(−)-Dioxosantadienic acid: hydrogen-bonding patterns in a bicyclic sesquiterpenoid keto acid and its monohydrate

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The anhydrous form, (I), of the title compound, (−)-2-(1,2,3,4,4a,7-hexahydro-4a,8-dimethyl-1,7-dioxo-2-naphthyl)-propionic acid, $C_{15}H_{18}O_4$, derived from a naturally occurring sesquiterpenoid, has two molecules in the asymmetric unit, (I) and (I′), differing in the conformations of the saturated ring and the carboxyl group. The compound aggregates as carboxyl-to-ketone hydrogen-bonding catemers [O···O = 2.776 (3) and 2.775 (3) Å]. Two crystallographically independent sets of single-strand hydrogen-bonding helices with opposite end-to-end orientation pass through the cell in the b direction, one consisting exclusively of molecules of (I) and the other entirely of (I′). Three C—H···O=C close contacts are found in (I). The monohydrate, $C_{15}H_{18}O_4 \cdot H_2O$, (II), with two molecules of (I) plus two water molecules in its asymmetric unit, forms a complex three-dimensional hydrogen-bonding network including acid-to-water, water-to-acid, water-to-ketone, water-to-water and acid-to-acid hydrogen bonds, plus three C—H···O=C close contacts. In both (I) and (II), only the ketone remote from the acid is involved in hydrogen bonding.

Comment

Our continuing interest in the crystallography of keto carboxylic acids lies in exploring the molecular characteristics that control the various hydrogen-bonding patterns. Functionally unelaborated acids, with one hydrogen-bond donor and one receptor, usually aggregate in the solid as dimers, rarely as catemers (chains). Appending a ketone function provides an excess of receptors and creates opportunities for at least three additional hydrogen-bonding modes. The commonest of these, the acid-to-ketone catemer, forms a sizeable overall minority of keto acid hydrogen-bonding cases and, in the presence of certain molecular features, becomes the dominant hydrogen-bonding mode (Brunskill et al., 1997).

As we have previously suggested, carboxyl dimerization is discouraged by the presence of conformational restrictions (Brunskill et al., 1999) or of only one enantiomer (Lalancette et al., 1998). A factor that may favour carboxyl-to-ketone hydrogen-bonding patterns is the presence of multiple ketone receptors for the hydrogen bond (Brunskill et al., 1999). The title compound, (I), derived from a sesquiterpene isolate of Artemisia, is a bicyclic γ,ζ-diketo acid, present as a single enantiomer, and we report here that (I) adopts the carboxyl-to-ketone catemeric hydrogen-bonding mode in the solid state and also crystallizes as a monohydrate, (II), with a complex hydrogen-bonding pattern.
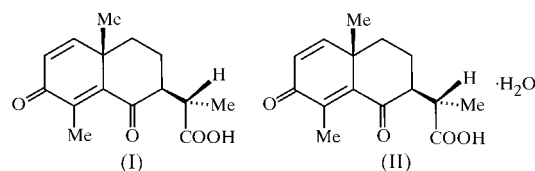

Fig. 1 shows the asymmetric unit of the anhydrous material, consisting of two molecules, (I) and (I′), which differ slightly in the flexure of the saturated ring and in the rotation of the carboxyl about the C9—C10 bond. The major conformational options lie in the branched chain attached at C2. Here, the substituents at C9, which has the S configuration, are staggered with respect to those at C2, so that the methyl is anti to C1; the C11—C9—C2—C1 torsion angle is 178.5 (2)° in (I) and −173.7 (2)° in (I′), a difference of 7.8 (2)°. In both (I) and (I′), the carboxyl group is turned so that its C=O group is away from the molecular face bearing the angular methyl, but in (I), the O3—C10—C9—C2 torsion angle is 41.3 (4)°, while in (I′), it is 26.6 (4)°, a difference of 14.7 (4)°. In both species, the dienone ring is essentially planar, providing strong conjugation for the O2 ketone, but the saturated-ring ketone is rotated significantly from the conjugation plane; the dihedral angle for C1—C2—C8a—O1 versus the dienone ring is 52.00 (12)° for (I) and 58.17 (9)° for (I′).

