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IRIDOID DIGLYCOSIDE MONOACYL ESTERS FROM THE LEAVES OF *PREMNA JAPONICA*

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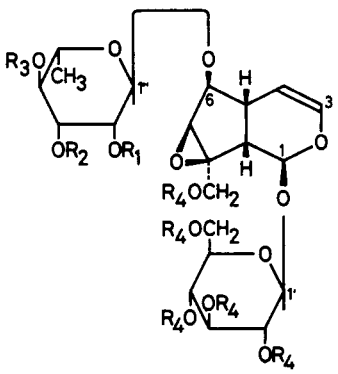
ABSTRACT.—By phytochemical investigation of the leaves of *Premna japonica*, four monoacyl 6-*O*-α-L-rhamnopyranosylcatalpols were isolated. The structures of these compounds were established to be 6-*O*-α-L-(2″-*O*-*trans*-*p*-coumaroyl)rhamnopyranosylcatalpol (saccatoside) [**1**], 6-*O*-α-L-(4″-*O*-*trans*- and *cis*-*p*-coumaroyl)rhamnopyranosylcatalpols [**3**], 6-*O*-α-L-(2″-*O*-caffeoyl)rhamnopyranosylcatapol [**5**], and 6-*O*-α-L-(3″-*O*-caffeoyl)rhamnopyranosylcatalpol [**7**].

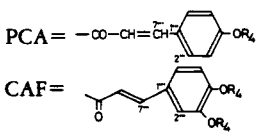
In previous papers, we reported the isolation of several acylated 6-*O*-α-L-rhamnopyranosylcatalpols from the Philippine medicinal plant, *Premna odorata* Blanco (Verbenaceae) (local name: Alagau) (1,2). This prompted us to examine another plant in the same genus, namely *Premna japonica* Miq., which grows in the southwestern part of Japan. On phytochemical investigation of this plant, two monoacyl 6-*O*-α-L-rhamnopyranosylcatalpols were isolated from the *n*-BuOH-soluble fraction of leaves (3). In further studies on this fraction, saccatoside [6-*O*-α-L-(2″-*O*-*p*-coumaroyl)rhamnopyranosylcatalpol] [**1**] (4), 6-*O*-α-L-(4″-*O*-*p*-coumaroyl)rhamnopyranosylcatalpol [**3**], a new compound, 6-*O*-α-L-(2″-*O*-caffeoyl)rhamnopyranosylcatalpol [**5**], and 6-*O*-α-L-(3″-*O*-caffeoyl)rhamnopyranosylcatalpol [**7**] (1) were isolated. This paper describes the isolation and structural elucidation of these iridoid diglycosides.

The MeOH extract of dried leaves of *P. japonica* was separated by a combination of highly porous polymer, Diaion HP-20, and Si gel chromatographic techniques, and by dccc.

Compound **1** (saccatoside) was obtained as a colorless amorphous powder. The physical and spectroscopic data for **1** and its octaacetate **2** matched well the reported data for saccatoside isolated from *Verbascum saccatum* L. (4). Compounds **5** and **7** were also obtained as colorless amorphous powders. The ^{1}H-nmr data proved that these compounds contain caffeoyl moieties that are attached to different hydroxyl groups of the



1 R_1=*E*-PCA, R_2=R_3=R_4=H
2 R_1=*E*-PCA, R_2=R_3=R_4=Ac
3 R_1=R_2=R_4=H, R_3=*E*,*Z*-PCA
4 R_1=R_2=R_4=Ac, R_3=*E*,*Z*-PCA
5 R_1=CAF, R_2=R_3=R_4=H
6 R_1=CAF, R_2=R_3=R_4=Ac
7 R_1=R_3=R_4=H, R_2=CAF
8 R_1=R_3=R_4=H, R_2=CAF
9 R_1=R_2=R_3=R_4=H



rhamnose unit of 6-*O*-α-L-rhamnopyranosylcatalpol. From the spectroscopic data for **5** and **7** and their nonaacetates **6** and **8**, the compounds were determined to be 6-*O*-α-L-(2″-*O*-caffeoyl)- and 6-*O*-α-L-(3″-*O*-caffeoyl)rhamnopyranosylcatalpols, respectively (1).

