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Dihydroparthenolide diol, a novel sesquiterpene lactone

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Key indicators

Single-crystal X-ray study
T = 300 K
Mean σ(C–C) = 0.003 Å
R factor = 0.044
wR factor = 0.128
Data-to-parameter ratio = 15.6

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

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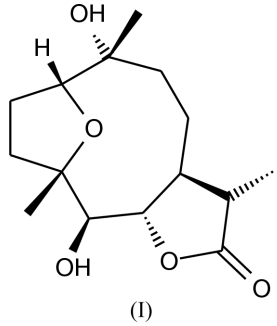
The title compound, 2,10-dihydroxy-1,6,10-trimethyl-4,14-dioxatricyclo[9.2.1.$0^{3,7}$]tetradecan-5-one, $C_{15}H_{24}O_5$, a novel sesquiterpene lactone synthesized from dihydroparthenolide, has a 1,4-furano bridge in the 10-membered ring and a *trans*-fused α-methyl-γ-lactone.

Comment

α,β-Unsaturated lactones have aroused much interest in medicine because of their remarkable biological properties, mainly as cytotoxic, antitumor, and bactericidal agents (El-Feraly & Chan, 1978). Among these compounds, sesquiterpenes (α-methylene-γ-lactones) have been intensively studied using both medicinal and chemical approaches (Picman, 1986). Recently, it has been shown that sesquiterpene lactones stimulate germination of Striga seeds at concentrations lower than 10^{-5} M (Rugutt, 1996). Striga (witchweed) are parasitic weeds that cause severe damage to graminaceous and leguminous crops in tropical and semi-tropical areas of the eastern hemisphere (Nour *et al.*, 1983).



(I)

We have recently begun a program aimed at the synthesis and separation (Shamsi & Warner, 1997) of antimycobacterial agents. Specifically, a long-range goal of our efforts in this area is to rationally design novel classes of drugs against the multidrug-resistant *Mycobacterium tuberculosis* and *M. avium*. It is important to recognize that dihydroparthenolide contains the 4,5-epoxide as a reactive receptor site. Although this epoxide function is not directly accessible due to steric hindrance of the associated medium ring structure, it provides increased reactivity as well as regio- and stereospecificity of subsequent intramolecular cyclizations. We envision that the reaction of dihydroparthenolide with OsO_4 leads to the formation of a 1,10-diol (both OH α-oriented). This diol undergoes a Markovnikov-type transannular cyclization to afford dihydroparthenolide diol, (I). In the 400 MHz ^{1}H NMR spectrum of (I), a doublet at δ 3.66 was attributed to H-5 which coupled with H-6. The signal of H-6 (δ 4.17) appeared as a well

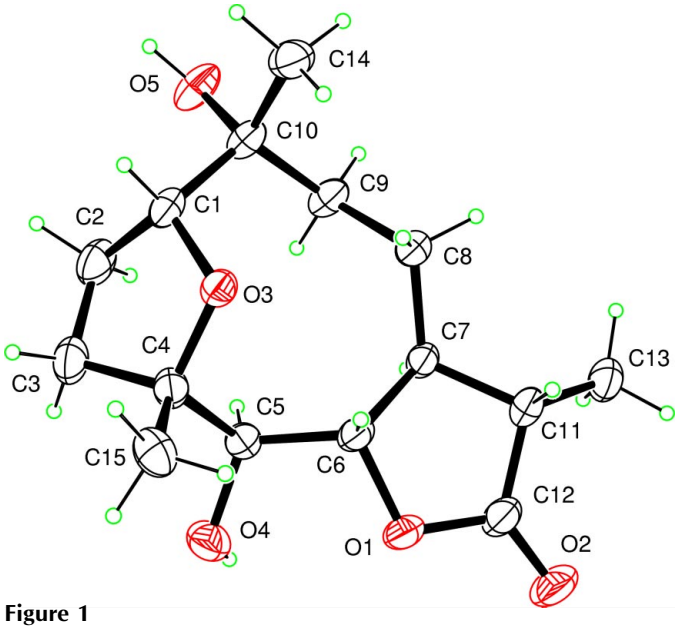


Figure 1
The atom-numbering scheme for (I) with ellipsoids at the 30% probability level.

defined one-proton doublet of doublets with large coupling constants ($J_{5,6}$ = 10.4 Hz; $J_{6,7}$ = 7.2 Hz). This indicated a *trans*-axial relationship between H-5, H-6 and H-7, *i.e.* H-5 α, H-6 β, and H-7 α-oriented. The stereochemistry of methylene proton resonances (which overlapped at δ 1.4–2.3) could not be determined from the NMR data. In order to unambiguously assign the stereochemistry of dihydroparthenolide diol, the crystal structure was determined.

The structure (Fig. 1) is identical to that of the naturally occurring achillifolin (Ulubelen *et al.*, 1990), except that the title compound has a β-methyl group and an α-OH at C10 rather than an exocyclic CH_2 group. The tetrahydrofuran ring has the half-chair conformation with O3 on the twist axis, and asymmetry parameter (Duax & Norton, 1995) $\Delta C_2 = 3.5^\circ$. The α-methyl-γ-lactone is *trans*-fused at C6—C7, and has its methyl group α-oriented, with C11 having the *S* configuration. The conformation of the lactone ring is an envelope, with C7 at the flap position, and asymmetry parameter $\Delta C_s = 1.0^\circ$. O—H···O hydrogen bonding (Table 2) forms chains in the [010] direction. The crystal structure of dihydroparthenolide has been reported (Rugutt & Rugutt, 1997).

