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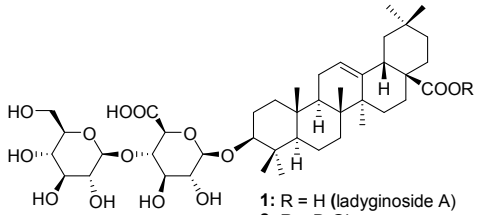
ACCEPTED MANUSCRIPT

Stereocontrolled Synthesis of Oleanolic Saponin Ladyginoside A Isolated from *Ladyginia Bucharica*

Matylda Stefaniak[a], Grzegorz Łopatkiewicz[a], Magdalena Antkowiak[a] and Jacek Mlynarski*[a,b]

Abstract: Efficient stereocontrolled synthesis of ladyginoside A isolated from *Ladyginia bucharica* is described. The presented methodology bases on the β-selective glycosylation to construct oleanate-3-*O*-β-glycoside from selectively protected D-cellobiose comprising desired β-linkage in carbohydrate unit. By using this procedure, dimethyl ester of ladyginoside A (**1**) (methyl oleanate 3-*O*-(β-D-glucopyranosyl)-(1→4)-β-D-glucuronide methyl ester) was obtained in 16% overall yield. Elaborated synthesis is also demonstrated as useful methodology *en route* to saponin **2** with additional glucose unit, namely 3-*O*-[β-D-glucopyranosyl-(1→4)-β-D-glucuronide] oleanolic acid 28-*O*-β-D-glucopyranosyl ester.



1: R = H (ladyginoside A)
2: R = D-Glc

Introduction

Naturally occurring triterpenoid saponins isolated from plants and marine organisms attract the attention of biologists and chemists due to broad spectrum of well-defined biological and pharmacological activities. For the synthetic chemists saponins are interesting targets as their synthesis requires joint effort of specialist in the synthesis of triterpenoids and specialist in the field of carbohydrates.[1,2] Interestingly, more than half of triterpene saponins are glycosides of oleanolic acid or its derivatives, with one or more sugar chain attached through an ether glycosyl linkage at C-3.[3,4] One of such compounds – ladyginoside A (**1**) was initially isolated from *Laginoside bucharcia*[5] and its structure was proved by Abubakirov in early 70s.[6] Interestingly, the same compound was isolated in 1998 from *Polyscias fruticosa* with other saponins named polysciosides A-H.[3] *Polyscias fruticosa* named also Ming aralia is widely cultivated in several countries of southeastern Asia and the tropical islands of the Pacific region. A tonic from leaves have anti-inflammatory, antibacterial and antitoxin properties and helps in digestion. The root is also used due to diuretic, febrifuge and anti-dysentery properties. It is also used in neuralgia and rheumatic pains treatment.[7] However, during the chromatographic isolation of extract from *Polyscias fruticose* Chau found also another oleanolic saponin **2**,[3b] that was originally isolated from *Swartzia simplex* and previously identified as 3-*O*-[β-D-glucopyranosyl-(1→4)-β-D-glucuronide] oleanolic acid 28-*O*-β-D-glucopyranosyl ester (**2**).[8] *Swartzia simplex* extract was also shown to be a potential candidate as a natural molluscicide active compound. In traditional medicine of South America region alcoholic extract of leaves of this plant is used for treatment of liver inflammation.[9] An interesting wide range of pharmacological properties makes these saponins interesting synthetic target.[10] Below, we report a short protocol for stereocontrolled synthesis of **1** and **2** from readily available cellobiose and oleanolic acid.

Results and Discussion

Retrosynthetic analysis of ladyginoside A (1) and 3-*O*-[β-D-glucopyranosyl-(1→4)-β-D-glucuronide] oleanolic acid 28-*O*-β-D-glucopyranosyl ester (2).

The synthetic pathways to ladyginioside A (**1**) and also to 3-*O*-[β-D-glucopyranosyl-(1→4)-β-D-glucuronide] oleanolic acid 28-*O*-β-D-glucopyranosyl ester (**2**) are presented in Scheme 1. Our retrosynthetic analysis of ladyginoside A skeleton illustrates that the structure could be reduced to simple starting materials such as oleanolic acid and protected cellobiose. Thinking in the forward direction, it was envisaged that the stereochemistry control during the crucial glycosylation step might be achieved by using trichloroacetimidate (TCA) donor (**3**), being convenient for the coupling of triterpenoids[2] with sugars by using Schmidt protocol.[11] The application of this concept oleanate 3-*O*-β-glycoside (**4**) could be obtained from distinct fragments: the natural oleanolic acid and the commercially available D-(+)-cellobiose being desired disaccharide fragment (Scheme 1). The idea behind this strategy was to use natural disaccharide with internal β-linkage. Such strategy seems to be far more efficient when compared to broadly used step-by-step monosaccharide coupling.

Using the same protection for all OH groups but one in **4** (Bz vs. 6-*O*-Ac) allows for selective deprotection-oxidation sequence at C-6 position *en route* to glucuronic acid. As a triterpenoid acceptor was chosen selectively protected oleanolic acid. The free carboxyl group at C-28 group in aglycone moiety gives a possibility to functionalize this position with various sugar moieties. The compound (**6**) – direct precursor of another natural saponine **2**, could be obtained by esterification **4** with D-glucose bromide (**7**). Such a strategy is the most convenient methodology *en route* to another natural compound from oleanolic saponin group and also for a broad family of similar saponins in the future.

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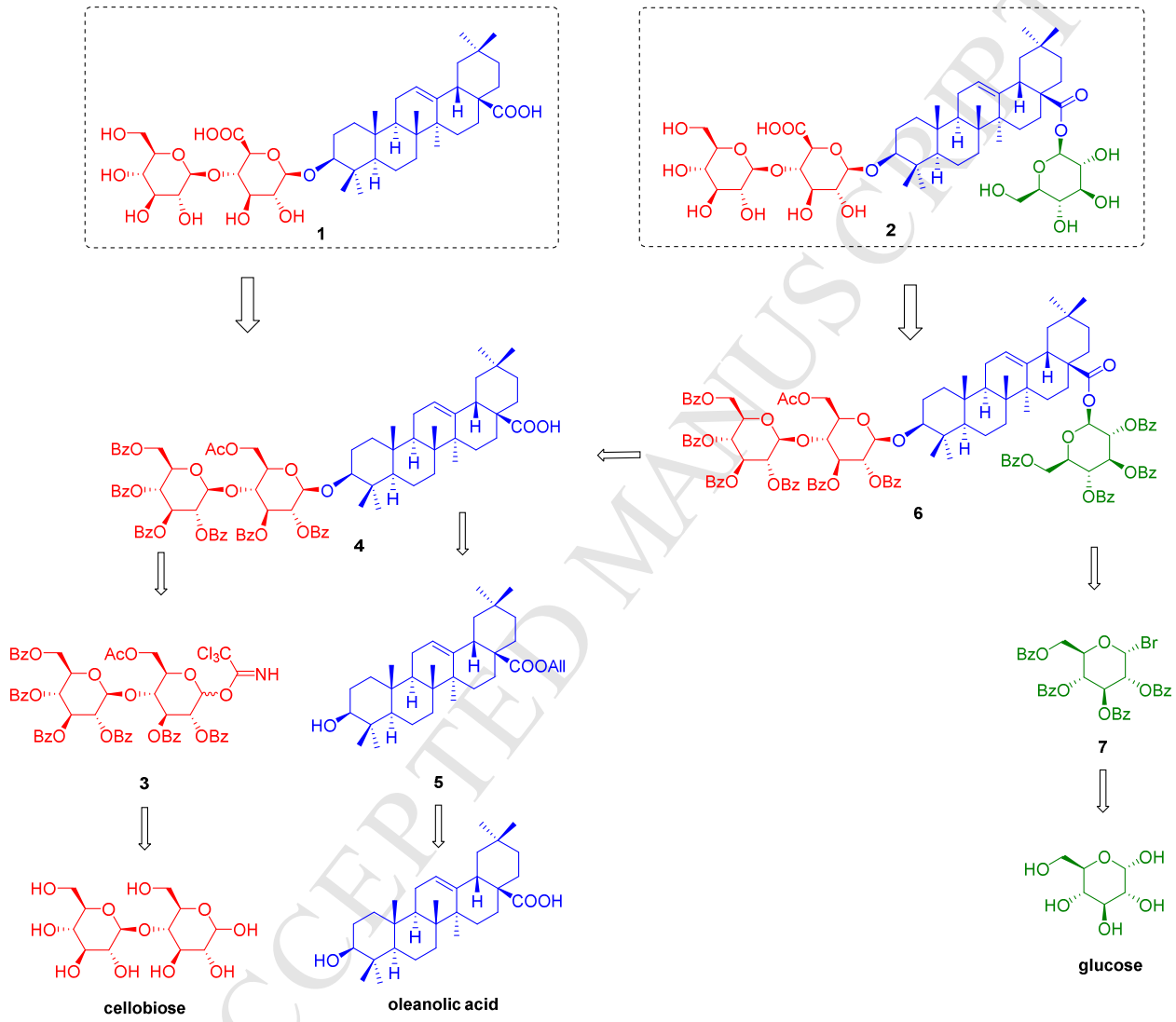
Synthesis of Ladyginoside A (1)