Compound **3**, $C_{30}H_{38}O_{16}$, was isolated as a colorless amorphous powder and showed a single band on tlc [$CHCl_3$-MeOH-H_2O (15:6:1) and EtOAc-EtOH-H_2O (8:2:1)] and also on dccc. The ir and uv absorption maxima suggested that **3** has similar functional groups to those of **1**. In its fabms, **3** showed a quasi-molecular ion peak at *m/z* 655 $[MH]^+$ and cluster ion peaks at *m/z* 677 $[M + Na]^+$ and 693 $[M + K]^+$ on the addition of NaI and KI, respectively. The ^{1}H-nmr signals (100 MHz, MeOH-d_4) indicated the presence of a trans double bond [δ 6.37 (d, J = 16 Hz) and 7.66 (d, J = 16 Hz)] and aromatic protons coupled in an AA′BB′ system [6.81 (d, J = 8 Hz) and 7.43 (d, J = 8 Hz)]. From these data, the acyl portion of **3** was presumed to be *trans-p*-coumaric acid. The extra signals at δ 5.82 (d, J = 13 Hz) and 6.92 (d, J = 13 Hz) are characteristic of a cis double bond, while aromatic proton signals also appeared with satellites [δ 6.75 (d, J = 9 Hz) and 7.66 (d, J = 9 Hz)], which were assumed to be due to the cis isomer. The ^{13}C-nmr spectrum of **3** also indicated the presence of *trans*- and *cis-p*-coumaric acid moieties (Table 1). A set of nine signals was unequivocally assigned to *trans-p*-coumaric acid, as compared with those in the case of **1**, and another set of nine minor peaks, which accompanied the major peaks, corresponded to the reported data for *cis-p*-coumaric acid (5). The remaining ^{13}C-nmr signals, except for the rhamnopyranosyl carbon signals, were essentially the same as those of **1**, and five signals (C-6, -7, -1″, -4″, and -5″), which were due to carbons close to the acyl moiety, were split in two, due to the co-existence of a cis isomer. From the integrals of several cis and trans pairs of proton signals, the *E-Z* ratio was determined to be 71:29.

The position of esterification was established by comparison of the rhamnose signals of **3** with those of **9** (Table 1). Because the anomeric carbon signals of **3** (δ 100.3 and 100.5) were not affected by acylation, the 2″ position was excluded as the site of esterification. The 3″ position could also be excluded by the comparison of the rhamnosyl carbon signals of **3** with those of **7**. Therefore, the position of acylation was concluded to be 4″. This was confirmed by calculation of the substitution-induced shift in the case of **3** caused by acylation [3″, Δδ **3**–**9** −1.9 ppm; 4″, Δδ **3**–**9** +1.5 (and +1.2) ppm; and 5″, Δδ **3**–**9** −1.8 (and −2.0) ppm]. Thus the structure of **3** was elucidated to be 6-*O*-α-L-(4″-*O*-*trans-p*-coumaroyl)- and 6-*O*-α-L-(4″-*O*-*cis-p*-coumaroyl)rhamnopyranosylcatalpol. On acetylation of **3**, its octaacetate **4** was obtained. The physical and spectroscopic data for **4** also supported the proposed structure.

In monoacyl 6-*O*-α-L-rhamnopyranosylcatalpols, the 2″ and 3″ positions are generally the location of acylation (1,3,6). As far as we know, compound **3** is the second example of the 4″ position of rhamnopyranose in 6-*O*-α-L-rhamnopyranosylcatalpol being esterified. The precedent is 6-*O*-α-L-(4″-*O*-*p*-methoxycoumaroyl)rhamnopyranosylcatalpol, which was isolated from *Verbascum georgicum* (7).

