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MONOTERPENE GLYCOSIDES FROM *PAEONIA SUFFRUTICOSA*

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Key Word Index—*Paeonia suffruticosa*; Ranunculaceae; monoterpene glycoside; mudanpiosides; mudanpi.

Abstract—Six new monoterpene glycosides, namely mudanpioside-A to -F, were isolated as minor components from an ethanol extract of the root cortex of *Paeonia suffruticosa*. Their structures have been established on the basis of spectral evidence. In addition, five known glycosides, paeoniflorin, oxypaeoniflorin, benzoylpaeoniflorin, benzoyloxypaeoniflorin and apiopaeonoside, were also isolated and characterized.

INTRODUCTION

The root cortex of *Paeonia suffruticosa* Anhr. (P. moutan SIM) (Chinese name: mudanpi) is a well known traditional Chinese medicine and has been used as an analgesic, sedative and anti-inflammatory agent, and as a remedy for cardiovascular, extravasated blood, stagnated blood and female genital diseases [1–4]. Chemical and pharmacological studies on *P. suffruticosa* have been carried out by many investigators since 1887 [5–23]. In the previous paper, we reported on the isolation and structural identification of several acetophenones from the root cortex of the same plant [21]. In a continuation of our phytochemical studies on the constituents of this plant, we present here the isolation and structural elucidation of six new monoterpene glycosides, mudanpioside-A (**1**), -B (**2**), -C (**3**), -D (**4**), -E (**5**) and -F (**6**), in addition to five known glycosides, paeoniflorin (**7**) [24], oxypaeoniflorin (**8**) [10], benzoylpaeoniflorin (**9**) [10], benzoyloxypaeoniflorin (**10**) [11] and apiopaeonoside (**11**) [13], from the polar fraction of an ethanol extract.

RESULTS AND DISCUSSION

The IR, ^{1}H and ^{13}C NMR spectral data for compounds **1**–**5** resembled closely those for the known compounds **7**–**10** which were also isolated in the course of this work from *P. suffrucitcosa* (Tables 1 and 2). This suggested that compounds **1**–**5** were mono- or di-benzoates of monoterpene glycosides, the difference between them being in the substitution pattern of the aromatic rings. However, compound **6** was a monoterpene glycoside without any acyloxy substituent.

Compound **1** gave rise to a quasimolecular ion peak at *m/z* 613 $[M-H]^-$ on FAB-mass spectroscopy. High mass measurement established the molecular formula as $C_{31}H_{34}O_{13}$. The ^{1}H NMR spectrum revealed signals assignable to a monoterpene i.e. signals for: two methylenes at δ2.26 and 2.39 (*d*, J = 11.8 Hz) (H-3) and δ2.19 (*d*, J = 10.6 Hz) and 2.83 (*dd*, J = 10.6, 6.7 Hz) (H-6), a methylene bearing an acyloxy functionality at δ5.00 and 5.15 (*d*, J = 12.1 Hz) (H-8), one methine at δ3.02 (*d*, J = 6.7 Hz) (H-5), a methine adjacent to two heteroatoms at δ5.89 (*s*) (H-9) and a methyl at δ1.67 (*s*) (H-10). In addition, the glucose moiety accounted for signals at δ4.02 (*t*, J = 7.3 Hz) for H-2′, 4.07 (*t*, J = 7.3 Hz) for H-4′, 4.09 (*t*, J = 7.3 Hz) for H-5′, 4.19 (*t*, J = 7.3 Hz) for H-3′, 5.10 (*d*, J = 7.3 Hz) for H-1′, 4.95 (*dd*, J = 10.8, 7.3 Hz) and 5.17 (*d*, J = 10.8 Hz) for two H-6′. The remaining signals disclosed the presence of two aryloxy groups; one set for a simple benzoyloxy unit at δ7.27 (*t*, J = 7.6 Hz, H-3″ and H-5″), 7.41 (*t*, J = 7.6 Hz, H-4″) and 8.09 (*d*, J = 7.6 Hz, H-2″ and H-6″), and the other for a *p*-methoxybenzoyloxy unit at δ6.98 (*d*, J = 8.8 Hz, H-3‴ and H-5‴), 8.23 (*d*, J = 8.8 Hz, H-2‴ and H-6‴) and 3.65 (*s*, 4‴-OMe). The presence of these groups was also supported by the fragment ion peaks at *m/z* 121 and 151, the former due to the benzoyloxy fragment, the latter to the *p*-methoxybenzoyloxy fragment. COSY, HMQC, HMBC and NOESY experiments (HMBC and NOESY, Fig. 1) allowed the complete connectivities and assignments of the ^{1}H and ^{13}C NMR spectral data and established the location of substitution on the monoterpene and benzene ring systems. Further, the HMBC experiment showed a notable cross-peak between C-7″ and H-8. This phenomenon proved the attachment of the benzoyloxy group to C-8 of the monoterpene, and, of course, the other *p*-methoxybenzoyloxy to C-6′ of glucose. Based on above spectral analyses, the structure of mudanpioside-A was deduced as **1** with six chiral centres.

