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Feroniellins A–C, novel cytotoxic furanocoumarins with highly oxygenated C_{10} moieties from *Feroniella lucida*

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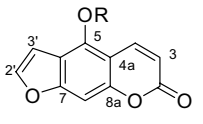
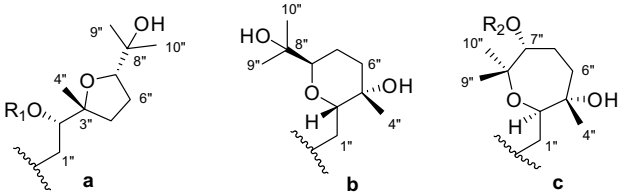
Abstract—Three new furanocoumarins, named feroniellins A (**1**), B (**2**), and C (**3**), were isolated from the roots of *Feroniella lucida*. Compounds **1**–**3** are novel structures having an oxolane, oxane, and oxepane moiety. Their overall structures and configurations were determined by spectral and chemical methods. The cytotoxicities of **1**–**3** were evaluated against human KB and HeLa carcinoma cells.

Feroniella lucida (Rutaceae) is a medium-sized tree distributed widely in the Northeast of Thailand. The genus *Feroniella* is categorized into the subtribe Balsamocitrinae, which includes the genera *Swinglea, Aegle*, *Afraegle*, *Aeglopsis*, *Balsamocitrus* and *Feronia*.[1] Anthranilic-derived alkaloids, such as quinolines and acridones[2] and coumarins encompassing modified C_5 and C_{10} moieties,[3] have been exemplified as principal secondary metabolites of this subtribe. Although *F. lucida* is now popularly cultivated as an ornamental plant, its ethnopharmacological use and phytochemical investigation have not been recorded. In our ongoing search for bioactive metabolites from Thai medicinal plants,[4] we have discovered distinct cytotoxicity in the CH_2Cl_2 extract of *F. lucida* roots. Bioassay-guided fractionation resulted in the isolation of three new isomeric furanocoumarins, named feroniellins A–C (**1**–**3**). The present paper describes the isolation and structure elucidation of **1**–**3**.

Feroniella lucida roots (3 kg), collected from Roi Et, in April 2005, were extracted with MeOH (4 L × 3). The combined extracts were partitioned between H_2O and CH_2Cl_2 to afford the cytotoxic CH_2Cl_2 extract. A portion (70 g) of the extract was chromatographed on silica gel with CH_2Cl_2–*n*-hexane (1:1–1:0) and MeOH–CH_2Cl_2 (1:99–10:90) to yield seven fractions. Fraction 4 (520 mg) was subsequently purified on Sephadex LH-20 [*n*-hexane–CH_2Cl_2–MeOH (2.5:2.0:0.5)] followed by ODS HPLC (80% MeOH–H_2O) to furnish three new isomeric furanocoumarins, named feroniellins A (94 mg), B (56 mg), and C (8 mg).



1 R = a, R_1 = H
1a R = a, R_1 = Ac
1b R = a, R_1 = *S*-(-)-MTPA
1c R = a, R_1 = *R*-(-)-MTPA
2 R = b
3 R = c, R_2 = H
3a R = c, R_2 = Ac



Feroniellin A (**1**)[5] was obtained as a pale yellow powder and had the molecular formula $C_{21}H_{24}O_7$ as established by HRESIMS. The UV (MeOH) absorbances at 252 and 309 nm suggested the presence of a coumarin moiety.[6] It also showed the characteristic ^{1}H NMR signals[7]

Keywords: *Feroniella lucida*; Rutaceae; Coumarin; Cytotoxic.
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of a 3,4-unsubstituted coumarin (δ 6.29, d, $J = 9.6$ Hz, H-3 and 8.22, d, $J = 10.0$ Hz, H-4), which had a furan moiety attached (δ 7.60, d, $J = 2.0$ Hz, H-2′ and 7.01, d, $J = 1.6$ Hz, H-3′). The ^{13}C NMR spectrum revealed 21 signals; eleven of, which were accounted for by the furanocoumarin nucleus (Table 1). The remaining proton and carbon signals were ascribable to a geranyl-derived portion on the basis of 2D NMR data analysis.

The COSY spectrum of **1** displayed two spin systems, O–CH_2–CH–O and C–CH_2–CH_2–CH–O, which were flanked by an oxygenated quaternary C-3″, as suggested by the cross peaks of H-2″/C-3″ and H-5″/C-3″. Acetylation of **1** with Ac_2O in pyridine yielded feroniellin A acetate (**1a**),[8] indicating the presence of one secondary hydroxyl group, which was located at C-2″ based on HMBC correlation of H-2″/CO_2CH_3. Two singlet methyls (δ 1.16, CH_3-10″ and 1.26, CH_3-9″) were accommodated at C-8″ (δ 70.5), which was in turn connected to C-7″ (δ 87.6). The remaining singlet methyl (δ 1.24) was placed at C-3″ (δ 83.9) on the basis of HMBC cross peaks between these protons and C-2″, 3″, and 5″.