EXPERIMENTAL

INSTRUMENTS.—^{1}H- (100 MHz) and ^{13}C- (25 MHz) nmr spectra were recorded on a JEOL FX-100 spectrometer with TMS (δ = 0) as an internal standard. Ir spectra were recorded on a Shimadzu IR-408 spectrophotometer in KBr tablets, and uv spectra were measured with a Shimadzu UV-200S spectrophotometer with MeOH as a solvent. Ms spectra were recorded on a JEOL DX-300 with a JMA-3100 computer (eims at 70 eV). Optical rotation was measured with a Union automatic digital polarimeter PM-101. The droplet counter-current chromatograph (Tokyo Rikakikai Co., Ltd., Tokyo) was equipped with 500 glass columns (40 cm length, 2 mm i.d.), and the ascending method was used. Precoated Si gel 60 F_{254} plates (0.2 mm, Merck) were used for tlc.

PLANT MATERIAL.—Leaves of *P. japonica* were collected in the southeastern part of Tokushima Pre-

TABLE 1. ^{13}C-nmr Data for Compounds **1**, **3**, **5**, **7**, and **9** (25 MHz, MeOH-d_4).

Carbon	1	3		5	7	9[a]
		E	*Z*			
Aglycone						
1	95.3	95.2		95.2	95.2	95.1
3	142.3	142.3		142.3	142.2	142.1
4	103.5	103.4		103.5	103.6	103.6
5	37.3	37.3		37.2	37.2	37.2
6	84.4	84.1	83.9	84.4	83.8	83.5
7	59.6	59.5	59.4	59.6	59.4	59.3
8	66.6	66.6		66.5	66.6	66.5
9	43.3	43.3		43.3	43.3	43.2
10	61.5	61.5		61.5	61.5	61.4
Glucose						
1′	99.8	99.7		99.7	99.7	99.7
2′	74.9	74.8		74.8	74.8	74.8
3′	78.6	78.6		78.6	78.6	78.5
4′	71.8	71.7		71.7	71.7	71.7
5′	77.7	77.6		77.7	77.7	77.6
6′	63.0	62.9		62.9	62.9	62.9
Rhamnose						
1″	97.8	100.3	100.5	97.8	100.3	100.3
2″	74.2	72.4		74.2	70.3	72.2
3″	70.6	70.3		70.5	75.3	72.2
4″	74.2	75.3	75.0	74.2	71.4	73.8
5″	70.3	68.3	68.1	70.3	70.3	70.1
6″	18.1	17.9		18.0	18.0	18.0
Acyl moiety						
1‴	127.2	127.2	127.6	127.7	127.9	
2‴	131.3	131.2	133.7	114.9	115.4	
3‴	116.9	116.9	115.8	149.6	149.5	
4‴	161.3	161.3	160.0	146.7	146.7	
5‴	116.9	116.9	115.8	116.5	116.5	
6‴	131.3	131.2	133.7	123.1	122.9	
7‴	147.2	146.9	145.6	147.6	147.1	
8‴	115.0	115.1	116.7	115.3	115.3	
9‴	168.7	168.9	167.8	168.7	168.9	

[a]Data taken from Otsuka *et al.* (1).

fecture in May 1988. The voucher specimen (88-PJ-Tokushima-1) was deposited at the Herbarium of the Department of Pharmacognosy, Institute of Pharmaceutical Sciences, Hiroshima University School of Medicine.

ISOLATION PROCEDURE.—Dried and powdered leaves of *P. japonica* (1.45 kg) were extracted with *n*-hexane (18 liters × 2) and then MeOH (18 liters × 3). The MeOH extract (285 g) was dissolved in 95% aqueous MeOH (1.5 liters) and then extracted with *n*-hexane. The concentrated MeOH layer was suspended in H_2O (1.5 liters) and then extracted with EtOAc (1.5 liters) and *n*-BuOH (1.5 liters × 2), successively. The *n*-BuOH extract (84.4 g) was chromatographed on a column of highly porous polymer (Diaion, Hp-20; Mitsubishi Chemical) with a stepwise increase of MeOH content in H_2O (20, 40, 60, 80, and 100%).

