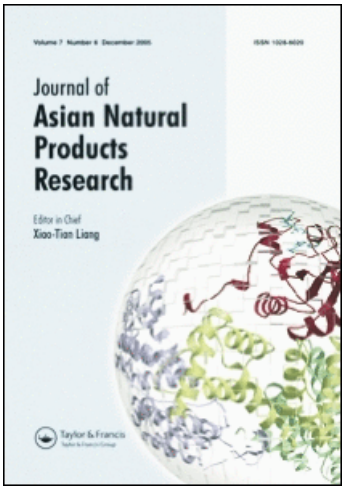

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Three new triterpenoid saponins from the seeds of *Aesculus turbinata*

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Three new triterpenoid saponins, named isoescins VIIa (**1**), VIa (**2**), and VIIIa (**3**), were isolated from the seeds of *Aesculus turbinata* and identified by spectroscopic analysis and chemical hydrolysis. Their structures were established as 21β-*O*-tigloyl-28-*O*-acetylprotoaescigenin 3β-*O*-[β-D-galactopyranosyl(1 → 2)][β-D-glucopyranosyl(1 → 4)]-β-D-glucopyranosiduronic acid (Isoescin VIIa, **1**), 21β-*O*-(2-methylbutyryl)-28-*O*-acetylprotoaescigenin 3β-*O*-[β-D-glucopyranosyl(1 → 2)] [β-D-glucopyranosyl(1 → 4)]-β-D-glucopyranosiduronic acid (Isoescin VIa, **2**), and 21β-*O*-angeloyl-28-*O*-acetylbarringtogenol C 3β-*O*-[β-D-glucopyranosyl(1 → 2)] [β-D-glucopyranosyl(1 → 4)]-β-D-glucopyranosiduronic acid (Isoescin VIIIa, **3**).

Keywords: Hippocastanaceae; *Aesculus turbinata*; isoescin VIa; isoescin VIIa; isoescin VIIIa

1. Introduction

Aesculus turbinata Bl. (Hippocastanaceae) is a cultivated plant to China and a native plant to Japan. Escins, the saponin mixtures from the seeds, have shown prominent anti-inflammatory activity and are of great medicinal importance. In the course of our characterisation studies on bioactive saponin constituents in genus *Aesculus*, 17 saponins have been isolated from the seeds of *A. chinensis* and identified by spectroscopic techniques.[1–7] Recently, detailed chemical work has been undertaken on escins from the seeds of *A. turbinata*. Repeated chromatography of the escins afforded three new triterpenoid oligoglycosides, named isoescins VIIa (**1**), VIa (**2**), and VIIIa (**3**). The present paper describes the isolation and structural elucidation of the new compounds.

2. Results and discussion

The 70% EtOH extract of the seeds of *A. turbinata* yielded compounds **1**, **2**, and **3** after being subjected to D-101 macroreticular resin and high-performance liquid chromatographic column.

Compound **1** was isolated as an amorphous powder. The IR spectrum of **1** showed absorption bands ascribable to carboxyl and α,β-unsaturated ester at 1730, 1710, 1691, 1653 and 1271 cm^{-1}, and broad bands at 3385 and 1076 cm^{-1} suggestive of oligoglycosidic structure.[1] The MALDI-TOF-MS showed the quasi-molecular ion peak at *m/z* 1153 $[M + Na]^+$. Its molecular formula $C_{55}H_{86}O_{24}$ was determined by the high-resolution MALDI-TOF-MS at *m/z* 1153.5417 $[M + Na]^+$. In the NMR spectra of **1** (Tables 1 and 2), in addition to ^1H NMR and ^{13}C NMR signals due to a tigloxyl group [^1H NMR: δ 6.98 (1H, dq, $J = 1.5, 7.3$ Hz, H-3′′′′), 1.58 (3H, br d, $J = 7.5$ Hz, H_3-4′′′′), and 1.84 (3H, br s, H_3-5′′′′); ^{13}C NMR: δ 168.5 (C-1′′′′), 129.7 (C-2′′′′), 136.3 (C-3′′′′), 14.1 (C-4′′′′) and 12.3 (C-5′′′′)] and an acetoxyl group [^1H NMR: δ 1.84 (H_3-2′′′′′); ^{13}C NMR: δ 170.7 (C-1′′′′′) and 20.0 (C-2′′′′′)], signals ascribable to a pentacyclic triterpenoid sapogenol were observed. Those at δ 123.1 (C-12) and 142.6 (C-13) with the corresponding proton at δ 5.35 (1H, m, H-12), were indicative of a double bond at the 12-position of the oleanane skeleton (Figure 1). Compared with isoescin IIa,[8] both ^1H NMR and ^{13}C NMR spectral data of sapogenol moiety in **1** were same as those of isoescin IIa except for the signals of a oligoglycosidic structure unit. The number of monosaccharides in the structure was suggested by three anomeric carbon resonances at δ 104.5 (C-1′, C-1″ and C-1‴) with the corresponding protons at δ 4.89 (H-1′, d, $J = 7.5$ Hz), 5.61 (H-1″, d, $J = 7.5$ Hz) and 4.20 (H-1‴, d, $J = 7.5$ Hz) from its HMQC spectrum. ^1H NMR and ^{13}C NMR signals of the trisaccharide moiety were coincident with those of isoescin IIIa,[8] which suggested the same trisaccharide moiety and linkage sites as isoescin IIIa. Also, acid hydrolysis of **1** also yielded glucose, galactose, and glucuronic acid. The linkage positions of the tigloxyl, acetoxyl, and trisaccharide groups with the aglycone were further characterised by a HMBC experiment on **1**. Namely, the HMBC

