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FOETIDIN, AN 8,9-SECO-17-NOR-KAURANE DITERPENOID FROM *ELAEOSELINUM FOETIDUM*

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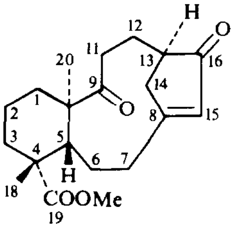
Key Word Index—*Elaeoselinum foetidum*; Umbelliferae; diterpenoid; new seco-nor-kaurane derivative; foetidin; methyl *ent*-8,9-seco-9,16-diketo-17-nor-kaur-8 (15)-en-19-oate.

Abstract—A new seco-nor-kaurane diterpenoid, foetidin, has been isolated from the aerial part of *Elaeoselinum foetidum*. Its structure, methyl-*ent*-8,9-seco-9,16-diketo-17-nor-kaur-8(15)-en-19-oate, was established mainly by spectroscopic means.

INTRODUCTION

In our search for new natural products in plants endemic in the Iberian Peninsula [1–4], we have now investigated *Elaeoselinum foetidum* (L.) Boiss. From the aerial part of this plant, a new 8,9-seco-*ent*-17-nor-kaurane diterpenoid (**1**) has been isolated, for which we propose the name foetidin, together with the known *ent*-kaur-16-en-19-oic acid [5]. The structure of foetidin (**1**) was established on the basis of spectroscopic evidence and by comparison with closely related compounds.



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RESULTS AND DISCUSSION

Combustion analysis and mass spectrometry indicated the molecular formula $C_{20}H_{28}O_4$ for foetidin (**1**). Its IR spectrum was consistent with the presence of an ester group and two additional carbonyl groups, one of them being an α,β-unsaturated ketone group (see Experimental). The presence of the latter was also revealed by the UV spectrum (λ_{max}^{EtOH} 235 nm, log ε 4.11).

However, it was the 360 MHz ^1H NMR spectrum of foetidin (**1**) that provided the most information (Table 1). In addition to showing signals of two tertiary methyl groups at δ 0.85 and 1.28, of a methyl ester group at δ 3.69 and of an olefinic proton at δ 5.97, the *quasi* first-order appearance of the spectrum allowed the identification of the three separate moieties:

$$-CH_2(1)-CH_2(2)-CH_2(3)-,$$
$$-CH(5)-CH_2(6)-CH_2(7)- \text{ and}$$
$$-CH_2(11)-CH_2(12)-CH(13)-CH_2(14)-C(8)=CH(15)-CO(16)-.$$

The existence of a long-range coupling between one of the protons at C-7 and the olefinic proton H-15 ($J_{7\alpha,15}$ = 1.5 Hz) established a connection between the latter two fragments. All these assignments were confirmed by double resonance experiments and checked by spectral simulations. Although some of the proton signals were partially overlapped (see Table 1), the corresponding coupling constants could in most cases be determined from the multiplets of the coupling partners. Two of the coupling constants in the fragment $-CH_2(1)-CH_2(2)-CH_2(3)-$ could not be determined owing to the strong coupling of protons H-1β and H-2α, as well as to the overlapping of the H-1α and H-2β signals with other signals. However, the values of the coupling constants which could be determined in this fragment are in accordance with those expected for a six-membered ring in a chair conformation. Irradiation of the high-field methyl signal at δ 0.85 produced a sharpening of the signals at δ 1.55 (H-5) and 1.83 (H-1β), presumably due to the disappearance of non-resolved long-range couplings with the methyl protons. On the basis of this, the assignments for H-1α and H-1β could be made and subsequently those for the remaining protons of the $-CH_2(1)-CH_2(2)-CH_2(3)-$ fragment. These assignments were confirmed by the ^{13}C NMR data (see below).

Although no particular conformation for the ten-membered ring of foetidin (**1**) could be postulated *a priori*, a Dreiding molecular model of this compound was of great assistance in rationalizing the ^1H NMR data. The chemical shift and coupling data for the protons at C-5 and C-6 suggest a considerable deviation of the values of the torsion angles H_5–C(5)–C(6)–$H_{6\alpha}$ and H_5–C(5)–C(6)–$H_{6\beta}$ from those found in related *trans*-decalin-type systems. The coupling constants of $H_{6\alpha}$ and $H_{6\beta}$ with

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Table 1. ^{1}H NMR spectral data of compound **1** (360 MHz, $CDCl_3$, TMS as internal standard)*