The residue of the 60% MeOH eluent (24.1 g) was subjected to Si gel cc with $CHCl_3$-MeOH-H_2O (15:6:0.1) and then $CHCl_3$-MeOH (90:10) as eluents to yield two fractions (0.88 g and 0.88 g, respectively). Final purification of these fractions by dccc with $CHCl_3$–MeOH–H_2O–*n*-PrOH (45:60:40:10) afforded compound **1** (51 mg) and compound **3** (201 mg) as amorphous powders. From the 40% MeOH eluent on Diaion column chromatography, compounds **5** (125 mg) and **7** (120 mg) were obtained by repeated Si gel cc [$CHCl_3$-MeOH-H_2O (15:6:0.5) and $CHCl_3$-MeOH (85:15)] and dccc [$CHCl_3$–MeOH–H_2O–*n*-PrOH (45:60:40:10)].

Compound **1** *(saccatoside).*—A colorless amorphous powder: $[\alpha]_D$ −117.4° (*c* = 0.38, MeOH); uv (MeOH) λ max (log ε) 227 (4.09) 302 (4.38) inf, 314 (4.44) nm; ir ν max (KBr) 3350, 1690, 1725, 1600, 1510, 1440, 1260, 1165, 1125, ~1070, 920, 835 cm^{-1}; ^1H nmr (100 MHz, MeOH-d_4) δ 1.31 (3H, d, *J* = 6 Hz, H-6″), ~2.5 (2H, m, H-5, H-9), 3.65 (1H, br s, H-7), 6.38 (H, d, *J* = 16 Hz, H-8‴), 6.39 (H, br d, *J* = 6 Hz, H-3), 6.81 (2H, d, *J* = 9 Hz, H-3‴, -5‴), 7.48 (2H, d, *J* = 9 Hz, H-2‴, -6‴), 7.67 (H, d, *J* = 16 Hz, H-7‴); ^{13}C nmr see Table 1; fabms *m/z* $[MH]^+$ 655, $[M+Na]^+$ 677 (+ NaI), $[M+K]^+$ 693 (+ KI); calcd for $C_{30}H_{38}O_{16}\cdot 1/2H_2O$, C 54.30, H 5.92, found C 54.05, H 6.12.

Saccatoside octaacetate [**2**].—Compound **1** (19 mg) was treated with a mixture of Ac_2O (1.5 ml) and pyridine (1.5 ml) at 25° overnight. The usual workup gave 20 mg of a colorless amorphous powder: $[\alpha]_D$ −35.8° (*c* = 0.24, $CHCl_3$); uv (MeOH) λ max (log ε) 217 (4.24), 223 (4.17) inf, 283 (4.46) nm; ir ν max (KBr) 1745, 1630, 1500, 1365, 1220, 1155, 1040, 905 cm^{-1}; ^1H nmr (100 MHz, $CDCl_3$) δ 1.25 (3H, d, *J* = 6 Hz), 1.99, 2.02, 2.03, 2.05, 2.06, 2.11, 2.13, 2.30 (3H, each, s, Ac × 8), ~2.5 (2H, m), 3.59 (H, br s), 6.32 (H, br d, *J* = 6 Hz), 6.51 (H, d, *J* = 16 Hz), 7.16 (2H, d, *J* = 9 Hz), 7.60 (2H, d, *J* = 9 Hz), 7.72 (H, d, *J* = 16 Hz); ^{13}C nmr (25 MHz, $CDCl_3$) δ 17.4, 20.6, 20.7 (×5), 20.8, 21.1, 35.4, 41.7, 58.0, 61.1, 62.2, 62.3, 66.9, 68.2, 68.9, 70.1, 70.6, 71.1, 72.2, 72.6, 83.5, 94.2, 96.5 (×2), 102.4, 117.2, 122.2 (×2), 129.5 (×2), 131.6, 141.1, 145.2, 152.4, 165.9, 169.1, 169.3 (×2), 170.0 (×2), 170.3, 170.6, 170.7; eims *m/z* 375, 331, 189, 169, 147, 109; fabms *m/z* $[MH]^+$ 991, $[M+Na]^+$ 1013 (+ NaI), $[M+K]^+$ 1029 (+ KI); calcd for $C_{46}H_{54}O_{24}$, C 55.75, H 5.49, found C 55.31, H 5.49.

