Phytochemistry Letters 5 (2012) 309–312

Contents lists available at ScienceDirect

Phytochemistry Letters

journal homepage: www.elsevier.com/locate/phytol

Lucidafuranocoumarins B and C from the twigs of *Feroniella lucida*: Absolute configurations of lucidafuranocoumarin C

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ARTICLE INFO

Article history:
Received 26 October 2011
Received in revised form 6 February 2012
Accepted 10 February 2012
Available online 25 February 2012

Keywords:
Feroniella lucida
Rutaceae
Furanocoumarins
Cytotoxicity

ABSTRACT

Two new furanocoumarins, lucidafuranocoumarins B (**1**) and C (**2**), were isolated from the twigs of *Feroniella lucida*, together with five known compounds (**3**–**7**). The structures of these compounds were identified on the basis of extensive spectroscopic methods. The absolute configurations of lucidafuranocoumarin C at C-2″ and C-5″ were established as *R*- and *S*-configurations, respectively, by applying Mosher's method. Some isolates were also evaluated for their cytotoxicity against KB, MCF-7 and NCI-H187 cell lines.

1. Introduction

Feroniella lucida is an ornamental plant in the family Rutaceae locally known as "Masung" in Thai. It is a medium-sized tree distributed widely in Northeast of Thailand. Previous phytochemical investigations of this plant have revealed the presence of various types of secondary metabolites, including coumarins (Phoopichayanun et al., 2011; Phuwapraisirisan et al., 2006, 2008; Sripisut et al., 2011), benzo[*c*]phenanthridine alkaloids (Sripisut et al., 2011), amide derivatives (Sripisut et al., 2011) and triterpenes (Phuwapraisirisan et al., 2007). Many of them showed interesting pharmacological activities including antibacterial (Kongkathip and Kongkathip, 2009), antitumor (Ito et al., 2005; Su et al., 2009), antimycobacterial (Sunthitikawinsakul et al., 2003), antifungal (Sunthitikawinsakul et al., 2003), anti-HBV (Su et al., 2009), and anti-HIV-1 activities (Kongkathip and Kongkathip, 2009). We previously reported a new coumarin, as well as its cytotoxic activity from the roots of *F. lucida* (Sripisut et al., 2011). In continuation of our study, we report herein the isolation and structural elucidation of two new furanocoumarins (**1** and **2**) and five known compounds (**3**–**7**). The absolute configurations at C-2″ and C-5″ of **2** were also determined as well. Some isolates were evaluated for cytotoxic activities against three human cancers cell lines, KB, MCF-7 and NCI-H187.

2. Results and discussion

The acetone extract of the twigs of *F. lucida* was purified by silica gel column chromatography to afford two new furanocoumarins, lucidafuranocoumarins B (**1**) and C (**2**) together with five known compounds, bergamottin (**3**) (Girennavar et al., 2006), anisolactone (**4**) (Lakshmi et al., 1984), 2″,3″-dihydroxyanisolactone (**5**) (Phuwapraisirisan et al., 2007), imperatorin (**6**) (Masuda et al., 1998) and umbelliferone (**7**) (Ngadjui et al., 1991).

Lucidafuranocoumarin B (**1**) was obtained as a light yellow gum and its molecular formula was determined as $C_{21}H_{20}O_6$ ([M]$^+$ *m*/*z* 368.1256, calcd. for $C_{21}H_{20}O_6$, 368.1260) based on HR-EI-MS. The IR spectrum displayed the carbonyl lactone functionalities at 1735 and 1765 cm^{-1}, and the UV spectrum showed the typical absorbances at λ_{max} 267 and 282 nm, suggesting the presence of a coumarin moiety in the molecule (Phuwapraisirisan et al., 2006). The ^{1}H NMR spectral data (Table 1) of **1** showed the characteristic of furanocoumarin framework (Girennavar et al., 2006) at δ_H 8.16 (1H, *d*, *J* = 9.6 Hz, H-4), 7.61 (1H, *d*, *J* = 2.4 Hz, H-2′), 7.17 (1H, *s*, H-8), 6.95 (1H, *d*, *J* = 2.4 Hz, H-3′), and 6.29 (1H, *d*, *J* = 9.6 Hz, H-3) indicative a substituent at C-5. This finding was supported by the ^2J and ^3J HMBC correlations (Fig. 2) of H-8 to C-4a (δ 107.4), C-6 (δ 114.1), C-7 (δ 158.1) and C-8a (δ 152.6). In addition, the units of –OCH$_2$CH=C(Me)–CH$_2$– [δ_H 5.64 (1H, *br t*, *J* = 9.6 Hz, H-2″), 4.97 (2H, *d*, *J* = 9.6 Hz, H-1″), 2.46 (1H, *m*, H-4″a),

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doi:10.1016/j.phytol.2012.02.008

Table 1
NMR data (400 MHz) of **1** and **2** in $CDCl_3$ (mult., *J* in Hz).

