Two Novel Compounds from *Paeonia suffruticosa*

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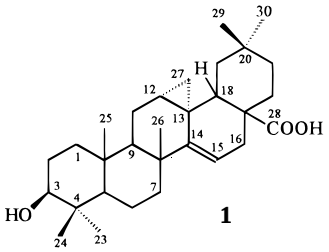
A new hexacyclic triterpenoid, mudanpinoic acid A (**1**), and a new gallic acid glycoside, mudanoside B (**2**), along with nine known compounds—benzoic acid, resacetophenone, paeoniflorigenone, β-sitosterol, betulinic acid, oleanoic acid, quercetin, β-sitosterol-β-D-glucoside, and *trans*-caffeic acid stearyl ester—were isolated from the dried root cortex of *Paeonia suffruticosa*. The structures of the novel compounds were elucidated on the basis of spectral methods, and that of compound **1** was confirmed by X-ray crystallographic analysis.

"Mudanpi" the root cortex of *Paeonia suffruticosa* Andrews (Ranunculaceae), is an important crude drug used in Chinese traditional medicine as an analgesic, sedative, antiinflammatory agent, and remedy for female diseases,[1−4] and it is prescribed in various Chinese preparations for the treatment of blood stagnation. We have reported previously the structural determination of four paeonol derivatives[5] and six mudanpiosides[6] from *P. suffruticosa*. Further phytochemical studies on the constitutents of this plant have afforded a new hexacyclic triterpenoid, mudanpinoic acid A (**1**), and a new gallic acid glycoside, mudanoside B (**2**), and nine known compounds—benzoic acid, resacetophenone, paeoniflorigenone, β-sitosterol, betulinic acid, oleanoic acid, quercetin, β-sitosterol-β-D-glucoside, and trans-caffeic acid stearyl ester—were also isolated and characterized. The present paper deals with the structural elucidation of the two new compounds, **1** and **2**.



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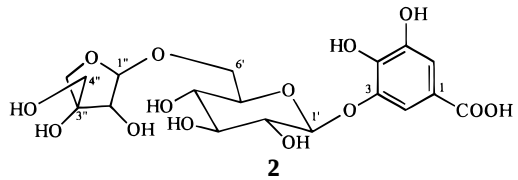

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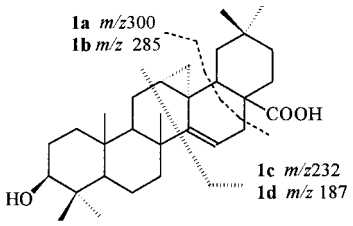

Figure 1. Major mass spectral fragmentation of mundanpinoic acid A (**1**).

Results and Discussion

Mudanpinoic acid A (**1**) was crystallized as colorless prisms from MeOH and exhibited $[\alpha]_D$ +20.6° (MeOH). HR MS revealed an $[M^+]$ at *m/z* 454.3448, corresponding to the molecular formula $C_{30}H_{46}O_3$ (calcd 454.3447). The IR spectrum of **1** revealed absorption bands at λ_{max} 3200−3400, 1745, and 1705 cm^{-1}, indicating hydroxyl and carboxyl groups, respectively.

The presence of a carboxyl group at C-17 and a Δ^{14} double bond was established from the mass spectral fragmentation pattern of mudanpinoic acid A (**1**). It exhibited a fragment peak at *m/z* 300 (Figure 1, 1a) comprising rings A, B, and C. This ion peak was accompanied by a peak 15 mass units lower (Figure 1, 1b), which was formed by the loss of the allylically activated methyl group at C-8. Moreover, the mass spectrum of compound **1** showed a peak at *m/z* 232 (Figure 1, 1c), derived from rings D and E. This fragment (1c) loses the carboxyl substituent at C-17, giving rise to a prominent peak at *m/z* 187 (Figure 1, 1d). Such fragmentation is consistent with the mass spectral data of Δ^{14}-taraxerene derivatives, as reported by Djerassi et al.[7,8] Accordingly, compound **1** was tentatively assigned with the structure 3-hydroxy-12,13-cyclo-taraxerene-14-en-28-oic acid.

