Saponins from the Leaves of *Aralia elata* SEEM. (Araliaceae)

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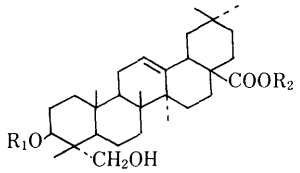
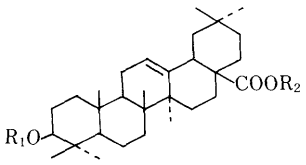
Eleven triterpenoidal saponins having oleanolic acid or hederagenin as the aglycone and two flavonoidal glycosides were isolated from the leaves of *Aralia elata* SEEM. (Araliaceae). The structures of four new saponins (1, 2, 3, and 4) were established to be 3-*O*-α-L-rhamnopyranosyl(1→2)-α-L-arabinopyranosyl-hederagenin 28-*O*-β-D-xylopyranosyl-(1→6)-β-D-glucopyranosyl ester, 3-*O*-α-L-rhamnopyranosyl(1→2)-α-L-arabinopyranosyl-oleanolic acid 28-*O*-β-D-xylopyranosyl(1→6)-β-D-glucopyranosyl ester, 3-*O*-β-D-glucopyranosyl(1→3)-α-L-rhamnopyranosyl(1→2)-α-L-arabinopyranosyl-hederagenin 28-*O*-β-D-glucopyranosyl(1→6)-β-D-glucopyranosyl ester, and 3-*O*-β-D-glucopyranosyl(1→3)-α-L-rhamnopyranosyl(1→2)-α-L-arabinopyranosyl-hederagenin, respectively, on the basis of spectroscopic and chemical evidence.

Keywords *Aralia elata*; Araliaceae; triterpenoidal saponin; hederagenin glycoside; oleanolic acid glycoside; bisdesmoside; monodesmoside

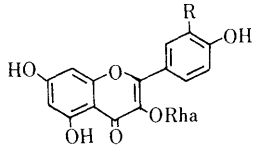
The roots and bark of *Aralia elata* SEEM. (Araliaceae) (Japanese name "taranoki") have been used as a folk medicine in Japan and China as a tonic, anti-gastric ulcer agent, and antidiabetes agent. Isolation and structural studies of various triterpenoidal saponins from *Aralia* species have been reported by the three groups as follows: tarasaponins from the roots of *A. elata* by Shoji *et al.*,[1] araloside A, B, and C from *A. mandsurica* by Kochetkov *et al.*,[2] and saponin AC's from *A. cordata* by Kawai *et al.*[3] This paper describes the structural elucidation of four new triterpenoidal saponins (**1**—**4**) isolated from the leaves of *A. elata*.



	R_1	R_2
1:	–Ara²Rha	–Glc⁶Xyl
3:	–Ara²Rha³Glc	–Glc⁶Glc
4:	–Ara²Rha³Glc	H
6:	–Ara²Rha	–Glc⁶Glc
8:	–Ara²Rha	–Glc⁶Glc⁴Rha
10:	–Ara²Rha	H
14:	H	H
41:	–Ara	–Glc



	R_1	R_2
2:	–Ara²Rha	–Glc⁶Xyl
5:	–Ara²Rha	–Glc⁶Glc
7:	–Ara²Rha³Glc	–Glc⁶Glc
9:	–Ara²Rha	H
11:	–Ara²Rha³Glc	H
15:	H	H



12: R=OH, **13**: R=H

Ara = α-L-arabinopyranose Rha = α-L-rhamnopyranose Glc = β-D-glucopyranose Xyl = β-D-xylopyranose

Fig. 1

TABLE I. ^{1}H-NMR Spectral Data for Saponins **1**—**4** (270 MHz, Pyridine)[a]

