H, PhCH*H*), 5.01 (s, 1H, H-1″), 4.97 (d, *J* = 5.0 Hz, 1H, H-1‴), 4.74 (br s, 1H, H-1′), 4.35 (dd, *J* = 12.7, 3.8 Hz, 1H, H-5‴-1), 4.10 (dd, *J* = 9.9, 3.8 Hz, 1H, H-5′-1), 3.88–3.92 (m, 2H, H-3′, H-4′), 3.83–3.87 (m, 2H, H-2′, H-5″), 3.71–3.75 (m, 2H, H-4″, H-5′-2), 3.61 (dd, *J* = 11.5, 4.4 Hz, 1H, H-5‴-2), 3.10 (dd, *J* = 11.5, 4.4 Hz, 1H, H-3), 2.91 (dd, *J* = 13.7, 3.8 Hz, 1H, H-18), 2.09, 1.80 (s each, 3H each, Ac ×2), 1.12 (d, *J* = 6.6 Hz, 3H, H-6″), 1.11, 0.94, 0.92, 0.89, 0.88, 0.78, 0.60 (s each, 3H each, CH_3 ×7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 177.5 (C-28), 170.5, 169.8, 165.6, 165.5, 165.0, 143.8 (C-13), 136.5, 133.5, 133.4, 130.0, 129.9, 128.5, 128.4, 128.1, 122.5 (C-12), 101.7 (C-1′), 101.3 (C-1‴), 98.0 (C-1″), 90.5 (C-3), 75.8, 75.6, 71.9, 71.8, 70.2, 70.1, 69.9, 68.9, 67.3, 66.0, 64.9, 61.1, 60.4, 55.5, 47.7, 46.8, 46.0, 41.8, 41.5, 39.4, 39.2, 38.6, 36.8, 33.9, 33.2, 32.7, 32.5, 30.8, 29.8, 28.2, 27.7, 25.9, 25.8, 23.7, 23.5, 23.1, 21.1, 20.6, 18.3, 17.5, 16.9, 16.5, 15.4; HRMALDIMS: calcd for [M + Na^+] $C_{78}H_{96}O_{20}Na$: 1375.6371; found: *m*/*z* 1375.6387.

*4.1.4.2. Benzyl oleanolate 2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl-(1 → 4)-2,3-di-O-benzoyl-β-D-xylopy-ranosyl-(1 → 3)-2,4-di-O-acetyl-α-L-rhamnopyranosyl-(1 → 2)-α-L-arabinopyranoside (**38**).* Yield: 90%; $[\alpha]_D^{22}$ −0.6° (*c* 0.85, $CHCl_3$); IR (KBr) ν_{max} 3451, 2922, 1735, 1447, 1256, 1093, 1062, 1023, 711 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.26–7.94 (m, 35H, Ph–H), 5.82 (t, *J* = 9.9 Hz, 1H, H-3‴′), 5.61 (t-like, *J* = 7.7, 7.1 Hz, 1H, H-3‴), 5.47 (dd, *J* = 9.9, 7.7 Hz, 1H, H-2‴′), 5.41 (t, *J* = 9.4 Hz, 1H, H-4‴′), 5.28 (t-like, *J* = 3.8, 3.3 Hz, 1H, H-12), 5.18 (dd, *J* = 3.4, 1.1 Hz, 1H, H-2″), 5.14 (dd, *J* = 7.7, 5.5 Hz, 1H, H-2‴), 5.10 (d, *J* = 12.6 Hz, 1H, PhC*H*H), 5.06 (d, *J* = 12.7 Hz, 1H, PhCH*H*), 5.01 (t, *J* = 9.9 Hz, 1H, H-4″), 4.97 (d, *J* = 7.7 Hz, 1H, H-1‴′), 4.93 (d, *J* = 1.7 Hz, 1H, H-1″), 4.74 (d, *J* = 5.5 Hz, 1H, H-1‴), 4.70 (d, *J* = 2.8 Hz, 1H, H-1′), 4.22 (dd, *J* = 11.6, 1.6 Hz, 1H, H-6‴′-1), 4.03–4.08 (m, 2H, H-4‴, H-5‴′), 3.96–4.02 (m, 3H, H-3″, H-5‴-1, H-6‴′-2), 3.82–3.86 (m, 3H, H-2′, H-3′, H-4′), 3.79 (dq, *J* = 9.9, 6.6 Hz, 1H, H-5″), 3.70 (dd, *J* = 11.5, 8.8 Hz, 1H, H-5′-1), 3.70 (dd, *J* = 11.5, 4.9 Hz, 1H, H-5′-2), 3.40 (dd, *J* = 12.1, 7.7 Hz, 1H, H-5‴-2), 3.08 (dd, *J* = 11.5, 4.4 Hz, 1H, H-3), 2.90 (dd, *J* = 13.7, 3.8 Hz, 1H, H-18), 2.04, 2.01 (s each, 3H each, Ac ×2), 1.08 (d, *J* = 6.1 Hz, 3H, H-6″), 1.10, 0.91, 0.90, 0.89, 0.87, 0.76, 0.59 (s each, 3H each, CH_3 ×7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 177.4 (C-28), 170.4, 169.6, 165.9, 165.8, 165.7, 165.1, 165.0, 164.8, 143.7 (C-13), 136.4, 133.4, 133.2, 133.0, 129.7, 129.6, 129.5, 129.4, 129.2, 128.9, 128.5, 128.3, 127.9, 127.8, 122.4 (C-12), 101.6 (C-1′), 101.5 (C-1‴′), 101.4 (C-1‴), 98.0 (C-1″), 90.4 (C-3), 75.7, 75.3, 72.9, 72.3, 71.8, 71.6, 70.7, 70.5, 70.0, 69.4, 67.1, 65.9, 62.9, 61.9, 60.1, 55.4, 47.6, 46.7, 45.9, 41.7, 41.3, 39.2, 39.0, 38.4, 36.7, 33.8, 33.1, 32.6, 30.7, 29.7, 28.1, 27.6, 25.8, 25.6, 23.6, 23.4, 23.0, 20.9, 20.4, 18.2, 17.3, 16.8, 16.4, 15.3; HRMALDIMS: calcd for [M + Na^+] $C_{105}H_{118}O_{28}Na$: 1849.7706; found: *m*/*z* 1849.7702.

*4.1.5. General procedure for synthesizing compounds **42**–**44***

A solution of Mbp thioglycoside **34** (40 mg, 0.112 mmol) and 4 Å MS (80 mg) in CH_2Cl_2 (5 mL) was stirred at room temperature under argon for 30 min, and then cooled to −78 °C. At this temperature, a solution of TMSOTf (0.2 equiv.) in dry CH_2Cl_2 was injected and after 10 min a trichloroacetimidate **32**, **39** or **40** (2.1 equiv.) in dry CH_2Cl_2 was added. The mixture was stirred for additional 30 min and then warmed up to −10 °C. To the above mixture was added a solution of saponin acceptor **41** (99 mg, 0.112 mmol, 1.0 equiv.) in CH_2Cl_2 (2 mL) followed by NIS (50 mg, 0.112 mmol, 2.0 equiv.). After being stirred for 1 h, the reaction mixture was quenched with Et_3N, and then filtered through a pad of Celite. The filtrate was concentrated. The residue was purified silica gel column chromatography (2.5:1, petroleum ether–EtOAc) to give the fully protected saponin. The amounts of the reactants and the yields of the saponin products were calculated based on saponin accepter **41**.

*4.1.5.1. Benzyl oleanolate 3β-O-2,3,4-tri-O-benzoyl-β-D-xylopyranosyl-(1 → 3)-2,4-di-O-acetyl-α-L-rhamno-pyranosyl-(1 → 2)-3,4-di-O-benzoyl-β-D-xylopyranoside (**42**).* Yield: 67%; Mp: 140–142 °C; $[\alpha]_D^{25}$ −28.1 (*c* 2.04, $CHCl_3$); IR (KBr) ν_{max} 2945, 1731, 1603, 1451, 1256, 1093, 711 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.27–8.10 (m, 30H, Ph–H), 5.59 (t, *J* = 7.1, 6.6 Hz, 2H, H-3′, H-3‴), 5.29 (t, *J* = 3.8 Hz, 1H, H-12), 5.20–5.22 (m, 2H, H-2″, H-2‴), 5.14–5.17 (m, 2H, H-4′, H-4‴), 5.10 (d, *J* = 12.7 Hz, 1H, PhC*H*H), 5.05 (s, 1H, H-1″), 5.04 (d, *J* = 12.7 Hz, 1H, PhCH*H*), 5.03 (m, 1H, H-4″), 4.78 (d, *J* = 4.9 Hz, 1H, H-1′), 4.60 (d, *J* = 5.0 Hz, 1H, H-1‴), 4.37 (dd, *J* = 12.1, 3.9 Hz, 1H, H-5′-1), 4.11 (dd, *J* = 12.1, 3.8 Hz, 1H, H-5‴-1), 4.01–4.04 (m, 2H, H-3″, H-5″), 3.97 (t, *J* = 5.5 Hz, 1H, H-2′), 3.62 (dd, *J* = 12.1, 6.6 Hz, 1H, H-5′-2), 3.33 (dd, *J* = 12.1, 6.6 Hz, 1H, H-5‴-2), 3.15 (dd, *J* = 11.5, 4.4 Hz, 1H, H-3), 2.91 (dd, *J* = 13.2, 4.4 Hz, 1H, H-18), 1.92, 1.77 (s each, 3H each, Ac ×2), 1.13 (d, *J* = 6.6 Hz, 3H, H-6″), 1.12, 0.95,

0.92, 0.90, 0.89, 0.74, 0.60 (s each, 3H each, CH_3 ×7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 177.6 (C-28), 169.9, 169.5, 165.8, 165.6, 165.5, 165.4, 165.2, 143.8 (C-13), 136.5, 133.5, 133.4, 129.9, 129.8, 128.6, 128.5, 128.4, 122.6 (C-12), 103.1 (C-1′), 101.1 (C-1‴), 97.6 (C-1″), 89.4 (C-3), 75.9, 74.1, 71.4, 71.2, 70.3, 69.5, 69.1, 67.2, 66.0, 60.9, 55.7, 47.7, 46.8, 46.0, 41.8, 41.5, 39.4, 39.2, 38.8, 36.8, 33.9, 33.2, 32.8, 32.5, 30.8, 28.1, 27.7, 26.0, 25.9, 23.7, 23.5, 23.1, 20.9, 20.6, 18.3, 17.5, 16.9, 16.4, 15.5; HRMALDIMS: calcd for [M + Na^+] $C_{92}H_{104}O_{22}Na$: 1583.6952; found: *m*/*z* 1583.6912.

