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EUDESMANOLIDES FROM *MELANOSELINUM DECIPIENS*

GUILLERMO M. MASSANET,* FRANCISCO M. GUERRA, JAVIER M. DORADO, ZACARÍAS D. JORGE and PEDRO VALERGA†

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Cádiz, Apdo. 40, 11510 Puerto Real, Cádiz, Spain; †Departamento de Química Inorgánica, Facultad de Ciencias, Universidad de Cádiz, Apdo. 40, 11510 Puerto Real, Cádiz, Spain

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Key Word Index—*Melanoselinum decipiens*; Umbelliferae; Apiaceae; sesquiterpene lactones; eudesmanolides.

Abstract—The aerial part of *Melanoselinum decipiens* yielded, in addition to the previous known decipienin A, two sesquiterpene lactones whose structures were elucidated by spectroscopic methods. Both substances belong to a stereostructural type of eudesmanolides which is described for the first time from Umbelliferae. The stereochemistry of one of the lactones was confirmed by X-ray diffraction analysis. The biogenetic relevance is discussed.

INTRODUCTION

Sesquiterpene lactones [1] constitute an important group of secondary metabolites, which show a wide range of biological activities [2–4] and are encountered principally in plants belonging to the Asteraceae (Compositae) family. The Apiaceae (Umbelliferae) are another significant source of sesquiterpene lactones [5, 6].

Holub *et al.* [6–9] proposed that sesquiterpene lactones from Umbelliferae have a different stereostructure from the analogous skeletal type of this group of metabolites from Compositae species (Scheme 1). The stereostructure of sesquiterpene lactones isolated from Umbelliferae species after Holub's work seemed to confirm his hypothesis. (See reviews by Fraga, B. M. in *Nat. Prod. Rep.* from 1985). On the other hand, from *Melanoselinum decipiens* (Schader–Wendl) Hoffm. (Umbelliferae, tribe Laserpitieae), González *et al.* [10–12] isolated several eudesmanolides to which the Compositae type of stereostructures were assigned. Holub *et al.* [6] using Holub's above commented proposal, revised their stereostructures and suggested that they should have the stereochemical pattern of Umbelliferae shown in Scheme 1.

As a part of our synthetic programme directed towards the elucidation of the structure and stereochemistry of sesquiterpenoids of the Umbelliferae family, we reinvestigated *Melanoselinum decipiens* with the aim of isolating decipienin A(**3**) [10], a metabolite, from this plant which we have synthesized in both stereostructural forms [13] (Massanet, G. M., unpublished results).

In the course of our reinvestigation we isolated, in addition to decipienin A, two new eudesmanolides which show a new stereochemical pattern different from those shown by Umbelliferae and Compositae species. The results and biogenetic implications are discussed.

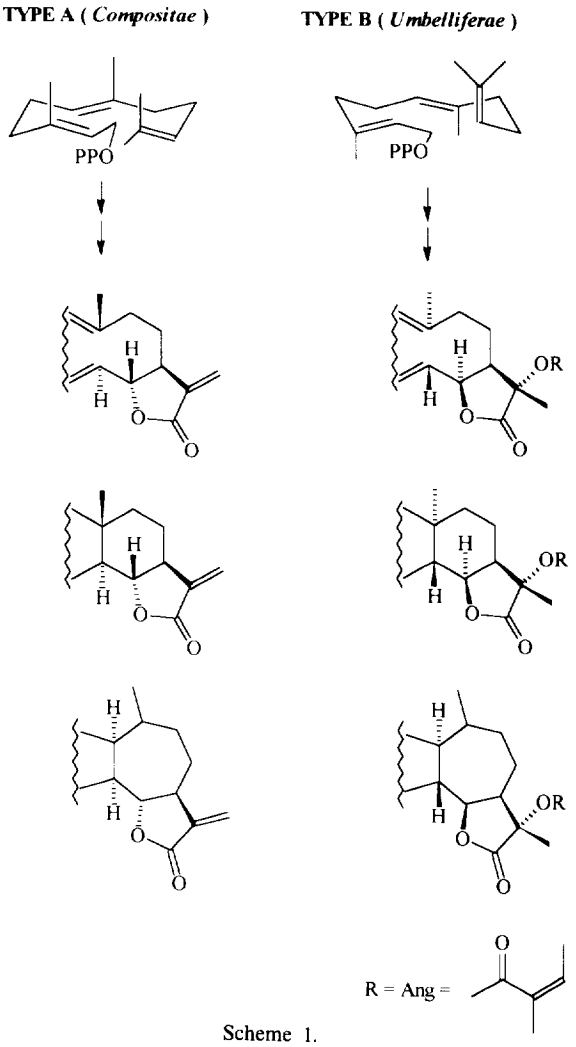
RESULTS AND DISCUSSION

The IR of **1** showed bands for γ-lactone (υ_{max} 1792 cm^{-1}) α, β-unsaturated ester (υ_{max} 1734 cm^{-1}), acetate (υ_{max} 1734 and 1737 cm^{-1}) and double bonds (υ_{max} 1653 cm^{-1}). Its mass spectrum exhibited no molecular peak but characteristic fragments *m/z* 330 $[M - HOAc]^+$, 230 $[M - (HOAc + HOAng)]^+$, 83 $[C_4H_7CO]^+$, 55 $[C_4H_7]^+$.

