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Caffeoyl arbutin and related compounds from the buds of *Vaccinium dunalianum*

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ABSTRACT

Dunalianosides A-I (**1**–**9**), esters of arbutin and related phenolic glucosides, were isolated from the buds of *Vaccinium dunalianum* Wight (Ericaceae) together with 20 known compounds, and their structures were established on the basis of 1- and 2D NMR spectroscopic evidence. Dunalianosides F–H were dimers of *p*-hydroxyphenyl 6-*O*-*trans*-caffeoyl-β-D-glucopyranoside (**10**). The latter was obtained in extraordinary high yield (22% of dry weight), and dunalianoside I (**9**) was found to be a conjugate of arbutin with an iridoid glucoside.

1. Introduction

Vaccinium dunalianum Wight (Ericaceae) is an evergreen perennial shrub distributed in the Southwest of China, Myanmar and Vietnam. The local people of its growing area in China use the leaf of this plant as a folk medicine for the treatment of articular rheumatism, and also substitute its dried buds for tea to prepare a traditional folk beverage. It is well known that the *Vaccinium* species are rich sources of naturally occurring dietary phenolics, such as flavonoids, anthocyanins, proanthocyanidins and other phenolic compounds (Prior et al., 1998; Moyer et al., 2002; Taruscio et al., 2004), which have been identified as antioxidants, with the potential to prevent oxidative damage caused by reactive oxygen species. However, no chemical investigation has been reported on the title plant. In continuing studies on phenolic constituents from medicinal plants, the occurrence of significant amounts of phenolics in the buds of this plant has been suggested by TLC analysis in our preliminary analysis. Further study of phenolics in the buds of this plant has led to the isolation of eight novel caffeoyl derivatives of arbutin, namely dunalianosides A–H (**1**–**8**), and a new conjugate of arbutin with an iridoidal glycoside, dunalianoside I (**9**), together with 20 known compounds (**10**–**29**). Of these, *p*-hydroxyphenyl 6-*O*-*trans*-caffeoyl-β-D-glucopyranoside (**10**) was isolated in 22% yield from the dried buds. This study investigated the isolation and structural elucidation of these compounds.

2. Results and discussion

A 60% aqueous acetone extract of the air-dried buds of *V. dunalianum* was first defatted by partitioning with diethyl ether, and then the aqueous layer was concentrated to yield large amounts of off-white crystalliferous solids. The solids were collected by filtration and re-crystallized to yield *p*-hydroxyphenyl 6-*O*-*trans*-caffeoyl-β-D-glucopyranoside (robustaside B, **10**) (22% of the dry weight) (Machida et al., 1991). The filtrate was concentrated, and the residue was chromatographed successively on Diaion HP-20, Sephadex LH-20, MCI gel CHP20P, Chromatorex ODS, Toyopearl HW-40F, and silica gel to give dunalianosides A–I (**1**–**9**), along with 19 known compounds. By comparisons of the physical and spectroscopic data with those of previously reported data and direct comparison with authentic standards, the known compounds, in addition to **10**, were characterized as *p*-hydroxyphenyl β-D-glucopyranoside (arbutin, **11**) (Dommisse et al., 1986), *p*-hydroxyphenyl 6-*O*-acetyl-β-D-glucopyranoside (pyroside, **12**) (Machida and Kikuchi, 1993), *p*-hydroxyphenyl 6-*O*-(4-β-D-glucopyranosyl-*trans*-caffeoyl)-β-D-glucopyranoside (robustaside C, **13**) (Ahmed et al., 2000), *p*-hydroxyphenyl 6-*O*-*trans*-coumaroyl-β-D-glucopyranoside (robustaside A, **14**) (Machida and Kikuchi, 1993), monotropein (**15**) (Jensen et al., 2002) and scandoside (**16**) (Kim et al., 2005), benzyl alcohol β-D-glucopyranoside (**17**) (Kitajima et al., 1998), icariside F_2 (**18**) (Ono et al., 1996), parasorboside (**19**), methyl (3*S*,5*S*)-5-hydroxy-3-(β-D-glucopyranosyl)-hexanoate (**20**) (Numata et al., 1990), 6-*O*-*trans*-caffeoyl-D-glucopyranose (**21**) (Shimomura et al., 1987), ferulic acid 4-*O*-β-D-glucoside (**22**) (Shoyama et al., 1987), kaempferol 3-*O*-β-D-glucopyranoside (**23**) (Vvedenskaya et al., 2004), caffeic acid (**24**), chlorogenic acid (**25**), 3-*O*-feruloylquinic

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Table 1
^{1}H (500 MHz) and 13C (125 MHz) NMR spectroscopic data for compounds **1–5** measured in CD_3OD

