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Efficient synthesis of glycyrrhetinic acid glycoside/glucuronide derivatives using silver zeolite as promoter ☆

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ABSTRACT

3-*O*-Glycopyranosides of glycyrrhetinic acid have been synthesized in good to high yields and excellent stereoselectivity using glycosyl bromide donors and silver zeolite as promoter. In addition to the preparation of glycosides containing β-linked glucosyl, 2-deoxy-2-trichloroacetamido-glucosyl, galactosyl, cellobiosyl and lactosyl residues, also the deactivated acetylated methyl glucopyranosyluronate bromide donor could be coupled to triterpene aglycon ester derivatives in good yields. The ester protecting group located at C-30 of the oleanolic acid scaffold exerted an influence on the overall yield, with the methyl-ester-protected glycosyl acceptor giving better yields compared to the allyl, benzyl as well as diphenylmethyl ester aglycon. The acetyl-protected glucuronides were differently deblocked in high yields via Zemplén deacetylation or via hydrogenolysis followed by Zemplén deacetylation, and alkaline hydrolysis, respectively, to allow for a selective liberation of the ester groups from either the glucuronide or the glycyrrhetinic acid unit, respectively. The target glycosides/glucuronides serve as probes for pharmaceutical studies aimed at defining structure–activity relationships of glycoside/glucuronide triterpenes.

1. Introduction

Glycyrrhizin constitutes a major component of the natural saponins isolated from licorice roots (*Glycyrrhiza radix*) and has been used since many centuries in traditional Asian medicines for treatment of pulmonary and inflammatory diseases. Glycyrrhizin harbors a broad spectrum of bioactivities such as anti-viral, cytotoxic, endocrine and anti-inflammatory, but also hepatoprotective properties, and is being exploited in the treatment of chronic hepatitis.[1,2] The carbohydrate portion of glycyrrhizin comprises a β-(1→2)-linked glucuronic acid disaccharide linked to O-3 of the triterpene. Several studies have addressed the modification of the disaccharide unit as well as the de novo attachment of sugar residues to the 3-β hydroxy group of the olean-11-oxo-12-ene scaffold.[3,4] The biological results obtained with these compounds regarding the contribution of the carbohydrate portion towards biological activities such as haemolytic or anti-viral activities have been elusive.[5,6] Furthermore, previously published glycosylation reactions of glycyrrhetinic acid acceptor derivatives have suffered from low yields in both the coupling and deprotection steps. As examples, Koenigs–Knorr and Helferich-type reactions of glycosyl bromide donors have been performed using silver carbonate,[7] silver triflate[8] or $Hg(CN)_2/HgBr_2$[9] or by employing TMS-bromide and $CoBr_2$ as promoters in the coupling step with reducing sugars.[10] Also condensation of sugar peracetates in the presence of $SnCl_4$ with a glycyrrhetinic acid aglycon has been reported.[10] These approaches proceeded either in low yields, additional orthoester formation or with low anomeric selectivity. Also formation of the corresponding enol-glycosides at position 11 was observed as a side reaction.[11]

By contrast, use of trifluoroacetimidate donors proved to be effective for the coupling of 2-amino-2-deoxy-sugars to allyl ester protected oleanolic acid.[12] Similarly, trichloroacetimidate donors have been successfully coupled to the 3-OH group of oleanolic acid and glycyrrhetinic acid in high yields, albeit with concomitant formation of small amounts of the 11-enol glycoside in the latter case.[13,14] Finally, the glucuronide moiety has been formed in most cases by TEMPO oxidation of suitably protected intermediate glucopyranosyl units in a late stage of the synthetic scheme, requiring additional protecting group manipulation, while direct glycosylation using glucopyranosyluronate donors proceeded with low anomeric selectivity.[15,16] Within the framework of ongoing investigations on bioactivities of glycosylated triterpenes, we have therefore set out to study efficient procedures for the generation

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of glycyrrhetinic acid glycosides which should also be applicable to the synthesis of glucuronide derivatives of glycyrrhetinic acid.

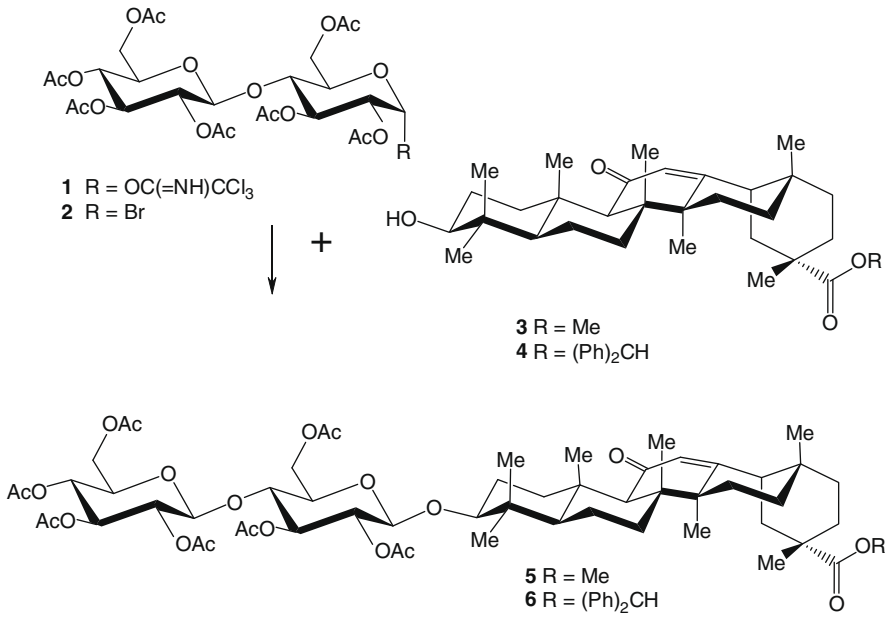
2. Results and discussion

2.1. Glycosylation of glycyrrhetinic acid derivatives

In order to explore the reactivity of commonly used donors in the synthesis of glycosylated triterpenes, hepta-*O*-acetyl cellobiosyl trichloroacetimidate and bromide donors **1** and **2**, respectively, were used in model reactions with the glycyrrhetinic acid methyl ester derivative **3** in the presence of various Lewis acid promoters in dichloromethane (Scheme 1, Table 1). The reactions proceeded with exclusive formation of the desired β-linked disaccharide derivatives, albeit in poor to modest yields, with TMSOTf as promoter giving the best result followed by tris(trifluorophenyl)borane (entries 1 and 2), whereas boron trifluoride etherate as promoter afforded a very low yield (entry 3).[17] When $ZnBr_2$ was used as catalyst, the reaction proceeded in two stages.[18] Initially, the triterpene acceptor **3** was consumed and after 2 h at room temperature, a putative intermediate orthoester could be visualized by thin-layer chromatography. Eventually the orthoester was converted in poor yield (13%) into the product **8** upon continued exposure to $ZnBr_2$ (Table 1, entry 4). Next the hepta-*O*-acetyl cellobiosyl bromide **2** was tested as glycosylating agent for the diphenylmethyl ester derivative **4** under Helferich conditions (in the presence of 1.5:2 $Hg(CN)_2/HgBr_2$), which did not lead to satisfactory results either (Table 1, entry 5).[5a] The stereochemistry of the glycosidic linkage of the glycoside **5** was determined in all cases to be β based on the value of the coupling constant of H-1′ ($J_{1',2'}$ 8.0 Hz).

Finally, Koenigs–Knorr conditions were applied in model reactions using the acetylated glucopyranosyl bromide **7**, in the presence of Ag_2CO_3/I_2 (5:1) (Scheme 2). Reaction of **7** with acceptor **4** furnished the orthoester **8** in 51% and the β-glycoside **9** in 29% yield.[19] The structural assignment of the orthoester **8** was based on the observed high-field shifted signal of the methyl group of the orthoacetate (δ 1.74, *endo*-CH_3).[20] Applying a large excess of donor **7** (6 equiv) and 9:1 Ag_2CO_3/I_2 as promoter afforded the glycoside **9** in 60% yield without formation of the orthoester. Eventually, silver zeolite, which has previously been proven as versatile promoter for related glycosylation reactions,[21–23] proved to be an efficient alternative and the β-glucopyranoside **9** was isolated in 60% yield. The reaction was performed in dichloromethane in the presence of molecular sieves 4 Å and using 3 equiv of the bromide donor **7**. The coupling reaction proceeded slowly but in a stereoselective fashion, without orthoester formation and with only trace amounts of α-glycoside being formed. Using these conditions, glycosylation of the methyl ester aglycon **3** afforded the monoglucopyranoside derivative **10** in 65% yield (Scheme 2).

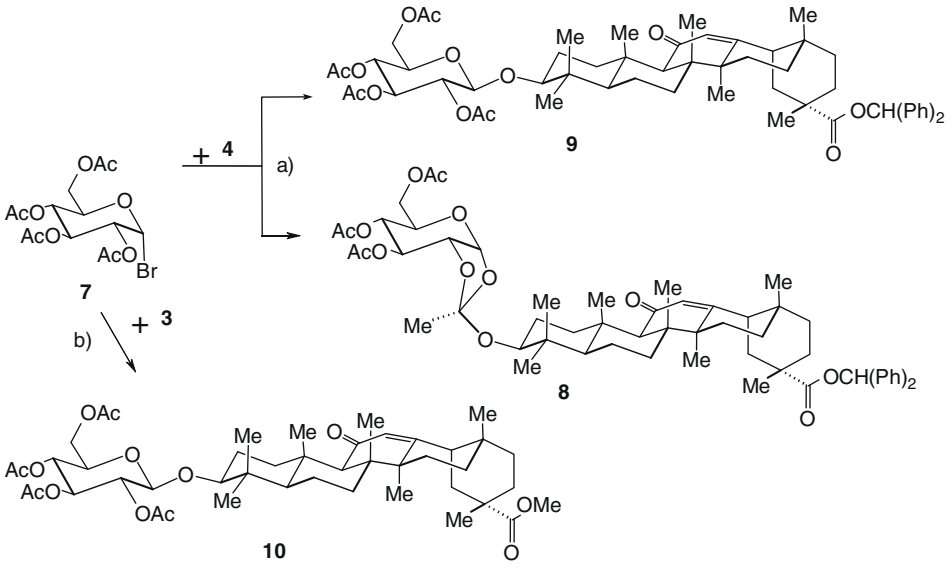
Due to the easy set-up and simple work-up of the reaction, a series of mono- and disaccharide glycoside derivatives could be prepared (Table 2, entries 1–14, Scheme 3). The cellobiosyl glycosides **5** and **6** could be isolated in substantially better yields (Table 2, entries 1 and 2) compared to the use of the trichloroacetimidate donor **1** (Table 1, entry 1) or in comparison to the coupling reaction of the bromide donor **2** under Helferich conditions (Table 1, entry 5). The results were confirmed by similar glycosylation reactions using glycopyranosyl bromide donors **13**–**15** and methyl (2,3,4-tri-*O*-acetyl-glucopyranosyl bromide)uronate (**16**). Thus, the β-D-galactopyranosyl derivatives **17** and **18** were prepared in good



Scheme 1. Glycosylation of glycyrrhetinic acid derivatives with cellobiosyl donors. For conditions and yields see Table 1.