Position	**1**		**2**	
	δ_C	δ_H	δ_C	δ_H
2	161.0	–	161.5	–
3	112.8	6.29, *d* (9.6)	112.4	6.17, *d* (10.0)
4	139.4	8.16, *d* (9.6)	139.5	8.14, *d* (10.0)
4a	107.4	–	106.9	–
5	148.6	–	148.4	–
6	114.1	–	113.9	–
7	158.1	–	158.0	–
8	94.4	7.17, *s*	94.3	6.99, *s*
8a	152.6	–	152.1	–
2′	145.1	7.61, *d* (2.4)	145.3	7.59, *d* (2.4)
3′	104.9	6.95, *d* (2.4)	104.8	6.98, *d* (2.4)
1″	69.3	4.97, *d* (9.6)	74.0	4.64, *dd* (10.0, 2.4) 4.39, *dd* (10.0, 8.4)
2″	122.8	5.64, *br t* (9.6)	76.0	4.10, *br d* (8.4)
3″	137.6	–	72.5	–
4″	45.0	2.46, *m* 2.33, *m*	41.2	2.21, *m* 1.61, *m*
5″	76.1	4.66, *m*	78.1	5.30, *m*
6″	35.1	2.12, *m* 2.00, *m*	150.1	7.15, *br s*
7″	33.7	2.70, *m*	129.3	–
8″	179.6	–	174.1	–
9″	17.1	1.77, *s*	23.3	1.41, *s*
10″	15.8	1.29, *d* (7.2)	10.5	1.91, *s*

2.33 (1H, *m*, H-4″b) and 1.77 (1H, *s*, H-9″)] and α-methyl-γ-lactone ring [δ_H 4.66 (1H, *m*, H-5″), 2.70 (1H, *m*, H-7″), 2.12 (1H, *m*, H-6″a), 2.00 (1H, *m*, H-6″b) and 1.29 (3H, *d*, *J* = 7.2 Hz, H-10″)] were also observed in the ^{1}H NMR spectrum. On the basis of COSY and HMBC spectra (Fig. 2), both units are linked to each other at C-4″ and C-5″. The relative stereochemistry of **1** was established by NOE difference spectra. The methyl protons Me-10″ (δ 1.29) were enhanced when irradiated at H-5″ (δ 4.66). This result implied that H-5″ and Me-10″ had the *syn* relative orientation. Additionally, the geometry of double bond at C-2″ and C-3″ was assigned as *E*-configuration according to the enhancement of H_2-4″ (δ 2.46 and 2.33) upon the irradiation of H-2″ (δ 5.64). Therefore, the structure of **1** was identified to be lucidafuranocoumarin B.

Lucidafuranocoumarin C (**2**) was isolated as a light yellow gum and its molecular formula, $C_{21}H_{22}O_9$, was determined by the pseudo ion peak at *m*/*z* 423.1052 ($C_{21}H_{20}O_8Na$ $[M-H_2O+Na]^+$, calcd for 423.1050) in the ESI-TOF-MS. The IR spectrum showed two carbonyl (1700 and 1734 cm^{-1}) and hydroxy (3426 cm^{-1}) functionalities. The ^{1}H and ^{13}C NMR spectral data of **2** (Table 1) displayed C_{10} terpenoidal furanocoumarin skeleton similar to those of **3**, except the double bond at C-2″, C-3″ and Me-10″ were oxidized to diol and carboxylic acid, respectively (Fig. 1). The ^{1}H and ^{13}C NMR chemical shifts were very similar to those of feroniellic acid A (Fig. 1), isolated from the same plant by Phuwapraisirisan et al. (2008). However, some of ^{1}H NMR signals of these compounds, lucidafuranocoumarin C and feroniellic acid A, showed significant chemical shift differences. For example, the ^{1}H NMR spectrum at H-2″, H-4a″, H-4b″ and H-9″ of lucidafuranocoumarin C resonated at δ_H 4.10, 2.21, 1.61 and 1.40, respectively, whereas feroniellic acid A appeared at δ_H 4.43, 2.36,

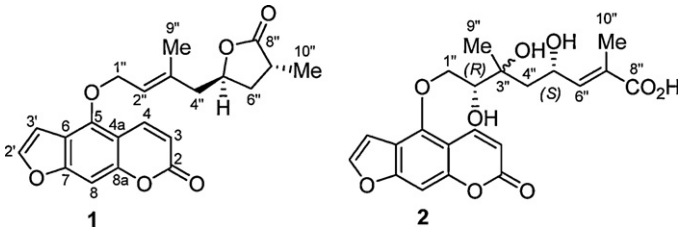

Fig. 1. Chemical structures of compounds **1** and **2**.

