Phytochemistry, Vol. 23, No 9, pp. 1971–1974, 1984
Printed in Great Britain.

0031–9422/84 $3.00 + 0.00

THE CRYSTAL STRUCTURE OF 6-*EPI*-DESACETYLLAURENOBIOLIDE, A GERMACRA-1(10),4-DIENE-12,8α-OLIDE FROM *MONTANOA GRANDIFLORA**

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(*Revised received* 10 *February* 1984)

Key Word Index—*Montanoa grandiflora*; Compositae; germacrolide; sesquiterpene lactone, 6-*epi*-desacetyllaurenobiolide.

Abstract—A chloroform extract of *Montanoa grandiflora* afforded a novel 6β-hydroxy-germacradien-8,12-olide. Its structure was shown to be 6-*epi*-desacetyllaurenobiolide by spectral studies, chemical transformations and single crystal X-ray diffraction. The X-ray data demonstrate that the ten-membered ring exists in the crystal in the highly unusual [$_{15}D^{5}$, $_{1}D^{14}$] conformation, in which the methyl group at C-4 is α-oriented and the methyl group at C-10 is β-oriented. The two double bonds are approximately parallel rather than crossed.

INTRODUCTION

As part of our continuing study on *Montanoa*, we have previously described the isolation of sesquiterpene lactones of the germacrolide type from *Montanoa frutescens* [1] and of the heliangolide and guaianolide type from *M. tomentosa* [2, 3]. Now we wish to report the results of our investigation on *Montanoa grandiflora*, by describing the isolation and structure elucidation of a novel *trans, trans*-germacra 1(10),4-dien-*trans*-8,12-olide by chemical and spectral methods as well as by single crystal X-ray diffraction.

To our knowledge this is the first germacradienolide with a β-hydroxy group at C-6, its structure corresponding to 6-*epi*-desacetyllaurenobiolide (**1a**). Some other germacradienolides with a β-oxygen function have also been isolated from other species of *Montanoa*, but they are *cis*-germacradien-6,12-olides [4]. These compounds found in *M. hibiscifolia* and *M. pteropoda* might be derived from a precursor with a C-6 β-hydroxy group of the type of **1a** isolated from *M. grandiflora*.

RESULTS AND DISCUSSION

6-*Epi*-desacetyllaurenobiolide (**1a**), $C_{15}H_{20}O_3$, mp 117–118°, is an α,β-unsaturated γ-lactone with a strong UV end absorption and IR bands at 1762, 1662 and a hydroxyl absorption at 3455 cm^{-1}.

The ^1H NMR spectrum (Table 1) showed the typical doublets of an exocyclic methylene at δ5.70 (J = 2.6 Hz) and 6.42 (J = 3.0 Hz). The magnitude of the allylic coupling constant suggested a *trans*-fused lactone ring, according to Samek's rule [5]. Two doublets at δ1.55 and 1.66 ($J \sim 1.0$ Hz) indicated the presence of two vinyl methyl groups at C-10 and C-4. A four-proton complex signal at δ4.5–5.1 was assigned to the vinyl protons (H-1, H-5) and to the lactonic proton (H-8) and the proton on the carbon bearing a hydroxy group (H-6).

Sodium borohydride reduction of **1a** afforded the dihydro derivative **2a**, in whose ^1H NMR the exocyclic methylene doublets were replaced by a methyl doublet at δ1.33. Acetylation of **1a** and its dihydro derivative **2a** gave the corresponding monoacetates **1b** and **2b**, confirming the presence of a hydroxy group in the molecule. The spectral data of the isolated material **1a**, the dihydro derivative **2a** and their acetates, indicated that the new compound must be a monohydroxy germacrolide, with a 7,8-lactone ring closure, very closely related to desacetyllaurenobiolide (**4**). The chemical shift and the coupling constants of the exocyclic methylene proton signals strongly suggested that the compound isolated from *M. grandiflora* must be the C-6 epimer of **4**. Whereas in the ^1H NMR spectrum of **4** the exocyclic methylene proton signals appeared both as multiplets (two overlapping doublets of doublets) at δ6.3 due to the α-orientation of the hydroxy group at C-6 [6], the spectrum of **1a** showed these signals as two doublets with different chemical shifts, suggesting a β-orientation of the hydroxy group at C-6.

