organic compounds

Dehydroleucodin: a guaiane-type sesquiterpene lactone

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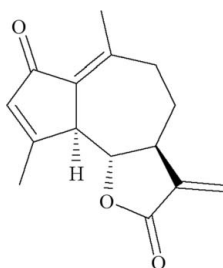Correspondence e-mail: barbieri@fiu.edu

Dehydroleucodin [systematic name: (1S,6S,2R)-9,13-dimethyl-5-methylene-3-oxatricyclo[8.3.0.0^{2,6}]trideca-9,12-diene-4,11-dione], $C_{15}H_{16}O_3$, is a guanolide isolated from *Artemisia douglasiana*. The fused-ring system contains a seven-membered ring that adopts a chair conformation, a fused planar cyclopentenone ring and a five-membered lactone ring fused in envelope conformation. The absolute structure determined by X-ray analysis agrees with that previously assigned to this compound by NMR studies [Bohlmann & Zdero (1972). *Tetrahedron Lett.* **13**, 621–624] and also with that of leucodine, a closely related guaianolide [Martinez *et al.* (1988). *J. Nat. Prod.* **51**, 221–228].

Related literature

For NMR studies of dehydroleucodin and leucodine, see: Bohlmann & Zdero (1972); Martinez *et al.*, (1988). For the pharmacological activity of dehydroleucodin and related compounds, see Giordano *et al.* (1992).

Experimental

Crystal data

$C_{15}H_{16}O_3$	V = 1253.07 (8) Å^3
M_r = 244.28	Z = 4
Orthorhombic, $P2_12_12_1$	Cu $K\alpha$ radiation
a = 7.5101 (3) Å	μ = 0.73 mm^{-1}
b = 11.1065 (4) Å	T = 100 K
c = 15.0228 (6) Å	$0.29 \times 0.07 \times 0.05$ mm

Data collection

Bruker APEXII DUO diffractometer	10896 measured reflections
Absorption correction: integration (*SADABS*; Bruker, 2008)	2166 independent reflections
T_{min} = 0.820, T_{max} = 0.962	2150 reflections with $I > 2\sigma(I)$
	R_{int} = 0.064

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.027	$\Delta\rho_{max}$ = 0.19 e Å^{-3}
$wR(F^2)$ = 0.068	$\Delta\rho_{min}$ = −0.14 e Å^{-3}
S = 1.05	Absolute structure: Flack (1983), 879 Friedel pairs
2166 reflections	Flack parameter: 0.00 (17)
165 parameters	
H-atom parameters constrained	

Data collection: *APEX2* (Bruker, 2008); cell refinement: *SAINT* (Bruker, 2008); data reduction: *SAINT*; program(s) used to solve structure: *SHELXTL* (Sheldrick, 2008); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

References

Bohlmann, F. & Zdero, C. (1972). *Tetrahedron Lett.* **13**, 621–624.
Bruker (2008). *APEX2, SAINT* and *SADABS*. Bruker AXS Inc., Madison, Wisconsin, USA.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Giordano, O. S., Pestchanker, J. M., Guerreiro, E., Saad, J. R., Enriz, R. D., Rodriguez, A. M., Jauregui, E. A., Maria, A. O. M. & Wendel, G. H. (1992). *J. Med. Chem.* **35**, 2452–2458.
Martinez, M. V., Munoz-Zamora, A. & Joseph-Nathan, P. (1988). *J. Nat. Prod.* **51**, 221–228.
Sheldrick, G. M. (2008). *Acta Cryst.* A**64**, 112–122.