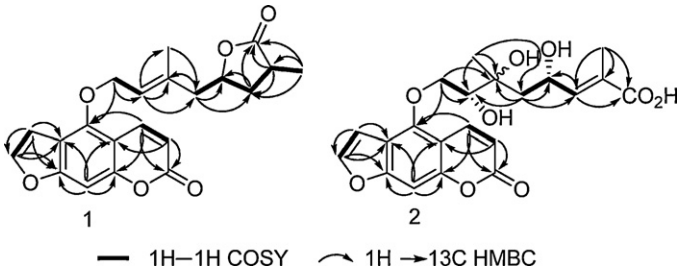

Fig. 2. COSY and selective HMBC correlations of compounds **1** and **2**.

1.94 and 1.25. In addition, the ^{13}C NMR signal of C-9″ of both compounds was also significant difference (δ 29.9 for feroniellic acid A and δ 23.3 for lucidafuranocoumarin C). From the above information, lucidafuranocoumarin C is an isomer of feroniellic acid A..

To determine the absolute configurations of **2**, it was treated separately with (*R*)- and (*S*)-α-methoxy-α-trifluoromethyl-phenylacetyl chloride (MTPA-Cl) in the presence of pyridine, yielding the (*S*)- and (*R*)-bis-MTPA esters **2a** and **2b**, respectively. Based on the ^{1}H NMR of (*S*)- and (*R*)-bis-MTPA esters **2a** and **2b**, the differences between the chemical shifts for **2a** and **2b**, $\Delta\delta_{SR}$, are demonstrated in Fig. 3. The negative signs around C-2″ and C-5″ led to the assignments of 1,4-*syn* diols with the *R*- and *S*-configurations at C-2″ and C-5″, respectively, when directly compared with Mosher's model (Freire et al., 2005; Ohtani et al., 1991).

Compounds **1**–**3**, **6**, and **7** were evaluated for their cytotoxicity against oral cavity cancer (KB), breast cancer (MCF-7) and small cell lung cancer (NCI-H187). Unfortunately, compounds **1**, **2**, and **7** were inactive in all cell lines. Compounds **3** and **6** were selectively active against NCI-H187 (IC_{50} 24.82 μM) and KB (IC_{50} 35.51 μM) cells, respectively.

It should be noted that the relative biogenetic pathway of the side chain of furanocoumarins **1**, **2**, **4** and **5** could be derived from furanocoumarin **3** (Fig. 4). The furanocoumarin **2** could be derived from dihydroxylation (C-2″ and C-3″) and allylic oxidation (Me-10″) of **3**. On the other hand, the oxidation of allylic position, C-5″, to an alcohol and C-8″ to carboxylic acid of **3** and followed by the cyclization to give **4**. Compound **5** was either selective dihydroxylation (C-2″ and C-3″) yielding diols **5** or selective reduction at α,β-unsaturated γ-lactone furnishing **1**.

3. Experimental

3.1. General

The $[\alpha]_D$ value was determined with a Bellingham & Stanley ADP440 polarimeter. The UV spectra were recorded with PerkinElmer UV–Vis spectrophotometer. The IR spectra were recorded with PerkinElmer FTS FT-IR spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded using 400 MHz Bruker FTNMR Ultra Shield spectrometer. Chemical shifts were recorded in parts per million (δ) in $CDCl_3$ with tetramethylsilane (TMS) as an internal reference. The HRMS were obtained from microTOF, Bruker Daltonics or MAT 95 XL mass spectrometers. Column chromatography was performed by using quick column chromatography

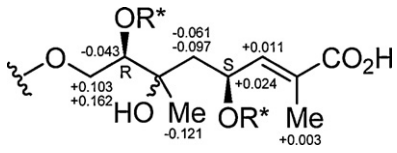

Fig. 3. $\Delta\delta_{SR}$ sign distribution of syn-1,4 of bis-MTPA esters **2**.