A strategy for convenient preparation of disaccharide fragment is based on the modification of naturally occurring disaccharide D-(+)-cellobiose. This sugar contains fixed β-(1→4)-glycosylic bond and could be directly used for the synthesis of saponins containing this motive in the molecule. Our concept reduce the number of steps in this total synthesis of **1** due to removal of stereo-problematic glycosylation step between two monosaccharide units and acceptor. Most of the previous studies describe the synthesis of similar compound with creating a new bond between two glucose molecules (β-D-Glc-(1→4)-D-Glc,4-O-β-D-Glucopyranosyl-D-glucose) in typical glycosylation (Schmidt or Koenigs–Knorr) reactions.[12,13]



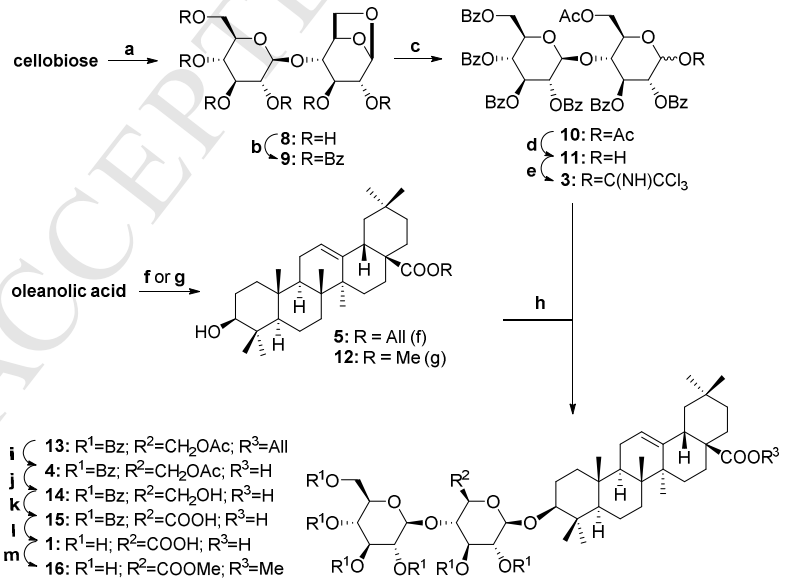
Scheme 1. Retrosynthesis of Ladyginoside A (**1**) and 3-*O*-[β-D-glucopyranosyl-(1→4)-β-D-glucuronide] oleanolic acid 28-*O*-β-D-glucopyranosyl ester (**2**)

So as to use this concept, it was necessary to distinguish between two primary hydroxyl group in 6 and 6' position in sugar unit. To provide efficient access to direct precursor of natural compound **1**, we decided to apply Schmidt glycosylation for **3** and **5** coupling. Keeping the retrosynthetic analysis in mind, we started the synthesis of **3** from the 1,6-anhydrocellobiose (**8**),[14] prepared following Shoda's procedure[15] from commercially available D-(+)-cellobiose (Scheme 2). For synthesis 2-chloro-1,3-dimethyl imidazolinium chloride (DMC) was used as dehydrative condensing agent in the presence of triethylamine (TEA) and water. Next, treatment of compound **8** with benzoyl chloride (BzCl) in pyridine lead to 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→4)-1,6-anhydro-2,3-di-*O*-benzoyl-β-D-glucopyranose (**9**) in 79% yield after two steps. Application of benzoyl groups improves the stereoselection of glycosylation step providing the exclusively formation of β-anomer in the next synthetic steps.[16,17] Differentiation of 6-OH groups took place in the reaction of compound (**9**) with trifluoroacetic acid (TFA) and acetic anhydride (Ac_2O) which affords 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→4)-1,6-di-*O*-acetyl-2,3-di-*O*-benzoyl-α/β-D-glucopyranose (**10**) as a mixture of α- and β-anomer (α:β, 2.85:1.00). In this approach, the application of only two various protecting groups (benzoyl and acetyl) in the whole synthesis is significant facilitation. Benzoyl groups are present in the

molecule to the last step of the synthesis. Acetyl group attached to 6-OH position was maintained during the glycosylation and removed selectively after aglycone coupling. However, deprotection of acetyl residue from the anomeric center was required to convert compound **10** into trichloroacetimidate donor **3**. The selective deacetylation of anomeric position occurred easily by treatment of compound **10** with hydrazine acetate in *N*,*N*-dimethylformamide (DMF) with high yield (89%). Finally, we carried out the trichloroacetimidate formation of free hydroxyl group using modified procedure outlined by Schmidt and co-worker.[16] The preparation of trichloroacetimidate donor **3** (α:β, 5.00:1.00) was achieved in four steps in overall 55% yield (Scheme 2).

Our synthetic strategy assumed coupling of trichloroacedamidate donor (**3**) with triterpenoid acceptor obtained by simple modification of oleanolic acid**.** Direct glycosylation of oleanolic acid (without any protecting group at C-28 position) with various sugar donors resulted in an unselective formation of products. After some trials, we selected allyl ester as the best protecting group for the C-28 position.[10a,d] The methyl group has also been tested as a successful candidate but removal of the methyl ester required harsh conditions. Only halogenolysis of 28-*O*-methyl oleanate (**12**)[18] with lithium iodide (LiI) in refluxing *N,N*-dimethylformamide (DMF) using reported procedure[19] led to deprotection of the carboxylic group in oleanolic acid. Therefore, this method could not be applied for 3-*O*-glycoside because of the sensitive glycosidic bond. Finally the allyl ester **5** was obtained in very good yield (97%) (Scheme 2). Subsequent deprotection of the allyl ester in **5** and then in **13** using tetrakistriphenylphosphine palladium(0) [$Pd^0(PPh_3)_4$], triphenylphosphine (PPh_3) and pyrrolidine in dry tetrahydrofuran (THF) under reported conditions[10] was carried out with good yields 88% and 83% respectively. As is presented on Scheme 2, the assembly of the benzoyl and allyl-protected saponin **13** was achieved by successive glycosylation steps. The coupling of oleanolic ester **5** with trichloroacetimidate **3** was completed in the presence of the catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf) at low temperature in dry dichloromethane (DCM) with molecular sieves (MS) during 3 hours. To our delight this methodology resulted in the exclusive formation of β-anomer of compound **13** in 81%.

Further transformation of compound **13** into the final structure **1** was also collected at Scheme 2. Following the synthetic plan, we converted the glycoside-product **13** to C-28 deprotected acid **4**.[10a] Next step required the deacetylation at 6-OH position. The 6-*O*-acetyl group in compound **4** was removed selectively with acetyl chloride (AcCl) in the mixture of methanol and dichloromethane (DCM). Next, we performed the oxidation of **14** into carboxylic acid with (2,2,6,6-tetramethyl-1-piperidinyl)oxy (TEMPO) and (diacetoxyiodo)benzene (BAIB) under phase-transfer catalyzed condition. The product **15** was obtained with 76% yield. To optimize the whole synthesis, we tested the reverse order of deacetylation-oxidation sequence. In doing so, we have begun with 6-*O*-acetyl group removal followed by 28-*O*-deallyliation gave the product **14** with lower yield. Nevertheless, free COOH group opens the way to functionalization of this position by other sugar chains. Such alternative approach ending up with saponin **2** will be described in the further part of this manuscript. The final deprotection gave access to natural compound **1**. Removal of benzoyl groups in sugar moiety with NaOH in MeOH/DCM, followed by methylation with methyl iodide (MeI) in *N,N*-dimethylformamide (DMF) provided dimethyl ester **16** in good overall yield (98%). The methylation step was necessary to facilitate the isolation, characterization and comparison of obtained compound with literature data.