Saponin	Sugar anomeric	Vinyl (C-12)	Rha-CH_3	CH_3
1	6.26 (d, J=7.7 Hz, Glc-1)	5.40 (br s)	1.43 (d, J=5.9 Hz)	1.19, 1.16
	6.21 (s, Rha-1)			0.95, 0.95
	5.11 (d, J=5.5 Hz, Ara-1)			0.88, 0.88
	4.92 (d, J=7.3 Hz, Xyl-1)			
2	6.21 (d, J=7.7 Hz, Glc-1)	5.39 (br s)	1.57 (d, J=6.2 Hz)	1.24, 1.13
	6.16 (s, Rha-1)			1.06, 1.02
	4.87 (d, J=5.1 Hz, Ara-1)			0.89, 0.89
	4.85 (d, J=7.3 Hz, Xyl-1)			0.88
3	6.30 (s, Rha-1)	5.41 (br s)	1.55 (d, J=6.2 Hz)	1.19, 1.16
	6.28 (d, J=8.1 Hz, Glc-1)			1.13, 0.99
	5.52 (d, J=7.7 Hz, Glc-1)			0.87, 0.87
	5.05 (d, J=7.3 Hz, Glc-1)			
	5.00 (d, J=5.9 Hz, Ara-1)			
4	6.15 (s, Rha-1)	5.40 (br s)	1.43 (d, J=5.9 Hz)	1.19, 1.05
	5.39 (d, J=7.7 Hz, Glc-1)			0.95, 0.95
	4.95 (d, J=6.6 Hz, Ara-1)			0.88, 0.87

a) Only assignable signals are listed. Glc = β-D-glucopyranose, Rha = α-L-rhamnopyranose, Ara = α-L-arabinopyranose, Xyl = β-D-xylopyranose.

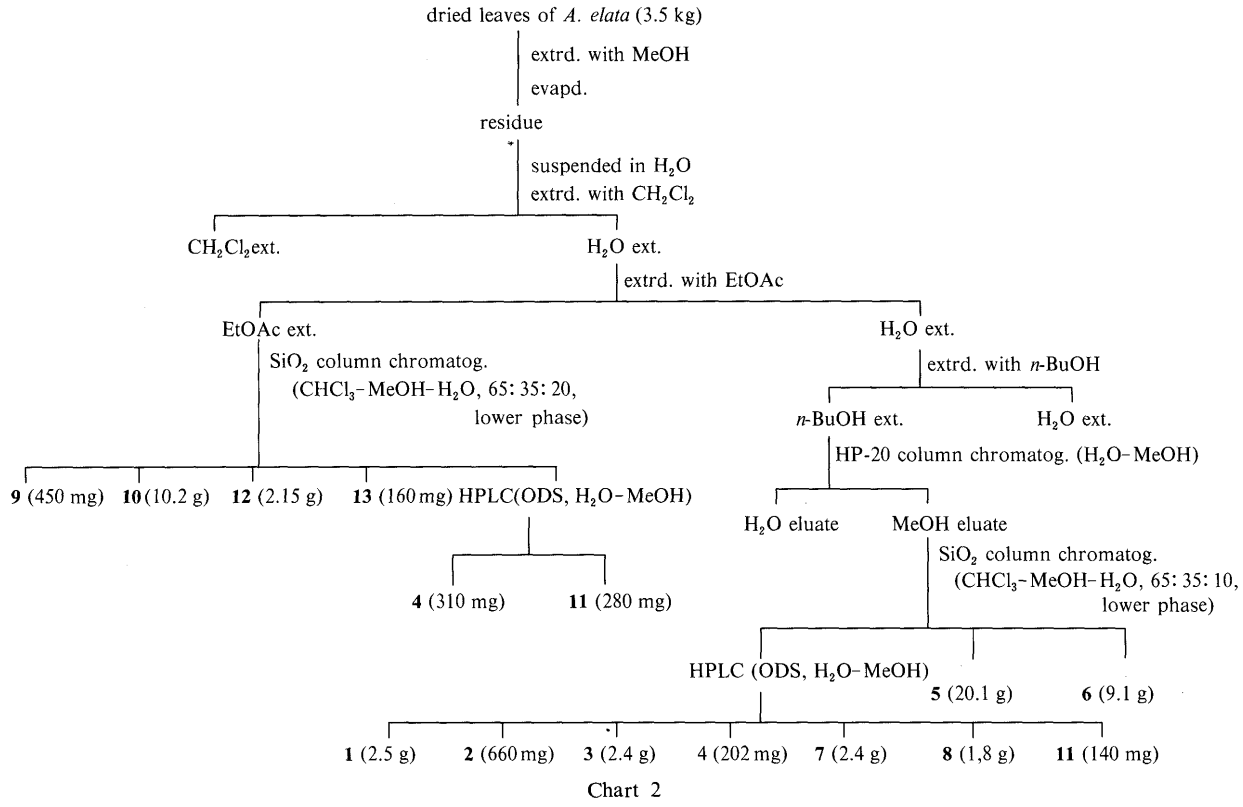
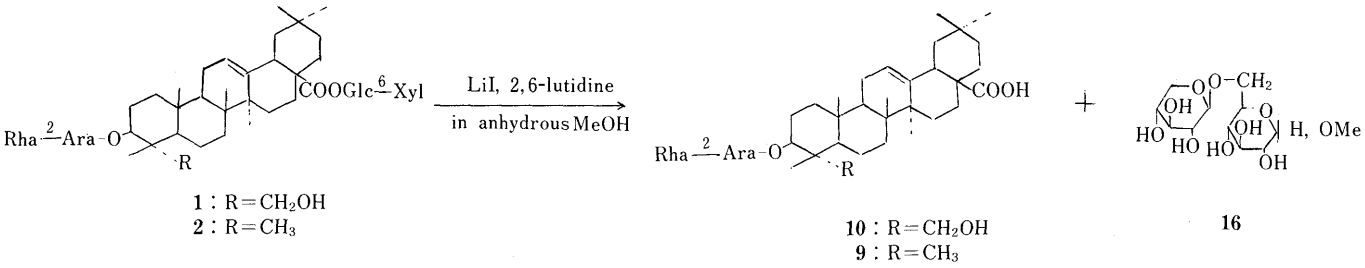


