Studies on the Constituents of *Heloniopsis orientalis* (THUNB.) C. TANAKA

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The constituents of the fresh whole plants of *Heloniopsis orientalis* (THUNB.) C. TANAKA (Liliaceae) were investigated and five steroidal components were obtained. Their chemical structures were characterized as dioscin (1), pennogenin 3-*O*-*β*-chacotrioside (T-c) (2), pregnadienolone 3-*O*-*β*-chacotrioside (P-d) (3), 26-*O*-*β*-D-glucopyranosyl 17-dehydrokryptogenin 3-*O*-*β*-chacotrioside (4) and 12-*O*-*β*-D-galactopyranosyl heloniogenin 3-*O*-*β*-D-allomethylopyranosyl-(1→5)-*β*-D-apiofuranoside (5).

Keywords *Heloniopsis orientalis*; Liliaceae; steroidal glycoside; dioscin; pennogenin glycoside; 17-dehydrokryptogenin glycoside; pregnadienolone glycoside; heloniogenin bisdesmoside; allomethylose; *β*-chacotrioside

In the previous paper,[1] we reported the isolation of four acylated sucrose derivatives from the fresh whole plants of *Heloniopsis orientalis* (THUNB.) C. TANAKA. Further examination led to the isolation of a new spirostanol bisdesmoside (**5**) along with four steroidal glycosides (**1**—**4**). The present paper describes the isolation and structural characterization of these compounds **1**—**5**.

The AcOEt- and BuOH-soluble fractions previously obtained[1] from the methanolic extract of the title plant were subjected to a combination of Sephadex LH-20 and silica gel chromatographies with various solvent systems to afford compounds **1**—**5**, together with H_{a-d}, which were isolated by Kawasaki *et al.*[2]

Compounds **1** and **2** showed strong absorptions due to hydroxyl groups (3500 cm^{-1}) and a (25 *R*)-spiroketal moiety in the infrared (IR) spectra,[3] and peaks due to $(M+Na)^+$ at *m/z* 891 and 907, respectively, in the fast atom bombardment mass spectra (FAB-MS). They were identified respectively as dioscin[4] and T-c[5]: 3-*O*-α-L-rhamnopyranosyl-(1→4)-[α-L-rhamnopyranosyl-(1→2)]-*β*-D-glucopyranosides (*β*-chacotriosides) of diosgenin and pennogenin, respectively, by the IR, FAB-MS and carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectral evidence.

Compound **3** showed absorptions of α,*β*-unsaturated ketone (1650 cm^{-1}) and hydroxyl groups (3400 cm^{-1}), but none due to a spirostanol side chain in the IR spectrum. The FAB-MS of **3** exhibited a peak at *m/z* 791 that originated from $(M+Na)^+$. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum showed signals due to C-19 and -18 methyls (each 3H, s, at δ 0.92 and 1.07), two rhamnosyl C-6 methyls (each 3H, d, $J=6.1$ Hz, at δ 1.23 and 1.26), one keto-methyl (3H, s, at δ 2.25) and two olefinic protons (each 1H, br s, at δ 5.39 and 6.91). From the above evidence, **3** was presumed to be a pregnane triglycoside and it was found to be 3*β*-hydroxypregna-5,16-dien-20-one 3-*O*-*β*-chacotrioside by direct comparison with an authentic specimen synthesized from methyl proto-dioscin according to Marker's degradation[6]; this compound had been isolated from *Paris polyphylla* SM. and named P-d[7] by Kawasaki *et al.*

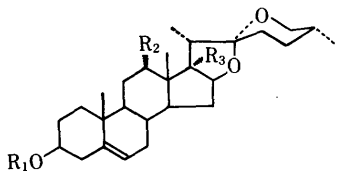
Compound **4** gave quite similar IR, ultraviolet (UV) and optical rotatory dispersion (ORD) spectra to those of Hc, *i.e.* the 3, 26-*O*-bisglycoside of 17(20)-dehydrokryptogenin. The FAB-MS of **4** gave the $(M+Na)^+$ ion peak at *m/z* 1067. Signals ascribable to the sugar residue of **4** were superimposable on those of proto-dioscin in the ^{13}C-NMR spectra. Therefore, **4** could be represented as 26-*O*-*β*-D-glucopyranosyl 17(20)-dehydrokryptogenin 3-*O*-*β*-chacotrioside.