The partial averaging of C—O bond lengths and C—C—O angles by disorder, often seen in acids, is unique to the carboxyl-pairing pattern of hydrogen bonding, whose geometry permits transposition of the two carboxyl O atoms.
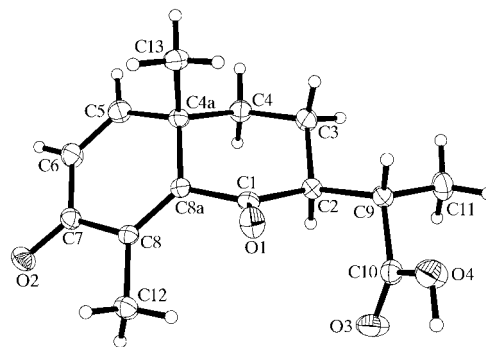
Figure 1
The molecular view of one of the two molecules in the asymmetric unit of (I), with the atom-numbering scheme. Displacement ellipsoids are drawn at the 20% probability level and H atoms are shown as spheres of arbitrary radii.

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As in other catemers, no significant averaging is observed for (I), whose bond lengths are 1.196 (3) and 1.333 (4) Å, with angles of 124.8 (3) and 112.1 (3)°. For (I′), the bond lengths are 1.196 (3) and 1.328 (3) Å, with angles of 124.8 (3) and 112.7 (2)°. Our own survey of 56 keto acid structures which are not acid dimers gives average values of 1.20 (1) and 1.32 (2) Å, and 124.5 (14) and 112.7 (17)° for these bond lengths and angles, in accord with the typical values of 1.21 and 1.31 Å, and 123 and 112° cited for highly ordered dimeric carboxyls (Borthwick, 1980). The three methyl groups are fully ordered in both (I) and (I′), and staggered relative to the substituents at their points of attachment.

Fig. 2 illustrates the packing of (I) and (I′) in the cell, with extracellular molecules included to show the two crystallographically independent single-strand hydrogen-bonding catemers; one chain consists entirely of molecules of (I), while the other is made up exclusively of (I′). Each chain proceeds from the carboxyl of one molecule to the remote ketone (O2) of a neighbour. Among hydrogen-bonding catemers, the observed prevalence of subtypes, describing the relation of adjacent molecules, is screw > translation > glide, with the chains often following a cell axis. Here, the components of each chain are related by a twofold screw axis along **b**; the axis for helices of type (I) lies in the *ab* face of the chosen cell, while the counterdirectionally aligned type (I′) helices follow an axis lying in the *bc* face. The intermolecular O···O distance
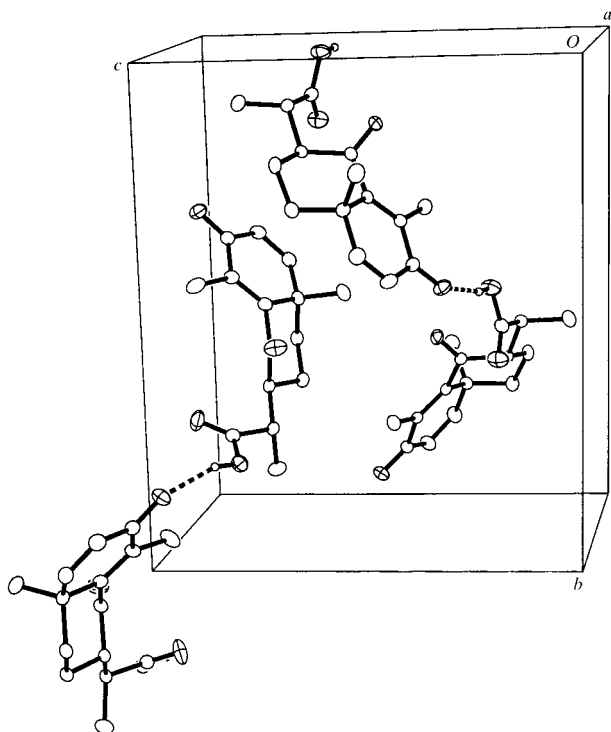

