Fern Constituents: Four New Diterpenoid Glycosides from Fresh Leaflets of *Gleichenia japonica*

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From the fresh leaflets of a fern, *Gleichenia japonica*, four new labdane-type diterpenoid glycosides, 18-*O*- α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)- β -D-glucopyranosyl-13-epitorreferol (1), 3-*O*- α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)- β -D-glucopyranosyl-3 β -hydroxymanool (2), 3-*O*- α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)- β -D-glucopyranosyl-3 β -hydroxy-13-epimanool (3), and 3-*O*- α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)- β -D-glucopyranosyl-(13*E*)-labda-8(17),13-diene-3 β ,15-diol (4), were isolated together with two known compounds, (6*S*,13*S*)-6-*O*- α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)- β -D-glucopyranosyl-6,13-dihydroxycleroda-3,14-diene (5) and 3-*O*- β -D-glucopyranosyl-13-*O*- α -L-rhamnopyranosyl-3 β -hydroxymanool (6), and their structures were determined.

Keywords fern; *Gleichenia japonica*; labdane diterpenoid; glycoside

Gleichenia japonica SPR. [= *Diplopterygium glaucum* (THUNB. ex HOUTT.) NAKAI, urajiro in Japanese, Gleicheniaceae] is a common fern distributed in southern Honshû, Shikoku and Kyushû, Japan, and throughout in south-east Asia. This fern grows as a large unit colony, and has been used as a diuretic.¹⁾ In previous papers,²⁾ we have reported the isolation and identification of four triterpenoids belonging to the hopane and migrated hopane groups, such as hydroxyhopane (diplopterol), trisnorhopane, fern-9(11)-ene and hop-22(29)-ene, from a hexane extract of fresh leaflets of this fern. Further investigations of a methanol extract of fresh leaflets resulted in the isolation of four new labdane-type diterpenoid glycosides, 18-*O*- α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)- β -D-glucopyranosyl-13-epitorreferol (1), 3-*O*- α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)- β -D-glucopyranosyl-3 β -hydroxymanool (2), 3-*O*- α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)- β -D-glucopyranosyl-3 β -hydroxy-13-epimanool (3), and 3-*O*- α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)- β -D-glucopyranosyl-(13*E*)-labda-8(17),13-diene-3 β ,15-diol (4) (Chart 1), together with two known compounds, (6*S*,13*S*)-6-*O*- α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)- β -D-glucopyranosyl-6,13-dihydroxycleroda-3,14-diene (5),³⁾ and 3-*O*- β -D-glucopyranosyl-13-*O*- α -L-rhamnopyranosyl-3 β -hydroxymanool (6).⁴⁾ This paper deals with the structural elucidation and identification of these glycosides.

Results and Discussion

The methanol extract of the fresh leaflets was separated by various kinds of chromatography (see Experimental) to give 1, 2, 3, 4, 5 and 6. Compounds 5 and 6 were identified by comparison of the optical rotations, and the ¹H- and ¹³C-NMR data with those published.^{3,4)}

Compound 1 showed the molecular ion peak at *m/z* 615 [M + H]⁺, and the characteristic fragment ion at *m/z* 288 due to the aglycone part in the FAB-MS. Further, the high-resolution FAB-MS (HR-FAB-MS) indicated the molecular formula to be C₃₂H₅₅O₁₁ (*m/z* 615.3787). The ¹H-NMR spectrum of 1 indicated the presence of three tertiary, one secondary and one hydroxy methyls, one vinyl group, one exocyclic double bond and two anomeric protons (Table I). The ¹³C-NMR spectrum of 1 coincided with that of 3-*O*- α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)- β -D-glucopyranosyl-13-*O*- α -L-rhamnopyranosyl-3 β -hydroxymanool (7),⁴⁾ except for the signals of C-3, C-13, C-18, and adjoining atoms of the aglycone part (Table II). The sugar part of 1 was characterized as the 18-*O*- α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)- β -D-glucopyranosyl on the basis of the ¹H- and ¹³C-NMR spectra.^{4,5)} Further, the enzymatic hydrolysis of 1 with crude hesperidinase gave 13-epitorreferol (8) as the aglycone.⁶⁾ Thus, 1 was determined to be 18-*O*- α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)- β -D-

