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Two (+)-α,4-dimethyl-2-oxocyclohexaneacetic acids: hydrogen bonding in a terpenoid γ-keto acid and in a diastereomeric lactol

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The (+)-(α*S*,1*S*,4*R*)-diastereomer of the title structure, $C_{10}H_{16}O_3$, aggregates in the solid as non-symmetric dimers with disorder in both carboxyl groups [O···O = 2.710 (5) and 2.638 (5) Å]. The two molecules constituting the asymmetric unit pair around a pseudo-twofold rotational axis and differ only slightly in their distances and angles, but one methyl group displays rotational disorder absent in the other molecule. Five intermolecular C—H···O close contacts exist, involving both ketone groups. The (+)-(α*R*,1*R*,4*R*)-diastereomer exists in the crystal in its closed-ring lactol form, (3*R*,3a*R*,6*R*,7a*R*)-2,3,3a,4,5,6,7,7a-octahydro-7a-hydroxy-3,6-dimethylbenzo[*b*]furan-2-one, $C_{10}H_{16}O_3$, and aggregates as hydrogen-bonded catemers that extend from the hydroxyl group of one molecule to the carbonyl group of a neighbor screw-related along *b* [O···O = 2.830 (3) Å and O—H···O = 169°]. One close intermolecular C—H···O contact exists involving the carbonyl group.

Comment

Our study of hydrogen bonding in solid ketocarboxylic acids has included several γ- and δ-keto acids that crystallize as lactols (Thompson *et al.*, 1985; Papadakis *et al.*, 2003). We now report results for a diastereomeric pair of γ-keto acids having the title structure, of which one crystallizes in the open-chain and the other in the lactol form. Both are derived from the same source, an optically active conjugated terpene lactone isolatable from oil of peppermint and reported to have analgesic properties. Given the fixed configuration at one of the three stereogenic centers in our compounds, the remaining two, the configurations of which are alterable, can generate four diastereomeric permutations. Two of these four compounds are evidently liquids at room temperature (Foote *et al.*, 1967). We describe here the remaining two, which are crystalline (Foote *et al.*, 1967; Woodward & Eastman, 1950; Takahashi *et al.*, 1980). One, (+)-(α*S*,1*S*,4*R*)-, is the monocyclic keto acid, (I), while its diastereomer, (+)-(α*R*,1*R*,4*R*)-, crystallizes in the bicyclic lactol ('pseudo-acid') form, (II).

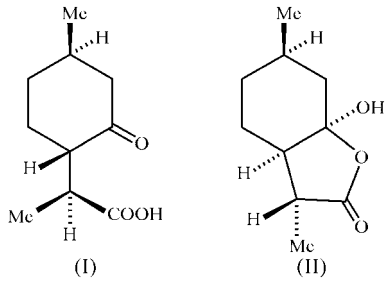

Fig. 1 shows the asymmetric unit of compound (I). The two molecules, designated (I*A*) and (I*B*), differ slightly in their conformations. Both ring substituents of (I) lie on equatorial bonds, and the specific staggered conformation about C1—C7 is energetically advantageous in placing both C7 substituents in *anti* relationships relative to the ring bonds. The one remaining conformationally significant option is rotation of the carboxyl group, which differs in molecules (I*A*) and (I*B*) by 5.2 (8)° (for the C1—C7—C8—O2 torsion angles). The resulting dihedral angle between the plane of the carboxyl group (O2/O3/C8/C7) and that of the ketone (C1/C2/C3/O1) is 82.35 (18)° for (I*A*) and 80.51 (17)° for (I*B*). Superimposing