Epoxidation of **1a** with *m*-chloroperbenzoic acid gave the 4,5-monoepoxy derivative **3**, mp 167–168°. The ^1H NMR spectrum of **3** was particularly informative; it showed a sharp singlet at δ1.3 and a doublet at 2.49 (J = 8.0 Hz) due to the methyl group and H-5, on the carbon bearing the epoxy function. The other proton signals of the basic skeletal arrangement of **3**, were mainly assigned by spin–spin decoupling experiments. The doublet of quartets at δ2.89 (J = 4.5 Hz, J = 3.0 Hz) was assigned to H-7, since irradiation of this signal collapsed the exocyclic methylene doublets to singlets. The doublet of doublets of

*Contribution No. 631 from Instituto de Química, U.N.A.M. (México).

Table 1. ^{1}H NMR data of 6-epi-desacetyllaurenobiolide and derivatives (80 MHz, , TMS as int. standard)

H	1a	1b	2a	2b	3
1	4.5–5.1	4.45–5.1	4.5–5 1	4.35–5.2	5.41 *t* (*br*) (8.0)*
5	4.5–5.1	4.45–5.4	4.5–5.1	4.35–5 2	2.51 *d* (8.0)
6	4.5–5.1	5.29 *d* (*br*) (8.0)	4.5 *dd* (8.0, 2.0)	5.55 *dd* (8.0, 2.2)	3.77 *dd* (8.0, 2.8)
7	2.75 *dq* (4.0, 3.0)	2.85 *m*	obs	obs	2.89 *dq* (4.5, 3 0)
8	4.5–5.1	4.45–5.4	4.5–5.1	4.35–5.2	4.77 *ddd* (12.0, 3.0, 3.0)
13a	5.70 *d* (2.6)	5 69 *d* (2.6)	1.33 *d* (7.0)	1.35 *d* (7 0)	5.65 *d* (2.6)
13b	6 41 *d* (3.0)	6.35 *d* (3.0)			6.47 *d* (3.0)
14	1.55 *d* (~ 1.0)	1.65 *s* (*br*)	1.49 *s* (*br*)	1.57 *s* (*br*)	1 77 *s* (*br*)
15	1.64 *d* (~ 1.0)	1.65 *s* (*br*)	1 67 *s* (*br*)	1.64 *s* (*br*)	1.30 *s*
9α					2 06 *dd* (12.0, 12 0)
9β					2.77 *dd* (12.0, 3.5)
AcO		1.97 *s*		2.08 *s*	

*Numbers in parentheses are coupling constants or line separations in Hz.

doublets at 4.77 (J = 12.0 Hz, J = 3.0 Hz, J = 3.0 Hz) changed to a doublet of doublets (J = 12.0, J = 3.0 Hz) and a doublet of doublets at δ3.77 collapsed to a doublet (J = 8.0 Hz), assigning these signals to H-8 and H-6. Conversely irradiation confirmed these assignments, since saturation at the H-8 signal (δ4.77) converted the H-7 signal to a quartet (J = 3.0 Hz) and a doublet of doublets at 2.77 (J = 12.0, J = 3.5 Hz) and a triplet at 2.06 (J = 12.0 Hz) to doublets (J = 12.0 Hz) assigning these signals to the H-9β and H-9α, respectively. On the other hand, irradiation at the frequency of H-6 (δ3.77) indeed changed the H-7 signal to a quartet and the H-5 doublet (δ2.49) to a singlet. All the above spectral data are in good agreement with the skeletal arrangement proposed for **3**.

