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Synthesis of two natural betulinic acid saponins containing α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranose and their analogues

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ABSTRACT

A concise synthesis of naturally occurring betulinic acid saponins bearing an α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranoside moiety at the C-3 position is described. Betulinic acid 3β-*O*-α-L-rhamnopyranosyl-(1→2)-[β-D-glucopyranosyl-(1→4)]-α-L-arabinopyranoside isolated from *Pulsatilla koreana* and 28-*O*-β-D-glucopyranosyl betulinic acid 3β-*O*-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranoside isolated from *Schefflera rotundifolia* were easily synthesized for the first time using a stepwise glycosidation approach. The overall syntheses involved eight linear steps starting from allyl betulinate and commercially available L-arabinose, L-rhamnose and D-glucose. The syntheses of betulin and betulinic acid *O*-glycoside analogues containing an α-L-arabinose moiety are also reported. These results open the way to the synthesis of various lupane-type saponin derivatives as potentially bioactive compounds.

1. Introduction

Natural products (NPs) have attracted increased attention over the last century as an important source of new drug leads for the pharmaceutical industry.[1–4] In the domain of cancer research, 47% of antitumour compounds approved from 1940 to 2006 are either NPs or their semi-synthetic derivatives.[5] Saponins are a specific class of NPs widely distributed in the plant kingdom, which consist of a triterpenoid or steroid skeleton bearing one or more sugar chains.[6] They exhibit numerous pharmacological and biological properties such as anti-inflammatory,[7] haemolytic,[8] cytotoxic and antitumour[9] activities. Since many commonly used traditional Chinese drugs are rich in saponins,[10] some authors considered them responsible along with polyphenols for the majority of biological effects observed in the Chinese medical literature.[11] However, the isolation of saponins from plant extracts is often a long and fastidious process and usually only small amounts of products are obtained in a pure and homogeneous form.[12] Therefore, chemical syntheses are needed and appear to be a realistic way to gain access to a broad library of saponin glycoforms in order to study the structure–activity relationships (SARs) of this important class of NPs.[13]

Betulin (**1**) and its C-28 carboxylic derivative betulinic acid (**2**) (Fig. 1) are naturally occurring pentacyclic lupane-type triterpenoids that possess multiple pharmacological activities.[14,15] Betulinic acid (**2**) has the ability to inhibit the growth of various cancerous cell lines in vitro without affecting normal cells.[16] The in vivo antitumour activity of betulinic acid (**2**) was also confirmed whereas no other toxicity was observed on tumour-bearing mice at doses of 500 mg/kg body weight after intraperitoneal injections.[17,18] Thus, due to the selective cytotoxicity and favourable therapeutic index, which are in contrast with the majority of antitumour agents actually used in chemotherapy, betulinic acid (**2**) is considered a promising anticancer agent.[19,20] Nonetheless, further clinical development of betulin (**1**), betulinic acid (**2**) and lupane-type analogues is strongly hampered since they are virtually insoluble in water (0.02 μg/mL for **2**)[21,22] and possess high partition coefficient values (log P>6), which complicate the preparation of injectable formulations for biological assays and decrease their bioavailability in the organism.[23] The introduction of polar groups at either C-3 or C-28 positions such as phthalates,[24] amino acids[25,26] or sugar moieties[27,28] is an interesting avenue to increase the hydrosolubility of lupane-type triterpenoids **1** and **2**. Recently, our preliminary SAR studies have shown that adding an α-L-rhamnopyranose moiety at the C-3 position of **2** resulted in a significant increase of both the water solubility and the in vitro cytotoxic activity against human lung carcinoma (A549) and human colon adenocarcinoma (DLD-1) cancer cell lines.[27] Therefore, it was

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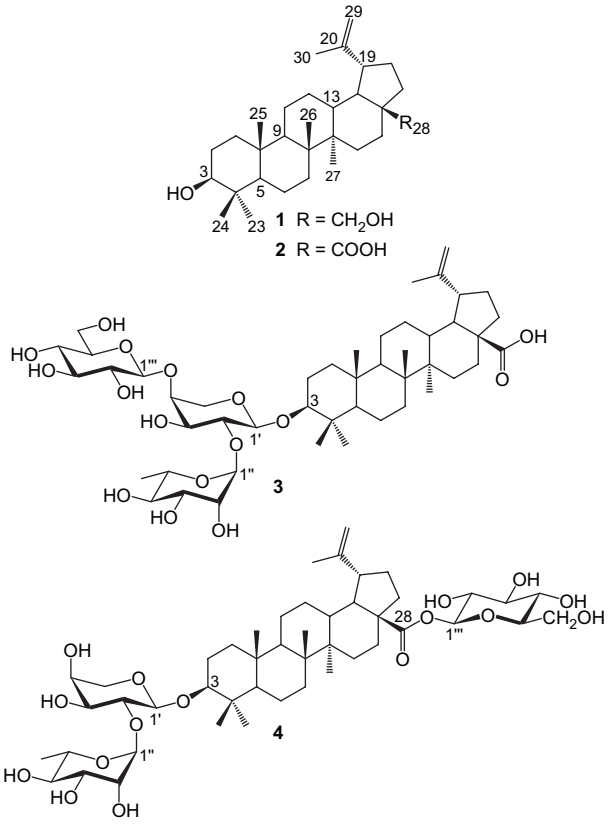


Figure 1. Structures of betulin (**1**), betulinic acid (**2**) and natural betulinic acid saponins (**3**, **4**).

postulated that betulinic acid saponins represent an interesting class of potent anticancer agents and require additional investigations.

Lupane-type saponins having betulin (**1**) or betulinic acid (**2**) as aglycones are rarely isolated from a natural source[29–31] and their chemical syntheses are very scarce in the literature.[27,28,32–37] Betulinic acid 3β-*O*-α-L-rhamnopyranosyl-(1→2)-[β-D-glucopyranosyl-(1→4)]-α-L-arabinopyranoside (**3**) (Fig. 1) is a naturally occurring monodesmosidic saponin isolated from the roots of *Pulsatilla koreana*, which is a plant widely used in Chinese traditional medicine for the treatment of malaria, amoebic dysentery and various cancers.[31] Saponin **3** exhibited moderate in vitro cytotoxicity against A549, SK-OV-3, SK-MEL-2 and HCT15 cancer cell lines and significant in vivo anticancer activity against BDF1 mice bearing Lewis lung carcinoma (LLC).[38,39] The particular trisaccharide chain at the C-3 position of saponin **3** has been shown to be a nontoxic moiety, which would increase the activity and water solubility once conjugated to NPs.[40] Another similar naturally occurring bidesmosidic saponin, 28-*O*-β-D-glucopyranosyl betulinic acid 3β-*O*-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranoside (**4**) (Fig. 1) isolated from the aerial parts of *Schefflera rotundifolia*, a plant used as folk remedies for the treatment of pain, rheumatic arthritis and lumbago in Asian countries, exhibited noticeable antiproliferative activity against J774.A1, WEHI-164 and HEK-293 cancer cell lines (IC_{50} 0.32–0.79 μM).[30] Furthermore, betulinic acid and 23-hydroxybetulinic acid saponins bearing an α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranose moiety at the C-3 position have already been isolated from *Pulsatilla chinensis*, which is one of the most well-known plants used in traditional Chinese medicine.[29,41–43] Hence, as part of our efforts to prepare lupane-type saponins as anticancer agents,[27,28] this report describes the first synthesis of two naturally occurring betulinic acid saponins (**3**, **4**). The syntheses of betulin (**15a**, **15b**, **23a**) and betulinic acid (**19a**, **19b**, **23b**) saponin analogues containing α-L-arabinose are also reported.

2. Results and discussion

To our knowledge, the synthesis of betulinic acid saponins bearing a unique α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranosyl moiety at the C-3 position such as natural saponins **3** and **4** has never been reported until now. Two general synthetic approaches exist in the literature for this particular type of intersugar linkage.[13] One strategy consists in preparing the disaccharide donor followed by coupling with the triterpene or steroid aglycone.[44,45] Since, in this case, the arabinose residue does not contain a neighbouring participating group at the C-2 position, the main inconvenience of this convergent glycosidation is the formation of an α/β anomeric mixture, which complicates the further purification of intermediates.[13,44,45] In this work, we adopted the stepwise glycosidation approach in which the arabinose residue containing a C-2 neighbouring participating group was first coupled with the aglycone. This linear strategy was shown to form a stereospecific 1,2-trans glycosidic bond[13] usually found in the linkage of natural triterpenoid saponins.[12] Moreover, stepwise extension of the sugar chain allows the preparation of a great variety of analogues by simply altering the monosaccharide donors.[46] Thus, such an approach to provide saponin glycoforms may be of further interest for studies regarding the SAR of natural and non-natural saponins and their development as pharmaceutical or biological agents.

Saponins **3** and **4** can be retrosynthetically (Fig. 2) disconnected into distinct fragments: the natural lupane-type betulinic acid (**2**) and the commercially available monosaccharides L-arabinose, L-rhamnose and D-glucose. As shown in Figure 2, the benzoyl participating groups were selected as protecting groups for the sugar donors **5**–**8** since they avoid the formation of trans-esterification products[47,48] in comparison with the acetyl groups and can be easily removed under alkaline conditions without hydrolysis of the C-28 ester in the aglycone.[49] In addition, the anomeric position of sugar donors **5**, **6** and **8** was activated by the trichloroacetimidate (TCA) group, which was first devised by R.R. Schmidt in the early 1980s[50] and shown to be ideal donors for the coupling with steroids and triterpenoids using various Lewis acids as promoters such as trimethylsilyl trifluoromethanesulfonate (TMSOTf) or boron trifluoride diethyl etherate ($BF_3 \cdot OEt_2$).[51] While TCA donors are usually used for the preparation of ether-glycosides,[13,47] we planned to employ the sugar donor bromide **7**[52] in order to selectively glycosylate the C-28 carboxylic acid function and produce the ester-glycoside at a later stage of the synthesis after assembly of the disaccharide.[53]

As depicted in Scheme 1, the starting point of our synthesis consisted in the preparation of the known 2,3,4-tri-*O*-benzoyl-β-L-arabinopyranosyl trichloroacetimidate (**8**).[51,54] Accordingly, the commercial L-arabinose was subjected to perbenzoylation with benzoyl chloride (BzCl) using a catalytic amount of 4-dimethylaminopyridine (DMAP) at 60 °C. The crude residue was then brominated (33% HBr/HOAc) at the anomeric position, hydrolyzed with silver carbonate (Ag_2CO_3) in an acetone/water 20:1 solution and activated using trichloroacetonitrile (CCl_3CN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to furnish **8** in 38% yield after four steps. However, two anomeric protons signals at δ 6.67 ppm (s) and 6.82 ppm (d, $J_{1,2}$ 3.0 Hz) were visualized in the ^1H NMR spectrum indicating that, unexpectedly, the resulting product was an inseparable mixture of **8** and 2,3,5-tri-*O*-benzoyl-α-L-arabinofuranosyl trichloroacetimidate (**9**)[55] (R_f 0.67, hexanes/EtOAc 3:1) in a 5:1 ratio. The strong HMBC cross-peaks between the proton H-1 (δ 6.67 ppm) and the carbon C-4 (δ 84.3 ppm) confirmed the presence of the TCA **9** in the mixture. It was further postulated that the furanosyl form of the arabinose residue was produced during the benzoylation step since the conversion of pyranose to furanose in hot pyridine is not unprecedented.[56] To confirm this hypothesis, in a separate experiment, L-arabinose was perbenzoylated under

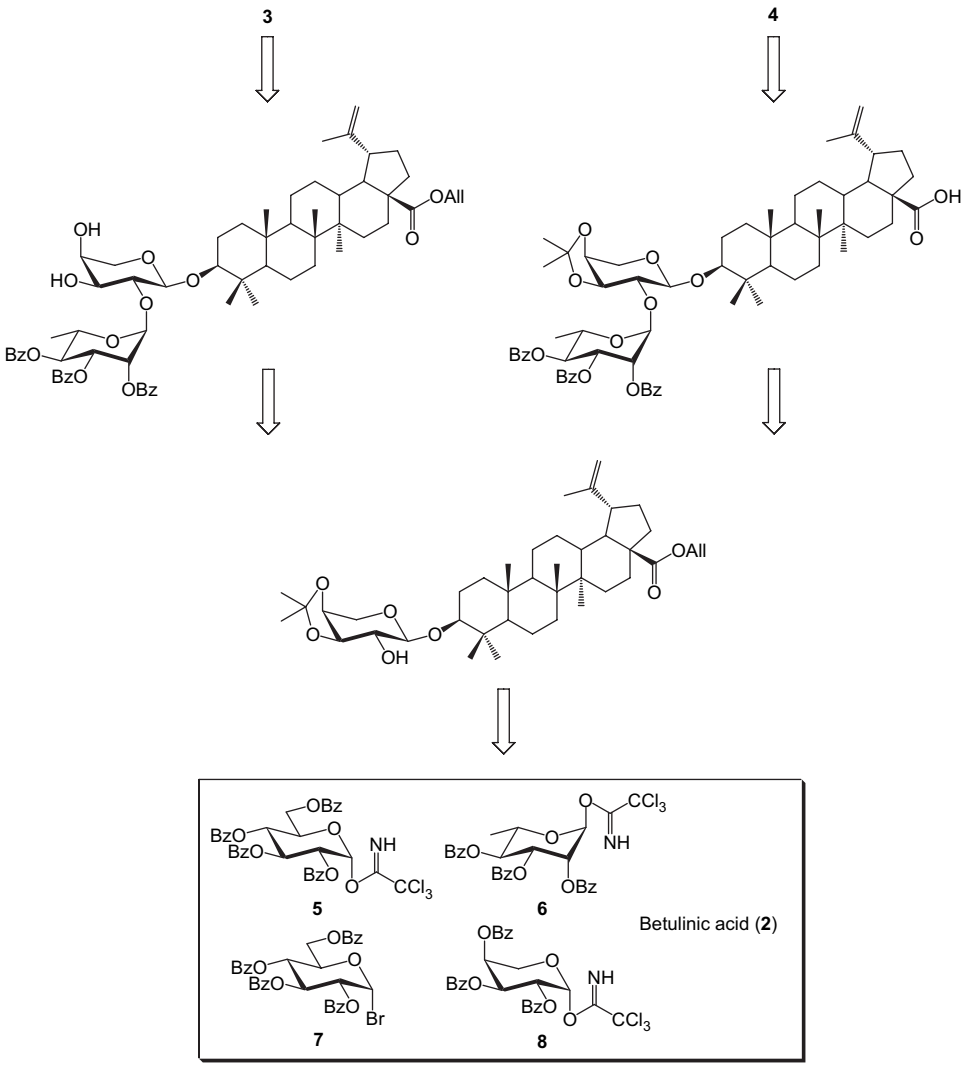
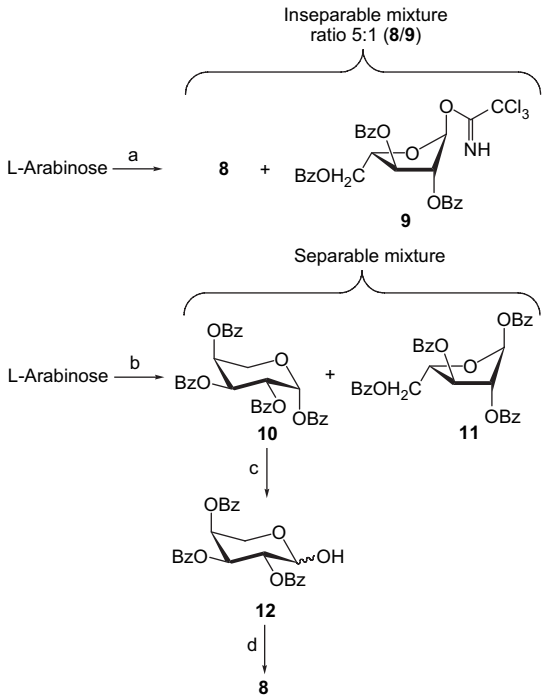


Figure 2. Retrosynthetic analysis of betulinic acid 3β-*O*-α-L-rhamnopyranosyl-(1→2)-[β-D-glucopyranosyl-(1→4)]-α-L-arabinopyranoside (**3**) and 28-*O*-β-D-glucopyranosyl betulinic acid 3β-*O*-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranoside (**4**).

the previously mentioned conditions but keeping the temperature under 25 °C throughout the overnight reaction to afford 1,2,3,4-tetra-*O*-benzoyl-β-L-arabinopyranose (**10**, 91%) along with 1,2,3,5-tetra-*O*-benzoyl-α-L-arabinofuranose (**11**)[56] in only 1% yield. This time, the purification by silica gel (SiO_2) column chromatography allowed the separation because both products **10** and **11** presented a significant difference in their retention factors according to TLC (hexanes/EtOAc 3:1). Afterwards, **10** was brominated and hydrolyzed to furnish **12** (73%, two steps), which was activated with CCl_3CN and DBU to yield **8** (80%) as a pure β-anomeric form without any trace of **9**.