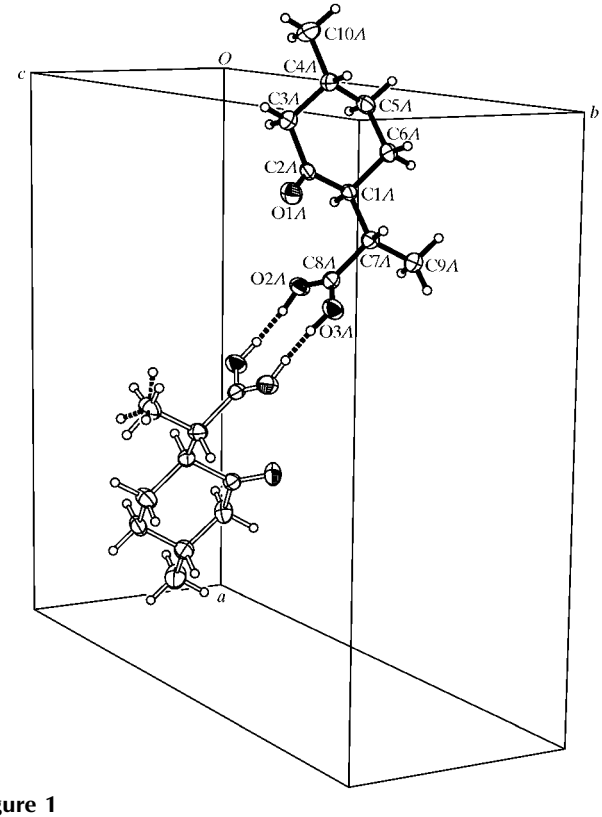

Figure 1
The asymmetric unit in (I), with the unit cell and with the atom numbering shown only for molecule (I*A*); molecule (I*B*) is highlighted by open bonds. The disordered carboxyl groups are depicted with half-occupancy H atoms. For the partially disordered methyl group in (I*B*), the major contributor is shown with open bonds. Displacement ellipsoids are drawn at the 20% probability level.

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the two halves of the asymmetric unit shows that the positional differences for correlated atom pairs range from 0.017 (for atom C4) to 0.092 Å (for atom O2). The largest variation in torsion angle between (I*A*) and (I*B*) is 3.27 (6)° for C3—C4—C5—C6. The superimposition for the full molecules of (I*A*) and (I*B*) produces an overall r.m.s. deviation of 0.10 Å, which diminishes to 0.06 Å when the H atoms are omitted. Consistent with many of the differences residing in the H-atom positions, in (I*B*), the methyl group adjacent to the carboxyl group is disordered, with an 86 (6):14 (6) distribution of contributors, while molecule (I*A*) lacks this methyl disorder.

All these minor conformational differences are only part of a larger constellation of non-symmetric 'flaws', which conspire to thwart what would otherwise constitute a twofold axis of rotation relating (I*A*) and (I*B*). For example, the two halves of the dimer are also imperfectly aligned about their potential twofold axis by a slight central folding of the dimer, an out-of-plane 'hinging', with a dihedral angle of 2.7 (13)° rather than exactly 0°. Thus, even forcing the identity of (I*A*) and (I*B*) does not create a true twofold axis (and fails to produce any additional symmetry), nor does a contrived twofold axis align with any crystallographic element. Such an absence of any element of symmetry in carboxyl dimers (Lalancette *et al.*, 1991, 1996; Lalancette & Thompson, 2003) is much more commonly encountered in chiral non-racemic cases, such as (I), than where centrosymmetric arrangements are possible (Gavezzotti & Filippini, 1994; Allen *et al.*, 1999; Sørensen & Larsen, 2003).

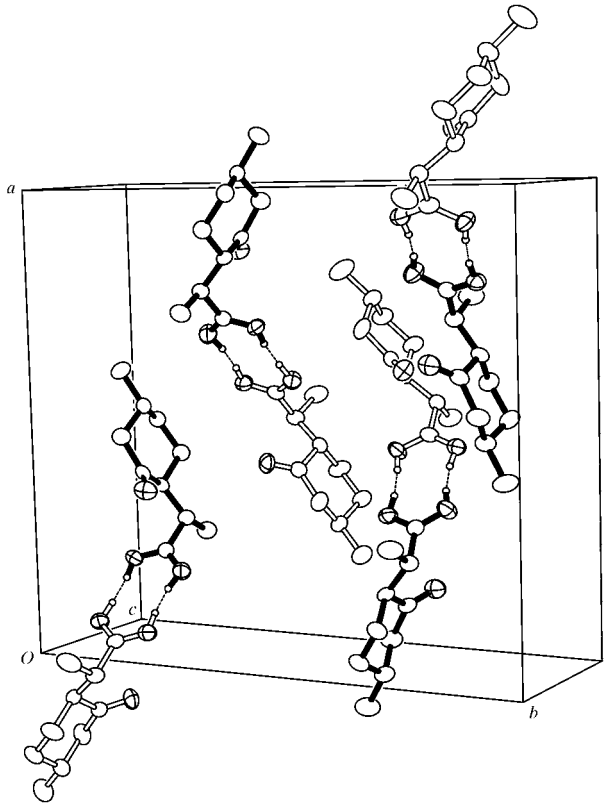

Figure 2
A packing diagram for (I). For clarity, all C-bound H atoms have been omitted and molecules of type (I*B*) are represented with open bonds. Displacement ellipsoids are drawn at the 30% probability level.