Chart 1

TABLE I. ^1H -NMR Spectral Data for Diterpenoid Alcohols and Glycosides (500 MHz, $\text{C}_5\text{D}_5\text{N}$ or CDCl_3 , δ)

	1	2	3	4	5 ^{a)}
H-3		3.377 (dd, 4.0, 11.8)	3.396 (dd, 3.9, 11.9)	3.384 (dd, 3.9, 11.7)	5.150 (m)
H-6					3.708 (dd, 4.3, 10.4)
H-14	6.173 (dd, 10.4, 17.4)	6.216 (dd, 10.7, 17.4)	6.238 (dd, 10.7, 17.4)	5.808 (dt, 0.9, 6.2)	6.169 (dd, 10.7, 17.2)
H-15a	5.152 (dd, 1.8, 10.4)	5.193 (dd, 2.1, 10.7)	5.192 (dd, 1.9, 10.7)	4.529 (brs)	5.117 (dd, 2.1, 10.8)
H-15b	5.572 (dd, 1.8, 17.4)	5.614 (dd, 2.1, 17.4)	5.600 (dd, 1.9, 17.4)		5.578 (dd, 2.1, 17.2)
H-16	1.457 (3H, s)	1.511 (3H, s)	1.511 (3H, s)	1.718 (3H, s)	1.511 (3H, s)
H-17a	4.879 (brs)	4.783 (brs)	4.848 (brs)	4.612 (brs)	0.733 (d, 5.5)
H-17b	4.934 (brs)	4.933 (brs)	4.933 (brs)	4.909 (brs)	
H-18	3.152 (d, 9.1)	1.250 (3H, s)	1.261 (3H, s)	1.247 (3H, s)	2.199 (3H, s)
	3.954 (d, 9.1)				
H-19	0.849 (3H, s)	1.170 (3H, s)	1.180 (3H, s)	1.181 (3H, s)	0.723 (3H, s)
H-20	0.764 (3H, s)	0.673 (3H, s)	0.681 (3H, s)	0.657 (3H, s)	1.462 (3H, s)
H-1'	4.780 (d, 7.3)	4.959 (d, 7.3)	4.975 (d, 7.4)	4.968 (d, 7.3)	
H-2'	ca. 4.35	ca. 4.30	ca. 4.32	ca. 4.30	ca. 4.35
H-3'	ca. 4.30	ca. 4.30	ca. 4.31	ca. 4.30	ca. 4.33
H-4'	4.147 (t, 7.6)	4.185 (t, 9.0)	4.192 (t, 8.2)	4.183 (t, 8.2)	ca. 4.21
H-5'	3.913 (m)	3.957 (m)	3.962 (m)	3.968 (m)	ca. 3.96
H-6'	4.370 (m)	4.403 (m)	4.413 (m)	4.400 (m)	ca. 4.36
	4.534 (m)	4.577 (m)	4.579 (m)	4.584 (m)	ca. 4.54
H-1''	6.654 (brs)	6.601 (brs)	6.612 (brs)	6.606 (brs)	6.593 (brs)
H-2''	4.804 (brs)	4.868 (d, 1.8)	4.871 (brs)	4.872 (brs)	4.858 (brs)
H-3''	4.634 (d, 9.2)	4.690 (m)	4.697 (m)	4.694 (m)	ca. 4.70
H-4''	ca. 4.34	ca. 4.35	ca. 4.36	ca. 4.36	ca. 4.36
H-5''	4.837 (m)	4.800 (m)	4.809 (m)	4.811 (m)	ca. 4.88
H-6''	1.785 (d, 6.1)	1.714 (d, 6.4)	1.720 (d, 6.1)	1.724 (d, 5.8)	1.767 (d, 6.1)

