

# The anti-inflammatory triterpenoid methyl 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oate methanol solvate hydrate

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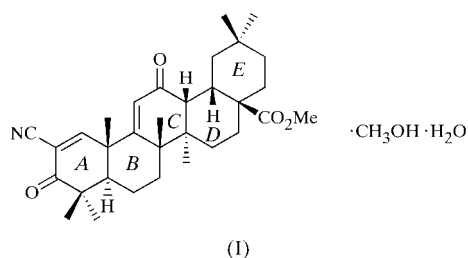
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The title compound,  $C_{32}H_{43}NO_4 \cdot CH_3O \cdot H_2O$ , has a nearly planar cyano-enone *A* ring in an otherwise normal oleanane triterpenoid. Rings *A*, *B* and *C* are non-chairs, but rings *D* and *E* adopt essentially cyclohexane chair conformations. The structure clearly establishes the *C-D-E* ring stereochemistry as *trans-syn-cis*, as predicted from a nuclear Overhauser effect (NOE) NMR measurement.

## Comment

We have found that several synthetic triterpenoids derived from the naturally occurring oleanolic and ursolic acids, with an enone functionality in the *A* and *C* rings, have significant biological activity. For example, 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO) exhibits potent anti-inflammatory, differentiating and antiproliferative activity (Honda *et al.*, 1997, 1998, 1999; Suh *et al.*, 1998, 1999; Honda, Gribble *et al.*, 2000; Honda, Rounds *et al.*, 2000). Furthermore, CDDO is a ligand for the peroxisome proliferator-activated  $\gamma$  receptor



(Wang *et al.*, 2000), and it also induces apoptosis in human myeloid leukemia cells (Ito *et al.*, 2000). In order to probe the possible receptor proteins for which CDDO may be a ligand, we now report the crystal structure determination of the title compound, (I), which is the methyl ester of CDDO. This is the first crystal structure to be reported for a member of these synthetic oleanane-enones. We have synthesized CDDO

methyl ester in ten steps (Honda, Rounds *et al.*, 2000) from the naturally occurring oleanolic acid, whose absolute configuration is known (Simonsen & Ross, 1957). Only a few oleanane crystal structures have been recorded previously, including 18-(*H*)-oleanane (Fowell *et al.*, 1978), methyl 3,16-dihydroxy-12-oxo-13-oleanan-28-oate dihydrate (Dhaneshwar *et al.*, 1987) and methyl 3-acetoxy-12-oxo-18-olean-28-oate (Gzella, 2000).

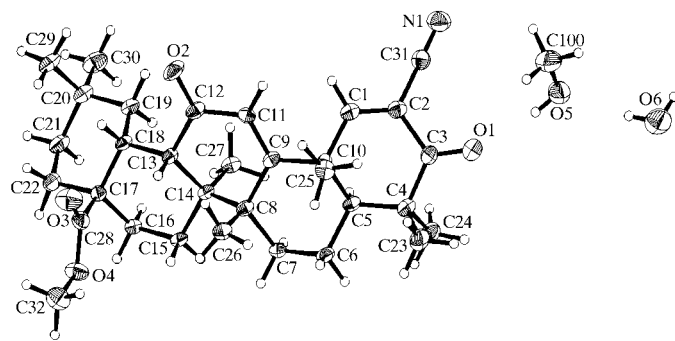
The crystal structure determination reported herein supports our structural assignments for both CDDO methyl ester, (I), and CDDO, which were based solely on spectral data and the method of synthesis. The X-ray structure of (I) confirms the ketone functionalities at C3 and C12, the cyano group at C2, the methyl ester at C17, and the C=C double bonds at C1=C2 and C9=C11.

The unsaturated carbonyl bond distances, C3—O1 [1.215 (6) Å] and C12—O2 [1.231 (5) Å], are similar to the corresponding values reported for the saturated ketones in allobetulone [C3—O1 1.206 (3) Å; Klinot *et al.*, 1989], 12 $\alpha$ -hydroxy-3-oxooleanano-28,13-lactone [C3—O1 1.201 (4) Å; Eggleston, 1987] and avenestergenin A-2 [C12—O2 1.20 (1) Å; Begley *et al.*, 1986]. The carbonyl bond distances in (I) and the cyano group triple-bond distance [C31 $\equiv$ N1 1.137 (7) Å] are normal.

The C=C double bonds at C1=C2 [1.327 (7) Å] and C9=C11 [1.353 (6) Å] are similar to the value for a simple alkene C=C double bond (1.316 Å; Batsanov, 2000), which again perhaps reflects the enone character of these double bonds.

