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Synthesis of Saponins with Allobetulin and Glycyrrhetic Acid as Aglycones

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Procedures for the synthesis of branched Xylβ(1–3)[Galβ(1–2)]Glc and Xylβ(1–3)[Galβ(1–2)]GlcA trisaccharides β-linked to the 3-*O* moieties of allobetulin and glycyrrhetic acid, respectively, were developed. To this end, β-selective glucosylation of the two triterpenes with a glucosyl donor permitting selective access to 2a-*O*, 3a-*O*, and 6a-*O*, was studied; this led to glucoside intermediates. Xylosylation of the 2a,3a-*O*-unprotected glucoside was straightforward because, under inverse procedure conditions, exclusively 3a-*O*-reaction was observed. Subsequent 2a-*O*-galactosylation followed by 4a,6a-*O*-debenzylidenation and chemoselective oxidation of the glucose hydroxymethyl group gave the target molecule **1** in high yield after deprotection. The high nucleophilicity of the glycyrrhetinate keto group required a variation in the sequential attachment of the galactosyl and xylosyl residues, so the 2a-*O*-unprotected glucoside was selected. Initial 2a-*O*-galactosylation, affording mainly a disaccharide, and subsequent protecting group manipulation and 3a-*O*-xylosylation gave the target molecule **2b** after deprotection. Transformation of the glucose residue in the trisaccharide intermediate into a glucuronate residue furnished target molecule **2a**, with the Xylβ(1–3)[Galβ(1–2)]GlcA β-linked to 3-*O* of the glycyrrhetic acid.

Introduction

Many microbial cell wall constituents act as antigens and stimulate the production of antibodies and cellular immune responses in a host, thus protecting against infectious diseases.[1] Some antigens, however, exert only a weak effect on the immune system when used in vaccines, so immunostimulants are required in order to elicit the required immune response.[2] Typical immunoadjuvants are Freund's complete and incomplete adjuvant, bacterial endotoxins, mineral salts (for instance, aluminium-based mineral salts = alums) and saponins.[3] Of particular interest are compounds displaying specific immunomodulatory effects, such as, for instance, the immune stimulating complexes (ISCOMs),[4] consisting of saponins, cholesterol and phospholipids.[5–7] Amongst the saponins, the Quillaja saponin QS 21 (Figure 1), extracted from the cortex of the tree *Quillaja saponaria* Molina,[8–10] exhibits particularly strong immunoadjuvant properties.[11,12] QS 21, an acylated bisdesmosidic triterpenoid saponin, has been shown to enhance both humoral and cell-mediated immune responses in a host of vaccine formation assays.[13] Various clinical trials have been performed with QS 21[9–14] and it appears highly effective as an adjuvant in vaccines intended to induce a potent cytotoxic T-lymphocyte response against a variety of target antigens including cancer antigens.[15–17]

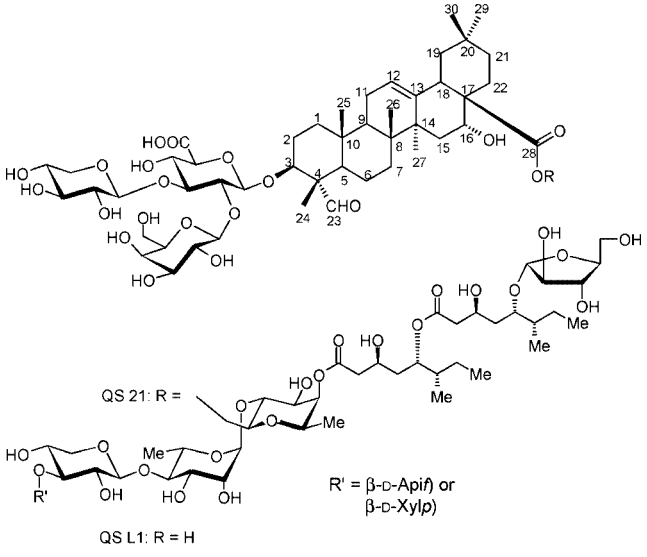

Figure 1. Structures of saponins QS 21 and QS L1.

QS 21 consists of a triterpene (quillaic acid) with two attached oligosaccharide chains and a sugar residue containing a dimeric fatty acyl group linked to the tetrasaccharide moiety (Figure 1).[15,18,19] The fatty acyl chains seem to play a critical role in immune stimulation, as inferred from alkaline hydrolysis of QS 21.[10,14,20,21] For instance, strong alkaline hydrolysis gave QS L1,[9] which was demonstrated

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greatly to increase both humoral immunity and cellular immune response when administered in the presence of alum-precipitated recombinant hepatitis B surface antigen, yet in the presence of only the antigen it showed low antigen activity.[22] Besides that, QS L1 is less toxic than QS 21 in vivo and in vitro, due to the lack of a lipophilic chain.[22] Hence, QS L1 should use a different mechanism from QS 21 for immune stimulation, and so the synthesis of QS L1 analogues containing the Xylβ(1–3)[Galβ(1–2)]-GlcUA trisaccharide moiety attached to structurally closely related aglycones – thus avoiding the use of the not readily accessible quillaic acid – became of interest.[23–25]

In this paper, allobetulin and glycyrrhetic acid have been selected as structurally related triterpene aglycones, thus giving compounds **1** and **2a** as target compounds (Figure 2); for comparison studies compound **2b** was also prepared. For the 3-*O*-glycosylation of the aglycones, a linear strategy (i.e., construction of the trisaccharide moiety at the aglycon) was chosen because a convergent strategy (i.e., glycosylation of the aglycon with a preprepared trisaccharide donor[23,26]) lacking anchimeric assistance in the glycosylation step did not provide satisfactory anomeric selectivities.[23,27] Through this approach, with the help of anchimeric assistance,[25] good glycosylation results were expected. Success in this endeavour should also greatly facilitate the total synthesis of QS 21 and analogues.[28]

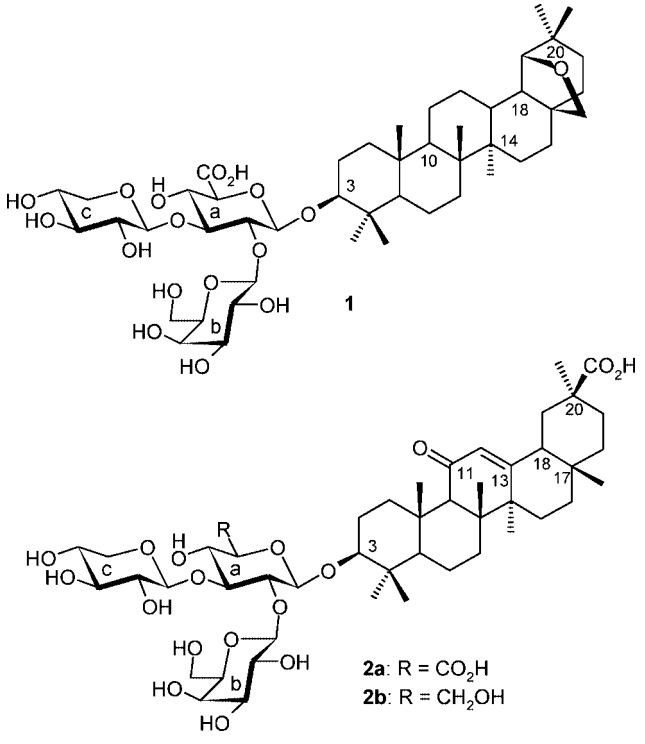
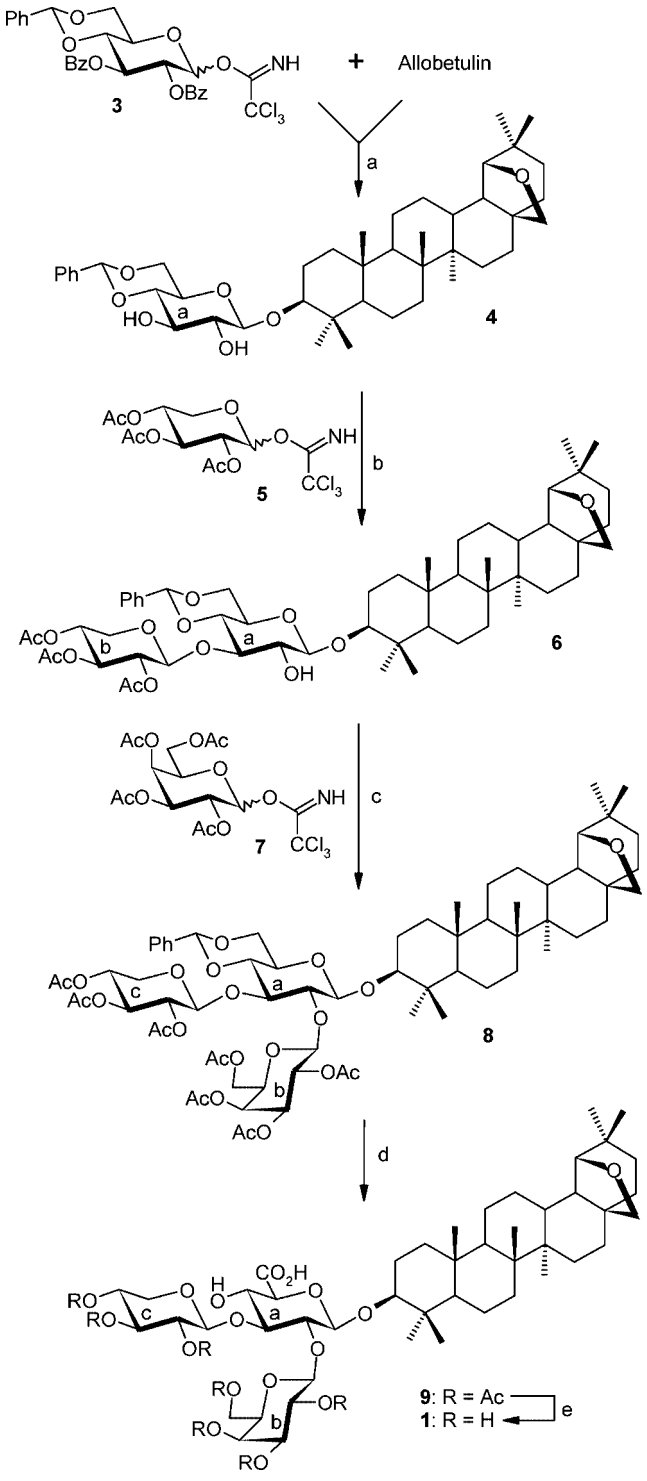


Figure 2. Structure of target molecules **1**, **2a** and **2b**.

Results and Discussion

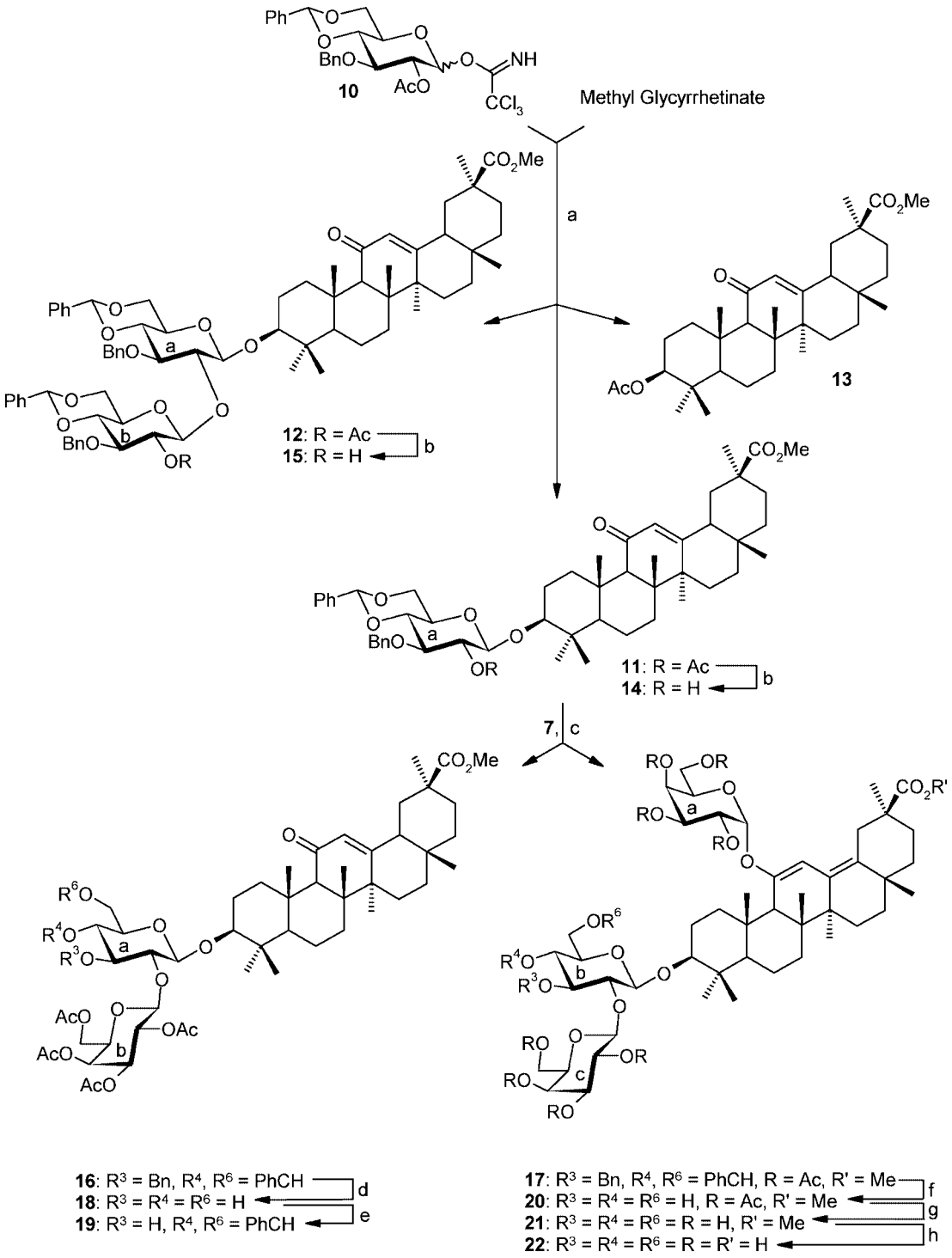
Synthesis of Allobetulin-Based Saponin 1

Previous studies had suggested that glucopyranosyl donor **3**[29] (Scheme 1) should be suitable for the efficient attachment of the trisaccharide moiety to the aglycon in a linear strategy, and so glycosylation of commercially available allobetulin with donor **3** in the presence of trimethyl-



Scheme 1. Synthesis of target molecule **1**. Reagents and conditions: a) TMSOTf (0.05 equiv.), CH_2Cl_2; NaOMe, MeOH/CH_2Cl_2 (72%). b) TMSOTf (0.005 equiv.), IP, CH_2Cl_2, –75 → –58 °C (73%). c) TMSOTf (0.03 equiv.), IP, CH_2Cl_2, room temp. (qu). d) EtSH, TsOH, CH_2Cl_2 (89%); TEMPO, NaOCl, TBAC, KBr, CH_2Cl_2/H_2O/$NaHCO_3$ (69%). e) NaOMe, MeOH/CH_2Cl_2. IR-120 (H^+) (qu).

silyl trifluoromethanesulfonate (TMSOTf) as catalyst was performed; subsequent cleavage of the *O*-benzoyl protecting groups under Zemplén conditions afforded the 2a,3a-*O*-unprotected β-linked glycoside **4** in very good overall yield (^{1}H NMR: $J_{1a,2a}$ = 7.5 Hz). Glycosylation of acceptor **4** with xylopyranosyl donor **5**[30] by the inverse procedure (IP: i.e., addition of donor **5** to a mixture of **4** and TMSOTf)[31,32] exclusively furnished the β(1–3)-linked disaccharide **6** [^{13}C NMR: δ = 105.2 (C-1a), 100.3 ppm (C-1b); ^{1}H NMR: δ = 2.46 ppm (d, HO-2a)]; this result is in accordance with the frequently observed higher nucleophilicity of 3-OH over 2-OH in glucopyranosyl residues. The 2a-*O*-galactosylation