Position	**1**		**2**		**3**		**4**		**5**	
	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)
1	152.1		140.0		152.4		152.6		152.1	
2	119.5	6.91 *d* (8.7)	147.2		106.5	6.64 *d* (1.8)	104.1	6.70 *d* (1.8)	119.6	6.95 *d* (9.0)
3	116.8	6.65 *d* (8.7)	105.8	6.27 *d* (2.7)	146.5		149.2		116.7	6.67 *d* (9.0)
4	153.7		155.3		141.5		142.5		153.9	
5	116.8	6.65 *d* (8.7)	107.1	6.09 *dd* (8.7, 2.7)	116.0	6.63 *d* (8.4)	116.0	6.60 *d* (8.8)	116.7	6.67 *d* (9.0)
6	119.5	6.91 *d* (8.7)	121.0	6.93 *d* (8.7)	108.8	6.46 *dd* (8.4, 1.8)	110.3	6.53 *dd* (8.8, 1.8)	119.6	6.95 *d* (9.0)
3-OCH_3							56.4	3.74 *s*		
1′	103.5	4.70 *d* (7.2)	104.4	4.54 *d* (7.8)	103.3	4.73 *d* (7.2)	103.8	4.70 *d* (7.0)	103.6	4.78 *d* (8.0)
2′	74.8	3.41 *t* (7.2)	74.8	3.39 *t* (7.8)	74.6	3.38 *t* (7.2)	74.9	3.39 *t* (7.0)	74.9	3.54 *t* (8.0)
3′	77.7	3.43 *t* (7.2)	77.5	3.43 *t* (8.5)	77.6	3.41 *t* (8.6)	77.8	3.41 *t* (8.8)	75.5	3.67 *t* (9.5)
4′	71.6	3.38 *t* (7.2)	71.6	3.36 *t* (8.5)	71.4	3.36 *t* (8.6)	71.8	3.35 *t* (8.8)	72.4	4.90 *t* (9.5)
5′	75.2	3.61 *ddd* (7.2, 6.6, 1.8)	75.7	3.59 *ddd* (8.5, 6.6, 1.8)	75.2	3.66, *ddd* (8.6, 6.3, 1.8)	75.6	3.61 *ddd* (8.8, 6.8, 1.8)	73.1	3.82 *ddd* (9.5, 9.5, 5.5)
6′	64.3	4.49 *dd* (11.7, 1.8)	64.5	4.50 *dd* (12.3, 1.8)	64.4	4.54 *dd* (11.7, 1.8)	64.8	4.51 *dd* (12.0, 1.8)	63.7	4.27 *dd* (12.5, 5.5)
		4.30 *dd* (11.7, 6.6)		4.31 *dd* (12.3, 6.6)		4.32 *dd* (11.7, 6.3)		4.28 *dd* (12.0, 6.8)		4.24 *dd* (12.5, 9.5)
CH_3CO									20.9	2.10 *s*
CH_3CO									172.1	
1″	128.0		127.7		127.5		127.6		127.6	
2″	116.1	7.40 *d* (2.1)	115.0	7.02 *d* (1.8)	114.8	7.07 *d* (1.5)	115.0	7.00 *d* (1.5)	115.1	7.05 *d* (2.5)
3″	148.2		149.6		149.3		149.2		149.6	
4″	145.5		146.8		146.5		146.8		146.7	
5″	118.5	6.72 *d* (8.1)	116.5	6.75 *d* (7.8)	116.2	6.79 *d* (8.4)	116.6	6.74 *d* (8.4)	116.5	6.79 *d* (8.5)
6″	125.2	7.08 *dd* (8.1, 2.1)	123.1	6.92 *dd* (7.8, 1.8)	122.9	6.96 *dd* (8.4, 1.5)	123.1	6.89 *dd* (8.4, 1.5)	123.2	6.93 *dd* (8.5, 2.5)
7″	145.5	6.82 *d* (12.9)	147.2	7.55 *d* (15.9)	146.9	7.57 *d* (16.0)	147.2	7.51 *d* (16.0)	147.3	7.56 *d* (16.0)
8″	115.7	5.77 *d* (12.9)	114.8	6.26 *d* (15.9)	114.6	6.32 *d* (16.0)	114.8	6.23 *d* (16.0)	114.6	6.25 *d* (16.0)
9″	168.1		169.0		168.8		169.0		168.7	

acid (**26**) (Morishita et al., 1984), 3-*O*-*p*-coumarylquinic acid (**27**), (−)-shikimic acid (**28**) (Wada et al., 1992), and tryptophan (**29**).

Compound **1** was obtained as an off-white amorphous powder, and its molecular formula $C_{21}H_{22}O_{10}$ was confirmed by the positive HR-FAB-MS [*m/z* 434.1234 ($[M]^+$), calcd. 434.1213] and the number of ^{13}C NMR spectroscopic signals. The ^1H and ^{13}C NMR spectra closely resembled those of **10** (Machida et al., 1991), except for the signals due to the caffeoyl moiety. The olefin proton resonances of **1** were observed at δ 5.77 and 6.82 (each *d*, *J* = 12.9 Hz) (Table 1), which were up field compared to those of **10** ($\Delta\delta$ 0.51, 0.7, respectively), and the coupling constant was smaller (**10**: *J* = 15.6 Hz). This observation indicated that the geometry of the double bond in the caffeoyl moiety of **1** was the *cis* form. The chemical shifts of glucose H-6′ [δ 4.49 (*dd*, *J* = 11.7, 1.8 Hz) and 4.30 (*dd*, *J* = 11.7, 6.6 Hz)], and C-6′ (δ 64.3) confirmed the location of the *cis*-caffeoyl moiety at this position. On the basis of these spectroscopic data, compound **1** was determined to be *p*-hydroxyphenyl 6′-*O*-*cis*-caffeoyl-β-D-glucopyranoside, and named dunalianoside A.

Compound **2** was obtained as an off-white amorphous powder. Its molecular formula was deduced to be $C_{21}H_{22}O_{11}$ on the basis of the positive HR-FAB-MS [*m/z* 451.1213 ($[M+H]^+$, calcd. 451.1240)]. The ^1H and ^{13}C NMR spectroscopic data of **2** were closely related to those of **10**, which indicated the presence of a 6-*O*-caffeoyl-β-glucopyranoside residue in the molecule. However, instead of the aromatic AA′BB′ coupling system attributed to the *p*-substituted phenyl moiety in **10**, an ABX coupling system [δ 6.27 (1H, *d*, *J* = 2.7 Hz, H-3), 6.09 (1H, *dd*, *J* = 8.7, 2.7 Hz, H-5), 6.93 (1H, *d*, *J* = 8.7 Hz, H-6)] (Table 1) was observed in the ^1H NMR spectrum of **2**. Furthermore, the ^{13}C NMR spectrum of **2** (Table 1) showed signals arising from a 1,2,4-trisubstituted benzene ring (C-1–C-6). These findings indicated that **2** had an additional hydroxyl group in the phenyl moiety. The location of the glucose moiety and two hydroxyl groups in the aglycone moiety was confirmed by the NOESY experiment, which showed correlations between the glucose anomeric proton [δ 4.54 (1H, *d*, *J* = 7.8 Hz, H-1′)] and aglycone H-6 (δ 6.93), and between H-5 (δ 6.09) and H-6 (Fig. 1). Therefore, compound **2** was characterized as 2,4-dihydroxyphenyl 1-*O*-(6′-*O*-*trans*-caffeoyl)-β-D-glucopyranoside, and named dunalianoside B.

Compound **3** was obtained as an off-white amorphous powder. From the result of positive HR-FAB-MS [*m/z* 451.1224 ($[M+H]^+$, calcd. 451.1240)], its molecular formula was deduced to be $C_{21}H_{22}O_{11}$, which was identical to that of **2**. The ^1H NMR spectrum of **3** (Table 1) was also related to that of **2** and showed signals due to two sets of ABX-aromatic, *trans*-olefinic, and sugar proton resonances. A difference in the chemical shifts was observed in one of the ABX-spin systems due to presence of a trisubstituted benzene moiety. The substitution on the benzene ring was determined by the NOESY experiment, which showed correlations between the anomeric proton at δ 4.73 and both H-2 (δ 6.64) and H-6 (δ 6.46), and between H-6 and H-5 (δ 6.63) (Fig. 1). Therefore, compound **3** was established as 3,4-dihydroxyphenyl 1-*O*-(6′-*O*-*trans*-caffeoyl)-β-D-glucopyranoside, and named dunalianoside C.

