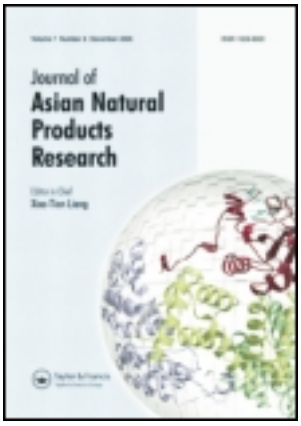

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New iridoid glycosides from the twigs and leaves of Callicarpa formosana var. formosana

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ORIGINAL ARTICLE

New iridoid glycosides from the twigs and leaves of *Callicarpa formosana* var. *formosana*

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Four new iridoid glycosides, 6-*O*-benzoylphlorigidoside B (**1**), 6-*O*-*trans*-cinnamoylphlorigidoside B (**2**), 6-*O*-*trans*-*p*-coumaroylshanzhiside methyl ester (**3**), and 4′-*O*-*trans*-*p*-coumaroylmussaenoside (**4**), were isolated from the EtOH extract of the twigs and leaves of *Callicarpa formosana* var. *formosana*. Their structures were elucidated by extensive spectroscopic analysis.

Keywords: *Callicarpa formosana* var. *formosana*; Verbenaceae; iridoid glycosides

1. Introduction

Callicarpa formosana Rolfe var. *formosana* (Verbenaceae) is a small shrub widely distributed from southern China to the Philippines, and its leaves have been used in traditional Chinese medicine for the treatment of many kinds of internal or external bleeding [1]. Previous chemical research on the genus *Callicarpa* has resulted in the isolation of some clerodane [2–5] and phyllocladane [6,7] diterpenoids. However, no systematic investigation on the chemical constituents of *C. formosana* var. *formosana* has appeared up to now. As part of our effort to assemble a natural compound library possessing thousands of structures [8], a general study on the EtOH extract of the twigs and leaves of this plant led to the isolation of four new iridoid glycosides, 6-*O*-benzoylphlorigidoside B (**1**), 6-*O*-*trans*-cinnamoylphlorigidoside B (**2**), 6-*O*-*trans*-*p*-coumaroylshanzhiside methyl ester (**3**), and 4′-*O*-*trans*-*p*-coumaroylmussaenoside (**4**) (Figure 1), together with two known ones, 6β-hydroxyipolamiide (**5**) [9] and phlorigidoside B (**6**) [10]. In addition, five known clerodane diterpenoids, hardwickiic acid (**7**) [11], monomethyl kolavate (**8**) [12], echinophyllin C (**9**) [13], clerodermic acid methyl ester (**10**) [14], and 15,16-dihydro-15-methoxy-16-oxo-hardwickiic acid (**11**) [15], were also isolated. To the best of our knowledge, there have been very few iridoid glycosides reported from the genus up to now. In this paper, we describe the isolation and structural elucidation of these new natural products.

2. Results and discussion

Compound **1**, obtained as an amorphous powder, had a molecular formula of $C_{26}H_{32}O_{14}$ based on HR-ESI-MS (pos.), showing a quasi-molecular ion peak at *m/z* 591.1705 (calcd for $C_{26}H_{32}O_{14}Na$,