Table 1
Summary of glycosylation reactions using cellobiosyl donors **1** and **2**

Entry	Donor	Acceptor	Product	Promoter	Equiv	*T* (°C)	*T* (h)	Yield (%)
1	**1**	**3**	**5**	TMSOTf	0.1	−80	1	43
2	**1**	**3**	**5**	$(F_5C_6)_3B$	0.15	−40	15	40
3	**1**	**3**	**5**	$BF_3 \cdot Et_2O$	0.5	−60	2	18
4	**1**	**3**	**5**	$ZnBr_2$	0.7	40	15	13
5	**2**	**4**	**6**	$Hg(CN)_2/HgBr_2$	3.5	20	16	20



Scheme 2. Reagents and conditions: (a) 5:1 Ag_2CO_3–I_2, CH_2Cl_2, rt, 4 days, 51% for **8**, 29% for **9**; (b) Ag zeolite, CH_2Cl_2, molecular sieves 4 Å, rt, 4 days, 65% for **9**, 65% for **10**.

Table 2
Summary of silver zeolite promoted glycosylation reactions

Entry	Donor	Acceptor	Product	Yield (%)
1	**2**	**3**	**5**	80
2	**2**	**4**	**6**	74
3	**7**	**3**	**10**	65
4	**7**	**4**	**9**	60
5	**13**	**3**	**17**	60
6	**13**	**4**	**18**	50
7	**14**	**3**	**19**	97
8	**14**	**4**	**20**	55
9	**15**	**3**	**21**	60
10	**15**	**4**	**22**	57
11	**16**	**3**	**23**	75
12	**16**	**4**	**24**	43
13	**16**	**11**	**25**	55
14	**16**	**12**	**26**	54

yields without formation of the corresponding α-isomers (Table 2, entries 5 and 6). The 2-deoxy-2-trichloroacetamido-D-glucopyranosyl bromide donor **14** furnished the β-glycoside **19** in near quantitative yield (Table 2, entry 7). The β-lactosyl derivatives **21** and **22** were isolated in 60% and 57% yields, respectively (Table 2, entries 9 and 10).

The broad scope of the procedure is evident from the successful coupling of the sterically hindered 3-OH group of the triterpene acceptor with a highly deactivated glycosyl donor such as the methyl (2,3,4-tri-*O*-acetyl-glucopyranosyl bromide)uronate (**16**), which furnished the monoglucuronide **23** in 75% yield.

It is worthy to note that the choice of the ester protecting group had an influence on the reaction yields: as seen in Table 2, the methyl ester acceptor **3** consistently gave the best yields, whereas the use of other ester protecting groups such as diphenylmethyl, allyl or benzyl groups resulted in slightly reduced yields (Table 2, entries 12–14). Since, however, the methyl ester group at position 30 of glycyrrhetinic acid is notoriously difficult to remove under alkaline conditions, the preparation of the fully deblocked glycosides is better being performed by deprotection via catalytic hydrogenation of benzyl ester type protecting groups.[5a,10] Alternative removal of the methyl ester group of glycyrrhetinic acid based on enzymatic treatment has not been tested thus far.

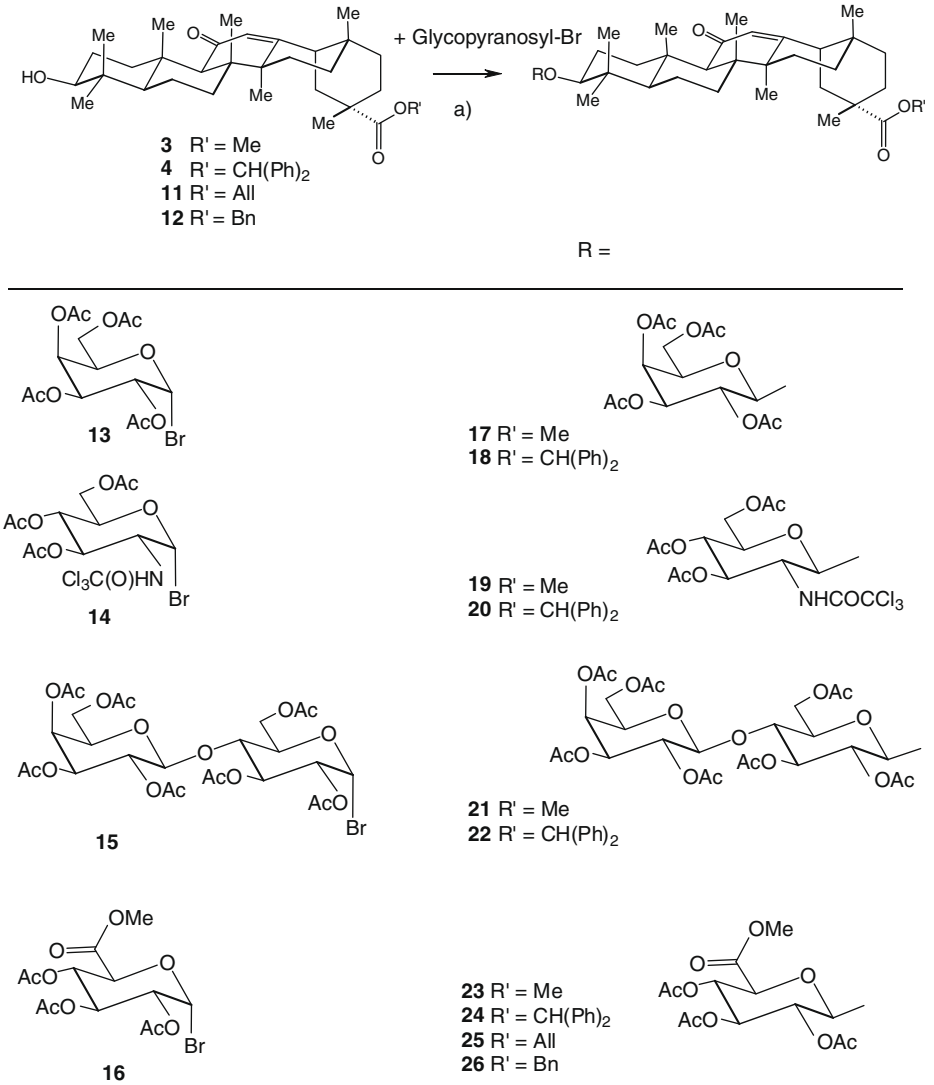
2.2. Deprotection of glucuronide derivatives

Based on the different ester protecting groups of the glucuronide derivatives **23** and **24**, a series of partially as well as fully deprotected glucuronide derivatives were prepared, in order to evaluate the influence of the carboxylic group located at the carbohydrate moiety versus the oleanolic acid part with respect to biological activities. Zemplén deacetylation of **23** gave the dimethyl ester **27** (Scheme 4). Subsequent saponification of **27** with methanolic NaOH furnished the monoacid **28**, whereas hydrogenolysis of **24** followed by Zemplén deacetylation gave the alternate monoacid **29**, which upon further alkaline treatment afforded the free diacid **30**, corresponding to the enzymatically formed monoglucuronide of glycyrrhetinic acid.[24] The ^{1}H and ^{13}C NMR data were in close in agreement with the published values of glycyrrhizin recorded for solutions in pyridine-d_5.[25]

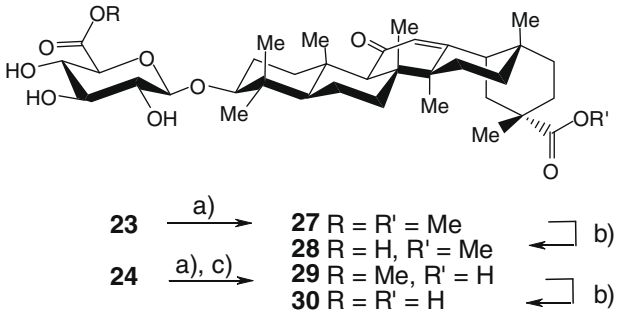
3. Experimental

3.1. General

Glycyrrhetinic acid ester derivatives **3**, **4**, **11** and **12** were prepared according to published procedures.[5a,10,7] Concentration of solutions was performed at reduced pressure at temperatures <40 °C. Dichloromethane was dried by stirring with CaH_2 (5 g per L) for 16 h, then distilled and stored under argon over molecular sieves 0.4 nm. Silver zeolite was prepared according to literature using powdered molecular sieves 4 Å (Merck) and was dried at 200 °C overnight prior to use.[21] Column chromatography was performed on Silica Gel 60 (230–400 mesh, Merck). Analytical TLC was performed using Silica Gel 60 F_{254} HPTLC plates with 2.5 cm concentration zone (Merck). Spots were detected by treatment with anisaldehyde–H_2SO_4. Ion exchange treatment was performed on Dowex 50 WX8 resin, H+ form, 50–100 mesh. Melting points were determined on a Kofler hot stage microscope and are uncorrected. Optical rotations were measured with a Perkin–Elmer 243 B polarimeter. NMR spectra were recorded at 297 K in CD_3OD and $CDCl_3$ with a Bruker DPX 300 or Avance 400 spectrometer (^{1}H at 300.13 MHz, ^{13}C at 75.47 MHz or ^{1}H at 400.13 MHz, ^{13}C at 100.61 MHz, respectively) using standard Bruker NMR software. ^{1}H NMR and ^{13}C NMR spectra were referenced to internal tetramethylsilane (δ 00). Signals assignments were based on COSY,



Scheme 3. Reagents and conditions: Ag zeolite, CH_2Cl_2, molecular sieves 4 Å, rt, 4 days; yields are given in Table 2.