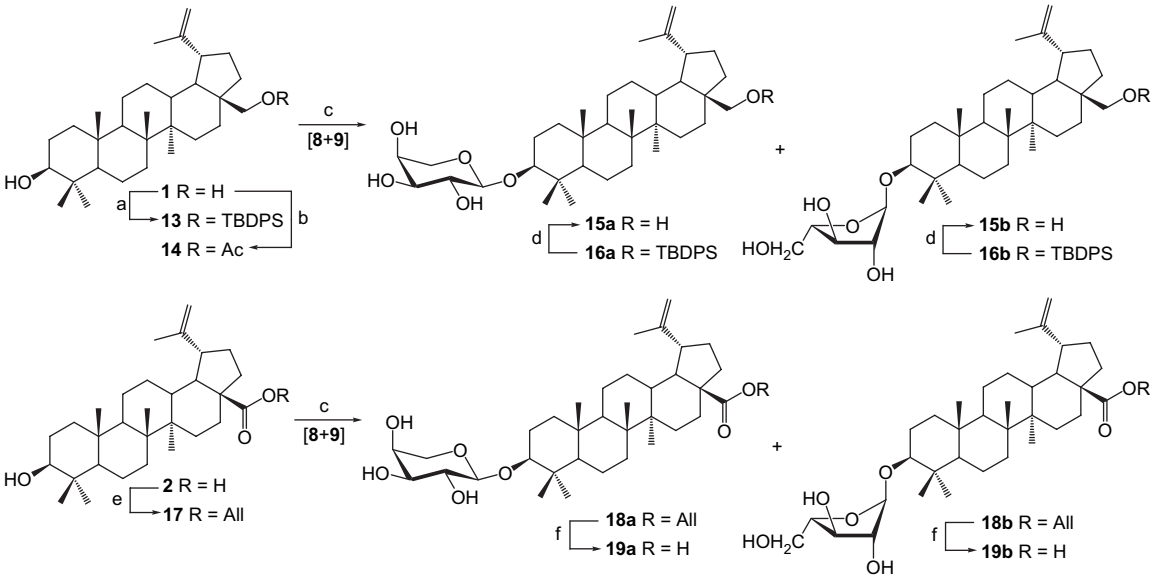
With TCA sugar donor **8** in hand, the next task was its linkage to the 3-OH of the lupane core of betulin (**1**) and betulinic acid (**2**). As previously described, pure **1** (>95%, GC–MS) was obtained by exhaustive extractions in dichloromethane (CH_2Cl_2) of the external bark of *Betula papyrifera* followed by recrystallization.[28] The natural carboxylic derivative **2** was then synthesized from **1** following known methodologies.[28] Here, the choice of the protecting groups at the C-28 position of triterpenoids **1** and **2** was crucial for the synthetic strategy since benzoyl groups have to be removed under basic conditions without affecting this position. Thus, as revealed in Scheme 2, we planned to temporarily protect the C-28 carboxylic acid position of betulinic acid (**2**) with an allyl ester as already reported by our laboratory in an earlier publication.[27] In addition, betulin (**1**) was treated with *tert*-butyldiphenylsilyl chloride (TBDPSCl) in the presence of imidazole and DMAP in refluxing tetrahydrofuran (THF) to yield the new compound **13** (90%) protected at the C-28 primary alcohol position by the most robust among silyl groups.[57] The regioselectivity of the silylation reaction was confirmed from the upfield shift in the ^{1}H NMR signal of the proton H-28 (δ 3.81 ppm in **1** to 3.68 ppm in **13**). For the introduction of the arabinose moiety, we chose to use the mixture of TCA donors **8** and **9** in order to obtain both arabinopyranoside and arabinofuranoside saponins, which could be of further interest for SAR investigations. Indeed, although the isolation of natural saponins bearing an α-L-arabinofuranosyl residue was already reported,[58,59] studies regarding their synthesis are scarce.[60–62] Consequently, according to Scheme 2, coupling of the acceptor **13** with a mixture of donors **8** and **9** under the catalytic promotion of TMSOTf in dry CH_2Cl_2 followed by subsequent removal of benzoyl groups using 0.25 N NaOH in a solution of MeOH/THF/H_2O 1:2:1 afforded the C-28 protected betulin 3β-*O*-α-L-arabinopyranoside **16a** (84%, two steps) along with the 3β-*O*-α-L-arabinofuranoside **16b** (13%, two steps). Moreover, similar treatment of acceptor **17**, i.e., coupling with donors **8** and **9** and deprotection of the benzoyl groups, furnished allyl betulinate 3β-*O*-α-L-arabinopyranoside (**18a**, 67%, two steps) together with the 3β-*O*-α-L-arabinofuranoside **18b** (11%, two steps). The non-natural betulinic acid saponins **19a** and



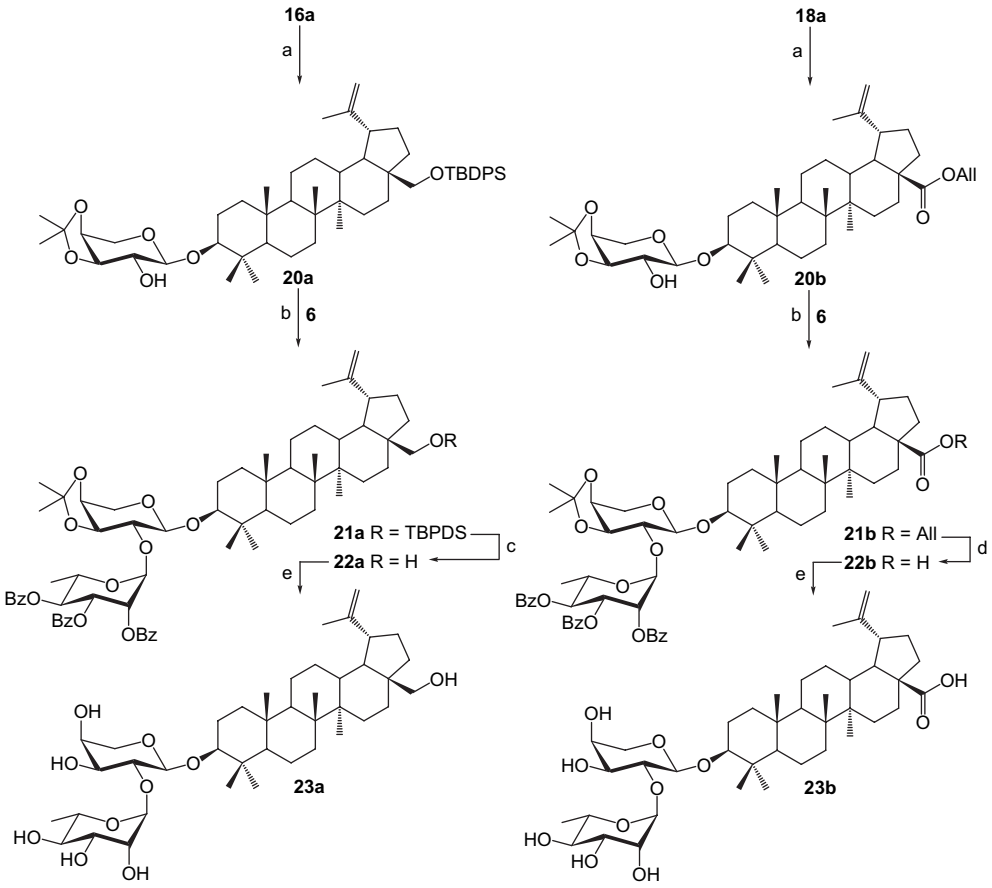
Scheme 1. Synthesis of L-arabinosyl donors (**8**, **9**). Reagents and conditions: (a) (i) BzCl (6.5 equiv), DMAP (0.01 equiv), Py, rt to 60 °C, overnight; (ii) HBr/HOAc 33%, CH_2Cl_2, rt, 2 h; (iii) Ag_2CO_3 (1.35 equiv), acetone/H_2O 20:1, rt, 1.5 h; (iv) CCl_3CN (8.0 equiv), DBU (0.5 equiv), CH_2Cl_2, rt, 4 days, 38% (four steps); (b) BzCl (6.5 equiv), DMAP (0.01 equiv), Py, rt, overnight, 91% for **10**; 1% for **11**; (c) (i) HBr/HOAc 33%, CH_2Cl_2, rt, 2 h; (ii) Ag_2CO_3 (1.35 equiv), acetone/H_2O 20:1, rt, 1.5 h, 73% (two steps); (d) CCl_3CN (8.0 equiv), DBU (0.5 equiv), CH_2Cl_2, rt, 45 min, 80%.

19b were obtained in good yields (66% and 71%, respectively) by the subsequent deprotection of the allylic ester in **18a** and **18b** using freshly prepared tetrakistriphenylphosphine palladium(0) [$Pd^0(PPh_3)_4$], triphenylphosphine (PPh_3) and pyrrolidine in dry THF.[44] On the other hand, the overnight desilylation of **16a** and **16b** by the action of 1 M tetrabutylammonium fluoride (TBAF) in HOAc 1:1 under reflux[57] was sluggish affording the target saponins **15a** and **15b** in unoptimized 42% and 37% yields, respectively. Thus, in order to increase the overall yields, the known acceptor 28-acetyl betulin (**14**)[27] was coupled with the donors **8** and **9** in a separate experiment and deprotected using the above mentioned methodology to access **15a** (73%, two steps) and **15b** (15%, two steps). As expected, the coupling constant data on the ^1H NMR spectra confirmed the α-anomeric configuration of the glycosidic linkage for all saponins (Ara*p*, d, $J_{1,2}$ 6.1–6.5 Hz, H-1′; Ara*f*, br s, H-1′).

In order to achieve the Rha*p*(1→2)Ara*p* intersugar linkage, the synthesis started with the regioselective protection of 3′- and 4′-OH of the arabinose moiety (Scheme 3). Accordingly, the treatment of **16a** under the catalytic action of pyridinium *p*-toluenesulfonate (PPTs) in conjunction with 2,2-dimethoxypropane (2,2-DMP)[48] afforded the isopropylidinated glycoside **20a** in 60% yield. The treatment of the arabinoside **18a** under similar reaction conditions furnished **20b** (74%). We first attempted to glycosylate the equatorial 2′-OH of **20b** with the known 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl trichloroacetimidate (**6**)[27] using TMSOTf as the promoter at −10 °C to room temperature. Unfortunately, the reaction was sluggish providing the target disaccharide glycoside **21b** in an unsatisfactory 22% yield. One possible explanation for the moderate yield was the rupture of the isopropylidene group, which led to the formation of a complex mixture of products.[63] Thus, by modifying the reaction conditions, it was found that the sugar donor **6** could be coupled with the acceptor **20b** under the promotion of the Lewis acid $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at a cryogenic temperature of −78 °C in a nearly quantitative yield (99%). Glycosidation of the acceptor **20a** with **6** using the same conditions proceeded smoothly to give the protected disaccharide saponin **21a** in a good yield (78%). Desilylation of **21a** (1 M TBAF/HOAc 1:1, THF, reflux, overnight) and deallylation of **21b** [$Pd^0(PPh_3)_4$, PPh_3, pyrrolidine, THF, room temperature] were then performed under standard experimental conditions to provide C-28 deprotected derivatives **22a** (72%) and **22b** (85%), respectively. The non-natural betulin and betulinic acid saponins **23a** and **23b** bearing an α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranosyl moiety at the C-3 position were successfully obtained after the deprotection of the isopropylidene group using *p*-toluenesulfonic acid monohydrate



Scheme 2. Synthesis of 3β-*O*-α-L-arabinopyranosides (**15a**, **19a**) and 3β-*O*-α-L-arabinofuranosides (**15b**, **19b**). Reagents and conditions: (a) TBDPSCl (1.5 equiv), imidazole (2.5 equiv), DMAP (0.1 equiv), THF, reflux, overnight, 90%; (b) Ac_2O (1.05 equiv), Py, DMAP (0.1 equiv), rt, 2 h, 73%; (c) (i) TCA (1.5 equiv), TMSOTf (0.1 equiv), 4 Å MS, CH_2Cl_2, rt, 2 h; (ii) NaOH (20 equiv), MeOH/THF/H_2O 1:2:1, rt, overnight, 73% for **15a** (two steps); 15% for **15b** (two steps); 84% for **16a** (two steps); 13% for **16b** (two steps); 67% for **18a** (two steps); 11% for **18b** (two steps); (d) 1 M TBAF/HOAc 1:1, THF, reflux, overnight, 42% for **15a**; 37% for **15b**; (e) AllBr (2.0 equiv), K_2CO_3 (3.0 equiv), DMF, 55 °C, 7 h, 84%; (f) $Pd^0(PPh_3)_4$ (0.3 equiv), PPh_3 (0.6 equiv), pyrrolidine (2.0 equiv), THF, rt, 4 h, 66% for **19a**; 71% for **19b**.

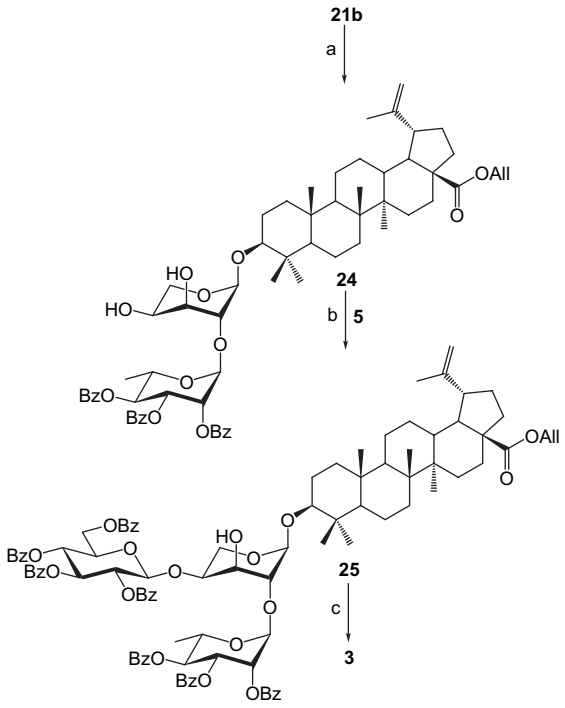


Scheme 3. Synthesis of 3β-*O*-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranosides **23a** and **23b**. Reagents and conditions: (a) PPTs (0.1 equiv), 2,2-DMP (10 equiv), acetone, rt, overnight and 60% for **20a**; 3.5 h and 74% for **20b**; (b) TCA (1.5 equiv), $BF_3{\cdot}OEt_2$ (0.7 equiv), 4 Å MS, CH_2Cl_2, −78 °C, 1.5 h, 78% for **21a**; 99% for **21b**; (c) 1 M TBAF/HOAc 1:1, THF, reflux, overnight, 72% for **22a**; (d) $Pd^0(PPh_3)_4$ (0.3 equiv), PPh_3 (0.6 equiv), pyrrolidine (2.0 equiv), THF, rt, 4 h, 85% for **22b**; (e) (i) $TsOH{\cdot}H_2O$ (0.7 equiv), CH_2Cl_2/MeOH 1:2, rt, overnight; (ii) NaOH (20 equiv), MeOH/THF/H_2O 1:2:1, rt, 4.5 h, 84% for **23a** (two steps); 61% for **23b** (two steps).

($TsOH{\cdot}H_2O$) in a dry CH_2Cl_2/MeOH 1:2 solution[63] followed by removal of the benzoyl groups (NaOH, MeOH/THF/H_2O 1:2:1) in 84% and 61% yields, respectively, over two steps. As expected, regarding saponins **23a** and **23b**, the two anomeric proton signals on the ^1H NMR spectra indicated the α-anomeric configuration of the rhamnopyranosyl (δ 6.19 ppm, br s, H-1″ for **23a**; δ 5.10 ppm, d, $J_{1,2}$ 1.1 Hz, H-1″ for **23b**) and arabinopyranosyl (δ 4.94 ppm, d, $J_{1,2}$ 5.4 Hz, H-1′ for **23a**; δ 4.54 ppm, d, $J_{1,2}$ 4.6 Hz, H-1′ for **23b**) moieties, which correspond to the natural 1,2-trans glycosidic linkage.[64] Moreover, the HMBC correlations between the proton H-1″ of the rhamnose moiety and the carbon C-2′ of the arabinose (δ 76.4 ppm for **23a**; δ 76.8 ppm for **23b**) clearly proved the (1→2) intersugar linkage.