6-O-α-L-(4″-O-trans- *and* cis-p-*Coumaroyl*)*rhamnopyranosylcatalpols* [**3**].—A colorless amorphous powder (*E*-to-*Z* ratio 71:29), $[\alpha]_D$ −70.8° (*c* = 0.48, MeOH); uv (MeOH) λ max (log ε) 226 (4.15), 302 (4.36) inf, 311 (4.41) nm; ir ν max (KBr) 3350, 1700, 1625, 1600, 1510, 1175, 1070, 1030, 920, 835 cm^{-1}; ^1H nmr (100 MHz, MeOH-d_4) δ 1.16 (d, *J* = 6 Hz, *Z*-H-6″), 1.17 (d, *J* = 6 Hz, *E*-H-6″), ~2.5 (2H, m, H-5, -9), 3.66 (H, br s, H-7), 5.82 (d, *J* = 13 Hz, *Z*-H-8‴), 6.37 (d, *J* = 16 Hz, *E*-H-8‴), 6.38 (H, br d, *J* = 6 Hz, H-3), 6.75 (d, *J* = 9 Hz, *Z*-H-3‴, -5‴), 6.81 (d, *J* = 8 Hz, *E*-H-3‴, -5‴), 6.92 (d, *J* = 13 Hz, *Z*-H-7‴), 7.43 (d, *J* = 9 Hz, *E*-H-2‴, -6‴), 7.66 (d, *J* = 9 Hz, *Z*-H-2‴, -6‴), 7.66 (d, *J* = 16 Hz, *E*-H-7‴); ^{13}C nmr see Table 1; fabms *m/z* $[MH]^+$ 655, $[M+Na]^+$ 677 (+ NaI), $[M+K]^+$ 693 (+ KI); calcd for $C_{30}H_{38}O_{16}\cdot H_2O$, C 53.57, H 5.99, found C 53.53, H 6.18.

6-O-α-L-(4″-O-trans- *and* cis-p-*Coumaroyl*)*rhamnopyranosylcatalpol octaacetates* [**4**].—Compound **3** (30 mg) was treated as usual to yield 38 mg of a colorless amorphous powder: $[\alpha]_D$ −70.8° (*c* = 0.48, $CDCl_3$); uv (MeOH) λ max (log ε) 217 (4.24), 224 (4.14) inf, 283 (4.41) nm; ir ν max (KBr) 1750, 1630, 1595, 1500, 1430, 1365, 1220, 1150, 1075, 1035, 980, 905 cm^{-1}; ^1H nmr (100 MHz, $CDCl_3$) δ 1.22 (d, *J* = 6 Hz, *Z*-H-6″), 1.26 (d, *J* = 6 Hz, *E*-H-6″), 1.96, 2.02, 2.03, 2.04, 2.11, 2.13, 2.16 and 2.18, 2.31 (Ac × 8), 3.59 (H, br s, H-7), 5.90 (d, *J* = 13 Hz, *Z*-H-8‴), 6.33 (H, br d, *J* = 6 Hz, H-3), 6.35 (d, *J* = 16 Hz, *E*-H-8‴), 6.99 (d, *J* = 13 Hz, *Z*-H-7‴), 7.10 (d, *J* = 9 Hz, *Z*-H-3‴, -5‴), 7.14 (d, *J* = 8 Hz, *E*-H-3‴, -5‴), 7.56 (d, *J* = 8 Hz, *E*-H-2‴, -6‴), 7.70 (d, *J* = 9 Hz, *Z*-H-2‴, -6‴), 7.83 (d, *J* = 16 Hz, *E*-H-7‴); ^{13}C nmr (25 MHz, $CDCl_3$) δ 17.4, 20.6 (×6), 20.9, 21.1, 35.5, 41.7, 58.0, 61.1, 62.2, 62.4, 67.0 (*Z*), 67.2 (*E*), 68.3, 68.8, 69.9 (*Z*), 70.1 (*E*), 70.6, 70.8 (*Z*), 71.1 (*E*), 72.3, 72.6, 83.4 (*Z*), 83.5 (*E*), 94.3, 96.5 (×2), 102.4, 117.0 (*E*-C-8‴), 118.4 (*Z*-C-8‴), 121.3 (*Z*-C-3‴, -5‴), 122.2 (*E*-C-3‴, -5‴), 129.4 (*E*-C-2‴, -6‴), 131.5 (*Z*-C-2‴, -6‴), 131.7 (*E*-C-1‴), 132.1 (*Z*-C-1‴), 141.1, 144.5 (*Z*-C-7‴), 145.0 (*E*-C-7‴), 151.4 (*Z*-C-4‴), 152.5 (*E*-C-4‴), 164.6 (*Z*-C-9‴), 165.8 (*E*-C-9‴), 169.0 (×2), 169.3, 169.9, 170.0, 170.2, 170.6 (×2); eims *m/z* 417, 331, 169, 147, 109; fabms *m/z* $[MH]^+$ 991, $[M+Na]^+$ 1013 (+ NaI), $[M+K]^+$ 1029 (+ KI); calcd for $C_{46}H_{54}O_{24}\cdot \frac{1}{2}H_2O$, C 55.25, H 5.54, found C 55.15, H 5.47.