Chart 2



1 : R=CH_2OH
2 : R=CH_3

10 : R=CH_2OH
9 : R=CH_3

16

Fig. 2

Dried leaves of *A. elata* were extracted with hot MeOH, and the extracts were fractionated as shown in Chart 1. Eleven saponins (**1**—**11**) and two flavonoidal glycosides (**12** and **13**) were isolated by repeated column chromatography and high performance liquid chromatography (HPLC). The known saponins **5**,[4] **6**,[5] **7**,[6] **8**,[7] **9**,[8] **10**,[7] and **11**,[6] and flavonoidal glycosides, quercetin 3-*O*-α-L-rhamnopyranoside (**12**)[9] and kaempferol 3-*O*-α-L-rhamnopyranoside (**13**),[10] were identified from chemical evidence and by comparison of the spectral data with published values for the compounds themselves and their derivatives.

Both saponins **1** and **2** showed the characteristic absorption band assigned to the ester group at 1740 cm^{-1} in the infrared (IR) spectra and four anomeric protons in the ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectra (Table I). The fast atom bombardment mass spectra (FAB-MS) of **1** and **2** revealed the pseudo molecular ion at *m/z* 1083 and 1067, $(M+K)^+$, respectively. On acid hydrolysis both **1** and **2** yielded the same monosaccharides, arabinose, xylose, rhamnose, and glucose (sugar ratio, 1 : 1 : 1 : 1, respectively) together with hederagenin (**14**) from **1** and oleanolic acid (**15**) from **2**. On selective cleavage of the ester glycosidic linkage with anhydrous LiI and 2,6-lutidine in anhydrous MeOH,[11] **1** and **2** gave the same methyl glycoside (**16**) (an anomeric mixture), and prosapogenin **10** and **9**, respectively, which suggested that **1** and **2** were bisdesmosides of **14** and **15**, respectively, having four monosaccharides. The prosapogenins **10** and **9** were identical with 3-*O*-α-L-rhamnopyranosyl(1→2)-α-L-arabinopyranosyl-hederagenin and -oleanolic acid, respectively, which were isolated in this work, based on the ^{1}H- and ^{13}C-NMR spectra and FAB-MS. The thin layer chromatography (TLC) of **16** was in accordance with that of synthetic methyl β-D-xylopyranosyl(1→6)-β-D-glucopyranoside (**17**) which was synthesized according to the method outlined in Fig. 3. The glycosidic oxygen linked to O-28 in **1** and **2** was determined to have the β-configuration from the coupling constant (J=7.7 Hz) of the anomeric proton of the glucopyranose in the ^{1}H-NMR spectra of **1** and **2**. These results together with the ^{13}C-NMR spectra (Table II) gave the formulas of **1** and **2** as shown in Fig. 1.