Compound **4** was obtained as an off-white amorphous powder, and had a molecular formula $C_{22}H_{24}O_{11}$, which was deduced from the positive HR-FAB-MS [*m/z* 464.1320 ($[M]^+$), calcd. 464.1318]. The ^1H and ^{13}C NMR spectroscopic data of **4** were very similar to those of **3** (Table 1), except for appearance of signals due to a methoxy group [δ_H 3.74 (3H, s), δ_c 56.4]. Analysis of the NOESY spectrum established the location of glucose at C-1 and the methoxyl group at C-3, which showed correlations between the anomeric proton at δ 4.70 (*d*, *J* = 7.0 Hz) and both H-2 [δ 6.70 (*d*, *J* = 1.8 Hz)] and H-6 [δ 6.53 (*dd*, *J* = 8.8, 1.8 Hz)], as well as between H-2 and the methoxyl group protons (Fig. 1). Therefore, compound **4** was established as 3-methoxy-4-hydroxyphenyl 1-*O*-(6′-*O*-*trans*-caffeoyl)-β-D-glucopyranoside, and named dunalianoside D.

Compound **5** was obtained as an off-white amorphous powder. Its molecular formula was deduced to be $C_{23}H_{24}O_{11}$ on the basis of the positive HR-FAB-MS [*m/z* 476.1303 ($[M]^+$), calcd. 476.1308]. From the ^1H, ^{13}C NMR and ^1H–^1H COSY spectroscopic data (Table 1, Fig. 1), occurrence of an arbutin moiety, along with a *trans*-caffeoyl and an acetyl [δ 2.10 (*s*)] group, was easily deduced. In

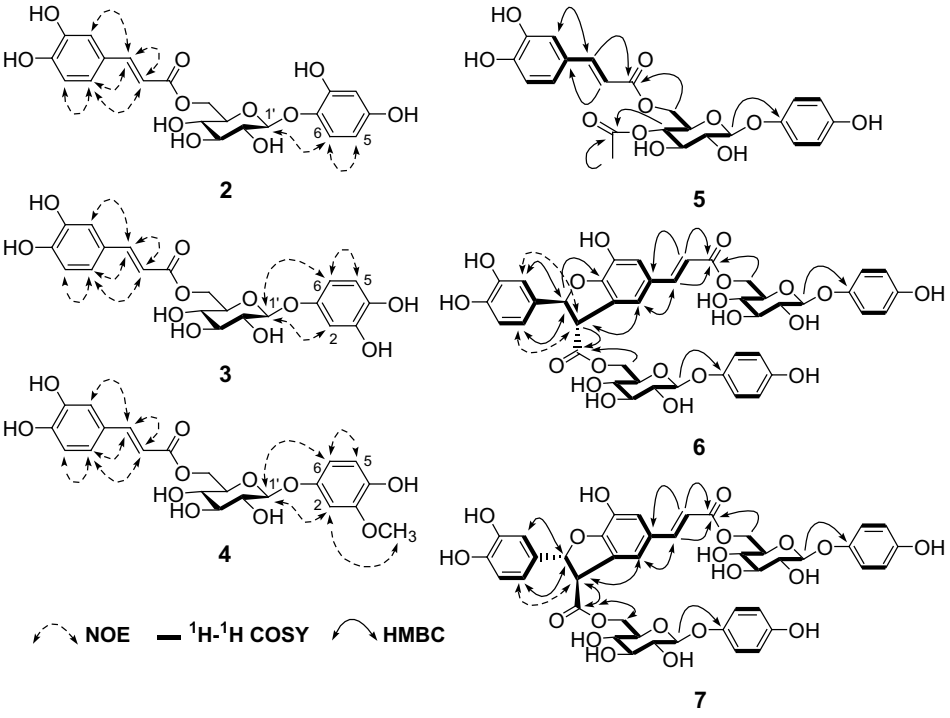


Fig. 1. Selected NOE correlations for **2**–**4**, and ^1H–^1H COSY and HMBC correlations for **5**–**7**.

addition, the downfield shifts of glucose H-4′ [δ 4.90 (1H, *t*, *J* = 9.5 Hz)] and H_2-6′ protons [δ 4.27 (1H, *dd*, *J* = 12.5, 5.5 Hz), 4.24 (1H, *dd*, *J* = 12.5, 9.5 Hz)] indicated acylation of hydroxyl groups at these positions. The locations of the caffeoyl and acetyl groups on the glucose core were determined by the heteronuclear multiple bond coherence (HMBC) analysis, which showed a long-range H–C correlation of glucose H_2-6′ with a carboxyl carbon (δ 168.7) of the caffeoyl group, as well as the glucose H-4′ with the carboxyl carbon (δ 172.1) of the acetyl group (Fig. 1). On the basis of the spectroscopic evidence, compound **5** was characterized as *p*-hydroxyphenyl 4′-*O*-acetyl-6′-*O*-*trans*-caffeoyl-β-D-glucopyranoside, and named dunalianoside E.

Compounds **6** and **7**, named as dunalianosides F and G, showed the same R_f value on silica gel TLC and similar chromatographic behavior during separation procedure. The final separation of these compounds was achieved by Toyopearl HW-40F column chromatography. The HR-FAB MS spectra of **6** [*m/z*, 866.2231 ($[M]^+$), calcd. 866.2269] and **7** [*m/z*, 867.2394 ($[M+H]^+$), calcd. 867.2347] established the same molecular formula $C_{42}H_{42}O_{20}$ for these compounds. The ^{1}H and ^{13}C NMR spectra of **6** and **7** were almost indistinguishable from each other, which indicated their structural similarity.

The ^{1}H NMR spectrum of compound **6** (Table 2) showed two sets of AA′BB′-aromatic doublets (H-2″, 6″, H-3″, 5″ and H-2‴, 6‴, H-3‴, H-5‴)] and two anomeric doublets (H-1‴) and H-1⁗). These signals were attributable to two arbutin moieties. In addition, a set of ABX-signal (H-2, H-5 and H-6)] and a pair of *meta*-coupled resonances (H-2′ and H-6′) were observed in the aromatic region, which were assignable to the discrete sets of protons of the 1,3,4- and 1,3,4,5-substituted phenyl units, respectively. Also observed were two doublets (*J* = 16.0 Hz) that arose from a pair of *trans*-olefinic protons, and two vicinally located methine protons (*d* each, *J* = 8.0 Hz) that were assigned to the protons of the dihydrobenzofuran skeleton in **6**. The dihydrobenzofuran skeleton was further confirmed by the HMBC experiment, which showed correlations of H-7 with C-1, C-2, C-6, C-9, C-4′ and C-5′, and correlations of H-8 with C-1, C-9, C-4′, C-5′ and C-6′ (Fig. 1). In the NOESY spectrum, the H-8 exhibited cross-peaks with H-2 and H-6, which indicated that the dihydrobenzofuran ring in **6** possessed a *trans* configuration. These spectroscopic characteristics were also