The ^1H NMR spectrum (Table 1) showed the presence of an angelate moiety [δ6.14 *qq* (1H), 1.95 *dq* (3H) and 1.85 *dq* (3H)] and an acetate [δ2.04 *s* (3H)]. Further, three methyl singlets appeared at δ1.79 (*br*), 1.67 and 0.94, respectively. The remaining significant signals were an olefinic proton at δ5.40 as a broad singlet, a triplet at δ4.87, a double doublet at δ4.71 and a threefold doublet at δ2.96.

All the above data accounted for a structure of $\Delta^{3,4}$-unsaturated eudesmanolide monoacetate with an angeloyloxy substituent at C-11, this being a characteristic functionality present in the sesquiterpene lactones isolated from Umbelliferae. The corresponding compound whose data fit for these structural features is isosilerolide [7], but the spectroscopic data were clearly diferent from those above described for lactone **1**. The most intriguing difference emerged from the coupling constants showed by the lactonic proton (H-6, $J_{5,6} = J_{6,7} = 3.8$ Hz). Furthermore, the ^1H–^1H COSY spectrum showed all the coupling relationships expected for a basic structure of 1-acetoxy-11-angeloyloxy-eudesm-3,4-en-6-12-olide.

*Author to whom correspondence should be addressed.



Scheme 1.

NOE experiments (Fig. 1) confirmed that we were dealing with a stereostructure which differs from the analogous skeletal types of eudesmanolides encountered in species of both Umbelliferae and Compositae families. Thus, *syn*-relationships were found between H-1, H-5, H-6 and H-7, while irradiation of the angular methyl affected only H-8β and H-2β signals. This led us to formulate the structure of this sesquiterpene lactone as 1β-acetoxy-11α-angeloyloxy-5αH,6αH,7αH,10βMe-eudesm-3,4-en-6,12-olide.

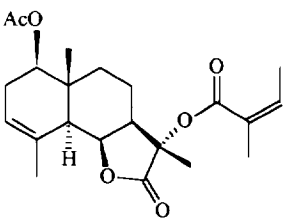
In order to remove any ambiguity concerning the structure and stereochemistry of this new compound,

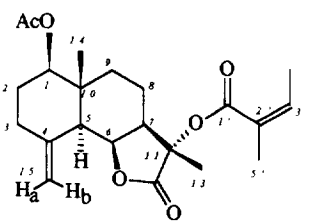
Table 1. ^{1}H NMR of compounds **1** and **2** (399.95 MHz, $CDCl_3$, signal of residual $CHCl_3$ centred at δ7.25 ppm)

H	1	2
1	4.71 *dd*	4.59 *dd*
2α	2.39 *br dd*	overlapped
2β	2.04 *br dd*	overlapped
3	5.40 *b*	—
3α	—	2.17 *ddd*
3β	—	2.36 *ddd*
5	2.19 *br s*	1.99 *br s*
6	4.87 *dd*	4.87 *dd*
7	2.96 *ddd*	2.96 *ddd*
8α	1.75 *m*	overlapped
8β	1.25 *m*	overlapped
13	1.67 *s*	1.66 *s*
14	0.94 *s*	0.90 *s*
15	1.79 *br s*	—
15a	—	5.11 *br s*
15b	—	4.98 *br s*
3′	6.14 *qq*	6.13 *qq*
4′	1.95 *dq*	1.95 *dq*
5′	1.85 *dq*	1.84 *dq*
Acetate	2.04 *s*	2.04 *s*

J(Hz): **1**: 1,2β = 10.0; 1,2α = 6.7; 2α,2β = 17.4; 5,6 = 6,7 = 3.8; 7,8α = 6.3; 7,8β = 12.3; 3′,4′ = 7.3; 3′,5′ = 1.4; 4′,5′ = 1.6. **2**: 1,2α = 4.5; 1,2β = 11.8; 3α,3β = 3α,2β = 13.7; 3α,2α = 4.7; 3β,2β* = 4.8; 3β,2α* = 2.3; 5,6 = 6,7 = 3.1; 7,8β = 9.8; 7,8α = 6.4; 3′,4′ = 7.3; 3′5′ = 4′,5′ = 1.5.