The ^{1}H NMR spectrum of **1** showed the presence of six methyl groups, in agreement with its ^{13}C NMR spectral data (δ 16.5, 16.5, 22.8, 28.8, 29.5, 32.6; Table

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Table 1. ^{13}C NMR and ^{1}H NMR Spectral Data of Mudanpinoic Acid A (1) (pyridine-d_5)

position	δ_C	δ_H (J in Hz)
1	39.0	0.84 (t, 8.0 Hz), 1α
		1.65 (t, 3.6 Hz), 1β
2	28.3	1.81−1.86, overlapped with H−11
3	78.1	3.41 (t, 8.0 Hz), 3α
4	39.5	
5	55.9	0.72 (d, 11.6 Hz), 5α
6	18.9	1.53−1.59, m
7	39.0	1.38 (dd, 10.8, 10.8 Hz), 7α
		1.87 (dd, 10.8, 2.8 Hz), 7β
8	37.4	
9	48.2	0.84 (t, 8.0 Hz)
10	37.4	
11	19.5	1.81−1.86, overlapped with H−2
12	15.2	1.18−1.20, overlapped with H−23
13	23.9	
14	156.6	
15	118.4	5.90 (dd, 7.2, 4.0 Hz)
16	33.1	2.12 (dd, 13.2, 4.0 Hz),16 α
		2.83 (dd, 13.2, 7.2 Hz),16 β
17	52.9	
18	35.1	3.13 (dd, 13.8, 3.8 Hz)
19	35.8	1.03−1.05, overlapped with H−27 B, 19α
		0.80 (dd, 13.0, 3.8 Hz), 19β
20	29.2	
21	34.4	1.31 (dt, 13.6, 3.6 Hz), 21α
		1.45 (td, 13.6, 3.6 Hz), 21β
22	31.2	1.62 (td, 13.6, 3.6 Hz), 22α
		2.09 (dt, 13.6, 3.6 Hz), 22β
23	28.8	1.01, s
24	16.5	1.20, s
25	16.5	0.89, s
26	22.8	1.16, s
27	11.8	0.12 (t, 4.8 Hz), 27A
		1.03−1.05, overlapped with H−19α, 27B
28	180.0	
29	32.6	1.07, s
30	29.5	0.96, s

1). The ABX-type signals at δ 5.90 (dd, 1H, J = 7.2, 4.0 Hz), 2.83 (dd, 1H, J = 13.2, 4.0 Hz), and 2.12 (dd, 1H, J = 13.2, 7.2 Hz) resulted from a group of related protons as observed in the $^{1}H-^{1}H$ COSY spectrum, which showed the presence of the partial structure $^{14}C{=}^{15}CH-^{16}CH_2$. The signal at δ 3.41 (t, 1H, J = 8.0 Hz, C*H*OH) indicated the presence of one methine group, which could be assigned to the C-3α proton. A signal at highfield (H-27A, δ 0.12, t, 1H, J = 4.8 Hz) was characteristic of the CH_2 unit in a cyclopropane ring.[8,9] The other cyclopropane proton signal at lower field (δ 1.03−1.05) overlapped with that of H-19α in the HMQC spectrum. In comparison with usual cyclopropane proton signal at δ 0.22, the unusual chemical shifts of H-27A and H-27B reflected respective shielding and deshielding effects of $\Delta^{14,15}$ in the D ring and suggested both hydrogens were affixed to C-27. The HMBC experiment showed diagnostic cross peaks between C-12 and H-27A, and C-13 and H-27A, respectively. These observations proved the attachment of the cyclopropane to C-12 and C-13 of the C ring. The protons and carbons of mudanpinoic acid A (**1**) could be assigned by the aid of 1D NMR (DEPT, HOHAHA) and 2D NMR (HMQC, $^{1}H-^{1}H$ COSY, HMBC) techniques. The ^{1}H NMR and ^{13}C NMR spectral data for **1** are shown in Table 1, except for the proton signals due to the overlapping of H-2 and H-11, H-12 and H-23, and H-19α and H-27B. The NOESY data resolved cross peaks corresponding to the NOEs between H-5α and four axial protons (H-1α, H-3α, H-7α, and H-9α) that suggested both the A and