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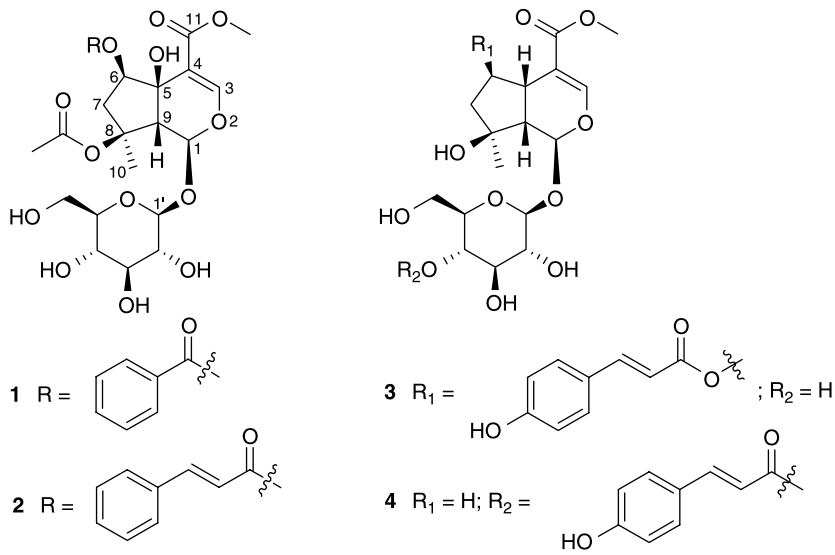

Figure 1. Structures of compounds **1**–**4**.

591.1689). The IR spectrum showed the absorption bands of hydroxy (3432 cm^{-1}), carbonyl (1717 cm^{-1}), and double bond (1629 cm^{-1}) groups. The NMR spectra exhibited the signals at δ_H 6.33 (br s, H-1), 7.71 (s, H-3), 3.18 (br s, H-9), 4.63 (d, $J = 8.0$ Hz, H-1′), 3.76 (s, OCH_3), and at δ_C 96.0 (d, C-1), 157.0 (d, C-3), 110.2 (s, C-4), 167.4 (s, C-11), 100.9 (d, C-1′), characteristic of a 5β-hydroxy iridoid glucopyranoside. On the whole, the NMR spectral data were in accordance with those of phlorigidoside B (**6**) [10], except that a set of additional resonances assignable to a benzoyloxy group appeared in **1**. By comparison of its ^{1}H NMR spectral data with those of **6**, a large downfield shift ($\Delta = 1.58$ ppm) from esterification was observed for H-6 proton, suggesting that a benzoyloxy group should be positioned at C-6. The deduction was further confirmed by the following HMBC correlations (Figure 2): from the H-6 proton signal at δ_H 5.92 (br d, $J = 3.7$ Hz) to δ_C 167.3 (s, C-1″), 110.2 (s, C-4), 74.6 (s, C-5), 87.7 (s, C-8), and 56.9 (d, C-9). The absolute configuration was deduced to be the same as that of **6**, based on the ROESY correlations of H-1/Me-10, H-1/H-1′,

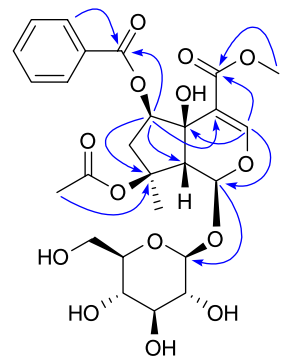

Figure 2. Key HMBC correlations of **1**.

H-7*a*/Me-10, and H-7*a*/H-6 and from the similar values of optical rotation [10]. Therefore, the structure of **1** was determined as 6-*O*-benzoylphlorigidoside B.

Compound **2**, an amorphous powder, possessed a molecular formula of $C_{28}H_{34}O_{14}$, determined by positive HR-ESI-MS showing a quasi-molecular ion peak at *m/z* 617.1855 (calcd for $C_{28}H_{34}O_{14}Na$, 617.1846). The NMR signals (Tables 1 and 2) were very similar to those of **1**, indicating that **2** was also a 5β-hydroxy iridoid glucopyranoside. However, a noticeable difference was that the

Table 1. ^{1}H NMR spectroscopic data for compounds **1**–**4** in CD_3OD.