Table 2
1H (500 MHz) and ^{13}C (125 MHz) NMR spectroscopic data for compounds **6**–**8** measured in CD_3OD

Position	**6**		**7**		**8**	
	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)
1	127.5		127.4		132.1	
2	114.0	6.84 *d* (2.5)	114.0	6.83 *d* (2.0)	116.4	6.41 *d* (2.0)
3	146.6		146.8		145.7	
4	146.6		146.6		144.7	
5	116.5	6.77 *d* (8.5)	116.5	6.76 *d* (8.5)	116.0	6.54 *d* (8.0)
6	118.9	6.74 *dd* (8.5, 2.5)	118.9	6.75 *dd* (8.5, 2.0)	120.6	6.32 *dd* (8.0, 2.0)
7	88.5	5.95 *d* (8.0)	88.5	5.95 *d* (8.0)	46.0	4.13 *dd* (10.0, 6.0)
8	57.2	4.36 *d* (8.0)	57.1	4.34 *d* (8.0)	45.3	3.75 *dd* (10.0, 6.0)
9	172.2		172.1		174.5	
1″	152.3		152.3		152.3[a]	
2″	119.7	6.94 *d* (9.5)	120.3	6.92 *d* (9.0)	119.6[b]	6.95 *d* (9.0)[a]
3″	116.8	6.65 *d* (9.5)	116.7	6.64 *d* (9.0)	116.8[c]	6.69 *d* (9.0)[b]
4″	153.9		154.1		153.8[d]	
5″	116.8	6.65 *d* (9.5)	116.7	6.64 *d* (9.0)	116.8[c]	6.69 *d* (9.0)[b]
6″	119.7	6.94 *d* (9.5)	120.3	6.92 *d* (9.0)	119.6[b]	6.95 *d* (9.0)[a]
1″-*O*-Glc-1‴	103.8	4.76 *d* (7.5)	104.3	4.76 *d* (7.5)	103.5[e]	4.73 *d* (7.5)[c]
2‴	74.9	3.40–3.50*	75.0	3.40–3.50*	74.9	3.36–3.40*
3‴	77.9	3.40–3.50*	77.9	3.40–3.50*	77.8[f]	3.43**
4‴	71.7	3.40–3.50*	71.8	3.40–3.50*	71.6	3.36–3.40*
5‴	75.4	3.64**	75.4	3.62**	75.3	3.56 *ddd* (7.0, 6.5, 2.0)
6‴	65.7	4.59 *dd* (12.0, 2.0) 4.37 *dd* (12.0, 6.0)	65.4	4.60 *dd* (12.0, 2.0) 4.37 *dd* (12.0, 6.0)	65.4	4.47 *dd* (12.0, 2.0) 4.25 *dd* (12.0, 6.5)
1′	129.9		129.9		132.0	
2′	117.4	7.01 *d* (2.0)	117.0	7.03 *d* (1.5)	116.4	6.40 *d* (2.0)
3′	143.0		143.0		145.7	
4′	150.7		150.8		144.6	
5′	133.1		133.0		116.0	6.54 *d* (8.0)
6′	118.5	7.08 *d* (2.0)	118.9	7.14 *d* (1.5)	120.6	6.31 *dd* (8.0, 2.0)
7′	146.9	7.50 *d* (16.0)	146.9	7.58 *d* (16.0)	45.9	4.10 *dd* (10.0, 6.0)
8′	116.0	6.25 *d* (16.0)	116.0	6.30 *d* (16.0)	44.7	3.79 *dd* (10.0, 6.0)
9′	168.9		168.8		174.4	
1⁗	152.1		152.2		152.2[a]	
2⁗	119.3	6.92 *d* (9.5)	119.6	6.92 *d* (9.0)	119.5[b]	6.91 *d* (9.0)[a]
3⁗	116.7	6.61 *d* (9.5)	116.7	6.61 *d* (9.0)	116.7[c]	6.67 *d* (9.0)[b]
4⁗	153.7		153.8		153.8[d]	
5⁗	116.7	6.61 *d* (9.5)	116.7	6.61 *d* (9.0)	116.7[c]	6.67 *d* (9.0)[b]
6⁗	119.3	6.92 *d* (9.5)	119.6	6.92 *d* (9.0)	119.5[b]	6.91 *d* (9.0)[a]
1⁗-*O*-Glc-1⁗′	103.3	4.72 *d* (7.5)	103.3	4.71 *d* (7.5)	103.4[e]	4.71 *d* (7.5)[c]
2⁗′	74.8	3.40–3.50*	74.9	3.40–3.50*	74.9	3.36–3.40*
3⁗′	77.8	3.40–3.50*	77.8	3.40–3.50*	77.7[f]	3.43**
4⁗′	71.6	3.40–3.50*	71.4	3.40–3.50*	71.5	3.36–3.40*
5⁗′	75.2	3.64**	75.1	3.62**	75.2	3.53 *ddd* (7.0, 6.5, 2.0)
6⁗′	64.6	4.50 *dd* (12.0, 2.0) 4.34 *dd* (12.0, 6.0)	64.6	4.49 *dd* (12.0, 2.0) 4.35 *dd* (12.0, 6.0)	65.2	4.54 *dd* (12.0, 2.0) 4.18 *dd* (12.0, 6.5)

*,** Overlapped signals in the same column, multiplicity could not be resolved.
[a–h, a–c] Interchangeable values in each vertical column.

observed in the ^{1}H, ^{13}C and 2D-NMR spectra of compound **7** (Fig. 1), which indicated that **6** and **7** possessed the same salient features. The full assignment of ^{1}H and ^{13}C NMR chemical shifts of **6** and **7** are shown in Table 2.

