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Structure of Evillosin, a Novel Labdane Diterpenoid Lactone from *Eupatorium villosum* Sw.[1]

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A novel labdane diterpenoid, evillosin (1), has been isolated from *Eupatorium villosum* (Compositae), and its stereostructure determined from spectral and X-ray crystallographic analyses. Evillosin possesses a normal labdane skeleton, but incorporates an unusual structural feature of a lactone between C-12 and C-15. The absolute stereochemistry of 1 was deduced from the positive Cotton effect displayed by ketone 3.

Various species of the widespread genus *Eupatorium* (Compositae) show significant antitumor and cytotoxic activities, which are often due to the presence of certain sesquiterpenoids that possess the α-methylene-γ-butyrolactone moiety.[2] Intrigued by the observation that *E. villosum* Sw. ("bitter bush" in Jamaican folklore)[3] is toxic to cattle and to goats, we undertook isolation studies aimed at identifying the toxic principles of this plant, and report in the present article the isolation and structural elucidation of a novel diterpenoid, evillosin (1). Evillosin was, however, inactive against sarcoma-180 in rats and was not toxic.[4]

Evillosin (1), $C_{22}H_{34}O_5$, mp 160–161 °C, was isolated from a methylene chloride extract of the leaves of *E. villosum* and showed strong IR absorptions typical of hydroxyl (3500 cm^{-1}) and carbonyl (1756, 1740 cm^{-1}) groups. The presence of a broad one-proton singlet at δ 3.44 in the ^{1}H-NMR spectrum of 1 suggested that the alcohol group was secondary. This was confirmed by conversion of 1 into the crystalline acetate 2, in which the absorption at δ 3.44 was shifted to δ 3.65 (triplet, J = 2 Hz), and by Jones oxidation,[5] which gave ketone 3.

Although evillosin had strong absorptions in its IR (1640 cm^{-1}) and Raman (1665 cm^{-1}) spectra characteristic of an olefinic double bond conjugated to a carbonyl group, the presence of an α,β-unsaturated carbonyl group was not immediately apparent from the UV spectrum (λ max 209, ϵ 15 210)[6] but was inferred from NMR spectral studies. Evil-

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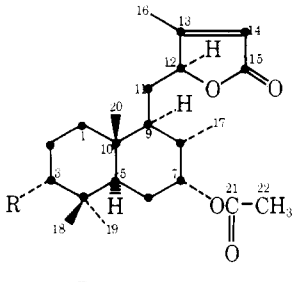
Table I. ^{13}C-NMR Spectra of Evillosin (1) and Derivatives 2 and 3[a]

carbon atom[b]	1[c]	2[d]	3[e]
C-1	31.6 (t)	32.5 (t)	34.1 (t)
C-2	25.1 (t)	22.6 (t)	37.7 (t)
C-3	75.2 (d)	77.4 (d)	214.0 (s)
C-4	36.8 (s)	36.0 (s)	47.0 (s)
C-5	40.9 (d)	42.2 (d)	47.2 (d)
C-6	30.7 (t)	30.6 (t)	30.7 (t)
C-7	74.2 (d)	74.0 (d)	73.5 (d)
C-8	35.4 (d)	35.3 (d)	35.3 (d)
C-9	47.8 (d)	47.7 (d)	47.9 (d)
C-10	38.4 (s)	38.4 (s)	38.2 (s)
C-11	26.6 (t)	26.5 (t)	27.5 (t)
C-12	86.3 (d)	86.0 (d)	85.6 (d)
C-13	168.8 (s)	168.4 (s)	168.3 (s)
C-14	116.5 (d)	116.6 (d)	116.7 (d)
C-15	170.8 (s)	170.3 (s)	170.3 (s)
C-16	22.0 (q)	21.6 (q)	21.6 (q)
C-17	14.1 (q)	14.0 (q)	14.1 (q)
C-18	16.2 (q)	16.2 (q)	16.1 (q)
C-19	28.0 (q)	27.5 (q)	25.1 (q)
C-20	13.0 (q)	13.1 (q)	12.6 (q)
C-21	172.8 (s)	172.5 (s)	172.4 (s)
C-22	21.3 (q)	21.3 (q)	21.1 (q)
C-23		170.6 (s)	
C-24		21.3 (q)	

