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Note

Synthesis of steroidal glycosides bearing the disaccharide moiety of OSW-1 and their antitumor activities

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Abstract

Nine glycosides bearing the disaccharide of OSW-1, namely 2-*O*-(4-methoxybenzoyl)-β-D-xylopyranosyl-(1→3)-2-*O*-acetyl-α-L-arabinopyranosides, were synthesized, and their antitumor activities were tested. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: 2-*O*-(4-Methoxybenzoyl)-β-D-xylopyranosyl-(1→3)-2-*O*-acetyl-α-L-arabinopyranosides; Synthesis; Antitumor

OSW-1 is the major component of a group of cholestane saponins isolated by Sashida et al. from the bulbs of *Ornithogalum saudersiae*, a species of the lily family.[1] In vitro assays showed that OSW-1 is extremely toxic to a broad spectrum of malignant tumor cells. Its IC_{50} is between 0.1 and 0.7 nM, which is about 10–100 times more potent than those of the traditional, clinically applied anticancer agents, such as mitomycin C, adriamycin, cisplatin, camptothecin, and taxol.[1b] Removal of the acetyl (Ac) and the 4-methoxybenzoyl (MBz) groups on the disaccharide moiety diminished the cytotoxicity 1000-fold.[1b] This result implies that the disaccharide moiety is essential to the antitumor activities of OSW-1. We have therefore synthesized glycosides bearing the acylated disaccharide of OSW-1 and have evaluated their antitumor activities.[2] Of these, the glycosides of simple alcohols, e.g., benzyl and nonyl alcohol, did not show any cytotoxic activity, and the glycosides of steroids showed only marginal cytotoxic activities against tumor cells. Recognizing that all the previously synthesized steroidal glycosides have the disaccharide attached at their 3-OH on the A ring, while in OSW-1, the disaccharide is attached at 16-OH on the D ring, we thought that the steroidal glycosides with the disaccharide of OSW-1 attached at a position at or close to the D ring (on the C ring or on the C_{17} side chain) would probably show strong cytotoxic activities against tumor cells. Here we reported the synthesis of such glycosides and their antitumor activities (Scheme 1).

We accomplished the first total synthesis of OSW-1 in 1998.[3] Recently, Jin and Yu reported the second synthetic route to this molecule.[4] Both routes completed the target

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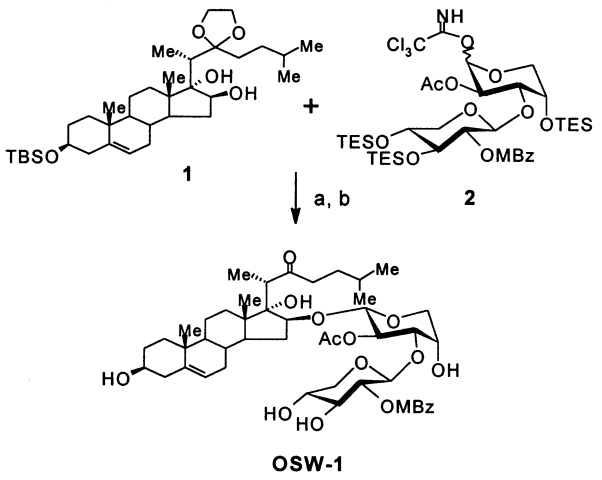
molecule with the coupling of aglycone **1** with a disaccharide imidate (**2** or its 3′,4′-di-*O*-*p*-methoxylbenzyl analog) and a similar protection strategy. In the previous synthesis of glycosides bearing the disaccharide of OSW-1, we found that coupling with the corresponding phenyl thio-disaccharide was not as effective as with the disaccharide imidate donor **2**, and the *tert*-butyldimethylsilyl (TBS) and triethylsilyl (TES) protective groups could be removed cleanly in 70% aqueous HOAc at 65 °C (Fig. 1).[2]



Scheme 1. Reagents and conditions: (a) TMSOTf (0.05 equiv), 4Å MS, CH_2Cl_2, −20 °C, 45 min, 69%. (b) $Pd(CN)_2Cl_2$, 20:1 acetone–water (v/v), , rt, overnight, 79%.