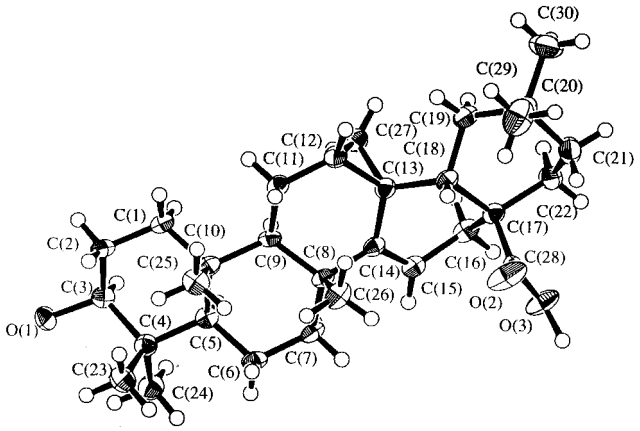

Figure 2. Molecular structure (relative configuration) of mundanpinoic acid **A** (**1**).

B rings are in the chair conformation and the A/B ring junction was in the *trans*-configuration. The NOEs between H-9α and H-27A, and H-27A and H-27B indicated that the configuration of the cyclopropane ring was cis to H-9α. The observation of NOEs between H-12β and H-18β suggested that the D/E ring junction was in the *cis*-configuration. Interestingly, the appearance of NOEs between H-18β and CH_3-29, CH_3-29 and H-21β, and the lack of NOEs between H-19β and H-21β, H-18β and H-22β, and H-22β and CH_3-29 indicated that the E ring was in a boat conformation. Similarily, the appearance of NOEs between H-16α and H-22α, H-16β and H-22β and the absence of NOEs between H-18β and H-16β revealed that the D ring was also in the boat form conformation. The relative configuration and the conformations of rings A, B, D, and E of mudanpinoic acid A (**1**) were confirmed by X-ray diffraction analysis (Figure 2).

Mudanoside B (**2**), pale crystals, $[\alpha]_D$ −66.2 (EtOH), $C_{18}H_{24}O_{14}$, showed the presence of an aromatic moiety and a disaccharide unit from its NMR spectra. A fragment at *m/z* 170 in the EIMS, a λ_{max} at 275 in the UV spectrum, and signals at δ 8.41 (1H, d, J = 2.0 Hz) and 7.90 (1H, d, J = 2.0 Hz) in the ^{1}H NMR spectrum provided evidence for a gallic acid moiety in the molecule of **2**. Comparison of the ^{13}C NMR spectrum of **2** with that of apiopaeonoside,[10] another constituent of *P. suffruticosa*, suggested that both compounds have the same apiosyl(1→6)-β-D-glucose moiety based on similar chemical shifts except for C-2 and C-3 of apiose. In apiopaeonoside, the signals at δ 77.2 and 80.1 were assigned to C-2″ and C-3″, respectively, while in mudanoside B (**2**), C-2″ and C-3″ appeared at δ_c 79.5 and 77.9, respectively, after the analysis of DEPT and HMQC spectra. The two singlets ascribable to H-2″ and H-1″ of apiose in the ^{1}H NMR of mudanoside B (**2**) clearly indicated that the two protons are trans to one another.[11] The NOESY experiment resolved the cross peaks corresponding to the NOEs between H-2″ and two methylene protons on C-4″, this suggesting a *cis*-configuration of the vicinal hydroxyl groups affixed to C-2″ and C-3″ of the apiose nuit. Thus, these data revealed the apiose unit of **2** has the configuration of D-apio-β-D-furanose or its enatiomer, L-apio-β-L-furanose. Although the isolated small quantity of **2** limited further identification of optical isomers, the naturally occurring apioses discovered only in D form and the

