

## Fabianane, an Unusual Secoamorphane from *Fabiana imbricata*

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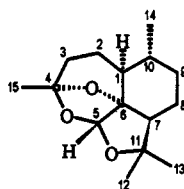
FABIANANE, AN UNUSUAL SECOAMORPHANE  
FROM *FABIANA IMBRICATA*G.D. BROWN<sup>1</sup>*Chemistry Department, Nottingham University, University Park, Nottingham NG7 2RD, UK*

**ABSTRACT.**—A novel seco-amorphane sesquiterpene incorporating a fully saturated furo[2,3-d]1,3-dioxole system was isolated from the aerial parts of *Fabiana imbricata*. Such functionality is unique within the sesquiterpene family, but does have one close relative in artemisinin (the antimalarial principle from *Artemisia annua*), which contains a saturated pyrano[3,2-e]1,2,4-trioxin system. The structure of fabianane [**1**] was elucidated by nmr spectroscopy and confirmed by comparison with nmr data for artemisinin.

*Fabiana imbricata* (Ruiz and Pavon) Romero is a solanaceous plant native to central Chile. It is used by the Mapuche Indians to treat kidney and urinary conditions (1,2).

Cc followed by hplc of a petroleum ether extract of the aerial parts of *Fabiana imbricata* yielded the novel compound fabianane [**1**]. Ms gave the composition of **1** as C<sub>15</sub>H<sub>24</sub>O<sub>3</sub> and it showed absorbances only for aliphatic functional groups in the diagnostic region of the spectrum. Compound **1** must therefore contain four rings incorporating three oxygen linkages. This analysis was confirmed by <sup>13</sup>C-nmr spectroscopy and DEPT, which showed 15 carbon signals with 24 directly attached protons (Table 1). Two of the carbon resonances had chemical shift values suggesting double substitution by oxygen (110.7 C and 103.9 CH), a further two signals were consistent with carbon atoms bearing a single oxygen substituent (94.2 C and 87.8 C), while the remainder of the spectrum comprised chemical shift values typical of aliphatic carbons. This interpretation of the <sup>13</sup>C-nmr data can only be accommodated if the three oxygen linkages occur in a linear sequence.

Single-bond <sup>13</sup>C-<sup>1</sup>H correlations were used to further assign carbon and proton resonances to discrete methyl, methyl-

**1**

ene, and methine units (Table 1). These individual units could then be correlated to one another by means of long-range <sup>13</sup>C-<sup>1</sup>H correlation spectroscopy (optimized for 10 Hz couplings to reveal 2- and 3-bond connectivities). These data are presented in Table 1 and have led to the proposed secoamorphane structure of [**1**].

The foregoing interpretation of the long-range <sup>13</sup>C-<sup>1</sup>H correlation nmr data was entirely confirmed by results of <sup>1</sup>H-<sup>1</sup>H COSY and by analysis of <sup>1</sup>H-<sup>1</sup>H *J*-coupling values. Although overlapping in the 1-dimensional <sup>1</sup>H-nmr spectrum, the multiplicity and coupling constants for most of the protons in the A and B rings could be extracted by performing a <sup>1</sup>H *J*-resolved experiment (Table 1), which then established all but one of the 2- and 3-bond <sup>1</sup>H-coupling constants for [**1**] (Experimental).

The coupling information extracted from the *J*-resolved experiment served not only to confirm the proposed structure, but also to define the relative stereochemistry of **1**. Thus, the 1-, 7- and 10-methine protons must all be axial, because each shows large trans-diaxial couplings to its neighbors and the relative

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TABLE 1. Nmr Data for Fabianane [1].