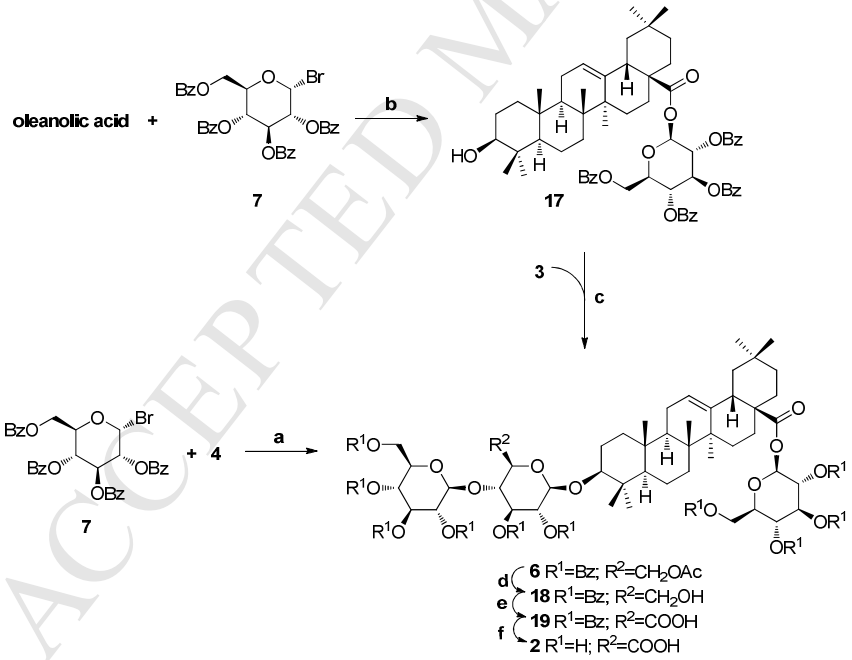


Scheme 2. Synthesis of ladyginoside A (**1**); (a) DMC, TEA, H_2O, 0 °C, 1 h; (b) BzCl, py, Ar, 24 h (79% over 2 steps); (c) Ac_2O, TFA, rt, Ar, 48 h (87%); (d) $H_2NNH_2{\cdot}AcOH$, DMF, rt, Ar, 3 h (89%); (e) Cl_3CCN, DBU, Ar, 3 h (90%); (f) AllBr, K_2CO_3, DMF, rt, Ar, 16 h (97%); (g) MeI, K_2CO_3, DMF, rt, Ar, 24 h (80%); (h) cat. TMSOTf, DCM, MS 4Å, -40 °C to rt, Ar, 3 h (81%); (i) PPh_3, $Pd^0(PPh_3)_4$, Pyr, rt, Ar, 18 h (83%); (j) AcCl, DCM:MeOH (1:1), rt, 18 h (59%); (k) TEMPO, BAIB, DCM:H_2O, rt, 5 h (76%); (l) NaOH, MeOH, rt, 1.5 h (99%); (m) MeI, K_2CO_3, DMF, rt, 18 h (99%).

The NMR spectra recorded for compound **16** in pyridine-d_5 was ultimate confirmation of saponine **1** as such data was described in the literature.[3b] To compare shifts in ^{1}H NMR spectra the signal 3.85 ppm (from 6-*O*-methyl group in sugar moiety of saponin) was chosen as a reference. The same procedure was applied for ^{13}C NMR spectra, as a reference signal 62.5 ppm (from C-6' in sugar moiety of saponin). The full information about NMR shifts are given in the Experimental Section and Supporting Information.

The synthesis 3-*O*-[β-D-glucopyranosyl-(1→4)-β-D-glucuronide] oleanolic acid 28-*O*-β-D-glucopyranosyl ester (2).

The 28-*O*-deallylation (before 6-*O*-acetyl group removal), as mentioned above, give a possibility to functionalize of this position with various sugar moieties. Introduction of glucose unit in C-28 position is the easiest method in this pathway to obtain another natural compound from oleanolic saponin group. According to our retrosynthetic analysis 28-*O*-2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl oleanate 3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→4)-6-*O*-acetyl-2,3-di-*O*-benzoyl-β-D-glucopyranoside (**6**) could be synthesized by simple esterification, this method was presented on Scheme 1. 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (**7**) was selected because of its high reactivity. Moreover, possessing of benzoyl protecting groups favors the formation of β form of 28-*O*-β-D-glucopyranosyl ester. Coupling of oleanolic acid 3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→4)-6-*O*-acetyl-2,3-di-*O*-benzoyl-β-D-glucopyranoside (**4**) with 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (**7**) under the optimized phase transfer-catalyzed conditions (K_2CO_3, Bu_4NBr, DCM-H_2O) gave the 28-*O*-glucosyl ester **6** (Scheme 3) with excellent yield 85%. Application of the previously used benzoyl groups in the glucose units would further facilitate the deprotection under the same condition like for **15** at the final step. Bromide **7** was prepared according to standard methodology with hydrobromic acid (HBr/AcOH) in dry dichloromethane (DCM).[20] Nevertheless, compound **6** could be synthesized in alternative way. This approach is presented at Scheme 3, as a sequence of *b-c* reactions. In this study ester **17** was prepared in the direct esterification between oleanolic acid and bromide **7**, under our previously mentioned conditions (in the phase transfer-catalyzed reaction conditions - K_2CO_3, Bu_4NBr, DCM-H_2O). In the next step we carried out the coupling of trichloroacedimidate **3** with **17**. This developed glycosylation procedure with TMSOTf resulted in the formation of compound **4** with 80% yield. Comparison of both attempts revealed that overall yield for thus presented sequence was lower than for previously presented pathway (first glycosylation **3** with **5** and then esterification **4** with **7**).



Scheme 3. Preparation of 3-*O*-[β-D-glucopyranosyl-(1→4)-β-D-glucopyranosyl] oleanolic acid 28-*O*-β-D-glucopyranosyl ester (**2**); (a) K_2CO_3, DMF, rt, Ar, 18 h (85%); (b) K_2CO_3, DMF, rt, Ar, 6 h (80%); (c) cat. TMSOTf, DCM, MS (4Å), -40 ^{0}C to rt, Ar, 3 h (80%); (d) AcCl, DCM:MeOH, rt, 18 h (63%); (e) TEMPO, BAIB, DCM:H_2O, rt, 5 h (75%); (f) NaOH; MeOH, rt, 2 h.

The last three steps include the same sequence: deacetylation-oxidation-debenzoylation as was described previously. The 6-*O*-acetyl group in 28-*O*-2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl oleanate 3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→4)-6-*O*-acetyl-2,3-di-*O*-benzoyl-β-D-glucopyranoside (**6**) was removed selectively with acetyl chloride (AcCl) in the mixture of methanol and dichloromethane (DCM). The resulting primary alcohol at position 6 was selectively oxidized into carboxylic acid with TEMPO/BAIB conditions (75%). The final removal of benzoyl groups in all sugars moieties with NaOH in MeOH/DCM provided ester **2**. Unfortunately, this additional synthesis of compound **2** ended up with only traces of desired compound and full characterization of final product was not possible. However, HRMS analysis confirmed the presence of **2**

in the reaction mixture. HRMS (negative ion mode) of saponin **2** showed a molecular ion at *m/z* 955.4885 $[M-H]^-$ indicated a M of 956.4903. ^{13}C NMR spectrum of compound **2** was also measured and compared with literature data.[3b] This also confirmed expected structure as presented in Experimental Section.

In conclusion, in this work naturally occurring saponin Ladyginioside A (**1**) and 3-*O*-[β-D-glucopyranosyl-(1→4)-β-D-glucuronide] oleanolic acid 28-*O*-β-D-glucopyranosyl ester (**2**) was successfully synthesized. This natural compound was isolated from *Ladyginia bucharica* in 70s and so far not chemically obtained. Application of oleanolic acid, D-(+)-cellobiose and α-D-glucose as starting material make the method efficient and available. Selection of appropriate protecting group and reactions conditions provided the excellence stereoselectivity and high yields in crucial steps. Saponin **1** was obtained in ten steps for the longest linear route with 16% of yield. The second saponin – compound **2** was synthesized in fully protected form. Therefore, the yield for the total synthesis of second saponin was calculated for protected compound **19**. This compound protected with ten OBz groups was obtained in ten steps for the longest linear route with 14% of yield. Last step deprotection of this compounds turned out to be inefficient and final saponin was obtained in small amount with insufficient purity. However, ^{13}C NMR spectra measured for this compound was identical with a data measured for compound **2** originally isolated from *Polyscias fruticose*.[3b] Described methodology can be a suitable and practical approach for preparing cellobiose derivatives and olenolic acid on a large scale. It opens the way for concise and efficient syntheses of a wide range of saponin analogues as pharmaceutical and biological agents that can be of further interest.

Experimental Section

General Information.

All starting materials and reagents were purchased from commercial sources and used without purification. Dry THF was distilled from potassium to prior to use. All reactions were performed under inert atmosphere. Reactions were controlled using analytical thin-layer chromatographies (TLC) using Merck Silica Gel 60 F254 precoated plates. Plates were visualized with UV light (254 nm) and by treatment with: aqueous cerium(IV) sulfate solution with molybdic and sulfuric acid followed by heating. All reagents and solvents were purified and dried according to common methods. All organic solutions were dried over anhydrous magnesium sulfate ($MgSO_4$). Reaction products were purified by normal phase flash chromatography, in air, using silica gel 60 (230–400 mesh) with n-Hx (Hx) and ethyl acetate (EA) as eluents, unless otherwise stated. ^1H spectra were recorded on 300 and 600 MHz (^1H) and referenced relative to tetramethylsilane in $CDCl_3$ (δ = 0 ppm), pyridine-d_5 residual solvent peak (δ = 3.85 ppm) and D_2O - acetonitrile (δ = 2.06 ppm). ^{13}C NMR spectra were recorded 150 and 75 MHz with complete proton decoupling. Chemical shifts were reported in ppm and reference signal was chosen as follow: $CDCl_3$ (δ = 77.16 ppm), pyridine-d_5 (for compound **16**; δ = 62.5 adequate to signal from C-6' in sugar moiety, and for compound **2**; δ = 176.4 adequate to signal from C-28 in aglycone moiety) and D_2O (acetonitrile δ = 1.47) for ^{13}C NMR. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet, t = triplet, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, dt = doublet of triplets, ddt = doublet of doublet of triplets, m = multiplet) and integration. High resolution mass spectra (HRMS) were recorded with an electrospray ionization time-of-flight (ESI-TOF) mass spectrometer. Infrared (IR) spectra were recorded with a Fourier transform infrared (FT-IR) spectrometer and are reported in wave numbers (cm^{-1}).Optical rotations were measured at room temperature with a digital polarimeter.

