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Arjunolic acid

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.008 Å
R factor = 0.050
wR factor = 0.164
Data-to-parameter ratio = 9.3

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

The title compound, 2α,3β-24-trihydroxyolean-12-en-28-oic acid, $C_{30}H_{48}O_5$, is a stereoisomer of hyptatic acid A (2α,3β-24-trihydroxyolean-12-en-28-oic methanolate). The central ring, which is flattened due to the presence of a C═C double bond, adopts a sofa conformation. All other six-membered rings adopt distorted chair conformations. The crystal structure is stabilized by O—H···O hydrogen bonds.

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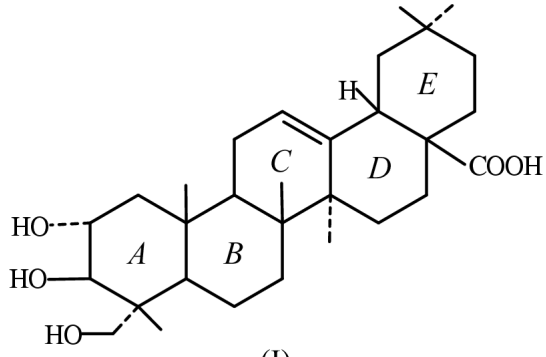
Comment

Arjunolic acid, (I), is the principal constituent of *Terminalia Arjuna*, which belongs to the family *combretaceae* and is an important medicinal plant found in India (Chopra *et al.*, 1956; Nadkarni & Nadkarni, 1976). It was first isolated from the plant by King *et al.* (1954). *Terminalia Arjuna* is used in the indigenous system of medicine, primarily as a cardiotonic.



(I)

Clinical evaluation of this plant indicates that it can be of benefit in the treatment of coronary artery disease, heart failures and possibly hypercholesterolemia, and it has also been found to have antibacterial and antimutagenic properties (Tripathi *et al.*, 1996). Arjunolic acid has been shown to provide significant cardiac protection in isoproterenol-induced myocardial necrosis in rats. Arjunolic acid treatment is also shown to prevent the decrease in the levels of superoxide dismutase, catalase, glutathione peroxidase, ceruloplasmin, α-tocopherol, reduced glutathione, ascorbic acid, lipid peroxide and myeloperoxidase, and the cardioprotection is confirmed by histopathological studies (Sumitra *et al.*, 2001). Arjunolic acid isolated from the rhizome of *Cocholspermum tinctorium*, its triacetate derivative and its methyl esters were tested using the short-term *in vitro* assay on EBV–EA activation in Raji cells induced by 12-*O*-tetradecanoylphorbol-13-acetate (TPA). Their inhibitory effects on skin-tumor promotors were found to be greater than those of the previously studied natural products (Diallo *et al.*, 1989). Also

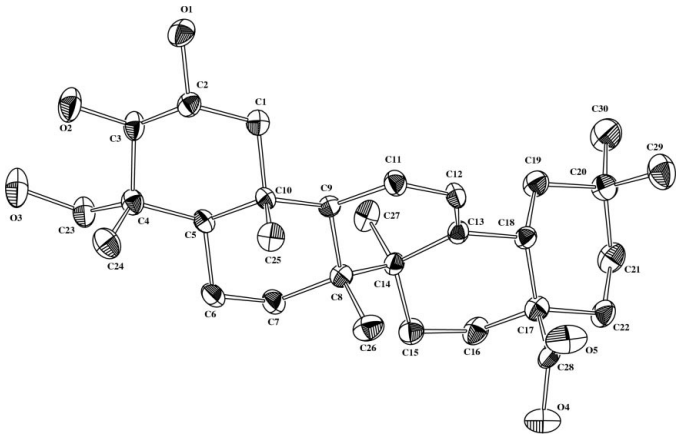


Figure 1
The molecular structure of the title compound, with 30% probability displacement ellipsoids

the compound demonstrated significant *in vitro* cytotoxicity in human colon HCT-8 tumor cells (Yamagishi *et al.*, 1988). In view of its medical importance, the crystal and molecular structure of arjunolic acid, (I), was determined.