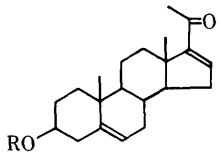
Compound **5** showed a strong absorption band due to the hydroxyl groups and characteristic absorption bands of the (25*R*)-spiroketal side chain in the IR spectrum. On acid hydrolysis, **5** liberated an aglycone (**6**), galactose, apiose and allomethylose,[8] which was identified by direct comparison with a specimen prepared[9] from rhamnose. Compound **6**, colorless needles, mp 208—211 °C, showed an M^+ peak at *m/z* 430.3068, giving the molecular formula $C_{27}H_{42}O_4$, and a characteristic prominent peak[10] at *m/z* 139.1124 ($C_9H_{15}O^+$) derived from the spiroketal side chain of the steroidal sapogenol in the electron-impact mass spectrum (EI-MS). The ^{1}H-NMR spectrum of **6** showed two singlets (3H each) at δ 0.83 and 1.02 assignable to the C-18 and -19 methyl groups, two doublets (3H each, $J=6.3$ and 7.1 Hz) at δ 0.78 and 0.99 ascribable to two secondary methyl groups at C-27 and -21, a signal at δ 3.38 (2H, m) due to the 26-methylene protons, a signal at δ 4.40 due to the 16α-H and a signal at δ 5.35 due to a vinyl proton. One of the other protons, a multiplet centered at δ 3.40, was associated with the α-hydrogen adjacent to the *β*-hydroxyl group at C-3, and the remaining proton appeared at δ 3.74 (1H, m, $W_{h/2}=7$ Hz); these signals shifted downfield to δ 4.60 and 4.96 on acetylation, respectively. The ^{13}C-NMR spectrum of **6** exhibited four carbon signals bearing a hydroxyl group or oxide ring at δ 66.9 (t), 71.3 (d), 71.5 (d) and 81.0 (d). These signals except for the one at δ 71.5 could be assigned to C-26, C-3 and C-16 by comparison with those in the ^{13}C-NMR spectrum of diosgenin. The signal at δ 71.5 was assigned to C-12 by taking into account the substituent effects of the hydroxyl group,[11] the configuration of which was determined to be α-axial on the basis of the half-height width of the above-mentioned proton signal at δ 3.74. Furthermore, the resonances of C-11 ($\Delta\delta$+8.4 ppm) and C-13 ($\Delta\delta$+4.8 ppm) were shifted downfield (*β*-effect) due to the introduction of the axial hydroxyl group at C-12, while the signals of the two carbons at C-14 ($\Delta\delta$ −12.1 ppm) and C-17 ($\Delta\delta$−8.2 ppm) were shifted upfield because of the γ-gauche interaction with the axial hydroxyl group at C-12. Consequently, **6** was assumed to be heloniogenin[12] which had been isolated from this plant by Okanishi *et al.*, and this was confirmed by

comparing the ^{1}H-NMR spectrum[13] and physical data with the reported values.

The FAB-MS of **5** gave a $(M+Na)^+$ peak at *m/z* 893. Thus, **5** was considered to be a triglycoside of heloniogenin possessing one each of galactosyl, apiosyl and allomethylosyl moieties.