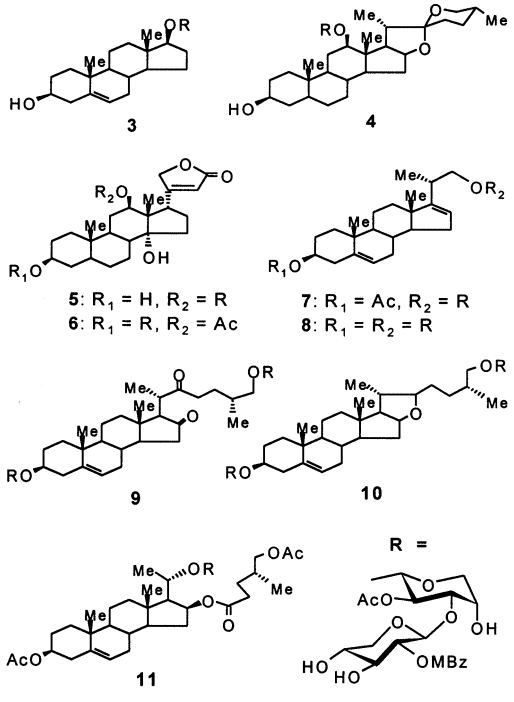


Fig. 1. Saponins bearing the OSW-1 disaccharide.

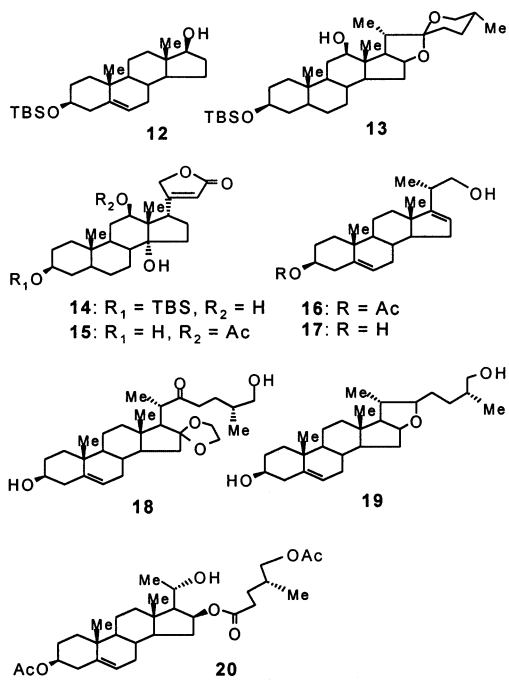


Fig. 2. Aglycones.

Employing similar coupling and deprotection conditions to these used in the previous synthesis of the glycosides bearing the OSW-1 disaccharide,[2] we synthesized compounds **3**–**11**. Aglycones **12**–**20** were either known compounds (**12**,[5] **13**,[6] **15**[7] and **19**[8]) or prepared in a few steps from the commercially available materials (Fig. 2).[9] Coupling of **12**, **13**, **16** and **20**, with one hydroxyl group free, with disaccharide imidate **2** (1.2 equiv) under the promotion of a catalytic amount of TMSOTf (0.02 equiv) gave the corresponding coupling products **21**, **22**, **25** and **29** in 51–76% yields. Of these, glycosylation of the 12-β-OH (**13**) led to relatively lower yields of the products, reflecting the steric hindrance of this position effected by the angular 19-methyl group. Coupling of digoxigenin derivatives **14** and **15** with imidate **2** (1.2 equiv) gave only the mono-glycosylated products **23** (51%) and **24** (74%), respectively; the hindered 14-α-OH remained intact. Coupling of diols **17**–**19** with imidate **2** (2.6 equiv) gave the corresponding bis-glycosylated products (**21**–**29**) in ~50% yields, equal to a per glycosylation of 70% yield. Treatment of the resulting coupling products (**21**–**29**)[9] with 70% aqueous HOAc at 65 °C afforded the final