The structure determination shows that (I) is a stereoisomer of hyptatic acid A ($2\alpha,3\beta$ 24-trihydroxyolean-12-en-28-oic methanolate), isolated from *Hyptis Capitata*, with the $-CH_3$ and $-CH_2OH$ attachments at the C4 atom interchanged (Fig. 1). Hyptatic acid A has been found to crystallize with two molecules (*A* and *B*) per asymmetric unit, with methanol as solvent of crystallization (Yamagishi *et al.*, 1988). Superposition of the non-H atoms of the arjunolic acid molecule (except O3) with each of the two independent molecules of hyptatic acid A, using *BIOSYM* (Biosym/MSI, 1995) shows that the r.m.s. deviation is 0.26 Å for molecule *A* and 0.28 Å for molecule *B*. Some of the bond lengths in (I) are found to be longer than the normal values and some angles are also widened due to steric overcrowding of axial methyl groups. However, these values are comparable with the corresponding values observed for molecules containing the same steroid skeleton. In the Cambridge Structural Database (1992), 29 structures were found to have the same steroid skeleton as arjunolic acid. Of these, 19 structures had an *R* factor less than 6.0% and, from the data for these structures, the mean geometry of the molecular skeleton was determined. The bond lengths and angles which have large values in arjunolic acid are compared with the corresponding values of the average molecular skeleton and are listed Table 1. This shows that the geometry of arjunolic acid is similar to the average molecular skeleton.

The puckering parameters, evaluated using *PARST* (Nardelli, 1995), show that the six-membered rings *A* and *E* adopt chair conformations [$Q_T = 0.552$ (6), $q_2 = 0.040$ (6) Å, $\varphi_2 = 96$ (7)° for ring *A*; $Q_T = 0.535$ (6), $q_2 = 0.066$ (6) Å, $\varphi_2 = -3$ (5)° for ring *E*] and rings *B* and *D* adopt slightly distorted chair conformations [$Q_T = 0.579$ (6), $q_2 = 0.158$ (6) Å, $\varphi_2 = 4$ (2)° for ring *B*; $Q_T = 0.513$ (6), $q_2 = 0.158$ (6) Å, $\varphi_2 = 29$ (2)° for ring *D*]. Ring *C* is in a slightly distorted sofa conformation due to the flattening caused by the C12═C13 double bond [$Q_T = 0.545$ (6), $q_2 = 0.404$ (6) Å, $\varphi_2 = 14.0$ (9)°]. All the fused rings have *trans* fusion except *D*/*E*, which is in *cis* fusion. The H atom at C18 and the carboxyl group at C17 are in β positions. The non-bonded distances between C atoms of diaxial methyl groups C24···C25 and C25···C26 are 3.323 (9) and 3.307 (9) Å, respectively. In a six-membered ring, the non-bonded distances between 1,3 diaxial methyl groups would be 2.52 Å if the ring adopted a regular chair form (Spirlet *et al.*, 1980). The structure is stabilized by O—H···O intra- and intermolecular hydrogen bonds (Table 2).

Experimental

The title compound was successively extracted from the dried and powdered heartwood (4 kg) of the plant *Terminalia Arjuna* with ethyl acetate in the cold (72 h). The extract was diluted with a little ethyl acetate and heated on a water bath to produce a dark red–brown solution which was allowed to stand overnight at room temperature. The pale-yellow solid which precipitated was filtered and washed with ethyl acetate (yield: 48 g). The crude arjunolic acid thus obtained was passed through a column of silica gel packed in chloroform. The column was eluted with chloroform and then with chloroform containing methanol in increasing proportions. Elution of the column with a chloroform–methanol (9:1) solvent mixture gave arjunolic acid (m.p. 569 K, 43 g) and crystals suitable for X-ray diffraction analysis were grown by slow evaporation from a methanol solution.