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Table 1. ^{1}H NMR spectral data for compounds **1**–**3** (pyridine-d_5, δ, ppm).

No.	1	2	3
1α	1.18 (1H, m)	1.18 (1H, m)	1.20 (1H, m)
1β	1.67 (1H, m)	1.67 (1H, m)	1.63 (1H, m)
2α	1.93 (1H, m)	1.92 (1H, m)	1.93 (1H, m)
2β	1.92 (1H, m)	1.91 (1H, m)	1.90 (1H, m)
3α	3.39 (1H, dd, J = 4.5, 11.5 Hz)	3.37 (1H, dd, J = 4.5, 11.5 Hz)	3.28 (1H, m)
5α	0.82 (1H, m)	0.76 (1H, m)	0.97 (1H, m)
6αβ	1.49 (2H, m)	1.48 (2H, m)	1.61 (1H, m)
7α	1.34 (1H, m)	1.34 (1H, m)	1.49 (1H, m)
7β	1.22 (1H, m)	1.22 (1H, m)	1.86 (1H, m)
9α	1.62 (1H, m)	1.64 (1H, m)	1.63 (1H, m)
11α	1.88 (1H, m)	1.89 (1H, m)	1.88 (1H, m)
11β	1.95 (1H, m)	1.93 (1H, m)	1.93 (1H, m)
12	5.35 (1H, m)	5.45 (1H, m)	5.35 (1H, m)
15α	1.69 (1H, m)	1.66 (1H, m)	1.63 (1H, m)
15β	2.24 (1H, m)	2.20 (1H, m)	2.28 (1H, m)
16β	4.58 (1H, br s)	4.71 (1H, br s)	4.67 (1H, br s)
18β	2.93 (1H, dd, J = 4.5, 12.8 Hz)	2.93 (1H, dd, J = 4.5, 12.8 Hz)	2.82 (1H, dd, J = 4.5, 12.5 Hz)
19α	1.39 (1H, dd, J = 4.5, 12.8 Hz)	1.38 (1H, dd, J = 4.5, 12.8 Hz)	1.34 (1H, dd, J = 4.5, 12.5 Hz)
19β	3.07 (1H, t, J = 12.8 Hz)	3.06 (1H, t, J = 12.5 Hz)	3.07 (1H, t, J = 12.5 Hz)
21α	6.43 (1H, d, J = 10.0 Hz)	6.38 (1H, d, J = 10.0 Hz)	6.38 (1H, d, J = 10.0 Hz)
22β	4.50 (1H, d, J = 10.0 Hz)	6.18 (1H, d, J = 10.0 Hz)	4.43 (1H, d, J = 10.0 Hz)
23	1.30 (3H, s)	1.37 (3H, s)	1.19 (3H, s)
24_a	3.31 (1H, d, J = 13.0 Hz)	3.35 (1H, d, J = 13.0 Hz)	1.10 (3H, s)
24_b	4.48 (1H, d, J = 13.0 Hz)	4.48 (1H, d, J = 13.0 Hz)	
25	0.63 (3H, s)	0.62 (3H, s)	0.65 (3H, s)
26	0.78 (3H, s)	0.88 (3H, s)	0.83 (3H, s)
27	1.80 (3H, s)	1.78 (3H, s)	1.79 (3H, s)
28_{ab}	4.27 (2H, d, J = 13.5 Hz)	4.27 (2H, d, J = 13.5 Hz)	4.25 (2H, d, J = 13.5 Hz)
29	1.09 (3H, s)	1.09 (3H, s)	1.10 (3H, s)
30	1.32 (3H, s)	1.28 (3H, s)	1.24 (3H, s)
$1'$	4.89 (1H, d, J = 7.5 Hz)	4.75 (1H, d, J = 7.5 Hz)	4.73 (1H, d, J = 7.5 Hz)
$1''$	5.61 (1H, d, J = 7.5 Hz)	5.49 (1H, d, J = 7.5 Hz)	5.61 (1H, d, J = 7.5 Hz)
$1'''$	4.20 (1H, d, J = 7.5 Hz)	5.20 (1H, d, J = 7.5 Hz)	5.19 (1H, d, J = 7.5 Hz)
$2''''$		2.50 (1H, m)	
$3''''$	6.98 (1H, dq, J = 1.5, 7.3 Hz)	1.79 (2H, m)	5.88 (1H, dq, J = 1.4, 7.3 Hz)
$4''''$	1.58 (3H, br d, J = 7.5 Hz)	0.95 (3H, t, J = 7.5 Hz)	1.97 (3H, br d, J = 7.5 Hz)
$5''''$	1.84 (3H, br s)	1.23 (1H, d, J = 7.5 Hz)	1.95 (3H, br s)
$2'''''$	1.84 (3H, s)	1.97 (3H, s)	1.93 (3H, s)