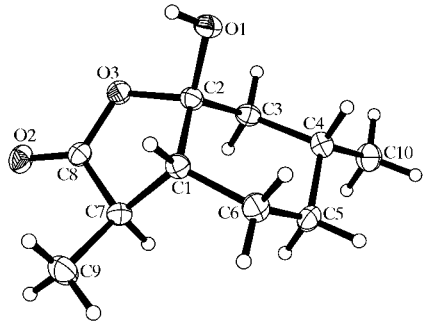

Figure 3
The asymmetric unit in (II), with skeletal numbering identical to that for (I). Displacement ellipsoids are drawn at the 20% probability level.

Many dimerized carboxyl groups have C—O bond lengths and C—C—O angles fully or partially averaged by disorder. The mechanisms involved in transposing the carboxyl O atoms require only local centrosymmetry within the dimerized carboxyl grouping itself, and thus may still operate, as in the present case, in dimers lacking overall centrosymmetry. Thus, within the conventional limits of experimental error, both groups display total carboxyl disorder (Table 1).

Fig. 2 illustrates the packing of the cell for (I) with the heterogeneous dimers of the asymmetric unit. This packing includes five intermolecular C—H···O close contacts (Table 2), involving both ketones of the system and lying within the 2.7 Å range normally employed for non-bonded C—H···O packing interactions (Steiner, 1997; Steiner & Desiraju, 1998).

Fig. 3 shows the asymmetric unit for the (+)-(αR,1*R*,4*R*)-isomer, (II), which crystallizes as the lactol. The numbering employed for (II) is identical to that used for (I), rather than the systematic but more complex benzofuran-based alternative (see *Abstract*), which obscures the parentage of (II) and its relationship to (I). Besides its new *R* lactol stereocenter at C2, compound (II) has configurations opposite to those in (I) at both C7 and C1; the latter creates a *cis*-1,4-disubstitution pattern for the cyclohexane, which requires that any chair conformation have an axial substituent. Placing the carboxyl-bearing substituent on an axial bond obviously allows the carboxyl group to approach the ketone from a direction favorable for the ring closure involved, but this will not automatically favor the lactol in the ring–chain equilibrium.

Many γ- and especially β-carboxy ketones and carboxy aldehydes whose geometries permitting it exist at least partly as the lactols in liquid phases (Chadwick & Dunitz, 1979; Dobson & Gerkin, 1996; Valente *et al.*, 1998). Although the factors affecting this tendency have been studied (Soffer *et al.*, 1950; Jones, 1963), the open and closed forms often lie so close energetically that small changes in the structure or the medium can shift the equilibria appreciably (Valters & Flitsch, 1985), so that predictions regarding equilibrium values for specific cases remain hazardous. Some such keto acids crystallize exclusively as lactols (Thompson *et al.*, 1985; Papadakis *et al.*, 2003). However, with low energy barriers, the equilibria involved may shift even during crystallization, so that the

particular tautomer obtained as the solid may actually depend more on crystallinity than on the position of the ring–chain equilibrium in the solution or melt. Our data (below) suggest that, in $CHCl_3$ solution, (II) exists as a mixture containing a minor proportion of the open form.

Fig. 4 shows the packing for (II) and the pattern for its hydrogen bonding. With no intramolecular hydrogen bonding possible, the molecule adopts the intermolecular mode commonly seen in such lactols, a hydroxyl-to-carbonyl catemer. As happens frequently (Papadakis *et al.*, 2003), the units of the chain are screw-related, in this case following the *b* axis in both directions. We characterize the geometry of hydrogen bonding to carbonyl groups using a combination of the H···O=C angle (ideal value 120°) and the H···O=C—C torsion angle (ideal value 0°). For the hydrogen bonding in (II), the above angles are 126 and 34°, respectively. A single C—H···O close contact (2.66 Å) was found, namely to the carbonyl O atom from atom H1*B* in the same screw-related neighbor involved in the catemeric hydrogen-bonding connection.