2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→4)-1,6-anhydro-2,3-di-*O*-benzoyl-β-D-glucopyranose (9);

A mixture of cellobiose (1.00 g, 2.92 mmol), 2-chloro-1,3-dimethylimidazolinium chloride (DMC) (1.48 g, 8.77 mmol) and Et_3N (3.66 mL, 2.63 mmol) in aqueous solution (5 mL) was stirred for 45 min at 0 °C. The product was extracted with DCM (3 × 50 mL). The combined water layers were concentrated. The crude product was purified by column chromatography (EA:EtOH:H_2O; 1:1:0.1) to give the compound **8**[14] as a white solid. **8** (1.00 g, 3.09 mmol) was dissolved in anhydrous pyridine (15 mL) and benzoyl chloride (2.14 mL, 18.5 mmol) was added dropwise to a solution at 0 °C. After 10 min solution was allowed to slowly gain rt and it was stirred for 24 h at rt. The reaction was quenched by addition of water (50 mL) and the product was extracted with EA (3 × 50 mL). The combined organic layers were washed with 1 M HCl (3 × 50 mL) followed by brine (50 mL) and then dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography Hx:EA (2:1) to give compound **9** as a white solid (2.60 g, 2.75 mmol, 89%). mp 121-122 °C; R_f = 0.28 (Hx:EA 2:1); $[\alpha]^{25}_D$ +1.7 (*c* 1.01, $CHCl_3$); IR (neat) 3072, 2560-2982, 1684, 1293, 1187 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.18 – 8.09 (m, 3H), 7.99 – 7.90 (m, 5H), 7.87 – 7.77 (m, 3H), 7.64 – 7.41 (m, 9H), 7.40 – 7.26 (m, 6H), 7.13 – 7.07 (m, 2H), 5.98 (t, *J* = 9.6 Hz, 1H), 5.78 (s, 1H), 5.64 (dd, *J* = 9.8, 8.1 Hz, 1H), 5.65 – 5.63 (m, 1H), 5.49 (dd, *J* = 9.8, 9.6 Hz, 1H), 5.41 (d, *J* = 8.1 Hz, 1H), 4.92 (d, *J* = 1.1 Hz, 1H), 4.51 (d, *J* = 5.4 Hz, 1H), 4.47 (dd, *J* = 11.9, 2.6 Hz, 1H), 4.43 (ddd, *J* = 10.0, 7.5, 2.5 Hz, 1H), 4.05 (dd, *J* = 11.9, 7.5 Hz, 1H), 3.95 (d, *J* = 7.5 Hz, 1H), 3.74 (dd, *J* = 7.6, 5.9 Hz, 1H), 3.73 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.9(2C), 165.5, 165.5, 165.4, 165.0, 133.8, 133.7, 133.6, 133.4, 132.9, 130.3, 130.0, 129.9, 129.8, 129.6, 129.5, 129.4, 129.3, 129.0, 129.0, 128.8, 128.7, 128.6, 128.6, 128.4, 128.2, 102.2, 99.0, 78.2, 74.4, 73.3, 72.7, 72.3, 69.9, 69.7, 68.8, 65.1, 63.5; HRMS *m/z* 971.2517 $[M + Na]^+$ (calcd for $C_{54}H_{44}O_{16}$, 971.2527).

2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→4)-1,6-di-*O*-acetyl-2,3-di-*O*-benzoyl-α/β-D-glucopyranose (10);

Trifluoroacetic acid (1.50 mL) was added to a stirred solution of **9** (1.80 g, 1.89 mmol) in Ac_2O (6.50 mL) in ice bath under argon. The reaction was allowed to reach rt. After 48 h the reaction was quenched with MeOH (20 mL) and neutralized with aq sat. $NaHCO_3$. The mixture was extracted with EA (3 × 50 mL) and combined organic phases were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography Hx:EA (2:1) to afford **10**

(1.73 g, 1.65 mmol, 87%) (α:β 2.85:1.00); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 – 7.20 (m, 115H), 6.45 (d, *J* = 3.7 Hz, 2.85H), 6.01 (dd, *J* = 10.1, 9.3 Hz, 2.85H), 5.86 (d, *J* = 8.3 Hz, 1H), 5.81 – 5.76 (m, 4.85H), 5.54 – 5.40 (m, 8.8H), 5.35 (dd, *J* = 10.3, 3.8 Hz, 2.85H), 4.92 (d, *J* = 7.9 Hz, 2.85H), 4.88 (d, *J* = 7.9 Hz, 1H), 4.38 – 4.33 (m, 3.85H), 4.20 – 4.13 (m, 7.7H), 4.06 (ddd, *J* = 10.1, 3.4, 2.0 Hz, 2.85H), 4.04 (dd, *J* = 11.8, 3.3 Hz, 2.85H), 4.01 – 3.98 (m, 1H), 3.93 – 3.84 (m, 7.7H), 3.82 (ddd, *J* = 9.9, 4.3, 1.9 Hz, 1H), 2.12 (s, 8.55H), 2.01 (s, 3H), 1.98 (s, 11.55H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.35, 169.01, 169.0, 165.8, 165.6, 165.4, 165.3, 165.2, 165.1, 164.9, 164.8, 133.7, 133.6, 133.5, 133.4, 133.3, 130.0, 129.9, 129.8, 129.8, 129.7, 129.5, 129.4, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 101.3, 101.2, 91.9, 89.1, 76.1, 73.0, 72.9, 72.4, 72.1, 72.0, 70.9, 70.4, 70.2, 69.5, 62.7, 61.7, 61.5, 60.50, 21.0, 20.9, 20.8, 20.8; HRMS *m/z* 1073.2830 $[M + Na]^+$ (calcd for $C_{58}H_{50}O_{19}$, 1073.2854).

2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→4)-6-*O*-acetyl-2,3-di-*O*-benzoyl-α/β-D-glucopyranose (11);

To a solution of **10** (3.24 g, 3.08 mmol) in anhydrous DMF (40 mL), hydrazine acetate (0.52 g, 5.70 mmol) was added and the reaction mixture was stirred at 50 °C for 20 min and then allowed to proceed for 3 h at rt. The solution was concentrated under diminished pressure, co-evaporated with toluene (2 × 30 mL) and the residue was dissolved in EA (50 mL). The organic phase was washed with aq sat. $NaHCO_3$ (2 × 30 mL) until neutral pH, brine (30 mL) and then dried over anhydrous $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography Hx:EA (2:1). **10** were obtained as white solid (2.70 g, 2.68 mmol, 87%) (α:β 2.20:1.00); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 – 7.17 (m, 96.0H), 6.10 (dd, *J* = 9.8, 9.6 Hz, 2.2H), 5.80 (dd, *J* = 9.7, 9.7 Hz, 2.2H), 5.83 – 5.77 (m, 2H) 5.57 (dd, *J* = 3.6, 3.6 Hz, 2.2H), 5.51 (dd, *J* = 9.8, 7.9 Hz, 2.2H), 5.52 – 5.42 (m, 2H), 5.46 (dd, *J* = 9.7, 9.7 Hz, 2.2H), 5.16 (dd, *J* = 9.9, 8.0 Hz, 1H), 5.13 (dd, *J* = 10.0, 3.6 Hz, 2.2H), 4.96 (d, *J* = 7.9 Hz, 2.2H), 4.90 (d, *J* = 7.9 Hz, 1H), 4.83 (t, *J* = 8.2 Hz, 1H), 4.40 (dd, *J* = 12.1, 1.9 Hz, 2.2H), 4.37 (dd, *J* = 12.0, 1.8 Hz, 1H), 4.25 (ddd, *J* = 10.0, 3.9, 1.9 Hz, 2.2H), 4.18 (dd, *J* = 12.0, 4.9 Hz, 1H), 4.17 (dd, *J* = 12.1, 4.0 Hz, 2.2H), 4.09 (dd, *J* = 12.1, 3.5 Hz, 2.2H), 4.09 (dd, *J* = 9.9, 9.4 Hz, 2.2H), 4.10 – 4.07 (m, 1H), 4.03 (dd, *J* = 11.9, 3.2 Hz, 1H), 3.99 (dd, *J* = 12.0, 4.9 Hz, 2.2H), 3.95 – 3.88 (m, 2H), 3.91 (ddd, *J* = 9.8, 4.9, 3.5 Hz, 2.2H), 3.72 (dddd, *J* = 11.0, 8.5, 6.9, 4.1 Hz, 1H), 3.09 (d, *J* = 3.6 Hz, 2.2H), 1.96 (s, 6.6H), 1.96 (s, 3H).^{13}C NMR (151 MHz, $CDCl_3$) δ 170.6, 170.5, 166.0, 165.9, 165.8, 165.8, 165.4, 165.4, 165.1, 164.9, 133.8, 133.6, 133.5, 133.5, 133.4, 133.3, 133.3, 130.1, 130.0, 130.0, 129.9, 129.8, 129.7, 129.6, 129.0, 128.8, 128.8 128.6, 128.6, 128.5, 128.4, 101.1, 100.9, 95.8, 90.3, 76.5, 74.5, 73.2, 73.0, 72.9, 72.4, 72.2, 72.1, 69.9, 69.6, 69.5, 68.5, 62.8, 62.0, 21.2, 20.9; HRMS *m/z* 1031.2734 $[M + Na]^+$ (calcd for $C_{56}H_{48}O_{18}$, 1031.2738).