[a] Determined in $CDCl_3$ with tetramethylsilane as an internal standard. Chemical shifts are in parts per million. [b] Assignments are based on chemical shifts and off-resonance decoupled spectra and are tentative. [c] Registry no. 69204-72-4. [d] Registry no. 69204-73-5. [e] Registry no. 69204-74-6.

losin displayed the following absorptions in its ^{13}C-NMR spectrum: a singlet at 170.8 ppm, attributed to a carbonyl carbon of the ester type (C-15); a doublet at 116.5 ppm, due to an olefinic carbon bearing one proton (C-14); and, significantly, a singlet at 168.8 ppm, ascribed to fully substituted sp^2 carbon β to a carbonyl group (C-13). In addition, a doublet at 86.3 ppm is due to an sp^3 carbon bearing a proton and an oxygen function and, from its chemical shift, appeared to be allylic, i.e., C-12. The corresponding methine proton appeared as a broad quartet (J = 1 Hz) at δ 5.05. The preceding spectral evidence, taken in conjunction with the aforementioned IR and Raman absorptions, indicated that evillosin incorporated an α,β-unsaturated carbonyl group but did not completely define the nature of this functionality. Other absorptions in the ^{13}C-NMR spectrum of evillosin, and its derivatives **2** and **3**, were in complete accord with structure **1** and are given in Table I.

The ^{1}H-NMR spectrum of **1** confirmed the presence of one olefinic proton (δ 5.78) but was surprisingly uninformative about the nature of the methyl groups. Thus, absorption due



1, R = OH
2, R = O–$\overset{23}{C}$O–$\overset{24}{C}$H$_3$
3, R = =O

to 12 protons appeared as an ill-defined doublet at 0.86, and that due to six protons appeared as a slightly broadened singlet at δ 2.08. Resolution of the latter into a sharp 3 H singlet at δ 2.25, assigned to an acetyl group, and a 3 H doublet at 2.12 (J = 2 Hz), attributed to a methyl group on a double bond coupled to a vinyl proton, was possible when the spectrum was determined in the presence of 15% Eu(fod)$_3$.[7] However, no significant resolution of the absorptions in the δ 0.86 region was observed. Differentiation of these absorptions into three quaternary methyl groups and one secondary methyl group was subsequently achieved when the ^{1}H-NMR spectrum of ketone **3** was determined in C_6D_6.

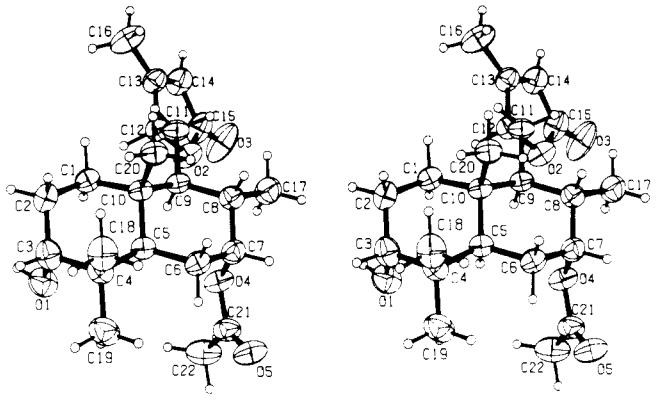


Figure 1. A stereoscopic drawing of evillosin (1).

Although the evidence presented above served to delineate the functionalities present in evillosin, it was considered insufficient to unambiguously define the stereostructure of this substance. Consequently, an X-ray structure determination of evillosin (**1**) was undertaken. A stereoscopic drawing of **1** as determined from the X-ray crystallographic analysis is displayed in Figure 1. This figure also represents the absolute stereochemistry as deduced from the positive Cotton effect shown by ketone **3**. Evillosin thus possesses a normal labdane skeleton but incorporates the unusual structural feature of a lactone between C-12 and C-15.[8] Details of the X-ray crystallographic data are given in the Experimental Section, and listings of final atomic parameters, final anisotropic thermal parameters, bond lengths, bond angles, and torsion angles are given as Supplementary Material.

Experimental Section

General. Melting points were determined in capillaries on a Thomas-Hoover melting point apparatus and are uncorrected. Unless otherwise indicated, infrared (IR) and nuclear magnetic resonance spectra (NMR) were determined in $CHCl_3$ and $CDCl_3$, respectively. ^{1}H- and ^{13}C-NMR spectra were recorded at 100 and 25.2 MHz, respectively. Chemical shifts are expressed in parts per million (ppm) with tetramethylsilane as an internal standard, and coupling constants (J) are expressed in hertz (s = singlet, d = doublet, t = triplet, m = multiplet). Mass spectra (MS) were determined using a direct inlet system with ionization energy of 70 eV; m/e values are given with relative intensities (%) in parentheses. Thin-layer chromatograms (TLC) were prepared from Merck (Darmstadt) silica gel G, and spots were made visible by spraying with 10% phosphomolybdic acid in ethanol and heating the plates to 110 °C.