*Interchangeable.





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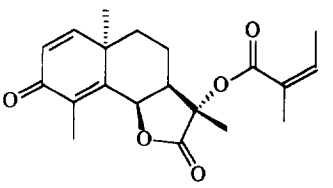

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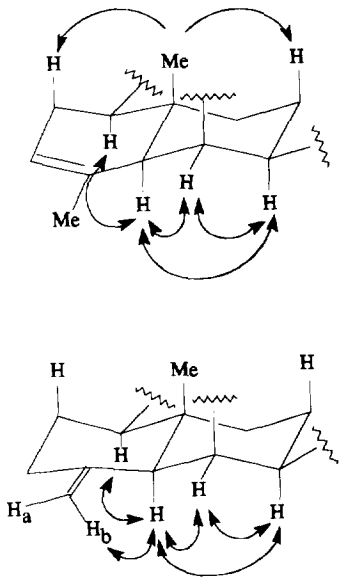

Fig. 1. More significant NOEs observed in **1** and **2**.

lactone **1** was subjected to X-ray analysis, which confirmed the constitution to be as shown in Fig. 2. The absolute configuration is proposed, assuming the β-orientation of C-7, C-11 bond on the basis of biogenetic grounds.

Another natural product (**2**) isolated from *Melanoselinum decipiens* was a closely related eudesmanolide, which also contained an acetate and an angelate group (IR, NMR).

Its mass spectrum showed a fragmentation pattern very similar to that **1**. The ^{1}H NMR spectrum (Table 1) differed from that of **1** in the absence of the vinylic methyl group and the appearance of the characteristic signals of the two protons belonging to an exomethylene double bond [δ5.11 *brs* (1H); δ4.98 *brs* (1H)]. The rest of the signals of both ^{1}H NMR were very similar. The stereostructure of **2** was further established by the difference NOE examinations (Fig. 1) and proved to be of the same type as that of compound **1**. The NOEs were observed betwen (i) H-1 and H5, (ii) H-5 and H-6, (iii) H-5 and H_{ax}-3, (iv) H-5 and H_b-15 (v) H-5 and H-7, (vi) H-6 and H-7. Thus, the structure of **2** was elucidated as 1β-acetoxy-11α-angeloyloxy-5αH,6αH,7αH,10βMe-eudesm-4,15-en-6,12-olide.

Holub *et al.* [6, 14] assumed that there is a separation of the biosynthetic pathways through which sesquiterpene lactones are formed in both Compositae and Umbelliferae families. This separation could take place during the formation of *trans-trans*-farnesyl diphosphate precursor which adopts a different conformation in both families.

It is interesting to point out that compounds **1** and **2** share stereostructural characteristics of both families (rings A and B of Compositae and lactonic ring of Umbelliferae: Scheme 1), and they occur together with other eudesmanolides typical of the Umbelliferae family. (Our unpublished synthetic work has demonstrated that decipienin A(**3**) has the stereostructure type A shown in Scheme 1.) This finding, together with the increasing number of sesquiterpene lactones isolated from Compositae species having stereostructures typical of Umbelliferae, indicates that the proposed separation of the biosynthetic pathways in both families [6] was a simplification.

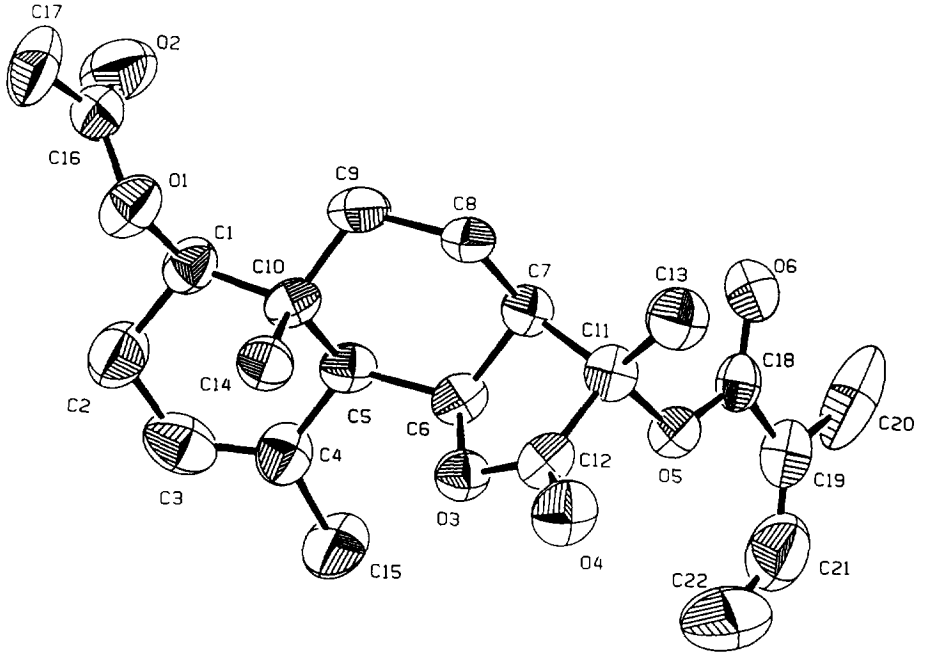

Fig. 2. ORTEP drawing of compound **1**.