Scheme 4. Reagents and conditions: (a) 0.1 M NaOMe, MeOH, 3 h, rt, 93% for **27**; (b) 0.2 M NaOH, MeOH, 0 °C, 3 h, 91% for **28**; 91% for **30**; (c) H_2, 10% Pd–C, 5:2 MeOH–EtOAc, then (a), 97% for **29**.

HSQC and HMBC measurements. For mass spectrometry analyses, samples were dissolved in the appropriate amount of MeCN to give a solution of approx. 1 nmol/μL. Just before analysis an aliquot of the respective sample was diluted in 50% aq acetonitrile containing 0.1% formic acid to give a final concentration of ~10 μmol/mL. This solution was subjected to offline ESI Q-TOFMS on a Waters Micromass Q-TOF Ultima Global. Capillary voltage was adjusted to obtain approx. 200 counts/s. The MS had been previously tuned with [Glu1]-fibrinopeptide B to give highest possible sensitivity and a resolution of ca. 10.000 (FWHM). Mass tuning of the TOF analyzer was done in the tandem MS mode using again [Glu1]-fibrinopeptide B.

3.2. Methyl 3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl)-18-β-glycyrrhetinate (5)

Method 1. A suspension of acceptor **3** (100 mg, 0.212 mmol) and powdered molecular sieves 4 Å (~100 mg) in dry CH_2Cl_2 (4 mL) was stirred at rt for 15 min under Ar, then cooled to −80 °C and TMSOTf (4 μL) was added dropwise. After 45 min of stirring, trichloroacetimidate donor **1** (332 mg, 0.425 mmol) dissolved in dry CH_2Cl_2 (2 mL) was slowly added into the reaction mixture. After 1 h, the reaction was stopped by the addition of Et_3N (100 μL). The suspension was diluted with CH_2Cl_2 (50 mL) and filtered through a pad of Celite. The filtrate was washed with satd aq $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel (3:1 → 1:1 toluene–EtOAc) afforded **5** (99.5 mg, 43%) as a white solid.

R_f 0.56 (1:1 *n*-hexane–EtOAc); ^1H NMR ($CDCl_3$, 300 MHz): δ 5.66 (s, 1H, H-12), 5.18 and 5.15 (2t, 2H, H-3″, H-3′), 5.05 (t, 1H,

$J_{3'',4''} = J_{4'',5''}$ 9.6 Hz, H-4″), 4.94 and 4.92 (2t, 2H, H-2″, H-2′), 4.49 (d, 2H, *J* 8.0 Hz, H-1′, H-1″), 4.44 (dd, 1H, $J_{5',6a'}$ 2.4, $J_{6a'',6b''}$ 11.6 Hz, H-6′a), 4.36 (dd, 1H, $J_{5'',6a''}$ 4.5, $J_{6a'',6b''}$ 12.6 Hz, H-6a″), 4.11 (dd, 1H, $J_{5',6b'}$ 6.5 Hz, H-6b′), 4.04 (dd, 1H, $J_{5'',6b''}$ 2.2 Hz, H-6b″), 3.73–3.55 (m, 6H, H-4′, OCH_3, H-5′, H-5″), 3.08 (dd, 1H, $J_{3,2a}$ 8.0, $J_{3,2b}$ 9.2 Hz, H-3), 2.79 (br d, 1H, *J* 13.7 Hz, H-1a), 2.31 (s, 1H, H-9), 2.10–1.73 (m, 28H, 7 × Ac, H-2a, H-2b, H-15a, H-16a, H-18, H-19a, H-21a), 1.68–1.50 (m, 3H, H-6a, H-7a, H-19b), 1.35 (s, 3H, C*H*$_3$-27), 1.14, 1.12 and 1.11 (3s, 9H, C*H*$_3$-29, C*H*$_3$-26, C*H*$_3$-25), 1.48-1.13 (m, 6H, H-6b, H-7b, H-15b, H-21b, H-22a, H-22b), 1.05–0.88 (m, 2H, H-1b, H-16b), 0.92 (s, 3H, C*H*$_3$-23), 0.80 (s, 3H, C*H*$_3$-28),0.75 (s, 3H, C*H*$_3$-24), 0.69 (br d, 1H, H-5); ^{13}C NMR ($CDCl_3$) δ: 200.05 (C-11), 175.81 (C-30), 170.43, 170.24, 170.10, 169.81, 169.23, 169.16, 169.02 (C-13, C*O*OCH$_3$), 128.33 (C-12), 102.67 (C-1′), 100.71 (C-1″), 90.39 (C-3), 77.90 (C-4′), 72.90, 72.58, 72.41 and 71.92, (C-5″, C-5′, C-3′, C-3″), 71.90 and 71.59 (C-2′, C-2″), 67.79 (C-4″), 62.14 (C-6′), 61.58 (C-6″), 60.36 (C-9), 55.21 (C-5), 51.77 (OCH_3), 48.37 (C-18), 45.35 (C-8), 44.01 (C-20), 43.14 (C-14), 41.07 (C-19), 39.16 (C-4), 39.00 (C-1), 37.70 (C-22), 36.77 (C-10), 32.69 (C-7), 31.81 (C-17), 31.10 (C-21), 28.49 (C-29), 28.31 (C-28), 27.65 (C-23), 26.44 (C-16), 26.37 (C-15), 25.66 (C-2), 23.32 (C-27), 21.03, 20.81, 20.69, 20.62, 20.51 (*C*H$_3$CO), 18.54 (C-26), 17.24 (C-6), 16.24 (C-24), and 16.20 (C-25).

Method 2. Acceptor **3** (46 mg, 0.095 mmol), donor **1** (150 mg, 0.192 mmol) and powdered molecular sieves 4 Å (~150 mg) were dissolved in dry CH_2Cl_2 (5 mL) under Ar. The reaction mixture was stirred at −40 °C for 30 min and a solution of $(C_6F_5)_3B$ (7.3 mg, 0.014 mmol) in dry CH_2Cl_2 (1 mL) was added dropwise into the solution. After 1 h at −40 °C the reaction was allowed to reach 20 °C and the reaction mixture was left overnight at rt. Then, the reaction was quenched by the addition of Et_3N (100 μL), and was processed as described above to furnish **5** (42 mg, 40%) as a white solid.

Method 3. A suspension of acceptor **3** (100 mg, 0.212 mmol) and powdered molecular sieves 4 Å (~100 mg) in dry CH_2Cl_2 (4 mL) was stirred at rt for 15 min under Ar, then cooled to −60 °C and $BF_3{\cdot}Et_2O$ (13 μL) was added dropwise. After stirring for 45 min, trichloroacetimidate donor **1** (332 mg, 0.425 mmol) dissolved in dry CH_2Cl_2 (2 mL) was slowly added into the reaction mixture. After 2 h, the reaction was stopped by the addition of Et_3N (100 μL). Work-up as described above afforded **5** (42 mg, 18%) as a white solid.

Method 4. Trichloroacetimidate donor **1** (50 mg; 0.064 mmol), acceptor **3** (26.5 mg, 0.056 mmol) and powdered molecular sieves 4 Å (100 mg) were dissolved in dry CH_2Cl_2 (5 mL) under Ar. The mixture was stirred at −30 °C for 4 h. Then anhydrous $ZnBr_2$ (8.5 mg; 0.038 mmol) was added in one portion into the suspension. The reaction was maintained at rt for 2 h and was monitored by TLC using 3:1 $CHCl_3$–EtOAc and 1:1 toluene–EtOAc. Stirring of the reaction was then continued under reflux for 15 h. Acetic anhydride (0.1 mL, 1.06 mmol) was added at rt and the reaction mixture was stirred for 3 h. Work-up as described above gave **5** (9 mg; 13%).

3.3. Diphenylmethyl 3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl)-18-β-glycyrrhetinate (6)

A suspension of **4** (112 mg, 0.18 mmol) in dry CH_2Cl_2 (8 mL) containing powdered molecular sieves 4 Å (~150 mg) and a mixture of $Hg(CN)_2$ (68 mg, 0.27 mmol) and $HgBr_2$ (130 mg, 0.36 mmol) was cooled to 0 °C. Hepta-*O*-acetyl-cellobiosyl bromide **2** (250 mg, 0.360 mmol) dissolved in 2 mL of dry CH_2Cl_2 was added dropwise with stirring. After stirring for 2 h at 0 °C the reaction was allowed to reach 20 °C and the suspension was stirred overnight at rt. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and filtered through a bed of Celite. The filtrate was washed with 1 M aq KI solution and satd aq $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated in vacuo. Silica gel chromatography of the crude mixture (2:1 → 1:1 toluene–EtOAc) afforded **6** as off-white powder (45 mg, 20%); R_f 0.45 (1:1 *n*-hexane–EtOAc); mp 188–192 °C, $[\alpha]_D^{20}$ +23 (*c* 0.5, $CHCl_3$); NMR data were identical to published data.[5]

3.4. 3,4,6-Tri-*O*-acetyl-{(*S*)-1,2-*O*-[1-(30-*O*-diphenylmethyloxycarbonyl-11-oxo-30-norolean-12-ene-3-yloxy)ethylidene]}-α-D-glucopyranose (8) and diphenylmethyl 3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-18-β-glycyrrhetinate (9)

To a suspension of **7** (50 mg, 0.121 mmol) in dry CH_2Cl_2 (3 mL) containing **4** (78 mg, 0.121 mmol) and powdered 4 Å molecular sieves (200 mg) were added Ag_2CO_3 (167 mg, 0.605 mmol) and I_2 (31 mg, 0.121 mmol). The suspension was stirred at rt for 4 days protected from light, then diluted with CH_2Cl_2 (50 mL) and filtered through Celite®. The filtrate was washed with satd aq $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (2:1 *n*-hexane–EtOAc) to afford **8** (60 mg, 51%) as colourless syrup. R_f 0.71 (1:1 *n*-hexane–EtOAc); $[\alpha]_D^{20}$ +91 (*c* 1.0, $CHCl_3$); selected ^{1}H NMR data ($CDCl_3$, 400 MHz): δ 7.38–7.27 (m, 10H, H-Ar), 6.93 (s, 1H, C*H*Ph$_2$), 5.69 (d, 1H, $J_{1',2'} \sim 4.0$ Hz, H-1′), 5.51 (s, 1H, H-12), 5.19 (t, 1H, H-3′), 4.90 (dd, 1H, H-4′), 4.19 (d, 1H, $J_{4',5'}$ 4.4 Hz, H-5′), 3.95 (m, 1H, H-6′), 3.23 (m, 1H, H-3), 2.79 (br d, 1H, *J* 13.6 Hz, H-1), 2.31 (s, 1H, H-9), 2.11, 2.09, 2.08 (3s, 9H, 3 × Ac), and 1.74 (s, 3H, CH_3-*endo*).