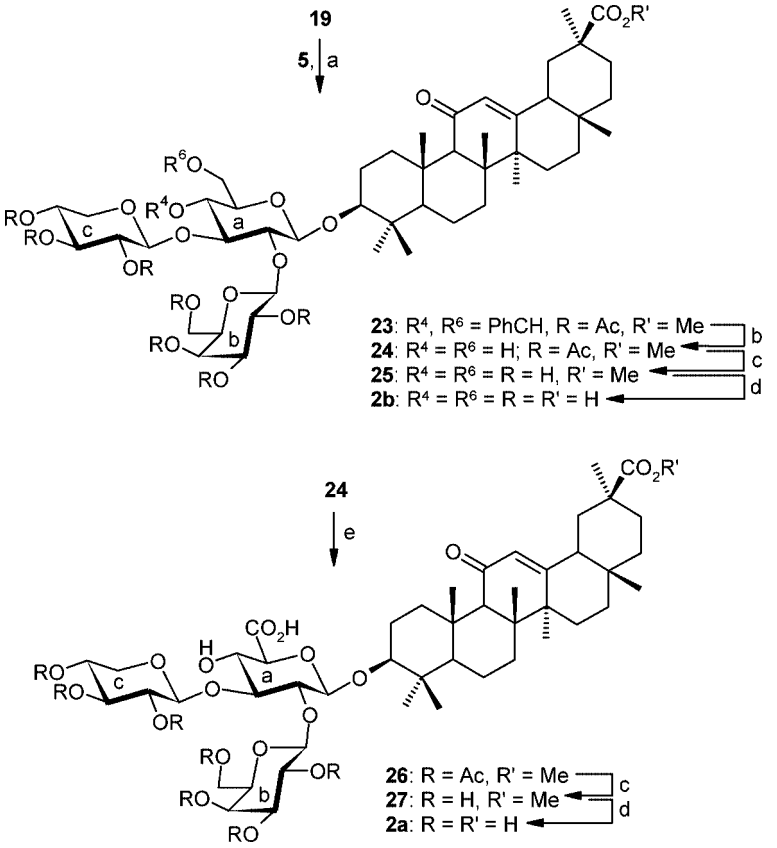


Scheme 2. Synthesis of intermediate **19**. Reagents and conditions: a) TMSOTf (0.06 equiv.), CH_2Cl_2, room temp. (**11**: 72%; **12**: 12%; **13**: 10%). b) NaOMe, MeOH, room temp. (**14**: 95%; **15**: 95%). c) TMSOTf (0.05 equiv.), IP, CH_2Cl_2, room temp. (**16**: 85%; **17**: 5%). d) Pd/C, H_2, MeOH/CH_2Cl_2 (qu). e) $PhCH(OMe)_2$, TsOH, MeCN, room temp. (85%). f) Pd/C, H_2, MeOH/CH_2Cl_2 (qu). g) KOH, EtOH/H_2O, room temp., 16 h (qu). h) KOH, EtOH/H_2O, refl, 3 h (70%).

could therefore be carried out immediately, and the desired trisaccharide **8** was obtained in practically quantitative yield with galactosyl donor **7**[33] under IP conditions, even though access to the 2a-OH group would be anticipated to be sterically hindered. The ^{1}H NMR spectroscopic data for **8** and also for the next compound indicate the presence of a $^1C_4 \rightleftharpoons {}^4C_1$ conformational equilibration of the xylopyranosyl residue, as was also observed previously;[25] however, the ^{13}C NMR spectroscopic data clearly indicate the generation of the β-anomer. For the transformation of the glucosyl residue into a glucuronic acid residue, the 4a,6a-*O*-benzylidene group was removed with ethyl mercaptan as nucleophile in the presence of *p*-toluenesulfonic acid (TsOH) as catalyst;[34] subsequent oxidation of the 4a,6a-*O*-unprotected intermediate with tetramethylpiperidine *N*-oxide (TEMPO)/sodium hypochlorite (NaOCl)[35,36] resulted in clean oxidation of the primary hydroxy group to furnish the uronic acid derivative **9**, which could be structurally fully assigned. As only *O*-acetyl protecting groups were present, final deprotection under Zemplén conditions to afford target molecule **1** could readily be carried out (Scheme 1).

Synthesis of the Glycyrrhetic Acid-Based Saponins 2a and 2b

For the synthesis of target molecules **2a** and **2b** the glycosylation sequence had to be changed because final galactosylation at the 2a-OH group met with difficulties due to the nucleophilicity of the glycyrrhetinate keto group (see below).[24] Therefore, for the glucosylation of methyl glycyrrhetinate, glucosyl donor **10**[23,25] with 2-*O*-acetyl and 3-*O*-benzyl protection was selected (Scheme 2). Glycosylation in the presence of TMSOTf as catalyst afforded mainly the desired β-linked glucoside **11** (^{1}H NMR: $J_{1a,2a}$ = 7.9 Hz), although small amounts of 3-*O*-acetyl glycyrrhetinate **13** were also obtained, which explains the concomitant formation of diglucosylated product **12**. Separation of **11** and **12** was more readily achieved after 2-*O*-deacetylation under Zemplén conditions, affording 2a- and 2b-*O*-unprotected derivatives **14** and **15**, respectively. Galactosylation of **14** with donor **7** under IP conditions in the presence of TMSOTf as catalyst furnished mainly the desired disaccharide **16** (^{1}H NMR: $J_{1a,2a}$ = 7.8, $J_{1b,2b}$ = 8.0 Hz). In addition, a small amount of keto group galactosylation, giving rise to compound **17**, was observed, in which the α configuration was unexpectedly found in the galactosyl residue at the dienol moiety (^{1}H NMR: $J_{1a,2a}$ = 3.3 Hz). Hydrogenolysis of disaccharide **16** with Pd/C as catalyst resulted in 3a-*O*-debenzylation and 4a,6a-*O*-debenzylidenation (→ **18**), and subsequent treatment with benzylidene dimethyl acetal in the presence of TsOH as catalyst installed the 4a,6a-*O*-benzylidene group to afford the 3a-*O*-unprotected acceptor **19**, suitable for the completion of the synthesis of the target molecules **2a** and **2b**. Compound **17** also seemed to be of



Scheme 3. Synthesis of target molecules **2a** and **2b**. Reagents and conditions: a) TMSOTf (0.05 equiv.), CH_2Cl_2, room temp. (86%). b) EtSH, TsOH, CH_2Cl_2, room temp. (83%). c) NaOMe, MeOH (qu). d) LiOH, MeOH, 54 °C (**2b**: 75%; **2a**: 55%). e) TEMPO, NaOCl, TBAB, NaBr, $CH_2Cl_2/H_2O/NaHCO_3$ (75%).

interest as a potential immunostimulant, so hydrogenolysis was performed (→ **20**); subsequent *O*-deacetylation (→ **21**) and methyl ester hydrolysis with KOH in an ethanol/water mixture provided the glycosylated glycyrrhetic acid **22**.

For the synthesis of target molecules **2a** and **2b**, xylosylation of **19** with xylosyl donor **5** was carried out in the presence of TMSOTf as catalyst (Scheme 3). In this way the β-linked trisaccharide **23** was obtained (^{13}C NMR: δ = 97.9, C-1c). 4a,6a-*O*-Debenzylidenation of **23** with ethyl mercaptan as nucleophile and TsOH as catalyst afforded the 4a,6a-*O*-unprotected compound **24**, and subsequent *O*-deacetylation under Zemplén conditions (→ **25**) and methyl ester hydrolysis with LiOH in methanol afforded target compound **2b** (^{1}H NMR: $J_{1a,2a} = J_{1b,2b} = J_{1c,2c}$ = 7.7 Hz). Oxidation of **24** with TEMPO/NaOCl in the presence of tetrabutylammonium bromide (TBAB) and NaBr resulted in chemoselective oxidation of the primary hydroxymethyl group, furnishing the glucuronate derivative **26**. *O*-Deacetylation (→ **27**) and subsequent methyl ester hydrolysis under the conditions described above afforded target molecule **2a** (^{1}H NMR: $J_{1a,2a}$ = 7.5, $J_{1c,2c}$ = 7.8 Hz).

In conclusion, the construction of branched trisaccharides of allobetulin and glycyrrhetic acid, containing β-linked glucopyranosyl or glucuronopyranosyl, galactopyranosyl, and xylopyranosyl residues, could be successfully accomplished in a stepwise fashion. The glucuronate derivatives were readily obtained by chemoselective oxidation of the glucose hydroxymethyl group. These results provide routes to the synthesis of more complex analogues of saponin QS L1 and finally to the synthesis of QS 21.

Experimental Section

Solvents were purified by standard procedures. NMR spectra were recorded at 22 °C on a Bruker AC 250 Cryospec or a Bruker DRX 600 spectrometer. Tetramethylsilane (TMS) or the resonance of residual undeuterated solvent was used as internal standard; solvent $CDCl_3$, δ = 7.24; D_2O, δ = 4.63; [D_6]DMSO, δ = 2.49 ppm. MALDI mass spectra were recorded on a Kratos Kompact Maldi 2 spectrometer and 2,5-dihydroxybenzoic acid (DHB) was used as matrix. FAB MS spectra were obtained with a Finnigan MAT 312/AMD 5000 instrument; +6 kV for positive ions, –4 kV for negative ions. Thin-layer chromatography was performed on Merck 60 F_{254} silica gel plastic plates or Merck RP-18 glass plates; compounds were visualized by treatment with a solution of [$(NH_4)_6Mo_7O_{24}\cdot 4H_2O$] (20 g) and $Ce(SO_4)_2$ (0.4 g) in 10% sulfuric acid (400 mL) and then heating to 120 °C. Flash chromatography was performed on J. T. Baker silica gel 60 (40–63 μm) at a pressure of 0.3 bar. Optical rotations were measured at 25 °C with a Perkin–Elmer 241/MS polarimeter at the sodium D line.

3β-*O*-(4,6-*O*-Benzylidene-β-D-glucopyranosyl)allobetulinol (4): TMSOTf solution (600 μL of a 0.05 M solution in CH_2Cl_2, 30 μmol, 0.05 equiv.) was added to a stirred solution of allobetulin (260 mg, 0.600 mmol) and the trichloroacetimidate donor **3**[29] (400 mg, 0.645 mmol) in dry CH_2Cl_2 (10 mL). After 15 min the reaction was complete (TLC: R_f = 0.54, PE/EtOAc 3:1). NEt_3 (2 drops) was added and the volume was reduced to 3 mL. Methanol (10 mL) and sodium methoxide (70 mg, 1.25 mmol) were added and the mixture was stirred for 16 h. The reaction was concentrated and the crude residue was subjected to flash chromatography (PE/EtOAc 2:1) to furnish the debenzoylated saponin **4** (300 mg, 0.433 mmol, 72% over two steps). R_f = 0.33 (petroleum ether/EtOAc 2:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.77 (s, 3 H, 24-H), 0.80 (s, 3 H, 29-H), 0.83 (s, 3 H, 23-H), 0.88 (s, 3 H, 27-H), 0.89 (s, 3 H, 30-H), 0.95/0.99 (2×s, 6 H, 25-, 26-H), 1.05–1.72 (24 H), 2.03 (br s, 1 H, 1×OH), 2.30 (br s, 1 H, 1×OH), 3.18 (m, 1 H, 5a-H), 3.40–3.47 (m, 2 H, 3-, 28-H_a), 3.50–3.85 (m, 6 H, 2a-, 3a-, 4a-, 19-H, 6a-H_a, 28-H_b), 4.29 (dd, $J_{6\text{-}H_b,6\text{-}H_a}$ = 10.4, $J_{6\text{-}H_b,5}$ = 5.0 Hz, 1 H, 6a-H_b), 4.44 (d, $J_{1,2}$ = 7.5 Hz, 1 H, 1a-H), 5.51 (s, 1 H, PhC*H*), 7.34 (m, 3 H, Ph), 7.46 (m, 2 H, Ph) ppm. $C_{43}H_{64}O_7\cdot 1.5H_2O$ (720.0): calcd. C 71.73, H 9.38; found C 71.41, H 9.54.

3β-*O*-[2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl-(1→3)-4,6-*O*-benzylidene-β-D-glucopyranosyl]allobetulinol (6): A solution of the monosaccharide saponin **4** (250 mg, 0.361 mmol) in dichloromethane (30 mL) was cooled to –75 °C and a TMSOTf solution (180 μL of a 0.01 M solution in CH_2Cl_2, 1.8 μmol, 0.005 equiv.) was added. A cold solution of the donor **5**[30,37] (170 mg, 0.400 mmol) in dry CH_2Cl_2 (10 mL) was then very slowly dropped into the vigorously stirred reaction mixture. During the addition the temperature was allowed to rise to –58 °C and the solution became turbid due to precipitated trichloroacetamide. Thorough TLC monitoring indicated quenching of the reaction after 1–2 h with NEt_3. The solvent was evaporated and the residue was purified by flash chromatography (PE/EtOAc 3:1 → 2:1) to give the disaccharide saponin **6** (250 mg, 0.263 mmol, 73%). R_f = 0.29 (petroleum ether/EtOAc 2:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.79 (s, 3 H, 24-H), 0.80 (s, 3 H, 29-H), 0.85 (s, 3 H, 23-H), 0.90 (s, 3 H, 27-H), 0.92 (s, 3 H, 30-H), 0.97/0.99 (2×s, 6 H, 25-, 26-H), 1.05–1.72 (24 H), 2.00–2.03 (3×s, 9 H, 3×H_3CCO), 2.46 (d, $J_{OH,2}$ = 2.4 Hz, 1 H, OH), 3.16 (m, 1 H, 3-H), 3.24 (dd, $J_{5\text{-}H_a,5\text{-}H_b}$ = 12.0, $J_{5\text{-}H_a,4}$ = 7.6 Hz, 1 H, 5b-H_a), 3.39 (m, 1 H, 5a-H), 3.43 (d, $J_{28\text{-}H_a,28\text{-}H_b}$ = 7.8 Hz, 1 H, 28-H_a), 3.52 (s, 1 H, 19-H), 79.4–75.2 (m, 2 H, 2a-, 4a-H), 3.76 (m, 2 H, 6a-H_a, 28-H_b), 3.82 (dd, $J_{3,4} = J_{3,2}$ = 9.0 Hz, 1 H, 3a-H), 4.15 (dd, $J_{5\text{-}H_b,5\text{-}H_a}$ = 12.1, $J_{5\text{-}H_b,4}$ = 4.7 Hz, 1 H, 5b-H_b), 4.29 (dd, $J_{6\text{-}H_b,6\text{-}H_a}$ = 10.4, $J_{6\text{-}H_b,5}$ = 4.8 Hz, 1 H, 6a-H_b), 4.42 (d, $J_{1,2}$ = 7.7 Hz, 1 H, 1a-H), 4.88 (ddd, $J_{4,3} = J_{4,5\text{-}H_a}$ = 7.6, $J_{4,5\text{-}H_b}$ = 4.7 Hz, 1 H, 4b-H), 4.93 (m, 2 H, 1b-, 2b-H), 5.09 (dd, $J_{3,4}$ = 7.7, $J_{3,2}$ = 4.7 Hz, 1 H, 3b-H), 5.51 (s, 1 H, PhCH), 7.35 (m, 3 H, Ph), 7.46 (m, 2 H, Ph) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, selected data): δ = 61.4 (C-5b), 66.4 (C-5a), 68.6 (C-4b), 68.7 (C-6a), 70.5 (C-3b), 70.8 (C-2b), 71.3 (C-28), 75.2 (C-2a), 79.4 (C-4a), 79.6 (C-3a), 88.0 (C-19), 90.2 (C-3), 100.3 (C-1b), 101.4 (PhCH), 105.2 (C-1a) ppm. $C_{54}H_{78}O_{14}$ (951.2). FAB-MS (positive mode, Matrix NBA + NaI, THF): 973 [M + Na]$^+$.