supporting information

Dehydroleucodin: a guaiane-type sesquiterpene lactone

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S1. Comment

The title compound, a guaiane-type sesquiterpene lactone, was isolated from *Artemisia douglasiana* Bess (Asteraceae). NMR studies have been reported previously (Bohlmann & Zdero, 1972). By using a lanthanide shift reagent [Eu(fod)3] the lower field signals of dehydroleucodin could be resolved and showed the 5S, 6R and 7S configurations at the chiral centers. Here we report the crystal structure of dehydroleucodin that resulted coherent with the absolute stereochemistry previously reported by Bohlmann and Zdero (1972). The molecular geometry of dehydroleucodin is illustrated in Fig. 1. Inspection of the crystal structure shows that the cyclopentenone carbons, C-9 and C-10 are almost coplanar. The seven-membered ring adopts approximately a chair conformation with the atoms C-6, C-7, and C-8 above the plane. The lactone ring shows a half-chair conformation. H-5 and H-7 are located below the plane (beta-orientation) whereas H-6 is above the plane (beta-orientation), hence the configurations at the chiral centers 5, 6 and 7, is confirmed as being S, *R* and S, respectively. Bond distances and bond angles are normal.

S2. Experimental

Aerial parts of *Artemisia douglasiana* were collected in San Carlos, Mendoza (Argentina). The dried crushed plant material (10 g, dry weight) was exhaustedly extracted with boiling $CHCl_3$. The $CHCl_3$ extract was chromatographed on silica gel and alumina columns using mixtures of ethyl acetate and chloroform as eluants to give white crystals of de-hydroleucodin (70 mg). This compound was identified by comparing the spectroscopic data with the previously published data (Bohlmann and Zdero, 1972). Crystals suitable for X-ray analysis were obtained by recrystallization from DMSO-water at 277K.

S3. Refinement

All the H atoms were placed in idealized positions and refined riding on their parent atoms, with C—H = 0.93-0.99 Å and $U_{iso}(H) = 1.5U_{eq}(C)$ for the methyl H atoms and $1.2U_{eq}(C)$ for the remaining ones. The Flack x parameter is 0.00 (17) confirming that the correct enantiomer is being reported.
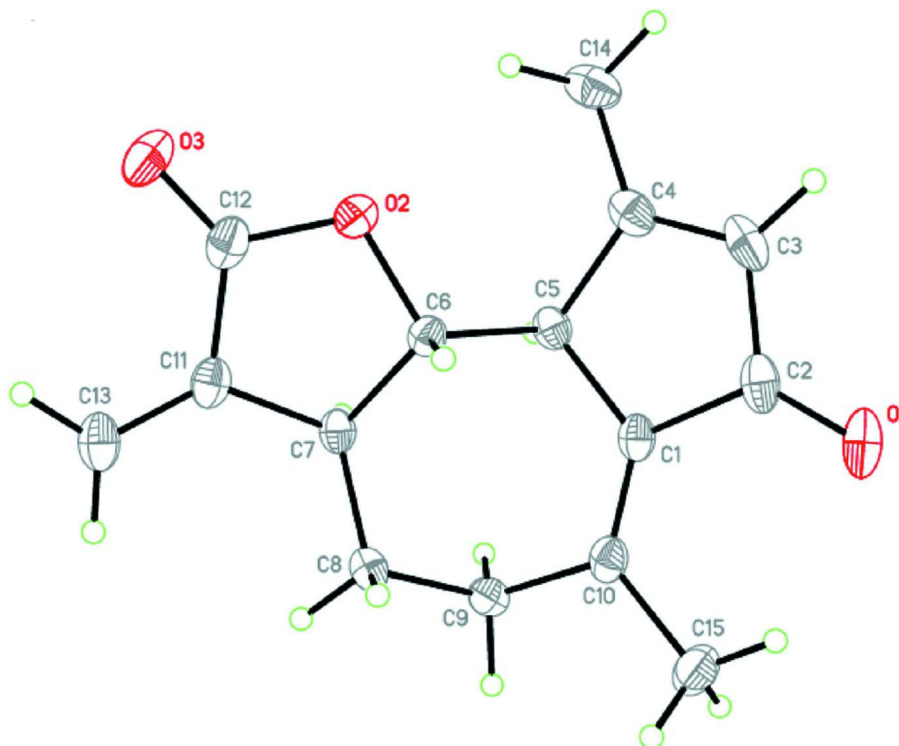
Figure 1

The molecular structure of the title molecule, showing 50% probability displacement ellipsoids.