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Table 1. ^{1}H NMR spectral data for compounds **1**–**6** (pyridine-d_5, δ, multi, J, Hz)

H	1	2	3	4	5	6
3	2.26 (*d*, 11.8) and 2.39 (*d*, 11.8)	2.25 (*d*, 12.2) and 2.40 (*d*, 12.2)	2.22 (*d*, 12.3) and 2.40 (*d*, 12.3)	2.31 (*d*, 12.2) and 2.49 (*d*, 12.2)	2.30 (*d*. 12.0) and 2.49 (*d*, 12.0)	5.78 (*quintet*, 1.8)
5	3.02 (*d*, 6.7)	3.04 (*d*, 6.7)	2.98 (*d*, 6.9)	3.09 (*d*, 6.8)	3.13 (*d*, 6.8)	2.95 (*dd*, 7.2, 2.5)
6	2.19 (*d*, 10.6) and 2.83 (*dd*, 10.6, 6.7)	2.18 (*d*, 10.7) and 2.85 (*dd*, 10.7, 6.7)	2.18 (*d*, 10.6) and 2.79 (*dd*, 10.6, 6.9)	2.32 (*d*, 10.5) and 2.91 (*dd*, 10.5, 6.8)	2.33 (*d*, 10.8) and 2.92 (*dd*, 10.8, 6.8)	2.63 (*d*, 9.3) and 3.55 (*dd*, 9.3, 7.2)
8	5.00 (*d*, 12.1) and 5.15 (*d*, 12.1)	5.01 (*d*, 16.5) and 5.17 (*d*, 16.5)	4.9–5.0 (*m*) and 5.10 (*d*, 11.5)	5.12 (*d*, 12.1) and 5.23 (*d*, 12.1)	5.16 (*d*, 12.1) and 5.28 (*d*, 12.1)	4.10 (*d*, 12.1) and 4.46 (*d*, 12.1)
9	5.89 (*s*)	5.90 (*s*)	5.85 (*s*)	5.94 (*s*)	5.97 (*s*)	1.31 (*s*)
10	1.67 (*s*)	1.64 (*s*)	1.63 (*s*)	1.67 (*s*)	1.68 (*s*)	2.12 (*d*, 1.8)
1′	5.10 (*d*, 7.3)	5.12 (*d*, 8.4)	5.07 (*d*, 8.3)	5.17 (*d*, 7.6)	5.20 (*d*, 8.5)	5.15 (*d*, 8.5)
2′	4.02 (*t*, 7.3)	4.02 (*t*, 8.4)	3.95–4.05 (*m*)	4.06 (*t*, 7.6)	4.06 (*t*, 8.5)	4.04 (*t*, 8.5)
3′	4.19 (*t*, 7.3)	4.22 (*t*, 8.4)	4.15 (*t*, 8.1)	4.22 (*t*, 7.6)	4.24 (*t*, 8.5)	4.20 (*t*, 8.5)
4′	4.07 (*t*, 7.3)	4.06 (*t*, 8.4)	3.95–4.05 (*m*)	4.18 (*t*, 7.6)	4.19 (*t*, 8.5)	4.16 (*t*, 8.5)
5′	4.09 (*t*, 7.3)	4.09 (*dd*, 8.4, 6.9)	3.95–4.05 (*m*)	3.94 (*dd*, 7.6, 6.0)	3.95 (*dd*, 8.5, 6.1)	3.90 (*m*)
6′	4.95 (*dd*, 10.8, 7.3) and 5.17 (*d*, 10.8)	4.96 (*dd*, 10.8, 6.9) and 5.19 (*d*, 10.8)	4.9–5.0 (*m*) and 5.14 (*d*, 10.0)	4.32 (*dd*, 10.8, 6.0) and 4.53 (*d*, 10.8)	4.34 (*dd*, 10.8, 6.1) and 4.54 (*d*, 10.8)	4.29 (*dd*, 11.7, 5.4) and 4.44 (*d*, 11.7)
2″	8.09 (*d*, 7.6)	8.12 (*d*, 8.3)	8.04 (*d*, 7.4)	8.13 (*d*, 8.6)	7.82 (*d*, 1.9)	
3″	7.27 (*t*, 7.6)	7.03 (*d*, 8.3)	7.23 (*t*, 7.4)	6.88 (*d*, 8.6)		
4″	7.41 (*t*, 7.6)		7.38 (*t*, 7.4)			
5″	7.27 (*t*, 7.6)	7.03 (*d*, 8.3)	7.23 (*t*, 7.4)	6.88 (*d*, 8.6)	7.11 (*d*, 8.3)	
6″	8.09 (*d*, 7.6)	8.12 (*d*, 8.3)	8.04 (*d*, 7.4)	8.13 (*d*, 8.6)	7.87 (*dd*, 8.3, 1.9)	
2‴,6‴	8.23 (*d*, 8.8)	8.23 (*d*, 8.3)	8.22 (*d*, 8.8)			
3‴,5‴	6.98 (*d*, 8.8)	6.98 (*d*, 8.3)	7.12 (*d*, 8.8)			
OMe	3.65 (*s*)	3.65 (*s*)		3.67 (*s*)	3.69 (*s*)	