3β-*O*-{2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl-(1→2)-[2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl-(1→3)]-4,6-*O*-benzylidene-β-D-glucopyranosyl}allobetulinol (8): A solution of the disaccharide saponin acceptor **6** (140 mg, 0.147 mmol) in dry CH_2Cl_2 (3 mL) was treated with a TMSOTf solution (250 μL of a 0.02 M solution in CH_2Cl_2, 5 μmol, 0.05 equiv.). The galactosyl donor **7**[4] (90 mg, 0.180 mmol) dissolved in CH_2Cl_2 (1 mL) was added dropwise to the reaction mixture at room temp. NEt_3 was used to quench the reaction and the solvent was evaporated. The residue was separated by flash chromatography (PE/EtOAc 2:1) to give the trisaccharide saponin **8** (90 mg, 0.070 mmol, 48%), together with unreacted recovered acceptor **6** (70 mg, 0.074 mmol). R_f = 0.086 (petroleum ether/EtOAc 2:1). R_f = 0.41 (petroleum ether/EtOAc 1:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.79 (s, 3 H, 29-H), 0.84 (2×s, 6 H, 23-, 24-H), 0.89 (s, 3 H, 25-H), 0.92 (s, 3 H, 27-H), 0.96 (s, 3 H, 30-H), 1.10 (s, 3 H, 26-H), 1.19–1.75 (24 H), 1.95 (1×s, 3 H, 1×H_3CCO), 1.99 (2×s, 6 H, 2×H_3CCO), 2.04 (2×s, 6 H, 2×H_3CCO), 2.08 (1×s, 3 H,

1×H_3CCO), 2.12 (1×s, 3 H, 1×H_3CCO), 3.07 (m, 1 H, 3-H), 3.14 (dd, $J_{5\text{-}H_a,5\text{-}H_b}$ = 12.3, $J_{5\text{-}H_a,4}$ = 5.9 Hz, 1 H, 5c-H_a), 3.40 (m, 1 H, 5a-H), 3.43 (d, $J_{28\text{-}H_a,28\text{-}H_{Hb}}$ = 7.7 Hz, 1 H, 28-H_a), 3.52 (s, 1 H, 19-H), 3.62 (dd, $J_{4,3}$ = $J_{4,5}$ = 9.2 Hz, 1 H, 4a-H), 3.75 (dd, $J_{6\text{-}H_a,6\text{-}H_b}$ = $J_{6\text{-}H_a,5}$ = 10.6 Hz, 1 H, 6a-H_a), 3.76 (d, $J_{28\text{-}H_{Hb},28\text{-}H_a}$ = 7.7 Hz, 1 H, 28-H_b), 3.94 (m, 2 H, 2a-, 5b-H), 3.97 (dd, $J_{3,4}$ = $J_{3,2}$ = 9.0 Hz, 1 H, 3a-H), 4.11 (m, 2 H, 6b-H_a, 6b-H_b), 4.18 (dd, $J_{5\text{-}H_b,5\text{-}H_a}$ = 12.3, $J_{5\text{-}H_b,4}$ = 3.8 Hz, 1 H, 5c-H_b), 4.28 (dd, $J_{6\text{-}H_b,6\text{-}H_a}$ = 10.6, $J_{6\text{-}H_b,5}$ = 4.9 Hz, 1 H, 6a-H_b), 4.42 (d, $J_{1,2}$ = 7.3 Hz, 1 H, 1a-H), 4.78 (ddd, $J_{4,3}$ = $J_{4,5\text{-}H_a}$ = 5.9, $J_{4,5\text{-}H_b}$ = 3.8 Hz, 1 H, 4c-H), 4.92 (d, $J_{1,2}$ = 7.8 Hz, 1 H, 1b-H), 4.95–4.97 (m, 3 H, 1c-, 2c-, 3c-H), 5.11 (dd, $J_{2,3}$ = 10.1, $J_{2,1}$ = 7.8 Hz, 1 H, 2b-H), 5.24 (dd, $J_{3,2}$ = 10.3, $J_{3,4}$ = 3.4 Hz, 1 H, 3b-H), 5.34 (dd, $J_{4,3}$ = 3.4, $J_{4,5}$ < 1 Hz, 1 H, 4b-H), 5.46 (s, 1 H, PhCH), 7.35 (m, 3 H, Ph), 7.44 (m, 2 H, Ph) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, selected data): δ = 60.4 (C-5c), 61.0 (C-6b), 66.0 (C-5a), 67.5 (C-4b), 67.6 (C-4c), 69.3 (C-6a), 69.7 (C-3c, C-2c), 70.3 (C-2b), 70.5 (C-3b), 70.7 (C-5b), 71.6 (C-28), 77.9 (C-2a), 78.7 (C-3a), 79.5 (C-4a), 88.2 (C-19), 91.2 (C-3), 97.8 (C-1c), 99.1 (C-1b), 102.0 (PhCH), 104.5 (C-1a) ppm. $C_{68}H_{96}O_{23}$ (1281.4). FAB-MS (positive mode, matrix NBA + NaI, THF): *m/z* = 1303 $[M + Na]^+$, 1319 $[M + K]^+$, 1454 $[(M + NaI)Na]^+$.

3β-*O*-{2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl-(1→2)-[2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl-(1→3)]-β-D-glucuronopyranosyl}-allobetulinol (9): Compound **8** (60 mg, 0.047 mmol) was dissolved in CH_2Cl_2 (1 mL) and treated with ethanethiol (20 μL). The solution was acidified with *p*-toluenesulfonic acid and stirred until TLC (R_f = 0.85, toluene/acetone 1:3) indicated complete removal of the benzylidene group. Addition of NEt_3, concentration and flash chromatographic separation (PE/EtOAc 1:1 → 1:2) yielded the debenzylidenated saponin (50 mg, 0.042 mmol, 89%), which was directly used for the oxidation step. For this the saponin was redissolved in a CH_2Cl_2/H_2O/satd. $NaHCO_3$ mixture (12:1:1, 3.5 mL). Tetrabutylammonium chloride (0.6 mg, 2.3 μmol), potassium bromide (0.9 mg, 7.4 μmol) and TEMPO (0.25 mg, 1.6 μmol) were added, and NaOCl solution (70 μL) was added dropwise to the vigorously stirred mixture at 0 °C. After 1 h the oxidation was complete, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and quenched with Na_2SO_3 solution (5 mL), the organic layer was washed with HCl (0.25 M), and the combined water phases were extracted with CH_2Cl_2. The organic layers were combined and concentrated, and the residue was separated by repeated flash chromatography (toluene/acetone 1:3, followed by SiO_2 2×5, toluene/acetone 1:1 → 1:3 + 0.5% TFA, followed by EtOAc → toluene/acetone 1:3 + 0.5% TFA) to give the oxidized trisaccharide saponin **9** (35 mg, 0.029 mmol, 69%) as a colourless solid. R_f = 0.43 (toluene/acetone 1:3). ^{1}H NMR (600 MHz, $CDCl_3$/MeOD 20:1): δ = 0.76 (s, 3 H, 29-H), 0.81 (2×s, 6 H, 23-, 24-H), 0.87 (s, 3 H, 25-H), 0.89 (s, 3 H, 27-H), 0.93 (s, 3 H, 30-H), 1.04 (s, 3 H, 26-H), 1.22–1.75 (24 H), 1.94 (1×s, 3 H, 1×H_3CCO), 2.02–2.11 (6×s, 18 H, 6×H_3CCO), 3.04 (m, 1 H, 3-H), 3.41 (d, $J_{28\text{-}H_a,28\text{-}H_{Hb}}$ = 7.7 Hz, 1 H, 28-H_a), 3.45 (dd, $J_{5\text{-}H_a,5\text{-}H_b}$ = 12.3, $J_{5\text{-}H_a,4}$ = 6.2 Hz, 1 H, 5c-H_a), 3.51 (s, 1 H, 19-H), 3.70–3.75 (m, 4 H, 3a-, 4a-, 5a-H, 28-H_b), 3.81 (dd, $J_{2,3}$ = $J_{2,1}$ = 7.8 Hz, 1 H, 2a-H), 3.88 (dd, $J_{5,6\text{-}H_a}$ = $J_{5,6\text{-}H_b}$ = 6.7, $J_{5,4}$ < 1 Hz, 1 H, 5b-H), 4.07 (m, 2 H, 6b-H_a, 6b-H_b), 4.36 (m, 2 H, 5c-H_b, 1a-H), 4.82 (d, $J_{1,2}$ = 6.8 Hz, 1 H, 1b-H), 4.92 (m, 2 H, 1c-, 4c-H), 5.00 (dd, $J_{2,3}$ = 6.6, $J_{2,1}$ = 4.5 Hz, 1 H, 2c-H), 5.06 (dd, $J_{3,2}$ = $J_{3,4}$ = 6.6 Hz, 1 H, 3c-H), 5.09 (m, 2 H, 2b-, 3b-H), 5.32 (dd, $J_{4,3}$ = 1, $J_{4,5}$ < 1 Hz, 1 H, 4b-H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, selected data): δ = 60.9 (C-6b), 61.0 (C-5c), 67.2 (C-4b), 68.1 (C-4c), 70.0 (C-3c), 70.0 (C-4a), 70.1 (C-2c), 70.4 (C-2b, C-3b, C-5b), 71.2 (C-28), 73.9 (C-5a), 76.4 (C-2a), 82.4 (C-3a), 88.2 (C-19), 91.1 (C-3), 98.9 (C-1c), 99.2 (C-1b), 103.6 (C-1a) ppm. $C_{61}H_{90}O_{24}$ (1207.3). FAB-MS (positive mode, matrix NBA + NaI, THF): *m/z* = 1209 $[M + H]^+$, 1229 $[M + Na]^+$, 1251 $[(M – H + Na)Na]^+$, 1267 $[(M – H + Na)K]^+$. MALDI-MS (positive mode, matrix DHB, THF): *m/z* = 1229.4 $[M + Na]^+$, 1245.0 $[M + K]^+$, 1267.6 $[(M – H + Na)K]^+$, 1284.1 $[(M – H + K)K]^+$, 1303.5 $[(M – 2 H + K + Na) K]^+$.

3β-*O*-{β-D-Galactopyranosyl-(1→2)-[β-D-xylopyranosyl-(1→3)]-β-D-glucuronopyranosyl}allobetulinol (1): A solution of the acetylated saponin **9** (5 mg, 4.1 μmol) in dichloromethane/methanol (1:1, 2 mL) was treated with solid sodium methoxide (1 mg). After complete deprotection, the solution was neutralized with ion exchange resin IR-120 (H^+), filtered and evaporated to furnish the pure deprotected neosaponin **1** (3.7 mg, 4.1 μmol, qu). R_f = 0.64 (chloroform/methanol/water 60:35:8). ^{1}H NMR (250 MHz, $CDCl_3$/MeOD/D_2O 65:35:3): δ = 0.54 (s, 3 H, 29-H), 0.56–0.57 (2×s, 6 H, 23-, 24-H), 0.64 (2×s, 6 H, 25-, 27-H), 0.70 (s, 3 H, 30-H), 0.75 (s, 3 H, 26-H), 0.98–1.55 (m, 24 H), 2.88 (m, 1 H, 3-H), 3.04–4.51 (m, 21 H, 1a-, 2a-, 3a-, 4a-, 5a-, 1b-, 2b-, 3b-, 4b-, 5b-, 1c-, 2c-, 3c-, 4c-H, 28-H_a, 28-H_b, 6b-H_a, 6b-H_b, 5c-H_a, 5c-H_b, 19-H) ppm. $C_{47}H_{76}O_{17}$ (913.1). MALDI-MS (positive mode, matrix DHB, MeOH): *m/z* = 951.9 $[M + K]^+$.

Methyl 3β-*O*-(2-*O*-Acetyl-3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranosyl)-18β-glycyrrhetinate (11) and Methyl 3β-*O*-[(2-*O*-Acetyl-3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranosyl)-(1→2)-(3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranosyl)]-18β-glycyrrhetinate (12): TMSOTf (0.03 M solution in CH_2Cl_2, 34 μL, 0.18 mmol) was added dropwise under nitrogen at room temp to a stirred solution of methyl glycyrrhetinate (1.24 g, 2.54 mmol) and donor **10**[23,25] (1.67 g, 3.08 mmol) in dry CH_2Cl_2 (61 mL). After 20 min the reaction mixture was neutralized with NEt_3, the solvent was evaporated in vacuo, and the residue was subjected to flash chromatography (petroleum ether/EtOAc 4:1) to afford a 6:1 mixture of compounds **11** (1.59 g, 72%) and **12** (454 mg, 12%), together with methyl 3-*O*-acetyl glycyrretinate **13** (134 mg, 10%). The separation of compounds **11** and **12** was achieved by MPLC (petroleum ether/EtOAc 5:1).

Compound 11: TLC (petroleum ether/EtOAc 3:1): R_f = 0.55. $[a]_D$ = +63.9 (*c* = 1, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.68 (d, $J_{5,6}$ = 11.9 Hz, 1 H, 5-H), 0.77 (s, 3 H, 24-CH_3), 0.80 (s, 3 H, 28-CH_3), 0.91–0.95 (m, 4 H, 23-CH_3, 1-H_a), 1.01 (br d, 1 H, 16-H_a), 1.11 (s, 3 H, 26-CH_3), 1.12 (s, 3 H, 25-CH_3), 1.14–1.15 (m, 4 H, 29-CH_3, 16-H_b), 1.30–1.31 (m, 2 H, 21-H_a, 22-H_a), 1.34 (s, 3 H, 27-CH_3), 1.38–1.64 (m, 3 H, 7-H_a, 22-H_b, 6-$H_{a,b}$, 6-Hb, 19-H_a, 7-H_b), 1.76–1.84 (m, 3 H, 2-$H_{a,b}$, 15-H_a), 1.91–1.95 (m, 1 H, 19-H_b), 1.95–2.08 (m, 6 H, 21-H_b, Ac, 15-H_b, 18-H), 2.30 (s, 1 H, 9-H), 2.78 (br d, *J* = 13.6 Hz, 1 H, 1-H_b), 3.09 (dd, $J_{3,2\text{-}H_a}$ = 5.3, $J_{3,2\text{-}H_b}$ = 11.0 Hz, 1 H, 3-H), 3.41 (ddd, $J_{5,4}$ = $J_{5,6\text{-}H_a}$ = 9.6, $J_{5,6\text{-}H_b}$ = 5.0 Hz, 1 H, 5a-H), 3.66–3.72 (m, 4 H, OCH_3, 3a-H), 3.77 (dd, $J_{4,3}$ = $J_{4,5}$ = 9.3 Hz, 1 H, 4a-H), 3.82 (dd, J_{gem} = $J_{6,5}$ = 9.3 Hz, 1 H, 6a-H_a), 4.32 (dd, $J_{6,5}$ = 5.0 Hz, 1 H, 6a-H_b), 4.50 (d, $J_{1,2}$ = 7.9 Hz, 1 H, 1a-H), 4.68 (d, J_{gem} = 12.2 Hz, 1 H, CH_2Ph), 4.87 (d, J_{gem} = 12.2 Hz, 1 H, CH_2Ph), 5.06 (dd, $J_{2,1}$ = $J_{2,3}$ = 7.9 Hz, 1 H, 2a-H), 5.57 (s, 1 H, C*H*Ph), 5.66 (s, 1 H, 12-H), 7.26–7.50 (m, 5 H, Ph) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 16.3 (2 C, C-24, C-25) 17.3 (1 C, C-6), 18.7 (1 C, C-26), 20.9 (1 C, *C*H_3CO), 23.3 (1 C, C-27), 25.9, 26.4, 26.5 (3 C, C-2, C-15, C-16), 27.7 (1 C, C-23), 28.3 (1 C, C-29), 28.5 (1 C, C-28), 31.1 (1 C, C-21), 32.7 (1 C, C-7), 37.7 (1 C, C-22), 39.0 (1 C, C-1), 41.1 (1 C, C-19), 48.4 (1 C, C-18), 51.8 (1 C, O*C*H_3), 55.3 (1 C, C-5), 61.8 (1 C, C-9), 66.1 (1 C, C-5), 68.8 (1 C, C-6), 73.3 (1 C, C-2), 73.9 (1 C, *C*H_2Ph), 78.5 (1 C, C-3), 81.5 (1 C, C-4), 89.9 (1 C, C-3), 101.1 (1 C, *C*HPh), 103.6 (1 C, C-1), 125.9, 126.0, 127.6, 127.9, 128.0, 128.1, 128.2, 128.4, 128.5, 129.0 (10 C,

2×Ph), 128.0 (1 C, C-12), 137.3, 138.3 (2 C, *ipso*-Ph), 169.1 (1 C, CH_3CO), 176.9 (1 C, C-30), 200.1 (1 C, C-11) ppm. MALDI-MS (positive mode, matrix DHB, THF): *m/z* = 890 $[M + Na]^+$, 906 $[M + K]^+$. $C_{53}H_{70}O_{10}$ (867.1): calcd. C 73.41, H 8.14; found C 73.07, H 8.28.