2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→4)-6-*O*-acetyl-2,3-di-*O*-benzoyl-α/β-D-glucopyranosyl trichloroacetimidate (3);

Trichloroacetonitrile (280 µL, 0.28 mmol) and DBU (84 µL, 56 µmol) were added to a solution of the **11** (250 mg, 280 µmol) in anhydrous DCM (10 mL) at 0 °C. After being stirred for 5 min at 0 °C, the reaction mixture was allowed to warm to rt over a period of 1 h, then concentrated in vacuum. The residue was purified column chromatography Hx:EA (3:1) afforded the compound **3** as a yellow solid (290 mg, 252 µmol, 90%) (α:β, 5.00:1.00); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.54 (s, 5H), 8.49 (s, 1H), 8.11 – 7.19 (m, 18 H), 6.83 (d, *J* = 3.7 Hz, 1H), 6.65 (d, *J* = 3.7 Hz, 5H), 6.45 (d, *J* = 3.7 Hz, 1H), 6.10 (dd, *J* = 9.9, 9.1 Hz, 6H), 6.04 – 5.96 (m, 2H), 5.82 – 5.77 (m, 1H), 5.79 (t, *J* = 9.7 Hz, 5H), 5.63 (dd, *J* = 8.4, 7.7 Hz, 1H), 5.54 (dd, *J* = 9.7, 7.9 Hz, 1H), 5.50 (dd, *J* = 9.7, 7.9 Hz, 5H), 5.46 (t, *J* = 9.7 Hz, 5H), 5.42 (dd, *J* = 10.1, 3.7 Hz, 5H), 5.37 (dd, *J* = 10.3, 3.7 Hz, 1H), 5.34 (dd, *J* = 10.3, 3.8 Hz, 1H), 4.97 (d, *J* = 7.9 Hz, 5H), 4.93 (dd, *J* = 9.8, 8.0 Hz, 1H), 4.41 (m, 5H), 4.35 (m, 2H), 4.24 – 4.16 (m, 15H), 4.04 (dd, *J* = 12.0, 3.6 Hz, 5H), 3.96 (dd, *J* = 12.0, 4.7 Hz, 5H), 3.87 (ddd, *J* = 9.7, 4.7, 3.6 Hz, 5H), 1.96 (s, 18H); For major anomer α: ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.3, 165.8(2C), 165.6, 165.2, 165.1, 164.9, 160.8, 133.7, 133.6, 133.5, 133.5, 133.4, 133.3, 130.0, 130.0 129.9, 129.9, 129.8, 129.7, 129.5, 128.8, 128.8, 128.7, 128.5, 128.5,128.5, 128.4, 101.3, 93.1, 90.8, 76.0, 73.0, 72.4, 72.2, 70.8, 70.2, 69.5, 62.7, 61.4, 20.8; HRMS *m/z* 1176.1820, $[M + Na]^+$ (calcd for $C_{58}H_{48}Cl_3O_{18}$, 1176.1805).

Oleanolic acid 28-*O*-allyl ester (5);

Allyl bromide (188 µL, 2.20 mmol) and K_2CO_3 (450 mg, 3.27 mmol) were added to a solution of oleanolic acid (500 mg, 1.10 mmol) in anhydrous DMF (7 mL). The reaction mixture was stirred for 16 h at rt. After cooling, EA (5 mL) was added and the organic layer was washed with 1 M HCl (10 mL). The aqueous layer was extracted with EA (3 × 20 mL) and the combined organic layers were washed with aq sat. NaHCO3 (5 mL) and brine (5 mL). After the solution was dried over anhydrous MgSO4, the solvents were evaporated under reduced pressure. The residue was purified by column chromatography Hx:EA (4:1). Compound **5** were obtained as white solid10d (527 mg, 1.09 mmol, 97%).

28-*O*-Allyl oleanate 3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→4)-6-*O*-acetyl-2,3-di-*O*-benzoyl-β-D-glucopyranoside (13);

To a solution of **3** (180 mg, 156 µmol) and **5** (52 mg, 104 µmol) in DCM (5 mL) was added MS 4Å (150 mg), the reaction mixture was stirred for 15 min at -40 °C. TMSOTf (6 µL, 34.3 µmol) was added in one portion and the reaction mixture was stirred for 3 h at rt. The reaction was finished by addition of Et_3N (5 µL, 34.3 µmol). Then poured on the short plug of Celite and washed with DCM. Filtrate was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product **13** was purified by column chromatography Hx:EA (4:1) to give white solid (125 mg, 84.2 µmol, 81%); mp 110-111 °C; $[\alpha]^{25}_D$: +11.3 (*c* 1.0 $CHCl_3$); IR (neat) 2944, 1729, 1452, 1263 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 – 7.87 (m, 7H), 7.80 – 7.73 (m, 4H), 7.57 – 7.50 (m, 2H), 7.48 – 7.40 (m, 4H), 7.40 – 7.31 (m, 6H), 7.30 – 7.26 (m, 2H), 7.26 – 7.18 (m, 5H), 5.88 (ddt, *J* = 17.1, 10.6, 5.6 Hz, 1H), 5.78 (t, *J* = 9.7 Hz, 1H), 5.73 (dd, *J* = 9.5, 9.4 Hz, 1H), 5.49 (dd, *J* = 9.8, 7.9 Hz, 1H), 5.42 (dd, *J* = 9.7, 9.5 Hz, 1H), 5.39 (dd, *J* = 9.7, 7.9 Hz, 1H), 5.29 (ddd, *J* = 17.2, 3.2, 1.6 Hz, 1H), 5.26 (t, *J* = 3.6 Hz, 1H), 5.18 (ddd, *J* = 10.5, 2.7, 1.3 Hz, 1H), 4.89 (d, *J* = 7.9 Hz, 1H), 4.64 (d, *J* = 8.0 Hz, 1H), 4.52 (dddd, *J* = 13.5, 5.6, 1.4, 1.4 Hz, 1H), 4.48 (dddd, *J* = 13.5, 5.6,

1.4, 1.4 Hz, 1H), 4.37 (dd, *J* = 11.8, 1.9 Hz, 1H), 4.16 (dd, *J* = 11.8, 5.1 Hz, 1H), 4.04 (dd, *J* = 9.5, 9.4 Hz, 1H), 4.02 (dd, *J* = 11.9, 3.1 Hz, 1H), 3.88 (ddd, *J* = 9.7, 5.2, 3.2 Hz, 1H), 3.82 (dd, *J* = 11.9, 5.2 Hz, 1H), 3.65 (ddd, *J* = 9.8, 5.1, 1.9 Hz, 1H), 3.00 (dd, *J* = 11.6, 4.6 Hz, 1H), 2.86 (dd, *J* = 13.8, 4.4 Hz, 1H), 1.95 (s, 3H), 1.08 (s, 3H), 0.92 (s, 3H), 0.89 (s, 3H), 0.83 (s, 3H), 0.66 (s, 3H), 0.62 (s, 3H), 0.58 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ* 177.5, 170.4, 165.9, 165.8, 165.5, 165.3, 165.1, 164.8, 143.8, 133.5, 133.4, 133.1, 132.7, 122.6, 117.8, 103.2, 101.1, 90.8, 73.0, 72.9, 72.8, 72.4, 72.3, 72.1, 69.5, 64.9, 62.7, 62.1, 55.5, 47.7, 46.9, 41.8, 41.4, 39.5, 38.9, 38.5, 36.8, 33.2, 32.8, 32.6, 30.8, 27.7, 26.0, 25.8, 23.8, 23.5, 23.2, 20.8, 18.2, 17.0, 16.3, 15.3; HRMS *m/z* 1509.6540 $[M + Na]^+$ (calcd for $C_{89}H_{98}O_{20}$, 1509.6549).