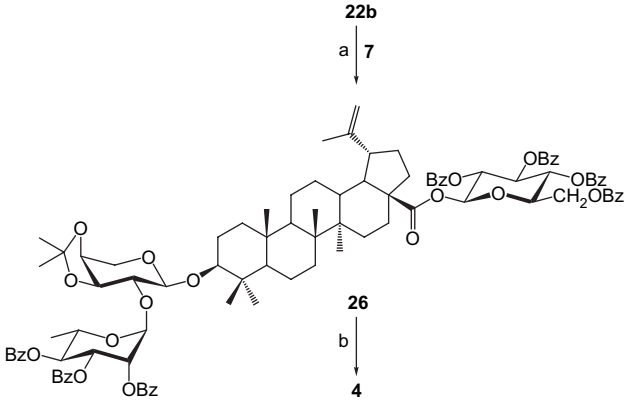
At this stage of the synthesis, we wished to prepare the natural betulinic acid saponin **3** starting from the fully protected derivative **21b**. According to Scheme 4, the deisopropylidination was achieved by treatment of **21b** with $TsOH{\cdot}H_2O$ (0.7 equiv) in a dry CH_2Cl_2/MeOH 1:2 solution to afford **24** in 70% yield. Surprisingly, the ^1H NMR spectrum of **24** showed that, once the isopropylidene was removed, the arabinopyranosyl moiety underwent a ring-flipping to adopt preferentially the $^1C_4$ chair conformation rather than the usual $^4C_1$ one.[46] Indeed, the coupling constant of the proton H-1′ was relatively small ($J_{1,2}$ 3.3 Hz) in comparison with **21b** ($J_{1,2}$ 7.5 Hz). Recently, this unusual $^1C_4$ chair conformation was reported in the literature for saponins containing an α-L-arabinopyranose moiety with a bulky group at the C-2′.[44–46,65] In the $^1C_4$ conformation, the 4′-OH is in the equatorial position while the 3′-OH is in the axial position. Since it is known that the equatorial hydroxyl groups are more reactive than the axial ones,[66] we planned to directly glycosylate this position in order to avoid tedious protection–deprotection reactions, which would increase the number of steps of the synthesis.[40,63] Therefore, as shown in Scheme 4, the acceptor **24** was coupled with the known donor 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl trichloroacetimidate (**5**)[27] under the promotion of TMSOTf (0.1 equiv) in CH_2Cl_2 at low temperature (−10 °C) to provide the desired protected **25** in 50% corrected yield along with the unreacted **24** (15%). The regioselectivity of this reaction was clearly proved by 2D NMR HMBC analyses, which showed a strong correlation between the proton H-1‴ of the glucopyranose (δ 5.12 ppm, d, $J_{1,2}$ 7.9 Hz) and the carbon C-4′ of the arabinose (δ 76.0 ppm). It is worth noting that the arabinose moiety of the protected saponin **25** adopted the unusual $^1C_4$ chair conformation as revealed by the small coupling constant of the proton H-1′ (δ 4.65 ppm, d, $J_{1,2}$ 3.8 Hz). Subsequent removal of the allyl and benzoyl groups of protected derivative **25** using the above mentioned methodology afforded the natural betulinic acid saponin **3** (60%, two steps) in which the arabinose residue retrieved the typical $^4C_1$ conformation (δ 4.79 ppm, d, $J_{1,2}$ 6.1 Hz, H-1′). The overall yield for the synthesis was 10% over eight linear steps from allyl betulinate (**17**). The physical and analytical data (^1H NMR, ^{13}C NMR and $[\alpha]_D^{25}$) of **3** were all consistent with those reported for the natural product isolated from the roots of *P. koreana*.[31]

The last step of our work was to incorporate a glucopyranosyl moiety at the C-28 position of **22b** with the aim of synthesizing the natural betulinic acid saponin **4**. As depicted in Scheme 5, the free carboxylic acid derivative **22b** was coupled with the known sugar donor 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (**7**)[52] under phase-transfer conditions[67] using potassium carbonate (K_2CO_3) and tetrabutylammonium bromide (Bu_4NBr) in a CH_2Cl_2/H_2O



Scheme 4. Completion of the synthesis of natural betulinic acid saponin **3**. Reagents and conditions: (a) $TsOH\cdot H_2O$ (0.7 equiv), CH_2Cl_2/MeOH 1:2, rt overnight, 70%; (b) TCA (1.5 equiv), TMSOTf (0.1 equiv), 4 Å MS, CH_2Cl_2, −10 °C to rt, 3 h, 50%; (c) (i) $Pd^0(PPh_3)_4$ (0.3 equiv), PPh_3 (0.6 equiv), pyrrolidine (2.0 equiv), rt, 4.5 h; (ii) NaOH (20 equiv), MeOH/THF/H_2O 1:2:1, rt, 6 h, 60% (two steps).

1:1 solution to give the fully protected derivative **26** (78%). Modifying the reaction conditions such as using the TCA sugar donor **5** in conjunction with TMSOTf or $BF_3\cdot OEt_2$ as the promoter did not increase the yield and led to a complex mixture of rearrangement products (data not shown). As expected, the strong HMBC correlation between the proton H-1‴ of the glucopyranose (δ 6.03 ppm, d, $J_{1,2}$ 9.7 Hz) and the carbon C-28 of the aglycone (δ 174.1 ppm) revealed that the reaction took place at the C-28 carboxylic acid position. The target natural betulinic acid saponin **4** was finally obtained after the removal of isopropylidene ($TsOH\cdot H_2O$, dry CH_2Cl_2/MeOH 1:2) and benzoyl groups (NaOH, MeOH/THF/H_2O 1:2:1) in an excellent 82% yield (two steps). The overall yield for the synthesis was 27% over eight linear steps from allyl betulinate (**17**). Surprisingly, it was found that the physical and analytical data (^{1}H NMR, ^{13}C NMR and $[\alpha]_D^{25}$) of **4** were not consistent with those reported for the natural product isolated from the aerial part of *S. rotundifolia*.[30] High-resolution electrospray ionization mass spectra (HR-ESI-MS) and extensive 1D and 2D NMR analyses (^{1}H, ^{13}C, DEPT-135, COSY, HSQC, HMBC, *J*-resolved, TOCSY, NOESY) on a 700 MHz NMR equipped with a cryogenic probe further proved that the structure of the synthetic saponin **4** was correct (Fig. 3).



Scheme 5. Completion of the synthesis of natural betulinic acid saponin **4**. Reagents and conditions: (a) sugar donor (1.5 equiv), K_2CO_3 (2.5 equiv), Bu_4NBr (0.4 equiv), CH_2Cl_2/H_2O 1:1, reflux, 6 h, 78%; (b) (i) $TsOH\cdot H_2O$ (0.7 equiv), CH_2Cl_2/MeOH 1:2, rt, overnight; (ii) NaOH (20 equiv), MeOH/THF/H_2O 1:2:1, rt, 4 h, 82% (two steps).

The ^{1}H NMR spectra of saponin **4** showed that the coupling constant of the proton H-1′ (δ 4.53 ppm, d, $J_{1,2}$ 4.6 Hz) in the arabinopyranose moiety was not characteristic of the standard $^4C_1$ conformation (δ 4.79 ppm, d, $J_{1,2}$ 6.1 Hz, H-1′ for **3**). This particularity was also observed for saponins **23a** and **23b** bearing the same disaccharide residue at the C-3 position (δ 4.52 ppm, d, $J_{1,2}$ 4.6 Hz, H-1′ in MeOD). In the course of this work, regarding the preparation of the sugar donor **8**, we found that using K_2CO_3 as a base instead of DBU led to the preferential formation of the known 2,3,4-tri-*O*-benzoyl-α-L-arabinopyranosyl trichloroacetimidate-$^1C_4$ (**27**)[44] (Table 1). The proton H-1′ of **27** was visualized like a broad singlet on the ^{1}H NMR spectrum (δ 6.33 ppm) as already reported in the literature for arabinose,[44–46,52,65] xylose[68,69] and fucose[65] adopting this unusual $^1C_4$ conformation. Hence, a $J_{1,2}$ coupling constant midway between $^4C_1$ and $^1C_4$ conformation suggested that the arabinose residue in saponins **4**, **23a** and **23b** were in a high conformational mobility.[70,71] It is worth noting that such a phenomenon was recently observed for naturally occurring saponins isolated from *Stryphnodendron fissuratum* having a terminal arabinose moiety.[72] In order to verify this hypothesis of conformational mobility, we performed a ^{1}H NMR analysis of saponin **4** in which the temperature was increased from 0 to 100 °C. As shown in Figure 4, the coupling constant values of the proton H-1′ decreased ($J_{1,2}$ 5.9–4.1 Hz) with an increase of the temperature. In comparison, the coupling constant values of the proton H-1‴ of the

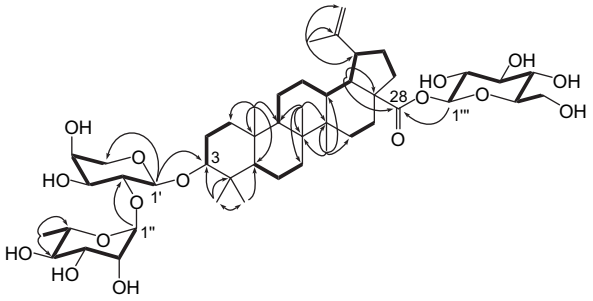
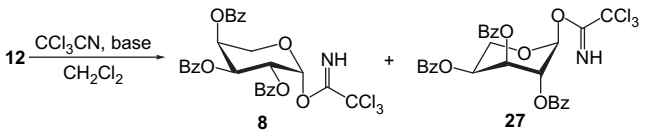


Figure 3. Selected key COSY (▬) and HMBC ($^1H\rightarrow{}^{13}C$) correlations of saponin **4**.

Table 1
Synthesis of 2,3,4-tri-*O*-benzoyl-L-arabinopyranosyl trichloroacetimidates $^4C_1$ (**8**) and $^1C_4$ (**27**)[a]



Entry	Base (equiv)	Yield (%)	
		8	**27**
1	DBU (0.5)	80	—
2	Cs_2CO_3 (0.2)	79	11
3	NaH (0.8)	42	42
4	K_2CO_3 (1.0)	20	66

[a] Reactions were performed overnight at room temperature with 8.0 equiv of CCl_3CN and 8 mL/mmol of CH_2Cl_2 at 0.22 mmol scale.

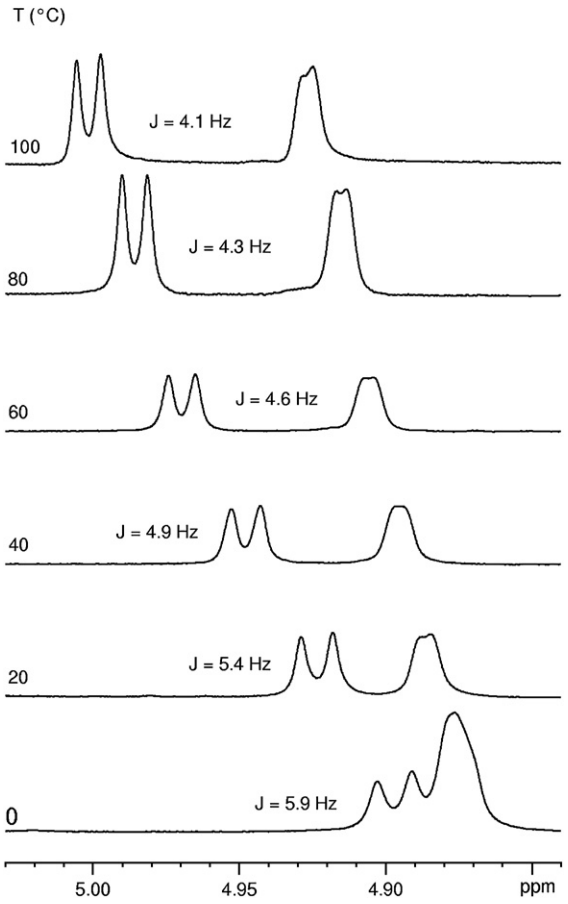


Figure 4. Temperature dependence of the H-1′ anomeric signal of the arabinopyranosyl moiety of saponin **4** suggesting its high conformational mobility (^{1}H NMR 500 MHz, C_5D_5N).

glucopyranose moiety were quite similar over the tested temperature range ($J_{1,2}$ 8.2–8.0 Hz). With regards to the saponin **4**, these ^{1}H NMR data suggested that the equilibrium between the $^4C_1$ and $^1C_4$ conformations of the arabinopyranose moiety tend to shift towards the $^1C_4$ conformation if the temperature is raised and vice versa.

3. Conclusion

In summary, this is the first report of the synthesis of naturally occurring lupane-type saponins bearing an α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranose sugar moiety. In this work, betulinic acid 3β-*O*-α-L-rhamnopyranosyl-(1→2)-[β-D-glucopyranosyl-(1→4)]-α-L-arabinopyranoside (**3**) and 28-*O*-β-D-glucopyranosyl betulinic acid 3β-*O*-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranoside (**4**) were synthesized using a stepwise glycosidation approach in 10% and 27% yields, respectively, over eight linear steps starting from allyl betulinate (**17**). It is noteworthy that the arabinose moiety of saponin **4** was in a high conformational mobility between $^4C_1$ and $^1C_4$ chair conformations as reflected by the unusual anomeric coupling constant of the proton H-1′. These results open the way for concise and efficient syntheses of a wide range of betulinic acid saponin analogues as pharmaceutical and/or biological agents that can be of further interest in the elaboration of meaningful SAR studies. Work is currently in progress in our laboratory in order to evaluate the in vitro haemolytic, anticancer and anti-inflammatory activities of these natural saponins (**3**, **4**) and their analogues (**15a**, **15b**, **19a**, **19b**, **23a**, **23b**) and results will be reported in due course.

4. Experimental

4.1. General methods

Chemical reagents were purchased from Sigma–Aldrich Co. Canada or Alfa Aesar Co. and were used as received. The usual solvents were obtained from VWR International Co. and were used as received. Air and water sensitive reactions were performed in flame-dried glassware under argon atmosphere. Moisture sensitive reagents were introduced via a dry syringe. Dichloromethane (CH_2Cl_2) and acetone were distilled from anhydrous CaH_2 under an argon atmosphere. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl under an argon atmosphere. Methanol (MeOH) was distilled from Mg and I_2 under an argon atmosphere. Analytical thin-layer chromatography was performed with silica gel 60 F_{254}, 0.25 mm pre-coated TLC plates (Silicycle, Québec, Canada). Compounds were visualized using UV_{254} and cerium molybdate (2 g $Ce(SO_4)_4(NH_4)_4$, 5 g $MoO_4(NH_4)_2$, 200 mL H_2O, 20 mL H_2SO_4) with charring. Flash column chromatography was carried out using 60–230 mesh silica gel (Silicycle, Québec, Canada) or high performance flash chromatography system (HPFC-Analogix F12-40) equipped with a silica gel column (F12-M, 8 g). All of the chemical yields generally represent the highest result obtained for three independent experiments. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance spectrometer at 400 MHz (^{1}H) and 100 MHz (^{13}C), equipped with a 5 mm QNP probe. Elucidations of chemical structures were based on ^{1}H, ^{13}C, COSY, TOCSY, HMBC, HSQC, *J*-resolved, NOESY and DEPT-135 experiments. Signals are reported as m (multiplet), s (singlet), d (doublet), t (triplet), dd (doublet of doublet), dq (doublet of quadruplet), ddd (doublet of doublet of doublet), ddt (doublet of doublet of triplet), br s (broad singlet) and coupling constants are reported in hertz (Hz). The chemical shifts are reported in parts per million (δ) relative to residual solvent peak or TMS. The labile O*H* NMR signals appearing sometimes were not listed. Optical rotations were obtained using sodium D line at ambient temperature on a Rudolph Research Analytical Autopol IV automatic polarimeter. High-resolution electrospray ionization mass spectra (HR-ESI-MS) and high field NMR analyses (500 and 700 MHz) were obtained at the Department of Chemistry, Université de Montréal, Québec, Canada.

4.2. 2,3,4-Tri-*O*-benzoyl-β-L-arabinopyranosyl trichloroacetimidate (8) and 2,3,5-tri-*O*-benzoyl-α-L-arabinofuranosyl trichloroacetimidate (9)

To a cooled solution (ice/water bath) of L-arabinose (10.0 g, 66.6 mmol) in anhydrous pyridine (140 mL) with DMAP (81 mg, 0.67 mmol) as catalyst was slowly added BzCl (46 mL, 400 mmol) over 30 min. The mixture was stirred overnight at 60 °C and then quenched with MeOH (20 mL). Then, the solvents were evaporated under reduced pressure to afford a yellow oily residue, which was taken up in EtOAc, washed with 10% HCl (4×), saturated $NaHCO_3$ solution and brine. The solvents of the dried solution ($MgSO_4$) were evaporated under reduced pressure to give a residue, which was used immediately for the next reaction without further purification. To a solution of the crude benzoylated arabinose derivative (32.5 g, 57.4 mmol) in anhydrous CH_2Cl_2 (168 mL) was added HBr/HOAc (40.2 mL, 33%) under an argon atmosphere. The mixture was stirred at room temperature for 2 h, then washed with saturated $NaHCO_3$ solution (3×) and brine. The solvents of the dried solution ($MgSO_4$) were evaporated under reduced pressure and the resulting residue was taken up in acetone (264 mL) and water (10.3 mL). Ag_2CO_3 (21.4 g, 77.4 mmol) was added portionwise and the hydrolysis was performed for 1 h at room temperature with constant stirring. The mixture was subsequently filtered through a bed of

Celite® and the solvents of the dried solution ($MgSO_4$) were evaporated under reduced pressure. The resulting crude residue was dissolved in wet CH_2Cl_2 (459 mL), then DBU (4.3 mL, 29 mmol) and CCl_3CN (46.0 mL, 459 mmol) were added sequentially. The mixture was stirred for 4 days at room temperature and the solvents were evaporated under reduced pressure to give a dark red oily residue, which was purified by flash chromatography (isocratic hexanes/EtOAc 9:1) to afford an inseparable mixture of **8** and **9** (15 g, 38%, four steps) as a white crystalline powder in a 5:1 ratio as confirmed by NMR. R_f 0.67 (hexanes/EtOAc 3:1). ^1H and ^{13}C NMR spectral data of **8**[44] and **9**[55] in the mixture were in agreement with those published in the literature.