Saponins **3** and **4** on acid hydrolysis, yielded the same monosaccharides, arabinose, rhamnose, and glucose. The sugar ratios, however, were different: 1 : 1 : 3 in **3** and 1 : 1 : 1 in **4**, respectively. FAB-MS of **3** and **4** revealed the pseudo molecular ion at *m/z* 1275 $(M+K)^+$ and 951 $(M+K)^+$, respectively, and the ^{1}H-NMR spectra showed five and

TABLE II. ^{13}C-NMR Chemical Shifts of Sugar Moieties of Saponins **1**—**11** in C_5D_5N

		1	2	3	4	5	6	7	8	9	10	11	41[13]
3-Ara	C-1	105.6	105.4	104.6	104.8	104.6	104.0	105.1	104.3	104.6	104.1	105.2	106.5
	C-2	75.9	75.8	75.6	75.6	75.9	75.9	75.8	76.0	75.8	75.2	75.9	73.0
	C-3	74.7[a]	73.8	74.6	74.8	73.4	74.0	74.3	74.5	73.5	74.4	74.1	74.6
	C-4	67.0	68.2	69.6	69.6	69.8	69.6	69.8	69.9	69.7	69.5	69.7	69.5
	C-5	64.0	64.2	66.0	66.2	64.3	65.1	65.6	65.5	64.4	65.4	65.4	66.9
3-Rha	C-1	101.7	101.6	101.2	101.4	101.6	101.6	101.6	101.8	101.6	101.4	101.6	
	C-2	72.3[b]	72.1[a]	71.4	71.6	72.4[a]	72.4[a]	71.6	72.4[a]	72.4[a]	72.4[a]	71.4	
	C-3	72.5[b]	72.4[a]	82.7	82.8	72.2[a]	72.1[a]	83.1	72.6[a]	72.2[a]	72.1[a]	83.0	
	C-4	74.5[a]	73.7	72.6	72.8	73.9	74.1	72.9	74.2	73.9	73.9	72.8	
	C-5	69.7	69.8	69.4	69.7	68.4	69.3	69.3	69.3	69.4	69.1	69.1	
	C-6	18.5	18.4	18.3	18.4	18.5	18.4	18.5	18.7	18.4	18.4	18.4	
3-Glc	C-1			106.4	106.5			106.6				106.4	
	C-2			75.3	75.6			75.7				75.7	
	C-3			78.4[a]	78.4[a]			78.4[a]				78.4[a]	
	C-4			71.3	71.6			71.5				71.5	
	C-5			78.1[a]	78.3[a]			78.5[a]				78.3[a]	
	C-6			62.4	62.5			62.6				62.4	
28-Glc	C-1	95.6	95.4	96.3		95.6	95.6	95.7	95.8				95.7
	C-2	73.9[c]	73.3[b]	73.7		73.8	73.8	73.8	74.1				74.0
	C-3	78.7	78.1	78.3[a]		78.5[b]	78.6	78.8[a]	78.5[b]				79.2
	C-4	71.0	70.9	70.6		70.7	70.7	70.9	70.9				71.0
	C-5	77.3	77.8	77.7		77.8	77.8	77.9	78.1				78.8
	C-6	69.2	69.0	69.2		69.2	69.2	69.2	69.3				62.2
28-Glc (Terminal)	C-1			104.9		105.0	105.0	105.3	104.9				
	C-2			74.9		75.0	75.0	75.0	75.5				
	C-3			78.2[a]		78.2[b]	77.8	78.2	76.7				
	C-4			71.1		71.4	71.5	71.4	78.7[b]				
	C-5			78.1[a]		78.2[b]	77.8	78.2	77.1				
	C-6			62.6		62.5	62.6	62.6	61.5				
28-Xyl	C-1	104.2	104.5										
	C-2	74.1[c]	73.7[b]										
	C-3	74.7	74.5										
	C-4	70.9	70.9										
	C-5	65.5	65.8										
28-Rha	C-1								102.8				
	C-2								72.6[c]				
	C-3								72.8[c]				
	C-4								74.1				
	C-5								70.5				
	C-6								18.7				