Further elution of the column with 1:1 *n*-hexane–EtOAc furnished the saponin **9** (35 mg, 29%) as a white solid. R_f 0.42 (3:2 *n*-hexane–EtOAc); $[\alpha]_D^{20}$ +84 (*c* 0.36, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.38–7.16 (m, 10H, H-Ar), 6.93 (s, 1H, C*H*Ph$_2$), 5.51 (s, 1H, H-12), 5.21 (t, 1H, $J_{3',4'} = J_{3',2'}$ 9.6, H-3′), 5.06–5.00 (m, 2H, H-4′, H-2′), 4.54 (d, 1H, $J_{1',2'}$ 8.0 Hz, H-1′), 4.24 (dd, 1H, $J_{5',6a'}$ 5.8, $J_{6a',6b'}$ 12.2 Hz, H-6a′), 4.10 (dd, 1H, $J_{6',5'}$ 2.5 Hz, H-6b′), 3.69 (ddd, 1H, H-5′), 3.12 (dd, 1H, $J \sim 8.2$ Hz, H-3), 2.80 (ddd, 1H, *J* 10.4 Hz, H-1a), 2.29 (s, 1H, H-9), 2.12–1.73 (m, 28H, 7 × Ac, H-2a, H-2b, H-15a, H-16a, H-18, H-19a, H-21a), 1.70–1.53 (m, 3H, H-6a, H-7a, H-19b), 1.34 (s, 3H, C*H*$_3$-27), 1.17, 1.12 and 1.08 (3s, 9H, C*H*$_3$-29, C*H*$_3$-25, C*H*$_3$-26), 1.46–1.13 (m, 6H, H-6b, H-7b, H-15b, H-21b, H-22a, H-22b), 1.03–0.85 (m, 2H, H-1b, H-16b), 0.93 (s, 3H, C*H*$_3$-23), 0.80 (s, 3H, C*H*$_3$-28), 0.77 (s, 3H, C*H*$_3$-24), and 0.69 (br d, 1H, H-5); ^{13}C NMR ($CDCl_3$) δ: 199.94 (C-11), 175.14 (C-30), 170.44, 170.24, 170.37, 170.21, 169.25, 168.87 (C*O*CH$_3$, C-13), 140.04 (C-arom.), 128.60, 128.42, 128.12, 127.80, 127.32, 126.93 (C-arom., C-12), 102.89 (C-1′), 90.51 (C-3), 76.63 (*C*HPh$_2$), 72.87 (C-3′), 71.76 (C-4′), 71.52 (C-5′), 68.79 (C-2′), 62.31 (C-6′), 61.73 (C-9), 55.27 (C-5), 48.04 (C-18), 45.32 (C-8), 44.00 (C-20), 43.12 (C-14), 41.07 (C-19), 39.23 (C-4), 39.08 (C-1), 37.52 (C-22), 36.79 (C-10), 32.74 (C-7), 31.72 (C-17), 31.09 (C-21), 28.29 (C-29), 28.20 (C-28), 27.66 (C-23), 26.43 (C-16), 26.30 (C-15), 25.72 (C-2), 23.32 (C-27), 20.67, 20.68, 20.69, 20.59 (*C*H$_3$CO), 18.66 (C-26), 18.42, 17.32 (C-6), 16.38 (C-24) and 16.26 (C-25).

3.5. General method for silver zeolite promoted glycosylation

Acetobromocellobiose **2** (100 mg, 0.143 mmol), acceptor **3** (34 mg, 0.0715 mmol), silver zeolite (~250 mg) and powdered 4 Å molecular sieves (~100 mg) were suspended in dry CH_2Cl_2 (3 mL) and stirred at rt while shielded from light for 4 days. The suspension was diluted with CH_2Cl_2 (50 mL), stirred under sonication for 5 min and filtered through a pad of Celite®. The filtrate was washed with 1 M $Na_2S_2O_3$ solution, satd aq $NaHCO_3$, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by silica gel chromatography (3:2 → 1:1 *n*-hexane–EtOAc) to afford 63 mg of **5** (80%) as a white solid.

Similarly, glycosidation of **2** (100 mg, 0.145 mmol) with **4** (46 mg, 0.071 mmol) was accomplished as described for the preparation of **5**. The product was purified by column chromatography (3:2 → 1:1 *n*-hexane–EtOAc) to yield **6** as a colourless syrup (65 mg, 74%).

In addition, coupling of acetobromoglucose **7** (100 mg, 0.243 mmol), acceptor **4** (75 mg, 0.121 mmol), silver zeolite (~250 mg) and powdered 4 Å molecular sieves (~200 mg) and work-up as described afforded 69 mg of **9** (60%) as a white solid.

3.5.1. Methyl 3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-18-β-glycyrrhetinate (10)

The compound was prepared according to the general procedure from bromide **7** (250 mg, 0.610 mmol), acceptor **3** (98 mg, 0.203 mmol), silver zeolite (~250 mg) and powdered 4 Å molecular sieves (~200 mg). Chromatography of the processed reaction mixture on silica gel (3:2 → 1:1 *n*-hexane–EtOAc) afforded 114 mg of **10** (65%) as a white solid; R_f 0.42 (3:2 *n*-hexane–EtOAc); $[\alpha]_D^{20}$ +84 (*c* 0.36, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.66 (s, 1H, H-12), 5.24 (t, 1H, $J_{3',4'}$ 9.6 Hz, H-3′), 5.06–5.01 (m, 2H, H-4′, H-2′), 4.54 (d, 1H, $J_{1',2'}$ 8.0 Hz, H-1′), 4.24 (dd, 1H, $J_{5',6a'}$ 5.8, $J_{6a',6b'}$ 12.2 Hz, H-6a′), 4.11 (dd, 1H, H-6b′), 3.71–3.67 (m, 4H, OCH_3, H-5′), 3.11 (t, 1H, $J \approx 8.2$ Hz, H-3), 2.80 (br d, 1H, J 10.4 Hz, H-1a), 2.31 (s, 1H, H-9), 2.11–1.75 (m, 19H, 4 × Ac, H-2a, H-2b, H-15a, H-16a, H-18, H-19a, H-21a), 1.70–1.53 (m, 3H, H-6a, H-7a, H-19b), 1.35 (s, 3H, CH_3-27), 1.14, 1.13 and 1.12 (3s, 9H, CH_3-29, CH_3-25, CH_3-26), 1.48–1.13 (m, 6H, H-6b, H-7b, H-15b, H-21b, H-22a, H-22b), 1.03–0.85 (m, 2H, H-1b, H-16b), 0.93 (s, 3H, CH_3-23), 0.80 and 0.77 (2s, 6H, CH_3-28, CH_3-24), and 0.69 (br d, 1H, H-5); ^{13}C NMR ($CDCl_3$): δ 200.04 (C-11), 176.86 (C-30), 170.64, 170.24, 170.36, 169.37, 169.14, 169.08 (C-13, *C*OCH_3), 128.51 (C-12), 102.86 (C-1′), 90.50 (C-3), 72.84 (C-4′), 71.65 (C-5′), 71.49 (C-3′), 68.78 (C-2′), 62.28 (C-6′), 61.74 (C-9), 55.24 (C-5), 51.76 (OCH_3), 48.36 (C-18), 45.34 (C-8), 44.00 (C-20), 43.12 (C-14), 41.06 (C-19), 39.17 (C-4), 39.01 (C-1), 37.69 (C-22), 36.78 (C-10), 32.69 (C-7), 31.79 (C-17), 31.09 (C-21), 28.47 (C-29), 28.31 (C-28), 27.67 (C-23), 26.44 (C-16), 26.37 (C-15), 25.68 (C-2), 23.31 (C-27), 20.73, 20.68, 20.61 and 20.58 (CH_3CO), 18.64 (C-26), 17.34 (C-6), 16.32 (C-24) and 16.27 (C-25). ESI-TOFMS: *m/z* = 815.5206 $[M+H]^+$; calcd 815.4581.

3.5.2. Methyl 3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-18-β-glycyrrhetinate (17)

Acetobromogalactose **13** (250 mg, 0.610 mmol), acceptor **3** (98 mg, 0.203 mmol), silver zeolite (~250 mg) and powdered 4 Å molecular sieves (~200 mg) were suspended in dry CH_2Cl_2 (5 mL) and treated as described for **5** to afford 105 mg (60%) of **17** as a white solid; R_f 0.51 (3:2 *n*-hexane–EtOAc); $[\alpha]_D^{20}$ +91.4 (*c* 0.33, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.67 (s, 1H, H-12), 5.36 (dd, 1H, $J_{3',4'}$ 3.4, $J_{5',4'}$ 1.2 Hz, H-4′), 5.26 (dd, 1H, $J_{2',3'}$ 10.6 Hz, H-2′), 5.02 (dd, 1H, H-3′), 4.50 (d, 1H, $J_{1',2'}$ 8.0 Hz, H-1′), 4.195 (dd, 1H, $J_{5',6a'}$ 6.8, $J_{6a',6b'}$ 11.2 Hz, H-6′a), 4.095 (dd, 1H, $J_{5',6'b}$ 6.8 Hz, H-6′b), 3.89 (ddd, 1H, H-5′), 3.69 (s, 3H, OCH_3), 3.11 (dd, 1H, J 5.8, J 10.8 Hz, H-3), 2.80 (ddd, 1H, J 13.6 Hz, H-1a), 2.30 (s, 1H, H-9), 2.16–1.77 (m, 19H, 4 × Ac, H-2a, H-2b, H-15a, H-16a, H-18, H-19a, H-21a), 1.68–1.53 (m, 3H, H-6a, H-7a, H-19b), 1.48–1.15 (m, 6H, H-6b, H-7b, H-15b, H-21b, H-22a, H-22b), 1.355 (s, 3H, CH_3-27), 1.15, 1.13 and 1.12 (3s, 9H, CH_3-29, CH_3-25, CH_3-26), 0.93 (s, 3H, CH_3-23), 1.05–0.88 (m, 2H, H-16b, H-1b), 0.80 and 0.79 (2s, 6H, CH_3-24, CH_3-28), 0.70 (br d, 1H, H-5); ^{13}C NMR ($CDCl_3$) δ: 200.11 (C-11), 176.91 (C-30), 170.46, 170.41, 170.25, 169.29, 169.16 (C-13, *C*OCH_3), 128.57 (C-12), 103.55 (C-1′), 90.64 (C-3), 71.38 (C-5′), 70.79 (C-3′), 69.62 (C-2′), 67.48 (C-4′), 62.13 (C-6′), 61.82 (C-9), 55.65 (C-5), 52.21 (OCH_3), 48.77 (C-18), 45.34 (C-8), 44.42 (C-20), 43.53 (C-14), 41.45 (C-19), 39.61 (C-4), 39.41 (C-1), 38.09 (C-22), 37.17 (C-10), 33.09 (C-7), 32.21 (C-17), 31.49 (C-21), 28.89 (C-29), 28.73 (C-28), 28.09(C-23), 26.84 (C-16), 26.76 (C-15), 26.23 (C-2), 23.72 (C-27), 21.27, 21.14, 21.09, 21.04 (*C*H_3CO), 19.04 (C-26), 17.75 (C-6), 16.76 (C-24), 16.70 (C-25). ESI-TOFMS: *m/z* = 815.5206 $[M+H]^+$; calcd 815.4581.