	6	8 ^{b)}	9 ^{b)}	10 ^{b)}	13 ^{b)}
H-3	3.487 (dd, 3.6, 11.6)		3.250 (m)	3.247 (dd, 4.4, 11.7)	3.253 (ddd, 4.7, 4.7, 11.6)
H-14	5.946 (dd, 11.0, 17.6)	5.910 (dd, 11.0, 17.5)	5.903 (dd, 10.7, 17.2)	5.906 (dd, 10.6, 17.4)	5.386 (m)
H-15a	5.174 (br d, 11.0)	5.052 (d, 11.0)	5.064 (dd, 1.3, 10.7)	5.053 (dd, 1.2, 10.6)	4.153 (dd, 3.5, 5.3)
H-15b	5.250 (br d, 17.6)	5.201 (d, 17.5)	5.207 (dd, 1.3, 17.2)	5.202 (dd, 1.2, 17.4)	
H-16	1.535 (3H, s)	1.274 (3H, s)	1.272 (3H, s)	1.273 (3H, s)	1.674 (3H, s)
H-17a	4.795 (brs)	4.526 (brs)	4.496 (br d, 1.2)	4.537 (br d, 1.2)	4.533 (br d, 1.2)
H-17b	4.929 (brs)	4.824 (br d, 1.2)	4.826 (br d, 1.2)	4.838 (br d, 1.2)	4.851 (br d, 1.2)
H-18	1.341 (3H, s)	3.106 (d, 10.9)	0.990 (3H, s)	0.992 (3H, s)	0.995 (3H, s)
		3.413 (d, 10.9)			
H-19	0.988 (3H, s)	0.748 (3H, s)	0.769 (3H, s)	0.771 (3H, s)	0.774 (3H, s)
H-20	0.669 (3H, s)	0.718 (3H, s)	0.679 (3H, s)	0.685 (3H, s)	0.688 (3H, s)
H-1'	4.980 (d, 7.6)				
H-2'	ca. 4.26				
H-3'	ca. 4.28				
H-4'	4.316 (t, 8.9)				
H-5'	ca. 4.06				
H-6'	ca. 4.40				
	4.605 (m)				
H-1''	5.478 (brs)				
H-2''	4.466 (brs)				
H-3''	4.551 (m)				
H-4''	ca. 4.24				
H-5''	ca. 4.39				
H-6''	1.661 (d, 7.4)				

Multiplicity and coupling constants are shown in parentheses. a) 270 MHz. b) Measured in CDCl_3 solution.

glucopyranosyl-13-epitorreferol. Assignments of the ^1H - and ^{13}C -NMR spectra of the compounds shown in Tables I and II were confirmed by proton-proton and ^{13}C -proton correlated spectroscopy (^1H - ^1H and ^{13}C - ^1H COSY), ^1H -detected heteronuclear multiple bond correlation (HMBC) spectrum, nuclear Overhauser effect spectroscopy (NOESY), and distortionless enhancement by polarization transfer (DEPT) spectrum methods.

Compounds **2** and **3** both showed the molecular ion peak at m/z 615 $[\text{M} + \text{H}]^+$, and the characteristic fragment ion

at m/z 288 due to the aglycone part in the FAB-MS. Further, the HR-FAB-MS of both **2** and **3** indicated the molecular formulae to be $\text{C}_{32}\text{H}_{55}\text{O}_{11}$ (m/z 615.3823 and m/z 615.3674, respectively). The ^1H -NMR spectra of **2** and **3** indicated the presence of four tertiary and one secondary methyls, one vinyl group, one exocyclic double bond, and two anomeric protons. The ^1H -chemical shifts of the two compounds were very similar except for the H-17a signals (Table I). The ^{13}C -NMR spectra of **2** and **3** also showed very similar signals, which were coincident

