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Feroniellic acids A–C, three new isomeric furanocoumarins with highly hydroxylated geranyl derived moieties from *Feroniella lucida*

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Abstract

Three new isomeric furanocoumarins named feroniellic acids A–C (**1**–**3**) were isolated from the BuOH extract of *Feroniella lucida* roots. They are diastereomerically different to each other in configuration at C-2″ and C-3″. The structures were elucidated on the basis of spectroscopic data while their configurations were established by synthesis of model compounds together with application of Mosher's method.

Keywords: *Feroniella lucida*; Feroniellic acid; Furanocoumarin

Furanocoumarins are plant metabolites predominantly distributed in the Moraceae, Umbelliferae, and Rutaceae families. They possess several intriguing biological activities such as enhancing the bioavailability of drugs,[1] reducing tumor invasion by inhibiting MMP-2 protease,[2] and disrupting HIV-1 replication.[3] In our continuing search for bioactive metabolites from *Feroniella lucida*,[4–7] we have reported furanocoumarins encompassing diverse oxygenated geranyl derived moieties such as feroniellins A–C, the three isomeric coumarins having different cyclic ether scaffolds. In this Letter, we report our phytochemical investigation of the polar extract of *F. lucida* roots, which showed inhibitory effects toward acetylcholinesterase (AchE), an enzyme responsible for Alzheimer's disease.

The roots collected in Roi Et in 2005 were extracted with MeOH using a Soxhlet extractor. The MeOH extract was suspended in water and partitioned with CH_2Cl_2 and BuOH, respectively. A portion of the BuOH extract (15 g) dissolved in water was loaded onto a Diaion HP-20® column and successively eluted with water, MeOH, and acetone. The MeOH eluent was subsequently purified using Sephadex LH-20 (1:9 MeOH–CH_2Cl_2) followed by preparative TLC (developed in 1:99 MeOH–CH_2Cl_2), yielding feroniellic acids A (**1**, 1.1 mg), B (**2**, 1.2 mg), and C (**3**, 1.1 mg).

Feroniellic acid A (**1**) was isolated as pale yellow gum.[8] The molecular formula $C_{21}H_{22}O_9$ was obtained by HRESIMS and consideration of the NMR data. The UV (MeOH) absorptions at 261 and 310 suggested the presence of a coumarin moiety.[9] A pair of doublet signals ($J = 9.8$ Hz) at δ 6.33 (H-3) and 8.14 (H-4), in conjunction with two broad singlets at 7.63 (H-2′) and 6.96 (H-3′), were indicative of a 3,4-unsubstituted furanocoumarin (Table 1). In the upfield region, two discrete spin systems could be constructed, based on 2D NMR data analysis (Fig. 1). The COSY spectrum confirmed the presence of –O–CH_2–CH–O– and –CH_2–CH(O)–CH= subunits, which were flanked by the oxygenated carbon at C-3″ (δ_C 73.5). The HMBC cross peaks between CH_3-10″/C-6″, CH_3-9″/C-2″, and CH_3-9″/C-4″ indicated that these two singlet methyls were attached to C-3″ and C-7″.

Feroniellic acid A revealed most ^{1}H NMR signals consistent with those of 2″,3″-epoxyanisolactone,[10] except for the oxygenated methylene and methine protons. A

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Table 1
NMR data of feroniellic acid A (**1**) in $CDCl_3$ (400 MHz ^1H and 100 MHz for ^{13}C)

Position	δ_C		δ_H (mult, *J* in Hz)
2	161.0		
3	113.4		6.33 (d, 9.8)
4	139.0		8.14 (d, 9.8)
4a	107.5		
5	148.5		
6	114.5		
7	158.0		
8	95.2		7.22 (s)
8a	152.4		
2′	145.4		7.63 (br s)
3′	104.2		6.96 (br s)
1″	73.6	a	4.67 (br d, 9.9)
		b	4.43 (br t, 8.8)
2″	77.4		4.20 (br d, 6.7)
3″	73.5		
4″	43.5	a b	2.36 (m) 1.94 (m)
5″	77.8		5.30 (m)
6″	148.5		7.10 (br s)
7″	130.5		
8″	173.5		
9″	29.5		1.25 (s)
10″	10.1		1.82 (s)