Table 2. ^{13}C NMR spectral data for compounds **1**–**10** (pyridine-d_5)

C	1	2	3	4	5	6	7	8	9	10
1	88.7	88.7	88.9	88.7	88.7	84.4	88.8	88.7	88.8	88.8
2	85.8	85.8	86.0	85.8	85.8	173.4	86.0	85.9	85.9	85.9
3	44.5	44.5	44.7	44.6	44.6	121.3	44.6	44.6	44.6	44.6
4	105.7	105.7	105.9	105.8	105.8	201.1	105.8	105.8	105.8	105.8
5	43.6	43.6	43.8	43.7	43.8	48.1	43.7	43.7	43.7	43.7
6	22.7	22.7	22.8	23.3	23.4	43.4	23.4	23.4	22.8	22.8
7	71.3	71.4	71.4	71.6	71.7	63.6	71.5	71.6	71.6	71.6
8	61.2	60.6	61.4	60.9	60.8	66.3	61.3	60.8	61.2	60.6
9	101.5	101.5	101.6	101.6	101.6	16.1	101.5	101.6	101.5	101.6
10	19.6	19.6	19.8	19.6	19.7	19.9	19.7	19.7	19.7	19.7
1′	100.1	100.1	100.3	100.1	100.2	99.8	100.2	100.2	100.1	100.1
2′	74.9	74.7	74.9	74.8	74.9	74.7	74.7	74.7	74.7	74.7
3′	78.0	78.0	78.3	78.3	78.4	78.5	78.2	78.1	78.0	78.0
4′	71.6	71.6	71.8	71.6	71.6	71.6	71.5	71.6	71.3	71.4
5′	75.0	74.9	75.0	78.2	78.2	78.5	78.2	78.1	74.9	74.9
6′	64.7	64.6	64.7	62.7	62.7	62.6	62.7	62.6	65.0	65.0
1″	130.4	121.1	130.6	122.7	121.3		130.4	121.1	130.5	121.1
2″	129.8	132.2	129.9	131.8	113.3		129.8	132.3	129.8	132.3
3″	128.6	115.9	128.7	113.9	148.1		128.7	116.0	128.8	116.0
4″	133.2	163.4	133.2	163.6	153.0		133.2	163.3	133.2	163.5
5″	128.6	115.9	128.7	113.9	115.9		128.7	116.0	128.8	116.0
6″	129.8	132.2	129.9	131.8	124.5		129.8	132.3	129.8	132.3
7″	166.2	166.4	166.6	166.1	166.5		166.4	166.5	166.4	166.6
1‴	122.7	123.3	121.6						130.7	130.7
2‴,6‴	131.8	131.8	132.4						129.8	129.8
3‴,5‴	114.1	114.0	116.2						128.6	128.8
4‴	163.6	163.7	163.7						133.2	133.3