(1S,6S,2R)-9,13-dimethyl-5-methylene-3- oxatricyclo[8.3.0.0²,⁶]trideca-9,12-diene-4,11-dione

Crystal data

$C_{15}H_{16}O_3$

$M_r = 244.28$

Orthorhombic, $P2_12_12_1$

Hall symbol: P 2ac 2ab

$a = 7.5101 (3)$ Å

$b = 11.1065 (4)$ Å

$c = 15.0228 (6)$ Å

$V = 1253.07 (8)$ Å³

$Z = 4$

$F(000) = 520$

Dehydroleucodin

$D_x = 1.295$ Mg m⁻³

Cu $K\alpha$ radiation, $\lambda = 1.54178$ Å

Cell parameters from 9973 reflections

$\theta = 2.9$–67.8°

$\mu = 0.73$ mm⁻¹

$T = 100$ K

Needles, colourless

$0.29 \times 0.07 \times 0.05$ mm

Data collection

Bruker APEXII DUO
diffractometer

Radiation source: IμS microsource

Graphite monochromator

phi and ω scans

Absorption correction: integration
(*SADABS*; Bruker, 2008)

$T_{min} = 0.820$, $T_{max} = 0.962$

10896 measured reflections

2166 independent reflections

2150 reflections with $I > 2\sigma(I)$

$R_{int} = 0.064$

$\theta_{max} = 66.4°$, $\theta_{min} = 5.0°$

$h = -8 \rightarrow 7$

$k = -13 \rightarrow 12$

$l = -17 \rightarrow 17$

Refinement

Refinement on F^2	Hydrogen site location: inferred from
Least-squares matrix: full	neighbouring sites
$R[F^2 > 2\sigma(F^2)] = 0.027$	H-atom parameters constrained
$wR(F^2) = 0.068$	$w = 1/[\sigma^2(F_o^2) + (0.0273P)^2 + 0.2735P]$
$S = 1.05$	where $P = (F_o^2 + 2F_c^2)/3$
2166 reflections	$(\Delta/\sigma)_{max} < 0.001$
165 parameters	$\Delta\rho_{max} = 0.19$ e Å^{-3}
0 restraints	$\Delta\rho_{min} = -0.14$ e Å^{-3}
Primary atom site location: structure-invariant	Absolute structure: Flack (1983), 879 Friedel
direct methods	pairs
Secondary atom site location: difference Fourier	Absolute structure parameter: 0.00 (17)
map	

Special details

Geometry. All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

Refinement. All H atoms were positioned geometrically (C—H=0.93/1.00 Å) and allowed to ride with $U_{iso}(H)=1.2/1.5U_{eq}(C)$. Methyl ones were allowed to rotate around the corresponding C—C. The Flack x parameter is 0.00 (17) confirming that the correct enantiomer is refined for this structure.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	y	z	$U_{iso}*/U_{eq}$
O1	0.81504 (13)	−0.02962 (8)	0.26751 (7)	0.0312 (2)
O2	0.80476 (13)	0.43297 (8)	0.09948 (6)	0.0248 (2)
O3	0.87294 (16)	0.62331 (10)	0.06281 (7)	0.0411 (3)
C1	0.68912 (15)	0.17287 (10)	0.25112 (8)	0.0192 (3)
C2	0.77553 (16)	0.05869 (11)	0.22172 (10)	0.0240 (3)
C3	0.79958 (18)	0.06797 (12)	0.12543 (10)	0.0278 (3)
H3A	0.8526	0.0072	0.0897	0.033*
C4	0.73794 (16)	0.17220 (12)	0.09389 (9)	0.0241 (3)
C5	0.66907 (16)	0.25183 (10)	0.16885 (8)	0.0192 (3)
H5A	0.5406	0.2712	0.1588	0.023*
C6	0.77492 (16)	0.36796 (10)	0.18300 (8)	0.0183 (3)
H6A	0.8926	0.3478	0.2104	0.022*
C7	0.68007 (16)	0.46068 (10)	0.24137 (8)	0.0190 (3)
H7A	0.5548	0.4662	0.2191	0.023*
C8	0.66895 (18)	0.43149 (11)	0.33978 (8)	0.0227 (3)
H8A	0.6197	0.5015	0.3723	0.027*
H8B	0.7899	0.4154	0.3631	0.027*
C9	0.55009 (17)	0.32097 (11)	0.35585 (8)	0.0224 (3)
H9A	0.5127	0.3202	0.4190	0.027*
H9B	0.4414	0.3286	0.3190	0.027*
C10	0.63981 (17)	0.20247 (11)	0.33441 (9)	0.0209 (3)
C11	0.77282 (17)	0.57383 (11)	0.21226 (9)	0.0215 (3)
C12	0.82427 (19)	0.55285 (12)	0.11838 (9)	0.0269 (3)
C13	0.80965 (17)	0.67457 (11)	0.25533 (10)	0.0266 (3)