Table 1
Synthesis of the glycosides **3**–**11**

Entry	Acceptor	Protected glycoside (yield %) [a]	Deprotected products (yield %) [a]
1	**12**	**21** (69)	**3** (94)
2	**13**	**22** (51)	**4** (92)
3	**14**	**23** (51)	**5** (93)
4	**15**	**24** (74)	**6** (93)
5	**16**	**25** (76)	**7** (95)
6	**17**	**26** (54)	**8** (96)
7	**18**	**27** (49)	**9** (94)
8	**19**	**28** (50)	**10** (96)
9	**20**	**29** (68)	**11** (95)

[a] Isolated yields.

glycosides (**3**–**11**) in excellent yields (> 92%). It is worth noting that not only the six TES groups but also the C_{16} ethylene glycol acetal on **27** were cleanly removed under these conditions. While all the acyl groups remained intact (Table 1, Scheme 2).

The in vitro antitumor activities of the resulting glycosides **3**–**11** against mouse leukemia P388 and human lung adenocarcinoma A-549 cell lines were tested using the MTT assay.[10] The results are listed in Table 2. In general, the present compounds showed stronger activities than those of the saponins bearing the disaccharide of OSW-1 at the C-3 position on the A ring,[2] with up to 100% growth inhibition at 10^{-5} M. However, they essentially lost their activity at 10^{-6} M. This activity is much less potent than that of OSW-1, which has been reported to have an IC_{50} around 10^{-4} μM.[1b] These results demonstrate that the aglycone is also essential to the antitumor activities of OSW-1. Synthesis of the compounds, structurally more closely related to OSW-1, and evaluation of their antitumor activities are our current interest, and the results of additional work will be reported in due course.

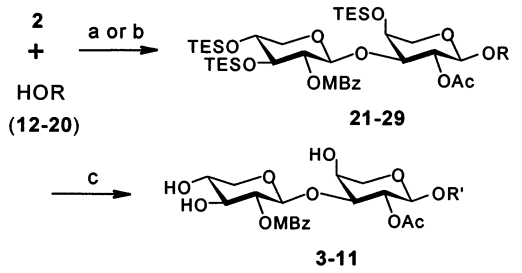
1. Experimental

General methods.—See Ref. 11.

Typical procedure for the glycosylation with donor **2** *to prepare the protected glycosides* **21**–**29**.—A solution of **2** (200 mg, 0.208 mmol), **18** (37 mg, 0.078 mmol), and 4Å MS (200 mg) in dry CH_2Cl_2 (7 mL) was stirred at rt for 20 min, and then cooled to −20 °C. To the above mixture, a solution of TMSOTf (0.03 M, 0.27 mL) in CH_2Cl_2 was added. After being stirred for another 50 min, the reaction was quenched with Et_3N and filtered. The filtrates were concentrated in vacuo to give a residue, which was purified by silica-gel column chromatography (6:1 then 4:1 petroleum ether–EtOAc) to give **27** (78 mg, 49%) as a white foam.

Typical procedure for the deprotection of glycosides (**21**–**29**) *to prepare glycosides* (**3**–**11**).—A solution of the protected glycosides **26** (47 mg, 0.025 mmol) in AcOH (1.4 mL) and water (0.6 mL) was warmed to 65 °C and stirred for 3 h. The solvent was then removed in vacuo. The residue was purified by flash-column chromatography (15:1 CH_2Cl_2–CH_3OH) to afford **8** (29 mg, 96%) as a white amorphous solid.

3β-Hydroxyandrost-5-en-17β-yl 2-O-(4-methoxybenzoyl)-β-D-xylopyranosyl-(1→3)-2-O-acetyl-α-L-arabinopyranoside (**3**).—White amorphous solid; R_f 0.40 (15:1 CH_2Cl_2–



Scheme 2. Reagents and conditions: (a) **2** (1.2 equiv), acceptor (**12**–**16**, **20**) (1.0 equiv), TMSOTf (0.02 equiv), 4Å MS, CH_2Cl_2, −20 °C, 30 min. (b) **2** (2.6 equiv), acceptor (**17**–**19**) (1.0 equiv), TMSOTf (0.05 equiv), 4Å MS, CH_2Cl_2, −20 °C, 50 min. (c) 70% aq HOAc, 65 °C, 3 h.