The stereochemistry of the epoxy group must be as depicted in **3**, according to the observed coupling constants of H-5, H-6 and H-7 ($J_{5,6}$ = 8 Hz, $J_{6,7}$ = 2.8 Hz). Hence the structure of the epoxy derivative **3** corresponds to that of 6-*epi*-spiciformin [6]. The formation of this epoxy derivative suggested that the major conformation of the molecule must be that with the C-4 methyl group below the plane of the medium ring. This assumption was confirmed by single crystal X-ray diffraction results, which showed that only one conformer is present in the crystalline state, with the C-4 methyl group below the plane of the ten-membered ring. This differs from the *cis*-6,12-germacra-(10),4-dieneolides isolated from *M. hibiscifolia*, in which both methyl groups are oriented below the plane of the ten-membered ring [4]. Finally, it is interesting to point out that all attempts to carry out the Cope rearrangement of **1a**, **1b**, **2a**, and **2b** were unsuccessful. This fact might be due to the adopted conformation of the ten-membered ring in which the double bonds are parallel rather than crossed. Some restriction in the rotation of the 4,5-double bond might be due to the β orientation of the hydroxyl group at C-6 that does not permit conversion into the chair-like transition state which is required for the thermal rearrangement of the 1,5-cyclodecadiene ring [7].

*X-ray crystallography**

Two crystallographically independent molecules exist in the asymmetric unit, both of which have the [$_{15}$D^5, $_1$D^{14}] conformation, illustrated in Fig. 1. The torsion angles characterize this conformation; the largest difference in an intraannular torsion angle between the two molecules is only 5.6°, and the RMS difference is 3.2°. The conformation is that in which the methyl group (C15) at the 4 position is α-oriented, and the methyl group (C14) at the 10 position is β-oriented, in contrast to the expected costunolide-type structure [8] in which both are β-directed. The fact that both of the independent molecules have this unexpected conformation is taken as evidence that it is the most stable for the isolated molecule and not due to intermolecular forces. Very recently, the germacrane lactol hallerol, obtained in the course of chemical transformation of some constituents of the Alpine plant *Laserpitium halleri* Crantz subsp. *halleri*, has been shown to exist in the [$_{15}$D^5, $_1$D^{14}] conformation [9]. Hallerol is

*Tables of nonhydrogen atom coordinates, hydrogen atom coordinates, and torsion angles (3 p.) have been deposited at the Cambridge Crystallographic Data Centre.

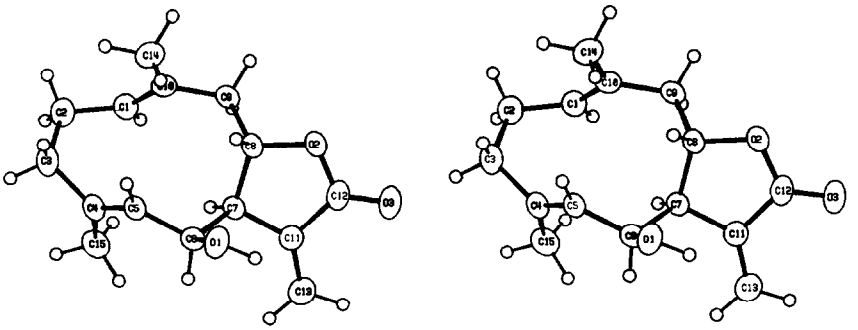
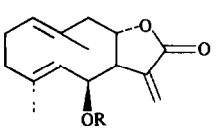


Fig. 1. The β face of 6-*epi*-desacetyllaurenobiolide, in stereopair.

identical to 6-*epi*-desacetyllaurenobiolide, except that it contains an α-methyl-γ-lactol *trans* fused at C(7)-C(8) rather than an α-methylene-γ-lactone. Hallerol exhibits an intramolecular hydrogen bond between the lactol hydroxyl group and the β-hydroxyl group at C6, which is thought to stabilize the boat-boat conformation [9]. The 6-*epi*-desacetyllaurenobiolide molecule attains the boat-boat conformation without the benefit of intramolecular hydrogen bonding.

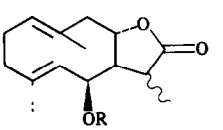
Bond distances and angles averaged over the two molecules are given in Tables 2 and 3. They are normal, with average C=C distance 1.319Å, average C(sp^2)–C(sp^3) distance 1.504Å, and average C(sp^3)–C(sp^3) distance 1.544Å. The lactone ring is only slightly non-planar, with a maximum torsion angle magnitude of only 6.6° (C11-C7-C8-O2), and a sum of 22.1°.