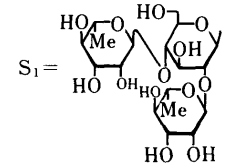
The nona-*O*-acetyl derivative (**5a**) of **5** exhibited peaks due to terminal galactosyl, allomethylosyl and allomethylosyl-apiosyl cations at *m/z* 331, 273 and 489, respectively, in the EI-MS. The ^{13}C-NMR spectrum of **5**, in comparison with the spectra of heloniogenin (**6**), methyl galactopyranoside, methyl apiofuranoside and methyl allomethylopyranoside,[14] exhibited significant glycosylation shifts[15] of the C-3 and C-12 signals of the aglycone, and of the C-5 signal of apiofuranoside. It also gave three anomeric carbon signals at δ 108.0, 107.1 and 102.5, reflecting all

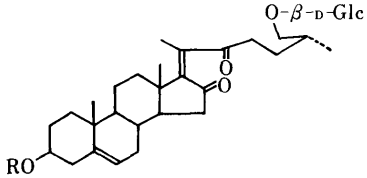




1 : $R_1=S_1$, $R_2=R_3=H$
2 : $R_1=S_1$, $R_2=H$, $R_3=OH$
5 : $R_1=S_2$, $R_2=O$-β-D-Gal, $R_3=H$
6 : $R_1=R_3=H$, $R_2=OH$
7 : $R_1=R_3=H$, $R_2=O$-β-D-Gal

3 : $R=S_1$





4 : $R=S_1$

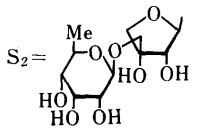


TABLE I. ^{13}C-NMR Data for **5**—**7** (in Pyridine-d_5)

	5	6	7		5	6	7
C-1	37.1	37.7	37.5	C-25	30.6	30.7	30.6
C-2	30.1	32.6	32.6	C-26	66.8	66.9	66.8
C-3	77.5	71.3	71.3	C-27	17.3	17.3	17.3
C-4	39.3	43.5	43.5	Gal			
C-5	141.2	142.1	142.3	C-1	107.1		107.2
C-6	121.5	121.2	120.9	C-2	72.9		72.9
C-7	32.0	32.3	32.0	C-3	75.4		75.5
C-8	31.7	32.1	31.9	C-4	70.5		70.0
C-9	49.0	48.4	49.1	C-5	76.6		76.8
C-10	36.8	36.8	36.8	C-6	62.0		62.1
C-11	27.5	29.3	27.6	Api			
C-12	82.6	71.5	82.6	C-1	108.0		
C-13	44.8	45.1	44.9	C-2	78.3		
C-14	44.3	44.5	44.5	C-3	78.9		
C-15	32.0	32.4	32.2	C-4	74.6		
C-16	80.9	81.0	81.0	C-5	72.9		
C-17	53.0	53.9	53.1	Allo			
C-18	17.0	17.3	17.1	C-1	102.5		
C-19	19.2	19.5	19.3	C-2	74.1		
C-20	42.2	42.3	42.3	C-3	72.3		
C-21	15.2	14.9	15.3	C-4	72.7		
C-22	109.3	109.3	109.3	C-5	69.8		
C-23	32.0	31.9	32.0	C-6	18.5		
C-24	29.3	29.4	29.4				

TABLE II. ^{13}C-NMR Data for **1**—**4** (in Pyridine-d_5)