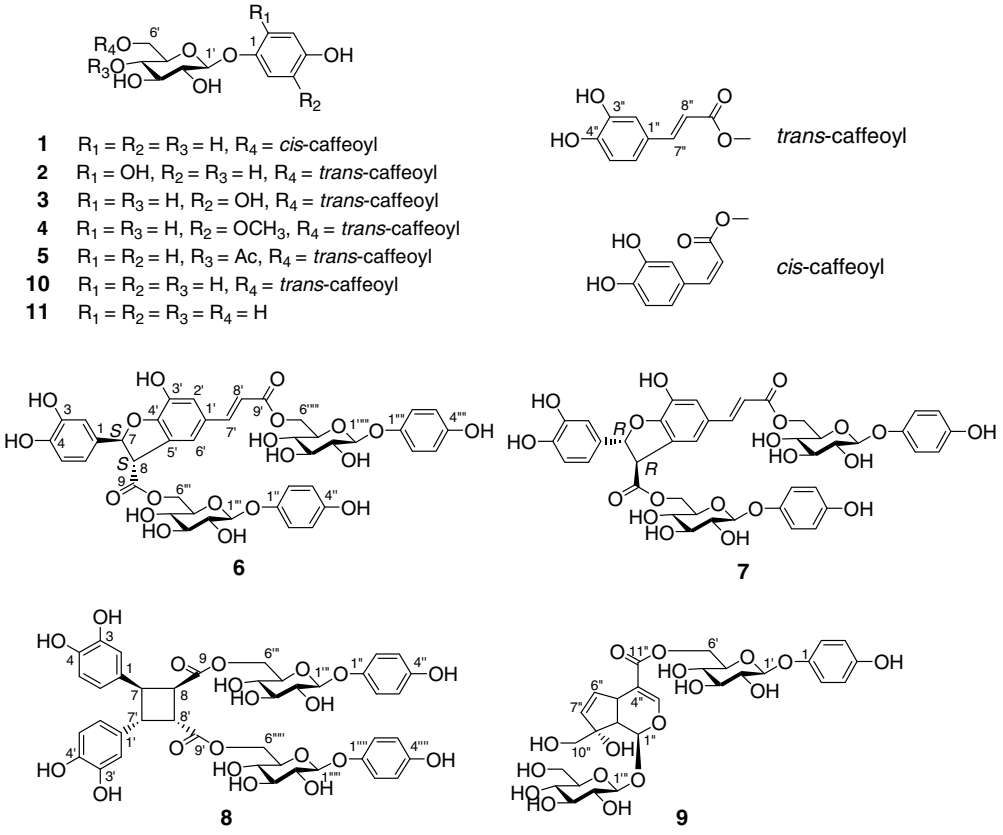
The absolute configuration in **6** was assigned by circular dichroism (CD) spectroscopy. The CD spectrum of **6** showed a negative Cotton effect at 254 nm and a positive one at 236 nm. Based on comparison of the spectrum with those of the known dihydrobenzofuran-type compounds (Lemière et al., 1995; Matsuda et al., 1996), the absolute stereochemistry at C-7 and C-8 was assigned to be in the 7*S* and 8*S* configurations. By contrast, compound **7** exhibited a positive Cotton effect at 256 nm and a negative one at 224 nm, and the configuration was assigned to be 7*R*, 8*R*. Therefore, the structures of **6** and **7** were established as shown in Scheme 1.

Compound **8** was obtained as an off-white amorphous powder. The molecular ion ([M]$^+$) observed in the positive HR-FAB-MS at *m/z* 868.2458 (calcd. 868.2425) and the ^{13}C NMR spectral data (Table 2) showed the molecular formula to be $C_{42}H_{44}O_{20}$. The ^{1}H and ^{13}C NMR spectral data of **8** were related to those of **1** and **10**, except for the appearance of the signals in duplicate. In addition, the olefinic resonances of caffeoyl moieties of **1** and **10** were replaced by four well-resolved double doublets (J = 10.0 and 6.0 Hz) at δ_H 4.13 (H-7), 4.10 (H-7′), 3.79 (H-8′) and 3.75 (H-8). Taking the molecular weight, which was exactly twice that of **1** or **10**, into account, these NMR data indicated that **8** was a dimer of **1** or **10,** and that **8** was a cyclobutane-type dimer formed by [2+2]-cycloaddition between two caffeoyl double bonds of **1** or **10**.

The structure was established by the following 2D NMR analysis. The COSY spectrum showed the connection between C-7–C-8, C-8–C-8′, C-8′–C-7′ and C-7′–C-7 (Fig. 2), which confirmed the presence of a cyclobutane ring in **8**. From the HMQC spectrum, the signals at δ 46.0 (C-7), 45.9 (C-7′), 45.3 (C-8) and 44.7 (C-8′) were assigned to the cyclobutane methine carbons. In the HMBC spectrum, the former two methine carbons correlated with the catechol ring protons, and conversely, the H-7 and H-7′ were correlated with the catechol ring carbons. The remaining two cyclobutane protons H-8 and H-8′ were coupled with carboxyl carbons (C-9 and C-9′). The HMBC spectrum also showed correlations of the carboxyl carbons with the glucose C-6 methylene protons. These results further confirmed that **8** was a dimer of **1** or **10** formed by cyclobutane formation between two caffeoyl groups. Concerning the dimerization reaction, there are two possible arrangements of the two caffeoyl arbutin moieties, that is, head-to-head (truxinic type) or head-to-tail (truxillic type) (Hartley et al., 1990). This was determined by the appearance of the HMBC correlations of H-7 with C-1 and C-1′; H-7′ with C-1′ and C-1; and H-8 and H-8′ with carboxyl carbons C-9 and C-9′, which showed that compound **8** was a truxinic-type dimer (Fig. 2).

The relative configuration of the cyclobutane ring was established by the NOESY experiment. The NOESY spectrum not only showed clear NOE correlations between H-7(H-7′) and H-2′,6′(H-2,6), but also between H-7(H-7′) and H-8(H-8′) (Fig. 2), which are only possible for a *trans* configuration between H-7 and H-7′, and *cis* configurations between H-7 and H-8 and between H-7′ and H-8′, which implied that the cyclobutane ring was in a μ-truxinate arrangement. Furthermore, the ^{1}H-^{1}H coupling of cyclobutane protons (10.0 and 6.0 Hz) was in agreement with that of a μ-truxinate-type-related compounds (Lu and Foo, 1999; Kamara et al., 2005). Therefore, compound **8** was deduced to be a μ-truxinic-type dimer of **1**, and its structure was established as shown in Scheme 1.

Compound **9**, named dunalianoside I, was obtained as an off-white amorphous powder. Its molecular formula was deduced to be $C_{28}H_{36}O_{17}$ on the basis of the positive HR-FAB MS [*m/z*



Scheme 1. Caffeoyl derivatives of arbutin isolated from *Vaccinium dunalianum*.

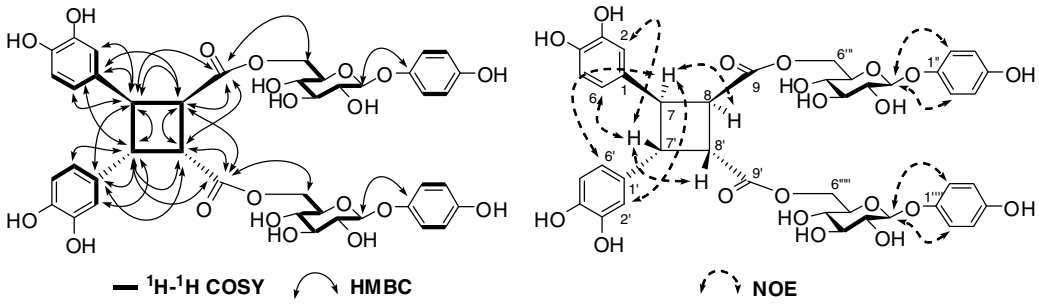


Fig. 2. Selected ^{1}H–^{1}H COSY, HMBC and NOE correlations for **8**.