7‴	166.4	166.0	166.6						166.3	163.3
OMe	55.2	55.2		55.2	55.5					

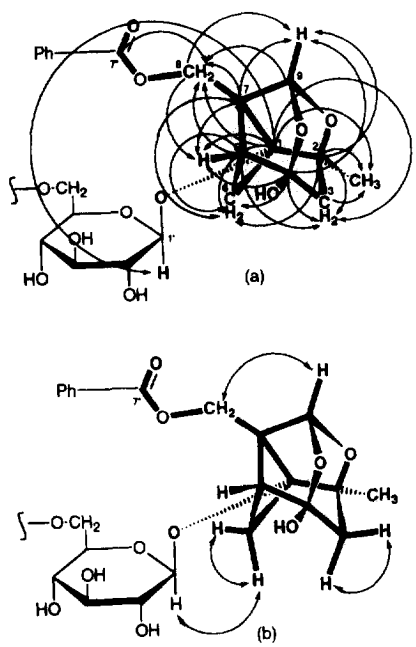


Fig. 1. Selected (a) HMPC (b) NOESY correlations for mudanpioside-A (**1**).

The four mudanpiosides -B (**2**), -C (**3**), -D (**4**) and -E (**5**) were indicated to have molecular formulae of $C_{31}H_{34}O_{14}$, $C_{30}H_{32}O_{13}$, $C_{24}H_{30}O_{12}$ and $C_{24}H_{30}O_{13}$, respectively, by negative HR FAB-mass spectrometry. The ^1H NMR data showed that compound **2** was made up of same monoterpene nucleus as **1**, a *p*-hydroxybenzoyloxy group and a *p*-methoxybenzoyloxy group. The positions of the two *para*-disubstituted benzene rings could be differentiated by the HMBC spectrum (Table 3). The one with the methoxyl substituent was attached to the glucose moiety as shown by the long-range couplings between C-7‴/H-6′, H-2‴, H-6‴ as well as C-4‴/H-2‴, H-6‴, 4‴-OMe while the other substituent was attached to the monoterpene nucleus. Thus, compared to **1**, the *p*-hydroxybenzoyl group in **3** replaced the *p*-methoxybenzoyl substituent on the glucose moiety. Compound **4** had a methoxybenzoyloxy group connected to C-8, but no benzoyl substituent on the glucose moiety. Similarly, **5** had a 4-hydroxy-3-methoxybenzoyloxy on C-8 and no benzoyl substituent. All the connectivities were further supported by HMBC (Table 3) and NOESY experiments. Consequently, the structures of mudanpioside-B to -E were established to be as shown by structures **2**–**5**.