Oleanolic acid 3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→4)-6-*O*-acetyl-2,3-di-*O*-benzoyl-β-D-glucopyranoside (4);

To a stirred solution of **13** (128 mg; 86.1 µmol) and PPh_3 (135 mg, 51.6 µmol) in anhydrous THF (4 mL) was added $Pd^0(PPh_3)_4$ (30 mg, 25.8 µmol) followed by pyrrolidine (14 µL, 172 µmol) at rt. The reaction mixture was stirred in the dark overnight. Then the solvents were evaporated under reduced pressure to give a red-yellow powder, which was purified by flash chromatography Hx:EA (2:1). **4** was obtained as a white amorphous powder (103 mg, 71.4 µmol, 83%); mp 195-200 °C; $[\alpha]^{25}_D$: +15.3 (*c* 1.0 $CHCl_3$); IR (neat) 3362, 2945, 2360, 1732, 1452, 1265 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.97 – 7.87 (m, 8H), 7.79 – 7.74 (m, 4H), 7.57 – 7.49 (m, 2H), 7.48 – 7.17 (m, 16H), 5.78 (t, *J* = 9.7 Hz, 1H), 5.74 (t, *J* = 9.5 Hz, 1H), 5.49 (dd, *J* = 9.8, 7.9 Hz, 1H), 5.42 (t, *J* = 9.7 Hz, 1H), 5.39 (dd, *J* = 9.8, 8.0 Hz, 1H), 5.24 (t, *J* = 3.6 Hz, 1H), 4.89 (d, *J* = 7.9 Hz, 1H), 4.64 (d, *J* = 8.0 Hz, 1H), 4.38 (dd, *J* = 11.8, 1.7 Hz, 1H), 4.16 (dd, *J* = 11.9, 5.1 Hz, 1H), 4.04 (t, *J* = 9.4 Hz, 1H), 4.03 (dd, *J* = 12.0, 3.2 Hz, 1H), 3.88 (ddd, *J* = 9.7, 5.1, 3.3 Hz, 1H), 3.81 (dd, *J* = 12.0, 5.2 Hz, 1H), 3.65 (ddd, *J* = 9.7, 5.0, 2.0 Hz, 1H), 2.99 (dd, *J* = 11.7, 4.5 Hz, 1H), 2.78 (dd, *J* = 13.7, 4.2 Hz, 1H), 1.94 (s, 3H), 1.07 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H), 0.81 (s, 3H), 0.67 (s, 3H), 0.60 (s, 3H), 0.54 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ* 183.3, 170.4, 165.9, 165.8, 165.5, 165.2, 165.1, 164.8, 143.7, 133.5, 133.4, 133.3, 133.1, 130.0, 129.9, 129.8, 129.7, 129.6, 128.8, 128.8, 128.6, 128.6, 128.5, 128.4, 128.4, 122.7, 103.2, 101.1, 90.8, 73.0, 72.9, 72.8, 72.4, 72.2, 72.1, 69.5, 62.7, 62.1, 55.5, 47.7, 46.6, 46.0, 41.7, 41.1, 39.3, 38.8, 38.5, 36.8, 33.9, 33.2, 32.6, 32.5, 30.8, 29.8, 27.7, 26.0, 25.7, 23.7, 23.5, 23.0, 20.8, 18.1, 17.1, 16.2, 15.3; HRMS *m/z* 1469.6213 $[M + Na]^+$ (calcd for $C_{86}H_{94}O_{20}$, 1469.6236).

Oleanolic acid 3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→4)-2,3-di-*O*-benzoyl-β-D-glucopyranoside (14);

The compound **4** (123 mg, 85.0 µmol) was dissolved in a solution of DCM (2 mL) and absolute MeOH (2 mL). Then AcCl (84.4 µL, 119 µmol) was added at 0 °C. The mixture was kept for 16 h at rt and then concentrated. The residue was purified by column chromatography Hx:EA (1:1). Compound **14** was obtained as yellow solid (71 mg, 50.2 µmol, 59%); mp 139-141 °C; IR (neat) 2925, 1729, 1451, 1437, 1261, 1176, 1092, 1069, 1027 cm^{-1}; $[\alpha]^{25}_D$: +16.5 (*c* 0.9, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 8.00 – 7.72 (m, 12H), 7.58 – 7.14 (m, 18H), 5.91 (s, 1H), 5.80 (t, *J* = 9.7 Hz, 1H), 5.72 (t, *J* = 9.6 Hz, 1H), 5.50 (dd, *J* = 9.8, 8.0 Hz, 1H), 5.40 (t, *J* = 9.7 Hz, 1H), 5.40 (dd, *J* = 9.9, 8.0 Hz, 1H), 5.24 (t, *J* = 3.6 Hz, 1H), 5.01 (d, *J* = 8.0 Hz, 1H), 4.69 (d, *J* = 8.0 Hz, 1H), 4.21 (t, *J* = 9.5 Hz, 1H), 4.04 (dd, *J* = 12.0, 3.1 Hz, 1H), 3.97 (ddd, *J* = 9.6, 5.4, 3.1 Hz, 1H), 3.80 (dd, *J* = 12.0, 5.4 Hz, 1H), 3.79 – 3.74 (m, 2H), 3.44 (dt, *J* = 9.8, 2.4 Hz, 1H), 3.01 (dd, *J* = 10.4, 5.9 Hz, 1H), 2.79 (dd, *J* = 13.6, 4.3 Hz, 1H), 1.07 (s, 3H), 0.91 (s, 3H), 0.89 (s, 3H), 0.82 (s, 3H), 0.68 (s, 3H), 0.61 (s, 3H), 0.57 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ* 182.7, 165.9, 165.8, 165.7, 165.3, 165.2, 164.8, 143.7, 129.9, 129.9, 129.9, 128.7, 128.6, 128.5, 128.4, 122.7, 103.3, 101.1, 90.7, 75.6, 75.0, 73.1, 72.9, 72.4, 72.3, 72.1, 69.6, 65.9, 62.9, 60.6, 55.5, 47.7, 46.6, 41.7, 41.1, 39.3, 38.9, 38.5, 36.8, 33.9, 33.2, 32.6, 32.5, 30.8, 27.7, 26.0, 23.9, 23.7, 23.5, 23.0, 18.1, 17.1, 16.2, 15.3; HRMS *m/z* 1428.6146 $[M + Na]^+$ (calcd for $C_{84}H_{92}O_{19}$, 1428.6146).

Oleanolic acid 3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→4)-2,3-di-*O*-benzoyl-β-D-glucuronide (15);

TEMPO (5 mg, 31.3 µmol) and BAIB (91 mg, 282 µmol) were added at rt to a stirred solution of compound **14** (176 mg, 125 µmol) in the mixture of H_2O:DCM (1:2, v/v) 3 mL. After 20 h, the solution was diluted with EA (3 mL), and the mixture was sequentially washed with aq 5% $Na_2S_2O_3$ (5 mL), aq sat. $NaHCO_3$ (5 mL) and brine (5 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography Hx:EA (1:2). Compound **15** was obtained as with solid (135 mg, 95.5 µmol, 76%); mp 189-194 °C; $[\alpha]^{25}_D$: +8.6 (c 0.93, $CHCl_3$); IR (neat) 2926, 1729, 1602, 1451, 1315, 1261, 1177, 1068, 1026 cm^{-1}c; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.99 – 7.87 (m, 7H), 7.79 – 7.66 (m, 5H), 7.59 – 7.28 (m, 13H), 7.25 – 7.14 (m, 5H), 5.82 (t, *J* = 9.6 Hz, 1H), 5.73 (t, *J* = 8.9 Hz, 1H), 5.48 – 5.42 (m, 2H), 5.37 (t, *J* = 9.5 Hz, 1H), 5.26 – 5.22 (m, 1H), 5.21 – 5.17 (m, 1H), 4.78 (d, *J* = 7.4 Hz, 1H), 4.42 (t, *J* = 8.7 Hz, 1H), 4.07 (d, *J* = 8.9 Hz, 1H), 4.09 – 3.96 (m, 2H), 3.76 – 3.70 (m, 1H), 3.06 (dd, *J* = 11.1, 4.0 Hz, 1H), 2.81 (dd, *J* = 13.4, 3.5 Hz, 1H), 1.09 (s, 3H), 0.93 (s, 3H), 0.90 (s, 3H), 0.79 (s, 3H), 0.67 (s, 3H), 0.63 (s, 3H), 0.56 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ* 184.0, 171.0, 165.9, 165.5, 165.3, 165.2, 143.6, 133.4, 133.3, 132.4, 132.3, 132.3, 130.0, 129.9, 129.8, 129.7, 129.6, 129.4, 129.3, 128.9, 128.9, 128.8, 128.5, 128.4, 128.4, 128.3, 122.7, 102.9, 100.7, 90.8, 73.1, 72.4, 72.3, 72.1, 71.8, 69.7, 63.0, 55.3, 47.6, 46.7, 46.0, 41.7, 41.1, 39.4, 38.7, 38.3, 36.7, 33.9, 33.2, 32.6, 32.0, 30.8, 30.4, 27.7, 26.0, 25.4, 23.7, 23.5, 23.0, 22.8, 18.1, 16.9, 16.3, 15.5, 14.3; HRMS *m/z* 1441.5899 $[M + Na]^+$ (calcd for $C_{84}H_{90}O_{20}$, 1441.5823).