H13A	0.8719	0.7376	0.2260	0.032*
H13B	0.7739	0.6839	0.3156	0.032*
C14	0.7232 (2)	0.20714 (14)	−0.00173 (9)	0.0321 (3)
H14A	0.7834	0.1469	−0.0387	0.048*
H14B	0.7792	0.2859	−0.0107	0.048*
H14C	0.5973	0.2116	−0.0186	0.048*
C15	0.6668 (2)	0.12277 (12)	0.41396 (9)	0.0304 (3)
H15A	0.5508	0.0977	0.4374	0.046*
H15B	0.7319	0.1671	0.4600	0.046*
H15C	0.7353	0.0515	0.3964	0.046*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0261 (5)	0.0160 (4)	0.0516 (6)	0.0001 (4)	−0.0029 (4)	0.0034 (4)
O2	0.0299 (5)	0.0231 (4)	0.0214 (4)	−0.0035 (4)	0.0023 (4)	0.0021 (4)
O3	0.0564 (7)	0.0322 (6)	0.0347 (6)	−0.0113 (5)	0.0045 (5)	0.0112 (5)
C1	0.0158 (6)	0.0158 (5)	0.0261 (6)	−0.0017 (5)	−0.0029 (5)	0.0001 (5)
C2	0.0158 (6)	0.0161 (6)	0.0401 (8)	−0.0039 (5)	−0.0027 (5)	−0.0029 (5)
C3	0.0244 (7)	0.0213 (6)	0.0377 (8)	−0.0010 (6)	0.0033 (6)	−0.0118 (6)
C4	0.0191 (6)	0.0257 (6)	0.0275 (7)	−0.0051 (5)	0.0011 (5)	−0.0076 (6)
C5	0.0169 (6)	0.0182 (6)	0.0225 (6)	−0.0011 (5)	−0.0013 (5)	−0.0027 (5)
C6	0.0186 (6)	0.0176 (6)	0.0186 (6)	−0.0002 (5)	−0.0010 (5)	0.0015 (5)
C7	0.0179 (6)	0.0156 (5)	0.0236 (6)	0.0019 (5)	−0.0008 (5)	−0.0001 (5)
C8	0.0275 (7)	0.0179 (6)	0.0227 (7)	0.0003 (5)	−0.0003 (5)	−0.0032 (5)
C9	0.0259 (6)	0.0215 (6)	0.0198 (6)	−0.0015 (6)	0.0017 (5)	−0.0022 (5)
C10	0.0193 (6)	0.0181 (6)	0.0253 (6)	−0.0041 (5)	−0.0037 (5)	0.0014 (5)
C11	0.0176 (6)	0.0179 (6)	0.0289 (7)	0.0018 (5)	−0.0032 (5)	0.0037 (5)
C12	0.0277 (7)	0.0223 (6)	0.0305 (7)	−0.0047 (6)	−0.0033 (6)	0.0050 (5)
C13	0.0219 (6)	0.0190 (6)	0.0389 (7)	0.0007 (5)	−0.0039 (6)	0.0003 (6)
C14	0.0315 (8)	0.0399 (8)	0.0251 (7)	−0.0044 (6)	0.0018 (6)	−0.0099 (6)
C15	0.0371 (8)	0.0252 (6)	0.0288 (7)	−0.0026 (6)	−0.0048 (6)	0.0075 (6)