The sixth optically active mudanpioside, -F (**6**) was shown to have the molecular formula $C_{16}H_{24}O_8$. Its

Table 3. HMBC spectral data for compounds **1**, **2** and **4**–**6** (pyridine-d_5)

C	1	2	4	5	6
1	H-3, -5, -6, -8, -10, -1′	H-3, -5, -6, -10, -1′	H-3, -5, -6, -10, -1′	H-3, -5, -6, -10, -1′	H-3, -5, -6, -8, -9, -10, -1′
2	H-3, -6, -9, -10	H-3, -6, -9, -10	H-3, -6, -9, -10	H-3, -6, -9, -10	H-3, -6, -10
3	H-10	H-10	H-10	H-10	H-10
4	H-3, -5, -6, -9	H-3, -5, -6, -9	H-3, -5, -6, -9	H-3, -5, -6, -9	H-5, -6
5	H-3, -6, -8	H-3, -6, -8	H-3, -6, -8	H-3, -6, -8	H-3, -6, -8, -9
7	H-5, -6, -8, -9	H-5, -6, -8, -9	H-5, -6, -8, -9	H-5, -6, -8, -9	H-5, -6, -8, -9
8	H-5, -9	H-5, -9	H-5, -9	H-5, -9	H-5, -9
9	H-8	H-8	H-8		H-6, -8
10					H-3
1′	H-2′	H-2′	H-2′	H-2′	H-2′
2′	H-4′	H-1′			H-3′
3′		H-2′	H-4′	H-4′	H-2′, -4′
4′	H-3′, -5′	H-3′	H-3′	H-3′	H-3′
5′	H-6′	H-3′, -4′, -6′	H-4′	H-4′	H-4′, -6′
6′					H-4′
1″	H-3″, -5″	H-3″, -5″	H-3″, -5″	H-5″	
2″	H-4″, -6″	H-6″	H-6″	H-6″	
3″	H-5″	H-5″	H-5″	H-5″, 3″-OMe	
4″	H-2″, -6″	H-2″, -3″, -5″, -6″	H-2″, -6″, 4″-OMe	H-2″, -5″, -6″	
5″	H-3″	H-3″	H-3″		
6″	H-2″, -4″	H-2″	H-2″	H-2″	
7″	H-8, -2″, -6″	H-8, -2″, -6″	H-8, -2″, -6″	H-8, -2″, -6″	
1‴	H-3‴, -5‴	H-3‴, -5‴			
2‴	H-6‴	H-6‴			
3‴	H-5‴	H-5‴			
4‴	H-2‴, -6‴, 4‴-OMe	H-2‴, -3‴, -5‴, -6‴, 4‴-OMe			
5‴	H-3‴	H-3‴			
6‴	H-2‴	H-2‴			
7‴	H-2‴, -6‴	H-6′, 2‴, -6‴			

^{1}H NMR spectrum contained the same glucose signals as **1**–**5**. However, the monoterpene moiety showed slight differences from those of the above. Thus, signals for one quaternary methyl at δ1.31 (*s*, H-9), one olefinic methyl at δ2.12 (*d*, J = 1.8 Hz, H-10), one vinyl proton at δ5.78 (*quintet*, J = 1.8 Hz, H-3), one methine at δ2.95 (*dd*, J = 7.2, 2.5 Hz, H-5), and two methylenes at δ2.63 (*d*, J = 9.3 Hz) and 3.55 (*dd*, J = 9.3, 7.2 Hz) (H-6)′and δ4.10 and 4.46 (*d*, J = 12.1 Hz) (H-8) showed the presence of a 2,7-dimethyl-7-hydroxymethyl-1-oxygenatedbicyclo[3.1.1]hept-2-en-4-one nucleus. The presence of an α,β-unsaturated carbonyl group was confirmed by the ^{13}C NMR signals for the double bond at δ121.3 and 173.4 along with the carbonyl at δ201.1. In a similar way, all the connectivities were supported by the HMBC spectrum (Table 3). The NOE relationships between Me-7 and H-3, Me-2 (H-10) accounted for the orientation of Me-7, which was suggested to be above the double bond (Fig. 2). Thus, mudanpioside-F possessed the structure **6**.