4.3. 1,2,3,4-Tetra-*O*-benzoyl-β-L-arabinopyranose (10) and 1,2,3,5-tetra-*O*-benzoyl-α-L-arabinofuranose (11)

To a cooled solution (ice/water bath) of L-arabinose (1.00 g, 6.66 mmol) in anhydrous pyridine (15.3 mL) with DMAP (8 mg, 0.07 mmol) as catalyst was slowly added BzCl (5.0 mL, 43 mmol) over 30 min. The mixture was stirred overnight at room temperature and then quenched with MeOH (2 mL) while keeping the temperature at 0 °C. Then, the solvents were evaporated under reduced pressure to afford a yellow oily residue, which was taken up in EtOAc, washed with 10% HCl (4×), saturated $NaHCO_3$ solution and brine. The solvents of the dried solution ($MgSO_4$) were evaporated under reduced pressure to give a residue, which was purified by flash chromatography (hexanes/EtOAc 9:1 to 7:3) to furnish **10** (3.44 g, 91%) as a white foam along with **11** (43 mg, 1%) as a colourless solid.

4.3.1. Compound *10*

R_f 0.50 (hexanes/EtOAc 3:1); $[\alpha]_D^{25}$ +291.2 (*c* 0.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.17–7.27 (m, 20H, H–Ar), 6.87 (br s, 1H, H-1), 6.07 (s, 2H, H-2, H-3), 5.90 (s, 1H, H-4), 4.41 (d, *J*=13.1 Hz, 1H, H-5), 4.19 (dd, *J*=13.4, 1.8 Hz, 1H, H-5). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.8–164.7 (4×*C*O), 133.8–128.4 (C–Ar), 91.1 (C-1), 69.5 (C-4), 68.2 (C-3), 67.8 (C-2), 65.0 (C-5). HR-ESI-MS *m*/*z* 589.1464 $[M+Na]^+$ (calcd for $C_{33}H_{26}O_9Na$: 589.1469).

4.3.2. Compound *11*

R_f 0.58 (hexanes/EtOAc 3:1); $[\alpha]_D^{25}$ −12.8 (*c* 0.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.17–7.27 (m, 20H, H–Ar), 6.77 (br s, 1H, H-1), 5.82 (d, *J*=0.6 Hz, 1H, H-2), 5.68 (dt, *J*=3.5, 0.9 Hz, 1H, H-3), 4.84 (m, 2H, H-4, H-5), 4.74 (dd, *J*=12.7, 6.5 Hz, 1H, H-5). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.2–164.6 (4×*C*O), 133.8–128.3 (C–Ar), 99.8 (C-1), 83.9 (C-4), 80.9 (C-2), 77.5 (C-3), 63.7 (C-5). HR-ESI-MS *m*/*z* 589.1466 $[M+Na]^+$ (calcd for $C_{33}H_{26}O_9Na$: 589.1469).

4.4. 2,3,4-Tri-*O*-benzoyl-α,β-L-arabinopyranose (12)

To a solution of **10** (3.00 g, 5.30 mmol) in anhydrous CH_2Cl_2 (12.7 mL) was added HBr/HOAc (2.9 mL, 33%) under an argon atmosphere. The mixture was stirred at room temperature for 2 h, then washed with saturated $NaHCO_3$ solution (3×) and brine. The solvents of the dried solution ($MgSO_4$) were evaporated under reduced pressure and the resulting residue was taken up in acetone (24.4 mL) and water (1.0 mL). Ag_2CO_3 (1.97 g, 7.15 mmol) was added portionwise and the hydrolysis was performed for 1 h at room temperature with constant stirring. The mixture was subsequently filtered through a bed of Celite® and the solvents of the dried solution ($MgSO_4$) were evaporated under reduced pressure. The resulting oily residue was purified by flash chromatography (hexanes/EtOAc 4:1 to 3:2) to afford **12** (1.78 g, 73%, two steps) as a white crystalline powder. R_f 0.24 and 0.14 (hexanes/EtOAc 3:1); $[\alpha]_D^{25}$ +291.4 (*c* 0.1, $CHCl_3$). HR-ESI-MS *m*/*z* 485.1206 $[M+Na]^+$ (calcd for $C_{26}H_{22}O_8Na$: 485.1207).

4.5. 2,3,4-Tri-*O*-benzoyl-β-L-arabinopyranosyl trichloroacetimidate-$^4C_1$ (8) and 2,3,4-tri-*O*-benzoyl-α-L-arabinopyranosyl trichloroacetimidate-$^1C_4$ (27)

To a solution of **12** (100 mg, 0.216 mmol) in wet CH_2Cl_2 (1.7 mL) was added DBU (16 μL, 0.108 mmol) followed by CCl_3CN (173 μL, 459 mmol). The mixture was stirred for 45 min at room temperature, then the solvents were evaporated under reduced pressure to give a dark red oily residue, which was purified by flash chromatography (hexanes/EtOAc 9:1 to 4:1) to furnish **8** (105 mg, 80%) as a white foam. If the reaction was performed overnight using K_2CO_3 (30 mg, 0.22 mmol) as a base instead of DBU, the TCA **27** (87 mg, 66%) was obtained as the major product (white amorphous powder) along with **8** (26 mg, 20%).

4.5.1. Compound *8*

R_f 0.67 (hexanes/EtOAc 3:1); $[\alpha]_D^{25}$ +229.2 (*c* 0.1, $CHCl_3$). ^1H and ^{13}C NMR spectral data of **8**[44] were in agreement with those published in the literature. HR-ESI-MS *m*/*z* 628.0298 $[M+Na]^+$ (calcd for $C_{28}H_{22}Cl_3NO_8Na$: 628.0303).

4.5.2. Compound *27*

R_f 0.37 (hexanes/EtOAc 3:1); $[\alpha]_D^{25}$ +94.0 (*c* 0.1, $CHCl_3$). ^1H and ^{13}C NMR spectral data of **27**[44] were in agreement with those published in the literature. HR-ESI-MS *m*/*z* 628.0296 $[M+Na]^+$ (calcd for $C_{28}H_{22}Cl_3NO_8Na$: 628.0303).

4.6. 28-*O*-*tert*-Butyldiphenylsilyl betulin (13)

To a cooled (ice/water bath) solution of **1** (2.00 g, 4.52 mmol), imidazole (769 mg, 11.3 mmol) and DMAP (55 mg, 0.45 mmol) in anhydrous THF (13.2 mL) was added dropwise TBDPSCl (1.8 mL, 6.8 mmol) under an argon atmosphere. The mixture was refluxed overnight or until TLC (hexanes/EtOAc 4:1) showed the disappearance of the initial product. Then, the solvents were evaporated under reduced pressure to give a residue, which was purified by flash chromatography (hexanes/Et_2O 19:1 to 4:1) to furnish **13** (2.762 g, 90%) as a white crystalline powder. R_f 0.59 (hexanes/EtOAc 3:1); $[\alpha]_D^{25}$ −11.2 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.68–7.39 (m, 10H, H–Ar), 4.59 (br s, 1H, H-29), 4.52 (br s, 1H, H-29), 3.68 (d, *J*=9.8 Hz, 1H, H-28), 3.32 (d, *J*=9.8 Hz, 1H, H-28), 3.16 (dd, *J*=10.9, 4.4 Hz, 1H, H-3), 2.26 (td, *J*=10.6, 5.6 Hz, 1H, H-19), 2.17–2.09 (m, 2H), 1.64 (s, 3H, H-30), 1.61–1.10 (m, 15H), 1.06 (s, 9H, $C(CH_3)_3$), 0.96 (s, 3H, H-23), 0.93 (s, 3H, H-27), 0.76 (s, 3H, H-25), 0.75 (s, 3H, H-24), 0.70 (s, 3H, H-26), 0.64 (d, *J*=8.8 Hz, 1H, H-5). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 150.8 (C-20), 135.7–127.6 (C–Ar), 109.4 (C-29), 78.9 (C-3), 61.0 (C-28), 55.2 (C-5), 50.3 (C-9), 48.4 (C-18), 48.4 (C-17), 47.8 (C-19), 42.6 (C-14), 40.7 (C-8), 38.8 (C-4), 38.6 (C-1), 37.2 (C-13), 37.1 (C-10), 34.5 (C-22), 34.1 (C-7), 29.8 (C-21), 29.5 (C-16), 28.0 (C-23), 27.4 (C-2), 27.0 (C-15), 26.9 ($C(CH_3)_3$), 25.1 (C-12), 20.7 (C-11), 19.4 ($C(CH_3)_3$), 19.1 (C-30), 18.3 (C-6), 16.1 (C-25), 15.7 (C-26), 15.4 (C-24), 14.7 (C-27). HR-ESI-MS *m*/*z* 703.4906 $[M+Na]^+$ (calcd for $C_{46}H_{68}O_2SiNa$: 703.4881).

4.7. 28-*O*-*tert*-Butyldiphenylsilyl betulin 3β-*O*-α-L-arabinopyranoside (16a) and 28-*O*-*tert*-butyldiphenylsilyl betulin 3β-*O*-α-L-arabinofuranoside (16b)

The acceptor **13** (1.400 g, 2.055 mmol) and a mixture of donors **8** and **9** (1.871 g, 3.082 mmol, ratio 5:1) were stirred in anhydrous CH_2Cl_2 (41.0 mL) with 4 Å MS under an argon atmosphere for 60 min. Then, the promoter TMSOTf (37 μL, 0.20 mmol) was injected in the medium via a dry syringe at room temperature while keeping rigorous anhydrous conditions. The reaction mixture was stirred for 2 h at room temperature and quenched by addition of Et_3N (1.15 mL, 8.22 mmol). The solvents were evaporated under

reduced pressure and the resulting residue was immediately dissolved in a solution of MeOH/THF/H_2O 1:2:1 (140 mL) to which was added NaOH (1.65 g, 41.1 mmol). The reaction mixture was stirred overnight at room temperature or until TLC (hexanes/EtOAc 2:3) showed the complete disappearance of the benzoylated products and then acidified to pH≈4 with 10% aqueous HCl. The solvents were evaporated under reduced pressure to give a solid residue, which was purified by flash chromatography (hexanes/EtOAc 2:3 to 100% EtOAc, then CH_2Cl_2/MeOH 9:1) to afford **16a** (1.404 g, 84%, two steps) and **16b** (225 mg, 13%, two steps) as white crystalline powders.

*4.7.1. Compound **16a***

R_f 0.62 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{25}$ −10.2 (*c* 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.74–7.34 (m, 10H, H–Ar), 4.59 (br s, 1H, H-29), 4.52 (br s, 1H, H-29), 4.26 (d, *J*=5.6 Hz, 1H, H-1′), 3.90 (m, 1H, H-4′), 3.88 (m, 1H, H-5′), 3.74 (m, 1H, H-2′), 3.68 (m, 1H, H-28), 3.63 (m, 1H, H-3′), 3.46 (m, 1H, H-5′), 3.32 (d, *J*=9.2 Hz, 1H, H-28), 3.07 (m, 1H, H-3), 2.26 (m, 1H, H-19), 2.19–2.08 (m, 2H), 1.90–1.72 (m, 2H), 1.64 (s, 3H, H-30), 1.62–1.11 (m, 13H), 1.05 (s, 9H, C(CH_3)$_3$), 0.95 (s, 3H, H-23), 0.91 (s, 3H, H-27), 0.76 (s, 3H, H-24), 0.74 (s, 3H, H-25), 0.70 (s, 3H, H-26), 0.63 (d, *J*=7.4 Hz, 1H, H-5). ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 150.7 (C-20), 135.6–127.6 (C–Ar), 109.4 (C-29), 105.2 (C-1′), 89.6 (C-3), 72.9 (C-3′), 71.4 (C-2′), 67.9 (C-4′), 65.0 (C-5′), 61.0 (C-28), 55.5 (C-5), 50.2 (C-9), 48.4 (C-18), 48.4 (C-17), 47.8 (C-19), 42.5 (C-14), 40.7 (C-8), 39.1 (C-4), 38.7 (C-1), 37.1 (C-13), 36.7 (C-10), 34.4 (C-22), 34.1 (C-7), 29.8 (C-21), 29.5 (C-16), 27.9 (C-23), 27.0 (C-15), 26.9 (C(CH_3)$_3$), 26.0 (C-2), 25.1 (C-12), 20.7 (C-11), 19.3 (C(CH_3)$_3$), 19.1 (C-30), 18.1 (C-6), 16.4 (C-24), 16.0 (C-25), 15.7 (C-26), 14.6 (C-27). HR-ESI-MS *m*/*z* 835.5292 $[M+Na]^+$ (calcd for $C_{51}H_{76}O_6SiNa$: 835.5303).

*4.7.2. Compound **16b***

R_f 0.69 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{25}$ −41.5 (*c* 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.72–7.35 (m, 10H, H–Ar), 5.10 (br s, 1H, H-1′), 4.59 (d, *J*=2.0 Hz, 1H, H-29), 4.52 (br s, 1H, H-29), 4.19 (m, 1H, H-4′), 4.03 (br s, 1H, H-3′), 3.99 (br s, 1H, H-2′), 3.89 (dd, *J*=11.7, 2.2 Hz, 1H, H-5′), 3.83 (dd, *J*=11.7, 1.4 Hz, 1H, H-5′), 3.68 (d, *J*=9.9 Hz, 1H, H-28), 3.32 (d, *J*=9.9 Hz, 1H, H-28), 3.10 (dd, *J*=11.8, 4.8 Hz, 1H, H-3), 2.27 (td, *J*=10.7, 5.4 Hz, 1H, H-19), 2.17–2.09 (m, 2H), 1.89–1.75 (m, 2H), 1.65 (s, 3H, H-30), 1.63–1.10 (m, 13H), 1.06 (s, 9H, C(CH_3)$_3$), 0.93 (s, 3H, H-27), 0.92 (s, 3H, H-23), 0.75 (s, 3H, H-25), 0.72 (s, 3H, H-24), 0.69 (s, 3H, H-26). ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 150.9 (C-20), 135.7–127.6 (C–Ar), 110.4 (C-1′), 109.4 (C-29), 87.9 (C-3), 87.2 (C-4′), 78.2 (C-2′), 78.1 (C-3′), 62.0 (C-5′), 61.0 (C-28), 55.4 (C-5), 50.2 (C-9), 48.4 (C-18), 48.4 (C-17), 47.8 (C-19), 42.6 (C-14), 40.7 (C-8), 38.8 (C-4), 38.5 (C-1), 37.2 (C-13), 36.8 (C-10), 34.5 (C-22), 34.1 (C-7), 29.8 (C-21), 29.5 (C-16), 28.0 (C-23), 27.0 (C-15), 26.9 (C(CH_3)$_3$), 25.9 (C-2), 25.1 (C-12), 20.7 (C-11), 19.4 (C(CH_3)$_3$), 19.1 (C-30), 18.2 (C-6), 16.1 (C-24), 16.0 (C-25), 15.7 (C-26), 14.7 (C-27). HR-ESI-MS *m*/*z* 835.5283 $[M+Na]^+$ (calcd for $C_{51}H_{76}O_6SiNa$: 835.5303).

4.8. Allyl betulinate (17)

Allyl bromide (0.19 mL, 2.2 mmol) and K_2CO_3 (454 mg, 3.28 mmol) were added to a solution of **2** (501 mg, 1.10 mmol) in DMF (7 mL). The reaction mixture was stirred for 7 h at 55 °C. After cooling, EtOAc was added and the organic layer was washed with 1 N HCl. The aqueous layer was extracted with EtOAc (3×) and the combined organic layers were washed with saturated $NaHCO_3$ and brine. After the solution was dried ($MgSO_4$), the solvents were evaporated under reduced pressure. The resulting residue was purified by flash chromatography (100% CH_2Cl_2) to give **8** as a white crystalline powder (458 mg, 84%). R_f 0.58 (CH_2Cl_2/MeOH 99:1); $[\alpha]_D^{20}$ +3.9 (*c* 1.00, $CHCl_3$). ^{1}H and ^{13}C NMR spectral data of **17**[27] were in agreement with those published in the literature. HR-ESI-MS *m*/*z* 497.3985 $[M+H]^+$ (calcd for $C_{33}H_{53}O_3$: 497.3995).

4.9. Allyl betulinate 3β-*O*-α-L-arabinopyranoside (18a) and allyl betulinate 3β-*O*-α-L-arabinofuranoside (18b)

These compounds were prepared from the acceptor **17** (1.250 g, 2.516 mmol) and a mixture of donors **8** and **9** (2.290 g, 3.774 mmol, ratio 5:1) in the same manner as that described for compounds **16a** and **16b**. Purification by flash chromatography (hexanes/EtOAc 2:3 to 100% EtOAc) gave **18a** (1.065 g, 67%, two steps) as a white crystalline powder and **18b** (176 mg, 11%, two steps) as a white amorphous powder.