correlations were observed between H-21 (δ_H 6.43) and C-$1''''$ (δ_C 168.5), H-28 (δ_H 4.27) and C-$1'''''$ (δ_C 170.7), H-$1'$ (δ_H 4.89) and C-3 (δ_C 90.5), suggesting a tigloxyl, an acetoxyl, and a *O*-$1'$-trisaccharide as substitution groups at C-21, C-28, and C-3 positions in aglycone, respectively. In addition, the HMBC correlations were also observed between H-$1''$ (δ_H 5.61) and C-$2'$ (δ_C 79.5), and H-$1'''$ (δ_H 4.20) and C-$4'$ (δ_C 83.3) similar to isoescin IIIa,[8] suggesting the linkage sequence of the monosaccharide units in the trisaccharide chain. The large J values (7.5 Hz) indicated β-glycosidic linkages in all cases. Consequently, the structure of **1** was elucidated as 21β-*O*-tigloyl-28-*O*-acetylprotoaescigenin 3β-*O*-[β-D-galactopyranosyl(1 → 2)] [β-D-glucopyranosyl(1 → 4)]-β-D-glucopyranosiduronic acid (**1**), named as isoescin VIIa.

Compound **2** was also isolated as an amorphous powder. The IR spectrum displayed absorption bands at 1720, 1691, 1606 and 1270 cm^{-1} for the carbonyl, ester group, and broad bands at 3386 and 1077 cm^{-1} possible for the oligoglycosidic structure moiety.[1] The positive MALDI-TOF-MS showed the quasi-molecular ion peak at *m/z* 1155 $[M + Na]^+$. Its molecular formula $C_{55}H_{88}O_{24}$ was determined by the negative high-resolution secondary ion mass spectrometry (HR-SI-MS) at *m/z* 1131.5579 $[M - H]^-$. By comparing the ^{1}H NMR and ^{13}C NMR spectral data of **2** with those of **1** (Tables 1 and 2), it was suggested that **2** has a 28-*O*-acetylprotoaescigenin skeleton (Figure 1), 2-methylbutyryloxy [^{1}H NMR: δ 2.50 (1 H, m, H-$2''''$), 1.79 (2H, m, H_2-$3''''$), 0.95 (3H, t, J = 7.5 Hz, H_3-$4''''$), and 1.23 (1H, d, J = 7.5 Hz, H_3-$5''''$); ^{13}C NMR: δ 176.8 s (C-$1''''$), 41.9 d (C-$2''''$), 27.9 t (C-$3''''$), 11.9 q (C-$4''''$) and 17.0 q (C-$5''''$)],[9] and a trisaccharide chain groups. Acid hydrolysis of **2** yielded glucose and glucuronic acid. In the HMBC spectrum of **2**, the correlations were observed

Table 2. ^{13}C NMR spectral data for compounds **1**–**3** (pyridine-d_5, δ, ppm).