No.	**1**	**2**	**3**	**4**
1	6.33 (br s)	6.30 (br s)	5.54 (d, 4.3)	5.47 (d, 4.0)
3	7.71 (s)	7.70 (s)	7.45 (s)	7.40 (s)
5	–	–	3.39 (m)	3.17 (m)
6	5.92 (br d, 3.7)	5.73 (br d, 3.9)	5.18 (m)	1.43, 2.29 (m)
7	1.95 (dd, 15.8, 3.7), 2.37 (br d, 15.8)	1.92 (dd, 15.8, 3.9), 2.33 (br d, 15.8)	1.87 (dd, 14.2, 4.8), 2.28 (dd, 14.2, 7.3)	1.68–1.75 (m)
9	3.18 (br s)	3.14 (br s)	2.53 (dd, 9.4, 4.3)	2.24 (dd, 9.2, 4.0)
10	1.47 (s)	1.46 (s)	1.34 (s)	1.33 (s)
1′	4.63 (d, 8.0)	4.63 (d, 7.8)	4.69 (d, 7.8)	4.75 (d, 7.7)
2′	3.21 (dd, 8.8, 8.0)	3.21 (dd, 9.2, 7.8)	3.20 (dd, 9.1, 7.8)	3.30 (dd, 9.2, 7.7)
3′	3.39 (dd, 8.8, 8.8)	3.40 (dd, 9.2, 8.8)	3.36 (dd, 9.1, 8.8)	3.64 (m)
4′	3.30 (dd, 9.4, 8.8)	3.29 (dd, 9.6, 8.8)	3.24 (dd, 9.5, 8.8)	4.81 (dd, 9.5, 9.5)
5′	3.37 (ddd, 9.4, 5.9, 2.0)	3.37 (ddd, 9.6, 6.1, 2.1)	3.33 (ddd, 9.5, 6.5, 2.2)	3.56 (m)
6′	3.71 (dd, 12.1, 5.9), 3.91 (dd, 12.1, 2.0)	3.70 (dd, 12.1, 6.1), 3.91 (dd, 12.2, 2.1)	3.64 (dd, 12.0, 6.5), 3.91 (dd, 12.0, 2.2)	3.54, 3.61 (m)
2″	–	6.60 (d, 16.0)	6.37 (d, 15.8)	6.36 (d, 15.9)
3″	8.11 (br d, 8.0)	7.78 (d, 16.0)	7.64 (d, 15.8)	7.66 (d, 15.9)
4″	7.50 (dd, 8.0, 7.4)	–	–	–
5″	7.62 (br t, 7.4)	7.60–7.65 (m)	7.47 (d, 8.6)	7.47 (d, 8.6)
6″	7.50 (dd, 8.0, 7.4)	7.39–7.44 (m)	6.80 (d, 8.6)	6.80 (d, 8.6)
7″	8.11 (br d, 8.0)	7.39–7.44 (m)	–	–
8″	–	7.39–7.44 (m)	6.80 (d, 8.6)	6.80 (d, 8.6)
9″	–	7.60–7.65 (m)	7.47 (d, 8.6)	7.47 (d, 8.6)
CH_3O	3.76 (s)	3.74 (s)	3.63 (s)	3.69 (s)
CH_3CO	1.83 (s)	1.95 (s)	–	–

Table 2. ^{13}C NMR spectroscopic data for compounds **1**–**4** in CD_3OD.

