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A dimer of α- and β-dihydroartemisinin: bis(3,6,9-trimethyl-3,12-epidioxy-3,4,5,5a,6,7,8,8a,9,10-decahydro-12*H*-pyrano[4,3-*j*][1,2]benzodioxepin-10-yl) ether

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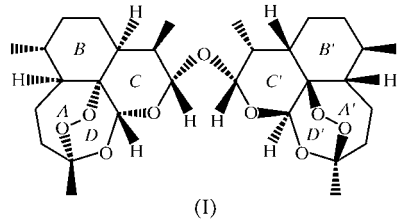
The title compound, $C_{30}H_{46}O_9$, prepared from a mixture of α- and β-dihydroartemisinin, has α- and β-arteether moieties linked *via* an –O– bridge, so that the molecule is asymmetric about the bridge. The endoperoxide bridges of the parent compounds have been retained in each half of the ether-bridged dimer. The rings exhibit chair and twist–boat conformations.

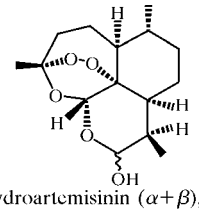
Comment

Dihydroartemisinin, (II), derived from artemisinin with retention of the endoperoxide bridge, is found to possess antimalarial activity (Posner & O'Neill, 2004). The dimers have both antimalarial and antitumor activities (Beekman *et al.*, 1997). The ether linkage itself can yield considerable cytotoxicity to EN2 tumor cells, particularly when the ether linkage is asymmetric (Beekman *et al.*, 1997). The endoperoxide group is also an important determinant for cytotoxicity. In the endoperoxides tested, the asymmetric dimer was 22 times more cytotoxic than artemisinin and 60 times more cytotoxic than dihydroartemisinin (Woerdenbag *et al.*, 1993). Hence, knowledge of the structure of the title compound, (I), is of interest.

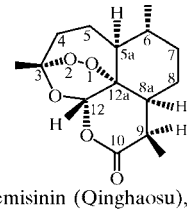
The crystal structures of artemisinin (Qinghaosu), (III) (Qinghaosu Research Group, 1980), and its derivatives have been reported, including dihydroartemisinin, artemether, artesunic acid (Luo *et al.*, 1984), both *cis*- (Brossi *et al.*, 1988) and *trans*-deoxyarteether (Dominguez Gerpe *et al.*, 1988), α-artesunate, β-artesunate (Haynes *et al.*, 2002), and the symmetric form of the ether dimer of deoxydihydroartemisinin (Flippen-Anderson *et al.*, 1989). Although the endoperoxide group is an important determinant for cytotoxicity, no crystal structure of an ether dimer of dihydroartemisinin with a peroxy unit has been reported previously. We report here the crystal structure of the title compound, which is an ether dimer of dihydroartemisinin with a unique 1,2,4-trioxane peroxy bridge.



(I)



Dihydroartemisinin (α+β), (II)



Artemisinin (Qinghaosu), (III)

A view of the molecular structure of (I) with the atom numbering is provided in Fig. 1. Attempts to determine the absolute configuration of the molecule were inconclusive, but the title compound can be placed in the illustrated configuration since the chirality of the starting materials is known (Qinghaosu Research Group, 1980). The overall conformation on each side of the ether linkage of (I) is essentially the same as that found in the crystal structure of dihydroartemisinin (Luo *et al.*, 1984). The orientation of the two dihydroartemisinin moieties about the ether linkage is such that the C10—H10 and C25—H25 bonds are almost parallel. This orientation gives the molecule almost pseudo-C_2 symmetry. The only configurational difference between the two halves of the molecule is that atom C10 has an *R* configuration, which corresponds to the situation in α-dihydroartemisinin (the H atoms at atoms C9 and C10 are *trans* oriented), while atom C25 has an *S* configuration of β-dihydroartemisinin (the H atoms at atoms C24 and C25 are *cis* oriented).

The seven-membered rings *A* (C1–C4/C12/O2/O1) and *A*′ (C16–C19/C27/O9/O8) include the key peroxy linkages [O1—O2 = 1.467 (4) Å and O8—O9 = 1.461 (3) Å]. The six-membered rings *B* (C4–C8/C12) and *B*′ (C19–C23/C27) have

