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1,10-Dehydrosalviarin

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Key indicators

Single-crystal X-ray study
T = 291 K
Mean σ(C–C) = 0.003 Å
R factor = 0.035
wR factor = 0.073
Data-to-parameter ratio = 9.5

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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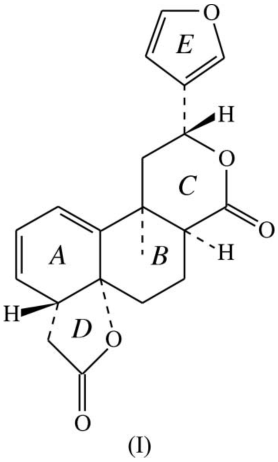
The title diterpenoid, $C_{20}H_{20}O_5$, is a plant metabolite from *Salvia wagneriana* Polak. The molecule is characterized by a pentacyclic structure derived from a rearranged clerodane skeleton and shows, in addition to *A* and *B* rings, two olide systems forming *C* and *D* rings. Moreover, a β-substituted furan ring is present on the *C* ring. The crystal packing is mainly governed by normal van der Waals interactions. In the crystal structure, one non-classical hydrogen bond is also present, involving the carbonyl O atom of the γ-lactone ring and one activated C atom of a screw-related furan system. The structure exhibits a remarkable isomorphism with that of the previously characterized salviarin. The antifeedant activity of dehydrosalviarin against the insect *Spodoptera littoralis*, a destructive pest for tropical and subtropical agriculture, is also reported.

Comment

Among plant diterpenoids, the class based on the clerodane skeleton is of great interest in alimentary, agricultural and cosmetic industries. Several of these substances present various biological activities, for example antitumoral, antimicrobial, antibacterial and, in particular, antifeedant against insects, well known for a long time and also used in folk medicine (Simmonds & Blaney, 1992; Enriz *et al.*, 2000). In consideration of possible utilizations in pharmacology and farming, these substances have been widely investigated, and a large number of clerodane diterpenoids have been isolated and characterized in recent years (Hanson, 2004, and previous reports). Their structural characterization is justified by problems associated with the stereochemistry of this class of molecules. In fact the revision of the absolute stereochemistry of clerodin (Rogers *et al.*, 1979), the first member of this series, and consequently those of structurally correlated ajugarins (Trivedi *et al.*, 1979; Kubo *et al.*, 1980), had extensive repercussions in the literature, causing confusion over the terms *ent*- and neo- or *ent*-neo-clerodanes. Besides, the stereochemical assignments were, in some cases, supported by a minimal amount of spectroscopic data and were, for this reason, doubtful (Merritt & Ley, 1992; Hayashi *et al.*, 2002; Prakash *et al.*, 2002).

Many clerodane diterpenoids have been isolated from different species of Salvia genus (Rodríguez-Hahn *et al.*, 1992; Simmonds *et al.*, 1996; Almanza *et al.*, 1997; Munro & Rizzacasa, 2003). Salvia species are widespread in both temperate and tropical zones and are able to develop various strategies to interact with the environment, synthesizing specific antifeedant secondary metabolites to defend themselves from herbivores (Simmonds *et al.*, 1996). As part of an ongoing search on bioactive clerodane diterpenoids (Bisio *et al.*, 2004, and references therein), we present here the three-dimensional structure of 1,10-dehydrosalviarin, (I), recently isolated (Bisio *et al.*, 2004), together with other correlated compounds, from the exuded aerial parts of an American species of *Salvia wagneriana* Polak (Laminaceae). This substance was proved to have an effective antifeedant activity against Mediterranean climbing cutworm *Spodoptera littoralis* (Boisd.) (Noctuidae), a destructive pest for tropical and subtropical agriculture. Compound (I) was at first obtained by chemical modification of a metabolite from *Salvia rubescens* HBK, but its stereochemistry was not assigned (Brieskorn & Stehle 1973). Subsequently, this substance was isolated from Mexican plants belonging to *S. lineata* Benth. species and characterized by means of spectroscopic and chemical data (Esquivel *et al.*, 1986). The present single-crystal X-ray study confirms the proposed relative stereochemistry.