	1	2	3	4
C-1	37.3	37.6	37.3	37.1
C-2	30.0	30.1	30.1	30.0
C-3	77.8	77.8	77.8	77.8
C-4	38.9	39.0	39.0	38.8
C-5	140.8	140.8	141.3	140.9
C-6	121.6	121.8	121.5	121.3
C-7	32.2	32.3	32.3	31.7
C-8	31.6	31.8	30.4	30.8
C-9	50.3	50.3	50.8	49.9
C-10	37.0	37.1	37.1	37.0
C-11	21.0	20.9	20.9	20.9
C-12	39.8	32.4	35.1	38.7
C-13	40.4	45.1	46.3	43.4
C-14	56.6	53.0	56.5	50.5
C-15	32.1	32.1	31.8	36.0
C-16	81.0	90.1	144.6	210.4
C-17	62.8	90.1	155.2	142.5
C-18	16.2	17.1	15.9	15.7
C-19	19.3	19.4	19.2	19.3
C-20	41.9	44.8	196.2	145.6
C-21	14.9	9.6	27.1	16.7
C-22	109.1	109.8		205.6
C-23	31.6	32.1		37.9
C-24	29.2	28.8		27.9
C-25	30.5	30.4		33.3
C-26	66.8	66.7		75.0
C-27	17.2	17.3		17.4
3-*O*-Glc				
C-1	100.2	100.2	100.2	100.2
C-2	78.9	78.8	78.8	78.8
C-3	76.6	76.8	76.8	76.8
C-4	78.1	78.1	78.1	78.0
C-5	77.7	77.9	77.8	77.8
C-6	61.3	61.3	61.3	61.3
Rha				
C-1	101.8	101.9	101.9	101.8
C-2	72.5	72.4	72.3	72.6
(Glc^2—) C-3	72.2	72.6	72.6	72.4
C-4	73.7	73.8	73.8	73.7
C-5	69.3	69.4	69.3	69.4
C-6	18.5	18.6	18.5	18.5
Rha′				
C-1	102.7	102.9	102.8	102.8
C-2	72.6	72.4	72.3	72.7
(Glc^4—) C-3	72.2	72.8	72.7	72.4
C-4	73.9	74.1	74.0	74.0
C-5	70.3	70.4	70.3	70.3
C-6	18.3	18.4	18.4	18.4
26-*O*-Glc				
C-1				104.7
C-2				75.0
C-3				78.3
C-4				71.4
C-5				78.5
C-6				62.8

β-configuration of the apiofuranosyl, the galactopyranosyl and the allomethylopyranosyl residues in **5** (Table I). Accordingly, **5** was suggested to be a bisdesmoside. Partial hydrolysis with 0.3 N HCl–MeOH of **5** provided a prosapogenin (**7**) together with methylsides of apiose and allomethylose. The ^{13}C-NMR spectrum of **7** showed the glycosylation shift of the C-12 signal and an anomeric carbon signal at δ 107.2 assignable to the galactopyranosyl moiety (Table I). Consequently, the structure of **5** was assigned as 3-*O*-β-D-allomethylopyranosyl-(1→5)-β-D-apiofuranosyl heloniogenin 12-*O*-β-D-galactopyranoside.

Compound **5** is the first heloniogenin bisdesmoside to be reported, and to our knowledge, the first example of a glycoside possessing an allomethylosyl unit except for cardenolide glycoside. The sugar moiety and the aglycone part of **1**—**4** are respectively identical and closely related chemically, and this suggests a close biogenetic relationship among these compounds.

Experimental

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Optical rotations were measured with a Union Giken PM-201 automatic digital polarimeter. ORD curve was measured with a JASCO J-600. IR and UV spectra were recorded with Hitachi 215 and 330 machines and ^{1}H- and ^{13}C-NMR spectra were taken with a JEOL FX-200 machine. EI- and FAB-MS were recorded on a JEOL JMS D-300 instrument. Column chromatography was carried out with Sephadex LH-20 (25—100 μ, Pharmacia Fine Chemical Co., Ltd.), MCI-gel CHP 20P (75—150 μ, Mitsubishi Chemical Industries, Ltd.), Kieselgel 60 silanisiert (70—230 mesh, Merck) and Kieselgel 60 (70—230 mesh, Merck). Thin-layer chromatography (TLC) was performed on precoated Kieselgel 60 F_{254} plates (0.2 mm thick, Merck) and spots were detected by spraying 10% H_2SO_4 followed by heating.