TABLE II. ^{13}C -NMR Spectral Data for Diterpenoid Alcohols and Glycosides (125 MHz, $\text{C}_3\text{D}_5\text{N}$ or CDCl_3 , δ)

	1	2	3	4	5 ^{a)}	6	8 ^{b)}
1	38.54	37.59	37.61	37.47	18.24	37.28	38.56
2	19.17	27.53	27.57	27.54	27.10	27.34	18.69
3	36.34	88.64	88.69	88.61	122.51	88.81	35.44
4	37.82	39.80	39.83	39.79	144.39	39.46	38.00
5	48.94	55.18	55.21	55.11	38.10	55.00	48.55
6	24.51	24.15	24.15	24.15	84.08	24.12	24.17
7	38.48	38.49	38.50	38.42	35.81	38.45	38.07
8	147.40	148.90	148.85	148.63	34.78	148.59	148.36
9	57.09	57.23	57.25	56.24	44.63	57.27	57.27
10	40.09	39.49	39.52	39.26	46.39	39.84	39.71
11	18.51	18.48	18.72	22.39	32.61	18.10	17.73
12	42.28	42.35	42.38	38.81	37.39	41.42	41.36
13	72.78	72.79	72.71	137.52	72.60	79.70	73.59
14	147.40	147.23	147.48	125.92	147.32	143.24	145.26
15	111.08	111.25	111.09	59.01	111.29	115.14	111.57
16	28.58	28.86	28.48	16.47	28.51	23.11	27.70
17	106.82	107.07	107.20	106.76	17.19	107.29	106.67
18	79.71	28.20	28.23	28.20	15.99	28.40	72.11
19	18.15	16.99	17.01	17.01	22.80	16.83	17.59
20	15.28	14.75	14.76	14.76	18.31	14.74	14.96
1'	103.77	105.42	105.47	105.42	102.77	106.95	
2'	76.60	77.60	77.59	77.62	78.01	75.79	
3'	80.12	79.96	80.00	79.96	79.76	78.74	
4'	72.01	72.09	72.11	72.11	72.43	71.79	
5'	78.46	78.25	78.27	78.27	78.52	78.35	
6'	62.84	62.81	62.83	62.83	62.93	63.01	
1''	101.47	101.66	101.68	101.68	102.01	96.70	
2''	72.58	72.48	72.52	72.49	72.48	73.48	
3''	72.65	72.52	72.55	72.54	72.63	72.88	
4''	74.06	74.12	74.16	74.12	74.18	74.20	
5''	69.61	69.59	69.62	69.61	69.59	69.74	
6''	19.17	18.69	18.51	18.70	18.71	18.65	

a) 67 MHz. b) Measured in CDCl_3 solution.

with those of **7** except for those of the C-13 hydroxy carbon and adjacent carbons.⁴⁾ The ^1H - and ^{13}C -NMR signals due to the sugar part of **2** and **3** were identical with those of **1**. Therefore, **2** and **3** have the same sugar sequence, 3-*O*- α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)- β -D-glucopyranosyl. The aglycones of **2** and **3** were determined by enzymatic hydrolysis with crude hesperidinase, giving 3 β -hydroxymanool (**9**) and 3 β -hydroxy-13-epimanool (**10**), respectively. The ^1H - and ^{13}C -NMR spectra of **9** and **10** supported their structures, and the configuration at C-13 was determined by comparison of the ^1H -NMR spectra with those of manool (**11**) and 13-epimanool (**12**).⁷⁾ The fact that the signals of H-17a appeared at δ 4.46 (d, $J=1.4$) in **11** and δ 4.50 (d, $J=1.5$) in **12**, but at δ 4.496 (d $J=1.2$) in **9** and δ 4.537 (d, $J=1.2$) in **10**, indicated the configurations at C-13 of **9** and **10** to be *R* and *S*, respectively. Therefore, compounds **2** and **3** were established as 3-*O*- α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)- β -D-glucopyranosyl-3 β -hydroxymanool and 3-*O*- α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)- β -D-glucopyranosyl-3 β -hydroxy-13-epimanool, respectively.