3.5.3. Diphenylmethyl 3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-18-β-glycyrrhetinate (18)

Acetobromogalactose **13** (100 mg, 0.243 mmol), acceptor **4** (98 mg, 0.121 mmol), silver zeolite (~150 mg) and powdered 4 Å molecular sieves (~100 mg) were suspended in dry CH_2Cl_2 (3 mL) and treated as described for **5** to afford 58 mg (50%) of **18** as a colourless syrup; R_f 0.64 (1:1 *n*-hexane–EtOAc); $[\alpha]_D^{20}$ +74 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.39–7.27 (m, 10H, H-Ar), 6.90 (s, 1H, C*H*Ph_2), 5.52 (s, 1H, H-12), 5.36 (dd, 1H, $J_{3',4'}$ 3.5, $J_{4',5'}$ 0.9 Hz, H-4′), 5.26 (dd, 1H, $J_{1',2'}$ 7.9, $J_{2',3'}$ 10.5 Hz, H-2′), 5.02 (dd, 1H, H-3′), 4.51 (d, 1H, H-1′), 4.195 (dd, 1H, $J_{5',6a'}$ 7.1, $J_{6a',6b'}$ 11.2 Hz, H-6′a), 4.10 (dd, 1H, $J_{5',6'b}$ 6.4 Hz, H-6′b), 3.90 (ddd, 1H, H-5′), 3.12 (dd, 1H, J 5.8, J 10.5 Hz, H-3), 2.80 (ddd, 1H, J 13.5 Hz, H-1a), 2.30 (s, 1H, H-9), 2.17–1.72 (m, 19H, 4 × Ac, H-2a, H-2b, H-15a, H-16a, H-18, H-19a, H-21a), 1.71–1.50 (m, 3H, H-6a, H-7a, H-19b), 1.45–1.15 (m, 6H, H-6b, H-7b, H-15b, H-21b, H-22a, H-22b), 1.365 (s, 3H, CH_3-27), 1.17, 1.13 and 1.08 (3s, 9H, CH_3-29, CH_3-25, CH_3-26), 0.93 (s, 3H, CH_3-23), 1.05–0.88 (m, 2H, H-16b, H-1b), 0.78 (s, 3H, CH_3-24), 0.66 (s, 3H, CH_3-28) and 0.70 (br d, 1H, H-5); ^{13}C NMR ($CDCl_3$): δ 199.91 (C-11), 175.15 (C-30), 170.44, 170.37, 170.21, 169.25, 168.87 (C-13, *C*OCH_3), 140.04 (C-arom.), 128.60, 128.42, 128.12, 127.80, 127.23, 126.93 (C-12, C-arom.), 103.47 (C-1′), 90.53 (C-3), 70.94 (C-5′), 70.35 (C-3′), 69.20 (C-2′), 67.05 (C-4′), 61.65 (C-6′), 61.42 (C-9), 55.20 (C-5), 47.97 (C-18), 45.26 (C-8), 43.94 (C-20), 43.06 (C-14), 41.05 (C-19), 39.18 (C-4), 39.03 (C-1), 37.41 (C-22), 36.73 (C-10), 32.66 (C-7), 31.68 (C-17), 31.09 (C-21), 28.25 (C-29), 28.20 (C-28), 27.66 (C-23), 26.38 (C-16), 26.30 (C-15), 25.79 (C-2), 23.24 (C-27), 20.83, 20.69, 20.59 (*C*H_3CO), 18.59 (C-26), 17.32 (C-6), 16.34 (C-24) and 16.26 (C-25). ESI-TOFMS: *m/z* = 967.560 $[M+H]^+$ calcd 967.5207.

3.5.4. Methyl 3-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranosyl)-18-β-glycyrrhetinate (19)

3,4,6-Tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-D-glucopyranosyl bromide **14** (260 mg, 0.506 mmol), acceptor **3** (82 mg, 0.170 mmol), silver zeolite (~ 250 mg) and powdered 4 Å molecular sieves (~150 mg) were suspended in dry CH_2Cl_2 (5 mL) and treated as described for **5** to give 150 mg (97%) of **19** as a colourless solid; R_f 0.37 (3:2 *n*-hexane–EtOAc); $[\alpha]_D^{20}$ +73.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.79 (d, 1H, J 8.7 Hz, NH), 5.66 (s, 1H, H-12), 5.34 (dd, 1H, $J_{2',3'}$ 10.6 Hz, H-3′), 5.06 (t, 1H, $J_{3',4'}$ 9.4 Hz, H-4′), 4.73 (d, 1H, $J_{1',2'}$ 8.2 Hz, H-1′), 4.27 (dd, 1H, $J_{5',6a'}$ 5.9, $J_{6a',6b'}$ 12.4 Hz H-6a′), 4.12 (dd, 1H, $J_{5',6ab'}$ 2.7 Hz, H-6b′), 3.97 (ddd, 1H, H-2′), 3.73 (ddd, 1H, H-5′), 3.69 (s, 3H, OCH_3), 3.12 (t, 1H, J 8.3 Hz, H-3), 2.80 (ddd, 1H, J 13.6 Hz, H-1a), 2.30 (s, 1H, H-9), 2.17–1.72 (m, 19H, 4 × Ac, H-2a, H-2b, H-15a, H-16a, H-18, H-19a, H-21a), 1.71–1.50 (m, 3H, H-6a, H-7a, H-19b), 1.45–1.15 (m, 6H, H-6b, H-7b, H-15b, H-21b, H-22a, H-22b), 1.35 (s, 3H, CH_3-27), 1.14, 1.13 and 1.08 (3s, 9H, CH_3-29, CH_3-25, CH_3-26), 0.92 (s, 3H, CH_3-23), 1.05–0.85 (m, 2H, H-16b, H-1b), 0.80 (2s, 6H, CH_3-24, CH_3-28) and 0.78 (br d, 1H, H-5); ^{13}C NMR ($CDCl_3$): δ 200.04 (C-11), 176.91 (C-30), 170.85, 170.64, 169.34, 169.58 (*C*OCH_3, C-13), 161.58 (*C*$OCCl_3$), 128.55 (C-12), 102.32 (C-1′), 90.51 ($COCCl_3$), 90.52 (C-3), 71.74 (C-5′), 71.49 (C-3′), 68.73 (C-4′), 62.34 (C-6′), 61.79 (C-9), 57.76 (C-2′), 55.34 (C-5), 51.79 (OCH_3), 48.41 (C-18), 45.38 (C-8), 44.05 (C-20), 43.17 (C-14), 41.13 (C-19), 39.29 (C-4), 39.11 (C-1), 37.74 (C-22), 36.81 (C-10), 32.73 (C-7), 31.84 (C-17), 31.14 (C-21), 28.51 (C-29), 28.36 (d.i., C-28, C-23), 26.49 and 26.42 (C-16, C-15), 25.69 (C-2), 23.36 (C-27), 20.77, 20.61, 20.56 (*C*H_3CO), 18.69 (C-26), 17.37 (C-6), and 16.32 (d.i., C-24, C-25). ESI-TOFMS: *m/z* = 916.386 $[M+H]^+$; calcd 916.349.

3.5.5. Diphenylmethyl 3-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-β-D-glucopyranosyl)-18-β-glycyrrhetinate (20)

3,4,6-Tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-D-glucopyranosyl bromide **14** (250 mg, 0.49 mmol), acceptor **4** (124 mg, 0.195 mmol), silver zeolite (~300 mg) and powdered 4 Å molecular sieves (~200 mg) were suspended in dry CH_2Cl_2 (5 mL) and treated as described for **5** to afford 115 mg (55%) of **20** as a white solid; R_f 0.43 (3:2 *n*-hexane–EtOAc); $[\alpha]_D^{20}$ −16.7 (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40–7.25 (m, 10H, H-Ar), 6.93 (s, 1H, C*H*Ph$_2$), 6.84 (d, 1H, $J_{2',NH}$ 8.8 Hz, NH), 5.51 (s, 1H, H-12), 5.35 (dd, 1H, $J_{2',3'}$ 11.2, $J_{3',4'}$ 9.2 Hz, H-3′), 5.06 (t, 1H, H-4′), 4.74 (d, 1H, $J_{1',2'}$ 8.0 Hz, H-1′), 4.27 (dd, 1H, $J_{5',6a'}$ 6.0, $J_{6a',6b'}$ 12.0 Hz H-6a′), 4.12 (dd, 1H, $J_{5',6ab'}$ 2.8 Hz, H-6b′), 3.98 (ddd, 1H, H-2′), 3.73 (ddd, 1H, H-5′), 3.13 (dd, 1H, *J* 9.2, *J* 7.2 Hz, H-3), 2.80 (ddd, 1H, *J* 13.6 Hz, H-1a), 2.28 (s, 1H, H-9), 2.14–1.73 (m, 19H, 4 × Ac, H-2a, H-2b, H-15a, H-16a, H-18, H-19a, H-21a), 1.69–1.50 (m, 3H, H-6a, H-7a, H-19b), 1.46–1.13 (m, 6H, H-6b, H-7b, H-15b, H-21b, H-22a, H-22b), 1.34 (s, 3H, CH_3-27), 1.17, 1.12 and 1.08 (3s, 9H, CH_3-29, CH_3-25, CH_3-26), 0.92 (s, 3H, CH_3-23), 1.00–0.88 (m, 2H, H-16b, H-1b), 0.79 (s, 3H, CH_3-24), 0.66 (s, 3H, CH_3-28) and 0.67 (br d, 1H, H-5); ^{13}C NMR ($CDCl_3$): δ 199.92 (C-11), 175.21 (C-30), 170.90, 170.67, 169.36, 168.91 (*C*OCH_3, C-13), 161.61 (*C*OCCl_3), 140.10 (C-arom.), 128.64, 128.51, 128.47, 128.16, 127.86, 127.29, 127.28 (C-arom., C-12), 102.28 (C-1′), 92.26 (CO*C*Cl_3), 90.47 (C-3), 71.72 and 71.48 (C-3′, C-5′), 68.73 (C-4′), 62.36 (C-6′), 61.73 (C-9), 56.72 (C-2′), 55.29 (C-5), 48.02 (C-18), 45.31 (C-8), 44.00 (C-20), 43.13 (C-14), 41.14 (C-19), 39.28 (C-4), 39.12 (C-1), 37.48 (C-22), 36.79 (C-10), 33.71 (C-7), 31.73 (C-17), 31.16 (C-21), 28.35 (C-29), 28.29 (C-28), 28.26 (C-23), 26.44 (C-16), 26.37 (C-15), 25.67 (C-2), 23.32 (C-27), 20.81, 20.63, 20.58 (*C*H_3CO), 18.66 (C-26), 17.35 (C-6), 16.32 (C-24), 16.31 (C-25). ESI-TOFMS: *m/z* = 1068.5415 $[M+H]^+$; calcd 1068.4198.