a—*c*) These values may be interchangeable in each column.

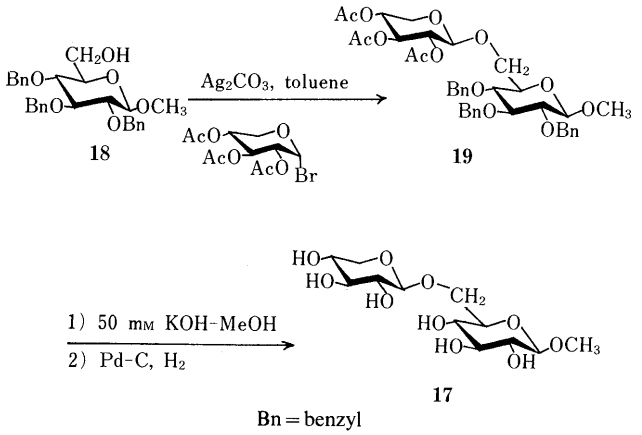


Fig. 3

three anomeric proton signals, respectively (Table I). Furthermore, the IR spectra of **3** and **4** demonstrated the characteristic bands due to the ester group at 1735 cm^{-1} and the COOH group at 1690 cm^{-1}. These findings indicated that **3** was 3,28-*O*-bisglycosidic hederagenin and **4** was 3-*O*-monoglycosidic hederagenin. The ^{13}C-NMR chemical shifts of the sugar moieties of **4** were in close accordance with those of saponin **11** (Table II), which, together with the chemical evidence, gave the formula of **4** as shown in Fig. 1. On alkaline hydrolysis, **3** yielded **4**. Comparison of the ^{1}H-NMR spectra of **3** and **4** (Table I) revealed that two doublets at δ 6.28 (J=8.1 Hz) and 5.05 (J=7.3 Hz) had disappeared in the spectrum of **4**. Based on a comparison of the sugar ratios obtained from the acid hydrolysis of **3** and **4**, it was inferred that the absent anomeric protons could be assigned to two β-D-glucopyranose linked to O-28. The ^{13}C-NMR chemical shifts of the sugar moieties of **3** agreed closely with those of **7** (Table II), in which the glycosylation shifts were observed at C-2 of arabinopyranose and C-3 of rhamnopyranose which were linked to O-3 of the aglycone, and C-6 of the inner glucopyranose linked to O-28. These findings gave the formula of **3** as shown in Fig. 1.

Saponins isolated from the roots and bark of *A. elata*, *A. mandshurica*, and *A. cordata* have a glucuronic acid as one of the sugar components of the glycosides. Although saponins isolated from *A. cordata* lack arabinose as a sugar component, L-arabinose (which is also one of the sugar

components in saponin molecules isolated from the roots and bark of *A. elata* and *A. mandshurica*) forms a furanose ring. Interestingly, on the other hand, saponins isolated from the leaves of *A. elata* have no glucuronic acid as a sugar component, and arabinose contained in the saponins forms a pyranose ring.