Table 2
Growth inhibition rate (%) of glycosides **3**–**11** on tumor cells (P388 and A-549)

Compound	P388			A-549		
	10^{-4} M	10^{-5} M	10^{-6} M	10^{-4} M	10^{-5} M	10^{-6} M
3	99.6	41.3	18.8	98.2	19.3	0
4	100.0	39.6	5.7	87.8	10.2	0
5	98.1	0	3.8	79.6	0	0
6	98.1	98.1	7.5	89.8	71.4	0
7	100.0	30.2	3.8	89.8	24.5	4.1
8	100.0	100.0	0	98.2	57.0	0
9	100.0	96.9	15.9	98.5	39.7	0
10	83.8	100.0	3.7	98.7	88.7	0
11	100.0	100.0	0	98.1	0	0

CH_3OH); $[\alpha]_D^{15}$ $-0.92°$ (*c* 1.41, $CHCl_3$); ^1H NMR (300 MHz, C_5D_5N): δ 8.21 (d, 2 H, *J* 9.1 Hz), 6.97 (d, 2 H, *J* 9.1 Hz), 5.78 (dd, 1 H, *J* 9.9, 7.7 Hz), 5.60 (t-like, 1 H, *J* 9.0, 7.9 Hz), 5.32 (d, 1 H, *J* 4.4 Hz), 5.09 (d, 1 H, *J* 7.9 Hz), 4.56 (d, 1 H, *J* 7.7 Hz), 4.42 (brs., 1 H), 4.28–4.14 (m, 3 H), 4.08 (dd, 1 H, *J* 9.9, 3.0 Hz), 4.14–4.04 (m, 1 H), 3.82–3.72 (m, 4 H), 3.64 (m, 3 H), 1.94 (s, 3 H), 0.97 (s, 3 H), 0.70 (m, 3 H). ^{13}C NMR (75 MHz, C_5D_5N): δ 169.1, 165.5, 163.8, 141.9, 132.4, 121.0, 114.0, 103.7, 103.2, 89.4, 81.5, 76.4, 75.3, 69.0, 67.1, 66.7, 64.3, 55.4, 51.1, 50.6, 43.5, 42.9, 37.9, 37.5, 36.9, 32.6, 31.9, 31.7, 29.5, 29.2, 24.0, 23.6, 20.9, 20.8, 19.6, 14.3, 11.6. ESIMS (*m*/*z*): 754 $[M + Na]^+$, 1116 $[1.5\ M + Na]^+$, 1484 $[2\ M + Na]^+$, 1848 $[2.5\ M + Na]^+$. Anal. Calcd for $C_{39}H_{54}O_{13}\cdot 1.5\ H_2O$: C, 61.81; H, 7.58. Found: C, 61.97; H, 7.39.

3β-Hydroxy-rocogenin-12β-yl 2-O-(4-methoxybenzoyl)-β-D-xylopyranosyl-(1→3)-2-O-acetyl-α-L-arabinopyranoside (**4**).—White amorphous solid; R_f 0.48 (15:1 CH_2Cl_2–CH_3OH); $[\alpha]_D^{15}$ $+11.9°$ (*c* 0.74, $CHCl_3$). ^1H NMR (300 MHz, C_5D_5N): δ 7.96 (d, 2 H, *J* 8.2 Hz), 6.86 (d, 2 H, *J* 8.2 Hz), 5.04 (m, 2 H), 4.69 (d, 1 H, *J* 5.8 Hz), 4.34 (d, 1 H, *J* 7.1 Hz), 4.28 (d, 1 H, *J* 7.7 Hz), 4.18–3.92 (m, 3 H), 3.86 (s, 3 H), 3.78–3.50 (m, 4 H), 3.50–3.24 (m, 6 H), 2.08 (s, 3 H), 1.02 (d, 3 H, *J* 6.9 Hz), 0.83 (s, 3 H), 0.77 (d, 3 H, *J* 5.5 Hz), 0.62 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 165.8, 163.8, 132.1, 121.6, 113.7, 109.5, 101.9, 97.1, 82.8, 80.9, 80.4, 74.2, 73.6, 71.1, 70.7, 69.6, 68.2, 66.8, 65.2, 64.8, 61.3, 55.5, 54.8, 52.7, 45.1, 44.8, 42.4, 38.0, 37.0, 35.6, 34.2, 31.8, 31.3, 30.2, 29.7, 28.8, 25.0, 20.3, 17.1, 13.5, 12.3, 11.0. ESIMS (*m*/*z*): 874 $[M + 1]$, 896 $[M + Na]^+$, 1329 $[1.5\ M + Na]^+$, 1769 $[2\ M + Na]^+$. Anal. Calcd for $C_{47}H_{68}O_{15}$: C, 62.09; H, 7.98. Found: C, 62.08; H, 7.96.