	$\delta^{13}\text{C}$	Mult. $^{13}\text{C}$	$\delta^1\text{H}$	Mult. $^1\text{H}$	Coupling constants (Hz)	$^{13}\text{C}$ - $^1\text{H}$ long-range correlation observed from C to:
1	44.0	CH	1.49	ddd	12.1, 10.6, 4.5	1.60 (H-9 $\beta$ ); 0.92 (H-14)
2 $\alpha$	23.6	CH <sub>2</sub>	1.90	dddd	13.2, 5.7, 4.5, 1.5	
2 $\beta$			1.30	dddd	13.2, 13.2, 12.1, 6.0	
3 $\alpha$	35.0	CH <sub>2</sub>	1.53	n.r. <sup>a</sup>		
3 $\beta$			1.72	ddd	13.2, 6.0, 1.5	
4	110.7	C	—			5.64 (H-5); 1.90 (H-2 $\alpha$ ); 1.54 (H-15)
5	103.9	CH	5.64	s		1.94 (H-7); 1.49 (H-1)
6	94.2	C	—			5.64 (H-5); 1.79 (H-8 $\alpha$ )
7	48.0	CH	1.94	dd	12.4, 6.2	1.60 (H-9 $\beta$ ); 1.26 (H-8 $\beta$ )
8 $\alpha$	26.5	CH <sub>2</sub>	1.79	dddd	13.6, 6.2, 3.6, 2.8	1.94 (H-7); 1.01 (H-9 $\alpha$ )
8 $\beta$			1.26	dddd	13.6, 13.6, 12.4, 3.4	
9 $\alpha$	33.0	CH <sub>2</sub>	1.01	dddd	13.6, 13.6, 11.3, 2.8	0.92 (H-14)
9 $\beta$			1.60	n.r. <sup>a</sup>		
10	35.2	CH	1.15	n.r. <sup>a</sup>		1.90 (H-2 $\alpha$ ); 1.26 (H-8 $\beta$ )
11	87.8	C	—			5.64 (H-5); 1.59 (H-12); 1.15 (H-13)
12	29.9	CH <sub>3</sub>	1.59	s		1.15 (H-13)
13	25.7	CH <sub>3</sub>	1.15	s		1.59 (H-12)
14	18.7	CH <sub>3</sub>	0.92	d	7.0	1.60 (H-9 $\beta$ ); 1.15 (H-10)
15	24.2	CH <sub>3</sub>	1.54	s		

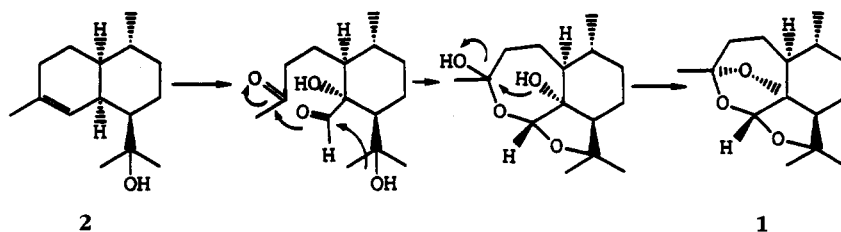
<sup>a</sup>n.r. = not resolved.

stereochemistry of fabianane is therefore (1 $\alpha$ , 7 $\alpha$ , 10 $\alpha$ ), as drawn. The configuration at these 3 chiral centers was confirmed by nOe enhancements, which also showed the 5-methine proton to be axial and positioned over both the A and B rings (enhancements observed upon irradiation of H-2 $\beta$  and H-10 $\beta$ ). The configuration at C-6 must be as shown to sterically accommodate the two five-membered rings.

Although the relative configuration of **1** was determined by nmr, its absolute configuration remained in doubt. The absolute configuration of fabianane is assumed to be as shown by analogy with other amorphanes which were recently isolated from *Fabiana imbricata* (3), such as **2**. Compound **1** could be formally

derived from **2** by oxidative cleavage of the 4,5-bond and hydroxylation at the 6-carbon followed by intramolecular cyclization to give the three ether linkages (Scheme 1).

