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Saponins from Leaves of *Acanthopanax hypoleucus* MAKINO

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From the leaves of *Acanthopanax hypoleucus* MAKINO (Araliaceae), five triterpenoidal saponins, having oleanolic acid and hederagenin as sapogenins, were isolated.

On the basis of chemical and spectral data, the structures of two new saponins, named hypoleucosides A (1), and B (5) were elucidated as follows: 1; 3-*O*-*β*-D-glucopyranosyl 11α-methoxy-oleanolic acid 28-*O*-*β*-D-glucopyranosyl ester, 5; 3-*O*-*β*-D-glucopyranosyl-(1→2)-α-L-arabinopyranosyl-(1→4)-*β*-D-glucopyranosyl oleanolic acid 28-*O*-*β*-D-glucopyranosyl-(1→6)-*β*-D-glucopyranosyl ester.

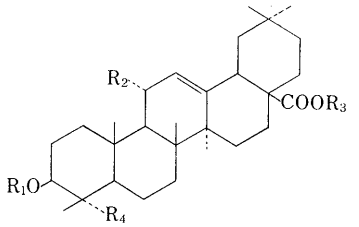
Keywords *Acanthopanax hypoleucus*; Araliaceae; hypoleucoside; oleanolic acid glycoside; hederagenin glycoside; 11α-methoxy-oleanolic acid

Many triterpenoid glycosides have already been isolated from *Acanthopanax* species, and their structures have been determined by Shoji and Tanaka *et al.*[1,2] Leaves of some *Acanthopanax* species have been used as a tonic, an anti-rheumatic and an anti-inflammatory in Korea and China.[3] As a continuation of our work on glycoside constituents with useful biological activities,[4] the chemical constituents of the leaves of *Acanthopanax hypoleucus* MAKINO (Japanese name: urajiro-ukogi), which grows widely in the moutainous regions of the middle and west districts of Japan, have been studied.

Air-dried leaves of *A. hypoleucus* collected in Yamanashi Prefecture were extracted with 50% aqueous methanol. A suspension of the methanolic extract in water was washed with ethyl ether. The aqueous layer was chromatographed on a column of highly porous polymer (Diaion HP-20) and the resulting crude saponin fraction was chromatographed repeatedly as described in the experimental section to give five saponins, **1**—**5**. Of these compounds, the new saponins **1** and **5** were named hypoleucosides A and B, respectively. Inspection of the proton and carbon-13 nuclear magnetic resonance (^{1}H- and ^{13}C-NMR) spectra indicated that saponins **2**, **3**, **4** and **5** were the 3,28-*O*-bisdesmoside of oleanolic acid (**6**) or hederagenin (**7**), having two to five monosaccharide units. The ^{13}C-NMR spectra were eventually assigned as shown in Table I by ^{1}H–^{1}H correlated spectroscopy (COSY) ^{1}H–^{13}C COSY, decoupling experiments and comparison with reported ^{13}C-NMR data.

The ^{13}C-NMR spectra of **2** and **4** indicated that these saponins are composed of the same sapogenin, hederagenin (**7**). In the ^{13}C-NMR spectra of **2** and **4**, the signals due to the aglycone moiety were in good agreement with those of the 28-glycosyl ester of the 3-*O*-glycosyl hederagenin. On acid hydrolysis, **2** and **4** afforded **7**, L-arabinose and D-glucose. On selective cleavage of the ester-glycoside linkage with anhydrous LiI and 2,6-lutidine in anhydrous methanol,[5] **2** gave a prosaponin (**8**) which was shown to be identical with akeboside Stb from *Akebia quinata* DECNE.[6] and a methyl disaccharide (**9**), and **4** gave a prosapogenin (**10**) and **9**. The product **9** was identified as a mixture of methyl *β*-D-glucopyranosyl-(1→6)-(α and *β*)-D-glucopyranosides by its ^{13}C-NMR data. Acid hydrolysis of **8** gave **7** and L-arabinose. Based on these results, the structure of **2**[7] was formulated as shown in Chart 1. Compound **10** was identified as saponin P_F[8] isolated from *A. quinata* by comparison of the reported spectra and physical data. The above evidence led to the formulation of **4**[7] as shown in Chart 1.