Digoxigenin-12β-yl 2-O-(4-methoxybenzoyl)-β-D-xylopyranosyl-(1→3)-2-O-acetyl-α-L-arabinopyranoside (**5**).—A white amorphous solid; R_f 0.44 (15:1 CH_2Cl_2–CH_3OH); $[\alpha]_D^{15}$ $+19.1°$ (*c* 0.42, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): 7.97 (d, 2 H, *J* 8.2 Hz), 6.86 (d, 2 H, *J* 8.2 Hz), 5.84 (s, 1 H), 5.24 (s, 1 H), 5.12 (m, 3 H), 5.03 (d, 1 H, *J* 6.9 Hz), 4.76 (m, 1 H), 4.28 (m, 1 H), 4.20–3.68 (m, 7 H), 3.87 (s, 3 H), 3.58–3.34 (m, 3 H), 3.00 (t, 1 H, *J* 9.2 Hz), 2.56 (m, 2 H), 2.05 (s, 3 H), 0.94 (s, 3 H), 0.71 (s, 3 H). ESIMS (*m*/*z*): 835 $[M - \text{water} + Na]^+$. Anal. Calcd for $C_{43}H_{58}O_{16}\cdot 2\ H_2O$: C, 59.57; H, 7.20. Found: C, 59.69; H, 6.98.

12β-O-Acetyl-digoxigenin-3β-yl 2-O-(4-methoxybenzoyl)-β-D-xylopyranosyl-(1→3)-2-O-acetyl-α-L-arabinopyranoside (**6**).—A white amorphous solid; R_f 0.33 (15:1 CH_2Cl_2–CH_3OH); $[\alpha]_D^{15}$ $+20.8°$ (*c* 1.60, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.98 (d, 2 H, *J* 8.7 Hz), 6.86 (d, 2 H, *J* 8.7 Hz), 5.89 (s, 1 H), 5.30 (s, 1 H), 5.03 (m, 2 H), 4.84 (d, 1 H, *J* 17.6 Hz), 4.78–4.58 (m, 2 H), 4.25 (m, 1 H), 4.16–3.92 (m, 2 H), 3.92–3.60 (m, 4 H), 3.89 (s, 3 H), 3.54 (d, 1 H, *J* 5.0 Hz), 3.40–3.24 (m, 3 H), 2.95 (t, 1 H, *J* 8.9 Hz), 2.62–2.40 (m, 2 H), 2.07 (s, 3 H), 2.04 (s, 3 H), 0.92 (s, 3 H), 0.84 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.8, 170.7, 169.3, 165.8, 163.8, 151.6, 132.1, 121.7, 118.9, 117.3, 113.7, 82.3, 80.3, 74.3, 73.7, 73.3, 70.7, 69.6, 67.6, 64.7, 64.5, 60.4,

55.5, 53.5, 50.0, 37.2, 36.2, 35.8, 34.9, 34.4, 30.0, 29.6, 27.2, 26.3, 23.9, 23.2, 21.5, 21.0, 20.4, 14.1. ESIMS (*m*/*z*): 878 [M − water + Na]$^+$, 894 [M + Na]$^+$. Anal. Calcd for $C_{45}H_{60}O_{17}$: C, 61.92; H, 6.93. Found: C, 62.07; H, 7.12.