Experimental

General Procedure All melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were obtained with a JEOL JNM-GX 270 FT NMR spectrometer at 270 and 67.8 MHz, respectively, and chemical shifts were given in ppm with tetramethylsilane as an internal standard. Electron impact- (EI-) and FAB-MS were recorded on a JEOL JMS-DX 300 mass spectrometer. Optical rotations were measured with a JASCO J-20A spectropolarimeter. Gas liquid chromatography (GLC) was run on a Shimadzu GC-9A with a flame ionization detector using a glass column (2.0 m × 4 mm) packed with 3% ECNSS-M (column temperature, gradient from 150 up to 190 °C; H_2 60 ml/min, N_2 80 ml/min). A Shimadzu LC-6A liquid chromatograph was employed for analytical HPLC, and was further equipped with an SSC-6310 autoinjector and an SSC-6320 fraction collector (Senshu Sci. Co., Ltd.) for preparative HPLC using ODS-H-4251 (250 mm × 10 mm). Thin-layer chromatograms utilized Kieselgel HF_{254} (Merck), and spots were detected by spraying with dilute H_2SO_4 followed by heating at 80 °C for 20 min. Column chromatograms were prepared with Wakogel C-200 and Diaion HP-20.

Extraction and Separation of Glycosides Dried leaves (3.5 kg) of *A. elata*, collected in June, 1987, at Hiki-gun, Saitama Prefecture, were extracted and separated as described in Chart 1.

Saponin 1 White powder, mp 209—213 °C, $[\alpha]_D^{18}$ −5.7° (c=0.88, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 1740. FAB-MS m/z: 1083 $(M+K)^+$. *Anal.* Calcd for $C_{52}H_{84}O_{21}\cdot H_2O$: C, 58.74; H, 8.15. Found: C, 58.75; H, 8.10.

Saponin 2 White powder, mp 208—212 °C, $[\alpha]_D^{18}$ −12.7 (c=0.86, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 1740. FAB-MS m/z: 1067 $(M+K)^+$. *Anal.* Calcd for $C_{52}H_{84}O_{20}\cdot 3H_2O$: C, 57.65; H, 8.37. Found: C, 57.74; H, 8.07.

Saponin 3 Colorless needles (*n*-BuOH), mp 219—221 °C, $[\alpha]_D^{20}$ −6.9° (c=1.44, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 1735. FAB-MS m/z: 1275 $(M+K)^+$. *Anal.* Calcd for $C_{59}H_{96}O_{27}\cdot 3H_2O$: C, 54.87; H, 7.96. Found: C, 54.86; H, 7.99.

Saponin 4 White powder, mp 240—245 °C, $[\alpha]_D^{22}$ +7.6 (c=1.34, pyridine). IR ν_{max}^{Nujol} 1690 cm^{-1}. FAB-MS m/z: 951 $(M+K)^+$. *Anal.* Calcd for $C_{47}H_{76}O_{17}\cdot 5/2H_2O$: C, 58.92; H, 8.52. Found: C, 58.67; H, 8.64.

Acid Hydrolysis of 1—4 Compound **1** (10 mg) was refluxed with 5 ml of 1 N H_2SO_4 in 1,4-dioxane–H_2O (3 : 1) for 5 h. The reaction mixture was diluted with H_2O (10 ml) and extracted with AcOEt (10 ml × 3). The combined AcOEt extracts were evaporated to give **14** (4.3 mg, 95.1%). The H_2O layer was neutralized with saturated aqueous Ba $(CO_3)_2$ solution, and centrifuged to provide a solution which was evaporated to give a syrup. The syrup was reacted with $NaBH_4$ and acetylated. The acetylated mixture was subjected to GLC, which revealed four peaks for the derivatives of arabinose, xylose, rhamnose, and glucose (1 : 1 : 1 : 1, respectively). Acid hydrolyses of **2**, **3**, and **4** were performed by the same method as for **1**, and the sugar components of each saponin were comfirmed by the same method as for **1**. The results are summarized Table III.

Reaction of 1 with LiI and 2,6-Lutidine in Anhydrous MeOH 2,6-Lutidine (1 ml) and LiI (10 mg) were added to a solution of **1** (50 mg) in anhydrous MeOH (5 ml), and the mixture was refluxed for 16 h under argon. The reaction mixture was diluted with H_2O (30 ml) and extracted with AcOEt (10 ml × 3). The combined AcOEt extracts were evaporated to afford a residue which was chromatographed on silica gel and eluted with a solution of $CHCl_3$–MeOH–H_2O (65 : 35 : 20, lower layer) to give **10** (28.1 mg, 78%). The H_2O layer was evaporated to afford a residue which was subjected to column chromatography (20% MeOH–$CHCl_3$) to give **16** (9.9 mg, 63%), which was identical with synthetic methyl β-D-xylopyranosyl(1→6)-β-D-glucopyranoside **17** by TLC and GLC.