*4.1.5.2. Benzyl oleanolate 3β-O-2,3,4,6,2′,3′,4′,6′-octa-O-benzoyl-β-D-cellobicopyranosyl-(1 → 3)-2,4-di-O-acetyl-α-L-rhamnopyranosyl-(1 → 2)-3,4-di-O-benzoyl-β-D-xylopyranoside (**43**).* Yield: 66%; Mp: 144–146 °C; $[\alpha]_D^{24}$ +26.2 (*c* 1.92, $CHCl_3$); IR (KBr) ν_{max} 2945, 1731, 1599, 1451, 1264, 1085, 707 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.27–8.07 (m, 50H, Ph–H), 5.65 (t, *J* = 9.4 Hz, 1H, H-3‴), 5.51–5.54 (m, 2H, H-2‴, H-3′), 5.40 (t-like, *J* = 9.9, 3.3 Hz, 1H, H-3′′′′), 5.27–5.31 (m, 2H, H-12, H-3″), 5.25 (dd, *J* = 9.6, 7.8 Hz, 1H, H-2′′′′), 5.15 (m, 1H, H-4′), 5.10 (d, *J* = 12.1 Hz, 1H, PhC*H*H), 5.06 (d, *J* = 12.6 Hz, 1H, PhCH*H*), 4.92–4.95 (m, 3H, H-1″, H-2″, H-4″), 4.74 (d, *J* = 7.7 Hz, 1H, H-1′′′), 4.66 (d, *J* = 4.9 Hz, 1H, H-1′), 4.34 (dd, *J* = 11.6, 3.8 Hz, 1H, H-5′-1), 4.28 (dd, *J* = 12.6, 2.7 Hz, 1H, H-6‴-1), 4.22 (t, *J* = 9.9 Hz, 1H, H-4′′′), 4.05 (d, *J* = 7.8 Hz, 1H, H-1′′′′), 4.03 (t, *J* = 9.6 Hz, 1H, H-4′′′′), 3.99 (dd, *J* = 12.1, 2.8 Hz, 1H, H-6′′′′-1), 3.89–3.92 (m, 1H, H-5″), 3.85–3.87 (m, 1H, H-5‴), 3.84 (t, *J* = 6.6 Hz, 1H, H-2′), 3.67 (m, 1H, H-5′′′′), 3.57 (dd, *J* = 12.1, 5.5 Hz, 1H, H-6′′′′-2), 3.51 (dd, *J* = 12.1, 5.6 Hz, 1H, H-5′-2), 3.12 (dd, *J* = 11.5, 4.4 Hz, 1H, H-3), 2.91 (dd, *J* = 13.7, 3.8 Hz, 1H, H-18), 2.71 (t, *J* = 10.5 Hz, 1H, H-6″-2), 1.74, 1.74 (s each, 3H each, Ac ×2), 1.04 (d, *J* = 6.1 Hz, 3H, H-6″), 1.12, 0.92, 0.90, 0.89, 0.86, 0.67, 0.59 (s each, 3H each, CH_3 ×7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 177.5 (C-28), 169.8, 169.7, 165.7, 165.6, 165.4, 165.3, 165.1, 143.8 (C-13), 136.5, 133.3, 129.8, 129.7, 128.5, 128.3, 128.1, 122.6 (C-12), 103.4 (C-1′), 100.9 (C-1‴), 100.5 (C-1′′′′), 97.9 (C-1″), 88.9 (C-3), 76.4, 75.4, 73.0, 72.4, 72.3, 71.9, 69.7, 69.6, 66.9, 66.6, 66.0, 62.7, 61.7, 55.7, 47.7, 46.8, 45.9, 41.8, 41.5, 39.4, 39.2, 38.8, 36.8, 33.2, 32.8, 30.8, 28.0, 26.0, 23.7, 23.1, 20.7, 20.1, 17.4, 16.9, 16.2, 15.5; HRMALDIMS: calcd for [M + Na^+] $C_{127}H_{132}O_{32}Na$: 2191.8557; found: *m*/*z* 2191.8594.

*4.1.5.3. Benzyl oleanolate 3β-O-2,3,4-tri-O-benzoyl-α-L-rhamnopyranosyl-(1 → 3)-2,4-di-O-acetyl-α-L-rha-mnopyranosyl-(1 → 2)-3,4-di-O-benzoyl-β-D-xylopyranoside (**44**).* Yield: 70%; Mp: 136–138 °C; $[\alpha]_D^{24}$ +36.9 (*c* 2.10, $CHCl_3$); IR (KBr) ν_{max} 2945, 1727, 1603, 1451, 1264, 1093, 707 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.28–8.12 (m, 30H, Ph–H), 5.57–5.62 (m, 3H, H-3′, H-3‴, H-4″), 5.38 (t-like, *J* = 2.3, 1.9 Hz, 1H, H-2′′′), 5.29 (t, *J* = 3.7 Hz, 1H, H-12), 5.24 (br s, 1H, H-2″), 5.13–5.19 (m, 2H, H-4′, H-4″), 5.09 (d, *J* = 12.4 Hz, 1H, PhC*H*H), 5.08 (s, 1H, H-1″), 5.06 (d, *J* = 12.9 Hz, 1H, PhCH*H*), 4.89 (s, 1H, H-1′′′), 4.81 (d, *J* = 4.6 Hz, 1H, H-1′), 4.48 (dd, *J* = 12.4, 4.1 Hz, 1H, H-5′-1), 4.12–4.15 (m, 3H, H-3″, H-5″, H-5′′′), 4.00 (t-like, *J* = 6.0, 5.0 Hz, 1H, H-2′), 3.63 (dd, *J* = 11.9, 6.4 Hz, 1H, H-5′-2), 3.18 (dd, *J* = 11.9, 4.6 Hz, 1H, H-3), 2.90 (dd, *J* = 13.8, 4.6 Hz, 1H, H-18), 2.22, 2.10 (s each, 3H each, Ac ×2), 1.23 (d, *J* = 5.9 Hz, 3H, H-6″), 1.12, 0.98, 0.92, 0.89, 0.89, 0.77, 0.60 (s each, 3H each, CH_3 ×7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 177.6 (C-28), 170.4, 170.0, 165.8, 165.9, 165.8, 165.4, 143.8 (C-13), 136.5, 133.7, 133.4, 133.1, 129.9, 128.8, 128.5, 128.1, 122.6 (C-12), 102.9 (C-1′), 98.7 (C-1′′′), 97.6 (C-1″), 89.5 (C-3), 74.7, 73.8, 72.5, 71.6, 71.0, 69.5, 67.5, 67.2, 66.0, 60.8, 55.7, 47.7, 46.8, 46.0, 41.8, 41.5, 39.4, 39.3, 38.8, 36.8, 33.9, 33.2, 32.7, 30.8, 28.1, 27.7, 26.1, 26.0, 23.7, 23.1, 21.0, 20.9, 18.3, 17.7, 17.4, 16.9, 16.5, 15.5; HRMALDIMS: calcd for [M + Na^+] $C_{93}H_{106}O_{22}Na$: 1597.7089; found: *m*/*z* 1597.7068.

*4.1.6. Benzyl oleanolate 3β-O-[3-O-(2,3,4-tri-O-benzoyl-α-L-rhamnopyranosyl)-3,4-di-O-benzoyl-β-D-xylo-pyranoside] (**45**)*

A mixture of compound **41** (120 mg, 0.14 mmol), powdered 4 Å molecular sieves and compound **40** (104 mg, 0.17 mmol) in dry CH_2Cl_2 (5 mL) was stirred at room temperature for 30 min then cooled to 0 °C. TMSOTf (10 μL, 0.02 mmol) was added dropwise and the reaction mixture was stirred for 30 min and then warmed to room temperature. The product was detected on TLC (2:1, petroleum ether–EtOAc). After completion of the reaction, the reaction mixture was quenched with Et_3N (0.05 mL) and filtered. The filtrate was concentrated and purified by a silica gel column chromatography (3:1, petroleum ether–EtOAc) to afford **45** (171 mg, 91%); $[\alpha]_D^{20}$ +63.2 (*c* 0.52, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 7.23–8.05 (m, 30H, Ph–H), 5.82 (dd, *J* = 10.1, 3.2 Hz, 1H, H-3″), 5.71 (t-like, *J* = 7.3, 6.9 Hz, 1H, H-3′), 5.60 (t-like, *J* = 10.1, 9.6 Hz, 1H, H-4″), 5.56 (dd, *J* = 3.2, 1.4 Hz, 1H, H-2″), 5.34 (d, *J* = 1.8 Hz, 1H, H-1″), 5.30 (t-like, *J* = 3.7, 3.2 Hz, 1H, H-12), 5.21–5.24 (m, 1H, H-4′), 5.09 (dd, *J* = 34.4, 12.8 Hz, 2H, CH_2–Ph), 4.87 (d, *J* = 5.5 Hz, 1H, H-1′), 4.48–4.52 (m, 1H, H-5″), 4.40 (dd, *J* = 12.4, 4.6 Hz, 1H, H-5′-1), 4.12 (dd, *J* = 6.9, 6.0 Hz, 1H, H-2′), 3.66 (dd, *J* = 12.4, 7.4 Hz, 1H, H-5′-2), 3.25 (dd, *J* = 11.9, 4.6 Hz, 1H, H-3), 2.91 (dd, *J* = 14.2, 4.6 Hz, 1H, H-18), 1.99 (dt, *J* = 13.2, 4.1 Hz, 1H, H-16), 1.31 (d, *J* = 5.9 Hz, 3H, H-6″), 1.13, 1.12, 0.92, 0.89, 0.89, 0.83, 0.62 (s each, 3H each, CH_3 ×7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 177.5 (C-28), 165.9, 165.8, 165.2, 143.8 (C-13), 136.6, 133.4, 130.0, 128.4, 122.6 (C-12), 103.5 (C-1′), 97.7 (C-1″), 89.6 (C-3), 74.2, 72.5, 71.9, 70.6, 66.0, 61.3, 55.8, 47.8, 46.8, 46.0, 39.4, 39.3, 36.9, 33.2, 30.8, 28.2, 25.9, 23.8, 17.5, 16.6, 15.5; ESI-MS (*m*/*z*): 1345.6 (M + H^+); HRMALDIMS: calcd for [M + Na^+] $C_{83}H_{92}O_{16}Na$: 1367.6309; found: *m*/*z* 1367.6278.