3.5.6. Methyl 3-*O*-[2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl]-18-β-glycyrrhetinate (21)

Acetobromolactose **15** (100 mg; 0.243 mmol), acceptor **3** (98 mg, 0.121 mmol), silver zeolite (~150 mg) and powdered 4 Å molecular sieves (~100 mg) were suspended in dry CH_2Cl_2 (3 mL) and treated as described for **5** to give 58 mg (60%) of **21** as a colourless solid; mp 135–139 (dec.); R_f 0.64 (1:1 *n*-hexane–EtOAc); $[\alpha]_D^{20}$ +120 (*c* 1.0, $CHCl_3$); ^{1}H NMR data were comparable to reported values.[9] ^{13}C NMR ($CDCl_3$): δ 200.03 (C-11), 176.84 (C-30), 170.30, 170.07, 169.97, 169.81, 169.35, 169.12, 169.08 (C-13, *C*OCH_3), 128.51 (C-12), 102.66 (C-1′), 101.06 (C-1″), 90.44 (C-3), 76.57 (C-4′), 72.91 (C-3′), 72.34 (C-5″), 72.04 (C-2′), 70.95 (C-3″), 70.67 (C-5′), 69.11 (C-2″), 66.63 (C-4″), 62.26 (C-6″), 61.73 (C-9), 60.83 (C-6′), 55.23 (C-5), 51.73 (OCH_3), 48.37 (C-18), 45.34 (C-8), 44.00 (C-20), 43.13 (C-14), 41.08 (C-19), 39.15 (C-4), 39.01 (C-1), 37.69 (C-22), 36.78 (C-10), 32.70 (C-7), 31.79 (C-17), 31.09 (C-21), 28.47 (C-29), 28.29 (C-28), 27.65 (C-23), 26.44 (C-16), 26.38 (C-15), 25.65 (C-2), 23.30 (C-27), 20.77, 20.68, 20.58, 20.45 (*C*H_3CO), 18.64 (C-26), 17.34 (C-6), 16.31 (C-24), 16.25 (C-25).

3.5.7. Diphenylmethyl 3-*O*-[2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl]-18-β-glycyrrhetinate (22)

Acetobromolactose **15** (100 mg, 0.143 mmol), acceptor **4** (36 mg, 0.057 mmol), silver zeolite (~150 mg) and powdered 4 Å molecular sieves (~100 mg) were suspended in dry CH_2Cl_2 (3 mL) and treated as described for **5** to afford 37 mg (57%) of **22** as a colourless syrup. R_f 0.52 (1:1 *n*-hexane–EtOAc); $[\alpha]_D^{20}$ +68.7 (*c* 0.3, $CHCl_3$). lit[5a] $[\alpha]_D^{20}$ +65.6 (*c* 0.1, CH_2Cl_2). NMR data were identical to published values.[5a]

3.5.8. Methyl 3-*O*-(methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosyluronate)-18-β-glycyrrhetinate (23)

Methyl 2,3,4-tri-*O*-acetyl-D-glucopyranosyluronate bromide **16** (500 mg, 1.21 mmol), acceptor **3** (190 mg, 0.392 mmol), silver zeolite (~750 mg) and powdered 4 Å molecular sieves (~400 mg) were suspended in dry CH_2Cl_2 (10 mL) and were processed as described for **5** to afford 232 mg (75%) of **23** as a colourless syrup; R_f 0.46 (3:2 *n*-hexane–EtOAc); $[\alpha]_D^{20}$ +55.5 (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.66 (s, 1H, H-12), 5.27–5.18 (m, 2H, H-3′, H-4′), 5.05 (dd, 1H, $J_{1',2'}$ 7.9, $J_{2',3'}$ 9.3 Hz, H-2′), 4.59 (d, 1H, H-1′), 4.00 (d, 1H, $J_{4',5'}$ 9.4 Hz, H-5′), 3.76 (s, 3H, 6′-OCH_3), 3.68 (s, 3H, 30-OCH_3), 3.12 (dd, 1H, *J* 6.6, *J* 9.7 Hz, H-3), 2.78 (ddd, 1H, *J* 13.5 Hz, H-1a), 2.31 (s, 1H, H-9), 2.10–1.78 (m, 16H, 3 × Ac, H-2a, H-2b, H-15a, H-16a, H-18, H-19a, H-21a), 1.69–1.50 (m, 3H, H-6a, H-7a, H-19b), 1.46–1.13 (m, 6H, H-6b, H-7b, H-15b, H-21b, H-22a, H-22b), 1.39 (s, 3H, CH_3-27), 1.19, 1.15 and 1.13 (3s, 9H, CH_3-29, CH_3-25, CH_3-26), 0.925 (s, 3H, CH_3-23), 1.05–0.88 (m, 2H, H-16b, H-1b), 0.80 (s, 3H, CH_3-28), 0.76 (s, 3H, CH_3-24) and 0.68 (br d, 1H, H-5); ^{13}C NMR ($CDCl_3$): δ 200.04 (C-11), 176.92 (C-30), 171.16 (C-6′), 170.64, 170.30, 169.34, 169.12, 169.03, 167.20 (*C*OCH_3, C-13), 128.56 (C-12), 102.84 (C-1′), 90.52 (C-3), 72.48 (C-5′), 72.21 (C-3′), 71.52 (C-2′), 69.52 (C-4′), 61.78 (C-9), 55.23 (C-5), 51.89 (6′-OCH_3), 51.80 (30-OCH_3), 48.38 (C-18), 45.38 (C-14), 44.05 (C-20), 43.15 (C-8), 41.11 (C-19), 39.3 (C-4), 39.015 (C-1), 37.74 (C-22), 36.79 (C-10), 32.73 (C-7), 31.83 (C-17), 31.14 (C-21), 28.51 (C-29), 28.35 (C-28), 27.73 (C-23), 26.48 and 26.42 (C-15, C-16), 25.63 (C-2), 23.37 (C-27), 20.68, 20.66, 20.53 (*C*H_3CO), 18.68 (C-26), 17.37 (C-6), 16.36 and 16.32 (C-24, C-25). ESI-TOFMS: *m/z* = 801.4869 $[M+H]^+$; calcd 801.4425.

3.5.9. Diphenylmethyl 3-*O*-[methyl (2,3,4-tri-*O*-acetyl-β-D-glucopyranosyluronate)]-18-β-glycyrrhetinate (24)

Methyl 2,3,4-tri-*O*-acetyl-D-glucopyranosyluronate bromide **16** (500 mg, 1.21 mmol), acceptor **4** (310 mg, 0.486 mmol), silver zeolite (~750 mg) and powdered 4 Å molecular sieves (~400 mg) were suspended in dry CH_2Cl_2 (10 mL) and were processed as described for **5** to give 208 mg (45%) of **24** as a colourless syrup; R_f 0.54 (1:1 *n*-hexane–EtOAc); $[\alpha]_D^{20}$ −8.3 (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.40–7.23 (m, 10H, H-Ar), 6.93 (s, 1H, C*H*Ph$_2$), 5.51 (s, 1H, H-12), 5.29–5.18 (m, 2H, H-3′, H-4′), 5.06 (t, 1H, $J_{2',3'}$ 8.6 Hz, H-2′), 4.59 (d, 1H, $J_{1',2'}$ 7.8 Hz, H-1′), 4.01 (d, 1H, $J_{4',5'}$ 9.3 Hz, H-5′), 3.76 (s, 3H, 6′-OCH_3), 3.15–3.10 (m, 1H, H-3), 2.81–2.77 (br d, 1H, *J* 13.4 Hz, H-1), 2.29 (s, 1H, H-9), 2.10–1.78 (m, 16H, 3 × Ac, H-2a, H-2b, H-15a, H-16a, H-18, H-19a, H-21a), 1.69–1.50 (m, 3H, H-6a, H-7a, H-19b), 1.46–1.13 (m, 6H, H-6b, H-7b, H-15b, H-21b, H-22a, H-22b), 1.34 (s, 3H, CH_3-27), 1.17, 1.16 and 1.08 (3s, 9H, CH_3-29, CH_3-25, CH_3-26), 0.92 (s, 3H, CH_3-23), 1.05–0.88 (m, 2H, H-16b, H-1b), 0.76 (s, 3H, CH_3-28), 0.66 (s, 3H, CH_3-24) and 0.68 (br d, 1H, H-5).^{13}C NMR ($CDCl_3$): δ 199.86 (C-11), 175.18 (C-30), 171.13 (C-6′), 170.28, 169.65, 169.62, 167.18, 166.65 (*C*OCH_3, C-13), 140.07 (C-arom.), 128.64, 128.53, 128.46, 128.15, 127.84, 127.26 (C-arom., C-12), 102.82 (C-1′), 90.46 (C-3), 76.64 (*C*HPh$_2$), 72.45 (C-3′), 72.21 (C-5′), 71.51 (C-2′), 69.48 (C-4′), 61.72 (C-9), 55.19 (C-5), 52.86 (6′-OMe), 48.02 (C-18), 45.29 (C-14), 43.99 (C-20), 43.10 (C-8), 41.11 (C-19), 39.21 (C-4), 39.08 (C-1), 37.74 (C-22), 36.76 (C-10), 32.73 (C-7), 31.73 (C-17), 31.14 (C-21), 28.28 (C-29), 28.24 (C-28), 27.71 (C-23), 26.44 (C-16), 26.37 (C-15), 25.63 (C-2), 23.31 (C-27), 20.81, 20.66, 20.59 (*C*H_3CO), 18.65 (C-26), 17.36 (C-6), 16.35 (C-24), 16.31 (C-25). ESI-TOFMS: *m/z* = 953.4869 $[M+H]^+$; calcd 953.5051.