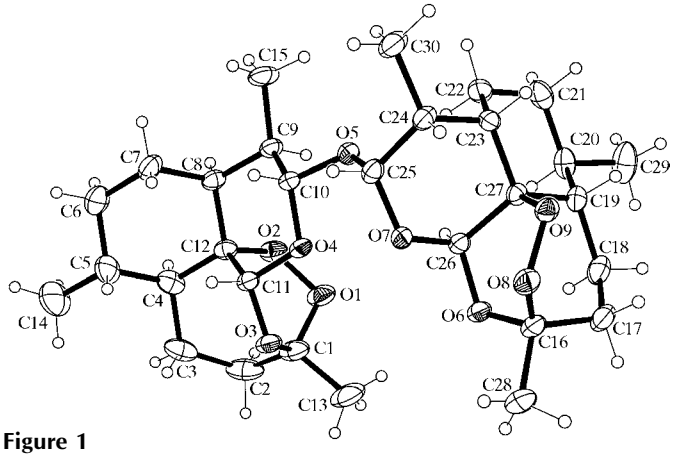


Figure 1
A view of the title compound, showing the atom-labeling scheme and displacement ellipsoids drawn at the 30% probability level.

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very slightly distorted chair conformations, with Cremer & Pople (1975) puckering parameters Q, θ and φ of 0.537 (5) Å, 175.4 (4)° and 327 (7)° for ring *B*, and 0.528 (4) Å, 173.4 (4)° and 330 (3)° for ring *B*′. For an ideal chair, θ has a value of 0 or 180°. The six-membered rings *C* (C8–C10/O4/C11/C12) and *C*′ (C23–C25/O7/C26/C27) have normal chair conformations, with puckering parameters Q, θ and φ of 0.550 (3) Å, 4.4 (3)° and 66 (4)° for ring *C*, and 0.536 (3) Å, 3.8 (3)° and 110 (5)° for ring *C*′. The same conformations were found in the corresponding six-membered rings of dihydroartemisinin (Luo *et al.*, 1984). The six-membered rings involving the endoperoxide bridges, *viz*. *D* (C1/O1/O2/C12/C11/O3) and *D*′ (C16/O8/O9/C27/C26/O6), are best described by a twist–boat conformation, for which the puckering parameters Q, θ and φ are 0.741 (4) Å, 85.6 (2)° and 36.7 (2)° for ring *D*, and 0.740 (3) Å, 85.5 (2)° and 35.5 (2)° for ring *D*′. For an ideal twist–boat conformation, θ and φ are 90 and $(60n + 30)$°, respectively. In contrast, the six-membered ring formed by the endoperoxide bridge in dihydroartemisinin has a somewhat distorted boat conformation.

Experimental

The title compound was prepared according to the procedure reported by Posner *et al.* (1997). To a solution of dihydroartemisinin (599 mg, 2.11 mmol) in toluene (60 ml) at 293–298 K 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 the same temperature for 3 h. The mixture was then diluted with methylene chloride and washed twice with water. The organic portions were collected, dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography (flash, 5–50% ethyl acetate/hexane) to produce compound (I) (203 mg, 0.368 mmol, yield 35%). Crystals were obtained from hexane by slow evaporation at room temperature. Analysis calculated for $C_{30}H_{46}O_9$: C 65.43, H 8.42%; found: C 65.40, H 8.38%.

Crystal data

$C_{30}H_{46}O_9$
M_r = 550.67
Monoclinic, $P2_1$
a = 10.338 (2) Å
b = 12.012 (2) Å
c = 12.065 (2) Å
β = 93.39 (3)°
V = 1495.6 (5) Å^3
Z = 2
D_x = 1.223 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 13709 reflections
θ = 3.0–27.5°
μ = 0.09 mm^{-1}
T = 295 (2) K
Block, colorless
0.42 × 0.30 × 0.23 mm

Data collection

Rigaku R-AXIS RAPID diffractometer
ω scan
Absorption correction: multi-scan (*ABSCOR*; Higashi, 1995)
T_{min} = 0.935, T_{max} = 0.972
14678 measured reflections
3576 independent reflections
2877 reflections with $I > 2\sigma(I)$
R_{int} = 0.069
θ_{max} = 27.5°
$h = -13 \rightarrow 13$
$k = -14 \rightarrow 15$
$l = -15 \rightarrow 15$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.058
$wR(F^2)$ = 0.156
S = 1.10
3576 reflections
358 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0947P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.29 e Å^{-3}
$\Delta\rho_{min}$ = −0.20 e Å^{-3}

The methyl H atoms were constrained to an ideal geometry [C—H = 0.96 Å and 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 0.97 and 0.98 Å for methylene and methine groups, respectively [U_{iso}(H) = 1.2U_{eq}(C)]. As there are no significant anomalous scatterers in the molecule, attempts to confirm the absolute structure by refinement of the Flack parameter (Flack & Bernardinelli, 2000) in the presence of 2761 sets of Friedel equivalents led to an inconclusive value for the parameter. Therefore, 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, 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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Supplementary data for this paper are available from the IUCr electronic archives (Reference: LN1194). Services for accessing these data are described at the back of the journal.

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