*4.9.1. Compound **18a***

R_f 0.54 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{25}$ +4.0 (*c* 0.5, $CHCl_3$/MeOH 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 5.93 (ddt, *J*=17.2, 10.5, 5.7 Hz, 1H, H-2$_{Allyl}$), 5.34 (dq, *J*=17.2, 1.1 Hz, 1H, H-3$_{Allyl}$), 5.23 (dq, *J*=10.3, 1.1 Hz, 1H, H-3$_{Allyl}$), 4.74 (d, *J*=1.4 Hz, 1H, H-29), 4.60 (m, 1H, H-29), 4.59 (m, 2H, H-1$_{Allyl}$), 4.27 (d, *J*=6.5 Hz, 1H, H-1′), 3.92 (m, 1H, H-4′), 3.90 (m, 1H, H-5′), 3.75 (t, *J*=8.1 Hz, 1H, H-2′), 3.65 (dd, *J*=8.4, 2.1 Hz, 1H, H-3′), 3.48 (d, *J*=11.3, 1H, H-5′), 3.09 (dd, *J*=11.3, 4.1 Hz, 1H, H-3), 3.02 (td, *J*=11.1, 4.9 Hz, 1H, H-19), 2.31–2.17 (m, 2H), 1.96–1.74 (m, 3H), 1.69 (s, 3H, H-30), 1.66–0.99 (m, 16H), 0.96 (s, 3H, H-23), 0.95 (s, 3H, H-27), 0.89 (s, 3H, H-26), 0.80 (s, 3H, H-25), 0.77 (s, 3H, H-24), 0.66 (d, *J*=9.7 Hz, 1H, H-5). ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 175.7 (C-28), 150.5 (C-20), 132.5 (C-2$_{Allyl}$), 118.1 (C-3$_{Allyl}$), 109.6 (C-29), 105.2 (C-1′), 89.7 (C-3), 72.8 (C-3′), 71.4 (C-2′), 67.8 (C-4′), 65.0 (C-5′), 64.6 (C-1$_{Allyl}$), 56.5 (C-17), 55.6 (C-5), 50.5 (C-9), 49.4 (C-18), 46.9 (C-19), 42.3 (C-14), 40.7 (C-8), 39.1 (C-4), 38.7 (C-1), 38.2 (C-13), 37.0 (C-22), 36.8 (C-10), 34.3 (C-7), 32.1 (C-16), 30.6 (C-21), 29.6 (C-15), 27.9 (C-23), 26.0 (C-2), 25.5 (C-12), 20.8 (C-11), 19.4 (C-30), 18.1 (C-6), 16.4 (C-24), 16.1 (C-25), 15.9 (C-26), 14.6 (C-27). HR-ESI-MS *m*/*z* 651.4221 $[M+Na]^+$ (calcd for $C_{38}H_{60}O_7Na$: 651.4231).

*4.9.2. Compound **18b***

R_f 0.59 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{25}$ −44.4 (*c* 0.5, $CHCl_3$/MeOH 1:1). ^{1}H NMR ($CDCl_3$/CD_3OD 1:1, 400 MHz) *δ*: 5.94 (ddt, *J*=16.7, 11.1, 5.6 Hz, 1H, H-2$_{Allyl}$), 5.35 (d, *J*=17.2 Hz, 1H, H-3$_{Allyl}$), 5.25 (d, *J*=10.5, 1H, H-3$_{Allyl}$), 4.99 (br s, 1H, H-1′), 4.73 (br s, 1H, H-29), 4.60 (m, 1H, H-29), 4.59 (m, 2H, H-1$_{Allyl}$), 4.04 (q, *J*=4.0 Hz, 1H, H-4′), 4.00 (m, 1H, H-2′), 3.89 (m, 1H, H-3′), 3.77 (dd, *J*=11.9, 2.5 Hz, 1H, H-5′), 3.68 (dd, *J*=11.4, 3.7 Hz, 1H, H-5′), 3.09 (dd, *J*=11.6, 4.3 Hz, 1H, H-3), 3.00 (td, *J*=11.3, 5.4 Hz, 1H, H-19), 2.32–2.17 (m, 2H), 1.96–1.76 (m, 3H), 1.70 (s, 3H, H-30), 1.67–1.00 (m, 16H), 0.99 (s, 3H, H-27), 0.95 (s, 3H, H-23), 0.92 (s, 3H, H-26), 0.84 (s, 3H, H-25), 0.76 (s, 3H, H-24), 0.72 (d, *J*=9.5 Hz, 1H, H-5). ^{13}C NMR ($CDCl_3$/CD_3OD 1:1, 100 MHz) *δ*: 176.6 (C-28), 150.7 (C-20), 132.8 (C-2$_{Allyl}$), 118.4 (C-3$_{Allyl}$), 110.7 (C-1′), 109.9 (C-29), 88.1 (C-3), 85.0 (C-4′), 81.4 (C-2′), 77.8 (C-3′), 65.1 (C-1$_{Allyl}$), 62.0 (C-5′), 57.1 (C-17), 56.0 (C-5), 51.0 (C-9), 49.8 (C-18), 47.5 (C-19), 42.8 (C-14), 41.1 (C-8), 39.3 (C-4), 39.1 (C-1), 38.7 (C-13), 37.3 (C-22), 37.3 (C-10), 34.7 (C-7), 32.5 (C-16), 30.9 (C-21), 30.0 (C-15), 28.1 (C-23), 26.2 (C-2), 25.9 (C-12), 21.3 (C-11), 19.4 (C-30), 18.6 (C-6), 16.4 (C-25), 16.4 (C-24), 16.2 (C-26), 14.9 (C-27). HR-ESI-MS *m*/*z* 651.4222 $[M+Na]^+$ (calcd for $C_{38}H_{60}O_7Na$: 651.4231).

4.10. Betulin 3β-*O*-α-L-arabinopyranoside (15a) and betulin 3β-*O*-α-L-arabinofuranoside (15b)

These compounds were prepared from the acceptor **14** (150 mg, 0.309 mmol) and a mixture of donors **8** and **9** (282 mg, 0.464 mmol, ratio 5:1) in the same manner as that described for compounds **16a** and **16b**. Purification by C-18 reversed phase flash chromatography (MeOH/H_2O 4:1 to 100% MeOH) gave pure **15a** (139 mg, 73%, two steps) as a white amorphous powder and pure **15b** (26 mg, 15%, two steps) as a white crystalline powder.

*4.10.1. Compound **15a***

R_f 0.47 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{25}$ +12.4 (*c* 0.4, $CHCl_3$/MeOH 1:1). ^{1}H NMR ($CDCl_3$/CD_3OD 1:1, 400 MHz) δ: 4.68 (d, *J*=1.6 Hz, 1H, H-29), 4.57 (br s, 1H, H-29), 4.33 (d, *J*=6.1 Hz, 1H, H-1′), 3.87 (m, 1H, H-5′), 3.86 (m, 1H, H-4′), 3.75 (d, *J*=11.0 Hz, 1H, H-2′), 3.64 (dd, *J*=8.3, 6.2 Hz, 1H, H-28), 3.57 (dd, *J*=8.3, 2.9 Hz, 1H, H-3′), 3.53 (m, 1H, H-5′), 3.28 (d, *J*=11.0 Hz, 1H, H-28), 3.14 (dd, *J*=11.4, 4.5 Hz, 1H, H-3), 2.41 (td, *J*=10.6, 5.7 Hz, 1H, H-19), 2.01–1.71 (m, 5H), 1.69 (s, 3H, H-30), 1.68–1.07 (m, 14H), 1.05 (s, 3H, H-26), 1.02 (s, 3H, H-23), 0.99 (s, 3H, H-27), 0.85 (s, 3H, H-25), 0.82 (s, 3H, H-24), 0.74 (d, *J*=12.2 Hz, 1H, H-5). ^{13}C NMR ($CDCl_3$/CD_3OD 1:1, 100 MHz) δ: 151.1 (C-20), 109.9 (C-29), 105.9 (C-1′), 90.2 (C-3), 73.3 (C-3′), 71.8 (C-2′), 68.1 (C-4′), 65.1 (C-5′), 60.0 (C-28), 56.2 (C-5), 51.0 (C-9), 49.3 (C-18), 48.4 (C-19), 48.2 (C-17), 43.2 (C-14), 41.5 (C-8), 39.7 (C-4), 39.3 (C-1), 37.9 (C-13), 37.4 (C-10), 34.7 (C-7), 34.5 (C-22), 30.2 (C-21), 29.7 (C-16), 28.1 (C-23), 27.5 (C-15), 26.5 (C-2), 26.1 (C-12), 21.4 (C-11), 19.3 (C-30), 18.7 (C-6), 16.5 (C-24), 16.5 (C-25), 16.2 (C-26), 15.0 (C-27). HR-ESI-MS *m*/*z* 597.4114 $[M+Na]^+$ (calcd for $C_{35}H_{58}O_6Na$: 597.4126).

*4.10.2. Compound **15b***

R_f 0.57 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{25}$ −32.2 (*c* 0.1, $CHCl_3$/MeOH 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.11 (br s, 1H, H-1′), 4.68 (d, *J*=1.8 Hz, 1H, H-29), 4.58 (br s, 1H, H-29), 4.20 (d, *J*=1.2 Hz, 1H, H-4′), 4.04 (s, 1H, H-3′), 4.01 (br s, 1H, H-2′), 3.89 (dd, *J*=11.8, 2.2 Hz, 1H, H-5′), 3.84 (dd, *J*=11.8, 1.4 Hz, 1H, H-5′), 3.81 (d, *J*=10.8 Hz, 1H, H-28), 3.34 (d, *J*=10.8 Hz, 1H, H-28), 3.12 (dd, *J*=11.5, 4.4 Hz, 1H, H-3), 2.39 (td, *J*=10.5, 5.7 Hz, 1H, H-19), 2.03–1.71 (m, 4H), 1.69 (s, 3H, H-30), 1.68–1.02 (m, 17H), 1.01 (s, 3H, H-26), 0.98 (s, 3H, H-27), 0.93 (s, 3H, H-23), 0.82 (s, 3H, H-25), 0.73 (s, 3H, H-24). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 150.5 (C-20), 110.4 (C-1′), 109.7 (C-29), 87.9 (C-3), 87.3 (C-4′), 78.2 (C-2′), 78.1 (C-3′), 62.0 (C-5′), 60.5 (C-28), 55.4 (C-5), 50.3 (C-9), 48.7 (C-18), 47.8 (C-19), 47.7 (C-17), 42.7 (C-14), 40.9 (C-8), 38.9 (C-4), 38.6 (C-1), 37.3 (C-13), 36.8 (C-10), 34.1 (C-22), 33.9 (C-7), 29.7 (C-16), 29.1 (C-21), 28.0 (C-23), 27.0 (C-15), 25.9 (C-2), 25.1 (C-12), 20.8 (C-11), 19.1 (C-30), 18.2 (C-6), 16.1 (C-24), 16.1 (C-25), 15.9 (C-26), 14.7 (C-27). HR-ESI-MS *m*/*z* 597.4116 $[M+Na]^+$ (calcd for $C_{35}H_{58}O_6Na$: 597.4126).

4.11. Betulinic acid 3β-*O*-α-L-arabinopyranoside (19a)

To a solution of **18a** (75 mg, 0.119 mmol) and PPh_3 (19 mg, 0.072 mmol) in anhydrous THF (0.84 mL) was added $Pd^0(PPh_3)_4$ (41 mg, 0.036 mmol) followed by pyrrolidine (20 μL, 0.239 mmol) at room temperature under an argon atmosphere. The reaction mixture was stirred in the dark overnight or until TLC (CH_2Cl_2/MeOH 9:1) showed the disappearance of the initial product. Then, the solvents were evaporated under reduced pressure to give a red-yellow powder, which was purified by flash chromatography (100% CH_2Cl_2 to CH_2Cl_2/MeOH 47:3) to afford pure **19a** (46 mg, 66%) as a white amorphous powder. R_f 0.46 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{25}$ +5.2 (*c* 0.2, $CHCl_3$/MeOH 1:1). ^{1}H NMR ($CDCl_3$/CD_3OD 1:1, 400 MHz) δ: 4.72 (d, *J*=1.6 Hz, 1H, H-29), 4.59 (br s, 1H, H-29), 4.33 (d, *J*=6.0 Hz, 1H, H-1′), 3.88 (m, 1H, H-5′), 3.87 (m, 1H, H-4′), 3.64 (dd, *J*=8.1, 6.1 Hz, 1H, H-2′), 3.58 (dd, *J*=8.1, 3.0 Hz, 1H, H-3′), 3.53 (dd, *J*=13.8, 3.7 Hz, 1H, H-5′), 3.13 (dd, *J*=11.6, 4.5 Hz, 1H, H-3), 3.03 (td, *J*=10.5, 4.3 Hz, 1H, H-19), 2.31–2.21 (m, 2H), 2.01–1.72 (m, 3H), 1.70 (s, 3H, H-30), 1.68–1.04 (m, 15H), 1.01 (s, 3H, H-23), 0.98 (s, 3H, H-27), 0.95 (s, 3H, H-26), 0.84 (s, 3H, H-25), 0.81 (s, 3H, H-24), 0.74 (d, *J*=9.7 Hz, 1H, H-5). ^{13}C NMR ($CDCl_3$/CD_3OD 1:1, 100 MHz) δ: 179.5 (C-28), 151.2 (C-20), 109.8 (C-29), 105.7 (C-1′), 90.2 (C-3), 73.2 (C-3′), 71.7 (C-2′), 67.9 (C-4′), 64.9 (C-5′), 56.7 (C-17), 56.2 (C-5), 51.1 (C-9), 49.7 (C-18), 47.5 (C-19), 42.9 (C-14), 41.2 (C-8), 39.6 (C-4), 39.2 (C-1), 38.8 (C-13), 37.6 (C-22), 37.4 (C-10), 34.8 (C-7), 32.7 (C-16), 31.0 (C-21), 30.1 (C-15), 28.1 (C-23), 26.4 (C-2), 26.0 (C-12), 21.4 (C-11), 19.5 (C-30), 18.6 (C-6), 16.4 (C-25), 16.4 (C-24), 16.2 (C-26), 14.9 (C-27). HR-ESI-MS *m*/*z* 611.3901 $[M+Na]^+$ (calcd for $C_{35}H_{56}O_7Na$: 611.3918).

4.12. Betulinic acid 3β-*O*-α-L-arabinofuranoside (19b)

This compound was prepared from **18b** (75 mg, 0.119 mmol) in the same manner as that described for compound **19a**. Purification by flash chromatography (100% CH_2Cl_2 to CH_2Cl_2/MeOH 47:3) gave pure **19b** (50 mg, 71%) as a white amorphous powder. R_f 0.54 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{25}$ −41.9 (*c* 0.2, $CHCl_3$/MeOH 1:1). ^{1}H NMR ($CDCl_3$/CD_3OD 1:1, 400 MHz) δ: 4.99 (br s, 1H, H-1′), 4.72 (m, 1H, H-29), 4.59 (br s, 1H, H-29), 4.04 (m, 1H, H-4′), 4.01 (dd, *J*=3.0, 1.6 Hz, 1H, H-2′), 3.88 (dd, *J*=5.1, 3.2 Hz, 1H, H-3′), 3.77 (dd, *J*=11.9, 3.2 Hz, 1H, H-5′), 3.68 (dd, *J*=11.9, 4.1 Hz, 1H, H-5′), 3.09 (dd, *J*=11.8, 4.8 Hz, 1H, H-3), 3.02 (td, *J*=11.0, 4.8 Hz, 1H, H-19), 2.31–2.22 (m, 2H), 2.01–1.89 (m, 2H), 1.81 (m, 1H, H-2), 1.70 (s, 3H, H-30), 1.68–1.01 (m, 16H), 0.99 (s, 3H, H-27), 0.96 (s, 3H, H-23), 0.95 (s, 3H, H-26), 0.85 (s, 3H, H-25), 0.77 (s, 3H, H-24), 0.73 (d, *J*=10.2 Hz, 1H, H-5). ^{13}C NMR ($CDCl_3$/CD_3OD 1:1, 100 MHz) δ: 179.6 (C-28), 151.2 (C-20), 110.9 (C-1′), 109.9 (C-29), 88.3 (C-3), 85.1 (C-4′), 81.7 (C-2′), 78.0 (C-3′), 62.2 (C-5′), 56.8 (C-17), 56.2 (C-5), 51.2 (C-9), 49.8 (C-18), 47.6 (C-19), 43.0 (C-14), 41.3 (C-8), 39.5 (C-4), 39.3 (C-1), 38.9 (C-13), 37.6 (C-22), 37.5 (C-10), 34.9 (C-7), 32.8 (C-16), 31.1 (C-21), 30.2 (C-15), 28.2 (C-23), 26.4 (C-2), 26.1 (C-12), 21.5 (C-11), 19.5 (C-30), 18.8 (C-6), 16.5 (C-25), 16.5 (C-24), 16.3 (C-26), 15.0 (C-27). HR-ESI-MS *m*/*z* 611.3898 $[M+Na]^+$ (calcd for $C_{35}H_{58}O_7Na$: 611.3918).

