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An angularly fused three-ring precursor to phytuberin

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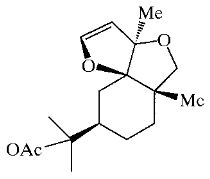
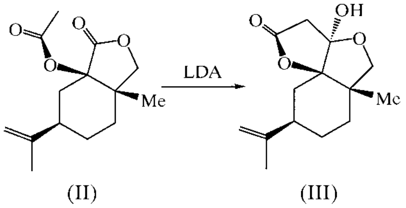
The title compound, 3,3a,5,5a,6,7,8,9-octahydro-3a-hydroxy-5a-methyl-8-(2-propenyl)furo[3,2-*c*]isobenzofuran-2-one, $C_{14}H_{20}O_4$, crystallizes with two independent molecules in the asymmetric unit. The molecules have similar metric parameters but differ in the conformations of the isopropenyl groups. The hydroxyl groups form one-dimensional chains of hydrogen bonds.

Comment

Phytuberin, (I), is a metabolite induced by stress on potato stems and tobacco leaves (Fujimori *et al.*, 1983). It is of interest from both a synthetic and a biological perspective since stress metabolites are a key part of certain signal transduction pathways (Preisig & Moreau, 1994). It also exhibits modest antifungal activity. An important step in the synthesis is the conversion of ester lactone (II) to lactone (III). Compound (II), upon treatment with 5 equivalents of lithium diisopropylamide (LDA) at 195 K afforded lactone (III) in 93% yield (Bull & Tuinman, 1976). This step set the stereochemistry for the eventual conversion to phytuberin.



(I)



(II) (III)

The title compound, (III), crystallizes in the chiral space group $P2_12_12_1$ with two independent molecules in the asymmetric unit. A drawing of one molecule is shown in Fig. 1.

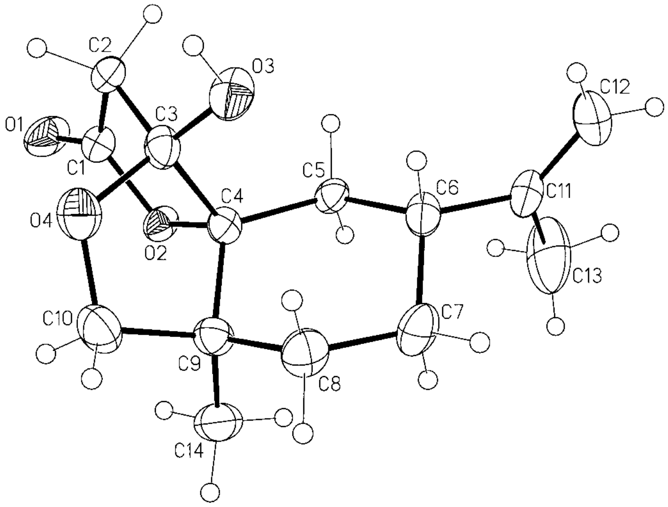


Figure 1
The molecular structure of one of the two independent molecules of (III) drawn with displacement ellipsoids at the 30% probability level.

Both molecules exhibit remarkably similar conformations of the fused three-ring system and differ only in the conformation of the isopropenyl group. This difference is illustrated by the values of the C5—C6—C11—C13 torsion angles, which are −62.1 (3) and 170.2 (2)° in the two molecules, respectively. The absolute configuration of the compound could not be determined directly from the X-ray data; however, the absolute configuration about atom C6 (*R*) was known since it remained unchanged from the starting material (*R*)-2-methyl-5-(2-propenyl)-2-cyclohexenone throughout the four synthetic steps leading to the formation of (III). The absolute configurations about the other three chiral centres, C3 (*R*), C4 (*R*) and C9 (*S*), were established relative to that of atom C6 from the structural data. In the following discussion, the structural parameters for one molecule will be given with those for the second molecule following in parentheses. The molecule of (III) contains two five-membered and one six-membered rings that have common vertices or edges. While all bond distances fall in the usual range for C—C and C—O distances, bond angles reflect strain present in the rings.