Dihydroparthenolide diol and dihydroparthenolide were tested against *Mycobacterium tuberculosis* and *M. avium*. Stock solutions (10.24 mg ml^{-1}) were dissolved in DMSO and filter sterilized. The bioassay was performed by a broth dilution method as previously reported (Franzblau, 1989). The MIC of both compounds against *M. tuberculosis* and *M. avium* was 128 µg ml^{-1}. The minimum inhibitory concentration (MIC) is the lowest concentration of the compound needed to inhibit 99% of the organisms.

Experimental

The leaves of *Ambrosia artemisifolia* (1.0 kg) were exhaustively extracted by percolation with methanol following the method described by El-Feraly & Chan (1978). The methanol was evaporated *in vacuo* to afford 72 g of gummy residue, which was chromatographed on 800 g of silica gel and eluted with hexane and increasing amounts of ethyl acetate (EtOAc). Hexane–EtOAc (15:85) afforded fractions, which after repeated crystallizations from methanol yielded dihydroparthenolide as colorless needles. Dihydroparthenolide diol was synthesized by subjecting dihydroparthenolide to dihydroxylation (Norby *et al.*, 1999) with OsO_4 under catalytic conditions. To a cold solution of 4-methylmorpholine *N*-oxide (0.8 g, 4.4 mmol) in water (2.5 ml) and acetone (1.0 ml) was added a solution of OsO_4 (1% in ^{t}BuOH, 0.33 ml, 1.3 × 10^{-5} mol). Dihydroparthenolide (1.1 g, 4.4 mmol) was added, and the reaction mixture stirred for 20 h. The reaction mixture was chromatographed on silica gel (hexane–EtOAc (1:4)) to afford colorless crystals of dihydroparthenolide diol in 85% yield.

Crystal data

$C_{15}H_{24}O_5$
M_r = 284.34
Orthorhombic, $P2_12_12_1$
a = 9.2706 (13) Å
b = 10.4565 (8) Å
c = 15.094 (3) Å
V = 1463.2 (4) Å^3
Z = 4
D_x = 1.291 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 21.3–42.2°
μ = 0.79 mm^{-1}
T = 300 K
Fragment, colorless
0.38 × 0.32 × 0.17 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
ω–2θ scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.808, T_{max} = 0.875
3269 measured reflections
2975 independent reflections
2731 reflections with $I > 2\sigma(I)$
R_{int} = 0.018
θ_{max} = 76.0°
$h = 0 \rightarrow 11$
$k = 0 \rightarrow 13$
$l = -18 \rightarrow 18$
3 standard reflections
frequency: 40 min
intensity decay: 3.3%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.044
$wR(F^2)$ = 0.128
S = 1.07
2975 reflections
191 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0780P)^2 + 0.2091P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.17 e Å^{-3}
$\Delta\rho_{min}$ = −0.15 e Å^{-3}
Extinction correction: *SHELXL97*
Extinction coefficient: 0.0042 (7)
Absolute structure: (Flack, 1983), 1217 Friedel pairs
Flack parameter = −0.3 (2)

Table 1
Selected geometric parameters (°).

C4—O3—C1—C2	−9.1 (2)	C5—C6—C7—C8	77.2 (2)
O3—C1—C2—C3	27.9 (2)	O1—C6—C7—C11	−38.4 (2)
C10—C1—C2—C3	149.75 (18)	C6—C7—C8—C9	−85.3 (2)
C1—C2—C3—C4	−35.5 (2)	C7—C8—C9—C10	123.2 (2)
C1—O3—C4—C3	−13.5 (2)	C2—C1—C10—C9	−73.0 (2)
C2—C3—C4—O3	30.6 (2)	C8—C9—C10—C1	−74.7 (3)
C2—C3—C4—C5	−84.1 (2)	C6—C7—C11—C12	37.16 (19)
C3—C4—C5—C6	159.33 (18)	C6—O1—C12—C11	−0.7 (3)
C12—O1—C6—C7	25.4 (2)	C7—C11—C12—O1	−24.2 (2)
C4—C5—C6—C7	−105.9 (2)		

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

D—H···A	D—H	H···A	D···A	D—H···A
O4—H4O···O5^{i}	0.90 (4)	2.06 (4)	2.895 (3)	154 (3)
O5—H5O···O2^{ii}	0.92 (4)	1.94 (4)	2.821 (2)	160 (3)

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

The absolute configuration was determined by refinement of the Flack parameter. The reported configuration, which agrees with that of sesquiterpene lactones from higher plants (Fischer *et al.*, 1979), yielded $x = -0.3\,(2)$, while the inverse configuration yielded $x = 1.3\,(2)$. The OH H-atom positions were located in a difference Fourier map and refined isotropically, with $U_{iso} = 1.5U_{eq}(O)$. Other H atoms were placed in calculated positions with C—H bond distances 0.97 (CH), 0.97 (CH_2) and 0.96 Å (CH_3), $U_{iso} = 1.2U_{eq}$ of the attached C atom (1.5 for methyl), and thereafter treated as riding. A torsional parameter was refined for each methyl group.

Data collection: *CAD*-4 *EXPRESS* (Enraf–Nonius, 1994); cell refinement: *CAD*-4 *EXPRESS*; data reduction: *maXus* (Mackay *et al.*, 1999); program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*III (Burnett & Johnson, 1996); software used to prepare material for publication: *SHELXL*97.

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