(I)

The molecule is characterized by a pentacyclic structure derived from a rearranged clerodane skeleton and shows, in addition to *A* and *B* rings, two olide systems, 12,17 and 19,18 olide forming *C* and *D* rings, respectively. Moreover, at C12 a β-substituted furan ring (*E* ring) in equatorial orientation is present. In the molecule there is an α-axial *cis* relationship between the H atom at C8 and the methyl group C20 at C9 (*B*/*C* rings *cis*-fused) as found in other correlated diterpenoids [*e.g.* salviarin (Savona *et al.*, 1978), splendidin (Savona *et al.*, 1979) and columbin (Overton *et al.*, 1966)], whereas the β-axial H atom at C4 is *trans* oriented to C19 of the γ-lactone *D* ring.

A perspective view of the molecule of (I) is shown in Fig. 1 together with the atomic labelling scheme. Bond lengths and angles are within the expected ranges and generally agree well with the values reported in the literature (Linden *et al.*, 1996; Almanza *et al.*, 1997; Bisio *et al.* 1999; Toscano *et al.*, 2001; Soundarya Devi *et al.*, 2003; Ravikumar *et al.*, 2005).

The *A* ring, which presents two conjugated double bonds in the 1,10- and 2,3-positions, adopts a distorted half-chair conformation, as does the δ-lactone ring *C*. The atomic displacements are 0.209 (2) (for C4) and 0.250 (2) Å (for C5) for the *A* ring, and 0.321 (2) (for C9) and 0.388 Å (for C11) for the *C* ring on the opposite side of the respective mean planes through the remaining ring atoms. In both rings the distortions are essentially toward twist-boat forms as shown by puckering parameters (Cremer & Pople, 1975): q_2 = 0.278 (2) Å, φ_2 = −27.5 (4)°, θ = 65.6 (4)° and q_2 = 0.303 (2) Å, φ_2 = 26.1 (3)°, θ = 40.3 (2)°, respectively. The deviations from the ideal HC symmetry can be measured by the asymmetry parameters (Duax *et al.*, 1976) ΔC_2(C1—C2) = 1.4 (4)° and ΔC_2(C9—C11) = 5.3 (4)°. The *B* ring approximates to an ideal chair with puckering parameters *Q* = 0.512 (2) Å, θ = 17.7 (3)° and φ_2 = −2.2 (2)°. With respect to the ideal chair form, C10 is flatter than C7, the distances from the average plane through the remaining endocyclic atoms being 0.444 (2) Å for C10 *versus* 0.694 (2) Å for C7. The γ-lactone (ring *D*) adopts an envelope form with apex at C5; this atom is 0.571 (2) Å out of the mean plane through the remaining atoms. The furan ring *E* is strictly planar (displacements less than 0.001 Å) and its orientation is defined by the torsion angle O2—C12—C13—C14 = 94.1 (4)°. The shortest non-1,4 intramolecular contacts are O3···C6 = 3.329 (4) Å and C1···C12 = 3.371 (4) Å.

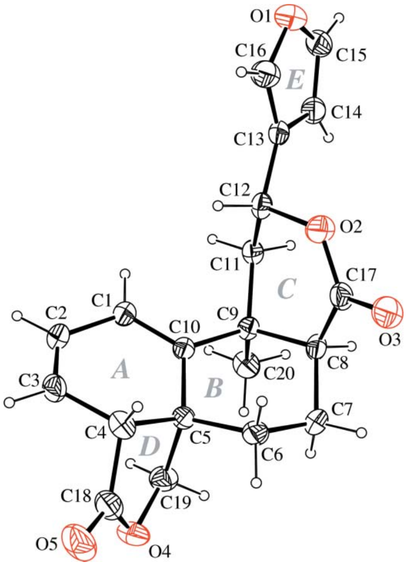
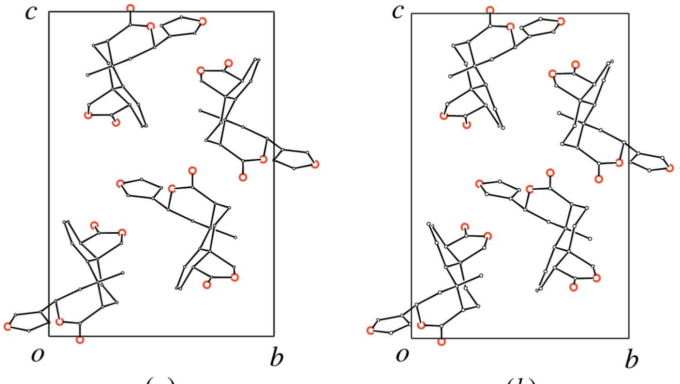


Figure 1

The molecular structure of (I), with the atomic labelling for non-H atoms. Displacement ellipsoids are drawn at 30% probability level.