The cyclohexyl ring has a chair conformation with atoms C4, C5, C7 and C8 in the equatorial plane and atom C6 −0.625 (3) Å [0.636 (3) Å] below and atom C9 0.646 (3) Å [−0.652 (3) Å] above the plane. Atoms C4, C5, C7 and C8 are planar within 0.05 Å (0.04 Å). The bond angles within the ring vary from 108.24 (18) to 115.95 (14)° [107.82 (15) to 115.56 (14)°]. The torsion angles are in the range 47.5 (2)–60.0 (3)° [49.2 (2)–59.8 (2)°]. These data are in good agreement with the corresponding values calculated for dihydro and 2α-hydroxydihydro derivatives of phytuberin (Hughes, 1976), the only other two structurally characterized compounds containing a three-ring system identical to that described here. Both five-membered rings in (III) exhibit envelope conformations. In the O2 ring, atoms C1, C2, C4 and O2 are planar within 0.003 Å (0.007 Å), while atom C3 is 0.465 (3) Å [0.390 (3) Å] above this plane. The dihedral angle between the C1—C2—C4—O2 plane and the 'flap' plane defined by C2—

C3—C4 is 30.1 (2)° [24.7 (2)°]. In the O4 ring, the equatorial plane contains atoms C3, C4, O4 and C10, which lie 0.05 Å (0.003 Å) within a plane, and atom C9, located 0.498 (4) Å [0.534 (3) Å] above that plane. The dihedral 'flap' angle is 69.0 (2)° [41.4 (2)°].

The hydroxyl group at atom C3 participates in intermolecular O—H···O hydrogen bonding, with an O···O separation of 2.853 (2) Å and an O—H···O angle of 162 (1)° (see Table 1). The analogous hydrogen bond formed by the hydroxyl group of the second molecule showed a similar O···O separation [2.856 (2) Å] but a significantly different O—H···O angle [140 (1)°] (see Table 1). In both cases, the hydrogen bonds link molecules of (3) into one-dimensional linear chains.

Experimental

To a solution of lithium diisopropylamide (5 equivalents) in tetrahydrofuran (THF) at 195 K was added dropwise over 1 min the lactone ester (II) (1 equivalent) in THF. The solution was stirred at 195 K for 1 h and the reaction was quenched and diluted with water. Methylene chloride (40 ml) was added and then the organic and aqueous layers were separated. The organic layer was dried over sodium sulfate, concentrated *in vacuo* and the residue purified by silica-gel flash chromatography.

Crystal data

$C_{14}H_{20}O_4$
$M_r = 252.30$
Orthorhombic, $P2_12_12_1$
$a = 9.3933$ (7) Å
$b = 9.3963$ (7) Å
$c = 30.329$ (2) Å
$V = 2676.9$ (3) Å^3
$Z = 8$
$D_x = 1.252$ Mg m^{-3}

Mo $K\alpha$ radiation
Cell parameters from 4161 reflections
$\theta = 3$–26°
$\mu = 0.091$ mm^{-1}
$T = 193$ (2) K
Plate, colourless
0.41 × 0.38 × 0.05 mm

Data collection

CCD area-detector diffractometer
ω scans
Absorption correction: empirical using intensity measurements (*SADABS*; Blessing, 1995)
$T_{\min} = 0.964$, $T_{\max} = 0.996$
12 722 measured reflections

3066 independent reflections
2383 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.026$
$\theta_{\max} = 26.37°$
$h = -11 \rightarrow 11$
$k = 0 \rightarrow 11$
$l = 0 \rightarrow 37$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.038$
$wR(F^2) = 0.079$
$S = 1.048$
3066 reflections
329 parameters

H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.03P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} = 0.001$
$\Delta\rho_{\max} = 0.15$ e Å^{-3}
$\Delta\rho_{\min} = -0.20$ e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O3—H3···O1$^{\rm i}$	0.84	2.04	2.853 (2)	162
O3A—H3A···O1$A^{\rm ii}$	0.84	2.17	2.856 (2)	140

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

The H atoms were idealized as follows: O3 and O3A with O—H = 0.84 Å; secondary CH_2 with C—H = 0.99 Å; tertiary Csp^3 with C—H = 1.00 Å; C12 and C12A as idealized terminal CH_2 with C—H = 0.99 Å; methyl groups with C—H = 0.98 Å.

Data collection: *SMART* (Siemens, 1996). Cell refinement: *SMART*. Data reduction: *SHELXTL* (Sheldrick, 1997). Program(s) used to solve structure: *SHELXTL*. Program(s) used to refine structure: *SHELXTL*. Molecular graphics: *SHELXTL*. Software used to prepare material for publication: *SHELXTL*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FR1250). Services for accessing these data are described at the back of the journal.

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