Isolation of Evillosin (1). Two kilograms of air-dried, finely ground leaves of *Eupatorium villosum* Sw. (Compositae), collected in Jamaica (1973), were steeped in 10.0 L of CH_2Cl_2 at room temperature for 4 days. The mixture was filtered and the filtrate was evaporated to give 48.3 g of a green gum. The latter was dissolved in 400 mL of methanol and stirred twice with 20.0 g of decolorizing charcoal (4 h each time), filtered, and evaporated to give 33.8 g of a light brown gum. A 25-g portion of this material was chromatographed on 350 g of neutral alumina (Woelm, Grade II, dry pack) with 75% ethyl acetate in hexane as eluent. Fractions containing **1** (ascertained by TLC using 70% ethyl acetate in hexane as eluent, R_f 0.26) were combined and rechromatographed on 100 g of adsorbent as described above to give 1.03 g of crude **1**. Crystallization from ethyl acetate in hexane (1:3) at 0 °C gave 841 mg of evillosin (**1**) as colorless crystals: mp 160–161 °C; $[\alpha]^{25}_D$ +135.5° ($CHCl_3$, c 0.994); UV (EtOH) 209 nm (ϵ 15 210); ORD (EtOH) $[\Phi]_{205}$ + 21689; CD (EtOH) $[\theta]_{220}$ −2283; IR

3500, 1756, 1740, 1640 cm^{-1}; Raman (neat) 3565, 1775–1755, 1735, 1665 cm^{-1}; ^1H NMR δ 0.86 (12 H, d), 2.08 (6 H, s), 3.29 (1 H, s, exchangeable with D_2O), 3.44 (1 H, s), 4.76 (1 H, d, J = 9 Hz), 5.05 (1 H, br q, J = 1 Hz), 5.78 (1 H, br s); MS m/e 378 (M^+, 0.001).

Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.79, H, 9.07.

Evillosin Acetate (2). A solution of 37.8 mg (0.1 mmol) of **1** in 0.5 mL of pyridine was treated with 0.2 mL of acetic anhydride. The mixture was stirred at 50 °C for 3 h and then at room temperature overnight. It was diluted with 25 mL of ice-cold water and extracted with ethyl acetate (2 × 25 mL). The extract was washed with 30 mL of ice-cold 0.1 N HCl followed by saturated brine (2 × 30 mL), dried ($MgSO_4$), and evaporated to give 39 mg of a gum, which was chromatographed on 50 g of neutral alumina (Woelm, Grade II, dry pack) with 50% ethyl acetate in hexane as eluent. Collection of the main band (ascertained by TLC using 50% ethyl acetate in hexane) and evaporation of the solvents gave a gum, which crystallized after 1 week. Trituration with hexane afforded 30 mg of **2** as colorless prisms: mp 133–135 °C; $[\alpha]^{25}_D$ +178.3 ($CHCl_3$, c 1.04); UV (EtOH) 209 nm (ϵ 15 000); IR 1755, 1740, 1725, 1640 cm^{-1}; ^1H NMR δ 0.78 (3 H, s), 0.90 (9 H, s), 2.0 (3 H, s), 2.09 (6 H, s), 4.65 (1 H, t, J = 2 Hz), 4.75 (1 H, d, J = 7 Hz), 5.05 (1 H, q, J = 1 Hz), 5.77 (1 H, s); MS m/e 360 ($M - CH_3CO_2H$, 0.5), the molecular ion was not observed.

Anal. Calcd for $C_{24}H_{36}O_6$: C, 68.55; H, 8.63. Found: C, 68.53; H, 8.60.