In contrast to previously-characterized germacranolides having 'crossed' double bonds, 6-*epi*-desacetyllaurenobiolide contains the two intraannular *trans* double bonds in approximately parallel arrangement. The C1-C10 and C4-C5 vectors form an angle of 20.0° in one molecule and 22.0° in the other. Despite this conformational difference, the two double bonds have the same separation in 6-*epi*-desacetyllaurenobiolide as in other germacranolides. The average distance between the two double bond centres is 2.947Å, as compared to 2.886Å in eupatolide [10], 2.918Å in tamaulipin-A [11], and 3.009Å in parthenolide [12] (average of two).



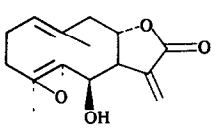
R

1a H
1b Ac



R

2a H
2b Ac



3

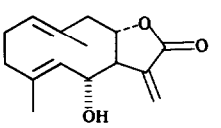


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Table 2. Average bond distances*

Atoms	Distance (Å)	Atoms	Distance (Å)
C1-C2	1.503	C7-C11	1.510
C1-C10	1.324	C8-O2	1.464
C2-C3	1.547	C8-C9	1.533
C3-C4	1.507	C9-C10	1.516
C4-C5	1.320	C10-C14	1.491
C4-C15	1.502	C11-C12	1.475
C5-C6	1.496	C11-C13	1.314
C6-O1	1.428	C12-O2	1.328
C6-C7	1.548	C12-O3	1.211
C7-C8	1.547		

*Averaged over the two independent molecules of the asymmetric unit. Individual esds are 0.003–0.005Å

Table 3 Average bond angles*

Atoms	Angle (deg)	Atoms	Angle (deg.)
C8-O2-C12	112.3	O2-C8-C7	106 1
C10-C1-C2	127.0	O2-C8-C9	106.3
C1-C2-C3	112.0	C7-C8-C9	115.9
C2-C3-C4	111.5	C8-C9-C10	111.1
C3-C4-C5	119.4	C1-C10-C9	119 5
C3-C4-C15	116.2	C1-C10-C14	124 9
C5-C4-C15	123.8	C9-C10-C14	115.4
C4-C5-C6	127.6	C7-C11-C12	107 9
O1-C6-C7	107 0	C7-C11-C13	129 4
O1-C6-C5	111.6	C12-C11-C13	122 7
C5-C6-C7	110.4	C11-C12-O2	110 2
C6-C7-C8	114.6	C11-C12-O3	128.3
C6-C7-C11	112 9	O2-C12-O3	121.5
C8-C7-C11	103.1		

*Averaged over the two independent molecules. Individual esds are 0.2–0.3°.

The two independent molecules pack such that they are related by a pseudo-2_1 situated at (0.40, 0.87, Z). The two are linked in chains along the *c* axis by hydrogen bonds involving the hydroxyl groups and the lactone carbonyl oxygen atoms. Intermolecular separations are O1 . . . O3′, 2.811(3)Å, and O1′ . . . O3, 2.852(3)Å.

EXPERIMENTAL

Montanoa grandiflora Alaman ex DC. was collected in Mexico City, in June 1982. A voucher is on deposit at the Herbarium of Instituto de Biologia (U.N.A.M.) Mexico. Dried leaves (110 g) were extracted with $CHCl_3$ at room temp giving 3.1 g crude extract which was percolated over silica gel (30 g) using $CHCl_3$ and mixtures of $CHCl_3$–Me_2CO as eluant. Fraction 2 (1.7 g) eluted with $CHCl_3$–Me_2CO (9:1) was chromatographed over 20 g silica gel and eluted with $CHCl_3$. From *M. grandiflora* collected in Izucar de Matamoros, Puebla, (Mexico) in September 1980 the known sesquiterpene lactone, encelin was isolated [14].