No.	**1**	**2**	**3**	**4**
1	96.0 (d)	95.8 (d)	95.0 (d)	95.5 (d)
3	157.0 (d)	157.0 (d)	153.4 (d)	152.0 (d)
4	110.2 (s)	110.1 (s)	109.9 (s)	113.5 (s)
5	74.6 (s)	74.4 (s)	39.1 (d)	32.0 (d)
6	78.4 (d)	78.1 (d)	79.2 (d)	30.7 (t)
7	43.8 (t)	43.8 (t)	47.7 (t)	40.7 (t)
8	87.7 (s)	87.4 (s)	79.1 (s)	80.5 (s)
9	56.9 (d)	56.8 (d)	51.5 (d)	52.3 (d)
10	22.1 (q)	22.1 (q)	25.5 (q)	24.6 (q)
11	167.4 (s)	167.2 (s)	168.9 (s)	169.3 (s)
1′	100.9 (d)	100.9 (d)	99.8 (d)	99.8 (d)
2′	74.4 (d)	74.4 (d)	74.7 (d)	74.9 (d)
3′	77.5 (d)	77.5 (d)	78.0 (d)	75.7 (d)
4′	71.6 (d)	71.6 (d)	71.7 (d)	72.4 (d)
5′	78.3 (d)	78.2 (d)	78.5 (d)	76.5 (d)
6′	62.9 (t)	62.9 (t)	62.9 (t)	62.6 (t)
1″	167.3 (s)	168.0 (s)	168.8 (s)	168.5 (s)
2″	131.7 (s)	119.1 (d)	115.5 (d)	114.7 (d)
3″	130.8 (d)	146.6 (d)	146.5 (d)	147.3 (d)
4″	129.6 (d)	135.7 (s)	127.1 (s)	127.1 (s)
5″	134.4 (d)	129.3 (d)	131.2 (d)	131.3 (d)
6″	129.6 (d)	130.1 (d)	116.9 (d)	116.9 (d)
7″	130.8 (d)	131.6 (d)	161.5 (s)	161.4 (s)
8″	–	130.1 (d)	116.9 (d)	116.9 (d)
9″	–	129.3 (d)	131.2 (d)	131.3 (d)
CH_3O	51.9 (q)	51.9 (q)	51.9 (q)	51.7 (q)
CH_3CO	22.0 (q)	22.1 (q)	–	–
CH_3CO	173.0 (s)	173.1 (s)	–	–

signals from a benzoyloxy group were absent and displaced by a set of newly arisen resonances at δ_H 7.78 (1H, d, $J = 16.0$ Hz), 6.60 (1H, d, $J = 16.0$ Hz), 7.60–7.65 (2H, m), 7.39–7.44 (3H, m), and δ_C 168.0 (s), 119.1 (d), 146.6 (d), 135.7 (s), 129.3 (2×d), 130.1 (2×d), 131.6 (d), assignable as a *trans*-cinnamoyloxy moiety. Similarly, the *trans*-cinnamoyloxy unit was also located at C-6 by the HMBC correlation from H-6 at δ_H 5.73 (br d, $J = 3.9$ Hz) to C-1″ at δ_C 168.0 (s). Stereochemically, it was in accord with that of **1** by observation of the ROESY spectrum. Thus, the structure of **2** was established as 6-*O*-*trans*-cinnamoylphlorigidoside B.

Compound **3**, an amorphous powder, gave an $[M+Na]^+$ quasi-molecular ion peak at *m/z* 575.1750 in the positive HR-ESI-MS, corresponding to the molecular formula $C_{26}H_{32}O_{13}$. The NMR spectra (Tables 1 and 2) were very similar to those of the known iridoid glycoside shanzhiside methyl ester [16], with the exception of the resonances at δ_H 6.37 (1H, d, $J = 15.8$ Hz), 7.64 (1H, d, $J = 15.8$ Hz), 7.47 (2H, d, $J = 8.6$ Hz), 6.80 (2H, d, $J = 8.6$ Hz); δ_C 168.8 (s), 115.5 (d), 146.5 (d), 127.1 (s), 131.2 (2× d), 116.9 (2×d), and 161.5 (s), assignable to a *trans-p*-coumaroyloxy group. An obvious downfield shift of H-6 proton suggested that the hydroxyl group at C-6 was substituted by the *trans-p*-coumaroyloxy group in **3**, which was supported by the HMBC correlations from H-6 at δ_H 5.18 (1H, m) to δ_C 168.8 (s, C-1″), 109.9 (s, C-4), 79.1 (s, C-8), and 51.5 (d, C-9). The configuration is the same as that of shanzhiside methyl

ester based on their accordant coupling constants. Thereupon, the structure of **3** was determined as 6-*O-trans-p*-coumaroylshanzhiside methyl ester.

