

MOLECULAR STRUCTURE OF 4-O-ETHYL ASCOFURANONE

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The molecular structure of a new antibiotic ascofuranone ( $C_{23}H_{29}O_5Cl$ ), which possesses serum lipid lowering property, has been elucidated by the aid of IR, NMR and mass spectroscopy<sup>1)</sup>. This letter presents the molecular structure and the absolute configuration of 4-O-ethyl ascofuranone determined by the X-ray crystal structure analysis. The sample ( $C_{25}H_{33}O_5Cl$ , mol.wt.=449.0, m.p.=66°C) was obtained by refluxing acetone solution of ascofuranone with ethyl iodide and potassium carbonate, and was crystallized from n-hexane-acetone. X-ray diffraction photographs indicated that the crystal was orthorhombic, space group  $P2_12_12_1$ , with four molecules in a unit cell of dimensions  $a=11.722$ ,  $b=34.629$ ,  $c=6.121$  Å,  $\rho_{ca1}=1.200$  g cm<sup>-3</sup>. Reflexion data were collected on a Philips PW 1100 X-ray diffractometer with graphite monochromated Cu K $\alpha$  radiation (number of observed independent reflexions=2653). The crystal structure was solved by the multi-solution method (MULTAN)<sup>2)</sup>, using 294 normalized structure factors ( $|E|\geq 1.45$ ). Origin and enantiomorph fixings were carried out automatically by the program. Sixteen sets of trial to determine the phases by a weighted tangent formula indicated that the correct phases were those obtained for the set of No.5, of which the absolute figure of merit and the residue<sup>3)</sup> were calculated to be 1.354 and 0.282, respectively.

The molecular structure, consistent with that given in the previous paper<sup>1)</sup>, was recognized readily except for two methyl carbon atoms on the E-map calculated with these phases. The structure was refined by the least-squares

method of block-diagonal approximations including anisotropic temperature factors for non-hydrogen atoms. The positions of 33 hydrogen atoms were obtained on the difference Fourier map. The R index was 0.06. The absolute configuration of 4-O-ethyl ascofuranone molecule was determined by Bijvoet's method using the anomalous dispersion of Cu  $K\alpha$  radiation by chlorine and oxygen atoms. The R indices<sup>4)</sup> for  $F_{\text{calc}}(hkl)$  and  $F_{\text{calc}}(\bar{h}\bar{k}\bar{l})$  were 0.069 and 0.059, respectively, which suggested the latter structure might represent the correct one. The same conclusion was obtained by the comparison of  $F_{\text{obs}}$  and  $F_{\text{calc}}$  for 1449 Friedel pairs of three dimensional reflexions. In Fig.1(a), the absolute configuration of 4-O-ethyl ascofuranone molecule is shown by an ORTEP<sup>5)</sup> drawing. The non-hydrogen atoms are drawn by the ellipsoids of thermal vibration at 50% probability. The numbering of the atoms is shown in Fig.1(b).