C	1	2	3	C	1	2	3
1	38.4	38.7	38.9	1′	104.5	104.4	104.5
2	26.3	26.5	26.4	2′	79.5	79.6	78.8
3	90.5	91.1	89.3	3′	76.7	76.7	76.6
4	43.7	43.5	39.7	4′	83.3	82.6	83.4
5	56.0	56.0	56.1	5′	75.5	75.6	75.6
6	18.4	18.4	18.5	6′	175.5	176.7	175.0
7	33.1	33.1	33.2	1″	104.5	104.1	104.5
8	39.8	39.8	39.9	2″	75.1	75.6	74.9
9	46.7	46.7	46.9	3″	74.8	78.3	78.3
10	36.2	36.2	36.3	4″	71.0	69.6	69.7
11	24.0	24.0	24.0	5″	76.7	78.0	78.0
12	123.1	123.4	123.0	6″	61.9	61.4	61.5
13	142.6	142.6	142.5	1‴	104.5	104.5	104.5
14	41.6	41.7	41.7	2‴	74.8	74.3	74.9
15	34.5	34.5	34.5	3‴	78.1	78.2	78.1
16	67.5	67.5	67.6	4‴	71.1	71.3	71.3
17	47.0	46.9	47.0	5‴	77.3	77.7	77.8
18	40.4	40.5	40.5	6‴	62.3	62.1	62.1
19	47.2	47.2	47.2	1⁗	168.5	176.8	168.5
20	36.0	36.6	36.0	2⁗	129.7	41.9	129.4
21	81.5	81.1	81.2	3⁗	136.3	27.9	135.7
22	71.1	71.0	71.3	4⁗	14.1	11.9	15.8
23	22.5	22.4	27.9	5⁗	12.3	17.0	20.9
24	63.3	63.2	16.7	1′′′′′	170.7	170.6	170.5
25	15.6	15.4	15.6	2′′′′′	20.0	20.6	20.6
26	16.8	16.7	16.9				
27	27.3	27.3	27.3				
28	66.3	66.3	66.4				
29	29.7	29.7	29.7				
30	20.7	20.1	20.1				

between H-21 (δ_H 6.38) and C-1⁗ (δ_C 176.8), and H-1′ (δ_H 4.75) and C-3 (δ_C 91.1) suggested the 2-methylbutyryloxy and a trisaccharide chain group were linked at C-21 and C-3 positions, respectively. Additionally, correlation peaks were observed between H-1″ (δ_H 5.49) and C-2′ (δ_C 79.6), and H-1‴ (δ_H 5.20) and C-4′ (δ_C 82.6) similar to escin IVe.[6] The large J values (7.5 Hz) indicated β-glycosidic linkages in all cases. Hence, the structure of **2** was elucidated as 21β-*O*-(2-methylbutyryl)-28-*O*-acetylprotoaescigenin 3β-*O*-[β-D-glucopyranosyl(1 → 2)] [β-D-glucopyranosyl(1 → 4)]-β-D-glucopyranosiduronic acid, named as isoescin VIa.

Compound **3** was also isolated as an amorphous powder. The IR spectrum of **3** displayed absorption bands at 1728, 1716, 1653, and 1275 cm^{-1} for the carbonyl group, the α,β-unsaturated ester and ester, and broad bands at 3419 and 1077 cm^{-1} suggestive of oligoglycosidic structure.[1] The positive MALDI-TOF-MS showed the quasi-molecular ion peak at *m/z* 1137 $[M + Na]^+$. Its molecular formula $C_{55}H_{86}O_{23}$ was determined by the negative HR-SI-MS *m/z* 1113.5475 $[M - H]^-$. Compared with isoescin IIIb,[8] both ^{1}H NMR and ^{13}C NMR spectral data (Tables 1 and 2) of sapogenol moiety of **3** were same to those of isoescin IIIb except for the signals of oligoglycosidic structure unit. Three monosaccharide residues in the structure were evident from anomeric carbon signals at δ_C 104.5 (C-1′, C-1″ and C-1‴) together with corresponding protons at δ_H 4.73 (H-1′, d, $J = 7.5$ Hz), 5.61 (H-1″, d, $J = 7.5$ Hz) and 5.19 (H-1‴, d, $J = 7.5$ Hz) from its HMQC spectrum. Acid hydrolysis of **3** yielded glucose and glucuronic acid. The chemical shifts for the three monosaccharide residues resembled those of escin Ia,[1,7] which suggested the same trisaccharide moiety as escin Ia. The HMBC experiment of **3** showed correlations between the following protons and carbons: H-21 (δ_H 6.38) and C-1⁗ (δ_C 168.5), H-28 (δ_H 4.25) and C-1⁗ (δ_C 170.5), H-1′ (δ_H 4.73) and C-3 (δ_C 89.3), H-1″ (δ_H 5.61) and C-2′ (δ_C 78.8), and H-1‴ (δ_H 5.19) and C-4′ (δ_C 83.4), which provided further evidence for the substituted or linkaged positions (Figure 1). The large coupling constants ($J = 7.5$ Hz) suggested that the glycosyl moiety existed in β orientation in all cases. The structure of **3** was consequently determined to be 21β-*O*-angeloyl-28-*O*-acetylbarringtogenol C 3β-*O*-[β-D-glucopyranosyl(1 → 2)] [β-D-glucopyranosyl (1 → 4)]-β-D-glucopyranosiduronic acid, named as isoescin VIIIa.