Figure 2
A packing diagram for (I), with two extracellular molecules to illustrate the two kinds of single-strand helical catemer proceeding in the *b* direction. Those of type (I) follow an axis in the *ab* face, and those of type (I′) an axis in the *bc* face. Methylene and methine H atoms have been omitted for clarity. Displacement ellipsoids are drawn at the 20% probability level.

and O—H···O angle are 2.776 (3) Å and 165°, respectively, within the type (I) chains, and 2.775 (3) Å and 160°, respectively, within the type (I′) chains.

Consistent with the 14.7 (4)° difference found between (I) and (I′) for the rotation of the COOH group about C9—C10, the intramolecular ketone *versus* carboxyl dihedral angles for (I) and (I′) differ by only 14.7 (4)°. However, the intermolecular ketone *versus* carboxyl dihedral angles for screw-related molecules involved in hydrogen bonding are markedly different for the two types of chains; these values are 26.4 (4)° for the type (I) chains and 78.9 (2)° for type (I′) chains. This difference is not related to the helical 'pitches' of the two helices (Coté *et al.*, 1997), which are found to be nearly identical, at 36.9° for (I) and 36.6° for (I′); it is a product of the different orientations of (I) and (I′) relative to the *b* axis, about which they are rotated in the symmetry operation that generates their hydrogen-bonding partners. The result is hydrogen-bonding helices with identical periods and pitches but significantly different footprints on the *ac* face for the two types of helices. Although the intermolecular dihedral angles cited above differ by more than 75°, the geometry of the hydrogen bonding itself for (I) *versus* (I′) is remarkably similar. We characterize the geometry of hydrogen bonding to carbonyls using a combination of the H···O=C angle and the H···O=C—C torsion angle. These describe the approach of the H atom to the O atom in terms of its deviation from, respectively, C=O axiality (ideal 120°) and planarity with the carbonyl (ideal 0°). In (I), these angles are 143.7 and 9.2°, respectively, while in (I′), the same angles are 141.3 and 5.6°.

Intermolecular C—H···O close contacts were found involving O3 (2.51 Å to H13*C* in a molecule in the *a* direction), O1 (2.55 Å to H6*A* in a molecule in the *b* direction), and O3′ (2.54 Å to H3*B* in a molecule in the *c* direction). These distances are less than the 2.7 Å range we usually employ for non-bonded H···O packing interactions (Steiner, 1997). Using compiled data for a large number of C—H···O contacts, Steiner & Desiraju (1998) find significant statistical directionality even as far out as 3.0 Å, and conclude that these are legitimately viewed as 'weak hydrogen bonds', with a greater contribution to packing forces than simple van der Waals attractions.

Fig. 3 shows the asymmetric unit for the monohydrate, which also contains two molecules, (II) and (II′), plus two molecules of water. The conformations of (II) and (II′) differ only slightly from one another and from those of (I) and (I′). The torsion angles C11—C9—C2—C1 and O3—C10—C9—C2 were used to illustrate this in the above discussion for (I) *versus* (I′); here, C11—C9—C2—C1 is −178.8 (4)° in (II) and 176.8 (4)° in (II′), a difference of 4.4 (4)°. In (II) and (II′), the O3—C10—C9—C2 torsion angles do not differ beyond experimental error; 38.9 (6)° in (II) and 37.9 (6)° in (II′). The dihedral angle for C1—C2—C8a—O1 *versus* the dienone ring is 55.7 (2)° in (II) and 58.3 (3)° in (II′).