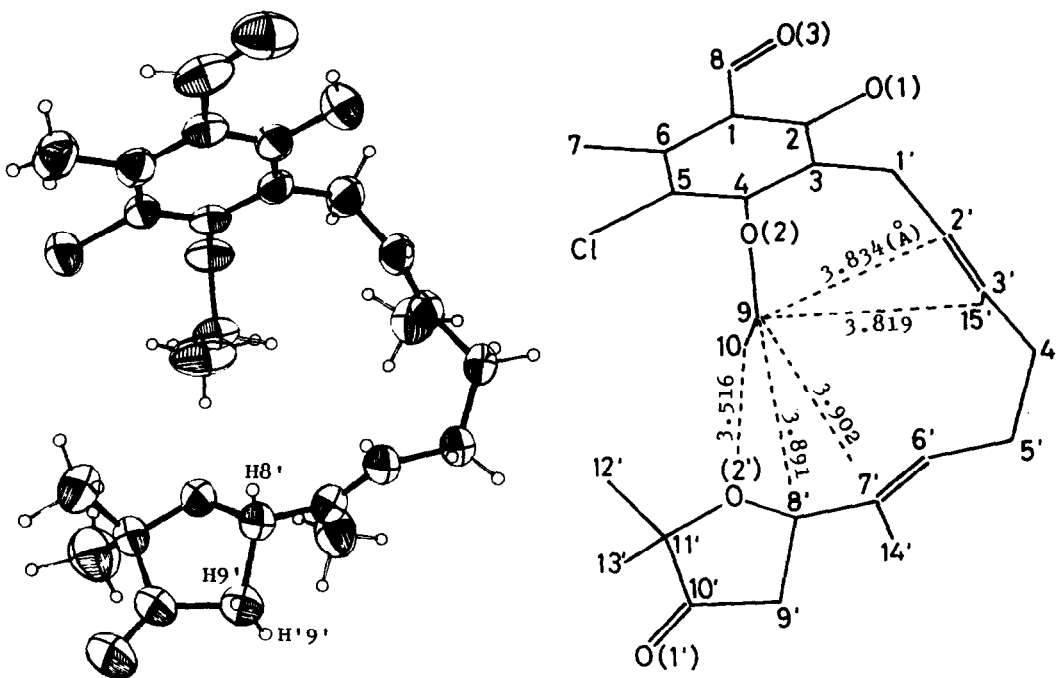


Fig.1. (a) ORTEP drawing of 4-O-ethyl ascofuranone molecule.

(b) Molecular projection along the crystallographic [001].

Intramolecular van der Waals contacts may contribute to stabilize the molecular conformation, having gauche arrangement around C4'-C5' bond in farnesyl side chain. The dihydrofuran-3-one ring in the molecule adopts an envelope conformation (C8' deviates ca. 0.5 Å from the best plane of O2', C9', C10' and C11'), and the spatial configuration around the asymmetric carbon C8' is Sinister according to the notation by Cahn, Ingold and Prelog<sup>6)</sup>. The ketone octant rule<sup>7)</sup> suggests a negative Cotton effect for the n- $\pi^*$  transition of the carbonyl group in the ring, when the conformation in the crystal structure is retained in the solution; alternatively, a positive Cotton effect can be expected if C8' be placed in the lower-right back octant by a ring puckering (Fig.2.). ORD and CD curves observed for ascocofuranone exhibited a negative Cotton effect; the molar ellipticity =  $-6.9 \times 10^3$  at 316 nm in CHCl<sub>3</sub>. Accordingly, it may be concluded that the dihydrofuran-3-one ring is rigid and its conformation in the chloroform solution is approximately identical to that in the crystal.

In the studies of NMR spectroscopy, two sharp singlets (unassigned) were observed for the protons of geminal methyl groups of C12' and C13':  $\delta$  1.20 and 1.26<sup>1)</sup> in chloroform solution. This magnetic none-equivalence should be attributed to the differences in the magnetic environments around the protons. The long-range shielding effect on the protons due to the diamagnetic anisotropies of the carbonyl (O1'=C10') and the ether (C8'-O2'-C11') groups, calcu-

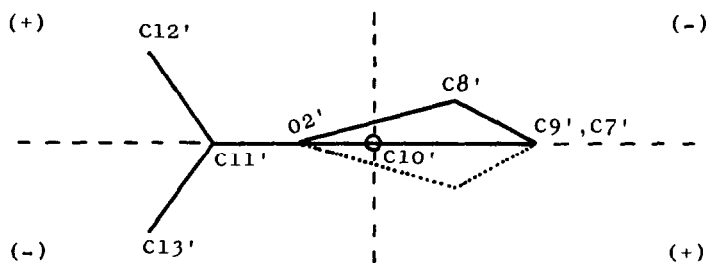


Fig.2. Projection of the dihydrofuran-3-one ring along the carbonyl O1'-C10' bond. (-) and (+) indicate negative and positive Cotton effects, predicted by the ketone octant rule.

lated by a point magnetic dipole approximation<sup>8</sup>), were negative (-0.103 ppm) and positive (+0.121 ppm) for the protons of methyl C12' and C13', respectively.

Two geminal protons (H9' and H'9') were approximately magnetically equivalent, and gave a first-order A<sub>2</sub>X spectrum by the vicinal spin coupling with the methine proton (H8'); namely a doublet due to the methylene protons (2H, δ 2.39,  $J_{H9',H8'} = J_{H'9',H8'} = 8.2$  Hz) and a triplet due to the methine proton (1H, δ 4.50,  $J_{H8',H9'} = J_{H8',H'9'} = 8.2$  Hz) were observed. In this connection, the parameters  $J^0$  and  $J^{180}$  in the Karplus equation, calculated using the dihedral angles (H9'-C9'-C8'-H8' = -3.3° and H'9'-C9'-C8'-H8' = -158.8°) and the original value of the constant C (-0.3 Hz), were 8.5 and 9.8 Hz, respectively, which were close to the original ones ( $J^0 = 8.5$  and  $J^{180} = 9.5$  Hz)<sup>9</sup>) chosen as most appropriate for an "unperturbed" H-C-C-H' fragment.

Calculations for the crystal structure analysis were carried out on the CDC 6600 computer at Century Research Center Corporation.

#### Footnote and References

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