Compound **4**, an amorphous powder, possessed the molecular formula $C_{26}H_{32}O_{12}$ from the positive HR-ESI-MS at *m/z* 559.1811 (calcd for $C_{26}H_{32}O_{12}Na$, 559.1791). The NMR spectra (Tables 1 and 2) also showed a set of *trans-p*-coumaroyloxy signals, and the remainder was generally in accord with those of mussaenoside [17], which suggested that **4** was a coumaroyl mussaenoside derivative. The significant HMBC correlations from a downfield oxygen-bearing methine proton at δ_H 4.81 (dd, 9.5, 9.5) to δ_C 168.5 (s, C-1″) and 62.6 (t, C-6′) were observed, indicating that the *trans-p*-coumaroyloxy group must be positioned at C-4′ in the glucose moiety. The variety trend ($\Delta \approx -2.3, +0.7$, and -2.0 ppm, respectively) of the ^{13}C NMR spectral data of C-3′, C-4′, and C-5′ also validated the esterifying at C-4′ by comparing with those of **3**. Considering the accordant coupling constants with those of mussaenoside, they possess the same configuration. Hence, the structure of **4** was elucidated to be 4′-*O-trans-p*-coumaroylmussaenoside.

3. Experimental

3.1 General experimental procedures

Optical rotations were measured on a Jasco P-1020 (Jasco International Co., Ltd, Tokyo, Japan) automatic digital polarimeter. IR spectra were recorded using a Bruker Tensor 27 FT-IR (Bruker Optics GmbH, Ettlingen, Germany) spectrometer with KBr pellets. UV spectroscopic data were obtained from online HPLC analysis. NMR spectra were carried out on either a Bruker DRX-500 or AV-400 (Bruker BioSpin GmbH, Rheinstetten, Germany) spectrometer with deuterated methanol signals (δ_H 3.30 ppm, δ_C 49.0 ppm) as the internal standard. ESI-MS (including HR-ESI-MS) were measured on an API QSTAR Pulsar i (MDS Sciex, Concord, Ontario, Canada) mass spectrometer. Silica gel (200–300 mesh; Qingdao Marine Chemical, Inc., Qingdao, China), Chromatorex C-18 (40–75 μm; Fuji Silysia Chemical Ltd, Kasugai, Aichi, Japan), and Sephadex LH-20 (Amersham Biosciences, Uppsala, Sweden) were used for normal pressure column chromatography. MPLC was performed on a Büchi Sepacore System equipped with pump manager C-615, pump modules C-605, and fraction collector C-660 (Büchi Labortechnik AG, Flawil, Switzerland), and columns packed with Chromatorex C-18 (40–75 μm; Fuji Silysia Chemical Ltd). Fractions were monitored and analyzed by TLC (Qingdao Marine Chemical, Inc.), in combination with an Agilent 1200 series HPLC system (Eclipse XDB-C18 column, 5 μm, 4.6×150 mm). Preparative HPLC was performed using an Agilent 1100 series (Zorbax SB-C18 column, 5 μm, 9.4×150 mm, 205 nm).

3.2 Plant material

The twigs and leaves of *C. formosana* var. *formosana* were collected in Maguan County of Yunnan Province, China, in April 2008, and identified by Mr Yu Chen of Kunming Institute of Botany, CAS. A voucher specimen (BBP2009007CF) has been deposited at BioBioPha Co., Ltd.

3.3 Extraction and isolation

Air-dried and powdered twigs and leaves (4.5 kg) of *C. formosana* var. *formosana* were extracted three times with EtOH at room temperature. After evaporation of the solvent under vacuum, the syrupy residue (320 g) was chromatographed over a silica gel column and eluted with petroleum ether, petroleum ether–acetone (20:1, 10:1, 6:1, 3:1, 1:1), acetone, and methanol, successively. The fraction eluted by acetone was repeatedly separated and purified by silica gel ($CHCl_3$–MeOH =