*4.1.7. 2,3,4-Tri-O-benzoyl-α-L-rhamnopyranosyl-(1 → 2)-1-(4-tolyl)thio-3,4-O-isopropylidene-α-L-arabino-pyranoside (**47**)*

A mixture of compound **46** (100 mg, 0.34 mmol), powdered 4 Å molecular sieves and compound **39** (314 mg, 0.51 mmol) in dry CH_2Cl_2 (5 mL) was stirred at room temperature for 30 min then cooled to −78 °C. TMSOTf (10 μL, 0.02 mmol) was added dropwise and the reaction mixture was stirred for 30 min and then warmed to room temperature. The product was detected on TLC (2:1, petroleum ether–EtOAc). After completion of the reaction, the reaction mixture was quenched with Et_3N (0.05 mL) and filtered. The filtrate was concentrated and purified by a silica gel column chromatography (5:1, petroleum ether–EtOAc) to afford **47** (221 mg, 86%); $[\alpha]_D^{23}$ +77.9 (*c* 0.95, $CHCl_3$); IR (KBr) ν_{max} 3364, 3231, 2979, 1726, 1448, 1255, 1109, 831, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.13–8.09 (m, 19H, Ph–H), 5.81 (dd, *J* = 9.9, 3.3 Hz, 1H, H-3′), 5.74 (dd, *J* = 3.3, 1.6 Hz, 1H, H-2′), 5.66 (t-like, *J* = 9.9, 9.8 Hz, 1H, H-4′), 5.49 (d, *J* = 1.7 Hz, 1H, H-1′), 4.82 (d, *J* = 8.3 Hz, 1H, H-1), 4.55 (dq, *J* = 9.9, 6.1 Hz, 1H, H-5′), 4.32 (m, 1H, H-4), 4.29 (t, *J* = 6.1 Hz, 1H, H-3), 4.20 (dd, *J* = 13.2, 3.8 Hz, 1H, H-5-1), 3.98 (dd, *J* = 8.3, 6.1 Hz, 1H, H-2), 3.80 (dd, *J* = 12.7, 3.8 Hz, 1H, H-5-2), 2.33 (s, 3H, STol–CH_3), 1.52, 1.35 (s each, 3H each, O–$(CH_3)_2$C–O), 1.32 (d, *J* = 6.6 Hz, 3H, H-6′); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 166.0, 165.8, 165.7, 138.1, 133.7, 133.5, 133.3, 132.8, 130.2, 130.0, 129.9, 129.8, 129.7, 129.6, 128.8, 128.7, 128.6, 128.5, 110.7 (C-1), 96.8 (C-1′), 86.9 (C-3′), 78.5, 76.0, 72.8, 71.9, 70.9, 70.3, 67.7, 65.1, 28.0, 26.3, 21.4, 17.7; HRMALDIMS: calcd for [M + Na^+] $C_{42}H_{42}O_{11}SNa$: *m*/*z* 777.2359; found: *m*/*z* 777.2340.

*4.1.8. Benzyl oleanolate 2,3,4-tri-O-benzoyl-α-L-rhamnopyranosyl-(1 → 2)-3,4-O-isopropylidene-β-L-arabinopyranoside (**49**)*

A mixture of compound **48** (80 mg, 0.15 mmol), powdered 4 Å molecular sieves and compound **47** (166 mg, 0.22 mmol) in dry CH_2Cl_2 (5 mL) was stirred at room temperature for 30 min then cooled to 0 °C. NIS (54 mg, 0.23 mmol) and AgOTf (5 mg, 0.02 mmol) was added, the reaction mixture was stirred for 30 min and then warmed to room temperature. The product was detected on TLC (3:1, petroleum ether–EtOAc). After completion of the reaction, the reaction mixture was quenched with Et_3N (0.20 mL) and filtered. The filtrate was diluted with CH_2Cl_2, and then washed with

saturated $Na_2S_2O_3$ and brine, respectively. The organic layer was dried over anhydrous Na_2SO_4, and then concentrated *in vacuo*. The resulting residue was purified by a silica gel column chromatography (3:1, petroleum ether–EtOAc) to afford **49** (60 mg, 35%); $[\alpha]_D^{23}$ +131.7 (*c* 0.50, $CHCl_3$); IR (KBr) ν_{max} 2919, 1726, 1441, 1255, 1096, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.10–8.10 (m, 20H, Ph–H), 5.84 (dd, *J* = 9.9, 3.3 Hz, 1H, H-3″), 5.77 (dd, *J* = 3.3, 1.7 Hz, 1H, H-2″), 5.64 (t, *J* = 9.9 Hz, 1H, H-4″), 5.34 (d, *J* = 1.7 Hz, 1H, H-1″), 5.29 (t-like, *J* = 3.8, 3.3 Hz, 1H, H-12), 5.11 (d, *J* = 12.7 Hz, 1H, PhCHH), 5.10 (d, *J* = 3.3 Hz, 1H, H-1′), 5.06 (d, *J* = 12.7 Hz, 1H, PhCHH), 4.44 (dd, *J* = 7.7, 6.0 Hz, 1H, H-3′), 4.27–4.30 (m, 2H, H-4′, H-5″), 4.11 (m, 1H, H-5′-1), 3.97 (d, *J* = 12.7 Hz, 1H, H-5′-2), 3.90 (dd, *J* = 7.7, 3.3 Hz, 1H, H-2′), 3.29 (dd, *J* = 11.5, 3.8 Hz, 1H, H-3), 2.90 (dd, *J* = 14.3, 3.8 Hz, 1H, H-18), 1.55, 1.36 (s each, 3H each, O–$(CH_3)_2$C–O), 1.35 (d, *J* = 6.4 Hz, 3H, H-6″), 1.13, 1.05, 0.95, 0.92, 0.92, 0.90, 0.62 (s each, 3H each, CH_3 ×7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 177.7 (C-28), 165.8, 143.9 (C-13), 136.6, 133.7, 133.5, 130.0, 129.5, 128.6, 128.5, 128.3, 128.2, 122.6 (C-12), 109.2, 99.3 (C-1″), 93.5 (C-1′), 88.8 (C-3), 81.1 (C-3″), 71.0, 70.4, 70.2, 69.9, 69.3, 67.2, 66.1, 62.7, 55.7, 47.8, 46.9, 41.9, 41.7, 39.5, 38.9, 38.1, 37.8, 33.3, 33.1, 32.8, 32.7, 31.5, 31.3, 31.2, 30.0, 29.9, 28.7, 28.0, 23.8, 23.7, 23.5, 23.3, 23.2, 18.0, 17.9, 16.5, 15.5, 14.2, 11.6; HRMALDIMS: calcd for [M + Na^+] $C_{72}H_{88}O_{14}Na$: *m*/*z* 1199.6078; found: *m*/*z* 1199.6066.

*4.1.9. Benzyl oleanolate 2,3,4-tri-O-benzoyl-α-L-rhamnopyranosyl-(1 → 2)-β-L-arabinopyranoside (**50**)*

A mixture of compound **49** (100 mg, 0.09 mmol) and *p*-TsOH (15 mg, 0.09 mmol) in CH_2Cl_2–MeOH (*V*:*V*/1:2, 6 mL) was stirred at r.t. When TLC (3:2, petroleum ether–EtOAc) showed that deprotection had completed, Et_3N (0.1 mL) was added and the mixture was concentrated and purified through a silica gel column chromatography (2:1, petroleum ether–EtOAc) to afford **50** (81 mg, 84%) as a white solid; $[\alpha]_D^{23}$ +156.2 (*c* 0.40, $CHCl_3$); IR (KBr) ν_{max} 2938, 1727, 1455, 1260, 1108, 1066, 707 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 7.27–8.07 (m, 20H, Ph–H), 5.80 (dd, *J* = 9.9, 3.3 Hz, 1H, H-3″), 5.75 (dd, *J* = 2.8, 1.6 Hz, 1H, H-2″), 5.66 (t, *J* = 9.9 Hz, 1H, H-4″), 5.28 (br s, 2H, H-1″, H-12), 5.22 (d, *J* = 3.8 Hz, 1H, H-1′), 5.12 (d, *J* = 12.7 Hz, 1H, PhCHH), 5.05 (d, *J* = 12.7 Hz, 1H, PhCHH), 4.38 (dq, *J* = 9.9, 6.0 Hz, 1H, H-5″), 4.20 (d, *J* = 8.8 Hz, 1H, H-3′), 4.09 (m, 1H, H-4′), 4.02 (dq, *J* = 9.3, 3.3 Hz, 1H, H-2′), 3.91 (d, *J* = 12.6 Hz, 1H, H-5′-1), 3.75 (d, *J* = 12.1 Hz, 1H, H-5′-2), 3.31 (dd, *J* = 11.6, 3.9 Hz, 1H, H-3), 2.89 (dd, *J* = 13.7, 4.4 Hz, 1H, H-18), 1.35 (d, *J* = 6.0 Hz, 3H, H-6″), 1.13, 1.07, 0.97, 0.91, 0.89, 0.87, 0.61 (s each, 3H each, CH_3 ×7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 177.7 (C-28), 171.4, 165.8, 144.0 (C-13), 136.7, 133.7, 133.6, 133.3, 130.1, 129.9, 128.8, 128.6, 128.5, 128.2, 122.6 (C-12), 99.3 (C-1″), 93.5 (C-1′), 88.7 (C-3), 81.2 (C-3″), 71.9, 70.8, 70.2, 69.9, 68.5, 67.2, 66.1, 62.7, 60.6, 55.7, 47.8, 46.9, 46.1, 41.9, 41.6, 39.5, 38.9, 38.3, 37.1, 34.1, 33.3, 32.9, 32.5, 30.9, 28.7, 27.8, 26.1, 23.8, 23.6, 23.2, 21.3, 21.1, 18.5, 17.9, 17.1, 16.9, 15.5, 14.4; ESI-MS: *m*/*z* 1159.7 (M + Na^+).

*4.1.10. General procedure for synthesizing compounds **52a–c** and **54a–c***

Compound **51** or **53** (0.13 mmol), trichloroacetimidate **40** (0.13 mmol) and powdered 4 Å molecular sieves (0.10 g) were stirred for 40 min at room temperature in dry CH_2Cl_2 (2 mL). TMSOTf (0.002 mL, 0.013 mmol) was added dropwise. The mixture was stirred for 10 min followed by addition of Et_3N and filtration. The filtrate was concentrated and purified by a silica gel column chromatography (5:1, petroleum ether–EtOAc) to afford the saponin products **52a–c** and **54a–c**.