EXPERIMENTAL

General. MPS: uncorr., HPLC: Hibar Si60 (Merck) column, flow rate 3 ml min^{-1} (10 × 250 mm); differential refractometer detector. HR-EIMS, and EIMS: directed inlet 70 eV. CC and TLC: silica gel.

Plant material. Melanoselinum decipiens was collected near Funchal (Madeira) in the summer of 1993 and was identified by Dr Susana Sá Fontinha. A voucher specimen (MADS no. 02676) is deposited in the Botanical Garden of Madeira.

The dried aerial parts of *M. decipiens* (1.2 kg) were extracted with EtOH in a Soxhlet apparatus for 12 hr, affording 25 g of syrup. This crude material was chromatographed on a silica gel column and eluted with mixtures of petrol and EtOAc of increasing polarity. Frs of 100 ml were taken and combined on the basis of TLC monitoring. The frs eluted with petrol–EtOAc (4:1) were combined and further separated by HPLC (petrol–EtOAc, 4:1) to give 6 mg of **1** and 4 mg of **2**.

1β-Acetoxy-11α-angeloyloxy-5αH,6αH,7αH,10βMe-eudesm-3,4-en-6,12-olide (**1**). Mp 119–121° (petrol). IR ν_{max}^{film} cm^{-1}: 1792 (γ-lactone), 1734 broad (angelate and acetate), 1653 (double bonds). MS *m/z* (rel. int.): 330.1824 $[M - HOAc]^+$ (18) (calc. for $C_{20}H_{26}O_4$: 330.1831), 230 $[M - HOAc - HOAng]^+$ (21), 83 $[C_4H_7CO]^+$ (100), 55 $[C_4H_7]^+$ (49).

1β-Acetoxy-11α-angeloyloxy-5αH,6αH,7αH,10βMe-eudesm-4,15-en-6,12-olide (**2**). Mp 151–153° (petrol). IR ν_{max}^{film} cm^{-1}: 1793 (γ-lactone), 1737 (acetate), 1722 (angelate), 1657 (double bonds). MS *m/z* (rel. int.): 330.1833 $[M - HOAc]^+$ (4) (calc. for $C_{20}H_{26}O_4$: 330.1831), 230 $[M - OAng]^+$ (12), 83 $[C_4H_7CO]^+$ (100).

Single crystal X-ray diffraction of **1**. Crystal data: $C_{22}H_{30}O_6$, M_r 390.48, monoclinic, space group $P2_1$ (No. 4), a = 12.997(5), b = 6.074(5), c = 13.718(5) Å, β = 101.21(3)°, V = 1062(2) $Å^3$, Z = 2, Dc = 1.221 g cm^{-1}, λ(Mo, K_α) = 0.71069 Å, F(000) = 420. A crystal of dimensions 0.29 × 0.18 × 0.57 mm was mounted in a glass fibre and transferred to an AFC6S-Rigaku diffractometer. The cell parameters were obtained from the settings of 25 reflections in the range $11.7 < 2\theta < 17.6°$. The space group was determined to be accentric $P2_1$ from the systematic absences. Data were collected at 17°, using ω-2θ scan method at 8° min^{-1}. A total of 1635 reflections were measured (unique set of 1558) in the interval $5 < 2\theta < 45°$. A set of 937 reflections with $I > 3\sigma(I)$ was used in refinements. The structure was solved using MITHRIL [15], and refined by full-matrix leastsquares methods with anisotropic thermal parameters for all non-hydrogen atoms. More than half of the hydrogen atoms were localized in difference Fourier maps and the rest were included at idealized geometric positions. The hydrogen atoms were not refined. Both enantiomorphs were checked and no significant difference has been found between them. The refinements led to the final values of $R = 0.045$ and $Rw = 0.050$ [weight scheme $w = \sigma^{-2}(F^2)$]. All calculations were made in a DEC VAX 3520 computer at the Servicios Centralizados de Ciencia y Tecnología, Universidad de Cádiz. The final fractional coordinates, thermal parameters, bond distances and angles have been deposited in the Cambridge Crystallographic Centre.

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