3.5.10. Allyl 3-*O*-[methyl (2,3,4-tri-*O*-acetyl-β-D-glucopyranosyluronate)]-18-β-glycyrrhetinate (25)

Bromide **16** (250 mg, 0.605 mmol), acceptor **11** (103 mg, 0.202 mmol), silver zeolite (~500 mg) and powdered 4 Å molecular sieves (~200 mg) were suspended in dry CH_2Cl_2 (5 mL) and treated

as described for **5** to give 92 mg (55%) of **25** as colourless syrup; R_f 0.57 (3:2 *n*-hexane–EtOAc); $[\alpha]_D^{20}$ +119 (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 5.92 (ddd, 1H, CH_2–C*H*=CH_2), 5.64 (s, 1H, H-12), 5.36–5.18 (m, 4H, CH_2–CH=C*H*$_2$, H-4′, H-3′), 5.05 (dd, 1H, $J_{4',5'}$ 8.0, $J_{2',3'}$ 8.8 Hz, H-2′), 4.65–4.54 (m, 3H, $J_{1',2'}$ 8.0 Hz, H-1′, OCH_2), 4.02 (d, 1H, $J_{4',5'}$ 9.6 Hz, H-5′), 3.75 (s, 3H, OCH_3), 3.13 (dd, 1H, *J* 7.6, *J* 8.8 Hz, H-3), 2.79 (br d, 1H, *J* 13.6 Hz, H-3a), 2.31 (s, 1H, H-9), 2.13–1.78 (m, 16H, 3 × Ac, H-2a, H-2b, H-15a, H-16a, H-18, H-19a, H-21a), 1.69–1.50 (m, 3H, H-6a, H-7a, H-19b), 1.46–1.13 (m, 6H, H-6b, H-7b, H-15b, H-21b, H-22a, H-22b), 1.35 (s, 3H, CH_3-27), 1.17, 1.12 and 1.11 (3s, 9H, C*H*$_3$-29, C*H*$_3$-25, C*H*$_3$-26), 0.93 (s, 3H, CH_3-23), 1.05–0.88 (m, 2H, H-16b, H-1b), 0.80 (s, 3H, C*H*$_3$-28), 0.77 (s, 3H, C*H*$_3$-24) and 0.69 (br d, 1H, H-5); ^{13}C NMR ($CDCl_3$): δ 199.95 (C-11), 175.97 (C-30), 171.05 (6′-C), 170.18, 169.28, 169.08, 168.97, 167.15 (*C*OCH_3, C-13), 132.18 (*C*H=CH_2), 128.50 (C-12), 118.38 (CH=*C*H_2), 102.78 (C-1′), 90.42 (C-3), 72.38 (C-5′), 72.17 (C-3′), 71.46 (C-2′), 69.46 (C-4′), 65.00 (O*C*H_2), 61.72 (C-9), 55.15 (C-5), 52.81 (6′- OCH_3), 48.25 (C-18), 45.32 (C-14), 43.96 (C-20), 43.12 (C-8), 41.05 (C-19), 39.17 (C-4), 38.99 (C-1), 37.67 (C-22), 36.74 (C-10), 32.68 (C-7), 31.78 (C-17), 31.10 (C-21), 28.47 (C-29), 28.32 (C-28), 27.68 (C-23), 26.43 (C-16), 26.36 (C-15), 25.58 (C-2), 23.33 (C-27), 20.76, 20.59, 20.48, 20.42 (*C*H_3CO), 18.63 (C-26), 17.32 (C-6), 16.32 and 16.28 (C-24, C-25). ESI-TOFMS: *m/z* = 827.4896 $[M+H]^+$; calcd 827.4581.

3.5.11. Benzyl 3-*O*-[methyl (2,3,4-tri-*O*-acetyl-β-D-glucopyranosyluronate)]-18-β-glycyrrhetinate (26)

Bromide **16** (250 mg, 0.605 mmol), acceptor **12** (113 mg, 0.202 mmol), silver zeolite (~500 mg) and powdered 4 Å molecular sieves (~200 mg) were suspended in dry CH_2Cl_2 (5 mL) and were processed as described for **5** to furnish 95 mg (54%) of **26** as a colourless solid; R_f 0.43 (3:2 *n*-hexane–EtOAc), $[\alpha]_D^{20}$ −59.7 (*c* 0.35, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40–7.31 (m, 5H, H-Ar), 5.54 (s, 1H, H-12), 5.28–5.07 (m, 4H, H-3′, H-4′, C*H*$_2$Ph), 5.05 (dd, 1H, $J_{3',2'}$ 9.2 Hz, H-2′), 4.59 (d, 1H, $J_{1',2'}$ 7.6 Hz, H-1′), 4.01 (d, 1H, $J_{4',5'}$ 9.6 Hz, H-5′), 3.75 (s, 3H, OCH_3,), 3.11 (dd, 1H, *J* 6.4, *J* 9.9 Hz, H-3), 2.79 (ddd, 1H, *J* 13.6 Hz, H-1a), 2.28 (s, 1H, H-9), 2.13–1.76 (m, 16H, 3 × Ac, H-2a, H-2b, H-15a, H-16a, H-18, H-19a, H-21a), 1.69–1.50 (m, 3H, H-6a, H-7a, H-19b), 1.46–1.13 (m, 6H, H-6b, H-7b, H-15b, H-21b, H-22a, H-22b), 1.33 (s, 3H, CH_3-27), 1.18, 1.16 and 1.14 (3s, 9H, C*H*$_3$-29, C*H*$_3$-25, C*H*$_3$-26), 0.92 (s, 3H, CH_3-23), 1.05–0.88 (m, 2H, H-16b, H-1b), 0.76 (s, 3H, C*H*$_3$-24), 0.73 (s, 3H, C*H*$_3$-28) and 0.69 (br d, 1H, H-5); ^{13}C NMR ($CDCl_3$): δ 199.92 (C-11), 176.16 (C-30), 170.26 (C-6′), 169.32, 169.00, 168.92, 167.18 (*C*OCH_3, C-13), 136.10 (C-arom.), 128.64, 128.53, 128.46, 128.15, 127.84, 127.26 (C-arom., C-12), 102.82 (C-1′), 90.47 (C-3), 76.72 (*C*HPh_2), 72.44 (C-5′), 72.20 (C-3′), 71.49 (C-2′), 69.48 (C-4′), 66.22 (*C*H_2Ph), 61.72 (C-9), 55.19 (C-5), 52.86 (OMe), 48.17 (C-18), 45.31 (C-14), 44.31 (C-20), 43.10 (C-8), 41.06 (C-19), 39.20 (C-4), 39.04 (C-1), 37.62 (C-22), 36.75 (C-10), 32.70 (C-7), 31.75 (C-17), 31.15 (C-21), 28.39 (C-29), 28.28 (C-28), 27.71 (C-23), 26.44 (C-16), 26.37 (C-15), 25.60 (C-2), 23.30 (C-27), 20.67, 20.64, 20.52 (*C*H_3CO), 18.65 (C-26), 17.36 (C-6), 16.35 and 16.31 (C-24, C-25). ESI-TOFMS: *m/z* = 877.4055 $[M+H]^+$; calcd 877.4738.

3.6. Methyl 3-*O*-(methyl β-D-glucopyranosyluronate)-18-β-glycyrrhetinate (27)

To a stirred solution of **23** (92 mg, 0.115 mmol) in dry MeOH (5 mL) 0.1 M NaOMe solution (0.9 mL) was added dropwise under ice cooling. The temperature of the reaction was raised to rt and the reaction mixture was stirred for 3 h. The solution was neutralized by the addition of DOWEX-50 H^+ resin, filtered and the filtrate was concentrated in vacuo to afford **27** (73 mg, 93%) as off-white powder; R_f 0.67 (5:1 EtOAc–MeOH); $[\alpha]_D^{20}$ +63.4 (*c* 0.33, MeOH); ^1H NMR (CD_3OD–$CDCl_3$ ≈ 5:1, 400 MHz): δ 5.56 (s, 1H, H-12), 4.38 (d, 1H, $J_{1',2'}$ 7.7 Hz, H-1′), 3.82 (d, 1H, $J_{4',5'}$ 9.7 Hz, H-5′), 3.77 and 3.69 (2s, 6H, 6′-OCH_3, 30-OCH_3), 3.52 (t, 1H, $J_{3',4'}$ 9.3 Hz, H-4′), 3.35 (dd, 1H, $J_{3',2'}$ 9.1 Hz, H-3′), 3.23 (dd, 1H, H-2′), 3.17 (br dd, 1H, *J* 5.7, *J* 10.6 Hz, H-3), 2.68 (ddd, 1H, *J* 13.3 Hz, H-1a), 2.44 (s, 1H, H-9), 2.12 (dd, 1H, *J* 4.2, *J* 13.6 Hz, H-18), 2.00–0.90 (m, 17H, H-2a, H-2b, H-15a, H-16a, H-19a, H-21a, H-6a, H-7a, H-19b, H-6b, H-7b, H-15b, H-21b, H-22a, H-22b, H-16b, H-1b), 1.41 (s, 3H, CH_3-27), 1.14, 1.13 and 1.06 (3s, 12H, C*H*$_3$-29, C*H*$_3$-25, C*H*$_3$-26, C*H*$_3$-23), 0.87 (s, 3H, C*H*$_3$-24), 0.82 (s, 3H, C*H*$_3$-28) and 0.79 (br d, 1H, H-5); ^{13}C NMR (CD_3OD–$CDCl_3$ ≈ 5:1): δ 202.67 (C-11), 178.67 (C-30), 177.04 (C-6′), 172.51 (C-13), 129.02 (C-12), 106.75 (C-1′), 90.31 (C-3), 78.09 (C-5′), 76.62 (C-3′), 75.58 (C-2′), 73.80 (C-4′), 63.20 (C-9), 56.46 (C-5), 52.34 (OMe), 49.94 (OMe), 48.40 (C-18), 46.80 (C-8), 45.35 (C-20), 44.63 (C-14), 42.34 (C-19), 40.61 (C-4), 40.30 (C-1), 39.03 (C-22), 38.11 (C-10), 33.86 (C-7), 33.00 (C-17), 32.03 (C-21), 29.17 (C-28), 28.53 (C-29), 28.47 (C-23), 27.58 (C-15), 27.40 (C-16), 26.89 (C-2), 23.83 (C-27), 19.31 (C-26), 18.46 (C-6), 17.03 (d.i., C-24, C-25). ESI-TOFMS: *m/z* = 675.4529 $[M+H]^+$; calcd 675.4108.