The new saponin **1** exhibited ions at *m/z* 833 $[M+Na]^+$, *m/z* 671 $[M+Na-hexose]^+$ and *m/z* 509 $[M+Na-hexose-hexose]^+$ in the positive fast atom bombardment mass spectrum (FAB-MS). On acid hydrolysis, **1** afforded a sapogenin and D-glucose. The ^{1}H-NMR spectrum of **1** showed a characteristic signal due to an olefinic proton at *δ* 5.70 (doublet, 3.85 Hz) of the olean-12-ene type triterpenes. The presence of a one methoxyl group was shown at *δ* 3.19 in the ^{1}H-NMR spectrum and *δ* 53.8 in the ^{13}C-NMR spectrum. In the ^{1}H-NMR spectrum of **1**, the downfield shift of 0.3 ppm of an olefinic proton (*δ* 5.70) compared with that of **6**. The coupling constant 8.06 Hz between H-9 (*δ* 1.82, d) and H-11 (*δ* 3.76, dd) suggested that a methoxyl group of **1** is located at 11-α. In the ^{13}C-NMR spectra, **1** demonstrated glycosylation shifts of signals of carbons around C-3 and C-28 as observed for the 3,28-*O*-bisdesmosides of oleanolic acid. On saponification, **1** gave a prosapogenin along with 1,6-anhydroglucose. Therefore,



	R_1	R_2	R_3	R_4
1	–glc	OMe	–glc	CH_3
2	–ara	H	–genti.	CH_2OH
8	–ara	H	–H	CH_2OH
3	–ara(2)–glc	H	–genti.	CH_3
11	–ara(2)–glc	H	–H	CH_3
4	–ara(2)–glc	H	–genti.	CH_2OH
10	–ara(2)–glc	H	–H	CH_2OH
5	–glc(4)–ara(2)–glc	H	–genti.	CH_3
12	–glc(4)–ara(2)–glc	H	–H	CH_3
6	–H	H	–H	CH_3
7	–H	H	–H	CH_2OH

genti. = gentiobiosyl = glc(6)–glc
ara = arabinopyranosyl
glc = glucopyranosyl

Chart 1

the structure of **1** was elucidated as 3-*O*-*β*-D-glucopyranosyl-11α-methoxy-oleanolic acid 28-*O*-*β*-D-glucopyranosyl ester. Amagaya *et al.*[9] suggested that the 11α-methoxyl group of oleanolic acid-type compounds might be an artifact derived from an 11α-hydroxy compound during extraction with methanol. Fresh leaves were extracted with ethanol following detection by thin layer chromatography (TLC) to give **1** as the major glycoside.

The saponins **3** and **5** gave **6**, D-glucose and L-arabinose on acid hydrolysis, respectively. In ^{13}C-NMR spectra of **3** and **5**, the signals due to the aglycone moiety were in good agreement with those of the 3,28-*O*-bisdesmoside of **6**. The signals due to the sugar moiety of **3** showed the presence of four monosaccharide units and **5** showed the presence of five monosaccharide units. On selective cleavage of the ester–glycoside linkage (*vide supra*), **3** also afforded a prosapogenin (**11**) and a methyl disaccharide, which was identified as **9**. The carbon signals due to the sugar moiety of **11** were found to be almost superimposable on those of **10**. These observations led to the formulation of **3**[7] as shown in Chart 1.