Isolation of Glycosidic Constituents The AcOEt- and BuOH-soluble fractions, previously obtained[1] from the methanolic extract of the fresh whole plants of *Heloniopsis orientalis* (Shojobakama) were rechromatographed over silica gel ($CHCl_3$–MeOH–H_2O (8:2:0.2), AcOEt–MeOH–H_2O (9:1:0.1), $CHCl_3$–MeOH–AcOEt–H_2O (2:2:5:1) upper phase), silanized silica gel (40% aqueous MeOH), Sephadex LH-20 (MeOH) and MCI-gel CHP 20P (30% aq. MeOH) to afford compounds **1** (1.2 g), **2** (40 mg), **3** (214 mg), **4** (420 mg) and **5** (305 mg).

Compound 1 Colorless needles, mp 277—279 °C. $[\alpha]_D^{24}$ −121.0° (c=1.00, MeOH). IR ν_{max}^{KBr} cm^{-1}: 3500. FAB-MS m/z: 891 $(M+Na)^+$. ^{13}C-NMR: Table II. Identical with an authentic sample on direct comparison.

Compound 2 Colorless needles, mp 275—277 °C (dec.). $[\alpha]_D^{22}$ −44.0° (c=1.00, MeOH). IR ν_{max}^{KBr} cm^{-1}: 3500, 980, 920, 900, 890 (900>920, (25*R*)-spiroketal). FAB-MS m/z: 907 $(M+Na)^+$. ^{13}C-NMR: Table II.

Compound 3 A white powder. $[\alpha]_D^{24}$ −85.6° (c=0.90, MeOH). IR ν_{max}^{KBr} cm^{-1}: 3400, 1650, 1590 (enone), no spiroketal absorption. UV λ_{max}^{MeOH} nm: 240 (ε=7600). FAB-MS m/z: 791 $(M+Na)^+$. ^{1}H-NMR (CD_3OD) δ: 0.92 (3H, s, 18-CH_3), 1.07 (3H, s, 19-CH_3), 1.23, 1.26 (each 3H, d, J=6.1 Hz, rha 5-CH_3), 2.25 (3H, s, CH_3–CO–), 4.50 (1H, d, J=7.8 Hz, glc 1-H), 5.20 (1H, d, J=1.5 Hz, rha 1-H), 5.39 (2H, br d, 6-H and rha 1-H), 6.91 (1H, br s, 16-H). ^{13}C-NMR: Table II. Identified as 3-hydroxypregna-5,16-dien-20-one 3-*O*-β-chacotrioside by direct comparison with an authentic sample prepared from methyl protodioscin.

Compound 4 A white powder. $[\alpha]_D^{22}$ −94.0° (c=1.0, MeOH). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1700 (C=O), 1630 (C=C). UV λ_{max}^{MeOH} nm: 247 (ε=3580). ORD (c=0.062, MeOH) [M] (nm): +4600° (322) (peak), −5200° (364) (trough). FAB-MS (m/z): 1067 $(M+Na)^+$, ^{13}C-NMR: Table II.

Compound 5 An amorphous powder. $[\alpha]_D^{24}$ −41.0° (c=1.00, MeOH). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 980, 960, 912, 900, 860, 840 (900>912, (25*R*)-spiroketal). FAB-MS m/z: 893 $(M+Na)^+$. *Anal.* Calcd for $C_{44}H_{70}O_{17}$ H_2O: C, 59.44; H, 8.16. Found: C, 59.73 H, 8.12. EI-MS m/z: 592, 430, 412, 394, 298, 139.