*4.1.10.1. Benzyl oleanolate 3β-O-[2-O-(2,3,4-tri-O-benzoyl-α-L-rhamnopyranosyl)-4,6-di-O-benzylidene-β-D-galactopyranoside] (**52a**).* Yield: 51%; $[\alpha]_D^{20}$ +70.8 (*c* 0.62, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 7.23–8.07 (m, 25H, Ph–H), 5.90 (dd, *J* = 10.6, 3.7 Hz, 1H, H-3″), 5.85 (d, *J* = 1.8 Hz, 1H, H-3′), 5.81 (m, 1H, H-4′), 5.65 (t, *J* = 10.1 Hz, 1H, H-4″), 5.55 (s, 1H, PhCHO), 5.30 (t, *J* = 3.6 Hz, 1H, H-12), 5.09 (dd, *J* = 40.8, 12.8 Hz, 2H, CH_2–Ph), 4.61–4.64 (m, 1H, H-5″), 4.52 (d, *J* = 7.3 Hz, 1H, H-1′), 4.32 (dd, *J* = 10.2, 1.8 Hz, 1H, H-6′-1), 4.18 (d, *J* = 2.8 Hz, 1H, H-1″), 4.08–4.10 (m, 2H, H-5′, H-6′-2), 3.96 (m, 2H, H-2′, H-2″), 3.20 (dd, *J* = 11.9, 4.1 Hz, 1H, H-3), 2.91 (dd, *J* = 13.3, 3.7 Hz, 1H, H-18), 1.1.36 (d, *J* = 6.4 Hz, 3H, H-6″), 1.14, 0.97, 0.93, 0.92, 0.90, 0.89, 0.63 (s each, 3H each, CH_3 ×7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 177.5 (C-28), 165.9, 165.6, 143.8 (C-13), 137.5, 136.5, 133.0, 128.3, 128.0, 122.7 (C-12), 104.0 (C-1′), 101.3 (PhC(O)), 97.2 (C-1‴), 89.9 (C-3), 72.1, 70.7, 70.1, 66.5, 56.1, 47.8, 46.9, 46.0, 41.5, 39.5, 39.3, 33.2, 30.8, 28.3, 26.0, 23.8, 17.6, 17.0, 16.9; HRMALDIMS: calcd for [M + Na^+] $C_{77}H_{90}O_{15}Na$: 1277.6202; found: *m*/*z* 1277.6172.

*4.1.10.2. Benzyl oleanolate 3β-O-[3-O-(2,3,4-tri-O-benzoyl-α-L-rhamnopyranosyl)-4,6-di-O-benzylidene-β-D-galactopyranoside] (**52b**).* Yield: 29%; $[\alpha]_D^{20}$ +80.8 (*c* 0.55, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 7.04–8.11 (m, 25H, Ph–H), 5.96 (dd, *J* = 10.5, 3.2 Hz, 1H, H-3″), 5.83 (t, *J* = 10.1 Hz, 1H, H-4″), 5.76 (m, 1H, H-2″), 5.58 (t, *J* = 10.1 Hz, 1H, H-3′), 5.53 (s, 1H, H-1″), 5.38 (s, 1H, PhCHO), 5.30 (br s, 1H, H-12), 5.10 (dd, *J* = 34.4, 12.5 Hz, 2H, CH_2–Ph), 4.91 (m, 1H, H-5″), 4.66 (d, *J* = 7.3 Hz, 1H, H-1′), 4.55 (m, 1H, H-4′), 4.43 (t, *J* = 8.7 Hz, 1H, H-2′), 4.33 (dd, *J* = 11.5, 5.0 Hz, 1H, H-6′-1), 4.11 (dd, *J* = 9.2, 6.8 Hz, 1H, H-6′-2), 3.86 (m, 1H, H-5′), 3.28 (dd, *J* = 11.4, 4.4 Hz, 1H, H-3), 2.92 (dd, *J* = 13.7, 3.2 Hz, 1H, H-18), 1.40 (d, *J* = 6.0 Hz, 3H, H-6″), 1.14, 0.93, 0.93, 0.92, 0.92, 0.90, 0.63 (s each, 3H each, CH_3 ×7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 177.5 (C-28), 165.8, 165.5, 163.4, 143.8 (C-13), 137.8, 136.5, 133.3, 129.8, 128.3, 122.7 (C-12), 105.3 (C-1′), 101.2 (PhC(O)), 99.9 (C-1‴), 89.9 (C-3), 81.8, 70.9, 70.3, 70.1, 66.0, 60.5, 55.8, 47.8, 46.8, 46.0, 41.8, 39.2, 36.9, 33.2, 30.8, 28.3, 26.0, 23.8, 19.2, 17.8, 16.8, 15.4; HRMALDIMS: calcd for [M + Na^+] $C_{77}H_{90}O_{15}Na$: 1277.6173; found: *m*/*z* 1277.6172.

*4.1.10.3. Benzyl oleanolate 3β-O-[2,3-di-O-(2,3,4-tri-O-benzoyl-α-L-rhamnopyranosyl)-4,6-di-O-benzyl-idene-β-D-galactopyranoside] (**52c**).* Yield: 7%; $[\alpha]_D^{20}$ +64.1 (*c* 0.65, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 7.15–8.11 (m, 40H, Ph–H), 5.90 (dd, *J* = 10.0, 3.6 Hz, 1H, H-3‴), 5.83 (dd, *J* = 10.1, 3.7 Hz, 1H, H-3″), 5.77 (m, 1H, H-4′), 5.70 (m, 1H, H-4‴), 5.62 (t, *J* = 10.1 Hz, 1H, H-4″), 5.56 (s, 1H, PhCHO), 5.32 (d, *J* = 1.9 Hz, 1H, H-1‴), 5.30 (t, *J* = 3.6 Hz, 1H, H-12), 5.08 (dd, *J* = 31.1, 12.4 Hz, 2H, CH_2–Ph), 4.48–4.50 (m, 1H, H-5″), 4.44–4.47 (m, 1H, H-5‴), 4.40 (d, *J* = 7.3 Hz, 1H, H-1′), 4.35 (d, *J* = 3.2 Hz, 1H, H-1″), 4.33 (dd, *J* = 11.5, 1.6 Hz, 1H, H-6′-1), 4.08–4.12 (m, 4H, H-2′, H-3′, H-5′, H-6′-2), 3.75 (dd, *J* = 7.0, 3.7 Hz, 1H, H-2″), 3.17 (dd, *J* = 11.9, 4.6 Hz, 1H, H-3), 2.91 (dd, *J* = 12.8, 4.1 Hz, 1H, H-18), 1.44 (d, *J* = 5.0 Hz, 3H, H-6‴), 1.34 (d, *J* = 5.9 Hz, 3H, H-6″), 1.12, 1.05, 0.91, 0.89, 0.86, 0.85, 0.60 (s each, 3H each, CH_3 ×7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 177.5 (C-28), 165.5, 165.2, 164.9, 143.8 (C-13), 137.6, 136.5, 129.8, 128.5, 128.3, 128.0, 122.7, 104.3 (C-1′), 101.2 (C-1″), 100.2 (PhC(O)), 97.7 (C-1‴), 89.6 (C-3), 85.8, 72.5, 71.6, 70.9, 66.0, 56.3, 47.9, 46.9, 46.0, 41.5, 39.5, 39.3, 33.2, 30.8, 28.3, 26.0, 23.8, 17.5, 17.1, 15.6; HRMALDIMS: calcd for [M + Na^+] $C_{104}H_{112}O_{22}Na$: 1735.7533; found: *m*/*z* 1735.7538.

*4.1.10.4. Benzyl oleanolate 3β-O-[2-O-(2,3,4-tri-O-benzoyl-α-L-rhamnopyranosyl)-4,6-di-O-benzylidene-β-D-glucopyranoside] (**54a**).* Yield: 45%; $[\alpha]_D^{20}$ +49.5 (*c* 0.50, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 7.29–8.09 (m, 25H, Ph–H), 5.91 (dd, *J* = 10.1, 3.2 Hz, 1H, H-3″), 5.83 (dd, *J* = 5.0, 1.8 Hz, 1H, H-2″), 5.76 (br s, 1H, H-1″), 5.69 (t, *J* = 10.1 Hz, 1H, H-4″), 5.53 (s, 1H, PhCH(O)), 5.30 (t, *J* = 3.6 Hz, 1H, H-12), 5.09 (dd, *J* = 37.6, 12.4 Hz, 2H, CH_2–Ph), 4.67 (d, *J* = 7.3 Hz, 1H, H-1′), 4.52–4.57 (m, 1H, H-5″), 4.35 (dd, *J* = 10.5, 5.5 Hz, 1H, H-6′-1), 4.07 (m, 1H, H-3′), 3.83–3.88 (m, 1H, H-2′), 3.78

(t, J = 10.1 Hz, 1H, H-6′-2), 3.56 (t, J = 9.6 Hz, 1H, H-4′), 3.45 (dt, J = 10.1, 5.0 Hz, 1H, H-5′), 3.25 (dd, J = 11.9, 4.6 Hz, 1H, H-3), 2.91 (dd, J = 13.1, 3.2 Hz, 1H, H-18), 1.35 (d, J = 6.0 Hz, 3H, H-6″), 1.14, 0.94, 0.93, 0.92, 0.91, 0.89, 0.63 (s each, 3H each, CH_3 ×7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 177.6 (C-28), 165.9, 165.7, 143.8 (C-13), 137.1, 136.5, 133.4, 129.8, 128.4, 122.6 (C-12), 104.7 (C-1′), 101.9 (PhC(O)), 97.7 (C-1‴), 89.9 (C-3), 80.8, 75.1, 72.5, 70.7, 69.5, 67.2, 66.1, 65.8, 56.0, 47.8, 46.8, 46.0, 41.8, 41.5, 39.4, 38.5, 34.1, 33.2, 30.8, 28.1, 26.0, 25.9, 23.8, 22.9, 21.6, 19.2, 17.6, 16.6, 15.5; HRMALDIMS: calcd for [M + Na^+] $C_{77}H_{90}O_{15}Na$: 1277.6210; found: m/z 1277.6172.

*4.1.10.5. Benzyl oleanolate 3β-O-[3-O-(2,3,4-tri-O-benzoyl-α-L-rhamnopyranosyl)-4,6-di-O-benzylidene-β-D-glucopyranoside] (**54b**).* Yield: 35%; $[\alpha]_D^{20}$ +35.9 (c 1.04, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.20–8.08 (m, 25H, Ph–H), 5.83 (dd, J = 10.1, 3.7 Hz, 1H, H-3″), 5.72 (dd, J = 3.7, 1.9 Hz, 1H, H-2″), 5.63 (s, 1H, PhCH(O)), 5.57 (t-like, J = 10.1, 9.6 Hz 1H, H-4″), 5.53 (d, J = 1.4 Hz, 1H, H-1″), 5.29 (t, J = 3.7 Hz, 1H, H-12), 5.08 (dd, J = 31.1, 12.8 Hz, 2H, CH_2–Ph), 4.53 (dt, J = 12.4, 6.4 Hz, 1H, H-5″), 4.47 (d, J = 7.8 Hz, 1H, H-1′), 4.35 (dd, J = 10.6, 5.0 Hz, 1H, H-6′-1), 4.01 (t-like, J = 9.2, 9.1 Hz, 1H, H-3′), 3.86 (t, J = 9.6 Hz, 1H, H-6′-2), 3.74–3.77 (m, 1H, H-2′), 3.72 (t-like, J = 9.7, 9.1 Hz, 1H, H-4′), 3.49 (dt, J = 9.6, 5.0 Hz, 1H, H-5′), 3.20 (dd, J = 11.5, 4.6 Hz, 1H, H-3), 2.9 (dd, J = 13.7, 4.1 Hz, 1H, H-18), 2.00 (dt, J = 13.7, 4.1 Hz, 1H, H-16), 1.00 (d, J = 6.0 Hz, 3H, H-6″), 1.11, 0.99, 0.91, 0.89, 0.89, 0.83, 0.60 (s each, 3H each, CH_3 ×7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 177.5 (C-28), 165.7, 143.8 (C-13), 137.3, 136.5, 133.5, 128.5, 128.2, 122.6 (C-12), 105.7 (C-1′), 101.8 (PhC(O)), 97.7 (C-1‴), 90.3 (C-3), 78.2, 71.5, 70.9, 70.2, 68.5, 66.9, 66.0, 55.6, 47.7, 46.8, 46.3, 41.8, 39.4, 36.8, 33.2, 30.8, 28.4, 27.6, 25.9, 23.8, 23.7, 23.5, 17.7, 17.1, 16.8, 15.4; HRMALDIMS: calcd for [M + Na^+] $C_{77}H_{90}O_{15}Na$: 1277.6201; found: m/z 1277.6172.