Selective cleavage of the C-28-sugar moiety of **5** gave a prosapogenin (**12**) and a methyl disaccharide, which was identified as **9**. Acid hydrolysis of **12** gave **6**, D-glucose and L-arabinose. The sugar sequence analysis of permethylated **12** by gas chromatography-mass spectrometry (GC-MS) showed the formation of 1,5-di-*O*-acetyl-2,3,4,6-tetra-*O*-methyl-glucitol, 1,4,5-tri-*O*-acetyl-2,3,6-tri-*O*-methyl-glucitol and 1,2,5-tri-*O*-acetyl-3,4-di-*O*-methyl-arabinitol, which were shown to be identical with authentic specimens.[10-12] Moreover, in the negative FAB-MS of **12**, ions at *m/z* 911 $[M-H]^-$, *m/z* 749 $[M-H-\text{hexose}]^-$, *m/z* 617 $[M-H-\text{hexose–pentose}]^-$, and *m/z* 455 $[M-H-\text{hexose–pentose–hexose}]^-$, indicated that the sugar moiety of **12** consists of a linear hexose–pentose–hexose unit. The mass spectrum (MS) of acetate of **12** exhibited fragment ions at *m/z* 331 [(glucose) Ac_4], 547 [(glucose) Ac_4–(arabinose) Ac_2] and 835 [(glucose) Ac_4–(arabinose) Ac_2–(glucose) Ac_3]. Consequently, the structure of **5** was concluded to be 3-*O*-*β*-D-glucopyranosyl-(1→2)-α-L-arabinopyranosyl-(1→4)-*β*-D-glucopyranosyl oleanolic acid 28-*O*-*β*-D-glucopyranosyl-(1→6)-*β*-D-glucopyranosyl ester.

We have already reported some results of preliminary screening for molluscicidal activity. However, **1**, **2**, **3**, **4** and **5** did not show molluscicidal activity against *Oncomelania nosophora*[4] at the concentration of 100 ppm.

Recently, Namba *et al.*[13] reported the inhibitory effect of oleanolic acid saponins obtained from *Anemone flaccida* Fr. SCHMIDT on the reverse transcriptase from a ribonucleic acid (RNA) tumor virus. Compounds **1**, **2**, **3**, **4** and **5** (10^{-4} M) did not have an inhibitory activity of reverse transcriptase of the avian myeloblastasis virus (AMV) in the presence of poly(rA)–oligo(dT) activated calf thymus deoxyribonucleic acid (DNA) or the 70S RNA template primer.

Experimental

All melting points were measured on a Yanagimoto micro melting points apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were measured on a JEOL GX-400 spectrometer in a C_5D_5N solution using tetramethylsilane (TMS) as an internal standard. GC-MS was taken on a JEOL JMS-SX 102 spectrometer: column, Neutra Bond-1 25 m × 0.25 mm i.d. 0.4 μm, ionizing volt 70 eV, accelerating volt 1.5 kV, carrier gas He 1 ml/min, injection temp. 200 °C, column temp. 100—200 °C, separator temp. 250 °C; electron impact-mass spectrum (EI-MS) was taken on a JEOL JMS-SX 102 spectrometer by the direct inlet method. For column chromatography, Kieselgel 60H (Art. 7736, Merck), LiChroprep RP-18 (25—40 μm, Merck) and Diaion HP-20 (Mitsubishi Chem. Ind. Co., Ltd., Tokyo, Japan) were used. All solvent systems for chromatography were homogeneous.

Extraction and Separation The air-dried leaves of *Acanthopanax hypoleucus* (100 g), collected in Hirogawara, Yamanashi, were extracted with a hot 50% aqueous MeOH. The 50% MeOH extract was concentrated and the residue (17.0 g) was partitioned between H_2O and Et_2O. The aqueous layer was chromatographed on a column of Diaion HP-20 by elution with H_2O, 50% aqueous MeOH, MeOH and finally with $CHCl_3$.