644.1965 ([M]$^+$), calcd. 644.1952], together with the ^{13}C NMR spectroscopic data (see Section 4.12). The ^{1}H and ^{13}C NMR spectroscopic data of **9** were very similar to those of compounds **11** and **15**, which suggested that compound **9** was a conjugate of arbutin with monotropein. The downfield shifts of the glucose C-6 (δ 64.6) and H_2-6 [δ 4.56 (*dd*, *J* = 12.0, 1.8 Hz) and 4.15 (*dd*, *J* = 12.0, 6.8 Hz)] signals of the arbutin moiety in **9** compared to those of **11** (δ_C 62.5, δ_H 3.87 and 3.68), and the upfield shift of the carboxyl carbon at δ 168.5 in **9** compared to δ 170.5 of **15**, indicating acylation at the glucose C-6 of the arbutin moiety by C-11 of the monotropein moiety. Therefore, the structure of **9** was established as shown in Scheme 1.

Compounds **6**–**8** described here are the first examples of the caffeoyl arbutin dimers, and the arbutin–iridoid conjugate **9** was also first isolated from a natural source. It is apparent that the compounds **6** and **7** with a dihydrobenzofuran skeleton are generated by oxidative dimerization of compound **10**. Many arylcoumaran neolignans formed by similar 8-5′ linkage have also been found in various plants (Whiting, 1985). On the other hand, compound **8** is presumed to be formed by a photochemical [2+2] cyclo-addition of **1** (D'Auria and Vantaggi, 1992). Similar phenylpropanoid dimers with a cyclobutane ring are also known in higher plants (Hartley et al., 1990; Magiatis et al., 2002; Wang et al., 2003; Katerere et al., 2004). Dimers with the μ-truxinate structures related to **8** have been isolated from *Stachys aegyptiaca* (El-Ansari et al., 1995), *Salvia officinalis* (Lu and Foo, 1999), and *Monochaetum multiflorum* (Isaza et al., 2001).

3. Concluding remarks

To the best of our knowledge, the present study is the first chemical investigation of *V. dunalianum*, which led to the isolation of nine new compounds, together with 20 known ones. The most important feature of this Chinese local herbal tea is an abundance of caffeoyl esters of arbutin and related compounds; in particular, compound **10** was isolated in 22% yield from the dried buds. So far, compound **10** has been isolated from the leaves of *Hakea saligna* (Proteaceae) (Manju et al., 1977), *Viburnum* sp. (Caprifoliaceae) (Iwagawa et al., 1988; Machida et al., 1991; Machida and Kikuchi, 1993), *Grevillea robusta* (Proteaceae) (Ahmed et al., 2000), *Bacopa procumbens* (Scrophulariaceae) (Pathak et al., 2005) and *Veronica turrilliana* (Plantaginaceae) (Kostadinova et al., 2007). However, the concentration in the buds of *V. dunalianum* seems to be highest, and the unusual accumulation of **10** was suggestive of its physiological role in this plant tissue.

In addition, it is well known that arbutin has been used as a diuretic and urinary anti-infective agent for centuries, either as a plant extract or in purified form (Robertson and Howard, 1987). The leaves of *Arctostaphylos uva-ursi* (Ericaceae) are used medicinally, as well as for preparing tea (Weiss and Fintelmann, 1997). Furthermore, arbutin is known to be an inhibitor of melanin biosynthesis (Akiu et al., 1988) and is used as a skin-whitening agent in cosmetics. Compound **10** and its analogues isolated in this study should be expected to possess similar properties, and detailed study of their bioactivities is now in progress.

4. Experimental

4.1. General experimental procedures

IR spectra were obtained with a JASCO FT/IR-410 spectrophotometer, and UV spectra were measured by a JASCO V-560 UV/VIS spectrophotometer. Optical rotations were measured with a JASCO DIP-370 digital polarimeter whereas CD spectra measured with JASCO J-720w apparatus. ^{1}H and ^{13}C NMR spectra were recorded in CD_3OD with Varian Unity plus 500 and Varian Gemini 300 spectrometers operating at 500 and 300 MHz for ^{1}H, and 125 and 75 MHz for ^{13}C, respectively. Coupling constants were expressed in Hz, and chemical shifts were given on a δ (ppm) scale. MS was recorded on a JEOL JMS DX-303 spectrometer, and glycerol was used as a matrix for FAB-MS measurement. Column chromatography was preformed with Kieselgel 60 (70–230 mesh; Merck), Diaion HP20SS (Mitsubishi Chemical), MCI gel CHP 20P (75–150 μm; Mitsubishi Chemical), Sephadex LH-20 (25–100 μm; Pharmacia Fine Chemical), Chromatorex ODS (100–200 mesh; Fuji Silysia Chemical) and TSK gel Toyopearl HW-40F (Tosoh). TLC was performed on precoated Kieselgel 60 F_{254} plates (0.2 mm thick; Merck), and spots were detected by UV illumination and by spraying with 2% ethanolic $FeCl_3$ and 10% sulfuric acid reagent, followed by heating.

4.2. Plant material

The air-dried buds of *V. dunalianum* Wight (Ericaceae) were collected from Wuding, Yunnan, People's Republic of China, and identified by Prof. Chong-Ren Yang. The voucher specimen (KUN No. 0800238) was deposit in Herbarium of Kunming Institute of Botany, Chinese Academy of Sciences.

4.3. Extraction and isolation

The air-dried buds (1.77 kg) of *V. dunalianum* were extracted with H_2O–acetone (4:6, v/v) at room temperature by maceration. After filtration, the extract was concentrated under reduced pressure at 40 °C until the acetone was removed, and then the aqueous solution was defatted by partition with Et_2O. The aqueous layer was further concentrated to remove residual organic solvent and left to stand at room temperature overnight to yield large amounts of off-white crystalline powder of compound **10** (316 g). TLC analysis showed that the crystalline powder was an almost pure compound. The filtrate remaining after the first crop of **10** was further concentrated to give another crop of **10** (155 g). The crystalline powder was combined and recrystallized from water to yield compound **10** as colorless needles (390 g).