The specific juxtaposition of (II) and (II′) illustrated was chosen to show that the carboxyl hydrogen-bonding in both (II) and (II′) precludes dimer pairing, so that disordering of the carboxyl groups is not expected. The C—O bond lengths

for (II) are 1.212 (5) and 1.313 (6) Å, with C—C—O angles of 123.2 (5) and 113.3 (4)°; for (II′), the bond lengths are 1.216 (5) and 1.320 (6) Å, with angles of 123.3 (4) and 112.9 (4)°. The direct acid-to-acid hydrogen bonding shown in Fig. 3 is the only hydrogen-bonding contact between (II) and (II′) not mediated by water molecules. The two water molecules present play different roles in the hydrogen-bonding scheme, as illustrated in Fig. 4. All three methyl groups are fully ordered and staggered in both (II) and (II′).

Fig. 4 illustrates the packing of the cell and the three-dimensional hydrogen-bonding network. Besides the acid-to-acid hydrogen bond shown in Fig. 3, this includes acid-to-water, water-to-acid, water-to-ketone and water-to-water hydrogen bonds. In both (II) and (II′), only the ζ-ketone (O2) remote from the acid is involved in the hydrogen bonding, as was the case for the anhydrous material. Two screw-related asymmetric units are shown, plus an extra molecule and peripheral waters. Besides the direct (two-bond) acid-to-acid hydrogen bond that distinguishes the chosen asymmetric unit, both three-bond and four-bond intermolecular carboxyl-to-ketone connections are found, mediated by single waters, and five-bond carboxyl-to-carboxyl and six-bond ketone-to-ketone connections are mediated through paired waters.

In (II), the criteria described above for characterizing the geometry of hydrogen bonding to carbonyls are applicable to four of the five hydrogen bonds present. Approach angles for the acid-to-acid hydrogen bond are H4′···O3=C10 155° and H4′···O3=C10—O4 −21°; angles for the water-to-acid hydrogen bond are HW1···O3=C10 159° and HW1···O3=C10—O4 30°; angles for the (acid-to-) water-to-ketone hydrogen bond are HW2′···O2=C7 118° and HW2′···O2=C7—C6 −20°; and angles for the (water-to-) water-to-ketone hydrogen bond are HW3′···O2=C7 127° and HW3′···O2=C7—C6 −31°.

One intermolecular C—H···O=C close contact was found for the O1′ ketone (2.50 Å to H3B in a molecule in the c direction), plus two for the O1 ketone (contacts of 2.49 Å to H3′A and 2.66 Å to H12F in separate molecules, both in the c direction).

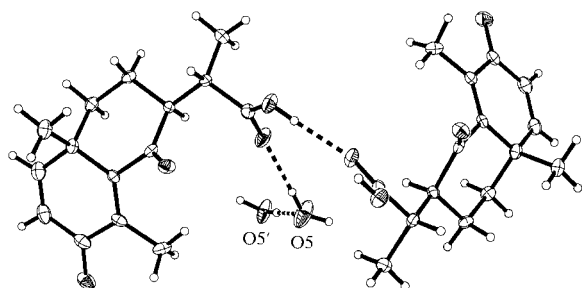The KBr IR spectrum of (I) displays absorptions at 1737 (acid), 1699 (free ketone), 1652 (hydrogen-bonded ketone) and 1616 cm^{-1} (C=C), consistent with known shifts due to the removal of hydrogen bonding from acid C=O and the addition of hydrogen bonding to a ketone. The monohydrate displays strong KBr absorptions at 1724 and 1652 cm^{-1}, with much weaker ones at 1674 and 1601 cm^{-1}. In CHCl$_3$ solution, where dimers predominate, a broad peak at 1706 cm^{-1} is accompanied by peaks at 1660 and 1633 cm^{-1}, and a typical carboxyl-dilution shoulder near 1750 cm^{-1}.
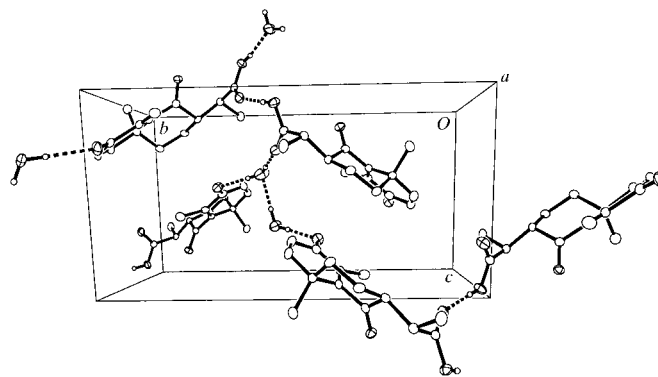