Acid Hydrolysis of 5 A solution of **5** (50 mg) in 2 N HCl–MeOH was refluxed for 2 h and the reaction mixture was neutralized with 3% KOH–MeOH and evaporated to dryness *in vacuo* to give a residue, which was chromatographed over silica gel (solv. $CHCl_3$–MeOH (10:1)→$CHCl_3$–MeOH–H_2O (7:3:0.5)) to afford an aglycone **6**, colorless needles (15 mg), mp 208—212 °C. $[\alpha]_D^{26}$ −60.0° (c=0.60, $CHCl_3$). MS m/z: 430.3068 ($C_{27}H_{42}O_4$), 412.2919 ($C_{27}H_{40}O_3$), 298.2288 ($C_{21}H_{30}O$), 139.1124 ($C_9H_{15}O$). ^{1}H-NMR ($CDCl_3$) δ: 0.78 (3H, d, J=6.3 Hz, 27-CH_3), 0.83 (3H, s, 18-CH_3), 0.99 (3H, d, J=7.1 Hz, 21-CH_3), 1.02 (3H, s, 19-CH_3), 3.38 (2H, m, 26-H_2), 3.40 (1H, m, 3-H), 3.74 (1H, br s, $W_{h/2}$=7 Hz, 12-H), 4.40 (1H, m, 16-H), 5.35 (1H, br d, 6-H). ^{13}C-NMR: Table I. Methylside of β-D-allomethylose (5 mg), colorless oil. ^{1}H-NMR (pyridine-d_5) δ: 1.60 (3H, d, J=6.3 Hz, 5-CH_3), 3.59 (3H, s, OMe), 3.68 (1H, dd, J=2.9, 9 Hz, 4-H), 3.95 (1H, dd, J=3.2, 7.8 Hz, 2-H), 4.30 (1H, m, 5-H), 4.67 (1H, dd, J=3.2, 2.9 Hz, 3-H), 5.12 (1H, d, J=7.8 Hz, 1-H), which was identified by comparison of the ^{1}H-NMR spectrum and *Rf* on TLC with those of methyl β-D-allomethyloside, prepared[9] from rhamnose, and a mixture of methylsides of galactose and apiose, which were identified by TLC comparison with authentic samples.

Acetylation of 6 Compound **6** (10 mg) was acetylated with acetic anhydride and pyridine (each 1 ml) in the usual manner to give a diacetate (**6a**, 6 mg). $[\alpha]_D^{26}$ −21.7°(c=0.46, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.78 (3H, d, J=6.1 Hz), 0.87 (3H, s), 0.91 (3H, d, J=7.1 Hz), 1.02 (3H, s), 2.03, 2.06 (each 3H, s), 3.36 (2H, m, 26-H_2), 4.40 (1H, m, 16-H), 4.60 (1H, m, 3-H), 4.96 (1H, br s, 12-H), 5.39 (1H, br d, 6-H).

Acetylation of 5 Compound **5** (10 mg) was acetylated in the same manner as described above to give a nonaacetyl derivative (**5a**, 5 mg). $[\alpha]_D^{27}$ +26.0° (c=0.50, $CHCl_3$). EI-MS m/z: 743 ($C_{41}H_{59}O_{12}$), 489 ($C_{21}H_{29}O_{13}$), 331 ($C_{14}H_{19}O_9$), 273 ($C_{12}H_{17}O_7$). ^{1}H-NMR ($CDCl_3$) δ: 0.78 (3H, d, J=5.4 Hz), 0.79 (3H, s), 0.95 (3H, d, J=6.5 Hz), 0.98 (3H, s), 1.20 (3H, d, J=6.4 Hz), 1.99—2.18 (OAc×9).

Partial Hydrolysis A solution of **5** (43 mg) in 0.3 N HCl–MeOH (3 ml) was refluxed for 20 min then diluted with water and extracted with *n*-BuOH. The BuOH layer was evaporated. The residue was subjected to column chromatography over silica gel with $CHCl_3$–MeOH–H_2O (8:1:0.1) to afford a prosapogenin **7** (17 mg), $[\alpha]_D^{24}$ +4.6° (c=1.31, MeOH). ^{13}C-NMR: Table I. The aqueous layer was neutralized by passage through Amberlite IRA-400, then evaporated *in vacuo* to give a mixture of sugars, apiose (*Rf* 0.64 on TLC, solv. benzene–EtOH–acetone–H_2O (7:5:3:0.5)) and allomethylose (*Rf* 0.60).

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