Table 2. ^{13}C NMR and ^{1}H NMR Spectral Data of Mudanoside B (2) (Pyridine-d_5)

unit	no	δ_C	δ_H (J in Hz)
gallic acid	1	120.8	
	2	111.3	8.44 (1H, d, J = 2.0 Hz)
	3	147.9	
	4	142.0	
	5	147.6	
	6	112.3	7.92 (1H, d, J = 2.0 Hz)
	7	166.4	
glucose	1′	103.9	5.56 (1H, d, J = 8.0 Hz)
	2′	74.6	4.33 (1H, t, J = 8.0 Hz)
	3′	79.4	4.37 (1H, t, J = 8.0 Hz)
	4′	72.7	3.96 (1H, dd, J = 9.6,8.0 Hz)
	5′	78.2	4.28 (1H, td, J = 9.6,2.4 Hz)
	6′	68.1	4.09 (1H, dd, J = 10.8,9.6 Hz)
			4.68 (1H, d, J = 10.8,2.4 Hz)
apiose	1″	111.6	5.61 (1H, s)
	2″	79.5	4.79 (1H, s)
	3″	77.9	
	4″	64.9	4.37 (1H, d, J = 10.8 Hz)
			4.74 (1H, d, J = 10.8 Hz)
	5″	75.2	4.28 (1H, d, J = 9.6 Hz)
			4.71 (1H, d, J = 9.6 Hz)

D-apiose moiety in apiopaeonoside isolated from this herb suggested that the apiose of **2** is likely to have the configuration of D-apio-β-D-furanose.[10,12] The chemical shift difference between mudanoside B and apiopaeonoside at C-2″ and C-3″ in the apiosyl unit may be due to different conformers or steric interactions that cause various shielding effects.[13] The connectivities between the gallic acid, β-D-glucose, and D-apiose moieties were based on the analysis of the HMBC spectrum, which showed two cross peaks corresponding to the long-range coupling between C-3 and H-1′} as well as C-6′} and H-1″. Consequently, the structure of mudanoside B was established as **2**. The ^{1}H NMR and ^{13}C NMR spectral data of **2** are shown in Table 2 and were assigned by 2D NMR (NOESY, HMQC, HMBC) and 1D NMR (DEPT) methods.

The identities of nine known compounds were verified by comparing melting points and UV, IR, ^{1}H NMR, ^{13}C NMR, and MS data with published values for paeoniflorigenone,[14,15] betulinic acid,[16] oleanolic acid,[17] quercetin,[18] β-sitosterol-β-D-glucoside,[16] and *trans*-caffeic acid stearyl ester[19] and by direct comparison with authentic samples for benzoic acid,[20] resacetophenone,[21] and β-sitosterol.[20] Compounds, β-Sitosterol, betulinic acid, oleanoic acid, quercetin, β-sitosterol-β-D-glucoside, and *trans*-caffeic acid stearyl ester were isolated for the first time from this Chinese herb.

Experimental Section

General Experimental Procedures. Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Optical rotations were determined on a JASCO DIP-370 polarimeter. The UV spectra were obtained on a Hitachi 200−20 spectrophotometer, and IR spectra were measured on a Hitachi 260−30 spectrophotometer. ^{1}H NMR spectra were recorded with a Varian Gemini NMR spectrometer at 400 MHz, and ^{13}C NMR spectra were recorded with a Varian Gemini NMR spectrometer at 100 MHz in $CDCl_3$, CD_3OD, and C_5D_5N. EIMS were obtained with a JEOL JMS−HX110 mass spectrometer at 70 eV, and FABMS were obtained with a JEOL TMSD-100 or JEOL JMS−HX110 spectrometer. Si gel 60 (Merck, 230−400 mesh) and Sephadex LH-20 were used for column chromatography. A preparative HPLC (Shimpack PREP-phenyl column, Shimadzu Corporation) was used for reverse chromatography.