*4.1.10.6. Benzyl oleanolate 3β-O-[2,3-di-O-(2,3,4-tri-O-benzoyl-α-L-rhamnopyranosyl)-4,6-di-O-benzylid-ene-β-D-glucopyranoside] (**54c**).* Yield: 20%; $[\alpha]_D^{20}$ +37.9 (c 0.64, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.16–7.97 (m, 40H, Ph–H), 5.86 (dd, J = 10.5, 3.7 Hz, 1H, H-3″), 5.79 (dd, J = 10.1, 3.2 Hz, 1H, H-3‴), 5.75 (dd, J = 3.2, 1.3 Hz, 1H, H-2″), 5.68 (t, J = 10.1 Hz, 1H, H-4″), 5.63 (dd, J = 3.2, 1.4 Hz, 1H, H-2‴), 5.62 (s, 1H, H-1‴), 5.58 (s, 1H, H-1″), 5.50 (t, J = 10.1 Hz, 1H, H-4‴), 5.37 (s, 1H, PhCH(O)), 5.30 (t, J = 3.2 Hz, 1H, H-12), 5.09 (dd, J = 34.3, 12.4 Hz, 2H, CH_2–Ph), 4.82 (d, J = 6.4 Hz, 1H, H-1′), 4.64–4.69 (dt, J = 12.4, 6.0 Hz, 1H, H-5″), 4.49 (dt, J = 12.4, 5.9 Hz, 1H, H-5‴), 4.40 (dd, J = 10.5, 5.0 Hz, 1H, H-6″-1), 4.24 (dd, J = 9.2, 7.3 Hz, 1H, H-3′), 4.10 (t-like, J = 7.3, 6.9 Hz, 1H, H-2″), 3.96 (t-like, J = 9.5, 9.2 Hz, 1H, H-4′), 3.82–3.88 (m, 1H, H-6′-2), 3.64 (td, J = 9.6, 4.6 Hz, 1H, H-5′), 3.32 (dd, J = 11.5, 4.1 Hz, 1H, H-3), 2.91 (dd, J = 13.7, 4.6 Hz, 1H, H-18), 1.37 (d, J = 6.0 Hz, 3H, H-6″), 0.88 (d, J = 5.9 Hz, 3H, H-6‴), 1.18, 1.14, 0.97, 0.92, 0.90, 0.89, 0.63 (s each, 3H each, CH_3 ×7); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 177.6 (C-28), 165.4, 165.3, 163.6, 143.8 (C-13), 137.2, 136.5, 132.9, 129.7, 128.4, 122.6 (C-12), 103.5 (C-1′), 102.2 (C-1″), 97.4 (PhC(O)), 97.1 (C-1‴), 91.9 (C-3), 89.1, 78.7, 77.5, 71.8, 70.0, 68.9, 67.1, 66.0, 55.9, 47.8, 46.9, 41.8, 39.2, 36.9, 33.2, 30.8, 28.3, 26.1, 25.8, 23.7, 17.5, 17.1, 15.5; HRMALDIMS: calcd for [M + Na^+] $C_{104}H_{112}O_{22}Na$: 1735.7564; found: m/z 1735.7538.

*4.1.11. General procedure for synthesizing compounds **14**–**26***

To a solution of **37**, **38**, **42**–**45**, **50**, **52a**–**c**, or **54a**–**c** (50 mg) in CH_2Cl_2–MeOH (V:V/1:1, 8 mL) was added 10% Pd–C (30 mg) and AcOH (2 drops) under 1 atm of H_2 for 4 h. The reaction mixture was then filtered and the filtrate was concentrated to dryness to give a white solid. The solid was dissolved in MeOH–CH_2Cl_2 (V:V/2:1, 8 mL), and then NaOMe (40 mg) was added. After stirring at room temperature for 8 h, the solution was neutralized with ion-exchange resin (H^+), then filtered and concentrated. The residue was purified by column chromatography on silica gel (3:1, $CHCl_3$–MeOH) to give the products **14**–**26**.

*4.1.11.1. Oleanolate 3β-O-β-D-xylopyranosyl-(1 → 3)-α-L-rhamnopyranosyl-(1 → 2)-α-L-arabinopyranoside (**14**).* Yield: 74% for two steps; $[\alpha]_D^{25}$ −4.30 (c 0.80, CH_3OH); Mp: 219–221 °C; IR (KBr) ν_{max} 3397, 2941, 1688, 1455, 1385, 1046 cm^{-1}; ^{1}H NMR (C_5D_5N, 600 MHz): δ 6.30 (br s, 1H, H-1″), 5.49 (t, J = 3.6 Hz, 1H, H-12), 5.39 (d, J = 7.4 Hz, 1H, H-1‴), 4.95 (br s, 1H, H-2″), 4.89 (d, J = 5.9 Hz, 1H, H-1′), 4.77 (dd, J = 9.6, 3.2 Hz, 1H, H-3″), 4.67 (dq, J = 9.6, 5.9 Hz, 1H, H-5″), 4.62 (t-like, J = 6.9, 6.4 Hz, 1H, H-2′), 4.52 (t-like, J = 9.7, 9.1 Hz, 1H, H-4″), 4.32–4.35 (m, 2H, H-4′, H-5‴-1), 4.26–4.30 (m, 2H, H-3′, H-5′-1), 4.23 (m, 1H, H-4‴), 4.19 (t-like, J = 8.7, 8.3 Hz, 1H, H-3‴), 4.11 (t, J = 8.2 Hz, 1H, H-2‴), 3.84 (d, J = 10.9 Hz, 1H, H-5′-2), 3.72 (t, J = 11.0 Hz, 1H, H-5‴-2), 3.30–3.33 (m, 3H, H-3, H-18), 1.57 (d, J = 6.0 Hz, 3H, H-6″), 1.34, 1.33, 1.16, 1.03, 1.00, 0.98, 0.85 (s each, 3H each, CH_3 ×7); ^{13}C NMR (C_5D_5N, 150 MHz): δ 180.8 (C-28), 145.3 (C-13), 122.5 (C-12), 107.9 (C-1‴), 105.8 (C-1′), 101.9 (C-1″), 89.3 (C-3), 83.4 (C-3″), 78.9, 76.1, 75.9, 73.5, 72.5, 71.6, 70.2, 67.9, 66.1, 56.5, 48.6, 47.2, 47.0, 42.7, 42.5, 40.3, 40.1, 39.4, 37.6, 34.8, 33.8, 33.7, 31.5, 30.5, 28.8, 28.7, 27.2, 26.7, 24.3, 18.9, 17.9, 17.7, 16.1; ESI-HRMS: m/z calcd for $C_{46}H_{73}O_{15}$ [M − H^+]: 865.4949; found: 865.4961.

*4.1.11.2. Oleanolate 3β-O-β-D-glucopyranosyl-(1 → 4)-β-D-xylopyranosyl-(1 → 3)-α-L-rhamnopyranosyl-(1 → 2)-α-L-arabinopyranoside (**15**).* Yield: 75% for two steps; $[\alpha]_D^{25}$ −17.9 (c 0.80, CH_3OH); IR (KBr) ν_{max} 3412, 2945, 1693, 1499, 1071 cm^{-1}; ^{1}H NMR (C_5D_5N, 500 MHz): δ 6.19 (s, 1H, H-1″), 5.49 (t, J = 3.6 Hz, 1H, H-12), 5.23 (d, J = 7.0 Hz, 1H, H-1‴), 5.01 (d, J = 7.9 Hz, 1H, H-1⁗), 4.87 (br s, 1H, H-2″), 4.85 (d, J = 5.0 Hz, 1H, H-1′), 4.67 (dd, J = 9.5, 3.0 Hz, 1H, H-3″), 4.60 (dq, J = 9.3, 5.5 Hz, 1H, H-5″), 4.53–4.56 (m, 2H, H-4″, H-6⁗-1), 4.47 (t, J = 9.5 Hz, 1H, H-3⁗), 4.37 (dd, J = 12.5, 2.7 Hz, 1H, H-6⁗-2), 4.24–4.33 (m, 5H, H-3′, H-4′, H-5′-1, H-4⁗, H-3⁗), 4.18 (t, J = 9.6 Hz, 1H, H-4⁗), 3.97–4.06 (m, 4H, H-2⁗, H-2⁗, H-5⁗-1, H-5⁗), 3.82 (dd, J = 12.1, 2.3 Hz, 1H, H-5⁗-2), 3.63 (m, 1H, H-5′-2), 3.28–3.31 (m, 2H, H-3, H-18), 1.55 (d, J = 6.0 Hz, 3H, H-6″), 1.29, 1.26, 1.10, 0.99, 0.96, 0.94, 0.82 (s each, 3H each, CH_3 ×7); ^{13}C NMR (C_5D_5N, 125 MHz): δ 180.2 (C-28), 145.0 (C-13), 122.7 (C-12), 106.8 (C-1‴), 104.9 (C-1′), 103.5 (C-1⁗), 101.4 (C-1″), 88.7 (C-3), 82.9 (C-3″), 78.7, 78.1, 77.7, 76.1, 75.5, 75.2, 74.2, 73.9, 72.7, 71.7, 71.6, 69.6, 64.7, 64.3, 62.6, 56.6, 48.0, 46.6, 46.4, 42.1, 41.9, 39.7, 39.5, 36.9, 34.2, 33.2, 33.1, 32.0, 30.9, 30.7, 29.8, 29.7, 29.5, 28.2, 28.1, 26.5, 26.1, 23.7, 23.6, 22.8, 18.4, 18.3, 17.3, 17.0, 15.4, 14.1; ESI-HRMS: m/z calcd for $C_{52}H_{83}O_{20}$ [M − H^+]: 1027.5478; found: 1027.5460.