Fabianane [**1**] is unique in the sesquiterpene family in that it incorporates a furo[2,3-d]1,3-dioxole system. It is also a member of the unusual secoamorphane class, with scission of the amorphane skeleton of **1** having occurred between the 4 and 5 carbons. To the best of my knowledge, only one other amorphane, the natural product artemisinin [**3**] (the antimalarial principle from *Artemisia annua*), shares this structural feature (4). Fabianane shares several other structural similarities with artemisinin, such as overall stereochemistry and level of oxygen-



SCHEME 1. Postulated Biogenetic Relationship Between **2** and **1**.

ation at carbons 4, 5, and 6 (5). The two compounds differ only in that a 4,6 ether linkage in fabianane is replaced by a peroxide linkage in artemisinin and that the 5,11 ether linkage of **1** is replaced by a 5,12 ester linkage in **3**.

Because of these similarities, a sample of artemisinin was isolated from *Artemisia annua* and subjected to the same series of nmr experiments as for **1**. These data gave very similar chemical shift values for **1** when compared with artemisinin (5), and this has lent further support to the unusual structure proposed for fabianane.

### EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—All nmr spectra were recorded on a Bruker 400 MHz spectrometer, with ir spectra recorded on a Perkin-Elmer 1600 Series Ft-ir, and ms on a Varian spectrograph (ei 70 eV).

PLANT MATERIAL.—*Fabiana imbricata* (Solanaceae) was collected while in flower from hillsides in the Cajon del Maipo, central Chile, in late November 1991. Plants were identified in the field by Mr. Rodrigo Villa, and a voucher specimen has been deposited at the Museo de Historia Natural, Santiago, Chile [No. (560) 126048]. *Artemisia annua* L. (Asteraceae) plants were grown from seed under greenhouse conditions. Seeds were kindly supplied and taxonomically verified by Dr. J. Twibell of the NCCPG Collection, Cambridge, UK.

EXTRACTION AND ISOLATION.—The aerial parts of *F. imbricata* (5 kg) were air-dried in the shade (10 days), ground to a fine powder, then Soxhlet extracted (8 h) with petroleum ether (bp 60–80°, twice distilled). Solvent was removed under reduced pressure to yield a yellow viscous fluid (167.8 g; 3.4% w/w yield). Fabianane (76 mg) was purified by cc (Si gel, 20% EtOAc/hexane;  $R_f=0.24$  by tlc with the same solvent) followed by hplc (YMC SIL-15 column; 20×250 mm; 10% EtOAc/hexane; flow 8.0 ml/min,  $R_t=18.7$  min).

Fresh stem and leaf material (1 kg) from *A. annua* was ground to a fine powder under liquid  $N_2$ , extracted in a Soxhlet apparatus (8 h) with  $Et_2O$ , and solvent removed *in vacuo* to yield a green, pleasant-smelling gum (9.0 g; 0.9% w/w yield). Artemisinin (40 mg) was obtained pure by cc (Si gel,  $Et_2O$ ;  $R_f=0.29$  by tlc in 30% EtOAc/hexane) followed by hplc (30% EtOAc/hexane,  $R_t=11.4$  min).

*Fabianane* [**1**].—Colorless oil.  $^1H$  nmr and  $^{13}C$  nmr, see Table 1. In the  $^1H$ -nmr spectrum irradiation at  $\delta$  1.30 led to a 4.0% nOe at  $\delta$  5.64; irradiation at  $\delta$  1.15 also led to a 1% enhancement at  $\delta$  5.64; ir ( $CCl_4$ )  $\nu$  max 2929, 2872  $cm^{-1}$ , eims  $m/z$   $[M-Me]^-$  237 (16), 206 (14), 192 (100), 177 (50), 165 (26), fabms  $m/z$   $[M+1]^+$  253 (11), 235 (22), 217 (18), 203 (16), 192 (22), 181 (21);  $[\alpha]_D -33.1^\circ$  ( $c=0.29$ ,  $CHCl_3$ ).

IDENTIFICATION OF KNOWN COMPOUND.—Artemisinin from *A. annua* gave good  $^1H$ - and  $^{13}C$ -nmr spectral agreement with published data (5).

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