Plant Material. The root cortex of *P. suffruticosa* was purchased from a local Chinese drug store (Chen-Yen Company) in July 1990, in Taipei. A specimen of the plant (NDMC-790701) has been deposited at the herbarium of the National Defense Medical Center, Taipei, Taiwan.

Extraction and Isolation. The root cortex (45 kg) was extracted with 95% EtOH, followed by 70% EtOH at room temperature. The combined EtOH extracts were concentrated under reduced pressure to yield a dark-brown syrup that was partitioned between hexane and 90% MeOH. The 90% MeOH layer was concentrated and partitioned with EtOAc and H_2O. The aqueous solution was again partitioned between *n*-BuOH and H_2O. The EtOAc layer was subjected to Si gel column chromatography and eluted with $CHCl_3$ and $CHCl_3$−MeOH (97:3) to afford acetophenones.[5] The residue after removal of acetophenones was rechromatography repeatedly on a Si gel column, eluted with $CHCl_3$−Me_2CO (97:3), to give sequentially β-sitosterol (1.3 g), resacetophenone (11.3 mg), betulinic acid (58.7 mg), paeoniflorigenone (51.0 mg), *trans*-caffic acid stearyl ester (73.2 mg), benzoic acid (9.9 g), oleanolic acid (365.4 mg), and mudanpinoic acid A (**1**) (25.6 mg). The residue from chromatography of the EtOAc extract was eluted with MeOH, combined with the *n*-BuOH extract, and subjected to column chromatography on Si gel with $CHCl_3$−MeOH (19:1, 9:1, 17:3, and 7:3). Rechromatography of the first fraction on Si gel, eluted with $CHCl_3$−MeOH (94:6), yielded sequentially a mixture of mudanpioside A and benzoyl paeoniflorin,[6] quercetin (29.8 mg), and β-sitosterol-β-D-glucoside (1.5 g). Rechromatography of the fourth fraction on a Sephedex LH-20 column, eluted with MeOH−H_2O (95:5), gave two fractions. The first fraction was further separated on a phenyl column in preparative HPLC, eluted with MeOH−H_2O (20:80) to give mudanoside B (**2**) (46.6 mg).

Mudanpinoic acid A (1): recrystallized from MeOH as transparent rectangular crystals; mp 310−312 °C; $[\alpha]_D$ +20.6° (c 0.07, MeOH); UV (EtOH) λ_{max} (log ϵ) 208 (3.83) nm; IR (KBr) ν_{max} 3395, 3256, 1745, 1705 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Table 1; EIMS m/z 454 (M^+, 28), 409 (8), 300 (15), 285 (23), 232 (3), 187 (84), 135 (77), 43(100); HREIMS m/z $[M]^+$ 454.3448 (calcd for $C_{30}H_{46}O_3$, 454.3447).

Single-Crystal X-ray Analysis of Mudanpinoic Acid A (1) as a Methanol Solvate.[22] Crystal data: $C_{31}H_{50}O_4$, space group $P2_1$, a = 14.663 (2) Å, b = 6.2756 (8) Å, c = 14.976 (1) Å, β = 94.129 (9)°, V = 1374.5 (3) Å}^{3}, Z = 2, D_{calcd} = 1.18 g/cm^3, $F(000)$ = 536.00. Intensity data were collected on a Rigaku AFC6S diffractometer using graphite monochromatized Mo Kα radiation (λ = 0.71069 Å) via the ω-2θ scan technique. A total of 2690 reflections were collected ($2\theta_{max}$ = 50.2°), from which 1784 reflections were observed [$I > 3\sigma(I)$]. The structure was solved by the direct method, and the final structure parameters were obtained by a full-matrix least-squares refinement. The refinement converged at $R(F)$ = 0.047, $R_w(F)$ = 0.037 and were anisotropic on all nonhydrogen atoms. The R test failed