Geometric parameters (Å, °)

O1—C2	1.2343 (17)	C7—H7A	1.0000
O2—C12	1.3692 (16)	C8—C9	1.5369 (17)
O2—C6	1.4649 (14)	C8—H8A	0.9900
O3—C12	1.2012 (17)	C8—H8B	0.9900
C1—C10	1.3456 (19)	C9—C10	1.5132 (17)
C1—C2	1.4914 (16)	C9—H9A	0.9900
C1—C5	1.5230 (17)	C9—H9B	0.9900
C2—C3	1.461 (2)	C10—C15	1.5009 (18)
C3—C4	1.334 (2)	C11—C13	1.3218 (18)
C3—H3A	0.9500	C11—C12	1.4808 (19)
C4—C14	1.4920 (19)	C13—H13A	0.9500
C4—C5	1.5225 (17)	C13—H13B	0.9500
C5—C6	1.5299 (16)	C14—H14A	0.9800

C5—H5A	1.0000	C14—H14B	0.9800
C6—C7	1.5286 (17)	C14—H14C	0.9800
C6—H6A	1.0000	C15—H15A	0.9800
C7—C11	1.5019 (16)	C15—H15B	0.9800
C7—C8	1.5158 (17)	C15—H15C	0.9800
C12—O2—C6	108.55 (9)	C7—C8—H8B	109.5
C10—C1—C2	127.08 (12)	C9—C8—H8B	109.5
C10—C1—C5	125.92 (11)	H8A—C8—H8B	108.1
C2—C1—C5	107.0 (1)	C10—C9—C8	113.74 (10)
O1—C2—C3	125.31 (13)	C10—C9—H9A	108.8
O1—C2—C1	127.97 (13)	C8—C9—H9A	108.8
C3—C2—C1	106.68 (11)	C10—C9—H9B	108.8
C4—C3—C2	111.72 (12)	C8—C9—H9B	108.8
C4—C3—H3A	124.1	H9A—C9—H9B	107.7
C2—C3—H3A	124.1	C1—C10—C15	123.99 (12)
C3—C4—C14	126.41 (12)	C1—C10—C9	122.21 (11)
C3—C4—C5	111.05 (12)	C15—C10—C9	113.80 (11)
C14—C4—C5	122.40 (12)	C13—C11—C12	123.01 (12)
C4—C5—C1	103.43 (10)	C13—C11—C7	131.52 (13)
C4—C5—C6	114.58 (10)	C12—C11—C7	105.47 (10)
C1—C5—C6	108.75 (9)	O3—C12—O2	121.46 (13)
C4—C5—H5A	110.0	O3—C12—C11	129.70 (13)
C1—C5—H5A	110.0	O2—C12—C11	108.82 (11)
C6—C5—H5A	110.0	C11—C13—H13A	120.0
O2—C6—C7	103.33 (9)	C11—C13—H13B	120.0
O2—C6—C5	112.09 (9)	H13A—C13—H13B	120.0
C7—C6—C5	113.92 (10)	C4—C14—H14A	109.5
O2—C6—H6A	109.1	C4—C14—H14B	109.5
C7—C6—H6A	109.1	H14A—C14—H14B	109.5
C5—C6—H6A	109.1	C4—C14—H14C	109.5
C11—C7—C8	119.24 (11)	H14A—C14—H14C	109.5
C11—C7—C6	100.4 (1)	H14B—C14—H14C	109.5
C8—C7—C6	116.17 (10)	C10—C15—H15A	109.5
C11—C7—H7A	106.7	C10—C15—H15B	109.5
C8—C7—H7A	106.7	H15A—C15—H15B	109.5
C6—C7—H7A	106.7	C10—C15—H15C	109.5
C7—C8—C9	110.86 (10)	H15A—C15—H15C	109.5
C7—C8—H8A	109.5	H15B—C15—H15C	109.5
C9—C8—H8A	109.5		