3-Ketoevillosin (3). A stirred solution of 94.5 mg (0.25 mmol) of **1** in 3.0 mL of acetone was oxidized with 0.1 mL of Jones reagent[5] during 5 min at room temperature. Isolation with ether in the usual manner gave 90 mg of a gum, which was subjected to preparative-scale TLC (silica gel, 70% ethyl acetate in hexane) to remove a slightly less polar substance, and afforded 75 mg of **3**. This solidified under high vacuum overnight: mp 65–70 °C; $[\alpha]^{25}_D$ +165.4 ($CHCl_3$, c 1.0); UV 209 nm (ϵ 14 800); ORD (EtOH) $[\Phi]_{315}$ +4295; CD (EtOH) $[\theta]_{295}$ +3285, $[\theta]_{215}$ −3782; IR 1755, 1730, 1710, 1640 cm^{-1}; ^1H NMR δ 0.93 (3 H, d, J = 5 Hz), 1.04 (6, H, s), 1.10 (3 H, s), 2.08 (3 H, s), 2.12 (3 H, d, J = 1 Hz), 4.71 (1 H, d, J = 5 Hz), 5.08 (1 H, s), 5.80 (1 H, s); ^1H NMR (C_6D_6) δ 0.66 (3 H, s), 0.80 (3 H, s), 0.82 (3 H, s), 1.02 (3 H, d, J = 6 Hz), 1.35 (3 H, d, J = 1 Hz), 1.73 (3 H, s), 4.13 (1 H, d, J = 7 Hz), 5.00 (1 H, q, J = 2 Hz), 5.22 (1 H, br s); MS m/e 376 (M^+, 2).

Anal. Calcd for $C_{22}H_{32}O_5$: C, 70.21; H, 8.25. Found: C, 70.31; H, 8.14.

X-ray Crystallographic Analysis of Evillosin (1). Evillosin belongs to space group $P2_12_12_1$, with a = 1.019 (1) Å, b = 10.738 (1) Å, c = 19.517 (2) Å, Z = 4, d_{calcd} = 1.197g cm^{-3}, μ(Cu Kα) = 6.8 cm^{-1}. The intensity data, uncorrected for absorption, were measured on a fully automated Hilger-Watts diffractometer (Ni filtered Cu Kα radiation, θ–2θ scans, pulse height discrimination) using a crystal of approximately 0.10 × 0.12 × 0.55 mm that was grown from ethyl acetate. Of 1637 independent reflections for $\theta < 57°$, 1496 were considered to be observed [$I > 2.5\sigma(I)$]. The structure and relative stereochemistry of **1** was solved by a multiple solution procedure[9] and was refined by full matrix least squares. In the final refinement, anisotropic thermal parameters and isotropic temperature factors were used for non-hydrogen and hydrogen atoms, respectively. The hydrogens were included in the structure factor calculations but their parameters were not refined. The final discrepancy indices were R = 0.042 and R_w = 0.048 for the 1496 observed reflections. The final difference map had no peaks greater than ±0.2 e A^{-3}. Listings of final atomic parameters, final anisotropic thermal parameters, bond lengths, bond angles, and torsion angles are given in Tables II–VI as Supplementary Material.

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Supplementary Material Available: Listings of final atomic parameters, final anisotropic thermal parameters, bond lengths, bond angles, and torsion angles for **1** are given in Tables II–VI (7 pages). Ordering information is given on any current masthead page.

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6,7-Benzomorphans. Stereospecific Synthesis of 2,9α- and 2,9β-Dimethyl-2'-methoxy-6,7-benzomorphans

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2,9α- and 2,9β-dimethyl-2'-methoxy-6,7-benzomorphans have been synthesized from *m*-methoxybenzaldehyde by a process involving the methylene lactam rearrangement of substituted nipecotic acids. Stereospecific hydrogenation of the intermediate 1-methyl-3-methylene-4-(3-methoxyphenyl)-2-piperidone gave the *cis*-3-methyl derivative. This was followed by replacement of the amide oxygen by a cyano group, a transformation effected by partial reduction to an iminium salt and nucleophilic attack by cyanide ion. Either 3-methyl isomer could be obtained stereospecifically by control of the latter process. The synthesis was completed by conversion of the cyano group to methyl ketone, acid-catalyzed ring closure into the aryl nucleus, oxidation of the resulting exo methylene to carbonyl, and reduction/hydrogenolysis to the final methoxy-6,7-benzomorphans, which were also cleaved to the corresponding phenols.

The 6,7-benzomorphans are of interest since as a class they show separation of the analgesic properties and adverse side effects characteristic of opiates.[1] In addition to the usual structure–activity relationships, the analgesic activity of the 6,7-benzomorphans depends on the stereochemistry at C-9 and to a lesser degree on the nature of the substituents at C-5

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