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9,10-Dehydrodeoxyartemisinin

Shu-Hui Li, Zheng-Yu Yue,* Po Gao and Peng-Fei Yan

School of Chemistry and Materials Science, Heilongjiang University, Harbin 150080, People's Republic of China

Correspondence e-mail: yuezhengyu@vip.sina.com

Key indicators

Single-crystal X-ray study
T = 295 K
Mean σ(C–C) = 0.003 Å
R factor = 0.035
wR factor = 0.101
Data-to-parameter ratio = 10.8

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

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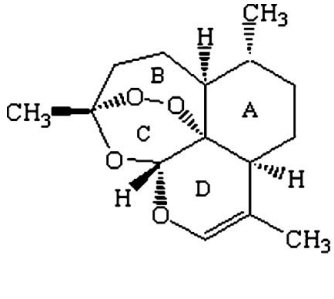
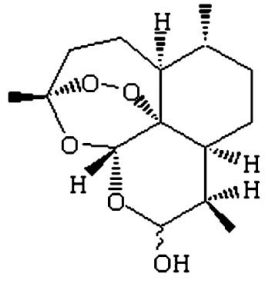
The title compound, $C_{15}H_{22}O_4$, obtained from the dehydration of dihydroartemisinin, has retained the endoperoxide bridge of the parent compound along with the C═C bond. The six-membered rings exhibit chair, twist–boat and envelope conformations.

Comment

Dihydroartemisinin, (II), derived from artemisinin, is found to possess antimalarial activity on account of the retention of the endoperoxide bridge of the parent compound (Posner & O'Neill, 2004). The title compound, 9,10-dehydrodeoxy-artemisinin, (I), a dehydrated product of (II), shows the same antimalarial activity as artemisinin (Li *et al.*, 1981). It is also a key intermediate in the synthesis of artemisinin derivatives (Lin *et al.*, 1990; El-Feraly *et al.*, 1990). The X-ray crystal structure of artemisinin (Qinghaosu Research Group, 1980) and artemisinin derivatives have been reported, including dihydroartemisinin, artemether, artesunic acid (Luo *et al.*, 1984), both *cis* (Brossi *et al.*, 1988) and *trans* (Dominguez Gerpe *et al.*, 1988) deoxyarteether, a symmetric form of the ether dimer of deoxydihydroartemisinin (Flippen-Anderson *et al.*, 1989), and α-artesunate and β-artesunate (Haynes *et al.*, 2002). We report here the crystal structure of the title compound, (I).



9,10-dehydrodeoxyartemisinin, (I)



Dihydroartemisinin (α+β), (II)

A view of the molecular structure of (I) is given in Fig. 1. Attempts to determine the absolute configuration of the molecule were inconclusive, but (I) can be assigned the illustrated configuration since the chirality of the starting material is known. Furthermore, the conformation of the compound is essentially the same as the corresponding conformation of the crystal structure of (II) (Luo *et al.*, 1984). Owing to the presence of the C═C bond in (I), the C1—O1—C14 bond angle of 118.78 (15)° is reduced from 124.2 (4)°, found for the corresponding angle in (II), while the C1—C2—C4 bond angle of 119.78 (17)° is expanded from that of 115.3 (4)° found in (II) (Qinghaosu Research Group, 1980).

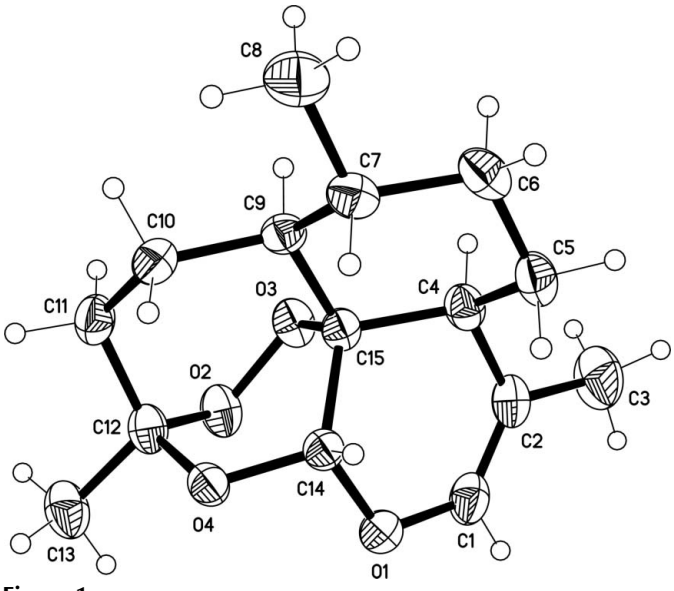


Figure 1
Molecular structure of (I), with displacement ellipsoids drawn at the 30% probability level.