4.13. 28-*O*-*tert*-Butyldiphenylsilyl betulin 3β-*O*-3,4-*O*-isopropylidene-α-L-arabinopyranoside (20a)

To a cooled (ice/water bath) solution of **16a** (1.000 g, 1.230 mmol) in anhydrous acetone (14.7 mL) were added PPTs (31 mg, 0.122 mmol) and 2,2-dimethoxypropane (1.52 mL, 12.3 mmol) under an argon atmosphere. The reaction mixture was stirred overnight at room temperature or until TLC (hexanes/EtOAc 7:3) showed the disappearance of the initial product. Then, the solvents were evaporated under reduced pressure and the resulting residue was taken up in CH_2Cl_2 and washed with saturated $NaHCO_3$ solution and brine. The organic solvents of the dried solution ($MgSO_4$) were evaporated under reduced pressure to give a residue, which was purified by flash chromatography (hexanes/EtOAc 9:1 to 4:1) to give **20a** (626 mg, 60%) as a white crystalline powder. R_f 0.38 (hexanes/EtOAc 3:1); $[\alpha]_D^{25}$ +1.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.72–7.35 (m, 10H, H–Ar), 4.60 (d, *J*=2.4 Hz, 1H, H-29), 4.53 (br s, 1H, H-29), 4.20 (m, 3H, H-1′, H-4′, H-5′), 4.06 (dd, *J*=7.6, 5.7 Hz, 1H, H-3′), 3.75 (dd, *J*=13.8, 3.5 Hz, 1H, H-5′), 3.68 (d, *J*=9.9 Hz, 1H, H-28), 3.63 (t, *J*=7.7 Hz, 1H, H-2′), 3.32 (d, *J*=9.9 Hz, 1H, H-28), 3.09 (dd, *J*=11.7, 4.6 Hz, 1H, H-3), 2.26 (td, *J*=11.0, 5.7 Hz, 1H, H-19), 2.17–2.08 (m, 2H), 1.91–1.66 (m, 3H), 1.65 (s, 3H, H-30), 1.54 (s, 3H, $(CH_3)_2C$), 1.36 (s, 3H, $(CH_3)_2C$), 1.06 (s, 9H, $C(CH_3)_3$), 0.96 (s, 3H, H-23), 0.92 (s, 3H, H-27), 0.80 (s, 3H, H-24), 0.76 (s, 3H, H-25), 0.69 (s, 3H, H-26), 0.66 (m, 1H, H-5). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 150.8 (C-20), 135.7–127.6 (C–Ar), 110.0 ($(CH_3)_2C$), 109.4 (C-29), 104.3 (C-1′), 89.0 (C-3), 78.1 (C-3′), 74.3 (C-2′), 73.2 (C-4′), 63.1 (C-5′), 61.0 (C-28), 55.5 (C-5), 50.3 (C-9), 48.4 (C-18), 48.4 (C-17), 47.8 (C-19), 42.6 (C-14), 40.8 (C-8), 39.1 (C-4), 38.7 (C-1), 37.2 (C-13), 36.8 (C-10), 34.5 (C-22), 34.1 (C-7), 29.8 (C-21), 29.5 (C-16), 28.2 (C-23), 28.0 ($(CH_3)_2C$), 27.0 (C-15), 26.9 ($C(CH_3)_3$), 26.1 ($(CH_3)_2C$), 26.1 (C-2), 25.1 (C-12), 20.7 (C-11), 19.4 ($C(CH_3)_3$), 19.1 (C-30), 18.1 (C-6), 16.5 (C-24), 16.1 (C-25), 15.7 (C-26), 14.7 (C-27). HR-ESI-MS *m*/*z* 875.5648 $[M+Na]^+$ (calcd for $C_{54}H_{80}O_6SiNa$: 875.5616).

4.14. Allyl betulinate 3β-*O*-3,4-*O*-isopropylidene-α-L-arabinopyranoside (20b)

This compound was prepared from **18a** (800 mg, 1.27 mmol) in the same manner as that described for compound **20a**. Purification by flash chromatography (hexanes/EtOAc 9:1 to 4:1) gave **20b** (630 mg, 74%) as a white crystalline powder. R_f 0.34 (hexanes/EtOAc

3:1); $[\alpha]_D^{25}$ +18.0 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ: 5.93 (ddt, *J*=17.2, 10.3, 5.7 Hz, 1H, H-2_{Allyl}), 5.34 (dq, *J*=17.2, 1.6 Hz, 1H, H-3_{Allyl}), 5.24 (dq, *J*=10.3, 1.2 Hz, 1H, H-3_{Allyl}), 4.74 (d, *J*=2.1 Hz, 1H, H-29), 4.60 (m, 1H, H-29), 4.59 (m, 2H, H-1_{Allyl}), 4.21 (d, *J*=7.6 Hz, 1H, H-1′), 4.20 (m, 2H, H-4′, H-5′), 4.06 (dd, *J*=7.6, 5.7 Hz, 1H, H-3′), 3.76 (dd, *J*=13.8, 3.5 Hz, 1H, H-5′), 3.63 (t, *J*=7.6 Hz, 1H, H-2′), 3.10 (dd, *J*=11.4, 4.6 Hz, 1H, H-3), 3.02 (td, *J*=11.3, 4.8 Hz, 1H, H-19), 2.29–2.17 (m, 2H), 1.95–1.75 (m, 2H), 1.69 (s, 3H, H-30), 1.54 (s, 3H, $(CH_3)_2C$), 1.37 (s, 3H, $(CH_3)_2C$), 0.96 (s, 3H, H-23), 0.95 (s, 3H, H-27), 0.90 (s, 3H, H-26), 0.82 (s, 3H, H-25), 0.80 (s, 3H, H-24), 0.69 (d, *J*=8.9 Hz, 1H, H-5). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 175.7 (C-28), 150.6 (C-20), 132.6 (C-2_{Allyl}), 118.2 (C-3_{Allyl}), 110.1 ($(CH_3)_2C$), 109.6 (C-29), 104.3 (C-1′), 89.1 (C-3), 78.2 (C-3′), 74.4 (C-2′), 73.3 (C-4′), 64.6 (C-1_{Allyl}), 63.2 (C-5′), 56.6 (C-17), 55.7 (C-5), 50.6 (C-9), 49.5 (C-18), 46.9 (C-19), 42.4 (C-14), 40.8 (C-8), 39.2 (C-4), 38.8 (C-1), 38.2 (C-13), 37.0 (C-22), 36.9 (C-10), 34.3 (C-7), 32.1 (C-16), 30.6 (C-21), 29.6 (C-15), 28.2 (C-23), 28.1 ($(CH_3)_2C$), 26.1 ($(CH_3)_2C$), 26.1 (C-2), 25.6 (C-12), 20.9 (C-11), 19.4 (C-30), 18.2 (C-6), 16.5 (C-24), 16.2 (C-25), 16.0 (C-26), 14.7 (C-27). HR-ESI-MS *m*/*z* 691.4538 $[M+Na]^+$ (calcd for $C_{41}H_{64}O_7Na$: 691.4544).

4.15. 28-*O*-*tert*-Butyldiphenylsilyl betulin 3β-*O*-2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl-(1→2)-3,4-*O*-isopropylidene-α-L-arabinopyranoside (21a)

The acceptor **20a** (500 mg, 0.586 mmol) and the donor **6** (546 mg, 0.879 mmol) were stirred in anhydrous CH_2Cl_2 (8.8 mL) with 4 Å MS under an argon atmosphere for 40 min. The temperature was lowered to −78 °C with an ice CO_2/acetone bath, then the promoter $BF_3{\cdot}Et_2O$ (52 μL, 0.41 mmol) was injected in the medium via a dry syringe while keeping rigorous anhydrous conditions. The reaction mixture was stirred for 1.5 h at −78 °C and quenched by addition of Et_3N (327 μL, 2.34 mmol). The solvents were evaporated under reduced pressure to give a residue, which was purified by flash chromatography (hexanes/EtOAc 47:3 to 17:1) to afford **21a** (600 mg, 78%) as a white crystalline powder. R_f 0.57 (hexanes/EtOAc 3:1); $[\alpha]_D^{25}$ +59.2 (*c* 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.13–7.21 (m, 25H, H–Ar), 5.87 (dd, *J*=10.2, 3.5 Hz, 1H, H-3″), 5.75 (dd, *J*=3.5, 1.7 Hz, 1H, H-2″), 5.67 (t, *J*=10.0 Hz, 1H, H-4″), 5.61 (d, *J*=1.5 Hz, 1H, H-1″), 4.60 (d, *J*=2.1 Hz, 1H, H-29), 4.53 (m, 1H, H-29), 4.51 (m, 1H, H-5″), 4.46 (d, *J*=7.5 Hz, 1H, H-1′), 4.25 (m, 2H, H-3′, H-4′), 4.15 (dd, *J*=13.3, 1.9 Hz, 1H, H-5′), 3.90 (t, *J*=7.1 Hz, 1H, H-2′), 3.79 (dd, *J*=12.6, 2.6 Hz, 1H, H-5′), 3.71 (d, *J*=9.9 Hz, 1H, H-28), 3.32 (d, *J*=9.9 Hz, 1H, H-28), 3.15 (dd, *J*=11.7, 4.5 Hz, 1H, H-3), 2.26 (td, *J*=10.9, 6.0 Hz, 1H, H-19), 2.18–2.09 (m, 2H), 1.88–1.68 (m, 3H), 1.66 (s, 3H, H-30), 1.55 (s, 3H, $(CH_3)_2C$), 1.35 (d, *J*=6.5 Hz, 3H, H-6″), 1.33 (s, 3H, $(CH_3)_2C$), 1.23 (s, 3H, H-23), 1.06 (s, 9H, $C(CH_3)_3$), 0.95 (s, 3H, H-27), 0.93 (s, 3H, H-24), 0.79 (s, 3H, H-25), 0.74 (s, 3H, H-26). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.8–165.4 (3×*C*O), 150.9 (C-20), 135.7–127.6 (C–Ar), 110.4 ($(CH_3)_2C$), 109.4 (C-29), 103.3 (C-1′), 95.3 (C-1″), 89.2 (C-3), 79.2 (C-3′), 75.4 (C-2′), 73.4 (C-4′), 72.0 (C-4″), 70.6 (C-2″), 69.9 (C-3″), 66.5 (C-5″), 62.7 (C-5′), 61.1 (C-28), 55.9 (C-5), 50.4 (C-9), 48.5 (C-18), 48.4 (C-17), 47.8 (C-19), 42.6 (C-14), 40.8 (C-8), 39.3 (C-4), 38.9 (C-1), 37.2 (C-13), 36.9 (C-10), 34.5 (C-22), 34.2 (C-7), 29.9 (C-21), 29.5 (C-16), 28.1 (C-23), 27.8 ($(CH_3)_2C$), 27.1 (C-15), 26.9 ($C(CH_3)_3$), 26.3 (C-2), 26.1 ($(CH_3)_2C$), 25.2 (C-12), 20.8 (C-11), 19.4 ($C(CH_3)_3$), 19.1 (C-30), 18.2 (C-6), 17.6 (C-6″), 16.5 (C-24), 16.2 (C-25), 15.8 (C-26), 14.7 (C-27). HR-ESI-MS *m*/*z* 1333.6971 $[M+Na]^+$ (calcd for $C_{81}H_{102}O_{13}SiNa$: 1333.6982).

4.16. Allyl betulinate 3β-*O*-2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl-(1→2)-3,4-*O*-isopropylidene-α-L-arabinopyranoside (21b)

This compound was prepared from the acceptor **20b** (500 mg, 0.747 mmol) and the donor **6** (696 mg, 1.12 mmol) in the same manner as that described for compound **21a**. Purification by flash chromatography (hexanes/EtOAc 9:1 to 17:1) gave **21b** (873 mg, 99%) as a white crystalline powder. R_f 0.51 (hexanes/EtOAc 3:1); $[\alpha]_D^{25}$ +81.5 (*c* 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.13–7.21 (m, 15H, H–Ar), 5.93 (ddt, *J*=17.2, 10.3, 5.8 Hz, 1H, H-2_{Allyl}), 5.87 (dd, *J*=10.0, 3.5 Hz, 1H, H-3″), 5.75 (dd, *J*=3.3, 1.6 Hz, 1H, H-2″), 5.66 (t, *J*=10.1 Hz, 1H, H-4″), 5.61 (d, *J*=1.3 Hz, 1H, H-1″), 5.35 (dq, *J*=17.3, 1.6 Hz, 1H, H-3_{Allyl}), 5.24 (dq, *J*=10.5, 1.3 Hz, 1H, H-3_{Allyl}), 4.75 (d, *J*=2.2 Hz, 1H, H-29), 4.61 (m, 1H, H-29), 4.58 (m, 2H, H-1_{Allyl}), 4.51 (dd, *J*=9.4, 5.8 Hz, 1H, H-5″), 4.47 (d, *J*=7.5 Hz, 1H, H-1′), 4.26 (m, 2H, H-3′, H-4′), 4.16 (dd, *J*=13.0, 1.9 Hz, 1H, H-5′), 3.90 (t, *J*=7.3 Hz, 1H, H-2′), 3.81 (dd, *J*=13.0, 3.0 Hz, 1H, H-5′), 3.16 (dd, *J*=11.9, 4.8 Hz, 1H, H-3), 3.03 (td, *J*=11.3, 4.5 Hz, 1H, H-19), 2.31–2.18 (m, 2H), 1.96–1.72 (m, 4H), 1.70 (s, 3H, H-30), 1.55 (s, 3H, $(CH_3)_2C$), 1.35 (d, *J*=5.8 Hz, 3H, H-6″), 1.34 (s, 3H, $(CH_3)_2C$), 1.23 (s, 3H, H-23), 0.98 (s, 3H, H-27), 0.93 (s, 3H, H-24), 0.92 (s, 3H, H-26), 0.84 (s, 3H, H-25), 0.77 (d, *J*=9.4 Hz, 1H, H-5). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 175.8 (C-28), 165.8–165.4 (3×*C*O), 150.6 (C-20), 133.4–133.0 (C–Ar), 132.6 (C-2_{Allyl}), 130.0–128.2 (C–Ar), 118.1 (C-3_{Allyl}), 110.4 ($(CH_3)_2C$), 109.6 (C-29), 103.3 (C-1′), 95.2 (C-1″), 89.2 (C-3), 79.2 (C-3′), 75.3 (C-2′), 73.4 (C-4′), 72.0 (C-4″), 70.6 (C-2″), 69.9 (C-3″), 66.5 (C-5″), 64.6 (C-1_{Allyl}), 62.7 (C-5′), 56.6 (C-17), 56.0 (C-5), 50.6 (C-9), 49.5 (C-18), 47.0 (C-19), 42.4 (C-14), 40.8 (C-8), 39.3 (C-4), 39.0 (C-1), 38.3 (C-13), 37.0 (C-22), 37.0 (C-10), 34.4 (C-7), 32.2 (C-16), 30.6 (C-21), 29.7 (C-15), 28.1 (C-23), 27.8 ($(CH_3)_2C$), 26.3 (C-2), 26.1 ($(CH_3)_2C$), 25.6 (C-12), 20.9 (C-11), 19.4 (C-30), 18.2 (C-6), 17.6 (C-6″), 16.6 (C-24), 16.2 (C-25), 16.0 (C-26), 14.7 (C-27). HR-ESI-MS *m*/*z* 1149.5898 $[M+Na]^+$ (calcd for $C_{68}H_{86}O_{14}Na$: 1149.5910).

4.17. Betulin 3β-*O*-2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl-(1→2)-3,4-*O*-isopropylidene-α-L-arabinopyranoside (22a)

To a solution of **21a** (250 mg, 0.191 mmol) in anhydrous THF (2.08 mL) was added HOAc (120 μL, 2.10 mmol) and 1 M TBAF in THF (2.08 mL) at room temperature under an argon atmosphere. The reaction mixture was refluxed overnight or until TLC (CH_2Cl_2/MeOH 9:1) showed the disappearance of the initial product. Then, the mixture was diluted with CH_2Cl_2, washed with H_2O, dried over anhydrous $MgSO_4$, filtered and the solvents were evaporated under reduced pressure. The resulting residue was purified by flash chromatography (hexanes/EtOAc 9:1 to 7:3) to furnish **22a** (125 mg, 72%, corrected yield) as a white amorphous powder along with **21a** (28 mg, 11%, recovery yield). R_f 0.20 (hexanes/EtOAc 3:1); $[\alpha]_D^{25}$ +91.2 (*c* 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.14–7.21 (m, 15H, H–Ar), 5.87 (dd, *J*=10.2, 3.5 Hz, 1H, H-3″), 5.75 (dd, *J*=3.3, 1.6 Hz, 1H, H-2″), 5.66 (t, *J*=10.0 Hz, 1H, H-4″), 5.57 (d, *J*=1.1 Hz, 1H, H-1″), 4.69 (d, *J*=1.4 Hz, 1H, H-29), 4.59 (br s, 1H, H-29), 4.51 (dq, 10.0, 6.3 Hz, 1H, H-5″), 4.47 (d, *J*=7.5 Hz, 1H, H-1′), 4.27 (m, 1H, H-3′), 4.26 (m, 1H, H-4′), 4.16 (d, *J*=13.4 Hz, 1H, H-5′), 3.90 (t, *J*=7.0 Hz, 1H, H-2′), 3.85 (m, 1H, H-28), 3.84 (m, 1H, H-5′), 3.34 (d, *J*=10.8 Hz, 1H, H-28), 3.16 (dd, *J*=11.9, 4.6 Hz, 1H, H-3), 2.40 (td, *J*=10.7, 5.7 Hz, 1H, H-19), 2.04–1.80 (m, 4H), 1.69 (s, 3H, H-30), 1.55 (s, 3H, $(CH_3)_2C$), 1.35 (d, *J*=6.2 Hz, 3H, H-6″), 1.34 (s, 3H, $(CH_3)_2C$), 1.24 (s, 3H, H-23), 1.03 (s, 3H, H-26), 0.99 (s, 3H, H-27), 0.93 (s, 3H, H-24), 0.85 (s, 3H, H-25), 0.77 (d, *J*=10.0 Hz, 1H, H-5). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.8–165.4 (3×*C*O), 150.5 (C-20), 133.4–128.2 (C–Ar), 110.4 ($(CH_3)_2C$), 109.7 (C-29), 103.3 (C-1′), 95.2 (C-1″), 89.2 (C-3), 79.2 (C-3′), 75.3 (C-2′), 73.4 (C-4′), 72.0 (C-4″), 70.6 (C-2″), 69.9 (C-3″), 66.5 (C-5″), 62.7 (C-5′), 60.6 (C-28), 55.9 (C-5), 50.4 (C-9), 48.8 (C-18), 47.8 (C-19), 47.8 (C-17), 42.7 (C-14), 41.0 (C-8), 39.3 (C-4), 39.0 (C-1), 37.3 (C-13), 36.9 (C-10), 34.2 (C-22), 34.0 (C-7), 29.8 (C-21), 29.2 (C-16), 28.1 (C-23), 27.8 ($(CH_3)_2C$), 27.0 (C-15), 26.3 (C-2), 26.1 ($(CH_3)_2C$), 25.2 (C-12), 20.8 (C-11), 19.1 (C-30), 18.2 (C-6), 17.5 (C-6″), 16.5 (C-24), 16.2 (C-25), 16.0 (C-26), 14.7 (C-27). HR-ESI-MS *m*/*z* 1095.5798 $[M+Na]^+$ (calcd for $C_{65}H_{84}O_{13}Na$: 1095.5804).