*4.1.11.3. Oleanolic acid 3β-O-β-D-xylopyranosyl-(1 → 3)-α-L-rhamnopyranosyl-(1 → 2)-β-D-xylopyranoside (**16**).* Yield: 78% for 2 steps; $[\alpha]_D^{25}$ −3.82 (c 0.50, CH_3OH); IR (KBr) ν_{max} 3412, 2938, 1696, 1536, 1455, 1385, 1046 cm^{-1}; ^{1}H NMR (C_5D_5N, 600 MHz): δ 6.62 (br s, 1H, H-1″), 5.50 (br s, 1H, H-12), 5.44 (d, J = 7.8 Hz, 1H, H-1‴), 5.06 (br s, 1H, H-2″), 4.88 (d, J = 7.8 Hz, 1H, H-1′), 4.83–4.87 (m, 2H, H-2′, H-5″), 4.58 (t, J = 9.1 Hz, 1H, H-3′), 4.36–4.39 (m, 2H, H-4′, H-4‴), 4.30 (t, J = 8.8 Hz, 1H, H-4″), 4.21–4.27 (m, 5H, H-3‴, H-4″, H-5′-1, H-5‴-1, H-5‴-2), 4.14 (dd, J = 8.7, 7.3 Hz, 1H, H-2‴), 3.74–3.79 (m, 2H, H-3, H-5′-2), 3.39 (dd, J = 11.5, 4.1 Hz, 1H, H-18), 1.69 (d, J = 5.9 Hz, 3H, H-6″), 1.43, 1.35, 1.26, 1.05, 0.99, 0.99, 0.88 (s each, 3H each, CH_3 ×7); ^{13}C NMR (C_5D_5N, 150 MHz): δ = 176.9 (C-28), 145.8 (C-13), 123.8 (C-12), 108.3 (C-1‴), 106.9 (C-1′), 102.4 (C-1″), 89.4 (C-3), 83.8 (C-3″), 80.6, 79.4, 78.1, 76.5, 73.7, 72.7, 72.4, 72.0, 70.5, 68.3, 67.9, 57.0, 48.9, 43.0, 40.5, 37.9, 35.1, 34.2, 31.8, 29.2, 29.0, 27.7, 27.0, 24.6, 19.5, 18.1, 16.4; ESI-HRMS: m/z calcd for $C_{46}H_{73}O_{15}$ [M − H^+]: 865.4949; found: 865.4980.

*4.1.11.4. Oleanolic acid 3β-O-β-D-glucopyranosyl-(1 → 4)-β-D-glucopyranosyl (1 → 3)-α-L-rhamnopyranosyl-(1 → 2)-β-D-xylopyranoside (**17**).* Yield: 78% for 2 steps; $[\alpha]_D^{25}$ −5.86 (c 0.50, CH_3OH); IR

(KBr) ν_{max} 3397, 2945, 1692, 1459, 1389, 1042 cm^{-1}; ^1H NMR (C_5D_5N, 600 MHz): δ 6.51 (br s, 1H, H-1″), 5.49 (d, J = 7.3 Hz, 1H, H-1‴), 5.47 (br s, 1H, H-12), 5.05 (br s, 1H, H-2″), 4.85 (dd, J = 9.6, 3.5 Hz, 1H, H-3″), 4.82 (d, J = 7.3 Hz, 1H, H-1′), 4.79 (dq, J = 9.3, 5.5 Hz, 1H, H-5″), 4.54–4.58 (m, 3H, H-2′, H-4″, H-6⁗-1), 4.42 (dd, J = 12.1, 5.2 Hz, 1H, H-6⁗-1), 4.33–4.37 (m, 2H, H-4‴, H-6⁗-2), 4.26–4.30 (m, 2H, H-3′, H-4′), 4.13–4.22 (m, 5H, H-3‴, H-3⁗, H-4⁗, H-5′-1, H-6⁗-2), 4.10 (t, J = 8.3 Hz, 1H, H-2‴), 4.07 (t, J = 8.3 Hz, 1H, H-2⁗), 4.10 (m, 1H, H-5⁗), 3.95 (m, 1H, H-5‴), 3.72 (m, 1H, H-5′-2), 3.32 (m, 2H, H-3, H-18), 1.67 (d, J = 5.9 Hz, 3H, H-6″), 1.39, 1.32, 1.22, 1.03, 0.98, 0.98, 0.86 (s each, 3H each, CH_3 ×7); ^{13}C NMR (C_5D_5N, 150 MHz): δ 178.9 (C-28), 145.5 (C-13), 122.9 (C-12), 107.0 (C-1‴), 106.7 (C-1′), 105.5 (C-1⁗), 102.1 (C-1″), 89.0 (C-3), 83.9 (C-3″), 81.6, 79.9, 79.0, 78.8, 77.3, 75.9, 75.3, 73.5, 72.0, 67.5, 62.9, 62.3, 56.6, 48.6, 47.2, 47.0, 42.7, 42.5, 40.3, 39.4, 37.6, 33.8, 31.5, 28.9, 28.7, 27.2, 26.7, 24.3, 19.2, 19.0, 17.9, 17.8, 16.1; ESI-HRMS: m/z calcd for $C_{53}H_{85}O_{21}$ [M − H^+]: 1057.5583; found: 1057.5569.

*4.1.11.5. Oleanolic acid 3β-O-α-L-rhamnopyranosyl-(1 → 3)-α-L-rhamnopyranosyl-(1 → 2)-β-D-xylopyranoside (**18**).* Yield: 73% for 2 steps; $[\alpha]_D^{25}$ −11.1 (*c* 0.65, CH_3OH); IR (KBr) ν_{max} 3350, 2922, 1595, 1544, 1424, 1042, 704 cm^{-1}; ^1H NMR (C_5D_5N, 600 MHz): δ 6.60 (br s, 1H, H-1″), 6.11 (br s, 1H, H-1‴), 5.47 (br s, 1H, H-12), 4.99 (br s, 1H, H-2″), 4.86 (d, J = 6.8 Hz, 1H, H-1′), 4.78–4.84 (m, 3H, H-2‴, H-3″, H-5‴), 4.74 (dq, J = 9.1, 6.4 Hz, 1H, H-5″), 4.67 (dd, J = 9.1, 3.2 Hz, 1H, H-5′-1), 4.49 (t, J = 9.6 Hz, 1H, H-4′), 4.30–4.36 (m, 3H, H-3′, H-3‴, H-4″), 4.27 (dd, J = 8.7, 7.2 Hz, 1H, H-2′), 4.19 (m, 1H, H-4′), 3.74 (t, J = 11.0 Hz, 1H, H-5′-2), 3.30–3.36 (m, 2H, H-3, H-18), 1.69 (d, J = 6.4 Hz, 3H, H-6‴), 1.62 (d, J = 6.4 Hz, 3H, H-6″), 1.38, 1.32, 1.23, 1.02, 0.97, 0.97, 0.85 (s each, 3H each, CH_3 ×7); ^{13}C NMR (C_5D_5N, 150 MHz): δ 176.4 (C-28), 143.5 (C-13), 123.7 (C-12), 106.5 (C-1′), 104.7 (C-1‴), 101.9 (C-1″), 89.0 (C-3), 80.1 (C-3″), 80.0 (C-3‴), 78.7, 74.7, 73.1, 72.8, 72.6, 72.4, 70.0, 68.5, 56.6, 49.3, 42.5, 40.1, 39.9, 37.4, 33.7, 31.3, 30.3, 28.7, 26.5, 24.2, 19.0, 17.6, 15.9; ESI-HRMS: m/z calcd for $C_{47}H_{75}O_{15}$ [M − H^+]: 879.5106; found: 879.5103.

*4.1.11.6. Oleanolic acid 3-O-α-L-rhamnopyranosyl-(1 → 2)-β-D-xylopyranoside (**19**).* Yield: 65% for 2 steps; $[\alpha]_D^{20}$ +5.96 (*c* 0.62, CH_3OH); ^1H NMR (CD_3OD, 600 MHz): δ 5.35 (s, 1H, H-1″), 5.27 (br s, 1H, H-12), 4.41 (d, J = 6.1 Hz, 1H, H-1′), 3.95–3.98 (m, 2H, H-2″, H-5‴), 3.87 (dd, J = 11.6, 5.5 Hz, 1H, H-5′-1), 3.25 (dd, J = 9.9, 3.3 Hz, 1H, H-3″), 3.48–3.51 (m, 1H, H-4′), 3.39–3.46 (m, 3H, H-2′, H-3′, H-5′-2), 3.20 (t, J = 9.9 Hz, 1H, H-4″), 3.14 (dd, J = 12.1, 4.4 Hz, 1H, H-3), 2.88 (dd, J = 13.7, 4.4 Hz, 1H, H-18), 1.25 (d, J = 6.0 Hz, 3H, H-6″), 1.19, 1.07, 0.97, 0.97, 0.94, 0.89, 0.85 (s each, 3H each, CH_3 ×7); ^{13}C NMR (CD_3OD, 150 MHz): δ 143.9 (C-13), 122.3 (C-12), 104.9 (C-1′), 100.6 (C-1″), 88.8 (C-3), 77.5, 77.3, 72.7, 70.8, 70.3, 68.7, 55.9, 41.6, 40.9, 39.3, 38.9, 36.6, 32.7, 32.3, 30.3, 27.2, 25.1, 22.7, 18.0, 16.7, 15.8, 14.7; ESI-HRMS: m/z calcd for [M + Na]$^+$ $C_{41}H_{66}O_{11}Na$: 757.4503; found: 757.4509.