The solid-state (KBr) IR spectrum of (I) has a single C=O absorption at 1704 cm^{-1} for both carboxyl and ketone, typical of unstrained dimeric cases lacking conjugation. This absorption is little changed in $CHCl_3$ solution (1707 cm^{-1}), where dimers predominate. For (II), the peak at 1736 cm^{-1} in the KBr spectrum conforms to C=O shifts typical for hydrogen bonding to a γ-lactone, whereas in $CHCl_3$ solution this peak is positioned normally, at 1764 cm^{-1}. Notably, the solution spectrum of (II) also contains a smaller peak, not present in the KBr spectrum, at a position (1708 cm^{-1}) consistent with both carbonyl groups in the open keto-acid form of the molecule. Assessing the relative concentrations of the open and closed forms of (II) from the C=O peak absorbance ratio (70:30), however, is limited by our lack of access to the pure open form, the peak of which at 1708 cm^{-1} is due to both C=O groups present, while that at 1764 cm^{-1} represents a single carbonyl group. ^1H NMR spectroscopy suggests the presence of about 5% of the minor tautomer in $CDCl_3$ solution.

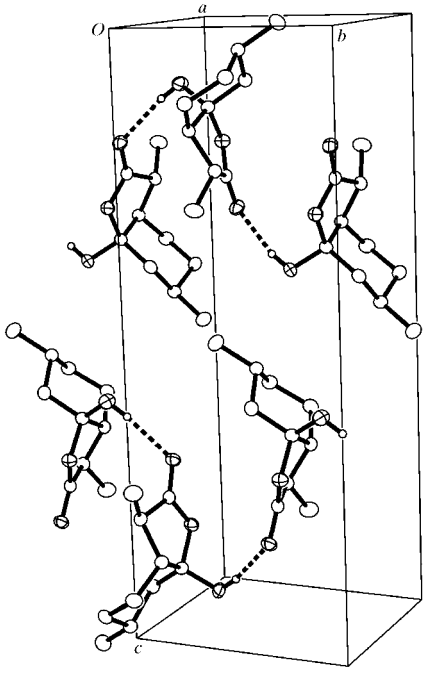

Figure 4
A packing diagram for (II) with extra molecules, illustrating the hydroxyl-to-carbonyl hydrogen bonding linking molecules screw-related along *b*. For clarity, all C-bound H atoms have been omitted.

Experimental

(−)-Menthalactone (99% pure) was purchased from Sigma–Aldrich Chemicals, Milwaukee, Wisconsin, USA. Aqueous saponification, as described by Foote *et al.* (1967), provided a concentrated oily product mixture that partially crystallized on refrigeration. Crystals of (I) suitable for X-ray analysis (m.p. 368 K) were obtained from diethyl ether, which was also used to separate (I) from (II) on the basis of differential solubility. Recrystallization of (II) from ethyl acetate gave material melting at 416 K suitable for analysis. The absolute configurations of both (I) and (II) have been established previously (Foote *et al.*, 1967; Takahashi *et al.*, 1979). Although no $[\alpha]_D$ optical rotations appear to have been reported for either (I) or (II), the positive optical rotatory dispersion (ORD) Cotton effects reported for both (Foote *et al.*, 1967) permit the assignment of positive signs to their $[\alpha]_D$ rotations.

Compound (I)

Crystal data

$C_{10}H_{16}O_3$
M_r = 184.23
Orthorhombic, $P2_12_12_1$
a = 16.740 (5) Å
b = 19.173 (5) Å
c = 6.632 (2) Å
V = 2128.4 (11) Å^3
Z = 8
D_x = 1.150 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 27 reflections
θ = 2.5–8.8°
μ = 0.08 mm^{-1}
T = 296 (2) K
Hexagonal plate, colorless
0.50 × 0.20 × 0.16 mm

Data collection

Siemens $P4$ diffractometer
$2\theta/\theta$ scans
Absorption correction: analytical (*SHELXTL*; Sheldrick, 1997*b*)
T_{min} = 0.980, T_{max} = 0.990
4249 measured reflections
2162 independent reflections
1007 reflections with $I > 2\sigma(I)$
R_{int} = 0.074
θ_{max} = 25.0°
$h = -19 \rightarrow 19$
$k = -22 \rightarrow 22$
$l = -6 \rightarrow 7$
3 standard reflections every 97 reflections
intensity variation: <3.0%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.059
$wR(F^2)$ = 0.093
S = 0.98
2162 reflections
238 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.012P)^2 +]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.14 e Å^{-3}
$\Delta\rho_{min}$ = −0.14 e Å^{-3}
Extinction correction: *SHELXL97* (Sheldrick, 1997*a*)
Extinction coefficient: 0.0033 (4)