A saponin mixture (3 g) eluted with MeOH was separated by chromatography on silica gel with $CHCl_3$–MeOH–H_2O (15:5:0.6, 15:6:1.0, 15:7:1.2, 15:8:1.2 and 15:9:2.0 successively) to give five fractions, Fr-A, -B, -C, -D and -E. Chromatography of Fr-A on a reverse phase column, LiChroprep RP-18 (solvent: 65% MeOH), gave a new saponin, **1** (42 mg). Fr-B was chromatographed on LiChroprep RP-18 (solvent: 65% MeOH) to give **2** (75 mg). Fr-C was separated by chromatography on LiChroprep RP-18 (solvent: 70% MeOH) to give **3** (48 mg). Fr-D was chromatographed on LiChroprep RP-18 (solvent: 65% MeOH) to give **4** (90 mg) and **5** (22 mg). Fr-E was chromatographed on LiChroprep RP-18 (solvent: 70% MeOH) to give a new saponin, **5** (60 mg).

1: A white powder, $[\alpha]_D^{16}$ 2.8° (*c*=0.29, MeOH). *Anal.* Calcd for $C_{43}H_{70}O_{14}\cdot 4H_2O$: C, 58.48; H, 8.90. Found: C, 58.28; H, 8.27. ^{1}H-NMR (C_5D_5N): δ: 0.87 (×2), 0.97, 1.01, 1.06, 1.31, 1.34 (each 3H, s), δ 3.19 (3H, s, OMe), δ 3.76 (1H, dd, *J*=8.06, 3.85 Hz) δ 4.91 (1H, d, *J*=7.69 Hz), δ 5.70 (1H, d, *J*=3.85 Hz, 12-H), δ 6.31 (1H, d, *J*=7.69 Hz).

2: A white powder, mp 208—212 °C (MeOH) $[\alpha]_D^{16}$ 32.6° (*c*=0.54, MeOH). ^{13}C-NMR data is given in Table I.

3: A white powder, mp 220—223 °C (MeOH) $[\alpha]_D^{16}$ 15.9° (*c*=0.57, MeOH). ^{13}C-NMR data is given in Table I.

4: A white powder, $[\alpha]_D^{16}$ 14.7° (*c*=0.35, pyridine). ^{13}C-NMR data is given in Table I.

5: A white powder $[\alpha]_D^{16}$ 2.1° (*c*=0.34, pyridine). *Anal.* Calcd for $C_{59}H_{96}O_{27}\cdot 8H_2O$: C, 51.29; H, 8.17. Found: C, 51.04; H, 7.49. ^{1}H-NMR (C_5D_5N): δ 0.83, 0.87, 0.86, 1.06 (×2), 1.21, 1.22 (each 3H, s), δ 4.80 (1H, d, *J*=6.96 Hz), δ 5.00 (1H, d, *J*=7.69 Hz), δ 5.27 (1H, d, *J*=7.33 Hz), δ 5.38 (1H, t-like, 12-H), δ 5.48 (1H, d, *J*=7.69 Hz), δ 6.22 (1H, d, *J*=7.88 Hz).

Selective Cleavage of the Ester Glycosyl Linkages of 2, 3, 4 and 5 A solution of **2** (48.0 mg), anhydrous LiI (50.0 mg) and 2,6-lutidine (1.2 ml) in anhydrous MeOH was refluxed for 40 h at 140 °C under a N_2 stream. After cooling, the reaction mixture was diluted with 50% MeOH (6 ml), neutralized with Amberlite MB-3 resin and evaporated to dryness. The residue was chromatographed on a column of Diaion HP-20 (50% MeOH and MeOH) to afford **8** (14 mg) and **9** (13 mg). The latter was identified as a mixture of methyl *β*-D-glucopyranosyl(1→6)-(α and *β*)-D-glucopyranosides by the ^{13}C-NMR spectrum data. By the same method, **3** (27 mg) gave **11** (9 mg) and **9** (7 mg); **4** (58 mg) gave **10** (21 mg) and **9** (13 mg); **5** (37 mg) gave **12** (18 mg) and **9** (6 mg).