Methyl oleanate 3-*O*-(β-D-glucopyranosyl)-(1→4)-β-D-glucuronide methyl ester (16);

The compound **15** (90 mg, 63.4 µmol) was dissolved in the mixture of MeOH:DCM (1:1, v/v) 2 mL. Then NaOH (30 mg, 76.1 µmol) was added. The reaction mixture was stirred for 4.5 h at rt and then acidified to pH=4 with 1 M HCl. The solvents were evaporated under reduced pressure to give a solid residue. This residue was poured on the short plug of Celite and washed with (EA:MeOH 3:2). Filtrate was dried over anhydrous Na_2SO_4 and solvents were removed under reduced pressure. Residue was

dried under high vacuum to afford crude **1** (42 mg, 52.9 µmol) which was dissolved in anhydrous DMF (1 mL). Then, K_2CO_3 (124 mg, 89.9 µmol) and MeI (6 µL, 89.9 µmol) were added. The mixture was stirred for 16 h, then the mixture was diluted with EA (3 mL), washed with H_2O (5 mL) and brine (2 mL). The solvents of the dried over anhydrous Na_2SO_4, organic solution were evaporated under reduced pressure. The residue was purified by flash chromatography (EA:MeOH 3:1 to 3:2). **16** (36 mg, 41.8 µmol, 78%) was obtained as a white amorphous powder; mp 205- 207 °C; $[\alpha]^{25}_D$ +4.6 (*c* 11.6, MeOH); IR (neat) 3367, 2924, 1729, 1439, 1364, 1162 cm^{-1}; ^{1}H NMR (600 MHz, Pyr)[3b] *δ* 5.34 (t, *J* = 3.2 Hz, 1H), 5.02 (d, *J* = 7.9 Hz, 1H), 4.96 (d, *J* = 7.9 Hz, 1H), 4.64 (d, *J* = 9.8 Hz, 1H), 4.50 (dd, *J* = 11.3, 1.9 Hz, 1H), 4.46 (t, *J* = 9.5, 9.1 Hz, 1H), 4.27 (t, *J* = 8.9 Hz, 1H), 4.24 (dd, *J* = 11.3, 5.8 Hz, 1H), 4.14 (t, *J* = 8.7 Hz, 1H), 4.10 (dd, *J* = 9.3, 9.1 Hz, 1H), 4.07 (t, *J* = 8.5 Hz, 1H), 3.99 – 3.95 (m, 1H), 3.97 (dd, *J* = 8.4, 8.3 Hz, 1H), 3.85 (s, 1H), 3.67 (s, 1H), 3.29 (dd, *J* = 11.8, 4.4 Hz, 1H), 3.06 (dd, *J* = 13.6, 4.0 Hz, 1H), 1.27 (s, 3H), 1.21 (s, 3H), 0.95 (s, 3H), 0.90 (s, 3H), 0.89 (s, 3H), 0.80 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (151 MHz, Pyr)[3b] *δ* 178.0, 170.0, 144.1, 122.8, 106.9, 105.1, 89.2, 82.7, 78.5, 78.2, 76.1, 75.1, 74.8, 74.5, 71.6, 62.5, 52.5, 46.9, 41.9, 41.8, 39.6, 39.5, 36.9, 33.1, 30.8, 28.1, 28.0, 26.5, 26.1, 23.7, 23.6, 23.4, 18.4, 17.1, 16.9, 15.4; HRMS *m/z* 845.4637 $[M + Na]^+$ (cald for $C_{44}H_{70}O_{14}$, 845.4663).

Oleanolic acid 28-*O*-2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl ester (17);

K_2CO_3 (151 mg, 1.1 mmol) were added to a stirred solution of oleanolic acid (240 mg, 0.52 mmol) and 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (**7**)[20] (723 mg, 1.1 mmol) in anhydrous DMF (1.5 mL). The suspension was vigorously stirred at rt for 6 h. Then, the mixture was diluted with EA (5 mL), washed with H_2O (3 × 10 mL) and brine (5 mL). Combined organic phases were dried over anhydrous $MgSO_4$, organic solution were evaporated under reduced pressure. The residue was purified by column chromatography (Hx:EA 2:1) to afford the product 1**7** (453 mg, 438 µmol, 80%) as a white solid.[10e]

28-*O*-2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl oleanate 3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→4)-6-*O*-acetyl-2,3-di-*O*-benzoyl-β-D-glucopyranoside (6);

K_2CO_3 (40 mg, 293 µmol) was added to a solution of **4** (106 mg, 73.3 µmol) and 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (**7**)[20] (97 mg, 146 µmol) in anhydrous DMF (2 mL). The resulting mixture was vigorously stirred at rt for 6 h. Then, the mixture was diluted with EA (7 mL), washed with H_2O (3 ×10 mL) and brine (10 mL). Combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (Hx:EA 3:2). **6** (123 mg, 62.3 µmol, 85%) was obtained as a white amorphous powder; mp 153-157 °C; $[\alpha]^{25}_D$ +40.3 (*c* 1.1, $CHCl_3$); IR (neat) 2925, 1729, 1451, 1437, 1261, 1176, 1261, 1092, 1269 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 8.03 – 7.18 (m, 50H), 5.96 (dd, *J* = 9.7, 9.6 Hz, 1H), 5.92 (d, *J* = 8.4 Hz, 1H), 5.77 (t, *J* = 9.7 Hz, 1H), 5.75 – 5.70 (m, 3H), 5.49 (dd, *J* = 9.8, 7.9 Hz, 1H), 5.42 (t, *J* = 9.7 Hz, 1H), 5.38 (dd, *J* = 9.8, 8.0 Hz, 1H), 5.25 (t, *J* = 3.6 Hz, 1H), 4.89 (d, *J* = 7.9 Hz, 1H), 4.62 (d, *J* = 7.9 Hz, 1H), 4.54 (dd, *J* = 12.2, 2.9 Hz, 1H), 4.45 (dd, *J* = 12.2, 5.0 Hz, 1H), 4.36 (dd, *J* = 11.7, 1.7 Hz, 1H), 4.24 (ddd, *J* = 9.8, 5.0, 3.1 Hz, 1H), 4.15 (dd, *J* = 11.7, 5.1 Hz, 1H), 4.04 (dd, *J* = 9.5, 9.3 Hz, 1H), 4.02 (dd, *J* = 11.9, 3.1 Hz, 1H), 3.87 (ddd, *J* = 9.7, 5.0, 3.3 Hz, 1H), 3.82 (dd, *J* = 11.9, 5.2 Hz, 1H), 3.64 (ddd, *J* = 9.8, 5.1, 2.1 Hz, 1H), 2.94 (dd, *J* = 11.7, 4.5 Hz, 1H), 2.76 (dd, *J* = 13.6, 3.9 Hz, 1H), 1.94 (s, 3H), 0.91 (s, 3H), 0.84 (s, 3H), 0.80 (s, 3H), 0.68 (s, 3H), 0.58 (s, 3H), 0.55 (s, 3H), 0.39 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ* 175.8, 170.4, 166.2, 165.8, 165.8, 165.8, 165.5, 165.2, 165.2, 165.1, 164.9, 164.8, 143.1, 133.5, 133.4, 133.3, 130.1, 130.0, 129.9, 129.9, 129.9, 129.8, 129.7, 129.6, 128.8, 128.8, 128.6, 128.6, 128.5, 128.4, 122.8, 103.2, 101.1, 92.0, 90.8, 73.0, 72.9, 72.8, 72.4, 72.3, 72.1, 70.5, 69.5, 69.4, 62.9, 62.7, 62.1, 55.4, 47.5, 46.9, 45.9, 41.6, 41.1, 39.0, 38.8, 38.4, 36.6, 33.8, 33.1, 32.1, 31.9, 31.8, 30.7, 27.9, 27.7, 25.7, 25.6, 23.6, 23.4, 22.8, 22.7, 20.8, 18.1, 16.5, 16.3, 15.2; HRMS *m/z* 1035.8868 $[M + 2Na]^{2+}$ (cald for $C_{120}H_{120}O_{29}$, 1035.8872).