Compound 12: TLC (petroleum ether/EtOAc 3:1): R_f = 0.56. MALDI-MS (positive mode, matrix DHB, THF): *m/z* = 1232 $[M + Na]^+$. $C_{73}H_{90}O_{15}$ (1207.5).

Methyl 3β-*O*-(3-*O*-Benzyl-4,6-*O*-benzylidene-β-D-glucopyranosyl)-18β-glycyrrhetinate (14) and Methyl 3β-*O*-[(3-*O*-Benzyl-4,6-*O*-benzylidene-β-D-glucopyranosyl)-(1→2)-(3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranosyl)]-18β-glycyrrhetinate (15): A solution of **11** (790 mg, 0.78 mmol) and **12** (114 mg, 0.09 mmol) in dry CH_3OH/CH_2Cl_2 (2.3:1, 100 mL) was treated with sodium methoxide (1 M solution in CH_3OH, 1 mL) and stirred at room temp. for 24 h. After neutralization with ion-exchange resin (Amberlite IR-120 H^+), the resin was filtered off and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc 3:1) to afford a mixture of **14** (612 mg 95%) and **15** (104 mg, 95%). The compounds were separated by MPLC (petroleum ether/EtOAc 3:1).

Compound 14: TLC (petroleum ether/EtOAc 3:1): R_f = 0.47. $[\alpha]_D$ = +4.4 (*c* = 0.5, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ = 0.72 (d, $J_{5,6}$ = 11.4 Hz, 1 H, 5-H), 0.81 (s, 3 H, 28-CH_3), 0.86 (s, 3 H, 24-CH_3), 0.93–1.04 (m, 2 H, 1-H_a, 16-H_a), 1.05 (s, 3 H, 23-CH_3), 1.12 (s, 3 H, 26-CH_3), 1.15–1.20 (m, 7 H, 25-CH_3, 29-CH_3, 16-H_b), 1.30–1.32 (m, 2 H, 21-H_a, 22-H_a), 1.35 (s, 3 H, 27-CH_3), 1.37–1.50 (m, 3 H, 7-H_a, 22-H_b, 6-H_a), 1.55–1.68 (m, 3 H, 6-H_b, 19-H_a, 7-H_b), 1.79–1.82 (m, 3 H, 2-$H_{a,b}$, 15-H_a), 1.91–2.08 (m, 4 H, 19-H_b, 21-H_b, 15-H_b, 18-H), 2.33 (s, 1 H, 9-H), 2.80 (br d, 1 H, 1-H_b), 3.20 (dd, $J_{3,2\text{-}H_a}$ = $J_{3,2\text{-}H_b}$ = 7.6 Hz, 1 H, 3-H), 3.43 (ddd, $J_{5,4}$ = $J_{5,6\text{-}H_a}$ = 9.6, $J_{5,6\text{-}H_b}$ = 5.0 Hz, 1 H, 5a-H), 3.61–3.73 [m, 6 H, H,H-COSY: 3.63 (2a-H), 3.66 (3a-H), 3.68 (OCH_3), 3.71 (4a-H)], 3.81 (dd, J_{gem} = $J_{6,5}$ = 10.3 Hz, 1 H, 6a-H_a), 4.32 (dd, J_{gem} = 10.3, $J_{6,5}$ = 4.9 Hz, 1 H, 6a-H_b), 4.46 (d, $J_{1,2}$ = 7.3 Hz, 1 H, 1-H), 4.80 (d, J_{gem} = 11.7 Hz, 1 H, CH_2Ph), 4.96 (d, J_{gem} = 11.7 Hz, 1 H, CH_2Ph), 5.56 (s, 1 H, C*H*Ph), 5.67 (s, 1 H, 12-H), 7.27–7.50 (m, 5 H, Ph) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 16.4 (1 C, C-25), 16.6 (1 C, C-24), 17.4 (1 C, C-6), 18.7 (1 C, C-26), 23.4 (1 C, C-27), 25.9, 26.4, 26.5 (3 C, C-2, C-15, C-16), 28.1 (1 C, C-23), 28.3 (1 C, C-29), 28.5 (1 C, C-28), 31.1 (1 C, C-21), 32.7 (1 C, C-7), 37.7 (1 C, C-22), 39.1 (1 C, C-1), 41.1 (1 C, C-19), 48.4 (1 C, C-18), 51.8 (1 C, OCH_3), 55.3 (1 C, C-5), 61.8 (1 C, C-9), 66.4 (1 C, C-5), 68.8 (1 C, C-6), 74.6 (1 C, CH_2Ph), 75.0 (1 C, C-2), 80.5 (1 C, C-3), 81.3 (1 C, C-4), 89.8 (1 C, C-3), 101.2 (1 C, C*H*Ph), 105.4 (1 C, C-1), 126.0, 127.7, 128.2, 128.4, 128.5, 128.9 (10 C, 2×Ph), 128.0 (1 C, C-12), 137.5, 138.5 (2 C, *ipso*-Ph), 169.2 (1 C, C-13), 176.9 (1 C, C-30), 200.1 (1 C, C-11) ppm. MALDI-MS (positive mode, matrix DHB, THF): *m/z* = 849 $[M + Na]^+$, 866 $[M + K]^+$. $C_{51}H_{68}O_9$ (825.1): calcd. C 74.24, H 8.31; found C 73.91, H 8.40.

Compound 15: TLC (petroleum ether/EtOAc 3:1): R_f = 0.48. $[\alpha]_D$ = +18.8 (*c* = 0.5, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ = 0.69 (d, $J_{5,6}$ = 11.6 Hz, 1 H, 5-H), 0.80 (s, 3 H, 28-CH_3), 0.84 (s, 3 H, 24-CH_3), 0.95–1.04 (m, 2 H, 1-H_a, 16-H_a), 1.06 (s, 3 H, 23-CH_3), 1.12, 1.13, 1.14 (3×s, 9 H, 26-CH_3, 25-CH_3, 29-CH_3), 1.15–1.17 (m, 1 H, 16-H_b), 1.30–1.31 (m, 2 H, 22-H_b, 21-H_b), 1.34 (s, 3 H, 27-CH_3), 1.38–2.07 (m, 11 H, 7-H_a, 22-H_b, 6-H_a, 6-H_b, 19-H_a, 7-H_b, 2-$H_{a,b}$, 15-H_a, 19-H_b, 21-H_b, 15-H_b, 18-H), 2.31 (s, 1 H, 9-H), 2.78 (br d, 1 H, 1-H_b), 3.17 (dd, $J_{3,2\text{-}H_a}$ = $J_{3,2\text{-}H_b}$ = 7.9 Hz, 1 H, 3-H), 3.37–3.40 (m, 2 H, 5a-H, 5b-H), 3.52 (br dd, 1 H, 2b-H), 3.59 (dd, $J_{3,2}$ = $J_{3,4}$ = 9.1 Hz, 1 H, 3b-H), 3.63 (dd, $J_{4,3}$ = $J_{4,2}$ = 9.1 Hz, 1 H, 4b-H), 3.68 (s, 3 H, OCH_3), 3.70–3.75 (m, 2 H, 4a-H, 6b-H_a), 3.78 (dd, J_{gem} = $J_{6,5}$ = 10.3 Hz, 1 H, 6a-H_a), 3.83–3.85 (m, 2 H, 2a-H, 3a-H), 3.95 (d, $J_{OH,2}$ = 1.9 Hz, 1 H, OH), 4.27–4.33 (m, 2 H, 6b-H_b, 6a-H_b), 4.54 (d, $J_{1,2}$ = 6.8 Hz, 1 H, 1a-H), 4.69 (d, $J_{1,2}$ = 7.5 Hz, 1 H, 1b-H), 4.75 (d, J_{gem} = 10.5 Hz, 1 H, 3b-OCH_2Ph), 4.76 (d, J_{gem} = 11.7 Hz, 1 H, 3a-OCH_2Ph), 4.81 (d, J_{gem} = 11.7 Hz, 1 H, 3b-OCH_2Ph), 5.00 (d, J_{gem} = 10.5 Hz, 1 H, 3a-OCH_2Ph), 5.54 (s, 1 H, 6b-OCH_2Ph), 5.58 (s, 1 H, 6a-OCH_2Ph), 5.66 (s, 1 H, 12-H), 7.26–7.49 (m, 20 H, 4 Ph) ppm. ROESY: 4.69 (1b-H)-3.83 (2a-H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 16.2 (1 C, C-24), 16.4 (1 C, C-25), 17.9 (1 C, C-6), 18.7 (1 C, C-26), 23.4 (1 C, C-27), 26.2, 26.4, 26.5 (3 C, C-2, C-15, C-16), 27.8 (1 C, C-23), 28.3 (1 C, C-29), 28.5 (1 C, C-28), 31.1 (1 C, C-21), 32.7 (1 C, C-7), 37.7 (1 C, C-22), 39.5 (1 C, C-1), 41.1 (1 C, C-19), 48.4 (1 C, C-18), 51.8 (1 C, OCH_3), 55.4 (1 C, C-5), 61.8 (1 C, C-9), 65.7, 66.7 (2 C, C-5a, C-5b), 68.6 (1 C, C-6b), 68.9 (1 C, C-6a), 74.5 (1 C, CH_2Ph), 75.8 (1 C, CH_2Ph), 76.9 (1 C, C-2b), 79.7 (1 C, C-3b), 80.7 (2 C, C-2a, C-3a), 81.0 (1 C, C-4b), 81.9 (1 C, C-4a), 89.6 (1 C, C-3), 101.1, 101.3 (2 C, 2 C*H*Ph), 104.9 (2 C, C-1a, C-1b), 125.9, 126.0, 127.5, 127.9, 128.2, 128.3, 128.4, 128.5, 128.6, 128.9, 129.0 (20 C, 4×Ph), 129.0 (1 C, C-12), 137.1, 137.3, 138.6 (4 C, *ipso*-Ph), 176.9 (1 C, C-30), 200.1 (1 C, C-11) ppm. MALDI-MS (positive mode, matrix DHB, THF): *m/z* = 1189 $[M + Na]^+$. $C_{71}H_{88}O_{14}$ (1165.5): calcd. C 73.17, H 7.71; found C 72.70, H 7.96.

Methyl 3β-*O*-[(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→2)-(3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranosyl)]-18β-glycyrrhetinate (16) and Methyl 3β-*O*-[(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→2)-(3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranosyl)]-11-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)-11(12),13(18)-dieno-glycyrrhetinate (17): TMSOTf (0.03 M solution in CH_2Cl_2, 6 μL, 32.9 μmol) was added dropwise under nitrogen at room temp to a solution of **14** (412 mg, 0.50 mmol) in CH_2Cl_2 (4 mL). After 5 min a solution of **7** (295 mg, 0.60 mmol) in dry CH_2Cl_2 (10 mL) was slowly added and the reaction mixture was stirred for 10 min. The mixture was then neutralized with NEt_3 and the solvent was evaporated in vacuo. Flash chromatography of the residue (petroleum ether/EtOAc 4:1 → 3:1 → 2:1) gave **16** (490 mg, 85%) and **17** (40 mg, 5%).

Compound 16: TLC (petroleum ether/EtOAc 3:1): R_f = 0.39. $[\alpha]_D$ = +30.5 (*c* = 1, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ = 0.71 (d, $J_{5,6}$ = 10.9 Hz, 1 H, 5-H), 0.80 (s, 3 H, 28-CH_3), 0.87 (s, 3 H, 24-CH_3), 0.94 (br ddd, 1 H, 1-H_a), 1.00 (br d, 1 H, 16-H_a), 1.15 (s, 3 H, 26-CH_3), 1.13–1.20 (m, 10 H, 25-CH_3, 23-CH_3, 29-CH_3, 16-H_b), 1.30–1.32 (m, 2 H, 22-H_a, 21-H_a), 1.35 (s, 1 H, 27-CH_3), 1.38–1.45 (m, 3 H, 22-H_b, 7-H_a, 6-H_a), 1.55–1.68 (m, 3 H, 6-H_b, 19-H_a, 7-H_b), 1.72–1.93 (m, 4 H, 2-$H_{a,b}$, 15-H_a, 19-H_b), 1.98–2.08 (m, 12 H, 21-H_b, 15-H_b, 3×Ac, 18-H), 2.13 (s, 3 H, Ac), 2.32 (s, 1 H, 9-H), 2.78 (br d, 1 H, 1-H_b), 3.13 (dd, $J_{3,2\text{-}H_a}$ = 5.5, $J_{3,2\text{-}H_b}$ = 10.8 Hz, 1 H, 3-H), 3.40 (ddd, $J_{5,4}$ = $J_{5,6\text{-}H_a}$ = 9.4, $J_{5,6\text{-}H_b}$ = 5.0 Hz, 1 H, 5a-H), 3.68–3.74 [m, 5 H, H,H-COSY: 3.69 (OCH_3), 3.70 (4a-H), 3.73 (3a-H)], 3.78–3.80 (m, 2 H, 5b-H, 6a-H_a), 3.86 (dd, $J_{2,1}$ = $J_{2,3}$ = 8.0 Hz, 1 H, 2a-H), 4.03–4.11 (m, 2 H, 6b-$H_{a,b}$), 4.32 (dd, J_{gem} = 10.6, $J_{6,5}$ = 5.0 Hz, 1 H, 6a-H_b), 4.47 (d, $J_{1,2}$ = 7.6 Hz, 1 H, 1a-H), 4.65 (d, J_{gem} = 10.4 Hz, 1 H, CH_2Ph), 4.92–4.95 (m, 2 H, CH_2Ph, 3b-H), 5.07 (d, $J_{1,2}$ = 8.0 Hz, 1 H, 1b-H), 5.18 (dd, $J_{2,1}$ = 8.0 Hz, $J_{2,3}$ = 10.3 Hz, 1 H, 2b-H), 5.32 (d, $J_{4,3}$ = 2.9 Hz, 1 H, 4b-H), 5.55 (s, 1 H, C*H*Ph), 5.66 (s, 1 H, 12-H), 7.31–7.48 (m, 10 H, 2×Ph) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 16.2, 16.3 (2 C, C-24, C-25), 17.6 (1 C, C-6), 18.7 (1 C, C-26), 20.6, 20.7 (4 C, 4×CH_3CO), 23.3 (1 C, C-27), 26.0, 26.4, 26.5 (3 C, C-2, C-15, C-16), 27.6, 28.3, 28.5 (3 C, C-23, C-29, 28), 31.1 (1 C, C-21), 32.7 (1 C, C-7), 37.7 (1 C, C-22), 39.1 (1 C, C-1), 41.1 (1 C, C-19), 48.4 (1 C, C-18), 51.8 (1 C, OCH_3), 55.4 (1 C, C-5), 61.1 (1 C, C-6b), 61.8 (1 C, C-9), 65.8 (1 C, C-5a), 67.2 (1 C, C-4b), 68.8 (1 C, C-6a),

69.6 (1 C, C-2b), 70.4 (1 C, C-5b), 71.1 (1 C, C-3b), 75.4 (1 C, CH_2Ph), 77.2 (1 C, C-2a), 81.5 (1 C, C-4a), 82.8 (1 C, C-3a), 90.7 (1 C, C-3), 100.1 (1 C, C-1b), 101.1 (1 C CHPh), 104.4 (1 C, C-1a), 125.9, 128.3, 128.6, 130.0 (10 C, 2×Ph), 128.0 (1 C, C-12), 137.3, 138.0 (2 C, *ipso*-Ph), 169.1, 169.3, 170.1, 170.3 (5 C, C-13, 4×CH_3CO), 176.9 (1 C, C-30), 200.2 (1 C, C-11) ppm. MALDI-MS (positive mode, matrix DHB, THF): *m/z* = 1179 $[M + Na]^+$, 1195 $[M + K]^+$. $C_{65}H_{86}O_{18}$ (1155.4): calcd. C 67.57, H 7.50; found C 67.17, H 7.52.