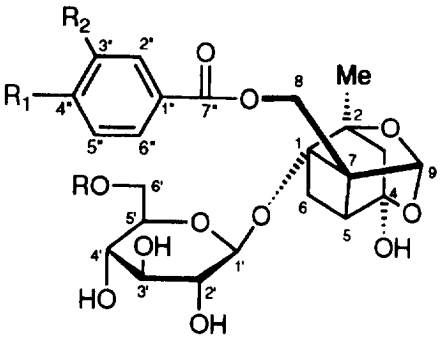
On the basis of the specific rotational values of compounds **1**–**5**, [α] $-5°$ to $-25°$, compared to those of **7**–**10**, [α] $-8°$ to $-15°$, these new compounds had to have the same absolute configuration as the known compounds **7**–**10** [10].

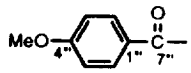
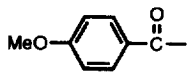
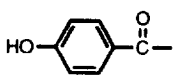
EXPERIMENTAL

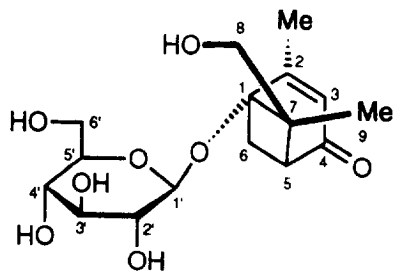
Mps: uncorr.; UV: EtOH; IR: KBr; ^{1}H NMR and ^{13}C NMR: pyridine-d_5, TMS as int. standard.

Plant material. The root cortex of *P. suffruticosa* was purchased from a local market. A specimen of the plant (NDMC-790701) has been verified by Prof. C. S. Kuoh and deposited at the herbarium of the National Defense Medical Center, Taipei, Taiwan.

Extraction and separation. The root cortex (45 kg) was extracted with 95% followed by 70% EtOH (×4) at room temp. The combined EtOH extracts were concd under red. pres. to yield a dark-brown syrup which was partitioned between hexane and 90% MeOH. The 90% MeOH layer was concd and partitioned with EtOAc and H_2O. The aq. soln was again partitioned between *n*-BuOH and H_2O. The EtOAc layer was subjected to silica gel CC and eluted with $CHCl_3$ and $CHCl_3$–MeOH (97:3) to afford acetophenones. The residue was eluted with MeOH, combined with the *n*-BuOH extract and subjected to CC on silica gel with $CHCl_3$–MeOH, 19:1, 9:1, 17:3. Re-chromatography of the 1st fr. on prep Lobar RP-8 followed by HPLC sepn gave **9** (20.7 g) and **1** (0.2 g). In the same manner, the 2nd fr. furnished **10** (6.6 g), **2** (0.2 g) and **3** (4.4 g), and the 3rd fr. gave **11** (1.7 g),



	R	R_1	R_2
1		H	H
2		OH	H
3		H	H
4	H	OMe	H
5	H	OH	OMe
7	H	H	H
8	H	OH	H
9	benzoyl	H	H
10	benzoyl	OH	H



6

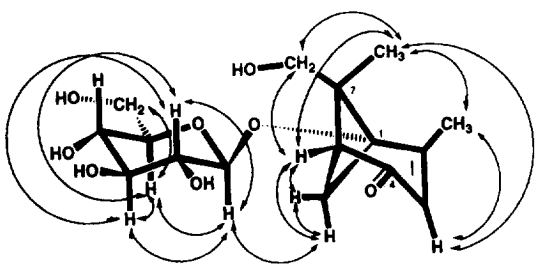


Fig. 2. NOESY correlations for mudanpioside-F (**6**).