Compound **12**: A white powder, $[\alpha]_D^{16}$ 11.7° (*c*=0.27, pyridine). *Anal.* Calcd for $C_{47}H_{76}O_{17}\cdot 5H_2O$: C, 56.27; H, 8.64. Found: C, 56.31; H, 8.02. ^{13}C-NMR data of **12** was listed in Table I.

Sequence Analysis by GC-MS To a solution of a saponin (5 mg) in dimethyl sulfoxide (DMSO) (300 μl) was added a saturated solution of NaH in DMSO (300 μl). The solution was sonicated at room temperature for 1 h. To this solution was added CH_3I (500 μl) under cooling and the mixture was further sonicated at room temperature for 30 min. The reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried, and concentrated to dryness. The residue was treated with 90% HCOOH (2 ml) at 100 °C for 1 h. The reaction mixture was evaporated to remove HCOOH. The residue was treated with 0.13 M–H_2SO_4 (2 ml) at 100 °C for 4 h. To the reaction mixture was added $BaCO_3$ and the resulting precipitate was filtered and washed with H_2O. The filtrate and washing were combined and concentrated, and 50% MeOH (2 ml) was added. To this solution was added $NaBH_4$ (or $NaBD_4$) (25 mg). After standing at room temperature for 2 h, the mixture was acidified by passage through a column of Dowex 50W-X8 (H^+ form) and concentrated to dryness. Boric acid in the residue was removed by repeated (four times) co-distillation with MeOH. The resulting methylated alditol mixture was acetylated with Ac_2O–C_5H_5N (1 : 1, 1 ml) at room temperature over night. The reagent was removed by co-distillation with *n*-hexane. The methylated alditol acetate mixture thus obtained was subjected to GC-MS.