Compound 17: TLC (petroleum ether/EtOAc 3:1): R_f = 0.48. $[\alpha]_D$ = +19.6 (*c* = 1, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.77 (s, 3 H, 28-CH_3), 0.82 (d, $J_{5,6}$ = 11.2 Hz, 1 H, 5-H), 0.86 (s, 3 H, 24-CH_3), 0.97, 0.98 (2×s, 6 H, 25-CH_3, 26-CH_3), 1.02–1.03 (m, 4 H, 27-CH_3, 16-H_a), 1.07 (s, 3 H, 23-CH_3), 1.14 (s, 3 H, 27-CH_3), 1.16–1.60 (m, 11 H, 1-H_a, 7-H_a, 22-H_a, 7-H_b, 6-H_a, 15-H_a, 22-H_b, 21-H_a, 15-H_b, 16-H_b, 6-H_b), 1.68–1.78 (m, 1 H, 2-H_a), 1.95–1.96 (m, 7 H, 2-H_b, 2×Ac), 2.00–2.03 (m, 10 H, 21-H_b, 3×Ac), 2.07, 2.14, 2.15 (3×s, 6 H, 3×Ac), 2.24–2.26 (m, 2 H, 9-H, 19-H_a), 2.47 (d, J_{gem} = 11.2 Hz, 1 H, 19-H_b), 2.84 (br d, 1 H, 1-H_b), 3.15 (dd, $J_{3,2\text{-}H_a}$ = 4.4, $J_{3,2\text{-}H_b}$ = 11.8 Hz, 1 H, 3-H), 3.44 (dd, $J_{5,6\text{-}H_b}$ = 5.1, $J_{5,6\text{-}H_a}$ = $J_{5,4}$ = 9.6 Hz, 1 H, 5b-H), 3.68–3.71 (m, 4 H, 4b-H, OCH_3), 3.75 (dd, $J_{3,4}$ = $J_{3,2}$ = 9.1 Hz, 1 H, 3b-H), 3.78–3.90 [m, 4 H, H,H-COSY: 3.78 (5c-H), 3.81 (6b-H_a), 3.85 (2b-H), 3.88 (6a-H_a)], 4.04–4.08 [m, 3 H, H,H-COSY: 4.03 (6c-H_a), 4.05 (5a-H), 4.08 (6c-H_b)], 4.15 (dd, $J_{6,5}$ = 5.3, J_{gem} = 11.2 Hz, 1 H, 6a-H_b), 4.44 (dd, $J_{6,5}$ = 4.6, J_{gem} = 10.2 Hz, 1 H, 6b-H_b), 4.50 (d, $J_{1,2}$ = 7.6 Hz, 1 H, 1b-H), 4.66 (d, J_{gem} = 10.3 Hz, 1 H, CH_2Ph), 4.93 (d, J_{gem} = 10.3 Hz, 1 H, CH_2Ph), 4.96 (dd, $J_{3,4}$ = 3.2, $J_{3,2}$ = 10.5 Hz, 1 H, 3c-H), 5.06 (d, $J_{1,2}$ = 7.9 Hz, 1 H, 1c-H), 5.18–5.23 (m, 2 H, 2c-H, 2a-H), 5.33 (d, $J_{4,3}$ = 2.8 Hz, 1 H, 4c-H), 5.42 (br s, 1 H, 4a-H), 5.45 (dd, $J_{3,4}$ = 3.2, $J_{3,2}$ = 10.8 Hz, 1 H, 3a-H), 5.55 (s, 1 H, CHPh), 5.70 (d, $J_{1,2}$ = 3.3 Hz, 1 H, 1a-H), 5.87 (s, 1 H, 12-H), 7.26–7.49 (m, 10 H, 2×Ph) ppm. ROESY: 5.70 (1a-H), 5.87 (12-H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 15.8 (1 C, C-24), 17.4, 17.8, 17.9 (3 C, C-6, C-25, C-28), 19.5 (1 C, C-27), 20.0 (1 C, C-26), 20.5, 20.6, 20.7, 20.8 (8 C, 8×CH_3CO), 24.7 (2 C, C-16, C-23), 27.0 (1 C, C-2), 27.7 (1 C, C-29), 30.2 (1 C, C-21), 32.5 (2 C, C-7, C-19), 36.7 (1 C, C-15), 37.7 (1 C, C-22), 40.8 (1 C, C-1), 51.7 (1 C, OCH_3), 55.0 (1 C, C-9), 55.9 (1 C, C-5), 61.2 (1 C, C-6c), 61.8 (1 C, C-6a), 65.7 (1 C, C-5b), 66.7 (1 C, C-5a), 67.2 (1 C, C-4c), 67.6 (1 C, C-3a), 67.7 (1 C, C-2a), 68.0 (1 C, C-4a), 68.8 (1 C, C-6b), 69.7 (1 C, C-2c), 70.3 (1 C, C-5c), 71.1 (1 C, C-3c), 77.0 (1 C, CH_2Ph), 77.2 (1 C, C-2b), 81.6 (1 C, C-4b), 82.8 (1 C, C-3b), 90.4 (1 C, C-3), 92.8 (1 C, C-1a), 100.2 (1 C, C-1c), 101.2 (1 C, CHPh), 102.8 (1 C, C-12), 104.5 (1 C, C-1b), 128.1, 128.3, 128.6, 129.0 (10 C, 2×Ph), 133.3 (1 C, C-18), 132.1 (1 C, C-13), 137.3, 137.9 (2 C, *ipso*-Ph), 154.3 (1 C, C-11), 169.2, 169.3, 170.1, 170.2, 170.3, 170.4 (8 C, 8×CH_3CO), 178.8 (1 C, C-30) ppm. MALDI-MS (positive mode, matrix DHB, THF): *m/z* = 1508 $[M + Na]^+$. $C_{79}H_{104}O_{27}$ (1485.7): calcd. C 63.87, H 7.06; found C 63.85, H 7.30.

Methyl 3β-*O*-[(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→2)-(β-D-glucopyranosyl)]-18β-glycyrrhetinate (18): Palladium on carbon (280 mg, 10% Pd) was added to a solution of compound **16** (514 mg, 0.45 mmol) in a mixture of CH_3OH/CH_2Cl_2 (2.2:1, 37 mL) and the suspension was vigorously stirred under hydrogen at room temp. After 2 h the mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc 2:1) to afford **18** (410 mg, qu) as a white powder. TLC (petroleum ether/EtOAc 1:1): R_f = 0.17. $[\alpha]_D$ = +7.9 (*c* = 1, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.72 (d, $J_{5,6}$ = 11.6 Hz, 1 H, 5-H), 0.80 (s, 3 H, 28-CH_3), 0.86 (s, 3 H, 24-CH_3), 0.94–0.96 (m, 1 H, 1-H_a), 1.00 (br d, 1 H, 16-H_a), 1.09 (s, 3 H, 23-CH_3) 1.12 (s, 3 H, 26-CH_3), 1.14 (s, 6 H, 25-CH_3, 29-CH_3), 1.15–1.19 (m, 1 H, 16-H_b), 1.27–1.30 (m, 2 H, 22-H_a, 21-H_a), 1.35 (s, 3 H, 27-CH_3), 1.39–1.42 (m, 3 H, 22-H_b, 7-H_a, 6-Ha), 1.58–1.64 (m, 3 H, 6-H_b, 19-H_a, 7-H_b), 1.75–1.91 (m, 4 H, 2-$H_{a,b}$, 15-H_a, 19-H_b), 1.99–2.08 (m, 13 H, 19-H_b, 21-H_b, 15-H_b, 3×Ac, 18-H), 2.14 (s, 3 H, Ac), 2.32 (s, 1 H, 9-H), 2.79 (br d, 1 H, 1-H_b), 3.16 (dd, $J_{3,2\text{-}H_a}$ = 4.9, $J_{3,2\text{-}H_b}$ = 10.8 Hz, 1 H, 3-H), 3.33–3.34 (m, 1 H, 5a-H), 3.49 (br s, 3 H, 3 OH), 3.55–3.56 (m, 3 H, 2a-H, 3a-H, 4a-H), 3.69 (s, 3 H, OCH_3), 3.79 (dd, J_{gem} = 11.8, $J_{6,5}$ = 4.8 Hz, 1 H, 6a-H_a), 3.88 (dd, J_{gem} = 11.8, $J_{6,5}$ = 3.5 Hz, 1 H, 6a-H_b), 3.92 (dd, $J_{5,6\text{-}H_a}$ = $J_{5,6\text{-}H_b}$ = 6.8 Hz, 1 H, 5b-H), 4.11–4.12 (m, 2 H, 6b-$H_{a,b}$), 4.45 (d, $J_{1,2}$ = 5.6 Hz, 1 H, 1a-H), 4.99 (d, $J_{1,2}$ = 7.9 Hz, 1 H, 1b-H), 5.01 (dd, $J_{3,2}$ = 10.5, $J_{3,4}$ = 3.1 Hz, 1 H, 3b-H), 5.23 (dd, $J_{2,1}$ = 8.0, $J_{2,3}$ = 10.3 Hz, 1 H, 2b-H), 5.37 (d, $J_{4,3}$ = 2.7 Hz, 1 H, 4b-H), 5.66 (s, 1 H, 12-H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 16.3, 16.4 (2 C, C-24, C-25), 17.4 (1 C, C-6), 18.7 (1 C, C-26), 20.6, 20.7, 21.0 (4 C, 4×CH_3CO), 23.4 (1 C, C-27), 26.4, 26.5 (3 C, C-2, C-15, C-16), 27.7 (1 C, C-23), 28.3, 28.5 (2 C, C-29, C-28), 31.1 (1 C, C-21), 32.7 (1 C, C-7), 37.7 (1 C, C-22), 39.2 (1 C, C-1), 41.1 (1 C, C-19), 48.4 (1 C, C-18), 51.8 (1 C, OCH_3), 55.4 (1 C, C-5), 60.7 (1 C, C-6b), 61.8 (1 C, C-9), 62.6 (1 C, C-6a), 66.8 (1 C, C-4b), 70.3 (1 C, C-2b), 70.6 (2 C, C-5b, C-3a), 74.7 (1 C, C-5a), 76.6 (1 C, C-2a), 80.3 (1 C, C-4a), 89.7 (1 C, C-3), 100.7 (1 C, C-1b), 103.7 (1 C, C-1a), 128.5 (1 C, C-12), 169.3, 170.1, 170.3 (4 C, 4×CH_3CO), 176.9 (1 C, C-30), 200.2 (1 C, C-11) ppm. MALDI-MS (positive mode, matrix DHB, THF): *m/z* = 1000 $[M + Na]^+$, 1116 $[M + K]^+$. $C_{51}H_{76}O_{18}\cdot 1H_2O$ (995.2): calcd. C 61.55, H 7.59; found C 61.74, H 8.11.

Methyl 3β-*O*-[(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→2)-(4,6-*O*-benzylidene-β-D-glucopyranosyl)]-18β-glycyrrhetinate (19): Benzaldehyde dimethyl acetal (78 μL, 0.53 mmol) and *p*-toluenesulfonic acid (5 mg, 0.02 mmol) were added to a solution of **18** (410 mg, 0.45 mmol) in dry acetonitrile (27 mL). The reaction mixture was stirred for 2 h and quenched with NEt_3, and the solvents were evaporated. Purification by flash chromatography (petroleum ether/EtOAc 2:1) afforded **19** (403 mg, 85%). TLC (petroleum ether/EtOAc 1:1): R_f = 0.40. $[\alpha]_D$ = +19.6 (*c* = 0.2, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.71 (d, $J_{5,6}$ = 11.6 Hz, 1 H, 5-H), 0.80 (s, 3 H, 28-CH_3), 0.87 (s, 3 H, 24-CH_3), 0.94–0.96 (m, 1 H, 1-H_a), 1.02 (br d, 1 H, 16-H_a), 1.2 (s, 6 H, 26-CH_3, 23-CH_3), 1.15 (s, 6 H, 25-CH_3, 23-CH_3), 1.18–1.19 (m, 1 H, 16-H_b), 1.30–1.32 (m, 2 H, 21-H_a, 22-H_a), 1.35 (s, 3 H, 27-CH_3), 1.39–1.44 (m, 3 H, 7-H_a, 22-H_b, 6-H_a), 1.58–1.64 (m, 3 H, 6-H_b, 19-H_a, 7-H_b), 1.77–1.83 (m, 3 H, 2-$H_{a,b}$, 15-H_a), 1.91–1.93 (m, 1 H, 19-H_b), 2.03, 2.06 (3×s, 9 H, 3×Ac), 2.07–2.08 (m, 1 H, 18-H), 2.13 (s, 3 H, Ac), 2.32 (s, 1 H, 9-H), 2.54 (d, $J_{OH,3}$ = 2.1 Hz, 1 H, 3-OH), 2.79 (br d, 1 H, 1-H_b), 3.15 (dd, $J_{3,2\text{-}H_a}$ = 5.7, $J_{3,2\text{-}H_b}$ = 10.5 Hz, 1 H, 3-H), 3.38 (ddd, $J_{5,4}$ = $J_{5,6\text{-}H_a}$ = 9.4, $J_{5,6\text{-}H_b}$ = 4.7 Hz, 1 H, 5a-H), 3.51 (dd, $J_{4,3}$ = $J_{4,5}$ = 9.3 Hz, 1 H, 4a-H), 3.69 (s, 3 H, OCH_3), 3.75–3.78 (m, 2 H, 2a-H, 6a-H_a), 3.81 (ddd, $J_{3,4}$ = $J_{3,2}$ = 9.0, $J_{3,OH}$ = 1.9 Hz, 1 H, 3a-H), 4.31 (dd, $J_{5,6\text{-}H_a}$ = $J_{5,6\text{-}H_b}$ = 6.7 Hz, 1 H, 5b-H), 4.11–4.12 (m, 2 H, 6b-$H_{a,b}$), 4.31 (dd, J_{gem} = 10.5, $J_{6,5}$ = 5.0 Hz, 1 H, 6a-H_b), 4.50 (d, $J_{1,2}$ = 7.4 Hz, 1 H, 1a-H), 5.01–5.04 (m, 2 H, 1b-H, 3b-H), 5.18 (dd, $J_{2,3}$ = 8.0, $J_{2,1}$ = 10.3 Hz, 1 H, 2b-H), 5.36 (d, $J_{4,3}$ = 2.7 Hz, 1 H, 4b-H), 5.51 (s, 1 H, CHPh), 5.66 (s, 1 H, 12-H), 7.37–7.49 (m, 5 H, Ph) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 16.3, 16.4 (2 C, C-24, C-25), 17.4 (1 C, C-6), 18.7 (1 C, C-26), 20.6, 21.0 (4 C, 4×CH_3CO), 23.4 (1 C, C-27), 26.1, 26.4, 26.5 (3 C, C-2, C-15, C-16), 27.6 (1 C, C-23), 28.3, 28.5 (2 C, C-28, C-29), 31.4 (1 C, C-21), 32.9 (1 C, C-7), 37.9 (1 C, C-22), 39.1 (1 C, C-1), 41.1 (1 C, C-19), 48.4 (1 C, C-18), 51.8 (1 C, OCH_3), 55.4 (1 C, C-5), 61.0 (1 C, C-6b), 61.8 (1 C, C-9), 65.7 (1 C, C-5a), 67.0 (1 C, C-4b), 68.9 (1 C, C-6a), 69.9 (1 C, C-2b), 70.4 (1 C, C-5b), 71.0 (1 C, C-3b), 74.6 (1 C, C-3a), 79.5 (1 C, C-2a), 80.4 (1 C, C-4a), 90.3 (1 C, C-

3), 100.7 (1 C, C-1b), 101.9 (1 C, *C*HPh), 104.1 (1 C, C-1a), 126.2, 128.4, 129.3 (5 C, Ph), 128.5 (1 C, C-12), 136.9 (1 C, *ipso*-Ph), 169.2, 169.8, 170.1, 170.4 (4 C, 4×CH_3CO), 176.9 (1 C, C-30), 200.2 (1 C, C-11) ppm. MALDI-MS (positive mode, matrix DHB, THF): *m*/*z* = 1088 $[M + Na]^+$, 1104 $[M + K]^+$. $C_{58}H_{80}O_{18}$ (1065.3): calcd. C 65.40, H 7.57; found C 65.52, H 7.77.