The slightly downfield shifts of oxygenated C-3″ (δ 83.9) and C-7″ (δ 87.6) coupled with the HMBC cross peak between H-7″ and C-3″ allowed us to construct a tetrahydrofuran or oxolane ring as a part of the C_{10} subunit. In fact, the NMR data of this portion were similar to those of dehydrovenustatriols, which were isolated from the red algae *Laurencia viridis*.[9] The C_{10} subunit was linked to the coumarin nucleus at C-5, as shown by an HMBC correlation of H_2-1″/C-5 and the presence of resonances typical of an unsubstituted C-8[7,10] (δ_C 94.7 and δ_H 7.17), thus completing the overall structure of **1**. The relative configuration of **1** was deduced by NOESY data

Table 1. ^{1}H and ^{13}C NMR data[a] for feroniellin A (**1**) in $CDCl_3$

No	δ_C	δ_H (mult, J in Hz)	HMBC (H → C)
2	161.2		
3	112.9	6.29 d (9.6)	C-2, 4a
4	139.3	8.22 d (10.0)	C-2, 5, 8a
4a	107.3		
5	148.6		
6	114.1		
7	158.1		
8	94.7	7.17 s	C-4a, 6, 7, 8a
8a	152.5		
2′	145.1	7.60 d (2.0)	C-6, 7, 3′
3′	104.8	7.01 d (1.6)	C-6, 7, 2′
1″	74.3	a 4.37 dd (2.8, 10.0)	C-5, 2″ C-5, 2″
		b 4.58 dd (2.8, 10.0)	
2″	75.9	4.04 dd (2.4, 8.0)	C-1″, 3″
3″	83.9		
4″	27.6	1.24 s	C-2″, 3″, 5″
5″	33.7	α 1.75 m	C-3″, 6″
		β 2.16 m	
6″	26.4	1.91 m	C-5″, 7″
7″	87.6	3.84 m	C-3″, 9″, 10″
8″	70.5		
9″	23.3	1.26 s	C-7″, 8″, 10″
10″	24.0	1.16 s	C-7″, 8″, 9″

[a] Measured at 400 MHz (^{1}H) and 100 MHz (^{13}C).

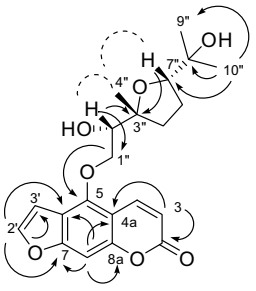

Figure 1. Key HMBC (solid arrows) and NOESY (dashed curves) correlations for **1**.

analysis (Fig. 1); the cross peaks between H-7″ and CH_3-4″, and between CH_3-4″ and H-2″ indicated that they were on the same face of the five-membered ring. To address the absolute configuration at C-2″, MTPA esters of **1** were prepared. Mosher analysis[11] of **1b** and **1c** resulted in the determination of the configuration as 2″*S*.[12]

Feroniellin B (**2**)[13] also had the molecular formula $C_{21}H_{24}O_7$, indicating that it was isomeric with **1**. The ^{1}H, ^{13}C NMR and COSY spectra resembled those of **1**, except for the subtle changes in the chemical shifts of the methyl and oxygenated protons and carbons in the C_{10} portion. Compound **2** did not yield any acetylated product on treatment with Ac_2O in pyridine, suggesting that the oxygenated resonances were that of ethers or tertiary hydroxyls. A downfield shift of C-2″ (δ_C 80.9 vs 75.9 in **1**), together with HMBC correlations between H-2″/C-7″ and H-7″/C-2″, indicated that C-2″ was fused to C-7″ through an ether bridge, thereby forming a tetrahydropyran or oxane moiety.[14]

The relative configuration of **2** (Fig. 2) was deduced from NOESY data and coupling constant analysis. CH_3-4″ (δ 1.24) was coupled to H-6″β (δ 1.61) and H-2″ (δ 4.12), which in turn was coupled to H-1″b (δ 4.72), thus indicating that CH_3-4″ and H-2″ resided in the same plane. The correlations of H-7″ to H-5″α and H-1″a to H-7″ along with a large coupling constant between H-7″ and H-6″β ($^3J_{7''/6''\beta} = 11.2$ Hz) indicated that H-7″ occupied a pseudo-axial position. Therefore, the relative configuration of **2** was described.

Feroniellin C (**3**)[15] was another isomeric coumarin of **1** and **2**. Interpretation of its COSY and HMBC data suggested that it differed from **1** and **2** in the nature of the

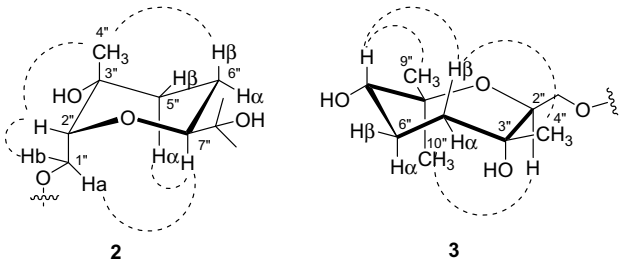

Figure 2. Key NOESY correlations in compounds **2** and **3**.