H-1α	1.30, partially overlapped
H-1β	1.83 *t*, $J_{1\alpha,1\beta} \cong -12$, $J_{1\beta,2\alpha} = 13.2$, strongly coupled with H-2α
H-2α	1.80, strongly coupled with H-3β
H-2β	1.57 *m*, $J_{2\alpha,2\beta} = -11.0$, $J_{1\alpha,2\beta} = 3.6$, partially overlapped
H-3α	2.27 *dq*, $J_{3\alpha,3\beta} = -13.4$, $J_{2\alpha,3\alpha} = 2.8$, $J_{2\beta,3\alpha} = 2.6$, $J_{1\alpha,3\alpha} = 2.4$
H-3β	1.13 *dt*, $J_{2\alpha,3\beta} = 13.2$, $J_{2\beta,3\beta} = 3.7$
H-5	1.55 *dd*, $J_{5,6\alpha} = 1.2$, $J_{5,6\beta} = 6.3$
H-6α	1.35, partially overlapped
H-6β	2.98 *m*, $J_{6\alpha,6\beta} = -16.0$, $J_{6\beta,7\alpha} = 4.3$, $J_{6\beta,7\beta} = 4.2$
H-7α	2.43 *m*, $J_{7\alpha,7\beta} = -13.0$, $J_{6\alpha,7\alpha} = 4.3$, $J_{6\beta,7\alpha} = 4.3$, $J_{7\alpha,15} = 1.5$
H-7β	2.58 *dq*, $J_{6\alpha,7\beta} = 12.8$, $J_{7\beta,15} \cong 0$
H-11α	1.87 *dd*, $J_{11\alpha,11\beta} = -17.4$, $J_{11\alpha,12\alpha} \cong 0$, $J_{11\alpha,12\beta} = 7.3$
H-11β	2.73 *dd*, $J_{11\beta,12\alpha} = 12.3$, $J_{11\beta,12\beta} \cong 0$
H-12α	2.55, partially overlapped
H-12β	1.91 *m*, $J_{12\alpha,12\beta} = -13.4$, $J_{12\beta,13} = 3.6$
H-13	2.66 *m*, $J_{12\alpha,13} = 4.1$, $J_{13,14A} = 2.6$, $J_{13,14B} = 3.7$
H_A-14	2.37 *m*, $J_{13,14A} = 2.6$, $J_{14A,14B} \cong -14$, $J_{14A,15} = 1.5$
H_B-14	2.34 *m*, $J_{14B,15} = 1.5$
H-15	5.97 *q*, $J_{7\alpha,15} = J_{14A,15} = J_{14B,15} = 1.5$
Me-18	1.28 *s*
Me-20	0.85 *s*
COOMe	3.69 *s*

*J in Hz. All the assignments have been confirmed by double resonance experiments.

$H_{7\alpha}$ and $H_{7\beta}$ are, however, consistent with the expected values for the usual *gauche* and *anti* orientations. Furthermore, the negligible value found for $J_{11\alpha,12\alpha}$ and that of $J_{11\alpha,12\beta} = 7.4$ Hz are in agreement with values of approximately 90° and 30° for the dihedral angles $H_{11\alpha}$–C(11)–C(12)–$H_{12\alpha}$ and $H_{11\alpha}$–C(11)–C(12)–$H_{12\beta}$, respectively, which are consistent with the Dreiding molecular model of foetidin (**1**). As a matter of fact, the geometry of the ten-membered ring of foetidin, estimated from its ^{1}H NMR data, agrees in general terms with that of the crystal structure of two recently reported 8,9-seco-*ent*-kaurenoids [6–8] in which the ten-membered ring has an approximate C_2 conformation with the conventional 2-fold axis passing through the midpoints of the C(5)–C(6) and C(12)–C(13) bonds.

The ^{13}C NMR of foetidin (**1**) (Table 2) confirmed all the above results. The assignment of the ^{13}C chemical shifts was based on the usual criteria of noise-decoupled spectra, single-frequency proton off-resonance (SFORD) spectra and application of known chemical shift rules. However, most important were the residual $^1J_{CH}$ coupling constants in the SFORD spectrum from which a proton–carbon-13 chemical shift correlation was made. The ^{13}C chemical shifts of C-18, C-19 and C-20 (29.40, 177.07 and 15.30 ppm, respectively) clearly indicate an axial orientation for the COOMe group [9].

Table 2. ^{13}C NMR chemical shifts of compound **1** (90.5 MHz, $CDCl_3$, TMS as internal standard)

C		C	
1	34.42 *t**	11	34.57 *t*
2	19.14 *t*	12	24.57 *t*
3	38.27 *dd*	13	47.26 *d*
4	45.19 *s*	14	33.12 *t*
5	47.13 *d*	15	132.89 *d*
6	22.92 *dd*	16	213.07 *s*
7	35.01 *t*	18	29.40 *q*
8	183.31 *s*	19	177.07 *s*
9	215.32 *s*	20	15.30 *q*
10	54.95 *s*	OMe	51.67 *q*

*SFORD multiplicity.