Methyl 3β-*O*-[(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→2)-(β-D-glucopyranosyl)]-11-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)-11(12),13(18)-dieno-glycyrrhetinate (20): Pd/C (18 mg) was added to a solution of saponin **17** (40 mg, 0.027 mmol) in CH_3OH/CH_2Cl_2 (2.8 mL, 2:1). The mixture was stirred at room temp. under hydrogen for 20 min and filtered, and the solvents were evaporated. The resulting residue was purified by flash chromatography (petroleum ether/EtOAc 1:2) to afford **20** (35 mg, qu). TLC (petroleum ether/EtOAc 1:2): R_f = 0.25. $[\alpha]_D$ = +26.7 (*c* = 1.0, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ = 0.77 (s, 3 H, 28-CH_3), 0.82–0.83 (m, 4 H, 5-H, 24-CH_3), 0.96, 0.97 (2×s, 6 H, 26-CH_3, 25-CH_3), 1.01–1.02 (m, 4 H, 27-CH_3, 16-H_a), 1.06, 1.08 (2×s, 6 H, 23-CH_3, 29-CH_3), 1.24–1.53 (m, 9 H, 1-H_a, 7-H_a, 22-H_a, 7-H_b, 6-H_a, 15-H_a, 22-H_b, 21-H_a, 15-H_b), 1.54–1.70 (m, 2 H, 16-H_b, 6-H_b), 1.72–1.87 (m, 1 H, 2-H_a), 1.96–2.02 (m, 13 H, 21-H_b, 4×Ac), 2.06 (s, 3 H, Ac), 2.13–2.15 (m, 10 H, 2-H_b, 3×Ac), 2.23–2.25 (m, 2 H, 9-H, 19-H_a), 2.44 (d, J_{gem} = 15.4 Hz, 1 H, 19-H_b), 2.88–2.90 (m, 1 H, 1-H_b), 3.17 (dd, $J_{3,2\text{-}H_a}$ = 4.3, $J_{3,2\text{-}H_b}$ = 11.8 Hz, 1 H, 3-H), 3.35–3.37 (m, 1 H, 5b-H), 3.44–3.45 (m, 1 H, 4b-H), 3.55–3.56 (m, 2 H, 2b-H, 3b-H), 3.69 (s, 3 H, OCH_3), 3.78 (dd, J_{gem} = 12.3, $J_{6,5}$ = 5.8 Hz, 1 H, 6b-H_a), 3.86–3.92 (m, 2 H, 6a-H_a, 5c-H), 3.96 (br d, *J* = 10.8 Hz, 1 H, 6b-H_b), 4.00 (dd, $J_{5,6\text{-}H_a}$ = $J_{5,6\text{-}H_b}$ = 6.4 Hz, 1 H, 5a-H), 4.10–4.15 (m, 3 H, 6c-$H_{a,b}$, 6a-H_b), 4.48 (d, $J_{1,2}$ = 6.6 Hz, 1 H, 1b-H), 4.97–5.00 (m, 2 H, 1c-H, 3c-H), 5.18 (dd, $J_{2,1}$ = 3.1, $J_{2,3}$ = 10.8 Hz, 1 H, 2a-H), 5.22 (m, $J_{2,1}$ = 8.0, $J_{2,3}$ = 10.3 Hz, 1 H, 2c-H), 5.34–5.36 (m, 2 H, 4a-H, 4c-H), 5.65 (dd, $J_{3,4}$ = 3.1, $J_{2,3}$ = 10.8 Hz, 1 H, 3a-H), 5.73 (d, $J_{1,2}$ = 3.1 Hz, 1 H, 1a-H), 5.79 (s, 1 H, 12-H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 16.0 (1 C, C-24), 17.4 (1 C, C-28), 18.0 (2 C, C-6, C-25), 19.4 (1 C, C-27), 20.0 (1 C, C-26), 20.6, 20.9 (8 C, 8×CH_3CO), 24.7 (2 C, C-16, C-23), 27.0 (1 C, C-2), 27.7 (1 C, C-29), 30.2 (1 C, C-21), 32.5 (2 C, C-7, C-19), 36.7 (1 C, C-15), 37.7 (1 C, C-22), 40.8 (1 C, C-1), 51.9 (1 C, OCH_3), 55.1 (1 C, C-9), 55.9 (1 C, C-5), 60.7 (1 C, C-6c), 61.6 (1 C, C-6a), 62.0 (1 C, C-6b), 66.8 (1 C, C-4c), 67.1 (1 C, C-5a), 67.5 (1 C, C-3a), 68.0 (1 C, C-2a), 68.2 (1 C, C-4a), 70.4 (2 C, C-4b, C-2c), 70.6 (1 C, C-5c), 71.0 (1 C, C-3c), 75.8 (1 C, C-5b), 76.6 (1 C, C-2b), 80.6 (1 C, C-3b), 89.5 (1 C, C-3), 92.3 (1 C, C-1a), 100.8 (1 C, C-1c), 102.5 (1 C, C-12), 104.0 (1 C, C-1b), 132.3 (1 C, C-18), 133.2 (1 C, C-13), 153.5 (1 C, C-11), 170.0, 170.1, 170.2, 170.3, 170.7 (8 C, 8 CH_3CO), 178.8 (1 C, C-11) ppm. MALDI-MS (positive mode, matrix DHB, THF): *m*/*z* = 1330 $[M + Na]^+$. $C_{65}H_{94}O_{27}$ (1307.4): calcd. C 59.71, H 7.25; found C 59.25, H 7.23.

Methyl 3β-*O*-[(β-D-Galactopyranosyl)-(1→2)-(β-D-glucopyranosyl)]-11-*O*-(α-D-galactopyranosyl)-11(12),13(18)-dieno-glycyrrhetinate (21): A solution of **20** (17.6 mg, 13.5 μmol) in 5% potassium hydroxide in EtOH/H_2O (1:1, 2 mL) was allowed to stir for 16 h at room temp. The reaction mixture was neutralized with ion-exchange resin (Amberlite IR-120 H^+) and the filtrate was concentrated in vacuo to give a residue that was subjected to flash chromatography ($CH_2Cl_2/CH_3OH/H_2O$ 7:3:1) to afford **21** (13 mg, qu). TLC ($CH_2Cl_2/CH_3OH/H_2O$ 7:3:1): R_f = 0.51. $[\alpha]_D$ = +18.3 (*c* = 0.7, $CHCl_3/CH_3OH$ 7:3). ^1H NMR (600 MHz, $CDCl_3/CD_3OD$ 7:3): δ = 0.73–0.85 (m, 7 H, 28-CH_3, 5-H, 24-CH_3), 0.93–1.03 (m, 14 H, 26-CH_3, 25-CH_3, 16-H_a, 23-CH_3, 29-CH_3), 1.07–1.15 (m, 4 H, 1-H_a, 27-CH_3), 1.21–1.55 (m, 10 H, 7-H_a, 22-H_a, 6-H_a, 7-H_b, 15-H_a, 21-H_a, 22-H_b, 15-H_b, 16-H_b, 6-H_b), 1.84–2.60 (m, 5 H, 2-$H_{a,b}$, 21-H_b, 19-H_a, 9-H, 19-H_b), 2.91–2.93 (m, 1 H, 1-H_b), 3.14 (br d, 1 H, 3-H), 3.20–3.35 [m, 5 H, H,H-COSY: 3.22 (5b-H), 3.29 (OCH_3), 3.35 (4b-H)], 3.43–3.75 [m, 12 H, H,H-COSY: 3.44 (5c-H), 3.47 (3c-H), 3.50 (2b-H), 3.53 (3b-H), 3.57 (6a-H_a), 3.58 (2c-H), 3.64 (5a-H), 3.67 (6b-H_a, 6c-H_a), 3.73 (6c-H_b, 6a-H_b), 3.75 (3a-H)], 3.84–3.97 [m, 4 H, H,H-COSY: 3.81 (6b-H_b), 3.84 (4c-H), 3.90 (2a-H), 3.98 (4a-H)], 4.40 (d, $J_{1,2}$ = 7.2 Hz, 1 H, 1b-H), 4.50 (d, $J_{1,2}$ = 7.2 Hz, 1 H, 1c-H), 5.43 (d, $J_{1,2}$ = 3.6 Hz, 1 H, 1a-H), 5.96 (s, 1 H, 12-H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 16.2 (1 C, C-24), 17.8 (1 C, C-28), 18.0 (2 C, C-6, C-25), 19.0 (1 C, C-27), 20.4 (1 C, C-26), 25.2 (2 C, C-16, C-23), 26.8 (1 C, C-2), 28.2 (1 C, C-29), 30.8 (1 C, C-21), 32.8 (1 C, C-19), 33.3 (1 C, C-7), 36.4 (1 C, C-15), 38.2 (1 C, C-22), 41.1 (1 C, C-1), 55.8 (1 C, C-9), 56.6 (1 C, C-5), 49.5 (1 C, OCH_3), 61.6 (2 C, C-6c, C-6a), 62.4 (1 C, C-6b), 69.2 (1 C, C-4a), 69.5 (2 C, C-2a, C-4c), 70.8 (1 C, C-5a), 70.9 (1 C, C-5a), 71.5 (1 C, C-3a), 73.4 (1 C, C-2c), 74.1 (1 C, C-3c), 75.9 (1 C, C-5c), 76.4 (1 C, C-5b), 77.4 (1 C, C-3b), 82.2 (1 C, C-2b), 90.5 (1 C, C-3), 96.7 (1 C, C-1a), 102.9 (1 C, C-12), 104.5 (1 C, C-1b), 105.2 (1 C, C-1c), 130.2 (1 C, C-18), 130.0 (1 C, C-13), 156.2 (1 C, C-11), 180.3 (1 C, C-11) ppm. MALDI-MS (positive mode, matrix CHCA, CH_3OH): *m*/*z* = 972 $[M + H]^+$, 996 $[M + Na]^+$, 1070 $[(M - H) + 2 K + Na]^+$. $C_{49}H_{78}O_{19}$ (971.1).

3β-*O*-[(β-D-Galactopyranosyl)-(1→2)-(β-D-glucopyranosyl)]-11-*O*-(β-D-galactopyranosyl)-11(12),13(18)-dieno-glycyrrhetinate (22): A solution of **21** (9 mg, 9.3 μmol) in 5% potassium hydroxide in EtOH/H_2O (1:1, 1 mL) was heated at reflux for 3 h. After cooling, the reaction mixture was neutralized with ion-exchange resin (Amberlite IR-120 H^+) and the filtrate was concentrated in vacuo to give a residue that was subjected to flash chromatography ($CH_2Cl_2/CH_3OH/H_2O$ 7:3:1) to afford **22** (6.2 mg, 70%). TLC ($CH_2Cl_2/CH_3OH/H_2O$ 7:3:1): R_f = 0.49. $[\alpha]_D$ = +15.9 (*c* = 0.6, $CHCl_3/CH_3OH$ 7:3). ^1H NMR (600 MHz, $CDCl_3/CD_3OD$ 7:3): δ = 0.78–0.89 (m, 7 H, 28-CH_3, 5-H, 24-CH_3), 0.95–1.13 (m, 17 H, 26-CH_3, 25-CH_3, 27-CH_3, 16-H_a, 23-CH_3, 29-CH_3, 1-H_a), 1.22–1.60 (m, 8 H, 7-H_a, 15-H_a, 22-$H_{a,b}$, 21-H_a, 15-H_b, 16-H_b, 6-H_b), 1.76–1.89 (m, 2 H, 2-$H_{a,b}$), 1.99–2.00 (m, 1 H, 21-H_b), 2.18–2.21 (m, 2 H, 19-H_a, 9-H), 2.50–2.56 (m, 1 H, 19-H_b), 2.91–2.93 (m, 1 H, 1-H_b), 3.18 (dd, $J_{3,2\text{-}H_a} \approx 4.3$, $J_{3,2\text{-}H_b} \approx 11.8$ Hz, 1 H, 3-H), 3.21–3.25 (m, 1 H, 5b-H), 3.30–3.37 (m, 1 H, 4b-H), 3.42–3.59 [m, 5 H, H,H-COSY: 3.46 (5c-H), 3.47 (3c-H), 3.51 (2b-H), 3.54 (3b-H), 3.56 (6a-H_a), 3.59 (2c-H)], 3.65–3.73 [m, 4 H, H,H-COSY: 3.65 (5a-H), 3.67 (6b-H_a), 3.69 (6c-H_a), 3.72 (6a-H_b), 3.73 (6c-H_b)], 3.78 (dd, $J_{3,4} \approx 3.8$, $J_{3,2} \approx 9.8$ Hz, 1 H, 3a-H), 3.84–3.96 [m, 4 H, H,H-COSY: 3.85 (6b-H_b), 3.86 (4c-H), 3.91 (2a-H), 3.96 (4a-H)], 4.43 (d, $J_{1,2}$ = 7.2 Hz, 1 H, 1b-H), 4.53 (d, $J_{1,2}$ = 7.8 Hz, 1 H, 1c-H), 5.43 (d, $J_{1,2}$ = 3.0 Hz, 1 H, 1a-H), 6.10 (s, 1 H, 12-H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 16.2 (1 C, C-24), 17.8 (1 C, C-28), 18.0 (1 C, C-25), 18.6 (1 C, C-6), 19.0 (1 C, C-27), 20.4 (1 C, C-26), 25.2 (1 C, C-23), 25.6 (1 C, C-16), 27.2 (1 C, C-2), 28.2 (1 C, C-29), 31.8 (1 C, C-21), 33.7 (1 C, C-7), 34.2 (1 C, C-19), 36.9 (1 C, C-15), 38.4 (1 C, C-22), 41.4 (1 C, C-1), 56.2 (1 C, C-9), 56.8 (1 C, C-5), 61.4 (2 C, C-6a, C-6c), 62.2 (1 C, C-6b), 69.2 (1 C, C-4c), 69.5 (1 C, C-2a), 69.8 (1 C, C-4a), 70.8 (1 C, C-4b), 71.0 (1 C, C-5a), 71.5 (1 C, C-3a), 73.4 (1 C, C-2c), 74.1 (1 C, C-3c), 76.2 (1 C, C-5c), 76.8 (1 C, C-5b), 77.6 (1 C, C-3b), 82.4 (1 C, C-2b), 90.3 (1 C, C-3), 97.0 (1 C, C-1a), 103.3 (1 C, C-12), 104.6 (1 C, C-1b), 105.5 (1 C, C-1c) ppm. MALDI-MS (positive mode, matrix CHCA, CH_3OH): *m*/*z*= 956 $[M - H]^+$. $C_{48}H_{76}O_{19}$ (957.1).

Methyl 3β-*O*-{(2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl)-(1→3)-[(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→2)]-(4,6-*O*-benzylidene-β-D-glucopyranosyl)}-18β-glycyrrhetinate (23): TMSOTf (0.02 M solution in CH_2Cl_2, 5 μL, 23.5 μmol) was added dropwise under nitrogen at room temp to a solution of **19** (404 mg, 0.38 mmol) and **5**[30,37] (191 mg, 0.46 mmol) in dry CH_2Cl_2 (8 mL).