Figure 4
A packing diagram for (II), with two asymmetric units, an extra molecule and several peripheral waters. The asymmetric units are distinguishable by their direct acid-to-acid hydrogen bonds (Fig. 3); the two shown are screw-related along **b**. Methylene and methine H atoms have been omitted for clarity. Displacement ellipsoids are drawn at the 20% probability level.

Experimental

Commercial (−)-α-santonin of known relative and absolute stereochemistry (Barton *et al.*, 1962; Nakazaki & Arakawa, 1962; Asher & Sim, 1965; Coggin & Sim, 1969) was obtained from the Aldrich Chemical Co., Milwaukee, Wisconsin, USA, and subjected to the basic hydrolysis and CrO$_3$ oxidation procedure described by Nishikawa *et al.* (1955). The optical rotation of (I) (m.p. 409 K) has been assigned (Nishikawa *et al.*, 1955; Yanagita & Ogura, 1957). Crystals of (I) (m.p. 401 K) were obtained by evaporation of an ether solution, while crystals of the monohydrate, (II) (m.p. 378 K), were obtained from an acetonitrile–water mixture.

Compound (I)

Crystal data

C$_{15}$H$_{18}$O$_4$	D_x = 1.251 Mg m^{-3}
M_r = 262.29	Mo $K\alpha$ radiation
Monoclinic, $P2$	Cell parameters from 30
a = 7.6790 (10) Å	reflections
b = 14.644 (2) Å	θ = 5.5–14.7°
c = 12.4610 (10) Å	μ = 0.09 mm^{-1}
β = 96.430 (10)°	T = 293 (2) K
V = 1392.4 (3) Å^3	Hexagonal prism, colourless
Z = 4	0.56 × 0.44 × 0.24 mm

Data collection

Siemens $P4$ diffractometer	R_{int} = 0.024
$2\theta/\theta$ scans	θ_{max} = 25°
Absorption correction: numerical	h = −9 → 9
(*SHELXTL*; Sheldrick, 1997)	k = −17 → 17
T_{min} = 0.95, T_{max} = 0.97	l = 0 → 14
5478 measured reflections	3 standard reflections
2553 independent reflections	every 97 reflections
2110 reflections with $I > 2\sigma(I)$	intensity variation: <1.5%

Figure 3
The molecular view of the asymmetric unit of (II) with the two associated water molecules; the atom-numbering scheme is the same as for (I). The molecule on the right is the primed species, (II′). Displacement ellipsoids are drawn at the 20% probability level and H atoms are shown as spheres of arbitrary radii.

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Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.033$
$wR(F^2) = 0.077$
$S = 1.08$
2553 reflections
355 parameters
H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0321P)^2 + 0.0377P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.13$ e Å^{-3}
$\Delta\rho_{min} = -0.10$ e Å^{-3}

Table 1
Selected geometric parameters (Å, °) for (I).