In the crystal structure, the molecular arrangement is mainly governed by normal van der Waals interactions (Fig. 2*a*). There is one intermolecular short hydrogen-bond-type contact, involving the γ-lactone carbonyl atom O5 and the activated atom C16 of a screw-related molecule: O5···C16 = 3.273 (4) Å and O5···H—C16 = 163°.

The title compound exhibits a remarkable isomorphism with salviarin (Savona *et al.*, 1978). In a least-squares superposition of the two molecules, the r.m.s. deviation of the corresponding atoms is 0.134 (5) Å and the largest differences are associated with atoms C1 and C10. The variations in molecular geometry, due to the different hibridization states of C1 and C10 (from Csp^3 in the *trans*-clerodane skeleton of salviarin to Csp^2 in dehydrosalviarin), are modest and do not affect the rest of the comparison. The high degree of



(*a*) (*b*)

Figure 2
Packing diagrams of title compound (*a*) and salviarin (*b*), showing the isomorphism between the two structures. H atoms have been omitted for clarity. The coordinates of salviarin are referred to the reduced cell and both the enantiomers have been chosen according to the reported stereochemistry of clerodin bromolactone (Rogers *et al.*, 1979).

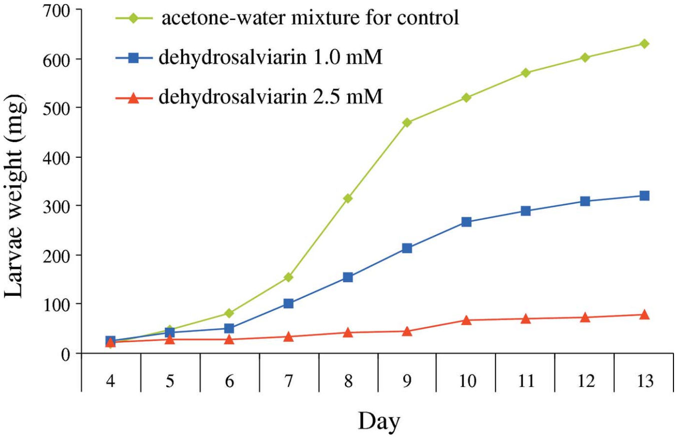


Figure 3
Antifeedant activity of (I) at concentration 1.0 m*M* and 2.5 m*M* (see *Comment* and *Experimental* sections). The control experiment is also reported for comparison. Each point is the mean of three experiments.

isomorphism between the two packings is shown in Fig. 2. The presence of two conjugated double bonds in (I) leads to a planar C10/C1/C2/C3 group favouring the approach between metabolite and receptor and so the ability of interaction, according to theoretical studies on structure–antifeedant activity relationships (Enriz *et al.*, 2000).

The antifeedant activity of 1,10-dehydrosalviarin against the insect *Spodoptera littoralis* (Besid.) has been tested and the results are reported in Fig. 3. In the control group, the larvae of *S. littoralis* showed a continuous increase in weight and at day 13 all larvae pupated. Larvae grown on leaves of lettuce *L. sativa* treated with a 2.5 m*M* solution of 1,10-dehydrosalviarin showed a dramatic loss of growth and their increase in weight was practically absent. Larvae grown on lettuce treated with a 1.0 m*M* solution of (I) showed a moderate increase in weight without ever reaching the critical weight for pupation. The present results fall into line with the literature data concerning significant antifeedant activity of neo-cleordanes aganist larvae of *S. littoralis* (Simmonds *et al.*, 1996) or other pests (Enriz *et al.*, 1994, 2000; Sosa *et al.*, 1994). The proven antifeedant activity of (I) can be useful for the development of new biorational pesticides of natural origin.

Experimental

The title compound was extracted and purified as previously reported (Bisio *et al.*, 2004). Crystals suitable for X-ray study were obtained by slow evaporation from an *n*-hexane–chloroform solution (3:1 *v*/*v*) at room temperature. For the biological essay the first-instar larvae of *S. littoralis* were grown on lettuce (*Lactuca sativa L.*) leaves available *ad libitum*. The leaves were sprayed with solutions of (I) in an acetone–water mixture (ratio 1:99), or a mixture of acetone–water alone (control). Starting from day 4, the larvae were weighed daily.