*4.1.11.7. Oleanolic acid 3β-O-α-L-rhamnopyranosyl-(1 → 2)-β-L-arabinopyranoside (**20**).* Yield: 74% for 2 steps; $[\alpha]_D^{20}$ +78.3 (*c* 0.84, CH_3OH); IR (KBr) ν_{max} 3420, 2941, 1688, 1455, 1139, 1066 cm^{-1}; ^1H NMR (CD_3OD, 600 MHz): δ 5.24 (t, J = 3.3 Hz, 1H, H-12), 5.05 (d, J = 3.3 Hz, 1H, H-1′), 4.95 (d, J = 1.1 Hz, 1H, H-1″), 3.95 (dd, J = 3.3, 1.6 Hz, 1H, H-2″), 3.91 (dd, J = 9.9, 3.3 Hz, 1H, H-3′), 3.87 (m, 2H, H-2′, H-4′), 3.85 (dd, J = 9.8, 3.3 Hz, 1H, H-5′-1), 3.75 (qd, J = 9.9, 6.0 Hz, 1H, H-5″), 3.66 (dd, J = 9.4, 3.3 Hz, 1H, H-3″), 3.57 (dd, J = 12.1, 1.6 Hz, 1H, H-5′-2), 3.40 (t-like, J = 9.9, 9.3 Hz, 1H, H-4″), 3.20 (dd, J = 12.1, 4.4 Hz, 1H, H-3), 2.84 (dd, J = 12.1, 3.8 Hz, 1H, H-18), 1.26 (d, J = 6.0 Hz, 3H, H-6″), 1.16, 1.03, 0.96, 0.94, 0.91, 0.85, 0.82 (s each, 3H each, CH_3 ×7); ^{13}C NMR (CD_3OD, 150 MHz): δ 182.1 (C-28), 145.4 (C-13), 123.7 (C-12), 103.8 (C-1″), 96.0 (C-1′), 83.3 (C-3), 77.3, 73.9, 72.5, 72.2, 71.4, 70.3, 64.8, 64.4, 57.2, 47.8, 47.4, 43.0, 42.9, 40.7, 39.8, 39.5, 38.3, 35.1, 34.2, 34.0, 33.7, 31.8, 29.4, 29.0, 26.6, 24.7, 24.2, 24.1, 22.8, 19.6, 18.2, 17.9, 17.4, 16.1; ESI-HRMS: m/z calcd for [M − H^+] $C_{41}H_{65}O_{11}$: 733.4527; found: 733.4543.

*4.1.11.8. Oleanolic acid 3-O-α-L-rhamnopyranosyl-(1 → 2)-β-D-galactopyranoside (**21**).* Yield: 56% for two steps; $[\alpha]_D^{20}$ −11.6 (*c* 0.64, CH_3OH); ^1H NMR (CD_3OD, 600 MHz): δ 5.24 (t, J = 3.7 Hz, 1H, H-12), 5.05 (d, J = 1.9 Hz, 1H, H-1″), 4.31 (d, J = 7.8 Hz, 1H, H-1′), 3.96 (dd, J = 3.8, 1.4 Hz, 1H, H-2″), 3.92 (d, J = 3.2 Hz, 1H, H-4′), 3.75–3.79 (m, 2H, H-3″, H-5″), 3.69–3.73 (m, 2H, H-6′-1, H-6′-2), 3.65 (dd, J = 9.7, 7.8 Hz, 1H, H-2′), 3.51 (dd, J = 9.6, 3.2 Hz, 1H, H-3′), 3.49 (t-like, J = 6.4, 5.9 Hz, 1H, H-5′), 3.39 (t-like, J = 9.7, 9.1 Hz, 1H, H-4″), 3.18 (dd, J = 11.5, 4.1 Hz, 1H, H-3), 2.86 (dd, J = 13.3, 3.2 Hz, 1H, H-18), 2.01 (dt, J = 14.2, 3.7 Hz, 1H, H-16), 1.24 (d, J = 6.4 Hz, 3H, H-6″), 1.16, 1.06, 0.95, 0.94, 0.91, 0.84, 0.81 (s each, 3H each, CH_3 × 7); ^{13}C NMR (CD_3OD, 150 MHz): δ 144.0 (C-13), 122.3 (C-12), 104.8 (C-1′), 100.7 (C-1″), 88.9 (C-3), 75.0, 74.9, 72.7, 70.7, 69.7, 61.1, 60.9, 56.1, 41.6, 39.3, 36.6, 32.7, 32.3, 30.3, 27.2, 25.1, 23.2, 22.7, 18.0, 16.7, 15.9, 14.7; ESI-HRMS: m/z calcd for [M + H]$^+$ $C_{42}H_{69}O_{12}$: 765.4789; found: 765.4783.

*4.1.11.9. Oleanolic acid 3-O-α-L-rhamnopyranosyl-(1 → 3)-β-D-galactopyranoside (**22**).* Yield: 58% for two steps; $[\alpha]_D^{20}$ +5.43 (*c* 0.56, CH_3OH); ^1H NMR (CD_3OD, 600 MHz): δ 5.37 (s, 1H, H-1″), 5.27 (t, J = 3.6 Hz, 1H, H-12), 4.40 (d, J = 7.7 Hz, 1H, H-1′), 3.98–4.03 (m, 2H, H-2″, H-5″), 3.80 (d, J = 3.3 Hz, 1H, H-4′), 3.78 (dd, J = 9.9, 3.3 Hz, 1H, H-3′), 3.74 (dd, J = 5.5, 2.8 Hz, 1H, H-3″), 3.70 (t-like, J = 8.8, 7.7 Hz, 1H, H-2′), 3.60–3.63 (m, 2H, H-6′-1, H-6′-2), 3.50 (t-like, J = 6.6, 6.1 Hz, 1H, H-5′), 3.41 (t-like, J = 9.9, 9.3 Hz, 1H, H-4″), 3.20 (dd, J = 12.1, 4.4 Hz, 1H, H-3), 2.87 (dd, J = 13.5, 3.2 Hz, 1H, H-18), 1.24 (d, J = 6.6 Hz, 3H, H-6″), 1.19, 1.08, 0.97, 0.97, 0.94, 0.89, 0.84 (s each, 3H each, CH_3 ×7); ^{13}C NMR (CD_3OD, 150 MHz): δ 143.9 (C-13), 122.3 (C-12), 105.9 (C-1′), 102.6 (C-1″), 89.5 (C-3), 80.5, 74.8, 72.8, 71.4, 70.8, 68.8, 60.8, 55.8, 41.4, 39.3, 38.3, 36.6, 32.3, 27.3, 25.7, 25.1, 23.2, 22.7, 16.7, 16.4, 15.7, 14.6; ESI-HRMS: m/z calcd for [M + Na]$^+$ $C_{42}H_{68}O_{12}Na$: 787.4608; found: 787.4595.

*4.1.11.10. Oleanolic acid 3-O-2,3-di-O-(α-L-rhamnopyranosyl)-4,6-di-O-benzylidene-β-D-galactopyranoside (**23**).* Yield: 51% for two steps; $[\alpha]_D^{20}$ −2.72 (*c* 0.75, CH_3OH); ^1H NMR (CD_3OD, 600 MHz): δ 5.56 (br s, 1H, PhC<u>H</u>O), 5.24 (t, J = 3.8 Hz, 1H, H-12), 5.13 (d, J = 1.1 Hz, 1H, H-1″), 4.90 (s, 1H, H-1‴), 4.53 (d, J = 7.7 Hz, 1H, H-1′), 4.38 (d, J = 3.3 Hz, 1H, H-4′), 3.97 (dq, J = 9.4, 6.1 Hz, 1H, H-5″), 3.91 (dd, J = 3.3, 1.2 Hz, 1H, H-2‴), 3.88 (br s, 1H, H-2″), 3.83–3.86 (m, 2H, H-2′, H-5‴), 3.77 (dd, J = 9.9, 3.3 Hz, 1H, H-3′), 3.68 (dd, J = 9.4, 3.3 Hz, 1H, H-3″), 3.66 (dd, J = 9.4, 3.3 Hz, 1H, H-3‴), 3.54 (br s, 1H, H-6′-2), 3.39 (t, J = 9.9 Hz, 1H, H-4‴), 3.36 (t, J = 9.3 Hz, 1H, H-4″), 3.20 (dd, J = 12.1, 4.4 Hz, 1H, H-3), 2.86 (dd, J = 13.7, 3.8 Hz, 1H, H-18), 1.21 (d, J = 6.0 Hz, 3H, H-6″), 1.19 (d, J = 6.1 Hz, 3H, H-6‴), 1.17, 1.08, 0.96, 0.94, 0.91, 0.89, 0.82 (s each, 3H each, CH_3 ×7); ^{13}C NMR (CD_3OD, 150 MHz): δ 182.6 (C-28), 162.7, 145.4 (C-13), 139.7, 130.0, 129.2, 127.6, 123.7 (C-12), 106.0 (C-1′), 104.9 (C-1‴), 102.7 (C-1″), 102.4 (Ph<u>C</u>HO), 90.8 (C-3), 84.4 (C-3″), 77.6 (C-3‴), 75.6, 74.0, 73.7, 72.5, 72.4, 71.9, 70.7, 70.5, 67.7, 57.6, 43.1, 42.9, 40.7, 40.5, 40.3, 38.1, 35.1, 34.2, 33.8, 31.8, 29.0, 28.6, 27.4, 26.6, 24.7, 24.2, 19.5, 18.3, 18.2, 18.0, 17.2, 16.2; HRMALDIMS: calcd for [M + Na^+] $C_{55}H_{82}O_{16}Na$: 1021.5507; found: m/z 1021.5495.

*4.1.11.11. Oleanolic acid 3-O-α-L-rhamnopyranosyl-(1 → 2)-β-D-glucopyranoside (**24**).* Yield: 55% for two steps; $[\alpha]_D^{20}$ +5.95 (*c* 1.00, CH_3OH); ^1H NMR (CD_3OD, 600 MHz): δ 5.37 (s, 1H, H-1″), 5.24 (t, J = 3.6 Hz, 1H, H-12), 4.41 (d, J = 7.7 Hz, 1H, H-1′), 3.98 (td, J = 9.4, 6.1 Hz, 1H, H-5″), 3.95 (dd, J = 3.4, 1.6 Hz, 1H, H-2″), 3.83 (dd, J = 11.5, 1.6 Hz, 1H, H-6′-1), 3.74 (dd, J = 9.3, 3.3 Hz, 1H, H-3″), 3.66

(dd, J = 12.1, 5.5 Hz, 1H, H-6′-2), 3.46 (t, J = 8.8 Hz, 1H, H-3′), 3.41 (t-like, J = 8.8, 7.7 Hz, 1H, H-2′), 3.38 (t-like, J = 9.8, 9.4 Hz, 1H, H-4″), 3.29 (t, J = 8.8 Hz, 1H, H-1-4′), 3.21–3.24 (m, 1H, H-5′), 3.18 (dd, J = 12.1, 4.4 Hz, 1H, H-3), 2.86 (dd, J = 14.3, 3.8 Hz, 1H, H-18), 1.21 (d, J = 6.6 Hz, 3H, H-6″), 1.16, 1.05, 0.95, 0.94, 0.91, 0.86, 0.82 (s each, 3H each, CH_3 ×7); ^{13}C NMR (CD_3OD, 150 MHz): δ 143.9 (C-13), 122.3 (C-12), 104.3 (C-1′), 100.5 (C-1″), 88.9 (C-3), 78.2, 77.6, 76.3, 70.8, 70.7, 68.7, 61.5, 56.0, 41.6, 39.3, 38.9, 36.6, 32.3, 30.3, 27.5, 25.9, 25.1, 22.7, 16.7, 16.4, 15.9, 14.7; ESI-HRMS: m/z calcd for $[M + Na]^+$ $C_{42}H_{68}O_{12}Na$: 787.4608; found: 787.4584.