7 (101.1 g), **8** (61.2 g), **4** (1.5 g), **5** (3.1 g) and **6** (0.6 g), successively.

Mudanpioside-A (**1**). Crystals, mp 115–121°, $[\alpha]_D$ − 6.885° (MeOH; *c* 0.061). Negative HRFAB-MS: calc. for $C_{31}H_{33}O_{13}$, *m/z* 613.1921 $[M-H]^-$, found 613.1932. UV λ_{max} nm (log ε): 233 (4.20), 257 (4.21); IR ν_{max} cm^{-1}: 3414, 1709, 1603, 1509; FAB-MS *m/z* (rel. int.): 613 $[M-H]^-$ (15), 151 (58), 137 (15), 121 (100).

Mudanpioside-B (**2**). Crystals, mp 140–144°, $[\alpha]_D$ − 12.055° (MeOH; *c* 0.0564). Negative HRFAB-MS: calc. for $C_{31}H_{33}O_{14}$, *m/z* 629.1875 $[M-H]^-$, found 629.1862; UV λ_{max} nm (log ε): 258 (4.52); IR ν_{max} cm^{-1}: 3393, 1702, 1604, 1510; FAB-MS *m/z* (rel. int.): 629 $[M-H]^-$ (100), 615 (14), 151 (12), 137 (32).

Mudanpioside-C (**3**). Crystals, mp 145–150°, $[\alpha]_D$ − 24.885° (MeOH; *c* 0.103). Negative HRFAB-MS: calc. for $C_{30}H_{31}O_{13}$, *m/z* 599.1764 $[M-H]^-$, found 599.15; UV λ_{max} nm (log ε): 231 (4.23), 258 (4.22); IR ν_{max} cm^{-1}: 3369, 1704, 1606, 1591, 1511; FAB-MS *m/z* (rel. int.): 599 $[M-H]^-$ (95), 281 (26), 239 (14), 179 (22), 153 (13), 137 (87), 136 (23), 121 (100).

Mudanpioside-D (**4**). Crystals, mp 122–127°, $[\alpha]_D$ − 15.238° (MeOH; *c* 0.105). Negative HRFAB-MS: calc. for $C_{24}H_{29}O_{12}$, *m/z* 509.1659 $[M-H]^-$, found 509.1659; UV λ_{max} nm (log ε): 258 (4.20); IR ν_{max} cm^{-1}: 3393, 1702, 1603, 1510; FAB-MS *m/z* (rel. int.): 509 $[M-H]^-$ (20), 151 (100), 137 (15), 121 (13).

Mudanpioside-E (**5**). Crystals, mp 134–140°, $[\alpha]_D$ − 19.800° (MeOH; *c* 0.100). Negative HRFAB-MS: calc. for $C_{24}H_{29}O_{13}$, *m/z* 525.1611 $[M-H]^-$, found 525.1605; UV λ_{max} nm (log ε): 221 (3.92), 265 (3.17), 291 (3.46); IR ν_{max} cm^{-1}: 3381, 1701, 1594, 1512; FAB-MS *m/z* (rel. int.): 525 $[M-H]^-$ (100), 197 (10), 167 (20).

Mudanpioside-F (**6**). Crystals, mp 153–159°, $[\alpha]_D$ + 3.306° (MeOH; *c* 0.0527). Negative HRFAB-MS: calc. for $C_{16}H_{23}O_8$, *m/z* 343.1393 $[M-H]^-$, found 343.1384; UV λ_{max} nm (log ε): 252 (3.84); IR ν_{max} cm^{-1}: 3463, 3311, 1671. FAB-MS *m/z* (rel. int.): 343 $[M-H]^-$ (100), 181 (15).

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