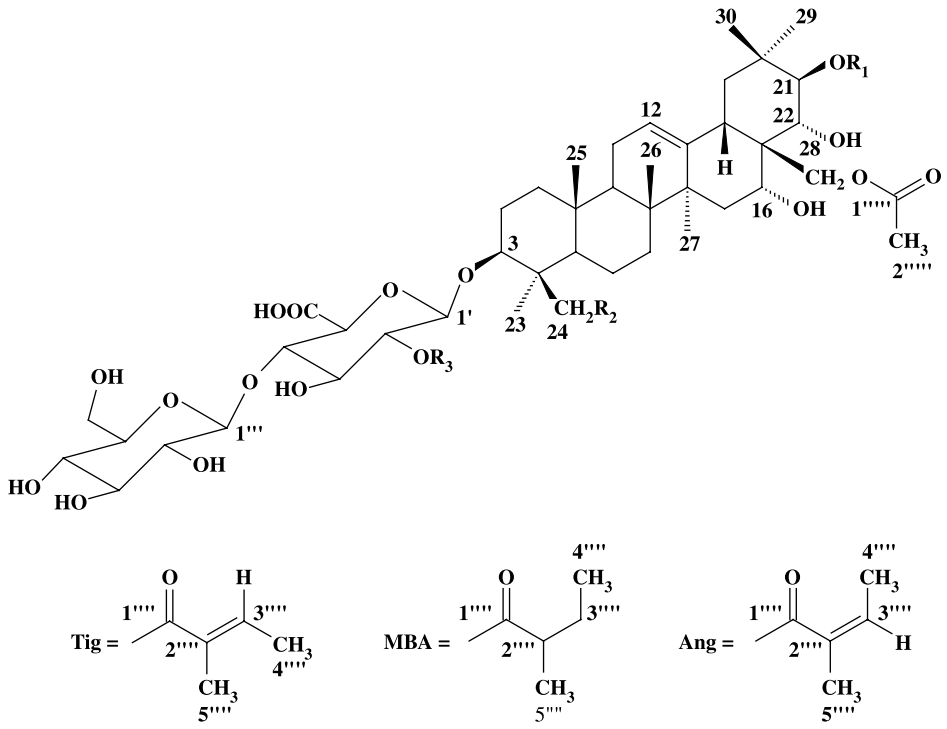
3. Experimental

3.1 General experimental procedures

Optical rotations were determined on a Perkin–Elmer 243B polarimeter in MeOH. IR spectra were recorded on a Thermo Nicolet Nexus 470 spectrophotometer with KBr disks. MALDI-TOF-MS (matrix assisted laser desorption ionisation MS) spectra were recorded on a BIFLEX III (Bruker) mass spectrometer and high-resolution secondary ion mass spectrometry (SI-MS) spectra were recorded on a APEX II (Bruker) mass spectrometer. NMR spectra were recorded in pyridine-d_5 using a Varian INOVA-500 spectrometer (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR including COSY, HMQC, HMBC, and NOESY) and chemical shifts are given in δ relative to TMS as internal standard. For preparative HPLC (pump, P2000; detector, UV 3000; software, PC 1000; Thermo Separation Products, USA) separation, the column used was a LUNA C18 (2) (Phenomenex 250 × 21.2 mm i.d., 10 μ), the mobile phase consisted of MeOH/1% HOAc aq. solution (70:30, v/v). The monitored wavelength was 220 nm. The flow rate was 3.5 ml/min.