Compound **4** showed the molecular ion peak at m/z 615 $[\text{M}+\text{H}]^+$, and the characteristic fragment ion at m/z 288 due to the aglycone part in the FAB-MS. Further, the HR-FAB-MS indicated the molecular formula to be $\text{C}_{32}\text{H}_{55}\text{O}_{11}$ (m/z 615.3731). The ^1H - and ^{13}C -NMR spectra of **4** indicated the presence of four tertiary and one hydroxy methyls, one vinyl group, one exocyclic

double bond, and two anomeric protons and carbons. The ^1H - and ^{13}C -NMR spectra of **4** coincided with those of **2** and **3** except for the signals of the side chain (Tables I, II). In the NOESY spectrum of **4**, cross peaks were observed between the H-16 methyl signals and H-15 hydroxymethyl signal. This result revealed the 13*E* configuration of the C-13 double bond. Further, the enzymatic hydrolysis of **4** with crude hesperidinase gave (13*E*)-labda-8(17),13-diene-3 β ,15-diol (**13**) as the aglycone, which was found to be the antipode of the diol (**14**) obtained from alepterolic acid⁸⁾ by LiAlH_4 reduction. Thus, **4** was determined to be 3-*O*- α -L-rhamnopyranosyl-(1 $\rightarrow$ 2)- β -D-glucopyranosyl-(13*E*)-labda-8(17),13-diene-3 β ,15-diol.

It is interesting to note that the leaflets of *Gleichenia japonica* afforded triterpenoids²⁾ only as hydrocarbons and free alcohols, while diterpenoids in this paper were isolated as glycosides of 3- and 18-hydroxyl compounds.

Experimental

Melting points were measured on a Yanagimoto micro apparatus and were uncollected. Specific rotations were observed at 22–24 °C. ^1H - and ^{13}C -NMR spectra were taken at 500 MHz and 125 MHz, respectively, by the Fourier-transform (FT) method with tetramethylsilane as an internal standard. FAB-MS and HR-FAB-MS were recorded at an emission current of 20 μA using glycerol + MeOH or *m*-nitrobenzyl alcohol as a matrix. HPLC was performed on a C-18 reverse phase column (detected by RI) with MeOH (75): H_2O (25) or MeOH (9): H_2O (1) as the eluent. Silica gel 60, 230–400 mesh (Merck) was used for column chromatography (CC). Precoated Silica gel 60 plates (Merck) were used for thin layer chromatography (TLC), and spots were detected by spraying with concentrated H_2SO_4 followed by heating.

Plant Material The leaflets of *Gleichenia japonica* were collected in December 1986, at Miyagahara, Nishiizu, Shizuoka Prefecture. Voucher specimens have been deposited in the Herbarium of Showa College of Pharmaceutical Sciences, Tokyo.