Crystal data

$C_{20}H_{20}O_5$
$M_r = 340.36$
Orthorhombic, $P2_12_12_1$
$a = 8.014\ (7)$ Å
$b = 11.970\ (12)$ Å
$c = 17.239\ (18)$ Å
$V = 1654\ (3)$ Å^3
$Z = 4$
$D_x = 1.367$ Mg m^{-3}

Mo $K\alpha$ radiation
Cell parameters from 5071 reflections
$\theta = 4.6$–$20.6°$
$\mu = 0.10$ mm^{-1}
$T = 291\ (2)$ K
Elongated prism, colourless
0.55 × 0.20 × 0.15 mm

Data collection

Nonius KappaCCD diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
$T_{\min} = 0.903$, $T_{\max} = 0.986$
12254 measured reflections
2149 independent reflections

1517 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.036$
$\theta_{\max} = 27.6°$
$h = -9 \rightarrow 10$
$k = -15 \rightarrow 15$
$l = -17 \rightarrow 22$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.035$
$wR(F^2) = 0.073$
$S = 1.00$
2149 reflections
227 parameters

H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0402P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} < 0.001$
$\Delta\rho_{\max} = 0.13$ e Å^{-3}
$\Delta\rho_{\min} = -0.17$ e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

O1—C15	1.348 (3)	C1—C2	1.457 (3)
O1—C16	1.369 (3)	C1—C10	1.330 (3)
O2—C12	1.474 (2)	C2—C3	1.315 (3)
O2—C17	1.325 (3)	C12—C13	1.494 (3)
O3—C17	1.209 (2)	C13—C14	1.421 (3)
O4—C18	1.343 (3)	C13—C16	1.341 (3)
O4—C19	1.453 (3)	C14—C15	1.323 (3)
O5—C18	1.207 (3)		
C15—O1—C16	106.13 (18)	O2—C12—C13	105.37 (15)
C12—O2—C17	122.98 (15)	C14—C13—C16	105.08 (19)
C18—O4—C19	109.34 (17)	C13—C14—C15	107.7 (2)
C2—C1—C10	122.81 (18)	O1—C16—C13	110.6 (2)
C1—C2—C3	121.58 (19)	O2—C17—O3	116.77 (19)
C2—C3—C4	120.69 (18)	O4—C18—O5	122.1 (2)
C10—C1—C2—C3	12.4 (3)	C17—C8—C9—C10	−81.0 (2)
C2—C3—C4—C5	−23.0 (3)	O2—C12—C13—C14	94.1 (2)
C18—C4—C5—C19	33.58 (18)	O2—C12—C13—C16	−83.1 (2)
C7—C8—C9—C11	171.48 (16)		

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Table 2
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
C16—H16···O5^{i}	0.93	2.37	3.273 (4)	163

Symmetry code: (i) $-x, y-\frac{1}{2}, -z+\frac{1}{2}$.

All H atoms were found in difference Fourier maps and were included in the final refinement assuming idealized geometry, with C—H distances = 0.98, 0.97, 0.96 and 0.93 Å for tertiary CH, secondary CH_2, methyl CH_3 and aromatic CH atoms, respectively, and were refined with U_{iso}(H) values equal to $1.2U_{eq}$(parent atom). In the absence of significant anomalous scattering, Friedel pairs were merged; the absolute configuration was chosen according to the known absolute configuration of clerodin (Rogers *et al.*, 1979).

Data collection: *COLLECT* (Hooft, 1999); cell refinement: *DIRAX* (Duisenberg, 1992); data reduction: *COLLECT*; program(s) used to solve structure: *SIR97* (Altomare *et al.*, 1999); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97*.

The X-ray experiments were performed at the ‘Centro di Metodologie Chimico-Fisiche’ of University Federico II of Naples, using the equipment of the ‘Centro Regionale di Competenza Nuove Tecnologie per le Attività Produttive’ of Campania Region. First-instar larvae of *S. littoralis* were obtained from cultures maintained at the Instituto Sperimentale per il Tabacco, Scafati, Italy. This work is part of the project of the Regional Centre of Competence ‘Analysis and Monitoring of the Environmental Risk’ supported by the European Community on Provision 3.16.

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