6-Epi-*desacetyllaurenobiolide* (**1a**). From chromatographic fractions 6–12, **1a** was crystallized from $CHCl_3$–petrol, mp 117–118°; IR ν_{max}^{film} cm^{-1}: 3455, 1762, 1662; UV λ_{max}^{MeOH} nm (ε): 205 (13045); CD (c 1.92×10^{-4}, MeOH): $[\theta]_{200} + 19633$, $[\theta]_{217} + 5425$, $[\theta]$ 255–15241; MS m/z (rel. int.): 248 $[M]^+$ (4.8), 230 $[M - H_2O]^+$ (13.4), 215 $[M - H_2O - Me]^+$ (6.0), 164 $[M - C_5H_8O]^+$ (11.6), 84 $[C_5H_8O]^+$ (100.0). (Calc. for $C_{15}H_{20}O_3$: 248.1411. Found: 248.1415). ^1H NMR (80 MHz, $CDCl_3$): δ4.5–5 1 (4H, *m*, H-1, H-5, H-6 and H-8) 2.75 (*dq*, J = 4.0 Hz, J = 3.0 Hz, H-7), 5.70 (*d*, J = 2.6 Hz, H-13a), 6.41 (*d*, J = 3.0 Hz, H-13b), 1.55 (3H, *d*, $J \sim$ 1.0 Hz, H-14), 1.64 (3H, *d*, $J \sim$ 1.0 Hz, H-15).

6-Epi-*laurenobiolide* (**1b**). Acetylation of 25 mg **1a** provided the acetate **1b** as a gum, after TLC purification (Et_2O–petrol, 4:1); IR ν_{max}^{film} cm^{-1}: 1760, 1745, 1662; UV λ_{max}^{MeOH} nm (ε): 207 (7279); MS m/z (rel. int.): 242 $[M - CH_2CO]^+$ (6.7), 230 $[M - AcOH]^+$ (62.1), 164 $[M - C_7H_{10}O_2]^+$ (12.7), 91 $[C_7H_7]^+$ (74.3), 84 $(C_5H_8O]^+$ (100.0), 43 $[Ac]^+$ (93.7); ^1H NMR (80 MHz, $CDCl_3$): δ4.45–5.4 (3H, *m*, H-1, H-5 and H-8), 5.29 (*d* (*br*), J = 8.0 Hz, H-6), 2.85 (*m*, H-7), 5.69 (*d*, J = 2.6 Hz, H-13a), 6.35 (*d*, J = 3.0 Hz, H-13b), 1.65 (6H, *s* (*br*), H-14 and H-15), 1.97 (3H, *s*, AcO).

11,13-*Dihydro*-6-epi-*desacetyllaurenobiolide* (**2a**). To a soln of 50 mg **1a** in MeOH was added 25 mg of $NaBH_4$ at 5°. After 1 hr the reaction mixture was diluted with H_2O, acidified with 5% aq. HCl and extracted with EtOAc. The solvent was evaporated *in vacuo* and the crude product purified by TLC ($CHCl_3$–Me_2CO, 9:1) to give 35 mg **2a** as a gum; IR ν_{max}^{film} cm^{-1}: 3450, 1752, 1595; UV λ_{max}^{MeOH} nm (ε): 201 (5750); MS m/z (rel. int.): 250 $[M]^+$ (5.6), 235 $[M - Me]^+$ (4.3), 232 $[M - H_2O]$ (2.1), 108 $[C_8H_{12}]^+$ (39.0), 84 $[C_5H_8O]^+$ (67.0); ^1H NMR (80 MHz, $CDCl_3$): δ4.5–5.1 (3H, *m*, H-1, H-5 and H-8), 4.5 (*dd*, J = 8.0 Hz, J = 2.0 Hz, H-6), 1.33 (3H, *d*, J = 7.0 Hz, H-13), 1 49 (3H, *s* (*br*), H-14), 1.67 (3H, *s* (*br*), H-15).

11,13-*Dihydro*-6-epi-*laurenobiolide* (**2b**). Acetylation of 12 mg **2a** yielded **2b** (10 mg), after TLC purification ($CHCl_3$–Me_2CO, 9:1): IR ν_{max}^{film} cm^{-1}: 1758 br, 1652, 890; MS m/z (rel. int.): 322 $[M]^+$ (0.2), 263 $[M - AcO]^+$ (1.0), 84 $[C_5H_8O]^+$ (12.1), 81 $[C_5H_5O]$ (89.7), 43 $[Ac]^+$ (100.0); ^1H NMR (80 MHz, $CDCl_3$): δ4.35–5.2 (3H, *m*, H-1, H-5 and H-8), 5.55 (*dd*, J = 8.0 Hz, J = 2.2 Hz, H-6), 1.35 (3H, *d*, J = 7.0 Hz, H-13), 1.57 (3H, *s* (*br*), H-14), 1.64 (3H, *s* (*br*), H-15), 2.08 (3H, *s*, AcO).