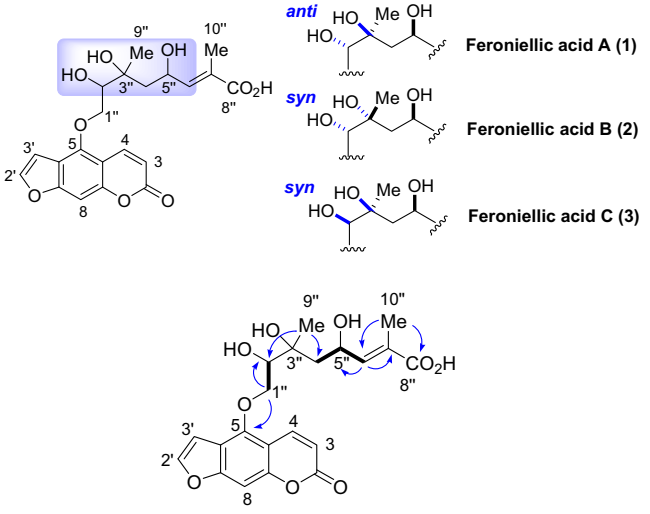


Fig. 1. Selected COSY (bold line) and HMBC (arrows) correlations of **1** in the geranyl derived region.

significant downfield shift of H-2″ (δ_H 4.20 vs 3.29) indicated that the epoxide ring in 2″,3″-epoxyanisolactone was replaced by a 1,2-diol motif in **1**. The presence of a carboxylic acid at C-8″ and a secondary alcohol at C-5″ was implied from a larger 36 amu, thus accounting for the molecular formula established for **1**. The $\Delta^{6''}$ was assigned to be *E*, based on the typical upfield shift of C-10″.[11]

Feroniellic acids B (**2**)[12] and C (**3**)[13] had the same molecular formula, $C_{21}H_{22}O_9$. They displayed ^1H and ^{13}C NMR spectra nearly identical to those of **1**, except for signals in the range 4.1–5.0 ppm (Fig. 2). A significant difference between **2** and **3** was the signal of H-2″, in which that of

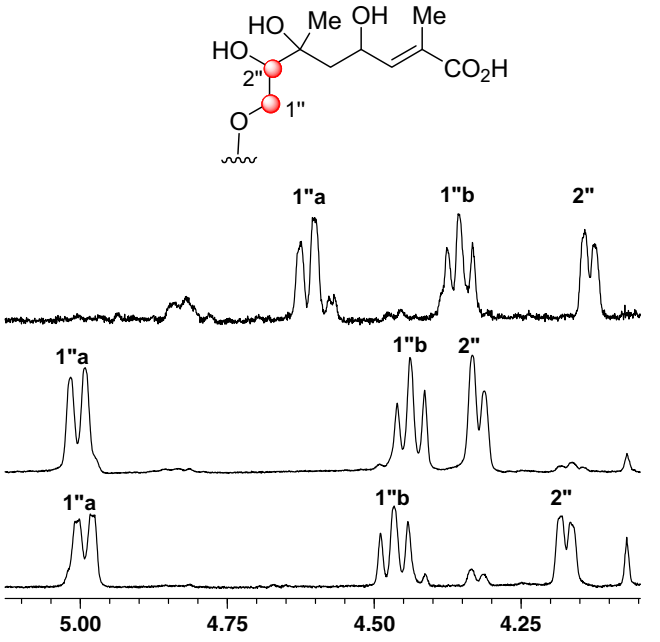
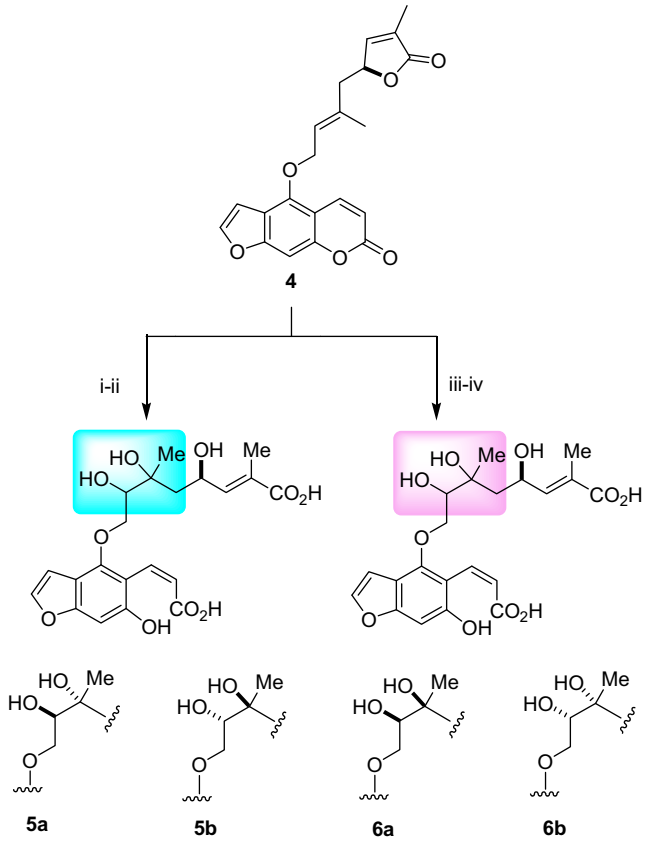