Crystal data

$C_{15}H_{22}O_4$
M_r = 266.33
Orthorhombic, $P2_12_12_1$
a = 6.2460 (12) Å
b = 9.0416 (18) Å
c = 25.132 (5) Å
V = 1419.3 (5) Å^3
Z = 4
D_x = 1.246 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 0.09 mm^{-1}
T = 295 (2) K
Prism, colorless
0.36 × 0.25 × 0.18 mm

Data collection

Rigaku R-AXIS RAPID diffractometer
ω scans
Absorption correction: multi-scan (*ABSCOR*; Higashi, 1995)
T_{min} = 0.962, T_{max} = 0.978
13861 measured reflections
1896 independent reflections
1658 reflections with $I > 2\sigma(I)$
R_{int} = 0.021
θ_{max} = 27.4°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.035
$wR(F^2)$ = 0.101
S = 1.09
1896 reflections
175 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0671P)^2 + 0.0449P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.22 e Å^{-3}
$\Delta\rho_{min}$ = −0.11 e Å^{-3}

The six-membered ring *A* (C4–C7/C9/C15; scheme 1) has a slightly distorted chair conformation, with Cremer & Pople (1975) puckering parameters of Q = 0.537 (2) Å, θ = 5.2 (2)° and φ = 79 (2)°. For an ideal chair, θ has a value of 0 or 180°. By contrast, the corresponding six-membered ring in (II) has a normal chair conformation (Luo *et al.*, 1984). The seven-membered ring *B* (C9–C12/O2/O3/C15) contains the key peroxy linkage [O2—O3 = 1.4670 (18) Å]. The six-membered ring *C* (O2/O3/C15/C14/O4/C12) including an oxygen bridge and a peroxy bridge is best described by a twist–boat conformation, for which the puckering parameters, Q, θ and φ, are 0.7441 (17) Å, 95.48 (12)° and 155.61 (12)°, respectively. For an ideal twist–boat conformation, θ and φ are 90° and $(60n + 30)$°, respectively. This conformation is consistent with those of artemisinin (Qinghaosu Research Group, 1980), (II), and artemether (Luo *et al.*, 1984). The six-membered ring *D* (O1/C1/C2/C4/C15/C14) has a double bond [C1═C2 = 1.314 (3) Å]. It is best described by an envelope conformation, for which the puckering parameters, Q, θ and φ, are 0.4322 (18) Å, 53.4 (3)° and 236.5 (3)°. For an ideal envelope conformation, θ and φ are 54.7° and $60n$°, respectively.

Experimental

Compound (I) was prepared according to a literature procedure (Posner *et al.*, 1997). To a solution of (II) (599 mg, 2.11 mmol) in toluene (60 ml) was added triethylene glycol (0.144 ml, 1.06 mmol) followed by $BF_3{\cdot}Et_2O$ (0.064 ml, 0.53 mmol). The reaction was stirred at room temperature for 3 h. The mixture was then diluted with CH_2Cl_2 and washed twice with water. The organic portion was collected, dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography (flash, 5–50% ethyl acetate/hexane) to produce (I) (125 mg, yield 22.3%). Crystals were obtained from a hexane solution of (I) by slow evaporation at room temperature. Analysis calculated for $C_{15}H_{22}O_4$: C 67.65, H 8.33%; found: C 67.62, H 8.35%.

The methyl H atoms were constrained to an ideal geometry [C—H = 0.96 Å, with U_{iso}(H) = 1.5U_{eq}(C)] but were allowed to rotate freely about the C—C bonds. All other H atoms were placed in geometrically idealized positions and constrained to ride on their parent C atoms at distances of 0.93, 0.97 or 0.98 Å for alkene, methylene or methine groups, respectively, and with U_{iso}(H) = 1.2U_{eq}(C). In the absence of significant anomalous scattering, Friedel pairs were merged before the final refinement and the absolute configuration was assigned to correspond to that determined for artemisinin (Qinghaosu Research Group, 1980).

Data collection: *RAPID-AUTO* (Rigaku Corporation, 1998); cell refinement: *RAPID-AUTO*; data reduction: *CrystalStructure* (Rigaku/MSC, 2002); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEPII* (Johnson, 1976); software used to prepare material for publication: *SHELXL97*.

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