20α-Methyl-3β-O-acetyl-androst-5,16(17)-diene-22-yl 2-O-(4-methoxybenzoyl)-β-D-xylopyranosyl-(1→3)-2-O-acetyl-α-L-arabinopyranoside (**7**).—A white amorphous solid; R_f 0.27 (15:1 CH_2Cl_2–CH_3OH); $[\alpha]_D^{15}$ −43.6° (*c* 1.24, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (d, 2 H, *J* 8.2 Hz), 6.86 (d, 2 H, *J* 8.2 Hz), 5.38 (d, 1 H, *J* 6.1 Hz), 5.26 (brs., 1 H), 5.09 (t, 1 H, *J* 7.4 Hz), 5.02 (t, 1 H, *J* 6.6 Hz), 4.71 (d, 1 H, *J* 6.6 Hz), 4.60 (m, 1 H), 4.28 (d, 1 H, *J* 7.4 Hz), 4.18–3.94 (m, 3 H), 3.85 (s, 3 H), 3.90-3.68 (m, 4 H), 3.48 (d, 1 H, *J* 11.8 Hz), 3.38 (m, 1 H), 3.10 (t, 1 H, *J* 9.2 Hz), 2.33 (t-like, 4 H, *J* 7.4 Hz), 2.03 (s, 3 H), 1.67 (s, 3 H), 1.05 (s, 3 H), 0.91 (d, 3 H, *J* 6.6 Hz), 0.72 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 169.6, 165.9, 163.8, 157.6, 139.9, 132.1, 122.4, 122.1, 121.6, 113.7, 101.7, 100.9, 80.0, 74.4, 74.1, 73.9, 73.6, 70.3, 69.7, 67.2, 64.8, 64.1, 56.9, 55.5, 50.6, 47.0, 38.1, 36.9, 36.8, 34.8, 32.2, 31.6, 31.2, 30.5, 27.7, 31.4, 20.7, 20.4, 19.2, 18.6, 16.1. ESIMS (*m*/*z*): 836 [M + Na]$^+$, 1239 [1.5 M + Na]$^+$, 1649 [2 M + Na]$^+$. Anal. Calcd for $C_{44}H_{60}O_{14}$: C, 63.59; H, 7.52. Found: C, 63.41; H, 7.63.

20α-Methyl-androst-5,16(17)-diene-3β,22-yl bis(2-O-(4-methoxybenzoyl)-β-D-xylopyranosyl-(1→3)-2-O-acetyl-α-L-arabinopyranoside) (**8**).—A white amorphous solid; R_f 0.37 (7:1 CH_2Cl_2–CH_3OH); $[\alpha]_D^{13}$ +14.0° (*c* 0.75, CH_3OH). ^{1}H NMR (300 MHz, C_5D_5N): δ 8.01 (d, 4 H, *J* 8.8 Hz), 6.80 (d, 4 H, *J* 8.8 Hz), 5.65 (m, 2 H), 5.46 (t-like, 2 H, *J* 7.3 Hz), 5.27 (brs., 1 H), 5.19 (brs., 1 H), 4.94 (d, 2 H, *J* 7.7 Hz), 4.53 (d, 1 H, *J* 7.2 Hz), 4.41 (d, 1 H, *J* 7.7 Hz), 4.27 (brs., 2 H), 3.46 (s, 6 H), 3.17 (t-like, 1 H, *J* 9.6, 8.6 Hz), 1.64 (s, 6 H), 1.11 (d, 3 H, *J* 7.1 Hz), 0.65 (s, 3 H), 0.47 (s, 3 H). ESIMS (*m*/*z*): 1234 [M + Na]$^+$. Anal. Calcd for $C_{62}H_{82}O_{24}$·4.5 H_2O: C, 57.62; H, 7.10. Found: C, 57.61; H, 7.38.