The relative configuration at C-13 in foetidin (**1**) cannot be established with certainty on the basis of the foregoing spectroscopic evidence alone. The configuration given here seems the most likely, taking into account that foetidin must be biogenetically derived from a kaurane hydrocarbon skeleton. Recently, the isolation of several diterpenoids having the 8,9-seco-*ent*-kaurane skeleton, but which were not 17-nor-derivatives, has been reported, as well as the crystal structure of two of them [6–8]. In these compounds, C-13 has the same configuration as the one proposed for foetidin (**1**). However, the presence of a ketone group in the α-position to C-13 in foetidin (**1**) does not completely rule out the occurrence of an epimerization. As regards the absolute configuration of this new diterpenoid, its unquestionable biogenetic origin from an *ent*-kaurane acid and the fact that *ent*-kauren-16-en-19-oic acid was isolated in the same plant strongly suggest that foetidin (**1**) has the absolute configuration of an *ent*-kaurane.

As a result of all the above data, foetidin can be assigned as methyl *ent*-8,9-seco-9,16-diketo-17-nor-kaur-8(15)-en-19-oate. To our knowledge this is the first 8,9-seco-17-nor-kaurane diterpenoid that has been isolated.

EXPERIMENTAL

Mps were determined on a Kofler apparatus and are uncorr. Elemental analyses were carried out with the help of an automatic

analyser. ^{1}H NMR and ^{13}C NMR spectra were measured at 360 and 90.5 MHz, respectively, in $CDCl_3$ soln with TMS as int. standard. The plant material was collected in June 1974 between Arcos de la Frontera and Tabernas de Rivera (Cádiz, Spain) and voucher specimens (No. 177215) have been deposited in the Herbarium of the Royal Botanical Garden of Madrid.

Extraction and isolation of the diterpenoids. Dried and finely powdered *Elaeoselinum foetidum* Boiss. aerial parts (300 g) were extracted overnight with *n*-hexane–Et_2O in a Soxhlet. The extract was chromatographed on a silica gel column (Merck, No. 7734, deactivated with 15% H_2O). Elution with *n*-hexane–EtOAc (99:1) yielded in order of elution: *ent*-kaur-16-en-19-oic acid (35 mg) and foetidin (14 mg), which were purified by prep. TLC on silica gel (Merck, No. 5554) developed with *n*-hexane–EtOAc (99:1) as eluant. The previously known *ent*-kaur-16-en-19-oic acid was identified by its physical (mp, $[\alpha]_D$) and spectroscopic (IR, ^{1}H NMR, MS) data, and by comparison with an authentic sample.

Foetidin (**1**). Colourless needles; mp 176–178° (from MeOH); $[\alpha]_D^{20}$ −280° ($CHCl_3$; *c* 1.04); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (ester), 1705 (ketone), 1695 (α,β-unsaturated ketone); ^{1}H NMR (360 MHz, $CDCl_3$): see Table 1; ^{13}C NMR (90.5 MHz, $CDCl_3$): see Table 2; EIMS (direct inlet) 75 eV, *m/z* (rel. int.): 332 $[M]^+$ (10), 304 (28), 276 (25), 273 (14), 261 (10), 245 (70), 217 (14), 216 (15), 163 (36), 150 (20), 137 (43), 135 (25), 124 (35), 123 (36), 122 (21), 121 (50), 109 (60), 108 (100), 107 (28). (Found: C, 72.27; H, 8.47. Calc. for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49%.)

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REFERENCES

1. Pinar, M., Rodríguez, B., Rico, M., Perales, A. and Fayos, J. (1983) *Phytochemistry* **22**, 987.
2. Fayos, J., Perales, A., Pinar, M., Rico, M. and Rodríguez, B. (1983) *Phytochemistry* **22** (in press).
3. Pinar, M., Rico, M. and Rodríguez, B. (1982) *Phytochemistry* **21**, 735.
4. Pinar, M., Rico, M. and Rodríguez, B. (1982) *Phytochemistry* **21**, 1802.
5. Henrick, C. A. and Jefferies, P. R. (1964) *Aust. J. Chem.* **17**, 915.
6. Taga, T., Osaki, K., Ito, N. and Fujita, E. (1982) *Acta Crystallogr. Sect. B* **38**, 2941.
7. Fujita, T., Takeda, Y., Shingu, M., Kido, M. and Taira, Z. (1982) *J. Chem. Soc. Chem. Commun.* 162.
8. Node, M., Ito, N., Fuji, K. and Fujita, E. (1982) *Chem. Pharm. Bull.* **30**, 2639.
9. Wehrli, F. W. and Nishida, T. (1979) *Fortschr. Chem. Org. Naturst.* **36**, 1.