to determine the chirality of mudanpinoic acid A (**1**). Therefore, the structure presented here and its mirror image are both equally possible. There is a MeOH solvate crystallized with a molecule of mudanpinoic acid A (**1**) in the asymmetric unit cell. The MeOH solvate is hydrogen-bonded to both the acid group on one mudanpinoic acid A molecule and the hydroxyl group on the other mudanpinoic acid A molecule. The distances involved are 2.79 Å (O3···O4) and 2.81 Å} (O1···O4). Hydroxyl hydrogen atoms found in the difference Fourier map (H45 and H46) were included in the final structural calculation but not refined. All other hydrogen atoms were fixed at their ideal positions with a C−H distance of 0.95 Å in the final calculation.

Mudanoside B (2): pale crystals; mp 305−307 °C (dec); $[\alpha]_D$ −66.2° (*c* 0.1, EtOH); UV (EtOH) λ_{max} (log ϵ) 218 (4.36), 275 (3.93) nm; IR (KBr) ν_{max} 3435, 3318, 3185, 1676, 1615, 1595, 1518 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 2; EIMS *m/z* 60 (100), 170 (80), 153 (73); negative FABMS *m/z* 445 $[M-H_2O-H]^-$.

Benzoic acid: white needles; mp 121−122 °C, UV (MeOH) λ_{max} (log ϵ) 227 (4.00) nm; IR (KBr) ν_{max} 1693 cm^{-1}; EIMS *m/z* 122 (M^+,100); spectral data consistent with that of authentic sample, which was isolated from *Paeonia lactiflora*.[20]

Resacetophenone: yellow needles; mp 143−145 °C; UV λ_{max} (log ϵ) 212 (4.18), 230 (3.88), 275 (4.06), 315 (3.78) nm; IR (KBr) ν_{max} 3547, 3421, 1625 cm^{-1}; EIMS *m/z* 152 (M^+, 40); spectral data consistent with authentic sample, which was from Aldrich Chemical Co.

Paeoniflorigenone: colorless viscous oil; $[\alpha]_D$ +14.8° (*c* 0.2, MeOH); UV (MeOH) λ_{max} (log ϵ) 229 (4.13) nm; IR (Nujol) ν_{max} 3403, 1735, 1625, 1278 cm^{-1}; EIMS *m/z* 319 $[M + 1]^+$; spectral data consistent with literature values.[14,15]

***β*-Sitosterol:** colorless needles; mp 137 °C; $[\alpha]_D$ +37.3° (*c* 2.0, $HClC_3$); spectral data consistent with authentic sample, which was isolated from *Paeonia lactflora*.[20]

Betulinic acid: colorless needles; mp 290−292 °C; $[\alpha]_D$ +6.8° (*c* 0.29, MeOH); spectral data consistent with literature values.[16]

Oleanolic acid: colorless needles; mp 305−307 °C; $[\alpha]_D$ +56.3° (*c* 0.28, $HClC_3$); spectral data consistent with literature values.[17]

Quercetin: yellow needles; mp 290−291 °C; spectral data consistent with literature values.[18]

***β*-Sitosterol-*β*-D-glucoside:** colorless needles; mp 286−289 °C; $[\alpha]_D$ −42.6 (*c* 2.0, $HClC_3$); spectral data consistent with literature values.[16]

***trans*-Caffeic acid stearyl ester:** white powder; mp 108−110 °C; spectral data consistent with literature values.[19]

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(22) Atomic coordinates, thermal parameters, bond distances and angles, and observed and calculated structure factors have been deposited with the Cambridge Crystallogrphic Data Centre and can be obtained upon request from Dr. Olga Kennard, University Chemical Laboratory, 12 Union Road, Cambridge CB2 1EZ, UK.

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