16,22-Dioxocholest-3β,26-yl bis(2-O-(4-methoxybenzoyl)-β-D-xylopyranosyl-(1→3)-2-O-acetyl-α-L-arabinopyranoside) (**9**).—A white amorphous solid; R_f 0.42 (6:1 CH_2Cl_2–CH_3OH). $[\alpha]_D^{13}$ −45.6° (*c* 1.01, CH_3OH); ^{1}H NMR (300 MHz, C_5D_5N): δ 8.06 and 6.80 (AB, 8 H), 5.66 (m, 2 H), 5.46 (q-like, 2 H, *J* 8.2 Hz), 5.10 (brs., 1 H), 4.94 (t-like, 2 H, *J* 8.5, 8.2 Hz), 4.56 (d, 1 H, *J* 7.4 Hz), 4.36 (d, 1 H, *J* 7.4 Hz), 4.27 (br., 2 H), 3.47 (s, 3 H), 3.46 (s, 3 H), 3.20 (m, 1 H), 1.67 (s, 6 H), 0.77 (d, 3 H, *J* 5.5 Hz), 0.68 (d, 3 H, *J* 5.4 Hz), 0.67 (s, 3 H), 0.45 (s, 3 H). ESIMS (*m*/*z*): 678 [0.5 M + Na]$^+$, 1333 [M + Na]$^+$. Anal. Calcd for $C_{67}H_{90}O_{26}$·6.5 H_2O: C, 56.33; H, 7.26. Found: C, 56.17; H, 7.26.

Dihydrodiosgenin-3β,26-yl bis(2-O-(4-methoxybenzoyl)-β-D-xylopyranosyl-(1→3)-2-O-acetyl-α-L-arabinopyranoside) (**10**).—A white amorphous solid; R_f 0.40 (8:1 CH_2Cl_2–CH_3OH); $[\alpha]_D^{22}$ +12.7° (*c* 0.60, CH_3OH); ^{1}H NMR (300 MHz, C_5D_5N): δ 8.06 and 6.80 (AB, 8 H), 5.64 (m, 2 H), 5.46 (q-like, 2 H, *J* 7.7, 9.1, 7.3 Hz), 5.12 (brs., 1 H), 4.94 (t-like, 2 H, *J* 9.1, 8.0 Hz), 4.55 (d, 1 H, *J* 7.1 Hz), 4.36 (d, 1 H, *J* 7.4 Hz), 4.27 (brs., 2 H), 3.47 (s, 6 H), 3.19 (dd, 1 H, *J* 9.4, 5.5 Hz), 3.08 (m, 1 H), 1.66 (s, 3 H), 1.65 (s, 3 H), 0.72 (d, 3 H, *J* 6.6 Hz), 0.65 (s, 3 H), 0.64 (d, 3 H, *J* 6.9 Hz), 0.61 (s, 3 H). ESIMS (*m*/*z*): 672 [0.5 M + Na]$^+$, 1320 [M + Na]$^+$. Anal. Calcd for $C_{67}H_{91}O_{25}$·9 H_2O: C, 55.17; H, 7.53. Found: C, 55.13; H, 7.51.

3β-O-Acetyl-16β-O-(4(R)-methyl-5-O-acetylpentoyl)-pregnene-20α-yl 2-O-(4-methoxybenzoyl)-β-D-xylopyranosyl-(1→3)-2-O-acetyl-α-L-arabinopyranoside (**11**).—A white amorphous solid; R_f 0.33 (15:1 CH_2Cl_2–CH_3OH); $[\alpha]_D^{22}$ −48.6° (*c* 0.99, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (d, 2 H, *J* 8.8 Hz), 6.91 (d, 2 H, *J* 8.8 Hz), 5.34 (d, 1 H, *J* 4.4 Hz), 5.00 (m, 3 H), 4.71 (d, 1 H, *J* 6.7 Hz), 4.61 (m, 1 H), 4.33 (d, 1 H, *J* 7.0 Hz), 4.14 (dd, 1 H, *J* 11.8, 4.7 Hz), 4.10–3.94 (m, 3 H), 3.90 (dd, 2 H, *J* 11.4, 9.3 Hz), 2.09 (s, 3 H), 2.05 (s, 3 H), 1.80 (s, 3 H), 1.05 (s, 3 H), 0.96 (d, 3 H, *J* 8.0 Hz). ESIMS (*m*/*z*): 996 [M + Na]$^+$. Anal. Calcd for $C_{51}H_{72}O_{18}$·1.5 H_2O: C, 61.24; H, 7.55. Found: C, 60.94; H, 7.09.

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