20:1) and Sephadex LH-20 ($CHCl_3$–MeOH = 1:1) to obtain **4** (27 mg). The fraction eluted by methanol was separated using a silica gel column and eluted with $CHCl_3$–MeOH (20:1, 10:1) to give subfractions I and II, respectively. Subfraction I was further isolated and purified by silica gel ($CHCl_3$–MeOH = 30:1), Sephadex LH-20 ($CHCl_3$–MeOH = 1:1), and normal pressure C-18 column to afford **1** (505 mg; C-18: 33% MeOH in H_2O) and **2** (20 mg; C-18: 41% MeOH in H_2O). Subfraction II was further isolated and purified by MPLC (5–7% MeOH in H_2O) to give **3** (120 mg).

In the process of purification of **3**, a 15% *cis-p*-coumaroyl isomer was concomitant with the goal all the while, and then preparative HPLC (15% MeCN in H_2O, 10 ml/min) was applied to further isolate the isomers to afford **3** (t_R = 12.5 min; UV: 230, 314 nm) and its *cis*-isomer (t_R = 10.2 min; UV: 230, 307 nm); however, the pair of isomers were already inter-transformed in subsequent HPLC analysis. In fact, the configuration of the cinnamoyl moiety in **2**–**4** is all inter-transformable in solvent, and only the *cis*-isomer always performs as a minor proportion from 3 to 15%. This is an interesting and worthwhile phenomenon in dealing with the isolation of cinnamoyl-containing molecules.

*3.3.1 6-O-Benzoylphlorigidoside B (**1**)*

Amorphous powder, $[\alpha]_D^{27}$ −92.4 (c = 0.28, MeOH). UV λ_{max} (MeOH): 231, 273 nm. IR (KBr): 3432, 1717, 1629, 1372, 1285, 1116, 1078, 1025 cm^{-1}. NMR spectral data, see Tables 1 and 2. ESI-MS (pos.): *m/z* 591 $[M+Na]^+$. HR-ESI-MS (pos.): *m/z* 591.1705 (calcd for $C_{26}H_{32}O_{14}Na$, 591.1689).

*3.3.2 6-O-trans-Cinnamoylphlorigidoside B (**2**)*

Amorphous powder, $[\alpha]_D^{26}$ −89.1 (c = 0.24, MeOH). UV λ_{max} (MeOH): 221, 280 nm. IR (KBr): 3422, 1712, 1632, 1372, 1287, 1172, 1079, 1022 cm^{-1}. NMR spectral data, see Tables 1 and 2. ESI-MS (pos.): *m/z* 617 $[M+Na]^+$. HR-ESI-MS (pos.): *m/z* 617.1855 (calcd for $C_{28}H_{34}O_{14}Na$, 617.1846).

*3.3.3 6-O-trans-p-Coumaroylshanzhiside methyl ester (**3**)*

Amorphous powder, $[\alpha]_D^{25}$ −102.1 (c = 0.22, MeOH). UV λ_{max} (MeOH): 230, 314 nm. IR (KBr): 3407, 1695, 1634, 1605, 1515, 1441, 1384, 1294, 1170, 1078 cm^{-1}. NMR spectral data, see Tables 1 and 2. ESI-MS (pos.): *m/z* 575 $[M+Na]^+$. HR-ESI-MS (pos.): *m/z* 575.1750 (calcd for $C_{26}H_{32}O_{13}Na$, 575.1740).

*3.3.4 4′-O-trans-p-Coumaroylmussaenoside (**4**)*

Amorphous powder, $[\alpha]_D^{22}$ −106.4 (c = 0.31, MeOH). UV λ_{max} (MeOH): 232, 314 nm. IR (KBr): 3420, 1713, 1636, 1606, 1516, 1440, 1382, 1284, 1167, 1085 cm^{-1}. NMR spectral data, see Tables 1 and 2. ESI-MS (pos.): *m/z* 559 $[M+Na]^+$. HR-ESI-MS (pos.): *m/z* 559.1811 (calcd for $C_{26}H_{32}O_{12}Na$, 559.1791).

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