6-O-α-L-(2″-O-*Caffeoyl*)*rhamnopyranosylcatapol* [**5**].—A colorless amorphous powder: $[\alpha]_D$ −103.3° (*c* = 0.29, MeOH) [lit. (1) −120°]; ^{13}C nmr see Table 1; ir, uv, ^1H-nmr, and fabms data were essentially the same as previously reported (1); calcd for $C_{30}H_{38}O_{17}\cdot 2H_2O$, C 50.99, H 5.99, found C 51.24, H 6.06.

6-O-α-L-(2″-O-*Caffeoyl*)*rhamnopyranosylcatapol nonaacetate* [**6**].—Compound **5** (33 mg) was treated as usual to give 44 mg of a colorless amorphous powder: $[\alpha]_D$ −37.1° (*c* = 0.42, $CHCl_3$) [lit. (1) −35.3°]; calcd for $C_{46}H_{54}O_{24}\cdot H_2O$, C 54.03, H 5.47, found C 54.00, H 5.34; ir, uv, ^1H- and ^{13}C-nmr, eims, and fabms data were essentially the same as previously reported (1).

6-O-α-L-(3″-O-*Caffeoyl*)*rhamnopyranosylcatapol* [**7**].—A colorless amorphous powder: $[\alpha]_D$ −114.2° (*c* = 0.30, MeOH) [lit. (1) −121°]; ^{13}C nmr see Table 1; ir, uv, ^1H-nmr, and fabms data were essentially the same as previously reported (1); calcd for $C_{30}H_{38}O_{17}\cdot 2H_2O$, C 50.99, H 5.99, found C 51.40, H 6.09.

6-O-α-L-(3″-O-*Caffeoyl*)*rhamnopyranosylcatapol nonaacetate* [**8**].—Compound **7** (34 mg) was treated as usual to afford 42 mg of a colorless amorphous powder: $[\alpha]_D$ −53.6°, (*c* = 0.44, $CHCl_3$) [lit. (1) −59.7°];

calcd for $C_{46}H_{54}O_{24}\cdot\frac{1}{2}H_2O$, C 54.49, H 5.43, found C 54.59, H 5.34; ir, uv, ^{1}H- and ^{13}C-nmr, eims, and fabms data were essentially as previously reported (1).

ANALYSIS OF THE SUGAR PORTION.—About 2 mg of each sample was heated in 1.5 ml of 5% hydrogen chloride in dry MeOH at 95° for 3 h. The reaction mixture was neutralized by the addition of Ag_2CO_3 and filtered. The filtrate was evaporated to dryness, and a few drops of trimethylsilyl imidazole were added. After 30 min at 60°, 1 ml of H_2O and 2 ml of *n*-hexane were introduced. The methyl glycoside trimethylsilyl ethers taken up in the *n*-hexane layer were analyzed by glc [column 1.5% OV-1 on Chromosorb W-AW (2 mm × 2 m); temperature 180° (isothermal); N_2 at 40 ml/min]: Rt rham 2.81 min, gluc 9.08 and 9.98 min; compound **1** rham 2.80 min, gluc 9.07 and 10.00 min; compound **3** rham 2.81 min, gluc 9.05 and 9.98 min; compound **5** rham 2.79, gluc 9.04 and 9.94 min; compound **7** rham 2.80, gluc 9.06 and 10.00 min.

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