Rings *A*–*C* are non-chairs, due to the presence of  $Csp^2$  atoms at C1, C2, C3, C9, C11 and C12, but rings *D* and *E* adopt essentially cyclohexane chair conformations. Ring *A* is nearly planar, with a mean deviation from the plane of 0.165 Å. The X-ray structure clearly establishes the *C-D-E* ring stereochemistry as *trans-syn-cis* and supports the stereochemistry of the H atom at C13, which was previously assigned from a nuclear Overhauser effect spectroscopy (NOESY) experiment on a precursor compound (Honda, Rounds *et al.*, 2000).

Methanol and water solvates both cocrystallize in the unit cell of (I) and provide unique hydrogen-bond intermolecular interactions. The methanol oxygen, O5, is hydrogen bonded



**Figure 1**

A view of the molecule of (I) with the cocrystallized moieties and the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

both to O1 in the oleanane and to the water molecule. In addition, the water molecule is also hydrogen bonded to atom O2 of a symmetry-related oleanane molecule.

## Experimental

Compound (I) was prepared in ten steps from oleanolic acid, as recently described by Honda, Rounds *et al.* (2000). Recrystallization from methanol gave colourless needles of (I) (m.p. 437–440 K).

### Crystal data

$C_{32}H_{43}NO_4 \cdot CH_4O \cdot H_2O$	Mo $K\alpha$ radiation
$M_r = 555.73$	Cell parameters from 56 reflections
Orthorhombic, $P2_12_12_1$	$\theta = 2.4\text{--}12.6^\circ$
$a = 6.5370$ (10) Å	$\mu = 0.08\text{ mm}^{-1}$
$b = 8.9500$ (10) Å	$T = 173$ (2) K
$c = 51.128$ (9) Å	Needle, colourless
$V = 2991.3$ (8) Å <sup>3</sup>	$0.8 \times 0.8 \times 0.3\text{ mm}$
$Z = 4$	
$D_x = 1.234\text{ Mg m}^{-3}$	

### Data collection

Siemens P4 diffractometer	$h = -8 \rightarrow 8$
$2\theta/\omega$ scans	$k = -11 \rightarrow 11$
10 610 measured reflections	$l = -65 \rightarrow 66$
3985 independent reflections	3 standard reflections
2825 reflections with $I > 2\sigma(I)$	every 197 reflections
$R_{\text{int}} = 0.065$	intensity variation: $\pm 2.0\%$
$\theta_{\text{max}} = 27.5^\circ$	

### Refinement

Refinement on $F^2$	$w = 1/[\sigma^2(F_o^2) + (0.1033P)^2 + 3.4110P]$
$R[F^2 > 2\sigma(F^2)] = 0.070$	where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.211$	$(\Delta/\sigma)_{\text{max}} = 0.004$
$S = 1.05$	$\Delta\rho_{\text{max}} = 0.37\text{ e \AA}^{-3}$
3985 reflections	$\Delta\rho_{\text{min}} = -0.34\text{ e \AA}^{-3}$
387 parameters	
H atoms treated by a mixture of independent and constrained refinement	

**Table 1**

Hydrogen-bonding geometry (Å, °).

$D-H \cdots A$	$D-H$	$H \cdots A$	$D \cdots A$	$D-H \cdots A$
O5–H5A $\cdots$ O1	0.84	2.04	2.846 (5)	160
O6–H6C $\cdots$ O2 <sup>i</sup>	0.87 (5)	2.07 (6)	2.895 (6)	160 (7)
O6–H6D $\cdots$ O5	0.87 (5)	2.07 (5)	2.910 (6)	166 (8)

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

The absolute configuration of (I) could not be determined. Water H atoms were refined, with O–H distances constrained to 0.86 Å. Other H atoms were treated as riding, with C–H = 0.98 Å for CH<sub>3</sub>, 0.99 Å for CH<sub>2</sub>, 1.00 Å for CH and 0.95 Å for aromatic CH, and O–H = 0.84 Å. A torsional parameter was refined for each methyl group, and a common  $U_{\text{iso}}$  value was refined for each H-atom type.

Data collection: XSCANS (Siemens, 1996); cell refinement: XSCANS; data reduction: XSCANS; program(s) used to solve structure: SHELXS97 (Sheldrick, 1997); program(s) used to refine structure: SHELXL97 (Sheldrick, 1997); molecular graphics: SHELXTL (Bruker, 1997); software used to prepare material for publication: SHELXTL.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FR1352). Services for accessing these data are described at the back of the journal.

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