The filtrate was concentrated, and the residue (472 g) was separated to three fractions (Frs. 1–3) by Diaion HP-20 column chromatography (CC) (10 cm i.d. × 35 cm), eluted with a gradient solvent system of H_2O/MeOH (1:0–0:1, v/v). Fr. 1 (366 g) was subjected to Diaion HP20SS column eluted with H_2O/MeOH (1:0–0:1, v/v) to give three fractions, and then Fr. 1–1 (256 g) was further fractionated into four (Frs. 1–1–1 to 1–1–4) by CC on Diaion HP20SS eluted with H_2O/MeOH (1:0–0:1, v/v) containing 0.1% TFA. Fr. 2 (91 g) was fractionated by Sephadex LH-20 CC eluted with H_2O/MeOH (1:0–0:1, v/v) to give four fractions (Frs. 2–1 to 2–4). Fr. 1–1–1 was subjected to Chromatorex ODS CC (H_2O/MeOH, 1:0–1:1, v/v), followed with silica gel CC ($CHCl_3$/MeOH/H_2O, 90:10:1–70:30:5, v/v) to yield **11** (9.3 g), **15** (1.48 g), **16** (15 mg) and **28** (947 mg). Fraction 1–1–2 was passed through Sephadex LH-20 (H_2O–MeOH, 1:0–0:1), Chromatorex ODS (H_2O/MeOH, 1:0–0:1, v/v), and a silica gel column ($CHCl_3$/MeOH/H_2O, 90:10:1–70:30:5, v/v) to yield **19** (448 mg) and **20** (227 mg). Repeated CC of Fr. 1–1–3 with Sephadex LH-20 (H_2O/MeOH, 1:0–0:1, v/v), Chromatorex ODS (H_2O/MeOH, 1:0–0:1, v/v), Toyopearl HW-40F (MeOH/H_2O (6:4, v/v)), and silica gel ($CHCl_3$/MeOH/H_2O, 90:10:1–70:30:5, v/v) to give **8** (25.7 mg), **9** (76.6 mg), **10** (31 mg) and **22** (7.3 mg). Fr. 1–1–4 was repeatedly subjected to Sephadex LH-20, and MCI-gel CHP20P chromatography eluting with H_2O/MeOH (1:0–0:1, v/v), respectively, and silica gel CC ($CHCl_3$/MeOH/H_2O, 90:10:1–70:30:5, v/v) to give **12** (614 mg), **17** (33.4 mg) **18** (51.7 mg) and **25** (22.4 g).

Fr. 2–1 (20 g) was repeatedly separated by CC with silica gel CC ($CHCl_3$/MeOH/H_2O, 90:10:1–70:30:5, v/v), Chromatorex ODS and MCI-gel CHP20P with H_2O/MeOH (1:0–0:1, v/v), respectively, to yield **4** (6.7 mg), **14** (6.7 mg), **21** (33.8 mg), **26** (2.0 g), **27** (33.3 mg) and **29** (30 mg). Similar separation for Fr. 2–2 (15 g) was performed to give **1** (278 mg), **2** (43 mg), **3** (43.7 mg), **13** (5.8 mg) and **24** (92 mg). Fr. 2–3 (10 g) was subjected to silica gel CC ($CHCl_3$/MeOH/H_2O, 90:10:1–70:30:5, v/v), followed by Chromatorex ODS (H_2O/MeOH, 1:0–0:1, v/v) to yield **5** (3.2 g) and a mixture of **6** and **7**. This mixture was further separated by CC with Sephadex LH-20 (EtOH) and Toyopearl HW-40F (MeOH/H_2O (6:4, v/v)) to yield **6** (83.2 mg) and **7** (46.4 mg). Fr. 2–4 (5 g) was subjected to silica gel CC ($CHCl_3$/MeOH/H_2O, 90:10:1–70:30:5, v/v) and MCI-gel CHP20P (H_2O/MeOH, 1:0–0:1, v/v) to yield **23** (54.3 mg).

4.4. Dunalianoside A (**1**)

Off-white amorphous powder, $[\alpha]_D^{26} = -64.6$ (*c* 0.1, MeOH); IR ν_{max} cm^{-1}: 3357, 1686, 1607, 1509, 1444, 1357, 1271, 1202, 1070, 827, 776; UV λ_{max} (MeOH) nm (log ε): 327 (4.14), 295 (4.09), 247sh (3.96), 220 (4.30). FAB-MS (positive ion mode): *m/z* 527 $[M+Gly]^+$, 457 $[M+Na]^+$, 435 $[M+H]^+$; HR-FAB MS (positive ion mode): *m/z* 434.1234 ($[M]^+$) for $C_{21}H_{22}O_{10}$ (calcd. for 434.1213). For ^1H and ^{13}C NMR spectroscopic data, see Table 1.

4.5. Dunalianoside B (**2**)

Off-white amorphous powder, $[\alpha]_D^{26} = -67.0$ (*c* 0.1, MeOH); IR ν_{max} cm^{-1}: 3372, 1686, 1607, 1510, 1446, 1367, 1284, 1200, 1075, 1034, 850, 805; UV λ_{max} (MeOH) nm (log ε): 328 (4.20), 290 (4.11), 245sh (4.00), 220 (4.32). FAB-MS (positive ion mode): *m/z* 473 $[M+Na]^+$, 451 $[M+H]^+$; HR-FAB MS (positive ion mode): *m/z* 451.1213 ($[M+H]^+$) for $C_{21}H_{23}O_{11}$ (calcd. for 451.1240). For ^1H and ^{13}C NMR spectroscopic data, see Table 1.

4.6. Dunalianoside C (**3**)

Off-white amorphous powder, $[\alpha]_D^{23} = -23.6$ (*c* 0.1, MeOH); IR ν_{max} cm^{-1}: 3386, 1690, 1608, 1513, 1446, 1353, 1281, 1185, 1071, 854, 810; UV λ_{max} (MeOH) nm (log ε): 327 (4.14), 294 (4.11), 248sh (3.99). FAB-MS (positive ion mode): *m/z* 473 $[M+Na]^+$, 451 $[M+H]^+$; HR-FAB MS (positive ion mode): *m/z* 451.1224 ($[M+H]^+$) for $C_{21}H_{23}O_{11}$ (calcd. for 451.1240). For ^1H and ^{13}C NMR spectroscopic data, see Table 1.

4.7. Dunalianoside D (**4**)

Off-white amorphous powder, $[\alpha]_D^{23} = -41.2$ (*c* 0.1, MeOH); IR ν_{max} cm^{-1}: 3362, 1693, 1604, 1511, 1451, 1370, 1261, 1197, 1070, 947, 801; UV λ_{max} (MeOH) nm (log ε): 329 (4.09), 289 (4.05), 248sh (3.90). FAB-MS (positive ion mode): *m/z* 557 $[M+Gly]^+$, 487 $[M+Na]^+$, 465 $[M+H]^+$; HR-FAB MS (positive ion mode): *m/z* 464.1320 ($[M]^+$) for $C_{22}H_{24}O_{11}$ (calcd. for 464.1318). For ^1H and ^{13}C NMR spectroscopic data, see Table 1.