Reaction of 2 with LiI and 2,6-Lutidine in Anhydrous MeOH 2,6-Lutidine (1 ml) and LiI (15 mg) were added to a solution of **2** (65 mg) in anhydrous MeOH (5 ml), and the mixture was refluxed for 20 h under argon. The reaction mixture was treated by the same method as for **1** to give **9** (37.6 mg, 81%) and **16** (12 mg, 58%).

Alkaline Hydrolysis of 3 A solution of **3** (100 mg) in 10 ml of 1 N KOH in H_2O–MeOH (1 : 1) was stirred at 60 °C for 2 d. The reaction mixture was neutralized with AcOH and evaporated to afford a residue which was subjected to column chromatography to give compound **4** (a white powder, 21 mg, 28%). Compound **4** was identical with the authentic saponin, which was isolated in this study, based on TLC and ^{13}C-NMR.

TABLE III. Products Obtained on Acid Hydrolysis of Saponins **1**—**4**

Saponin	Products	
	Aglycon	Sugars (molar ratios)
1	**14**	Arabinose (1), xylose (1), rhamnose (1), glucose (1)
2	**15**	Arabinose (1), xylose (1), rhamnose (1), gucose (1)
3	**14**	Arabinose (1), rhamnose (1), glucose (3)
4	**14**	Arabinose (1), rhamnose (1), glucose (1)

Methyl 2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl(1→6)-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (19) 2,3,4-Tri-*O*-acetyl-α-D-xylopyranosyl bromide (4.3 g) and Ag_2CO_3 (5.6 g) were added to a solution of methyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (**18**) (1 g) in toluene (30 ml) and the mixture was stirred overnight. The mixture was then poured into ice-water (100 ml), and extracted with CH_2Cl_2 (100 ml × 3). The combined extracts were washed successively with saturated aqueous $NaHCO_3$ and H_2O, dried over Na_2SO_4, filtered, and evaporated. The resultant residue was subjected to column chromatography (benzene–acetone, gradient up to 20% acetone) to obtain **19** (oil, 670 mg, 43%). EI-MS m/z (%): 690 (trace, M^+ −MeOH), 631 (4, M^+ $-CH_2C_6H_5$), 525 (3), 493 (5), 431 (5), 409 (5), 259 (68), *Anal.* Calcd for $C_{39}H_{46}O_{13}$: C, 64.81; H, 6.42. Found: C, 64.67; H, 6.50.

Methyl β-D-Xylopyranosyl(1→6)-β-D-glucopyranoside (17) A solution of **19** (600 mg) in 50 mM NaOH–MeOH (10 ml) was allowed to stand overnight. The reaction mixture was neutralized with AcOH, and evaporated to afford a residue. The residue was dissolved in MeOH (50 ml), and 10% Pd–C (50 mg) was added. The mixture was stirred for 20 h under hydrogen at atmospheric pressure. The catalyst was removed by filtration and washed with MeOH, and the solution was concentrated under reduced pressure to give **17** (a white powder, 154 mg, 57%). FAB-MS m/z (%): 365 $(M+K)^+$. ^{13}C-NMR (d_5-pyridine) δ: 105.8 (Xyl-1), 101.3 (Glc-1), 78.2 (Glc-3), 75.3 (Glc-5), 74.4 (Xyl-3), 73.6 (Xyl-2), 72.8 (Glc-2), 71.9 (Glc-4), 71.1 (Glc-6), 70.7 (Xyl-4), 67.0 (Xyl-5), 55.2 (OCH_3). *Anal.* Calcd for $C_{12}H_{22}O_{10}\cdot H_2O$: C, 41.86; H, 7.03. Found: C, 41.58; H, 7.09.

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