28-*O*-2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl oleanate 3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-(1→4)-2,3-di-*O*-benzoyl-β-D-glucopyranoside (18);

The compound **6** (134 mg, 66.2 µmol) was dissolved in a solution of DCM (2 mL) and absolute MeOH (2 mL). then AcCl (65 µL, 92.7 µmol) was added at 0 °C. The mixture was kept for 16 h at rt and then concentrated. The residue was purified by column chromatography Hx:EA (2:1) to give **18** as a yellow solid (83 mg, 41.7 µmol, 63%); mp 174-178 °C; $[\alpha]^{25}_D$ +11.4 (*c* 0.6; $CHCl_3$, IR (neat) 2941, 1727, 1603, 1451, 1316, 1260, 1177 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 8.12 – 7.66 (m, 20H), 7.64 – 7.08 (m, 30H), 5.96 (t, *J* = 9.7 Hz, 1H), 5.92 (d, *J* = 8.4 Hz, 1H), 5.80 (t, *J* = 9.7 Hz, 1H), 5.73 (dd, *J* = 10.4, 2.1 Hz, 1H), 5.71 (d, *J* = 9.7 Hz, 1H), 5.70 (d, *J* = 8.2 Hz, 1H), 5.50 (dd, *J* = 9.8, 8.0 Hz, 1H), 5.41 (t, *J* = 9.6 Hz, 1H), 5.41 – 5.37 (m, 1H), 5.24 (t, *J* = 3.5 Hz, 1H), 5.00 (d, *J* = 8.0 Hz, 1H), 4.67 (d, *J* = 8.0 Hz, 1H), 4.54 (dd, *J* = 12.2, 2.8 Hz, 1H), 4.45 (dd, *J* = 12.2, 5.0 Hz, 1H), 4.24 (ddd, *J* = 9.9, 4.8, 3.0 Hz, 1H), 4.20 (t, *J* = 9.6 Hz, 1H), 4.02 (dd, *J* = 11.9, 3.0 Hz, 1H), 3.97 (ddd, *J* = 9.7, 5.2, 3.3 Hz, 1H), 3.80 (dd, *J* = 12.0, 5.3 Hz, 1H), 3.77 – 3.73 (m, 2H), 3.42 (dt, *J* = 9.7, 2.3 Hz, 1H), 2.96 (dd, *J* = 10.8, 5.5 Hz, 1H), 2.76 (dd, *J* = 13.7, 3.9 Hz, 1H), 0.89 (s, 3H), 0.84 (s, 3H), 0.81 (s, 3H), 0.68 (s, 3H), 0.57 (s, 3H), 0.56 (s, 3H), 0.37 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ* 175.8, 166.2, 165.9, 165.8, 165.8, 165.6, 165.2(2C), 165.1, 164.8, 164.8, 143.1, 133.7, 133.5, 133.3, 133.2, 133.1, 130.0, 129.9, 129.9, 129.8, 129.7, 129.6, 129.5, 129.0, 128.8, 128.7, 128.7, 128.6, 128.5, 128.5, 128.4, 128.3, 122.7, 103.3, 101.1, 92.0, 90.7, 75.5, 75.5, 74.9, 73.0, 72.9, 72.8, 72.3, 72.2, 72.0, 70.4, 69.5, 69.3, 62.8, 60.6, 55.3, 47.4, 46.9, 45.8, 41.5, 41.0, 38.9, 38.7, 38.3, 36.6, 33.8, 33.1, 31.8, 31.7, 30.7, 29.8, 29.5, 27.8, 27.7, 26.0, 25.5, 23.6, 23.4, 22.8, 22.7, 21.2, 18.0, 16.5, 16.3, 15.2, 14.3; HRMS *m/z* 1014,8809 $[M + 2Na]^{2+}$ (cald for $C_{118}H_{118}O_{28}$, 1014.8820).

28-*O*-2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl oleanate 3-β-*O*-[(2,3-di-*O*-benzoyl-glucopyranosyl)uronate]-(1→4)-2,3,4,6-tetra-*O*-benzoyl-β-glucuronide (19);

2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (1 mg, 5.04 µmol) and (bisacetoxy)iodobenzene (BAIB) (15 mg, 45.4 µmol) was added at rt to a stirred solution of compound **18** (40 mg, 20.2

µmol) in the mixture of H_2O:DCM (1:2, 1.5 mL). After stirring for 20 h, the solution was diluted with EA (2 mL), and the mixture was washed with aq 5% $Na_2S_2O_3$ (3 mL), aq sat. $NaHCO_3$ (3 mL) and brine (3 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography Hx:EA (1:2) to give **19** (35.1 mg, 17.5 µmol 87%); mp 126-129 °C; IR (neat) 2940, 1603, 1439, 151315, 1261, 1177, 1120, 1091, 1068, 1026, 885 cm^{-1}; $[\alpha]^{25}_D$ +42.6 (*c* 1.6; $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 8.05 – 7.74 (m, 20H), 7.57 – 7.15 (m, 30H), 5.97 (t, *J* = 9.7 Hz, 1H), 5.92 (d, *J* = 8.4 Hz, 1H), 5.87 (t, *J* = 9.7 Hz, 1H), 5.85 – 5.78 (m, 1H), 5.77 – 5.70 (m, 3H), 5.48 (dd, *J* = 9.8, 8.2 Hz, 1H), 5.45 (dd, *J* = 8.9, 8.0 Hz, 1H), 5.40 (t, *J* = 9.7 Hz, 1H), 5.24 (m, 1H), 5.18 (d, *J* = 7.8 Hz, 1H), 4.79 (d, *J* = 7.5 Hz, 1H), 4.54 (dd, *J* = 12.2, 2.8 Hz, 1H), 4.48 – 4.39 (m, 2H), 4.24 (ddd, *J* = 9.8, 4.8, 3.1 Hz, 1H), 4.11 – 4.08 (m, 1H), 4.08 – 4.03 (m, 1H), 3.98 (dd, *J* = 12.0, 2.4 Hz, 1H), 3.78 (dd, *J* = 12.0, 5.4 Hz, 1H), 3.00 (dd, *J* = 11.4, 4.6 Hz, 1H), 2.76 (dd, *J* = 13.5, 3.7 Hz, 1H), 0.91 (s, 2H), 0.84 (s, 6H), 0.81 (s, 4H), 0.67 (s, 3H), 0.60 (s, 3H), 0.55 (s, 3H), 0.37 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 175.8, 169.4, 166.2, 166.0, 165.9, 165.8, 165.4, 165.2, 165.1(3C), 164.8, 143.1, 133.7, 133.5, 133.4, 133.2, 130.0, 129.9, 129.9, 129.8, 129.7, 129.6, 129.5, 129.4, 129.3, 129.3, 128.7, 128.6, 128.5, 128.5, 128.5, 128.4, 122.7, 103.2, 100.9, 92.0, 91.0, 74.0, 73.0, 72.9, 72.9, 72.2(2C), 72.0, 71.5, 70.4, 69.5, 69.3, 62.8, 55.2, 47.4, 46.9, 45.8, 41.5, 41.0, 38.9, 38.7, 38.2, 36.6, 33.8, 33.1, 31.8, 31.7, 30.7, 30.3, 27.8, 27.7, 25.5, 23.5, 23.3, 22.8, 22.7, 21.6, 18.0, 16.5, 16.3, 15.2, 14.3; HRMS *m/z* 1996.7574 $[M + Na]^+$ (cald for $C_{118}H_{116}O_{29}$, 1996.7558).

3-*O*-[β-D-Glucopyranosyl-(1→4)-β-D-glucuronide] oleanolic acid 28-*O*-β-D-glucopyranosyl ester (2);

(30 mg, 15.2 µmol) was dissolved in the mixture of MeOH:DCM (1:1, v/v) 1 mL. After 5 min of stirring NaOH (7.2 mg, 18 µmol) was added. The reaction mixture was stirred for 4.5 h at rt. Then mixture was acidified to pH=4 with 1 M HCl. The solvents were evaporated under reduced pressure to give a solid residue 12 mg, which was purified by column chromatography (EA:MeOH 3:1) to afford **2** as a white amorphous powder; ^{13}C NMR (151 MHz, Py)[3b] *δ* 176.4, 173.2, 144.2, 122.9, 106.8, 104.5, 95.8, 89.0, 83.6, 79.4, 78.9, 78.4, 77.8, 76.4, 75.2, 75.1, 74.1, 71.3, 71.6, 71.1, 62.5, 62.2, 55.6, 47.9, 47.0, 46.2, 42.1, 41.7, 39.9, 39.5, 36.9, 36.8, 34.0, 33.1, 33.1, 32.1, 30.7, 28.1, 28.0, 26.2, 26.1, 23.8, 23.6, 23.4, 18.5, 17.5, 17.0, 15.5; HRMS *m/z* 955.4886 $[M]^-$ (cald for $C_{48}H_{75}O_{19}$, 955.4903); 979.4890 $[M + Na]^+$ (cald for $C_{48}H_{76}O_{19}$, 979.4878).

Supporting Information Summary

The copies of ^1H, ^{13}C NMR are provided in the Supporting Information.

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Stereocontrolled Synthesis of Oleanolic Saponin Ladyginoside A Isolated from *Ladyginia Bucharica*

Matylda Stefaniak, Grzegorz Łopatkiewicz, Magdalena Antkowiak and Jacek Mlynarski*[a]

Stereoselective synthesis of two naturally occurring saponins Ladyginioside A (**1**) and 3-O-[β-d-glucopyranosyl-(1→4)-β-D-glucuronide] oleanolic acid 28-*O*-β-D-glucopyranosyl ester (**2**) is presented. Both compounds have been isolated from Ladyginia bucharica in 70s and so far not chemically obtained. Our strategy reduce the number of steps in this total synthesis of the saponine due to removal of stereo-problematic glycosylation step between two monosaccharide units and acceptor formation. It opens the way for concise and efficient syntheses of a wide range of saponin analogues as pharmaceutical and biological agents that can be of further interest.

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