4.8. Dunalianoside E (**5**)

Off-white amorphous powder, $[\alpha]_D^{26} = -67.3$ (*c* 0.1, MeOH); IR ν_{max} cm^{-1}: 3380, 1686, 1600, 1508, 1443, 1374, 1209, 1076, 1034, 829, 775; UV λ_{max} (MeOH) nm (log ε): 327 (4.22), 295 (4.14), 245sh (4.01), 220 (4.32). FAB-MS (positive ion mode): *m/z* 569 $[M+Gly]^+$, 499 $[M+Na]^+$, 477 $[M+H]^+$, 367 $[M-C_6H_5O_2]^+$; HR-FAB MS (positive ion mode): *m/z* 476.1303 ($[M]^+$) for $C_{23}H_{24}O_{11}$ (calcd. for 476.1308). For ^1H and ^{13}C NMR spectroscopic data, see Table 1.

4.9. Dunalianoside F (**6**)

Off-white amorphous powder, $[\alpha]_D^{26} = -32.6$ (*c* 0.1, MeOH), CD (MeOH) nm ($\Delta\varepsilon$): 236 (+4.13), 254 (–3.23), 275 (+1.15); IR ν_{max} cm^{-1}: 3424, 1722, 1690, 1610, 1512, 1450, 1344, 1285, 1220, 1139, 1077, 832, 777; UV λ_{max} (MeOH) nm (log ε): 330 (4.31), 289 (4.26), 223 (4.59). FAB-MS (positive ion mode): *m/z* 959 $[M+Gly]^+$, 889 $[M+Na]^+$, 867 $[M+H]^+$; HR-FAB MS (positive ion mode): *m/z* 866.2231 ($[M]^+$) for $C_{42}H_{42}O_{20}$ (calcd. for 866.2269). For ^1H and ^{13}C NMR spectroscopic data, see Table 2.

4.10. Dunalianoside G (**7**)

Off-white amorphous powder, $[\alpha]_D^{26} = -36.1$ (*c* 0.1, MeOH), CD (MeOH) nm ($\Delta\varepsilon$): 224 (–14.04), 256 (+1.74), 283 (–1.22); IR ν_{max} cm^{-1}: 3403, 1719, 1688, 1608, 1508, 1447, 1342, 1279, 1210, 1140, 1071, 831, 777; UV λ_{max} (MeOH) nm (log ε): 328 (4.32), 290 (4.26), 223 (4.60). FAB-MS (positive ion mode): *m/z* 959 $[M+Gly]^+$, 889 $[M+Na]^+$, 867 $[M+H]^+$; HR-FAB MS (positive ion mode): *m/z* 867.2394 ($[M+H]^+$) for $C_{42}H_{43}O_{20}$ (calcd. for 867.2347). For ^1H and ^{13}C NMR spectroscopic data, see Table 2.

4.11. Dunalianoside H (**8**)

Off-white amorphous powder, $[\alpha]_D^{26} = -37.2$ (*c* 0.1, MeOH); IR ν_{max} cm^{-1}: 3461, 1729, 1606, 1515, 1449, 1370, 1289, 1089, 831, 778; UV λ_{max} (MeOH) nm (log ε): 325sh (3.62), 285 (4.07). FAB-MS (positive ion mode): *m/z* 891 $[M+Na]^+$, 868 $[M]^+$; HR-FAB MS (positive ion mode): *m/z* 868.2458 ($[M]^+$) for $C_{42}H_{44}O_{20}$ (calcd. for 868.2425). For ^1H and ^{13}C NMR spectroscopic data, see Table 2.

4.12. Dunalianoside I (**9**)

Off-white amorphous powder, $[\alpha]_D^{26} = -117.0$ (*c* 0.1, MeOH); IR ν_{max} cm^{-1}: 3427, 1695, 1639, 1511, 1454, 1373, 1288, 1216, 1107, 948, 924, 874, 777; UV λ_{max} (MeOH) nm (log ε): 285 (3.41), 225 (4.14). FAB-MS (positive ion mode): *m/z* 737 $[M+Gly+H]^+$, 667 $[M+Na]^+$, 645 $[M+H]^+$, 644 $[M]^+$; HR-FAB MS (positive ion mode): *m/z* 644.1965 ($[M]^+$) for $C_{28}H_{36}O_{17}$ (calcd. for 644.1952). ^1H NMR

(CD_3OD, 300 MHz): arbutin moiety, δ 6.92 (2H, *d*, *J* = 9.0 Hz, H-2,6), 6.68 (2H, *d*, *J* = 9.0 Hz, H-3,5), 4.74 (*d*, *J* = 7.6 Hz, H-1′), 4.56 (*dd*, *J* = 12.0, 1.8 Hz, H-6′), 4.15 (*dd*, *J* = 12.0, 6.8 Hz, H-6′), 3.40 (*t*, *J* = 8.8 Hz, H-5′), 3.30∼3.38 (*m*, H-2′,3′,4′); monotropein moiety, δ 7.44 (*d*, *J* = 1.2 Hz, H-3″), 6.21 (*dd*, *J* = 5.8, 2.6 Hz, H-6″), 5.62 (*dd*, *J* = 5.8, 2.2 Hz, H-7″), 5.60 (*d*, *J* = 2.6 Hz, H-1″), 4.68 (*d*, *J* = 8.0 Hz, H-1‴), 3.88 (*dd*, *J* = 12.0, 1.5 Hz, H-6‴), 3.67 (*dd*, *J* = 12.0, 5.2 Hz, H-6‴), 3.61 (*d*, *J* = 2.2 Hz, H-10″), 3.58 (*dd*, *J* = 8.6, 2.6 Hz, H-5″), 3.40 (*t*, *J* = 8.8 Hz, H-5‴), 3.30–3.38 (*m*, H-3‴,4‴), 3.21 (*dd*, *J* = 8.8, 8.0 Hz, H-2‴), 2.72 (*dd*, *J* = 8.6, 2.6 Hz, H-9″). ^{13}C NMR (CD_3OD, 75 MHz): arbutin moiety, δ 153.9 (C-1), 152.2 (C-4), 119.4 (C-2,6), 116.7 (C-3,5), 103.4 (C-1′), 77.9 (C-3′), 75.4 (C-5′), 74.9 (C-2′), 71.4 (C-4′), 64.6 (C-6′); monotropein moiety, δ 168.5 (C-11″), 152.9 (C-3″), 137.9 (C-6″), 133.9 (C-7″), 110.9 (C-4″), 100.1 (C-1‴), 95.4 (C-1″), 86.1 (C-8″), 78.3 (C-5‴), 77.9 (C-3‴), 74.7 (C-2‴), 71.9 (C-4‴), 68.4 (C-10″), 62.6 (C-6‴), 45.7 (C-9″), 39.1 (C-5″).

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