Fig. 2. ^1H NMR spectra of feroniellic acids A (top), B (middle), and C (bottom) expanded in the range of 4.1–5.3 ppm.

2 had shifted more downfield. Significantly, H-1″a of **1** experienced a more upfield shift than those of **2** and **3**. These data suggested that **1**–**3** were stereoisomers of each other at the two asymmetric carbons, C-1″ and C-2″. An attempt to address the stereochemistry of these chiral centers failed due to the very small amount of samples (ca. 1 mg each). This problem was circumvented by constructing model compounds that enabled direct comparison with **1**–**3** through ^1H NMR spectroscopy. Starting from anisolactone (**4**), available in our laboratory,[6] all four possible stereoisomers of feroniellic acid were generated using two different routes (Scheme 1).

Epoxidation of **4** with *m*-CPBA followed by acid-catalyzed ring opening afforded the corresponding *anti*-diols **5a** and **5b** in a ratio of 9:1. The major product **5a** revealed a ^1H NMR spectrum essentially identical to that of feroniellic acid A (**1**), particularly the resonances of H-1″ and H-2″ (Fig. 3). Therefore the relative configuration of **1** was assigned as shown. In contrast, the two *syn*-diols **6a** and **6b** were prepared in moderate yield through oxidation with OsO_4. Although the desired products were an inseparable mixture, the oxygenated methine and methylene signals were consistent with those of **2** and **3**.[14] Given the sufficient amount of **5a** in hand, we further envisaged addressing the absolute configurations of C-1″, 2″, and 5″ using the modified Mosher's method.[15]

Although this methodology was originally developed to determine the absolute configuration of secondary monoalcohols, it has also been widely applied to polyols. Recently, Riguera has validated this approach for the configurational assignment of acyclic secondary/secondary 1,*n*-diols by examining the combined anisotropy effects of two phenylacetic acid derivatives such as MTPA.[16]



Scheme 1. Preparation of model compounds. Reagents and conditions: (i) *m*-CPBA, CH_2Cl_2; (ii) 0.75 M H_2SO_4, *t*-BuOH, reflux; (iii) NMO, OsO_4, 4:1 MeOH–H_2O, 18 h; (iv) 0.5 M H_2SO_4, *t*-BuOH, reflux.

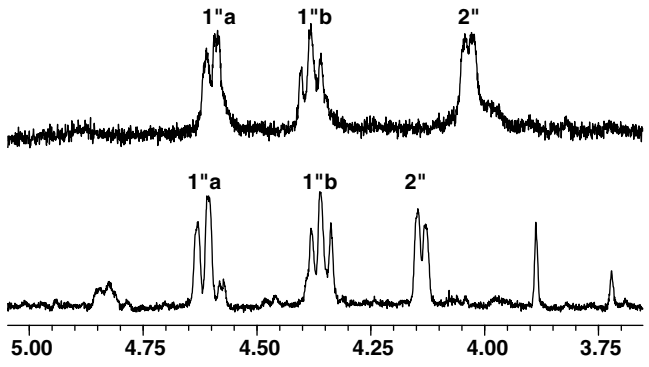


Fig. 3. Partial ^{1}H NMR spectra of *anti*-diol **5a** (upper) and feroniellic acid A (**1**, lower) illustrating the signals of H-1″ and H-2″.