3.7. Methyl 3-*O*-(β-D-glucopyranosyluronic acid)-18-β-glycyrrhetinate (28)

A solution of **27** (25 mg, 0.037 mmol) in MeOH (2 mL) was treated with 0.2 M methanolic NaOH solution (2 mL) at 0 °C for 3 h. The solution was treated with DOWEX-50 H^+ resin and was filtered. The filtrate was concentrated and lyophilized from dioxane to afford **28** (22 mg, 91%) as off-white powder; R_f 0.32 (10:1 MeCN–H_2O); $[\alpha]_D^{20}$ −66.7 (*c* 0.3, MeOH); ^1H NMR (CD_3OD, 300 MHz): δ 5.56 (s, 1H, H-12), 4.34 (d, 1H, $J_{1',2'}$ 7.7 Hz, H-1′), 3.69 (s, 3H, OCH_3), 3.56–3.19 (m, 5H, H-3′, H-4′, H-5′, H-2′, H-3), 2.69 (ddd, 1H, *J* 13.5 Hz, H-1a), 2.45 (s, 1H, H-9), 2.12 (dd, 1H, *J* 4.5, *J* 13.6 Hz, H-18), 2.00–0.90 (m, 17H, H-2a, H-2b, H-15a, H-16a, H-19a, H-21a, H-6a, H-7a, H-19b, H-6b, H-7b, H-15b, H-21b, H-22a, H-22b, H-16b, H-1b), 1.41 (s, 3H, CH_3-27), 1.21, 1.15 and 1.14 (3s, 9H, C*H*$_3$-29, C*H*$_3$-25, C*H*$_3$-26), 1.07 (s, 3H, C*H*$_3$-23), 0.82 (s, 3H, C*H*$_3$-24), 0.87 (s, 3H, C*H*$_3$-28) and 0.79 (br d, 1H, H-5); ^{13}C NMR (CD_3OD): δ 202.63 (C-11), 178.66 (C-30), 176.67 (C-6′), 172.45 (C-13), 129.03 (C-12), 106.76 (C-1′), 90.29 (C-3), 78.085 (C-5′), 76.66 (C-3′), 75.58 (C-2′), 73.79 (C-4′), 63.21 (C-9), 56.48 (C-5), 52.34 (OCH_3), 48.19 (C-18), 46.80 (C-8), 45.35 (C-20), 44.65 (C-14), 42.37 (C-19), 40.61 (C-4), 40.31 (C-1), 39.04 (C-22), 38.13 (C-10), 33.88 (C-7), 33.00 (C-17), 32.06 (C-21), 29.18 (C-28), 28.54 and 28.48 (C-29, C-23), 27.61 (C-15), 27.42 (C-16), 26.91 (C-2), 23.85 (C-27), 19.35 (C-26), 18.47 (C-6), and 17.03 (d.i., C-24, C-25). ESI-TOFMS: *m/z* = 661.4556 $[M+H]^+$; calcd 661.3951.

3.8. 3-*O*-(Methyl β-D-glucopyranosyluronate)-18-β-glycyrrhetinic acid (29)

A solution of **24** (90 mg, 0.103 mmol) in a mixture of dry MeOH (5 mL) and EtOAc (2 mL) was hydrogenated in the presence of 10% Pd–C (10 mg) for 12 h at atmospheric pressure at rt. After completion of the reaction, the catalyst was removed by filtration through a pad of Celite® and washed with MeOH. The combined filtrates were concentrated to give a colourless syrup (75 mg, 93%) which was used without any further purification. The syrup was dissolved in dry MeOH (4 mL) and 0.1 M NaOMe solution (1 mL) was added dropwise under ice cooling. The reaction mixture was stirred at rt for 5 h until the deacylation was complete. The solution was treated with DOWEX-50 H^+ resin, filtered and the resin was washed with MeOH. The filtrate was concentrated and the residue was lyophilized from dioxane to afford **29** as a white amorphous solid (61 mg, 97%); R_f 0.78 (1:1 EtOAc–MeOH); $[\alpha]_D^{20}$

+72 (*c* 0.27, MeOH); ^{1}H NMR (CD_3OD–$CDCl_3 \approx 5{:}1$, 400 MHz): δ 5.62 (s, 1H, H-12), 4.42 (d, 1H, $J_{1',2'}$ 7.6 Hz, H-1′), 3.83 (d, 1H, $J_{4',5'}$ 9.7 Hz, H-5′), 3.79 (s, 3H, OCH_3), 3.56 (t, 1H, $J_{3',4'}$ 9.3 Hz, H-4′), 3.39 (t, 1H, $J_{3',2'}$ 9.2 Hz, H-3′), 3.30 (dd, 1H, H-2′), 3.19 (dd, 1H, *J* 5.6, *J* 10.8 Hz, H-3), 2.71 (ddd, 1H, *J* 13.6 Hz, H-1a), 2.42 (s, 1H, H-9), 2.21 (dd, 1H, *J* 13.2, *J* 4.0 Hz, H-18), 2.16–0.90 (m, 17H, H-2a, H-2b, H-15a, H-16a, H-19a, H-21a, H-6a, H-7a, H-19b, H-6b, H-7b, H-15b, H-21b, H-22a, H-22b, H-16b, H-1b), 1.43 (s, 3H, CH_3-27), 1.19 and 1.16 (3s, 9H, CH_3-29, CH_3-25, CH_3-26), 1.10 (s, 3H, CH_3-23), 0.86 (s, 3H, CH_3-24), 0.83 (s, 3H, CH_3-28) and 0.81 (br d, 1H, H-5); ^{13}C NMR (CD_3OD–$CDCl_3 \approx 5{:}1$): δ 202.61 (C-11), 180.41 (C-30), 172.80 (C-6′), 171.36 (C-13), 128.94 (C-12), 107.02 (C-1′), 90.75 (C-3), 77.53 (C-3′), 76.66 (C-5′), 75.29 (C-2′), 73.18 (C-4′), 63.12 (C-9), 56.40 (C-5), 52.78 (OCH_3), 49.85 (C-18), 46.75 (C-8), 44.91 (C-20), 44.62 (C-14), 42.44 (C-19), 40.52 (C-4), 40.19 (C-1), 39.03 (C-22), 38.07 (C-10), 33.80 (C-7), 32.98 (C-17), 32.02 (C-21), 29.19 (C-28), 28.76 (C-29), 28.8 (C-23), 27.60 (C-15), 27.40 (C-16), 26.98 (C-2), 23.82 (C-27), 19.29 (C-26), 18.43 (C-6), 16.96 and 16.93 (C-24, C-25). ESI-TOFMS: *m/z* = 661.4347 $[M+H]^+$; calcd 661.3951.

3.9. 3-*O*-(β-D-Glucopyranosyluronic acid)-18-β-glycyrrhetinic acid (30)

A solution of **29** (33 mg, 0.05 mmol) in dry MeOH (3 mL) was stirred with 0.2 M methanolic NaOH (2 mL) for 3 h at rt. The solution was treated with DOWEX-50 H^+ cation-exchange resin. The resin was filtered off and the filtrate was concentrated and finally lyophilized to afford **30** as white amorphous powder (30 mg, 91%); R_f 0.44 (1:2 EtOAc–MeOH); $[\alpha]_D^{20}$ −40.6 (*c* 0.26, MeOH); ^{1}H NMR (CD_3OD–$CDCl_3 \approx 5{:}1$, 400 MHz): δ 5.65 (s, 1H, H-12), 4.38 (d, 1H, $J_{1',2'}$ 7.6 Hz, H-1′), 3.81 (d, 1H, $J_{4',5'}$ 9.6 Hz, H-5′), 3.54 (t, 1H, $J_{3',4'}$ 9.6 Hz, H-4′), 3.67 (t, 1H, $J_{3',2'}$ 9.2 Hz, H-3′), 3.27 (dd, 1H, H-2′), 3.22–3.16 (m, 1H, H-3), 2.69 (ddd, 1H, *J* 13.6 Hz, H-1a), 2.43 (s, 1H, H-9), 2.21 (dd, 1H, *J* 13.2, *J* 4.0 Hz, H-18), 2.16–0.90 (m, 17H, H-2a, H-2b, H-15a, H-16a, H-19a, H-21a, H-6a, H-7a, H-19b, H-6b, H-7b, H-15b, H-21b, H-22a, H-22b, H-16b, H-1b), 1.42 (s, 3H, CH_3-27), 1.18 and 1.14 (3s, 9H, CH_3-29, CH_3-25, CH_3-26), 1.07 (s, 3H, CH_3-23), 0.87 (s, 3H, CH_3-24), 0.84 (s, 3H, CH_3-28) and 0.78 (br d, 1H, H-5); ^{13}C NMR (CD_3OD–$CDCl_3 \approx 5{:}1$,): δ 202.60 (C-11), 180.26 (C-30), 172.59 (C-6′), 171.18 (C-13), 128.84 (C-12), 106.83 (C-1′), 90.66 (C-3), 77.45 (C-3′), 76.42 (C-5′), 75.02 (C-2′), 72.93 (C-4′), 62.96 (C-9), 56.27 (C-5), 46.60 (C-8), 44.73 (C-20), 44.43 (C-14), 42.23 (C-19), 40.38 (C-4), 40.09 (C-1), 38.83 (C-22), 37.89 (C-10), 33.67 (C-7), 32.82 (C-17), 31.88 (C-21), 29.14 (C-28), 28.76 (C-29), 28.31 (C-23), 27.44 (C-15), 27.26 (C-16), 26.82 (C-2), 23.83 (C-27), 19.34 (C-26), 18.27 (C-6), 16.92 and 16.86 (C-24, C-25). ESI-TOFMS: *m/z* = 647.3355 $[M+H]^+$; calcd 647.3795.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2009.04.015.

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