4.18. Betulinic acid 3β-*O*-2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl-(1→2)-3,4-*O*-isopropylidene-α-L-arabinopyranoside (22b)

This compound was prepared from **21b** (100 mg, 0.089 mmol) in the same manner as that described for compound **19a**. Purification by flash chromatography (hexanes/EtOAc 9:1 to 100% EtOAc) gave **22b** (82 mg, 85%) as a white amorphous powder. R_f 0.28 (hexanes/EtOAc 3:1); $[\alpha]_D^{25}$ +70.2 (*c* 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.13–7.20 (m, 15H, H–Ar), 5.86 (dd, *J*=10.2, 3.5 Hz, 1H, H-3″), 5.75 (dd, *J*=3.3, 1.6 Hz, 1H, H-2″), 5.66 (t, *J*=10.0 Hz, 1H, H-4″), 5.60 (d, *J*=1.2 Hz, 1H, H-1″), 4.76 (br s, 1H, H-29), 4.62 (br s, 1H, H-29), 4.50 (m, 1H, H-5″), 4.47 (d, *J*=7.5 Hz, 1H, H-1′), 4.26 (m, 2H, H-3′, H-4′), 4.16 (d, *J*=12.9 Hz, 1H, H-5′), 3.90 (m, 1H, H-2′), 3.80 (d, *J*=12.2 Hz, 1H, H-5′), 3.16 (dd, *J*=11.5, 4.3 Hz, 1H, H-3), 3.01 (td, *J*=10.6, 4.4 Hz, 1H, H-19), 2.31–2.14 (m, 2H), 2.05–1.80 (m, 3H), 1.71 (s, 3H, H-30), 1.55 (s, 3H, $(CH_3)_2$C), 1.34 (s, 3H, $(CH_3)_2$C), 1.33 (d, *J*=6.0 Hz, 3H, H-6″), 1.23 (s, 3H, H-23), 0.99 (s, 3H, H-27), 0.95 (s, 3H, H-26), 0.92 (s, 3H, H-24), 0.84 (s, 3H, H-25), 0.77 (d, *J*=9.4 Hz, 1H, H-5). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 181.4 (C-28), 165.8–165.4 (3×*C*O), 150.5 (C-20), 133.4–128.2 (C–Ar), 110.4 ($(CH_3)_2C$), 109.7 (C-29), 103.3 (C-1′), 95.3 (C-1″), 89.2 (C-3), 79.2 (C-3′), 75.4 (C-2′), 73.4 (C-4′), 72.0 (C-4″), 70.6 (C-2″), 69.9 (C-3″), 66.6 (C-5″), 62.7 (C-5′), 56.4 (C-17), 56.0 (C-5), 50.6 (C-9), 49.3 (C-18), 46.9 (C-19), 42.5 (C-14), 40.8 (C-8), 39.3 (C-4), 39.0 (C-1), 38.4 (C-13), 37.1 (C-22), 37.0 (C-10), 34.4 (C-7), 32.2 (C-16), 30.6 (C-21), 29.7 (C-15), 28.1 (C-23), 27.8 ($(CH_3)_2$C), 26.3 (C-2), 26.1 ($(CH_3)_2$C), 25.6 (C-12), 20.9 (C-11), 19.4 (C-30), 18.2 (C-6), 17.5 (C-6″), 16.5 (C-24), 16.2 (C-25), 16.0 (C-26), 14.7 (C-27). HR-ESI-MS *m*/*z* 1109.5589 $[M+Na]^+$ (calcd for $C_{65}H_{82}O_{14}Na$: 1109.5597).

4.19. Betulin 3β-*O*-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranoside (23a)

To a solution of **22a** (65 mg, 0.061 mmol) in anhydrous CH_2Cl_2/MeOH 1:2 (5.2 mL) was added TsOH·H_2O (9.0 mg, 0.048 mmol) at room temperature under an argon atmosphere. The reaction mixture was stirred overnight at room temperature or until TLC (hexanes/EtOAc 7:3) showed the complete disappearance of the initial product. Then, the mixture was quenched with Et_3N (49 μL, 0.35 mmol) and the solvents were evaporated under reduced pressure. The resulting residue was immediately dissolved in a solution of MeOH/THF/H_2O 1:2:1 (4.2 mL) to which was added NaOH (49 mg, 1.2 mmol). The reaction mixture was stirred for 4.5 h at room temperature or until TLC (CH_2Cl_2/MeOH 9:1) showed the complete disappearance of the benzoylated products and then acidified to pH≈4 with 10% aqueous HCl. The solvents were evaporated under reduced pressure to give a solid residue, which was purified by C-18 reversed phase flash chromatography (MeOH/H_2O 4:1 to 9:1) to afford pure **23a** (42 mg, 84%, two steps) as a white amorphous powder. R_f 0.84 (CH_2Cl_2/MeOH 3:1); $[\alpha]_D^{25}$ −32.8 (*c* 0.1, MeOH). ^{1}H NMR (C_5D_5N, 400 MHz) δ: 6.19 (s, 1H, H-1″), 4.94 (d, *J*=5.4 Hz, 1H, H-1′), 4.90 (br s, 1H, H-29), 4.79 (br s, 1H, H-2″), 4.74 (br s, 1H, H-29), 4.66 (m, 1H, H-3″), 4.62 (m, 1H, H-5″), 4.59 (m, 1H, H-2′), 4.34 (m, 1H, H-4″), 4.33 (m, 1H, H-5′), 4.31 (m, 1H, H-3′), 4.30 (m, 1H, H-4′), 4.10 (dd, *J*=10.2, 4.3 Hz, 1H, H-28), 3.84 (d, *J*=10.0 Hz, 1H, H-5′), 3.69 (dd, *J*=10.5, 4.7 Hz, 1H, H-28), 3.28 (dd, *J*=11.7, 4.1 Hz, 1H, H-3), 2.64 (td, *J*=10.8, 5.9 Hz, 1H, H-19), 2.52–2.40 (m, 2H), 2.23–2.11 (m, 2H), 1.97–1.85 (m, 2H), 1.77 (s, 3H, H-30), 1.66 (d, *J*=6.1 Hz, 3H, H-6″), 1.20 (s, 3H, H-23), 1.10 (s, 3H, H-24), 1.09 (s, 3H, H-27), 0.98 (s, 3H, H-26), 0.82 (s, 3H, H-25), 0.75 (d, *J*=10.8 Hz, 1H, H-5). ^{13}C NMR (C_5D_5N, 100 MHz) δ: 151.6 (C-20), 110.3 (C-29), 105.2 (C-1′), 102.2 (C-1″), 89.2 (C-3), 76.4 (C-2′), 74.5 (C-4″), 74.2 (C-3′), 73.0 (C-3″), 72.8 (C-2″), 70.3 (C-5″), 69.1 (C-4′), 65.1 (C-5′), 59.8 (C-28), 56.3 (C-5), 51.0 (C-9), 49.5 (C-18), 48.9 (C-17), 48.7 (C-19), 43.3 (C-14), 41.5 (C-8), 40.0 (C-4), 39.5 (C-1), 37.9 (C-13), 37.5 (C-10), 35.2 (C-22), 34.9 (C-7), 30.8 (C-21), 30.4 (C-16), 28.3 (C-23), 27.9 (C-15), 27.1 (C-2), 26.1 (C-12), 21.4 (C-11), 19.6 (C-30), 19.0 (C-6″), 18.9 (C-6), 17.2 (C-24), 16.8 (C-25), 16.5 (C-26), 15.3 (C-27). HR-ESI-MS *m*/*z* 743.4696 $[M+Na]^+$ (calcd for $C_{41}H_{68}O_{10}Na$: 743.4705).

4.20. Betulinic acid 3β-*O*-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranoside (23b)

This compound was prepared from **22b** (50 mg, 0.046 mmol) in the same manner as that described for compound **23a**. Purification by C-18 reversed phase flash chromatography (MeOH/H_2O 4:1 to 9:1) gave pure **23b** (20 mg, 61%, two steps) as a white amorphous powder. R_f 0.86 (CH_2Cl_2/MeOH 3:1); $[\alpha]_D^{25}$ −37.7° (*c* 0.1, MeOH). ^{1}H NMR (CD_3OD, 400 MHz) δ: 5.10 (d, *J*=1.1 Hz, 1H, H-1″), 4.70 (br s, 1H, H-29), 4.56 (br s, 1H, H-29), 4.52 (d, *J*=4.6 Hz, 1H, H-1′), 3.88 (dd, *J*=3.2, 1.6 Hz, 1H, H-2″), 3.84 (m, 1H, H-5′), 3.81 (m, 1H, H-5″), 3.79 (m, 1H, H-4′), 3.76 (m, 1H, H-2′), 3.74 (m, 1H, H-4″), 3.69 (m, 1H, H-3″), 3.48 (dd, *J*=11.4, 2.4 Hz, 1H, H-5′), 3.38 (t, *J*=9.5 Hz, 1H, H-3′), 3.10 (m, 2H, H-3, H-19), 2.43 (td, *J*=12.1, 2.7 Hz, 1H, H-13), 2.25 (dt, *J*=12.6, 3.0 Hz, 1H, H-16), 2.00–1.78 (m, 3H), 1.69 (s, 3H, H-30), 1.23 (d, *J*=6.2 Hz, 3H, H-6″), 1.00 (s, 6H, H-23, H-27), 0.99 (s, 3H, H-26), 0.87 (s, 3H, H-25), 0.82 (s, 3H, H-23), 0.75 (d, *J*=9.4 Hz, 1H, H-5). ^{13}C NMR (CD_3OD, 100 MHz) δ: 181.9 (C-28), 152.5 (C-20), 109.8 (C-29), 104.8 (C-1′), 102.0 (C-1″), 90.6 (C-3), 76.8 (C-2′), 73.9 (C-3′), 73.1 (C-4″), 72.2 (C-3″), 72.1 (C-2″), 70.2 (C-5″), 68.4 (C-4′), 63.8 (C-5′), 58.1 (C-17), 57.2 (C-5), 52.1 (C-9), 50.7 (C-18), 48.5 (C-19), 43.6 (C-14), 42.0 (C-8), 40.4 (C-4), 40.2 (C-1), 39.5 (C-13), 38.6 (C-22), 38.1 (C-10), 35.6 (C-7), 33.9 (C-16), 31.9 (C-21), 31.0 (C-15), 28.5 (C-23), 27.2 (C-2), 27.0 (C-12), 22.2 (C-11), 19.6 (C-30), 19.3 (C-6), 18.0 (C-6″), 16.9 (C-24), 16.9 (C-25), 16.8 (C-26), 15.2 (C-27). HR-ESI-MS *m*/*z* 757.4488 $[M+Na]^+$ (calcd for $C_{41}H_{66}O_{11}Na$: 757.4497).

4.21. Allyl betulinate 3β-*O*-2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranoside (24)

To a solution of **21b** (200 mg, 0.046 mmol) in anhydrous CH_2Cl_2/MeOH 1:2 (13.3 mL) was added TsOH·H_2O (23 mg, 0.12 mmol) at room temperature under an argon atmosphere. The reaction mixture was stirred overnight at room temperature or until TLC (hexanes/EtOAc 7:3) showed the complete disappearance of the initial product. Then, the mixture was quenched with Et_3N (124 μL, 0.887 mmol) and the solvents were evaporated under reduced pressure to give a solid residue, which was purified by flash chromatography (hexanes/EtOAc 4:1 to 2:3) to furnish **24** (133 mg, 70%) as a white crystalline powder. R_f 0.15 (hexanes/EtOAc 3:1); $[\alpha]_D^{25}$ +52.5 (*c* 0.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.12–7.23 (m, 15H, H–Ar), 5.93 (ddt, *J*=17.2, 10.4, 5.7 Hz, 1H, H-2_{Allyl}), 5.83 (dd, *J*=10.2, 3.4 Hz, 1H, H-3″), 5.71 (m, 1H, H-2″), 5.69 (m, 1H, H-4″), 5.38 (d, *J*=1.3 Hz, 1H, H-1″), 5.34 (dq, *J*=17.2, 1.5 Hz, 1H, H-3_{Allyl}), 5.24 (dq, *J*=10.4, 1.3 Hz, 1H, H-3_{Allyl}), 4.80 (d, *J*=3.3 Hz, 1H, H-1′), 4.74 (d, *J*=2.1 Hz, 1H, H-29), 4.61 (m, 1H, H-29), 4.58 (m, 2H, H-1_{Allyl}), 4.36 (ddt, *J*=9.7, 6.3, 6.2 Hz, 1H, H-5″), 4.03 (m, 1H, H-4′), 4.01 (m, 1H, H-3′), 3.99 (m, 1H, H-2′), 3.83 (dd, *J*=11.8, 7.6 Hz, 1H, H-5′), 3.68 (dd, *J*=11.7, 4.2 Hz, 1H, H-5′), 3.15 (dd, *J*=11.5, 4.5 Hz, 1H, H-3), 3.02 (td, *J*=11.1, 4.2 Hz, 1H, H-19), 2.30–2.18 (m, 2H), 1.95–1.83 (m, 3H), 1.69 (s, 3H, H-30), 1.34 (d, *J*=6.3 Hz, 3H, H-6″), 1.04 (s, 3H, H-23), 0.96 (s, 3H, H-27), 0.92 (s, 3H, H-26), 0.83 (s, 6H, H-23, H-25), 0.72 (d, *J*=8.9 Hz, 1H, H-5). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 175.7 (C-28), 165.8–165.5 (3×*C*O), 150.5 (C-20), 133.5–133.1 (C–Ar), 132.5 (C-2_{Allyl}), 129.9–128.3 (C–Ar), 118.1 (C-3_{Allyl}), 109.6 (C-29), 102.1 (C-1′), 98.2 (C-1″), 90.3 (C-3), 76.2 (C-2′), 71.6 (C-4″), 70.9 (C-3′), 70.7 (C-2″), 69.8 (C-3″), 67.2 (C-5″), 65.6 (C-4′), 64.6 (C-1_{Allyl}), 61.3 (C-5′), 56.5 (C-17), 55.6 (C-5), 50.5 (C-9), 49.4 (C-18), 46.9 (C-19), 42.4 (C-14), 40.7 (C-8), 39.2 (C-4), 38.8 (C-1), 38.2 (C-13), 37.0 (C-22), 36.9 (C-10), 34.2 (C-7), 32.1 (C-16), 30.6 (C-21), 29.6 (C-15), 28.0 (C-23), 26.0 (C-2), 25.5 (C-12), 20.9 (C-11), 19.4 (C-30), 18.2 (C-6), 17.5

(C-6″), 16.3 (C-24), 16.1 (C-25), 16.0 (C-26), 14.7 (C-27). HR-ESI-MS m/z 1109.5589 $[M+Na]^+$ (calcd for $C_{65}H_{82}O_{14}Na$: 1109.5597).