Generally, it appears that four possible stereoisomers (types A–D) of a diol with two asymmetric carbons have a specific and characteristic distribution of $\Delta\delta_{SR}$ signs. For acyclic 1,4-diols, the $\Delta\delta_{SR}$ distribution patterns used to predict the absolute configurations of the two chiral centers are shown Figure 4. Two bis-MTPA derivatives (**6c** and **6d**) were prepared separately by treating **6a** with (−)- and (+)-MTPACl in pyridine, and the $\Delta\delta_{SR}$ distribution is demonstrated in Figure 5. The unequal $\Delta\delta_{SR}$ sign distribution, negative signs around C-2″ and positive signs

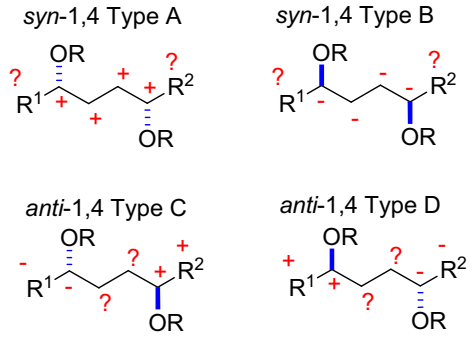


Fig. 4. $\Delta\delta_{SR}$ sign distribution model for the MTPA esters of the possibilities of a 1,4-diol. Atoms labeled "?" are not used for configurational assignments.

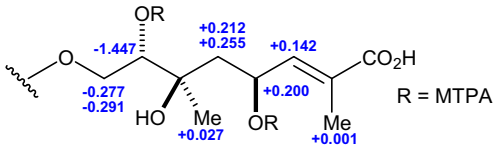


Fig. 5. $\Delta\delta_{SR}$ distribution of bis-MTPA esters **6c** and **6d**.

around C-5″, was consistent with *anti*-1,4-diol type C. Therefore the absolute configuration of feroniellic acid A (**1**) was confirmed.

In summary, we have succeeded in the characterization of three new isomeric furanocoumarins encompassing highly hydroxylated geranyl moieties. Using the model compounds prepared from anisolactone (**4**), a major component of *F. lucida* previously isolated in our laboratory, the relative configurations of **1**–**3** were easily determined. We have also demonstrated that applying the protocol developed by Riguera proved useful in addressing the absolute configuration of two asymmetric carbons of a diol. Coumarins having geranyl derived moieties are commonly encountered in the families Umbelliferae and Rutaceae;[17,18] however, highly hydroxylated geranyls that are terminated with a carboxylic acid are rare. From the biosynthetic point of view, investigation of the enzymes responsible for the synthesis of different stereomeric diols (*syn* and *anti*) is of great interest to understand the formation of **1**–**3** in Nature.

Acknowledgment

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13. *Feroniellic acid C* (**3**): $[\alpha]_D^{26}$ −21.2 (*c* 0.05, MeOH); UV (MeOH) λ_{max} (log ε) 268 (3.11) and 308 (3.53); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.24 (1H, d, $J = 9.6$ Hz, H-4), 7.62 (1H, br s, H-2′), 7.20 (1H, s, H-8), 7.10 (1H, br s, H-6″), 7.00 (1H, br s, H-3′), 6.32 (1H, d, $J = 9.6$ Hz, H-3), 5.24 (1H, m, H-5″), 5.06 (1H, br d, $J = 9.8$ Hz, H-1″a), 4.53 (1H, br t, $J = 8.4$ Hz, H-1″b), 4.24 (1H, br d, $J = 6.4$ Hz, H-2″), 2.33 (1H, br d, $J = 14.8$ Hz, H-4″a), 1.95 (3H, s, CH_3-10″), 1.83 (1H, dd, $J = 14.8$, 10.8 Hz, H-4″b), 1.49 (3H, s, CH_3-9″); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.0 (C-8″), 161.0 (C-2), 158.0 (C-7), 152.5 (C-8a), 148.5 (C-6″), 148.0 (C-5), 145.5 (C-2′), 139.1 (C-4), 130.2 (C-7″), 114.4 (C-6), 113.3 (C-3), 107.5 (C-4a), 104.5 (C-3′), 95.0 (C-8), 77.5 (C-5″), 73.8 (C-3″), 73.5 (C-1″), 66.0 (C-2″), 43.4 (C-4″), 22.1 (C-9″), 12.0 (C-10″); HRESIMS *m*/*z* $[M+Na]^+$ 441.1142 (calcd for $C_{21}H_{22}O_9Na$ 441.1162).
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