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THE ABSOLUTE CONFIGURATION OF FOMANNOSIN

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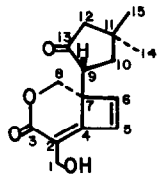
Still cultures of the wood-destroying Basidiomycete Fomes annosus produce an unusual sesquiterpene, fomannosin (1), with both phytotoxic and antibiotic activities.[1] The structure of fomannosin was originally determined by an X-ray study of the p-bromobenzoylurethane derivative 3 of dihydrofomannosin (2).[2] Attempts to determine the absolute configuration by the Bijvoet anomalous dispersion method[3] were unsuccessful. We have reported a biosynthetic study, involving incorporation of 1,2-^{13}C-acetate, which supports the mevalonoid origin of fomannosin and the intervention of a humulene intermediate.[4]



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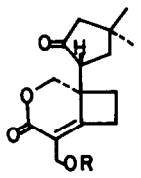
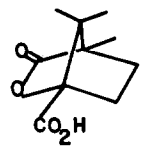


2 R = H
3 R = p-Br-C_6H_4CONHCO
4 R = (-)-Camphanyl



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In connection with our biosynthetic investigations, it became important to determine the absolute configuration of fomannosin. To this end we prepared an ester of dihydrofomannosin with an acid of known absolute configuration. (-)-Camphanic acid 5 was chosen, as its constitution and configuration are unambiguously determined by its synthesis[5] from (+)-camphor, whose structure and absolute stereochemistry are known.[6] The desired camphanate ester 4 was obtained by reacting dihydrofomannosin with 2 eq. camphanyl chloride in the presence of 2 eq. triethyl-

amine (THF, 25°, 2 hr). The camphanyl chloride was in turn prepared by treatment of 5 with excess thionyl chloride. After purification by PLC and recrystallization from acetone -- hexane, 4 exhibited the following properties: m.p. 147°; $[\alpha]_D$ + 101° (C = 0.8, $CHCl_3$); calc'd for $C_{25}H_{32}O_7$; C, 67.55, H 7.26, found C 67.57, H 7.20.

Crystals of dihydrofomannosin camphanate belonged to the triclinic space group P1 with a=6.248(3)Å, b=10.410(4)Å, c=10.243(3)Å, α=112.93(2)°, β=72.53(3)°, γ=105.12(3)°, and dcalc=1.28g/cc for one molecule in the asymmetric unit. A hemisphere of data with $2\theta \leq 114.1°$ was collected on a fully automated four-circle diffractometer using CuKα radiation (λ=1.5418Å). Reflections were measured in the w-scan mode with a scan width of one degree and a variable scan speed. After correction for Lorentz, polarization and background effects 1510 of the 1564 measured reflections (96.5%) were considered observed ($F_o^2 \geq 3\sigma(F_o^2)$).

The structure was solved with difficulty using a multiple-solution weighted tangent formula approach[8] followed by several Fourier syntheses.[9] Hydrogen positions were calculated and included in the structure. Anisotropic least-squares refinement of the heavy atoms and isotropic refinement of the hydrogens brought

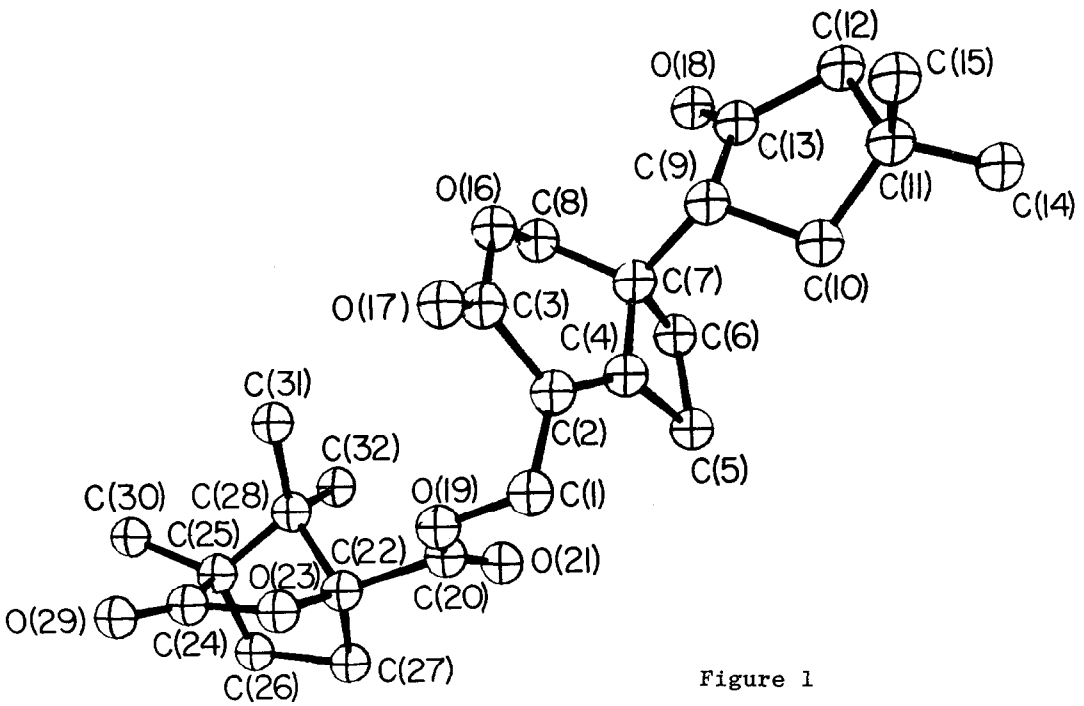

Figure 1

the R-factor to .072. There were no unusually short intermolecular contacts and the geometry generally agreed well with previous x-ray work.[10] The computer generated drawing of the molecule shows its correct absolute configuration.

The absolute configuration of fomannosin is therefore shown to be 7S, 9R. This result, coupled with a detailed spectroscopic study, allows a complete stereochemical analysis of fomannosin biosynthesis, the details of which will appear in a separate paper.[11]

References and Notes

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7. Nmr and ir spectra in full accord with the assigned structure were obtained for this compound.
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9. The following library of crystallographic programs was used: C. R. Hubbard, C. O. Quicksall, and R. A. Jacobson, "The Fast Fourier Algorithm and the Programs ALFF, ALFFDP, ALFFT and FRIEDEL", USAEC Report IS-2625, Iowa State University-Institute for Atomic Research, Ames, Iowa, 1971; W. R. Busing, K. O. Martin, and H. A. Levy, "A Fortran Crystallographic Least Squares Program", USAEC Report ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965; C. Johnson, "ORTEP, A Fortran Thermal-Ellipsoid Plot Program", U.S. Atomic Energy Commission Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965.
10. A computer generated drawing of the final X-ray model, fractional coordinates, bond distances, bond angles and observed and calculated structure

factors are available as a Supplement to Publication. To obtain a microfiche copy of the Supplement to Publication, contact the Photo Service, Iowa State University, Ames, Iowa, 50011, requesting Supplement to Publication No. __ and submitting $.50 in the form of check, cash or money order. Give your name and complete address (including zip code) for mailing.

11. This work was supported by the National Institutes of Health (GM 22172).