*4.1.11.12. Oleanolic acid 3-O-α-L-rhamnopyranosyl-(1 → 3)-β-D-glucopyranoside (**25**).* Yield: 54% for two steps; $[\alpha]_D^{20}$ +2.90 (*c* 0.65, CH_3OH); ^{1}H NMR (CD_3OD, 600 MHz): δ 5.27 (br s, 1H, H-12), 5.17 (s, 1H, H-1″), 4.35 (d, J = 8.2 Hz, 1H, H-1′), 4.01 (dq, J = 9.4, 6.6 Hz, 1H, H-5″), 3.97 (br s, 1H, H-2″), 3.86 (dd, J = 10.9, 3.5 Hz, 1H, H-6′-1), 3.71 (ddd, J = 9.4, 5.0, 3.3 Hz, 1H, H-5′), 3.49 (t, J = 8.8 Hz, 1H, H-3′), 3.42 (t-like, J = 9.9, 9.3 Hz, 1H, H-4″), 3.36 (t-like, J = 9.4, 9.3 Hz, 1H, H-2′), 3.28–3.32 (m, 2H, H-4′, H-6′-2), 3.21 (dd, J = 11.6, 4.4 Hz, 1H, H-3), 2.89 (dd, J = 12.1, 3.3 Hz, 1H, H-18), 1.27 (d, J = 6.1 Hz, 3H, H-6″), 1.19, 1.08, 0.98, 0.97, 0.93, 0.87, 0.84 (s each, 3H each, CH_3 ×7); ^{13}C NMR (CD_3OD, 150 MHz): δ 143.9 (C-13), 122.3 (C-12), 105.2 (C-1′), 101.6 (C-1″), 89.6 (C-3), 83.7, 74.8, 72.9, 71.1, 70.9, 69.0, 68.8, 61.4, 55.7, 41.6, 39.3, 38.8, 38.5, 36.6, 32.3, 30.3, 27.3, 25.1, 23.2, 22.7, 18.0, 16.6, 15.7, 14.6; ESI-HRMS: m/z calcd for $[M + H]^+$ $C_{42}H_{69}O_{12}Na$: 765.4789; found: 765.4806.

*4.1.11.13. Oleanolic acid 3-O-2,3-di-O-(α-L-rhamnopyranosyl)-β-D-glucopyranoside (**26**).* Yield: 57% for two steps; $[\alpha]_D^{20}$ −1.49 (*c* 0.75, CH_3OH); ^{1}H NMR (CD_3OD, 600 MHz): δ 5.24 (br s, 1H, H-12), 5.13 (s, 1H, H-1″), 4.92 (s, 1H, H-1‴), 4.48 (d, J = 7.1 Hz, 1H, H-1′), 3.99 (br s, 1H, H-2″), 3.90–3.96 (m, 3H, H-2‴, H-5′, H-5‴), 3.84–3.86 (m, 2H, H-3‴, H-4′), 3.64–3.71 (m, 3H, H-4″, H-5′, H-6′-1), 3.58 (t-like, J = 8.8, 8.3 Hz, 1H, H-3″), 3.42–3.49 (m, 3H, H-2′, H-4‴, H-6′-2), 3.39 (t-like, J = 9.9, 9.4 Hz, 1H, H-3′), 3.22 (dd, J = 12.1, 4.4 Hz, 1H, H-3), 2.87 (dd, J = 13.2, 3.3 Hz, 1H, H-18), 1.27 (d, J = 6.6 Hz, 3H, H-6″), 1.22 (d, J = 6.1 Hz, 3H, H-6‴), 1.16, 1.05, 0.95, 0.94, 0.91, 0.87, 0.82 (s each, 3H each, CH_3 ×7); ^{13}C NMR (CD_3OD, 150 MHz): δ 144.2 (C-13), 122.2 (C-12), 104.0 (C-1′), 102.2 (C-1‴), 100.7 (C-1″), 88.8 (C-3), 86.9, 77.4,76.1, 72.2, 71.9, 70.8, 70.5, 69.8, 68.9, 63.0, 61.3, 56.0, 41.6, 39.3, 39.0, 36.6, 32.5, 32.3, 30.3, 27.2, 25.1, 23.2, 22.7, 16.7, 16.5, 15.8, 14.7; ESI-HRMS: m/z calcd for $[M + Na]^+$ $C_{48}H_{78}O_{16}Na$: 933.5188; found: 933.5175.

4.2. Cytotoxic assay

The cytotoxicity of all synthesized oleanolic acid saponins was examined using a panel of human tumor cell lines, including one human promyelotic leukemia cell line (HL-60), one human non-small-cell lung cancer cell line (A549) and one human melanoma cancer cell lines (A375). Cells were seeded into 96-well plates and treated in triplicate with gradient concentrations of tested compounds at 37 °C for 72 h. Cytotoxicity to HL-60 cells was assessed by MTT assay, and cytotoxicity to A549 and A375 was assessed by SRB assay as previous described [34,35]. The cytotoxicity of tested compounds was expressed as an IC_{50}, determined by the Logit method from at least three independent experiments.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2013.04.016.

References

[1] K.R. Price, I.T. Johnson, G.R. Fenwick, CRC Crit. Rev. Food Sci. Nutr. 26 (1987) 27–133.
[2] R.A. Hill, J.D. Connolly, Nat. Prod. Rep. 28 (2011) 1087–1117.
[3] K. Papadopoulou, R.E. Melton, M. Legget, M.J. Daniels, A.E. Osbourn, Proc. Natl. Acad. Sci. U. S. A. 96 (1999) 12923–12928.
[4] K. Hostettmann, A. Marston, Saponins, Cambridge University Press, Cambridge, UK, 1995.
[5] L.P. Christensen, M. Jensen, U. Kidmose, J. Agric. Food Chem. 54 (2006) 8995–9003.
[6] K. Haralampidis, M. Trojanowska, A.E. Osbourn, Adv. Biochem. Eng. Biotechnol. 75 (2002) 31–49.
[7] B. Yu, J.S. Sun, Chem. J. Asian 4 (2009) 642–654.
[8] B. Yu, J.S. Sun, X.Y. Yang, Acc. Chem. Res. 45 (2012) 1227–1236.
[9] B. Yu, Y.C. Zhang, P.P. Tang, Eur. J. Org. Chem. 31 (2007) 5145–5161.
[10] C. Gauthier, J. Legault, A. Pichette, Mini-Rev. Org. Chem. 6 (2009) 321–344.
[11] J. Liu, J. Ethnopharmacol. 49 (1995) 57–68.
[12] Á. Guinda, M. Rada, T. Delgado, P. Gutiérrez-Adánez, J. Agric. Food Chem. 58 (2010) 9685–9691.
[13] H.Y. Cheung, Q.F. Zhang, J. Chromatogr. A 1213 (2008) 231–238.
[14] D.W. Jeong, Y.H. Kim, H.H. Kim, H.Y. Ji, S.D. Yoo, W.R. Choi, S.M. Lee, C.K. Han, H.S. Lee, Biopharm. Drug Dispos. 28 (2007) 51–57.
[15] F. Cao, J.H. Jia, Z. Yin, Y.H. Gao, L. Sha, Y.S. Lai, Q.N. Ping, Y.H. Zhang, Mol. Pharm. 9 (2012) 2127–2135.
[16] X.A. Wen, H.B. Sun, J. Liu, K.G. Cheng, P. Zhang, L.Y. Zhang, J. Hao, L.Y. Zhang, P.Z. Ni, S.E. Zographos, D.D. Leonidas, K.M. Alexacou, T. Gimisis, J.M. Hayes, N.G. Oikonomakos, J. Med. Chem. 51 (2008) 3540–3554.
[17] T.T. Guo, Q.C. Liu, P. Wang, L. Zhang, W. Zhang, Y.X. Li, Carbohydr. Res. 344 (2009) 1167–1174.
[18] Q.C. Liu, P. Wang, L. Zhang, T.T. Guo, G.K. Lv, Y.X. Li, Carbohydr. Res. 344 (2009) 1176–1181.
[19] Q.C. Liu, L. Zhang, X.P. Li, T.T. Guo, P. Wang, Y.X. Li, J. Carbohydr. Chem. 28 (2009) 506–519.
[20] T.T. Guo, Q.C. Liu, L. Zhang, P. Wang, Y.X. Li, Synth. Commun. 41 (2011) 357–371.
[21] M.S. Cheng, M.C. Yan, Y. Liu, L.G. Zheng, J. Liu, Carbohydr. Res. 341 (2005) 60–67.
[22] Q. Zheng, K. Koike, T. Nikaido, J. Nat. Prod. 67 (2004) 604–613.
[23] D. Panov, V. Grishkovets, V. Kachala, A.S. Shashkov, Chem. Nat. Compd. 42 (2006) 49–54.
[24] T. Kanchanapoom, R. Kasai, K. Yamasaki, Chem. Pharm. Bull. 49 (2001) 1195–1197.
[25] J. Tian, F. Wu, M. Qiu, R. Nie, Phytochemistry 32 (1993) 1539–1542.
[26] N. Ding, Z.H. Zhang, W. Zhang, Y.X. Chun, P. Wang, H.M. Qi, S. Wang, Y.X. Li, Carbohydr. Res. 346 (2011) 2126–2135.
[27] G.P. Song, H.C. Liu, W. Zhang, M.Y. Geng, Y.X. Li, Bioorg. Med. Chem. 18 (2010) 5183–5193.
[28] C.S. Yu, H.Y. Wang, L.W. Chiang, K. Pei, Synthesis 9 (2007) 1412–1420.
[29] R.F. Helm, J. Ralph, L. Anderson, J. Org. Chem. 56 (1991) 7015–7021.
[30] Q.C. Liu, Z. Fan, D. Li, W.H. Li, T.T. Guo, J. Carbohydr. Chem. 29 (2010) 386–402.
[31] D. Zheng, L. Zhou, Y.Y. Guan, X.Z. Chen, W.Q. Zhou, X.G. Chen, P.S. Lei, Bioorg. Med. Chem. Lett. 20 (2010) 5439–5442.
[32] C.S. Zhu, P.P. Tang, B. Yu, J. Am. Chem. Soc. 130 (2008) 5872–5873.
[33] M.C. Yan, Y. Liu, H. Chen, Y. Ke, Q.C. Xu, M.S. Cheng, Bioorg. Med. Chem. Lett. 16 (2006) 4200–4204.
[34] Z. Tao, Y. Zhou, J. Lu, W. Duan, Y. Qin, X. He, L. Lin, J. Ding, Cancer Biol. Ther. 6 (2007) 691–696.
[35] H.R. Lu, H. Zhu, M. Huang, Y. Chen, Y.J. Cai, Z.H. Miao, J.S. Zhang, J. Ding, Mol. Pharmacol. 68 (2005) 983–994.