O3—C10	1.196 (3)	O3′—C10′	1.196 (3)
O4—C10	1.333 (4)	O4′—C10′	1.328 (3)
O3—C10—C9	124.8 (3)	O3′—C10′—C9′	124.8 (3)
O4—C10—C9	112.1 (3)	O4′—C10′—C9′	112.7 (2)

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

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
O4—H4$\cdots$O2^i	0.82	1.98	2.776 (3)	165
O4′—H4′$\cdots$O2^{ii}	0.82	1.99	2.775 (3)	160

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

Compound (II)

Crystal data

$C_{15}H_{18}O_4 \cdot H_2O$
$M_r = 280.31$
Monoclinic, $P2$
$a = 8.7200$ (10) Å
$b = 18.170$ (3) Å
$c = 9.589$ (2) Å
$\beta = 100.13$ (2)°
$V = 1495.6$ (4) Å^3
$Z = 4$

$D_x = 1.245$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 20 reflections
$\theta = 2.2$–14.3°
$\mu = 0.09$ mm^{-1}
$T = 248$ (2) K
Plate, colourless
$0.4 \times 0.3 \times 0.2$ mm

Data collection

Siemens $P4$ diffractometer
$2\theta/\theta$ scans
5800 measured reflections
2725 independent reflections
1932 reflections with $I > 2\sigma(I)$
$R_{int} = 0.055$
$\theta_{max} = 25°$

$h = -10 \rightarrow 10$
$k = -21 \rightarrow 21$
$l = -11 \rightarrow 11$
3 standard reflections
    every 97 reflections
    intensity decay: variation <1.5%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.052$
$wR(F^2) = 0.103$
$S = 1.05$
2725 reflections
372 parameters
H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0291P)^2 + 0.2925P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.02$
$\Delta\rho_{max} = 0.29$ e Å^{-3}
$\Delta\rho_{min} = -0.27$ e Å^{-3}

Table 3
Selected geometric parameters (Å, °) for (II).

O3—C10	1.212 (5)	O3′—C10′	1.216 (5)
O4—C10	1.313 (6)	O4′—C10′	1.320 (6)
O3—C10—C9	123.2 (5)	O3′—C10′—C9′	123.3 (4)
O4—C10—C9	113.3 (4)	O4′—C10′—C9′	112.9 (4)

Table 4
Hydrogen-bonding geometry (Å, °) for (II).

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
O4—H4$\cdots$O3^{ri}	0.94 (6)	1.78 (6)	2.714 (5)	169 (5)
O4′—H4′$\cdots$O5^{ri}	0.82 (6)	1.75 (6)	2.565 (5)	170 (6)
O5—HW1$\cdots$O3	0.83	2.00	2.821 (5)	170
O5—HW2$\cdots$O2^i	0.84	2.05	2.844 (5)	159
O5′—HW3$\cdots$O2^{riii}	0.83	1.96	2.788 (5)	176
O5′—HW4$\cdots$O5	0.83	1.89	2.705 (6)	167

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

All H atoms for both (I) and (II) were found in electron-density difference maps, but were placed in calculated positions and allowed to refine as riding models. In (I), the phenyl H atoms were fixed at 0.93 Å, the methine H at 0.98 Å, the methylene H at 0.97 Å, the methyl H at 0.96 Å and the hydroxyl H at 0.82 Å from their respective C or O atoms. The isotropic displacement parameters of the two acid H atoms were allowed to refine but the other H atoms were refined as groups, with the phenyl H atom refining to 0.060 (4) Å, the methine H to 0.036 (3) Å, the methylene H to 0.050 (3) Å and the methyl H to 0.078 (3) Å^2. For (II), the phenyl H atoms were fixed at 0.94 Å, the methine H at 0.99 Å, the methylene H at 0.98 Å and the methyl H at 0.97 Å from their respective C atoms, and the hydroxyl H-atom positions were allowed to refine; the water H atoms were fixed to be 0.83 Å from their respective O atom. The isotropic displacement parameters of the two acid H atoms, as well as those of the water molecules, were held at 0.08 Å^2, while the displacement parameters of the remaining H atoms were tied to their respective C atoms.

For both compounds, data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXTL* (Sheldrick, 1997); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

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