Extraction and Separation of Compounds 1–6 Fresh leaflets of *G. japonica* were extracted with MeOH. The extract was concentrated to give a dark brown resin. The resin was suspended in H_2O , and the suspension was extracted with Et_2O and *n*-BuOH, successively. The *n*-BuOH solution was concentrated *in vacuo* to give a dark brown resin extract. The extract was chromatographed on silica gel with CHCl_3 (9): MeOH (1) [fr. A, B and C (1.93 g)], CHCl_3 (8): MeOH (2) [fr. D (600 mg), E (3.50 g), F (9.50 g), G], CHCl_3 (7): MeOH (3) (fr. H), CHCl_3 (1): MeOH (1) (fr. I), and MeOH (fr. J) to give ten fractions. Fraction F was repeatedly chromatographed on silica gel with EtOAc (12): MeOH (2): H_2O (1) [fr. K (640 mg), L (180 mg), M (900 mg), N (4.75 g), O (500 mg), P (395 mg)], and MeOH (fr. Q). One-third of fr. N was repeatedly separated by reversed-phase HPLC to give **1** (35 mg, amorphous powder, EtOAc), mp 115–118 °C, $[\alpha]_{\text{D}} -20.2^\circ$ ($c=0.2$, MeOH); **2** (38 mg, amorphous powder), mp 156–160 °C, $[\alpha]_{\text{D}} -26.3^\circ$ ($c=0.15$, MeOH); **3** (202 mg, amorphous powder, EtOAc), mp 144–147 °C, $[\alpha]_{\text{D}} -23.5^\circ$ ($c=0.2$, MeOH); **4** (39 mg, colorless needles, MeOH– H_2O), mp 128–132 °C, $[\alpha]_{\text{D}} -32.1^\circ$ ($c=0.15$, MeOH); **5** (35 mg, amorphous powder), $[\alpha]_{\text{D}} -39.9^\circ$ ($c=0.2$, MeOH); **6** (115 mg, amorphous powder), $[\alpha]_{\text{D}} -13.2^\circ$ ($c=0.3$, MeOH).

13-Epitorrefanol (8) Crude hesperidinase (55 mg) dissolved in citric acid buffer (pH 4.25, 10 ml) and toluene (1 ml) were added to a solution of **1** (18 mg) in EtOH (0.5 ml), and the mixture was incubated for 4 d at 37 °C. Then H_2O (15 ml) was added, and the whole was extracted with CHCl_3 three times. Removal of the solvent, and purification by reversed-phase HPLC gave **8** (7 mg, colorless needles, hexane), mp 144.5–146 °C, $[\alpha]_{\text{D}} +63.1^\circ$ ($c=0.2$, CHCl_3) (lit.⁶⁾ mp 145–146 °C, $[\alpha]_{\text{D}} +58.5^\circ$, MS: m/z 306 (M^+ , 1), 288 (14), 273 (27), 257 (100), 255 (10), 189 (48), IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3300, 3050, 1630, 1035, 980, 905.

3 β -Hydroxymanool (9) Enzymatic hydrolysis of **3** (18 mg) in the same way as described above gave **9** (0.5 mg, colorless needles, hexane), mp 91–94 °C, $[\alpha]_{\text{D}} +36.5^\circ$ ($c=0.1$, CHCl_3) (lit.⁹⁾ mp 97–98 °C, $[\alpha]_{\text{D}} +45.2^\circ$, MS: m/z 306 (M^+ , 9), 257 (43), 255 (32), 243 (14), 236 (100).

3 β -Hydroxy-13-epimanol (10) Enzymatic hydrolysis of **2** (28 mg) in the same way as described above afforded **10** (1.5 mg, colorless needles, hexane), mp 85–88 °C, $[\alpha]_D + 15.3^\circ$ ($c=0.1$, CHCl_3) (lit.⁷⁾ syrup, $[\alpha]_D + 17.6^\circ$, MS: m/z 306 (M^+ , 6), 257 (62), 255 (33), 243 (63), 236 (88), 69 (100).

(13E)-Labda-8(17),13-diene-3B,15-diol (13) Enzymatic hydrolysis of **4** (15 mg) in the same way as described above gave **13** (1 mg, colorless needles, hexane), mp 149–152 °C, $[\alpha]_D + 35.0^\circ$ ($c=0.1$, CHCl_3), MS: m/z 306 (M^+ , 4), 29 (26), 288 (12), 273 (45), 279 (7), 255 (21), 135 (100).

ent-(13E)-Labda-8(17),13-diene-3 β ,15-diol (14) LiAlH_4 reduction of alepterolic acid followed by recrystallization from hexane gave **14**, mp 158–159 °C, $[\alpha]_D - 40.4^\circ$ ($c=0.9$, CHCl_3).

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