3.2 Plant material

The seeds of *Aesculus turbinata* were collected in Akita county, Japan, September 1998, and identified by Dr Yamaji Seiichi, Institute of Natural Medicines, Toyama Medical and Pharmaceutical University. A voucher specimen (No. 17710) is deposited in the



	R_1	R_2	R_3
1	Tig	OH	Gla
2	MBA	OH	Glc
3	Ang	H	Glc

Figure 1. The structures of compounds **1**–**3**.

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3.3 *Extraction and isolation*

The powdered seeds (3.0 kg) were extracted four times with 70% EtOH under reflux for 2 h to give EtOH extract (730 g, 24.33%). The extract was further dissolved in H_2O and partitioned with EtOAc, followed by *n*-BuOH saturated with H_2O, to give EtOAc (26.8 g, 0.89%), *n*-BuOH (454.2 g, 15.14%), and H_2O (210 g, 7.00%) extracts.

The *n*-BuOH extract was subjected to D-101 macroreticular resin column and eluted successively with H_2O, 20% EtOH, 40–80% EtOH, and 95% EtOH, giving four saponin fractions of 15.2 g, 10.5 g, 19.1 g, and 66.7 g, respectively. A 10 g amount of the third fraction was separated repeatedly by preparative HPLC [MeOH/1% HOAc aq. (7:3, v/v)] to yield compounds **1** (55 mg, 0.0183‰), **2** (65 mg, 0.0216‰), and **3** (88 mg, 0.0293%), respectively.

3.3.1 *Isoescin VIIa (**1**)*

Amorphous powder; $[\alpha]_D^{23}$ −16.5 (*c* 1.00, MeOH); IR (KBr) ν_{max} (cm^{-1}): 3385, 2928, 1730, 1710, 1691, 1653, 1605, 1416, 1382, 1271, 1159, 1076, 1043; ^1H NMR (pyridine-d_5, 500 MHz) and ^{13}C NMR (pyridine-d_5, 125 MHz) spectral data: see Tables 1 and 2; positive MALDI-TOF-MS *m/z* 1153 $[M + Na]^+$, HR-MALDI-TOF-MS *m/z* 1153.5417 $[M + Na]^+$ (calcd for $C_{55}H_{86}O_{24}Na$, 1153.5401).

3.3.2 *Isoescin VIa (**2**)*

Amorphous powder; $[\alpha]_D^{23}$ −18.1 (*c* 1.22, MeOH); IR (KBr) ν_{max} (cm^{-1}): 3386, 2929, 1720, 1691, 1606, 1381, 1363, 1270, 1157, 1077, 1043; ^1H NMR (pyridine-d_5, 500 MHz) and ^{13}C NMR (pyridine-d_5, 125 MHz) spectral data: see Tables 1 and 2; positive MALDI-TOF-MS *m/z*

1155 $[M + Na]^+$, negative HR-SI-MS *m/z* 1131.5579 $[M - H]^-$ (calcd for $C_{55}H_{87}O_{24}$, 1131.5587).

*3.3.3 Isoescin VIIIa (**3**)*

Amorphous powder; $[\alpha]_D^{23}$ −12.1 (*c* 1.05, MeOH); IR (KBr) ν_{max} (cm^{-1}): 3419, 2927, 1728, 1716, 1653, 1608, 1414, 1385, 1275, 1242, 1162, 1077, 1043; ^1H NMR (pyridine-d_5, 500 MHz) and ^{13}C NMR (pyridine-d_5, 125 MHz) spectral data: see Tables 1 and 2; positive MALDI-TOF-MS *m/z* 1137 $[M + Na]^+$, negative HR-SI-MS *m/z* 1113.5475 $[M - H]^-$ (calcd for $C_{55}H_{85}O_{23}$, 1113.5481).

3.4 Acid hydrolysis of saponin

Each solution of compounds **1**, **2**, or **3** (each 10 mg) in a mixture of H_2O (1 ml) and 20% H_2SO_4 aq. (1 ml) was refluxed for 4 h. The hydrolysate was allowed to cool and then neutralised by saturated $NaHCO_3$, and extracted three times with EtOAc. The water layer was then condensed and subjected to PC (*n*-BuOH/H_2O/HOAc, 4:2:1) together with authentic glucose, galactose, and glucuronic acid.

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