TABLE I. ^{13}C-NMR Chemical Shifts of Saponins in C_5D_5N

	Compd. 1	2	8	3	11	4	10	5	12
C-1	39.68	38.61	38.74	38.71	38.77	38.61	38.70	38.75	38.80
C-2	26.75	25.86	26.01	26.36	26.49	25.74	25.89	26.50	26.64
C-3	88.72	81.82	81.90	88.80	88.88	82.07	82.20	88.93	89.01
C-4	39.68	43.25	43.43	39.43	39.55	43.30	43.46	39.59	39.73
C-5	55.78	47.40	47.60	55.78	55.88	47.70	47.90	55.82	55.93
C-6	18.59	18.00	18.12	18.47	18.54	18.07	18.18	18.43	18.52
C-7	33.43	32.32	32.86	33.92	33.31	32.61	33.18	33.03	33.30
C-8	38.22	39.74	39.74	39.84	39.79	39.74	39.72	39.81	39.78
C-9	53.31	47.98	48.12	48.00	48.08	47.98	48.09	47.97	48.07
C-10	43.25	36.75	36.91	36.92	37.04	36.74	36.89	36.92	37.05
C-11	75.88	23.67	23.81	23.74	23.84	47.98	23.65	23.31	23.74
C-12	122.41	122.69	122.51	122.78	122.56	122.70	122.51	122.77	122.56
C-13	148.67	143.97	144.76	144.08	144.87	143.99	144.77	144.04	144.84
C-14	42.22	41.94	42.12	42.07	42.20	41.97	42.12	42.05	42.18
C-15	28.26	28.09	28.28	28.16	28.27	28.12	28.30	28.19	28.34
C-16	23.23	23.17	23.70	23.33	23.75	23.69	23.81	23.72	23.80
C-17	46.57	46.83	46.60	47.00	46.72	46.86	46.60	46.92	46.70
C-18	41.25	41.48	41.93	41.63	42.05	41.51	41.94	41.60	42.02
C-19	46.08	46.03	46.37	46.21	46.54	46.07	46.40	46.19	46.52
C-20	30.68	30.52	30.86	30.68	30.99	30.55	30.88	30.65	30.98
C-21	33.84	33.77	34.16	33.05	34.28	33.81	34.18	33.92	34.28
C-22	32.33	32.60	33.16	32.48	33.25	32.37	32.85	32.44	33.24
C-23	28.26	64.32	64.51	28.20	28.35	64.70	64.89	27.97	28.08
C-24	16.86	13.37	13.51	16.67	16.80	13.24	13.37	16.64	16.77
C-25	19.10	16.03	16.03	15.53	15.50	16.02	16.01	15.50	15.48
C-26	17.18	17.39	17.41	17.44	17.43	17.40	17.40	17.41	17.41
C-27	25.34	25.86	26.08	25.98	26.18	25.88	26.10	25.95	26.18
C-28	176.38	176.35	180.09	176.46	180.20	176.38	180.10	176.42	180.21
C-29	32.92	32.90	33.16	33.05	33.31	32.92	33.18	33.03	33.30
C-30	23.56	23.49	23.63	23.62	23.81	23.52	23.73	23.59	23.80
OMe	54.18								
R_1									
a-1		106.29	106.54	104.84	104.65	103.64	103.84	105.27	105.46
a-2		74.43	74.63	81.05	80.79	80.94	81.29	83.21	83.33
a-3		72.84	73.06	73.44	73.27	73.37	73.56	72.29	72.44
a-4		69.33	69.50	68.29	68.13	68.05	68.21	68.62	68.77
a-5		66.63	66.81	64.95	64.75	64.70	64.89	65.81	65.96
g-1	106.73			106.03	105.82	105.59	105.88	104.24	104.40
g-2	75.67			76.41	76.22	75.96	76.17	76.00	76.15
g-3	78.75			78.24	78.10	78.05	78.22	77.35	77.46
g-4	71.07			71.67	71.55	71.35	71.37	78.17	78.32
g-5	78.62			78.16	78.02	77.98	78.17	77.29	77.46
g-6	62.82			62.66	62.55	62.36	62.50	62.45	62.59
g′-1								104.84	104.99
g′-2								75.16	75.30
g′-3								78.49	78.64
g′-4								71.44	71.58
g′-5								78.35	78.50
g′-6								63.12	63.26
R_3									
g-1′	95.71	95.43		95.59		95.46		95.57	
g-2′	74.02	73.63		73.81		73.68		73.79	
g-3′	79.21	78.11		78.62		78.47		78.59	
g-4′	71.68	71.31		71.49		71.22		71.44	
g-5′	78.04	78.11		78.32		78.16		78.26	
g-6′	62.17	69.14		69.35		69.20		69.31	
g-1″		104.90		105.13		104.96		105.09	
g-2″		74.88		75.06		74.92		75.03	
g-3″		78.42		77.86		77.72		77.85	
g-4″		70.66		70.88		70.73		70.86	
g-5″		77.68		78.29		78.16		78.26	
g-6″		62.41		62.58		62.45		62.55	

Acid Hydrolysis of 1, 2, 3, 4, 5 and 8 A solution of **1** (2 mg) in 7% HCl–dioxane (1 : 1, 1 ml) was refluxed for 4 h. The reaction mixture was diluted with H_2O and then extracted with Et_2O. The Et_2O layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. The H_2O layer was neutralized with Amberlite MB-3 ion exchange resin and evaporated to dryness. The resulting monosaccharides were trimethylsilylated with TMS and identified by gas-liquid chromatography (GLC) comparison with authentic samples. **1** afforded genin and D-glucose; **2**, **4** and **8** afforded hederagenin **7**, L-arabinose and D-glucose; **3**, **5** and **12** afforded oleanolic acid **6**, L-arabinose and D-glucose.

Saponification of 1 Saponification of **1** with 0.5 N aqueous KOH afforded prosapogenin along with 1,6-anhydroglucose.

AMV Reverse Transcriptase Assay The methods described by Nishio *et al.*[14] were modified to assay the reverse transcriptase activity of AMV.

Bioassay of Molluscicidal Activity Bioassay was done with snails of the species *Oncomelania nosophora*. The bioassay method was already reported in a previous paper.[15]

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