Crystal data

$C_{30}H_{48}O_5$
$M_r = 488.68$
Orthorhombic, $P2_12_12_1$
$a = 11.580$ (2) Å
$b = 14.623$ (2) Å
$c = 15.952$ (4) Å
$V = 2701.2$ (9) Å^3
$Z = 4$
$D_x = 1.202$ Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
$\theta = 14$–25°
$\mu = 0.63$ mm^{-1}
$T = 293$ (2) K
Needle, colorless
0.22 × 0.13 × 0.10 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
ω–2θ scans
Absorption correction: none
2962 measured reflections
2962 independent reflections
1388 reflections with $I > 2\sigma(I)$
$\theta_{max} = 71.9°$
$h = 0 \rightarrow 14$
$k = 0 \rightarrow 17$
$l = 0 \rightarrow 19$
3 standard reflections
frequency: 120 min
intensity decay: <1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.050$
$wR(F^2) = 0.164$
$S = 0.96$
2962 reflections
317 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0781P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.23$ e Å^{-3}
$\Delta\rho_{min} = -0.19$ e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0021 (4)

Table 1
Comparison of the unusually large bond lengths and angles (Å, °) in the skleton of arjunolic acid with those found in the average skeleton of related structures.

Bond	Arjunolic Acid	Average
C4—C5	1.570 (7)	1.563 (9)
C5—C10	1.557 (8)	1.552 (8)
C9—C10	1.562 (7)	1.570 (10)
C7—C8	1.551 (8)	1.541 (8)
C8—C9	1.565 (8)	1.553 (8)
C8—C14	1.578 (8)	1.589 (6)
C17—C22	1.559 (7)	1.546 (13)
C2—C3—C4	114.6 (5)	114.2 (12)
C1—C2—C3	110.9 (5)	111.0 (12)
C10—C1—C2	113.4 (5)	113.5 (11)
C4—C5—C10	117.1 (5)	117.0 (9)
C4—C5—C6	115.0 (4)	114.4 (5)
C6—C7—C8	115.5 (5)	114.1 (7)
C7—C8—C14	110.7 (4)	110.5 (5)
C8—C9—C10	118.2 (5)	117.5 (8)
C10—C9—C11	113.8 (4)	113.2 (6)
C14—C15—C16	115.7 (5)	114.6 (5)
C15—C16—C17	110.9 (5)	112.4 (7)
C16—C17—C18	109.9 (5)	108.7 (11)
C16—C17—C22	110.8 (5)	112.0 (13)
C18—C17—C22	111.7 (5)	110.2 (12)
C17—C18—C13	110.9 (5)	112.3 (9)
C17—C18—C19	112.5 (5)	112.8 (10)
C13—C18—C19	114.2 (5)	111.9 (15)
C18—C19—C20	114.1 (5)	114 (2)
C20—C21—C22	112.9 (5)	112.8 (14)
C21—C22—C17	114.0 (5)	114.4 (10)

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

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1O···O5^{i}	0.82	1.96	2.744 (6)	160
O3—H3O···O2	0.82	1.93	2.665 (6)	148
O4—H4O···O3^{ii}	0.82	1.82	2.642 (7)	174

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

All H atoms were placed in calculated positions, refined using a riding model, and given an isotropic displacement parameter equal to 1.2 times the equivalent isotropic parameter of their parent C atoms and 1.5 times the equivalent isotropic parameter of their parent O atoms. The C—H and O—H distances used depend on the type of atom. As a result of the poor diffraction quality of the crystal, the ratio of observed to unique reflections is low. The absolute configuration could not be determined by standard refinement of the Flack (1983) parameter in the absence of strong anomalous dispersion effects and Friedel opposites. It was established by a new technique based on reflections that are most affected by the anomalous dispersion of the O atoms (Parthasarathy & Abdul Ajees, 2002); the main conclusions of this report do not depend on the absolute configuration.

Data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989); cell refinement: *SDP* (Frenz, 1978); data reduction: *CAD*-4 *Software*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ZORTEP* (Zsolnai, 1995); software used to prepare material for publication: *PARST*97 (Nardelli, 1995) and *PLATON* (Spek, 2000).

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