After 10 min the reaction mixture was neutralized with NEt_3 and concentrated in vacuo. Flash chromatography of the residue (petroleum ether/EtOAc 1:1) gave compound **23** (432 mg, 86%) as a white solid. TLC (petroleum ether/EtOAc 1:1): R_f = 0.35. $[\alpha]_D$ = +1.6 (*c* = 1.0, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ = 0.70 (d, $J_{5,6}$ = 11.4 Hz, 1 H, 5-H), 0.80 (s, 3 H, 28-CH_3), 0.88 (s, 3 H, 24-CH_3), 0.93–0.95 (m, 1 H, 1-H_a), 1.00 (br d, 1 H, 16-H_a), 1.11 (s, 3 H, 26-CH_3), 1.13 (s, 9 H, 25-CH_3, 23-CH_3, 29-CH_3), 1.15–1.18 (m, 1 H, 16-H_b), 1.30–1.32 (m, 2 H, 21-H_a, 22-H_a), 1.34 (s, 3 H, 27-CH_3), 1.38–1.43 (m, 3 H, 22-H_b, 7-H_a, 6-H_a), 1.57–1.64 (m, 3 H, 6-H_b, 19-H_a, 7-H_b), 1.74–1.82 (m, 3 H, 2-$H_{a,b}$, 15-H_a), 1.90–1.93 (m, 1 H, 19-H_b), 1.95 (s, 3 H, Ac), 1.98–2.08 (m, 18 H, 21-H_a, 15-H_b, 5 × Ac, 18-H), 2.13 (s, 3 H, Ac), 2.31 (s, 1 H, 9-H), 2.78 (br d, 1 H, 1-H_b), 3.09–3.16 (m, 2 H, 3-H, 5c-H_a), 3.39 (ddd, $J_{5,6\text{-}H_b}$ = 4.9 Hz, 1 H, 5a-H), 3.63 (dd, $J_{4,3}$ = $J_{4,5}$ = 9.1 Hz, 1 H, 4a-H), 3.68 (s, 3 H, OCH_3), 3.76 (dd, J_{gem} = $J_{6,5}$ = 10.4 Hz, 1 H, 6a-H_a), 3.93–3.99 [m, 3 H, H,H-COSY: 3.95 (2a-H), 3.96 (5b-H), 3.97 (3a-H)], 4.12–4.13 (m, 2 H, 6b-$H_{a,b}$), 4.18 (dd, $J_{5,4}$ = 4.9, J_{gem} = 10.6 Hz, 1 H, 5c-H_b), 4.30 (dd, J_{gem} = 10.6, $J_{6,5}$ = 4.9 Hz, 1 H, 6a-H_b), 4.42 (d, $J_{1,2}$ = 7.1 Hz, 1 H, 1a-H), 4.77 (dd, $J_{4,3}$ = 9.3 Hz, 1 H, 4c-H), 4.93 (d, $J_{1,2}$ = 7.9 Hz, 1 H, 1b-H), 4.95–4.98 [m, 3 H, H,H-COSY; 4.95 (1c-H), 4.97 (2c-H, 3c-H)], 5.09 (dd, $J_{2,1}$ = 8.0, $J_{2,3}$ = 10.2 Hz, 1 H, 2b-H), 5.25 (dd, $J_{3,4}$ = 3.5, $J_{3,2}$ = 10.4 Hz, 1 H, 3b-H), 5.35 (d, $J_{4,3}$ = 3.1 Hz, 1 H, 4b-H), 5.46 (s, 1 H, C*H*Ph), 5.66 (s, 1 H, 12-H), 7.35–7.44 (m, 5 H, Ph) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 16.2, 16.3 (2 C, C-24, C-25), 17.3 (1 C, C-6), 18.7 (1 C, C-26), 20.6, 20.7 (7 C, 7 *C*H_3CO), 23.3 (1 C, C-27), 26.3, 26.4 (3 C, C-2, C-15, C-16), 27.7, 28.3, 28.5 (3 C, C-23, C-28, C-29), 31.2 (1 C, C-21), 32.7 (1 C, C-7), 37.7 (1 C, C-22), 39.1 (1 C, C-1), 41.1 (1 C, C-19), 48.4 (1 C, C-18), 51.8 (1 C, O*C*H_3), 55.4 (1 C, C-5), 60.1 (1 C, C-5c), 61.0 (1 C, C-6b), 61.8 (1 C, C-9), 65.8 (1 C, C-5a), 67.5 (1 C, C-4b), 67.4 (1 C, C-4c), 69.5 (2 C, C-2c, C-3c), 70.2 (1 C, C-2b), 70.4 (1 C, C-3b), 70.5 (1 C, C-5b), 77.6 (1 C, C-2a), 78.6 (1 C, C-3a), 79.4 (1 C, C-4a), 90.8 (1 C, C-3), 97.9 (1 C, C-1c), 99.0 (1 C, C-1b), 101.8 (1 C, *C*HPh), 104.1 (1 C, C-1a), 126.0, 128.3, 129.3 (5 C, Ph), 128.5 (1 C, C-12), 137.0 (1 C, *ipso*-Ph), 169.1, 169.2, 169.6, 169.8, 170.0, 170.1, 170.3 (7 C, 7 CH_3*C*O), 176.9 (1 C, C-30), 200.2 (1 C, C-11) ppm. MALDI-MS (positive mode, matrix DHB, THF): *m*/*z* = 1346 $[M + Na]^+$. $C_{69}H_{94}O_{25}$ (1323.5): calcd. C 62.62, H 7.16; found C 62.17, H 7.22.

Methyl 3β-*O*-{(2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl)-(1→3)-[(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→2)]-(β-D-glucopyranosyl)}-18β-glycyrrhetinate (24): A solution of **23** (364 mg, 0.28 mmol) in CH_2Cl_2 (25 mL) was treated with ethanethiol (2.5 mL, 0.033 mol) and *p*-toluenesulfonic acid (6.4 mg, 0.03 mmol) and stirred at room temp. After 2 h the solution was neutralized with NEt_3 and concentrated in vacuo, and the residue was purified by flash chromatography (petroleum ether/EtOAc 1:2) to give **24** (283 mg, 83%) as a white solid. TLC (petroleum ether/EtOAc 1:1): R_f = 0.05. TLC (CH_2Cl_2/CH_3OH 9:1): R_f = 0.68. $[\alpha]_D$ = +11.7 (*c* = 0.7, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ = 0.69 (d, $J_{5,6}$ = 11.4 Hz, 1 H, 5-H), 0.80 (s, 3 H, 28-CH_3), 0.88–0.93 (m, 4 H, 24-CH_3, 1-H_a), 1.00 (br d, 1 H, 16-H_a), 1.11 (s, 3 H, 26-CH_3), 1.13, 1.14 (3 × s, 9 H, 25-CH_3, 23-CH_3, 29-CH_3), 115–1.18 (m, 1 H, 16-H_b), 1.30–1.32 (m, 2 H, 21-H_a, 22-H_a), 1.35 (s, 3 H, 27-CH_3), 1.38–1.43 (m, 3 H, 22-H_b, 7-H_a, 6-H_a), 1.58–1.63 (m, 3 H, 6-H_b, 19-H_a, 7-H_b), 1.74–1.82 (m, 3 H, 2-$H_{a,b}$, 15-H_a), 1.88–1.90 (m, 1 H, 19-H_b), 1.97–2.10 (m, 18 H, 21-H_b, 15-H_b, 5 Ac, 18-H), 2.14 (s, 6 H, 2 × Ac), 2.31 (s, 1 H, 9-H), 2.78 (br d, 1 H, 1-H_b), 3.09 (dd, $J_{3,2\text{-}H_a}$ = 11.6, $J_{3,2\text{-}H_b}$ = 4.6 Hz, 1 H, 1 H, 3-H), 3.30–3.31 (m, 1 H, 5a-H), 3.47–3.50 (m, 2 H, 5c-H_a, 4a-H), 3.63–3.70 (m, 4 H, 3a-H, OCH_3), 3.74 (br d, 1 H, 6a-H_a), 3.79 (dd, $J_{2,3}$ = $J_{2,1}$ = 8.5 Hz, 1 H, 2a-H), 3.85–3.88 (m, 2 H, 5b-H, 6a-H_b), 4.11–4.14 (m, 2 H, 6b-$H_{a,b}$), 4.26 (dd, J_{gem} = 12.2, $J_{5,4}$ = 4.7 Hz, 1 H, 5c-H_b), 4.37 (d, $J_{1,2}$ = 7.7 Hz, 1 H, 1a-H), 4.82 (d, $J_{1,2}$ = 7.8 Hz, 1 H, 1b-H), 4.84 (d, $J_{1,2}$ = 5.7 Hz, 1 H, 1c-H), 4.99 (dd, $J_{4,3}$ = 7.0 Hz, 1 H, 4c-H), 5.04–5.08 (m, 2 H, 3b-H, 2c-H), 5.13–5.18 (m, 2 H, 2b-H, 3c-H), 5.35 (d, $J_{4,3}$ = 2.6 Hz, 1 H, 4b-H), 5.66 (s, 1 H, 12-H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 16.4 (2 C, C-24, C-25), 17.4 (1 C, C-6), 18.7 (1 C, C-26), 20.6, 21.0 (7 C, 7 × *C*H_3CO), 23.3 (1 C, C-27), 26.3 (3 C, C-2, C-15, C-16), 27.8, 28.3, 28.5 (3 C, C-23, C-28, C-29), 31.2 (1 C, C-21), 32.7 (1 C, C-7), 37.8 (1 C, C-22), 39.1 (1 C, C-1), 41.1 (1 C, C-19), 48.4 (1 C, C-18), 51.8 (1 C, O*C*H_3), 55.4 (1 C, C-5), 60.8 (1 C, C-6b), 61.8 (1 C, C-9), 62.1 (1 C, C-5c), 62.8 (1 C, C-6a), 67.0 (1 C, C-4b), 68.6 (1 C, C-4c), 69.6 (1 C, C-4a), 69.8 (1 C, C-2b), 70.5 (1 C, C-5b), 70.9 (2 C, C-2c, C-3c), 74.7 (1 C, C-5a), 76.0 69.8 (1 C, C-2a), 86.0 (1 C, C-3a), 90.5 (1 C, C-3), 99.3 (1 C, C-1b), 100.0 (1 C, C-1c), 103.6 (1 C, C-1a), 128.5 (1 C, C-12), 169.0, 169.1, 169.6, 169.8, 169.9, 170.1, 170.3 (7 C, 7 × CH_3*C*O), 176.9 (1 C, C-30), 200.2 (1 C, C-11) ppm. MALDI-MS (positive mode, matrix DHB, THF): *m*/*z* = 1258 $[M + Na]^+$, 1274 $[M + K]^+$. $C_{62}H_{90}O_{25}$ (1235.4): calcd. C 60.28, H 7.34; found C 60.41, H 7.38.

Methyl 3β-*O*-{(β-D-Xylopyranosyl)-(1→3)-[(β-D-galactopyranosyl)-(1→2)]-(β-D-glucopyranosyl)}-18β-glycyrrhetinate (25): Sodium methoxide (1 M solution in CH_3OH, 2 drops) was added to a solution of saponin **24** (58.0 mg, 0.047 mmol) in dry CH_3OH (2.5 mL). The mixture was stirred at room temp. for 24 h, neutralized by addition of ion exchange resin (Amberlite IR-120, H^+ form) and then filtered. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography (CH_2Cl_2/CH_3OH 4:1) to afford **25** (44.2 mg, qu). TLC (CH_2Cl_2/CH_3OH 2:1): R_f = 0.73. $[\alpha]_D$ = +17.9 (*c* = 0.3, CH_3OH). ^1H NMR (600 MHz, CD_3OD): δ = 0.77–0.82 (m, 4 H, 5-H, 28-CH_3), 0.89 (s, 3 H, 24-CH_3), 1.02–1.28 (m, 14 H, 1-H_a, 16-H_a, 26-CH_3, 25-CH_3, 23-CH_3, 29-CH_3, 16-H_b, 22-H_a), 1.38–1.46 (m, 7 H, 27-CH_3, 22-H_b, 21-H_a, 7-H_a, 6-H_a), 1.61–2.12 (m, 10 H, 6-H_b, 7-H_b, 19-H_a, 2-$H_{a,b}$, 19-H_b, 15-H_a, 21-H_b, 15-H_b, 18-H_a), 2.43 (s, 1 H, 9-H), 2.78 (br d, 1 H, 1-H_b), 3.09–3.33 [m, 6 H, H,H-COSY: 3.19 (3-H), 3.24 (2c-H), 3.25 (5c-H_a), 3.27 (5a-H), 3.31 (3c-H), 3.32 (4a-H)], 3.44–3.51 [m, 4 H, H,H-COSY: 3.44 (3b-H), 3.45 (5b-H), 3.47 (2b-H), 3.51 (4c-H)], 3.63–3.85 [m, 10 H, H,H-COSY: 3.63 (6b-H_a), 3.66 (3a-H), 3.68 (s, OCH_3), 3.71 (2a-H), 3.75 (6b-H_b, 6a-H_a), 3.79 (4b-H), 3.83 (6a-H_b)], 3.90 (dd, $J_{5,4}$ = 5.2, J_{gem} = 11.2 Hz, 1 H, 5c-H_b), 4.45 ($J_{1,2}$ = 7.7 Hz, 1 H, 1a-H), 4.58 ($J_{1,2}$ = 7.7 Hz, 1 H, 1c-H), 4.84 (d, $J_{1,2}$ = 7.2 Hz, 1 H, 1b-H), 5.56 (s, 1 H, 12-H) ppm. ^{13}C NMR (151 MHz, CD_3OD): δ = 16.9, 17.0 (2 C, C-24, C-25), 18.0 (1 C, C-6), 19.3 (1 C, C-26), 23.8 (1 C, C-27), 27.1–29.1 (6 C, C-2, C-15, C-16, C-23, C-28, C-29), 31.2 (1 C, C-21), 33.0 (1 C, C-7), 38.0 (1 C, C-22), 39.8 (1 C, C-1), 41.8 (1 C, C-19), 48.7 (1 C, C-18), 51.6 (1 C, O*C*H_3), 56.5 (1 C, C-5), 61.8 (2 C, C-6a, C-6b), 62.6 (1 C, C-9), 66.3 (1 C, C-5c), 69.5 (1 C, C-4b), 69.2 (1 C, C-4a), 70.2 (1 C, C-4c), 72.8 (1 C, C-2b), 74.3 (1 C, C-3b), 74.6 (1 C, C-2c), 76.3 (1 C, C-5b), 76.7 (1 C, C-5a), 77.5 (1 C, C-3c), 78.6 (1 C, C-2a), 87.0 (1 C, C-3a), 90.8 (1 C, C-3), 103.2 (1 C, C-1b), 104.3 (1 C, C-1c), 104.9 (1 C, C-1a), 129.0 (1 C, C-12), 172.6 (1 C, C-30), 202.6 (1 C, C-11) ppm. MALDI-MS (positive mode, matrix DHB, THF): *m*/*z* = 964 $[M + Na]^+$. $C_{48}H_{76}O_{18}\cdot 10H_2O$ (1121.3): calcd. C 51.42, H 8.63; found C 51.72, H 8.18.