4.22. Allyl betulinate 3β-*O*-2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl-(1→2)-[2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→4)]-α-L-arabinopyranoside (25)

The acceptor **24** (38.5 mg, 0.036 mmol) and the donor **5** (41 mg, 0.055 mmol) were stirred in anhydrous CH_2Cl_2 (1.5 mL) with 4 Å MS under an argon atmosphere for 40 min. The temperature was lowered to −10 °C with an ice water/acetone bath, then a solution of TMSOTf in CH_2Cl_2 (100 μL, 40 mM) was injected in the medium via a dry syringe while keeping rigorous anhydrous conditions. The reaction mixture was stirred while the temperature was gradually raised to room temperature over 3 h and quenched by addition of Et_3N (21 μL, 0.15 mmol). The solvents were evaporated under reduced pressure to give a residue, which was purified by flash chromatography (hexanes/EtOAc 9:1 to 1:1) to afford **25** (20 mg, 50%, corrected yield) as a white crystalline powder along with **24** (6 mg, 15%, recovery yield). R_f 0.32 (hexanes/EtOAc 3:1); $[\alpha]_D^{25}$ +52.0 (c 0.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.11–7.22 (m, 35H, H–Ar), 5.93 (m, 1H, H-3‴), 5.92 (m, 1H, H-2_{Allyl}), 5.79 (dd, J=10.2, 3.4 Hz, 1H, H-3″), 5.70 (t, J=9.7 Hz, 1H, H-4‴), 5.62 (m, 2H, H-2″, H-4″), 5.59 (m, 1H, H-2‴), 5.33 (dq, J=17.2, 1.5 Hz, 1H, H-3_{Allyl}), 5.23 (dq, J=10.4, 1.3 Hz, 1H, H-3_{Allyl}), 5.19 (d, J=1.6 Hz, 1H, H-1″), 5.12 (d, J=7.9 Hz, 1H, H-1‴), 4.74 (m, 1H, H-29), 4.71 (m, 1H, H-6‴), 4.65 (d, J=3.8 Hz, 1H, H-1′), 4.60 (m, 1H, H-29), 4.59 (m, 2H, H-1_{Allyl}), 4.51 (m, 1H, H-6‴), 4.31 (m, 1H, H-5″), 4.25 (m, 1H, H-5‴), 4.09 (m, 1H, H-5′), 4.07 (m, 1H, H-4′), 3.90 (m, 1H, H-3′), 3.83 (m, 1H, H-2′), 3.68 (m, 1H, H-5′), 3.07 (m, 1H, H-3), 3.02 (m, 1H, H-19), 2.30–2.12 (m, 2H), 1.95–1.70 (m, 3H), 1.69 (s, 3H, H-30), 1.29 (d, J=6.2 Hz, 3H, H-6″), 1.00 (s, 3H, H-23), 0.94 (s, 3H, H-27), 0.89 (s, 3H, H-26), 0.80 (s, 3H, H-25), 0.78 (s, 3H, H-24), 0.68 (d, J=9.1 Hz, 1H, H-5). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 175.7 (C-28), 166.1–165.1 (7×*C*O), 150.6 (C-20), 133.5–133.1 (C–Ar), 132.6 (C-2_{Allyl}), 129.9–128.3 (C–Ar), 118.1 (C-3_{Allyl}), 109.6 (C-29), 102.4 (C-1′), 101.9 (C-1‴), 97.9 (C-1″), 90.3 (C-3), 76.0 (C-4′), 76.0 (C-2′), 72.8 (C-3‴), 72.3 (C-5‴), 72.0 (C-2‴), 71.7 (C-4″), 70.7 (C-2″), 70.6 (C-3′), 69.8 (C-3″), 69.6 (C-4‴), 67.0 (C-5″), 64.6 (C-1_{Allyl}), 63.0 (C-6‴), 60.6 (C-5′), 56.6 (C-17), 55.7 (C-5), 50.6 (C-9), 49.5 (C-18), 46.9 (C-19), 42.4 (C-14), 40.7 (C-8), 39.2 (C-4), 38.8 (C-1), 38.2 (C-13), 37.0 (C-22), 36.9 (C-10), 34.3 (C-7), 32.1 (C-16), 30.6 (C-21), 29.6 (C-15), 28.1 (C-23), 25.9 (C-2), 25.5 (C-12), 20.9 (C-11), 19.4 (C-30), 18.2 (C-6), 17.5 (C-6″), 16.3 (C-24), 16.2 (C-25), 16.0 (C-26), 14.7 (C-27). HR-ESI-MS m/z 1687.7167 $[M+Na]^+$ (calcd for $C_{99}H_{108}O_{23}Na$: 1687.7174).

4.23. Betulinic acid 3β-*O*-α-L-rhamnopyranosyl-(1→2)-[β-D-glucopyranosyl-(1→4)]-α-L-arabinopyranoside (3)

To a solution of **25** (17 mg, 0.010 mmol) and PPh_3 (2.7 mg, 0.010 mmol) in anhydrous THF (>0.10 mL) was added $Pd^0(PPh_3)_4$ (5.9 mg, 0.005 mmol) followed by pyrrolidine (2.0 μL, 0.024 mmol) at room temperature under an argon atmosphere. The reaction mixture was stirred for 4.5 h in the dark at room temperature or until TLC (hexanes/EtOAc 7:3) showed the disappearance of the initial product. Then, the solvents were evaporated under reduced pressure and the resulting red-yellow residue was immediately dissolved in a solution of MeOH/THF/H_2O 1:2:1 (0.72 mL) to which was added NaOH (8.4 mg, 0.21 mmol). The reaction mixture was stirred for 6 h at room temperature or until TLC (CH_2Cl_2/MeOH 4:1) showed the complete disappearance of the benzoylated product and then acidified to pH ≈ 4 with 10% aqueous HCl. The solvents were evaporated under reduced pressure to give a solid residue, which was purified by C-18 reversed phase flash chromatography (MeOH/H_2O 3:2 to 4:1) to afford pure **3** (5.4 mg, 60%, two steps) as a white amorphous powder. R_f 0.68 (CH_2Cl_2/MeOH 3:1); $[\alpha]_D^{25}$ −24.6 (c 0.1, MeOH). ^1H NMR (C_5D_5N, 700 MHz) δ: 6.21 (br s, 1H, H-1″), 5.16 (d, J=7.9 Hz, 1H, H-1‴), 4.94 (m, 1H, H-29), 4.79 (d, J=6.1 Hz, 1H, H-1′), 4.76 (m, 2H, H-2″, H-29), 4.65 (m, 1H, H-5″), 4.64 (m, 1H, H-3″), 4.53 (m, 1H, H-2′), 4.52 (m, 1H, H-6‴), 4.42 (dd, J=12.2, 3.9 Hz, 1H, H-5′), 4.40 (dd, J=12.0, 5.0 Hz, 1H, H-6‴), 4.34 (t, J=9.4 Hz, 1H, H-4″), 4.30 (m, 1H, H-4′), 4.28 (t, J=9.3 Hz, 1H, H-4‴), 4.27 (m, 1H, H-3′), 4.23 (t, J=9.0 Hz, 1H, H-3‴), 4.07 (t, J=8.5 Hz, 1H, H-2‴), 3.92 (ddd, J=9.5, 5.1, 2.3 Hz, 1H, H-5‴), 3.81 (d, J=11.7 Hz, 1H, H-5′), 3.57 (td, J=10.7, 4.5 Hz, 1H, H-19), 3.22 (dd, J=11.7, 4.2 Hz, 1H, H-3), 2.78 (m, 1H, H-13), 2.66 (m, 1H, H-16), 2.29–2.22 (m, 2H), 2.08 (m, 1H, H-2), 1.95 (m, 1H, H-12), 1.87 (m, 1H, H-15), 1.78 (s, 3H, H-30), 1.76 (t, J=11.4 Hz, 1H, H-18), 1.65 (d, J=6.2 Hz, 3H, H-6″), 1.61–1.21 (m, 12H), 1.18 (s, 3H, H-23), 1.10 (s, 3H, H-27), 1.09 (s, 3H, H-24), 1.02 (s, 3H, H-26), 0.77 (s, 3H, H-25), 0.72 (d, J=11.9 Hz, 1H, H-5). ^{13}C NMR (C_5D_5N, 175 MHz) δ: 179.6 (C-28), 151.8 (C-20), 110.2 (C-29), 106.7 (C-1‴), 105.3 (C-1′), 102.1 (C-1″), 89.1 (C-3), 80.0 (C-4′), 79.1 (C-5‴), 78.8 (C-3‴), 76.7 (C-2′), 75.8 (C-2‴), 74.4 (C-4‴), 74.3 (C-4″), 72.8 (C-3″), 72.6 (C-2″), 71.5 (C-3′), 70.1 (C-5″), 64.9 (C-5′), 62.8 (C-6‴), 57.1 (C-17), 56.4 (C-5), 51.1 (C-9), 50.1 (C-18), 48.1 (C-19), 43.1 (C-14), 41.3 (C-8), 39.9 (C-4), 39.4 (C-1), 38.8 (C-13), 38.0 (C-22), 37.4 (C-10), 35.0 (C-7), 33.3 (C-16), 31.6 (C-21), 30.6 (C-15), 28.2 (C-23), 27.1 (C-2), 26.4 (C-12), 21.5 (C-11), 19.8 (C-30), 19.0 (C-6″), 18.8 (C-6), 17.1 (C-24), 16.7 (C-25), 16.7 (C-26), 15.1 (C-27). HR-ESI-MS m/z 919.5018 $[M+Na]^+$ (calcd for $C_{47}H_{76}O_{16}Na$: 919.5026).

4.24. 28-*O*-2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl betulinic acid 3β-*O*-2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl-(1→2)-3,4-*O*-isopropylidene-α-L-arabinopyranoside (26)

To a solution of the acceptor **22b** (30 mg, 0.028 mmol) and the donor **7** (27 mg, 0.041 mmol) in CH_2Cl_2 (0.32 mL) were added H_2O (0.32 mL), K_2CO_3 (9.5 mg, 0.069 mmol) and Bu_4NBr (3.6 mg, 0.011 mmol). The resulting mixture was vigorously stirred and refluxed for 6 h. Then, the mixture was diluted with CH_2Cl_2, washed with H_2O and brine. The solvents of the dried ($MgSO_4$) organic solution were evaporated under reduced pressure to give a brown residue, which was purified by flash chromatography (hexanes/EtOAc 9:1 to 3:2) to afford **26** (36 mg, 78%) as a white amorphous powder. R_f 0.20 (hexanes/EtOAc 3:1); $[\alpha]_D^{25}$ +93.0 (c 0.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.12–7.22 (m, 35H, H–Ar), 6.03 (d, J=9.7 Hz, 1H, H-1‴), 6.01 (t, J=8.3 Hz, 1H, H-3‴), 5.86 (dd, J=10.2, 3.5 Hz, 1H, H-3″), 5.76 (t, J=9.1 Hz, 1H, H-2‴), 5.75 (m, 1H, H-2″), 5.73 (t, J=9.7 Hz, 1H, H-4‴), 5.67 (t, J=10.0 Hz, 1H, H-4″), 5.61 (d, J=1.6 Hz, 1H, H-1″), 4.71 (d, J=1.8 Hz, 1H, H-29), 4.58 (m, 1H, H-29), 4.59 (m, 1H, H-6‴), 4.49 (m, 1H, H-6‴), 4.51 (m, 1H, H-5″), 4.45 (d, J=7.5 Hz, 1H, H-1′), 4.29 (m, 1H, H-5‴), 4.25 (m, 1H, H-4′), 4.25 (m, 1H, H-3′), 4.15 (dd, J=13.4, 1.6 Hz, 1H, H-5′), 3.89 (m, 1H, H-2′), 3.78 (dd, J=12.7, 2.6 Hz, 1H, H-5′), 3.11 (dd, J=11.5, 4.6 Hz, 1H, H-3), 2.93 (td, J=11.0, 4.7 Hz, 1H, H-19), 2.17 (m, 1H, H-16), 2.05 (td, J=12.1, 3.2 Hz, 1H, H-13), 1.96–1.66 (m, 4H), 1.64 (br s, 3H, H-30), 1.54 (s, 3H, (*C*H_3)$_2$C), 1.36 (d, J=6.2 Hz, 3H, H-6″), 1.33 (s, 3H, (*C*H_3)$_2$C), 1.18 (s, 3H, H-23), 0.90 (s, 3H, H-24), 0.80 (s, 3H, H-27), 0.71 (s, 3H, H-25), 0.63 (d, J=11.9 Hz, 1H, H-5), 0.49 (s, 3H, H-26). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 174.1 (C-28), 166.1–164.7 (7×*C*O), 150.3 (C-20), 133.6–128.3 (C–Ar), 110.4 ((*C*H_3)$_2$*C*), 109.6 (C-29), 103.3 (C-1′), 95.2 (C-1″), 91.4 (C-1‴), 89.1 (C-3), 79.2 (C-3′), 75.3 (C-2′), 73.4 (C-4′), 73.0 (C-5‴), 72.9 (C-3‴), 72.1 (C-4″), 70.6 (C-2″), 70.3 (C-2‴), 70.0 (C-3″), 69.4 (C-4‴), 66.5 (C-5″), 62.8 (C-6‴), 62.7 (C-5′), 56.8 (C-17), 55.8 (C-5), 50.4 (C-9), 49.1 (C-18), 46.7 (C-19), 42.2 (C-14), 40.3 (C-8), 39.2 (C-4), 38.9 (C-1), 38.0 (C-13), 36.8 (C-10), 36.3 (C-22), 33.4 (C-7), 31.5 (C-16), 30.3 (C-21), 29.9 (C-15), 28.1 (C-23), 27.8 ((*C*H_3)$_2$C), 26.2 (C-2), 26.1 ((*C*H_3)$_2$C), 25.5 (C-12), 20.8 (C-11), 19.5 (C-30), 17.9 (C-6), 17.6 (C-6″), 16.6 (C-24), 16.1 (C-25), 15.4 (C-26), 14.5 (C-27). HR-ESI-MS m/z 1687.7157 $[M+Na]^+$ (calcd for $C_{99}H_{108}O_{23}Na$: 1687.7174).

4.25. 28-*O*-β-D-Glucopyranosyl betulinic acid 3β-*O*-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranoside (4)

This compound was prepared from **26** (80 mg, 0.048 mmol) in the same manner as that described for compound **23a**. Purification by C-18 reversed phase flash chromatography ($MeOH/H_2O$ 3:2 to 3:1) afforded pure **4** (35 mg, 82%, two steps) as a white amorphous powder. R_f 0.49 (CH_2Cl_2/MeOH 3:1); $[\alpha]_D^{25}$ −36.0 (*c* 0.1, MeOH); ^1H NMR (CD_3OD, 400 MHz) δ: 5.49 (d, *J*=8.2 Hz, 1H, H-1‴), 5.10 (d, *J*=1.4 Hz, 1H, H-1″), 4.71 (d, *J*=1.6 Hz, 1H, H-29), 4.59 (br s, 1H, H-29), 4.53 (d, *J*=4.6 Hz, 1H, H-1′), 3.87 (dd, *J*=3.3, 1.7 Hz, 1H, H-2″), 3.84 (m, 1H, H-6‴), 3.83 (m, 1H, H-5′), 3.80 (m, 1H, H-5″), 3.78 (m, 1H, H-4′), 3.76 (m, 1H, H-2′), 3.74 (m, 1H, H-3′), 3.70 (m, 1H, H-6‴), 3.69 (m, 1H, H-3″), 3.47 (m, 1H, H-5′), 3.42 (m, 1H, H-3‴), 3.38 (m, 1H, H-5‴), 3.38 (m, 1H, H-4″), 3.37 (m, 1H, H-4‴), 3.32 (m, 1H, H-2‴), 3.08 (dd, *J*=11.4, 4.3 Hz, 1H, H-3), 3.00 (td, *J*=11.0, 4.6 Hz, 1H, H-19), 2.39–2.27 (m, 2H), 2.03–1.78 (m, 3H), 1.70 (s, 3H, H-30), 1.21 (d, *J*=6.2 Hz, 3H, H-6″), 1.00 (s, 3H, H-27), 0.99 (s, 3H, H-23), 0.96 (s, 3H, H-26), 0.87 (s, 3H, H-25), 0.82 (s, 3H, H-24), 0.74 (d, *J*=9.1 Hz, 1H, H-5). ^{13}C NMR (CD_3OD, 100 MHz) δ: 176.2 (C-28), 151.9 (C-20), 110.3 (C-29), 104.8 (C-1′), 102.1 (C-1″), 95.2 (C-1‴), 90.7 (C-3), 78.8 (C-5‴), 78.4 (C-3‴), 76.9 (C-2′), 74.1 (C-2‴), 73.9 (C-4″), 73.1 (C-3′), 72.2 (C-2″), 72.2 (C-3″), 71.1 (C-4‴), 70.2 (C-5″), 68.4 (C-4′), 63.8 (C-5′), 62.4 (C-6‴), 57.9 (C-17), 57.2 (C-5), 52.0 (C-9), 50.6 (C-18), 48.4 (C-19), 43.6 (C-14), 42.1 (C-8), 40.4 (C-4), 40.2 (C-1), 39.4 (C-13), 38.1 (C-10), 37.5 (C-22), 35.5 (C-7), 32.8 (C-16), 31.5 (C-21), 30.8 (C-15), 28.5 (C-23), 27.2 (C-2), 26.9 (C-12), 22.1 (C-11), 19.5 (C-30), 19.4 (C-6), 18.0 (C-6″), 16.9 (C-24), 16.9 (C-25), 16.7 (C-26), 15.2 (C-27). HR-ESI-MS *m*/*z* 919.5022 $[M+Na]^+$ (calcd for $C_{47}H_{76}O_{16}Na$: 919.5026).

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