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

O2*A*—C8*A*	1.278 (5)	O2*B*—C8*B*	1.275 (5)
O3*A*—C8*A*	1.262 (5)	O3*B*—C8*B*	1.277 (6)
O3*A*—C8*A*—C7*A*	119.3 (5)	O2*B*—C8*B*—C7*B*	118.0 (5)
O2*A*—C8*A*—C7*A*	118.6 (5)	O3*B*—C8*B*—C7*B*	118.8 (6)

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

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1A···O2^{i}	0.82	2.02	2.710 (5)	169
O1—H1A···O2^{i}	0.82	2.02	2.638 (5)	169
C6A—H6A1···O1A^{ii}	0.97	2.61	3.461 (6)	146
C7B—H7B···O1A^{iii}	0.98	2.51	3.475 (6)	170
C9A—H9A1···O1A^{ii}	0.96	2.65	3.558 (6)	158
C6A—H6A2···O1B^{iv}	0.97	2.61	3.501 (6)	152
C9B—H9B1···O1B^{v}	0.96	2.66	3.608 (6)	170

Symmetry codes: (i) $-x+\frac{5}{2}, y+\frac{1}{2}, -z+1$; (ii) $x, y, z+1$; (iii) $x-\frac{1}{2}, -y+\frac{1}{2}, -z$; (iv) $x+\frac{1}{2}, -y+\frac{1}{2}, -z+1$; (v) $x, y, z-1$.

Compound (II)

Crystal data

$C_{10}H_{16}O_3$
M_r = 184.23
Orthorhombic, $P2_12_12_1$
a = 6.728 (2) Å
b = 7.455 (2) Å
c = 19.829 (5) Å
V = 994.6 (5) Å^3
Z = 4
D_x = 1.230 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 29 reflections
θ = 1.9–10.6°
μ = 0.09 mm^{-1}
T = 296 (2) K
Plate, colorless
0.50 × 0.40 × 0.10 mm

Data collection

Siemens $P4$ diffractometer
$2\theta/\theta$ scans
Absorption correction: analytical (*SHELXTL*; Sheldrick, 1997*b*)
T_{min} = 0.958, T_{max} = 0.989
2100 measured reflections
1050 independent reflections
799 reflections with $I > 2\sigma(I)$
R_{int} = 0.030
θ_{max} = 25.0°
$h = -8 \rightarrow 8$
$k = -8 \rightarrow 8$
$l = -23 \rightarrow 23$
3 standard reflections
every 97 reflections
intensity variation: <1.6%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.038
$wR(F^2)$ = 0.082
S = 1.06
1050 reflections
119 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0322P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.11 e Å^{-3}
$\Delta\rho_{min}$ = −0.12 e Å^{-3}
Extinction correction: *SHELXL97* (Sheldrick, 1997*a*)
Extinction coefficient: 0.019 (3)

Table 3
Hydrogen-bond geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1A···O2^{i}	0.82	2.02	2.830 (3)	169
C1—H1B···O2^{i}	0.98	2.66	3.430 (4)	136

Symmetry code: (i) $-x+2, y+\frac{1}{2}, -z+\frac{3}{2}$.

All H atoms for both (I) and (II) were found in electron-density difference maps but were placed in calculated positions, with C—H distances of 0.97 Å for methylene H atoms, 0.98 Å for methine H atoms and 0.96 Å for methyl H atoms, and with O—H distances of 0.82 Å for both the disordered half-occupied acid H atoms in (I) and the hydroxyl H atom in (II), and allowed to refine as riding models on their respective atoms, with U_{iso}(H) = 1.2U_{eq}(C) for CH_2 groups or 1.5U_{eq}(C,O) for CH_3 and OH groups. The data for both (I) and (II) were merged, yielding 2087 Friedel pairs for (I) and 1050 for (II).

For both compounds, data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS*; data reduction: *XSCANS*; structure solution: *SHELXS97* (Sheldrick, 1997*a*); structure refinement: *SHELXL97* (Sheldrick, 1997*a*); molecular graphics: *SHELXP97* (Sheldrick, 1997*a*); publication software: *SHELXL97*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GG1241). Services for accessing these data are described at the back of the journal.

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