6-Epi-*specioformin* (**3**). To a soln of **1a** (50 mg) in $CHCl_3$, *m*-chloro-perbenzoic acid (30 mg) was added, and the reaction monitored by TLC. The $CHCl_3$ soln was washed with 5% NaOH, the solvent evaporated and the crude product purified by TLC ($CHCl_3$–Me_2CO, 9:1) giving 15 mg of **3** as a crystalline compound: mp 167–168° ($CHCl_3$–petrol); IR ν_{max}^{film} cm^{-1}: 3580, 3440, 1756, 1650; UV λ_{max}^{MeOH} nm (ε): 203 (5218); MS m/z (rel. int.): 246 $[M - H_2O]^+$ (0.1), 231 $[M - H_2O - Me]^+$ (0.2), 97 (25.3), 91 (10.2), 83 (14.6), 68 (100.0); ^1H NMR (80 MHz, $CDCl_3$): δ5.41 (*t* (*br*), J = 8.0 Hz, H-1), 2.51 (*d*, J = 8.0 Hz, H-5), 3.77 (*dd*, J = 8.0 Hz, J = 2.8 Hz, Hz, H-6), 2.89 (*dq*, J = 4.5 Hz, J = 3.0 Hz, H-7), 4.77 (*ddd*, J = 12.0 Hz, J = 3.0 Hz, J = 3.0 Hz, H-8), 5.65 (*d*, J = 2.6 Hz, H-13a), 6.47 (*d*, J = 3.0 Hz, H-13b), 1.77 (3H, *s* (*br*), H-14), 1.30 (3H, *s*, H-15), 2.06 (*dd*, J = 12.0 Hz, J = 12.0 Hz, H-9α), 2.77 (*dd*, J = 12.0 Hz, J = 3.5, Hz, H-9β).

X-Ray crystallography. A crystal of dimensions 0.34 × 0.48 × 0.72 mm was used for data collection in an Enraf-Nonius CAD4 diffractometer equipped with MoKα radiation and a graphite monochromator. *Crystal data.* $C_{15}H_{19}O_3$, MW = 247.3, orthorhombic space group $P2_12_12$, a = 20.050(3), b = 21.993(4), c = 6.157(2) Å, Z = 8, dc = 1.210 gcm^{-3}, λ = 0.71073Å, μ(MoKα) = 0.78 cm^{-1}. Data were collected by ω-2θ scans of variable speed, designed to yield $I \simeq 50\,\sigma$ (I) for all significant reflections. One octant of data having $1^0 \leqslant \theta \leqslant 25°$ was measured, yielding 2760 unique reflections of which 1881 had $I \geqslant 3\sigma$ (I) and were used in the refinement. Data reduction included corrections for background, Lorentz, and polarization effects; no absorption correction was necessary.

The structure was solved by direct methods (MULTAN 78) [13] and refined by full matrix, weighted least squares methods. Nonhydrogen atoms were refined anisotropically, while hydrogen atoms were located in difference maps and included as fixed contributions with isotropic B = 5.0 $Å^2$. Convergence was achieved with R = 0.038, R_w = 0.052 based on observed reflections, and the maximum residual was 0.16 e $Å^{-3}$.

Acknowledgements—We thank Mrs. T. German and Mr. F. Ramos, Herbarium of the Instiuto de Biologia (U.N.A.M.), for identification of the plant material, Messrs R. Saucedo, J Cardenas, H. Bojorquez, L. Velasco, R. Villena and A. Toscano for ^1H NMR, IR, UV and mass spectra, and M. Calleri, G. Chiari and D. Viterbo for communicating their results on hallerol to us prior to publication.

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