3β-*O*-{(β-D-Xylopyranosyl)-(1→3)-[(β-D-galactopyranosyl)-(1→2)]-(β-D-glucopyranosyl)}-18β-glycyrrhetic Acid (2b): Compound **25** (44.2 mg, 46.9 μmol) was dissolved in a methanolic lithium hydroxide solution (3%, 5 mL) and the mixture was heated at 54 °C for 24 h. The solution was neutralized with ion-exchange resin (Amberlite IR-120 H^+) and concentrated in vacuo, and the residue was purified by flash chromatography (CH_2Cl_2/CH_3OH 7:3) to afford

2b (32.6 mg 75%). TLC (CH_2Cl_2/CH_3OH 7:3): R_f = 0.20. $[\alpha]_D$ = +36.3 (*c* = 0.7, CH_3OH). ^1H NMR (600 MHz, $CDCl_3$/CD_3OD 5:1): δ = 0.77 (d, $J_{5,6}$ = 11.6 Hz, 1 H, 5-H), 0.82 (s, 3 H, 28-CH_3), 0.89 (s, 3 H, 24-CH_3), 0.99–1.04 (m, 2 H, 1-H_a, 16-H_a), 1.10, 1.13, 1.15 (3×s, 12 H, 29-CH_3, 23-CH_3, 26-CH_3, 25-CH_3), 1.23 (brd, 1 H, 16-H_b), 1.34–1.46 (m, 8 H, 21-H_a, 22-$H_{a,b}$, 27-CH_3, 7-H_a, 6-H_a), 1.61–1.95 (m, 8 H, 6-H_b, 19-H_a, 7-H_b, 2-$H_{a,b}$, 19-H_b, 21-H_b, 15-H_a), 2.14–2.21 (m, 2 H, 15-H_b, 18-H), 2.44 (s, 1 H, 9-H), 2.70 (brd, 1 H, 1-H_b), 3.21–3.33 [m, 6 H, H,H-COSY: 3.21 (3-H), 3.24 (2c-H), 3.25 (5c-H_a), 3.27 (5a-H), 3.30 (3c-H), 3.33 (4a-H)], 3.44–3.51 [m, 4 H, H,H-COSY; 3.44 (3b-H), 3.45 (5b-H), 3.48 (2b-H), 3.51 (4c-H)], 3.62–3.71 [m, 4 H, H,H-COSY; 3.62 (6b-H_a), 3.65 (6a-H_a), 3.66 (3a-H), 3.71 (2a-H)], 3.75–3.89 [m, 3 H, H,H-COSY: 3.75 (6b-H_b), 3.80 (4b-H), 3.84 (6a-H_b)], 3.91 (dd, $J_{5,4}$ = 5.8, J_{gem} = 11.6 Hz, 1 H, 5c-H_b), 4.46 (d, $J_{1,2}$ = 7.7 Hz, 1 H, 1a-H), 4.58 (d, $J_{1,2}$ = 7.7 Hz, 1 H, 1c-H), 4.85 (d, $J_{1,2}$ = 7.7 Hz, 1 H, 1b-H), 5.58 (s, 1 H, 12-H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$/CD_3OD 5:1): δ = 16.9, 17.0 (2 C, C-24, C-25), 18.0 (1 C, C-6), 19.3 (1 C, C-26), 23.8 (1 C, C-27), 27.4 (3 C, C-2, C-15, C-16), 28.3, 28.8, 29.2 (3 C, C-23, C-28, C-29), 32.9 (1 C, C-21), 33.8 (1 C, C-7), 39.0 (1 C, C-22), 40.1 (1 C, C-1), 42.2 (1 C, C-19), 50.0 (1 C, C-18), 56.5 (1 C, C-5), 62.4 (2 C, C-6a, C-6b), 63.0 (1 C, C-9), 66.9 (1 C, C-5c), 69.5 (1 C, C-4a), 70.0 (1 C, C-4b), 70.8 (1 C, C-4c), 73.3 (1 C, C-2b), 74.8 (1 C, C-3b), 75.0 (1 C, C-2c), 76.8 (1 C, C-5b), 77.3 (1 C, C-5a), 78.0 (1 C, C-3c), 78.9 (1 C, C-2a), 87.6 (1 C, C-3a), 91.5 (1 C, C-3), 103.8 (1 C, C-1b), 104.7 (1 C, C-1c), 105.2 (1 C, C-1a), 128.9 (1 C, C-12), 172.9 (1 C, C-30), 202.7 (1 C, C-11) ppm. MALDI-MS (positive mode, matrix DHB, THF): *m*/*z* = 951 $[M + Na]^+$, 967 $[M + K]^+$. $C_{47}H_{74}O_{18}\cdot 7H_2O$ (1053.2): calcd. C 53.60, H 8.42; found C 53.42, H 8.29.

Methyl 3β-*O*-{(2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl)-(1→3)-[(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→2)]-(6-β-D-glucopyranosyl uronic acid)}-18β-glycyrrhetinate (26): A mixture of NaOCl (0.18 mL), H_2O (0.15 mL) and $NaHCO_3$ (0.26 mL) was added at 0 °C to a mixture of compound **24** (56.4 mg, 0.046 mmol), NaBr (0.75 mg, 7.5 μmol), TBABr (0.75 mg, 2.34 μmol) and TEMPO (0.60 mg, 3.86 μmol) in CH_2Cl_2/H_2O (6:1, 0.94 mL). After the mixture had been stirred for 15 min, CH_3OH (0.3 mL) was added, and after extraction with CH_2Cl_2 the solvent was evaporated and the residue was purified by flash chromatography (CH_2Cl_2/CH_3OH 9:1) to afford **26** (43 mg, 75%). TLC (CH_2Cl_2/CH_3OH 9:1): R_f = 0.09. $[\alpha]_D$ = +6.1 (*c* = 1, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$/CD_3OD 10:1): δ = 0.78–0.82 (m, 4 H, 5-H, 28-CH_3), 0.92 (s, 3 H, 24-CH_3), 1.00–1.03 (m, 2 H, 1-H_a, 16-H_a), 1.14–1.15 (2×s, 12 H, 25-CH_3, 26-CH_3, 23-CH_3, 29-CH_3), 1.24–1.45 (m, 10 H, 6-H_a, 16-H_b, 22-H_a, 21-H_a, 6-H_b, 27-CH_3, 22-H_b, 7-H_a), 1.70–1.90 (m, 2 H, 19-H_a, 7-H_b, 2-$H_{a,b}$, 15-H_a, 19-H_b), 1.93–1.96 (m, 4 H, 21-H_b, Ac), 2.03, 2.05, 2.06, 2.09 (4×s, 12 H, 4×Ac), 2.12–2.13 (m, 8 H, 18-H, 9-H, 2×Ac), 2.68 (brd, 1 H, 1-H_b), 3.14 (brd, 1 H, 3-H), 3.51 (dd, $J_{5,4}$ = 5.7, J_{gem} = 11.5 Hz, 1 H, 5c-H_a), 3.62–3.65 (m, 1 H, 4a-H), 3.68–3.69 (m, 4 H, 5a-H, OCH_3), 3.78–3.80 (m, 2 H, 2a-H, 3a-H), 4.02–4.03 (m, 1 H, 5b-H), 4.09–4.18 (m, 2 H, 6b-$H_{a,b}$), 4.45–4.50 (m, 2 H, 5c-H_b, 1a-H), 4.86–4.88 [brs, 1 H, H,H-COSY: 4.88 (4c-H)], 4.94 (d, $J_{1,2}$ = 7.5 Hz, 1 H, 1b-H), 5.02–5.10 [m, 3 H, H,H-COSY: 5.01 (brd, 2c-H), 5.05 (brd, 3c-H), 5.08 (brs, 1c-H)], 5.13 (dd, $J_{2,3}$ = $J_{2,1}$ = 7.8 Hz, 1 H, 2b-H), 5.17 (brd, 1 H, 3b-H), 5.35 (brs, 1 H, 4b-H), 5.57 (s, 1 H, 12-H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$/CD_3OD 10:1): δ = 17.1, 17.2 (3 C, C-6, C-24, C-25), 18.5 (1 C, C-26), 20.5, 20.7, 20.8, 21.0, 21.2 (7 C, 7×*C*H_3CO), 24.0 (1 C, C-27), 27.4, 27.6 (3 C, C-2, C-15, C-16), 28.6–29.2 (3 C, C-23, C-28, C-29), 33.9, 33.8 (2 C, C-21, C-7), 39.0 (1 C, C-22), 40.7 (1 C, C-1), 42.3 (1 C, C-19), 48.6 (1 C, C-18), 52.1 (1 C, O*C*H_3), 56.5 (1 C, C-5), 61.4 (1 C, C-5c), 62.3 (1 C, C-9), 62.0 (1 C, C-6b), 68.4 (1 C, C-4b), 69.0 (1 C, C-4c), 70.7 (1 C, C-2c), 70.9 (1 C, C-3c), 71.1 (1 C, C-2b), 71.5 (2 C, C-4a, C-5b), 71.8 (1 C, C-3b), 76.1 (1 C, C-5a), 78.4 (1 C, C-2a), 83.0 (1 C, C-3a), 91.1 (1 C, C-3), 99.4 (1 C, C-1c), 100.2 (1 C, C-1b), 104.5 (1 C, C-1a), 129.1 (1 C, C-12), 171.0, 171.5, 171.6, 171.9, 172.1 (7 C, 7×CH_3*C*O), 172.3 (1 C, C-30), 178.6 (1 C, C-6a), 202.4 (1 C, C-11) ppm. MALDI-MS (positive mode, matrix DHB, THF): *m*/*z* = 1272 $[M + Na]^+$, 1288 $[M + K]^+$. $C_{62}H_{88}O_{26}\cdot 1H_2O$ (1267.4): calcd. C 58.76, H 7.16; found C 58.73, H 7.29.

Methyl 3β-*O*-{(β-D-Xylopyranosyl)-(1→3)-[(β-D-galactopyranosyl)-(1→2)]-(6-β-D-glucopyranosyl uronic acid)}-18β-glycyrrhetinate (27): Sodium methoxide (1 M solution in CH_3OH, 2 drops) was added to a solution of saponin **26** (24.3 mg, 0.019 mmol) in CH_3OH (1.0 mL). The mixture was stirred at room temp. for 16 h, neutralized by addition of ion exchange resin (Amberlite IR-120, H^+ form) and then filtered. After evaporation of the solvent the resulting residue was purified by flash chromatography (CH_2Cl_2/CH_3OH 2:1) to afford **27** (18.5 mg, qu). TLC (CH_2Cl_2/CH_3OH 1:1): R_f = 0.70. $[\alpha]_D$ = +23.2 (*c* = 0.5, CH_3OH). ^1H NMR (600 MHz, CD_3OD): δ = 0.77 (d, $J_{5,6}$ = 11.6 Hz, 1 H, 5-H), 0.81 (s, 3 H, 28-CH_3), 0.89 (s, 3 H, 24-CH_3), 1.02–1.03 (m, 2 H, 1-H_a, 16-H_a), 1.08, 1.13 (2×s, 12 H, 26-CH_3, 25-CH_3, 23-CH_3, 29-CH_3), 1.22–1.28 (m, 2 H, 16-H_b, 22-H_a), 1.40–1.44 (m, 9 H, 6-H_a, 27-CH_3, 22-H_b, 21-H_a, 7-H_a, 6-$H_{a,b}$), 1.61–2.12 (m, 10 H, 6-H_b, 7-H_b, 19-H_a, 2-$H_{a,b}$, 19-H_b, 15-H_a, 21-H_b, 15-H_b, 18-H), 2.43 (s, 1 H, 9-H), 2.78 (brs, 1 H, 1-H_b), 3.19–3.21 (m, 1 H, 3-H), 3.25–3.27 (m, 2 H, 5c-H_a, 2c-H), 3.30–3.32 (m, 1 H, 3c-H), 3.45–3.52 [m, 4 H, H,H-COSY: 3.45 (3b-H), 3.46 (5b-H), 3.50 (2b-H), 3.51 (4c-H)], 3.57–3.58 (m, 1 H, 4a-H), 3.63–3.65 (m, 1 H, 6b-H_a), 3.68–3.69 (m, 4 H, OCH_3, 5a-H), 3.72–3.81 [m, 4 H, H,H-COSY: 3.72 (3a-H), 3.74 (6b-H_b), 3.77 (2a-H), 3.81 (4b-H)], 3.91–3.93 (m, 1 H, 5c-H_b), 4.49 (d, $J_{1,2}$ = 7.5 Hz, 1 H, 1a-H), 4.62 (d, $J_{1,2}$ = 7.6 Hz, 1 H, 1c-H), 4.84–4.86 [br, 1 H, H,H-COSY: 4.84 (1b-H)], 5.56 (s, 1 H, 12-H) ppm. ^{13}C NMR (151 MHz, CD_3OD): δ = 16.9 (2 C, C-24, C-25), 18.0 (1 C, C-6), 19.3 (1 C, C-26), 23.8 (1 C, C-27), 27.3–29.1 (6 C, C-2, C-15, C-16, C-23, C-28, C-29), 31.2 (1 C, C-21), 33.0 (1 C, C-7), 38.0 (1 C, C-22), 39.8 (1 C, C-1), 41.8 (1 C, C-19), 48.6 (1 C, C-18), 52.1 (1 C, O*C*H_3), 56.5 (1 C, C-5), 56.5 (1 C, C-9), 62.4 (1 C, C-6b), 66.9 (1 C, C-5c), 70.0 (1 C, C-4b), 70.7 (1 C, C-4c), 71.5 (1 C, C-4a), 73.3 (1 C, C-2b), 74.9 (2 C, C-3b, C-2c), 76.8 (1 C, C-5b), 76.9 (1 C, C-5a), 77.9 (1 C, C-3c), 78.9 (1 C, C-2a), 86.6 (1 C, C-3a), 91.3 (1 C, C-3), 103.8 (1 C, C-1b), 104.6 (1 C, C-1c), 105.3 (1 C, C-1a), 129.0 (1 C, C-12), 172.6 (1 C, C-30), 178.7 (1 C, C-6a), 202.6 (1 C, C-11) ppm. MALDI-MS (positive mode, matrix DHB, THF): *m*/*z* = 978 $[M + Na]^+$, 993 $[M + K]^+$. $C_{48}H_{74}O_{19}\cdot 5H_2O$ (1045.2): calcd. C 55.16, H 8.10; found C 55.00, H 8.50.

3β-*O*-{(β-D-Xylopyranosyl)-(1→3)-[(β-D-galactopyranosyl)-(1→2)]-(6-β-D-glucopyranosyl uronic acid)}-18β-glycyrrhetic Acid (2a): A solution of saponin **27** (23.1 mg, 24.13 μmol) and lithium hydroxide (3% CH_3OH, 10 mL) was heated at 54 °C for 24 h, neutralized with ion-exchange resin (Amberlite IR-120 H^+) and concentrated in vacuo. Purification by flash chromatography (CH_2Cl_2/CH_3OH 2:1) afforded **2a** (12.5 mg, 55%). TLC (CH_2Cl_2/CH_3OH 2:1): R_f = 0.35. ^1H NMR (600 MHz, CD_3OD/D_2O 10:1): δ = 0.68 (d, $J_{5,6}$ = 7.5 Hz, 1 H, 5-H), 0.78 (s, 3 H, 28-CH_3), 0.84 (s, 3 H, 24-CH_3), 0.95–1.03 (m, 2 H, 1-H_a, 16-H_a), 1.03, 1.09, 1.12 (3×s, 12 H, 23-CH_3, 29-CH_3, 26-CH_3, 25-CH_3), 1.34 (s, 3 H, 27-CH_3), 1.22–2.00 (m, 18 H), 2.33 (s, 1 H, 9-H), 2.68 (brd, 1 H, 1-H_b), 3.14 (dd, $J_{3,2\text{-}H_a}$ = $J_{3,2\text{-}H_b}$ = 8.2 Hz, 1 H, 3-H), 3.22 (dd, J_{gem} = $J_{5,6}$ = 11.8 Hz, 1 H, 5c-H_a), 3.28–3.30 (m, 2 H, 2c-H, 3c-H), 3.44–3.52 [m, 4 H, H,H-COSY: 3.47 (3b-H), 3.49 (5b-H), 3.50 (2b-H), 3.52 (4c-H)], 3.59–3.80 [m, 6 H, H,H-COSY: 3.62 (4a-H), 3.64 (6b-H_a), 3.74 (3a-H), 3.75 (6b-H_b), 3.79 (2a-H), 3.80 (4b-H)], 3.87–3.90 (m, 1 H, 5c-H_b), 4.55 (d,

$J_{1,2}$ = 7.5 Hz, 1 H, 1a-H), 4.60 (d, $J_{1,2}$ = 7.8 Hz, 1 H, 1c-H), 4.83–4.89 [br, 1 H, H,H-COSY: 4.84 (1b-H)], 5.55 (s, 1 H, 12-H) ppm. ^{13}C NMR (151 MHz, CD_3OD/D_2O 10:1): δ = 16.0 (1 C, C-24), 16.3 (1 C, C-25), 17.5 (1 C, C-6), 18.7 (1 C, C-26), 23.4 (1 C, C-27), 26.5, 26.8 (3 C, C-2, C-15, C-16), 27.6, 28.2, 28.5 (3 C, C-23, C-28, C-29), 31.2 (1 C, C-21), 33.0 (1 C, C-7), 38.0 (1 C, C-22), 39.5 (1 C, C-1), 41.2 (1 C, C-19), 48.6 (1 C, C-18), 55.5 (1 C, C-5), 62.0 (1 C, C-9), 61.6 (1 C, C-6b), 66.1 (1 C, C-5c), 69.1 (1 C, C-4b), 69.5 (1 C, C-4c), 70.2 (1 C, C-4a), 73.9 (2 C, C-2c, C-3b), 75.1 (1 C, C-5a), 75.6 (1 C, C-5b), 77.1 (1 C, C-3c), 77.6 (1 C, C-2a), 86.2 (1 C, C-3a), 91.0 (1 C, C-3), 103.0 (1 C, C-1b), 104.0 (1 C, C-1c), 104.6 (1 C, C-1a) ppm. FAB-MS (positive mode, matrix: NBA, $CHCl_3$): *m/z* = 966 $[M + Na]^+$. $C_{47}H_{72}O_{19}$ (941.1).

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