

The Structure and Absolute Configuration of (5*R*)-5,6-Anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-5-*C*-(dimethoxyphosphinoyl)- α -D-xylo-hexofuranose

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Abstract

The absolute configuration of the title compound, C₁₈H₂₅O₈P, a derivative of the antibiotic fosfomicin, has been determined through the anomalous-dispersion effect. The crystals are orthorhombic, space group *P*2₁2₁2₁, with *a* = 15.658 (3), *b* = 20.158 (3), *c* = 6.205 (1) Å, *V* = 1958.5 (5) Å³, *Z* = 4, *D*_x = 1.358, *D*_m = 1.358 Mg m⁻³ (flotation in aqueous KI solution), *M*_r = 400.4, m.p. 380–381 K, [α]_D^{24°C} = -6.1° (*c* 1.27 g dm⁻³, CHCl₃), μ (Cu K α) = 1.62 mm⁻¹. Final *R* = 0.044 for 2834 reflexions. The furanoid ring takes a C(4)-*exo* envelope conformation (*E*₄) with *P* = 44.7° and τ_m = 36.7°. The benzyloxy group at C(3) is linked axially, and the C(5) atom of the epoxy group is bound equatorially to C(4). The chirality of *R* at C(5) clarifies the steric course of formation of the α,β -epoxyphosphinoyl compound.

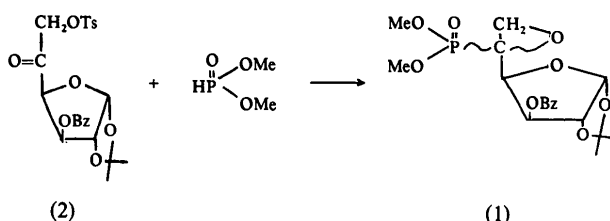
Introduction

Recently, (5*R*)- or (5*S*)-5,6-anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-5-*C*-(dimethoxyphosphinoyl)- α -D-xylo-hexofuranose (1), a derivative of the antibiotic fosfomicin (1,2-epoxypropylphosphonic acid), has been synthesized by a reaction of 3-*O*-benzyl-1,2-*O*-isopropylidene-6-*O*-(*p*-tolylsulphonyl)- α -D-xylo-5-hexulofuranose (2) with dimethyl phosphite (Inokawa, Kawata, Yamamoto, Kawamoto, Yamamoto, Takagi & Yamashita, 1981). The X-ray structural investigation of (1) has been undertaken in order to determine

the chirality at the C(5) atom. The results will clarify the absolute configuration of the derivatives of (1) and the mechanism of the formation of α,β -epoxyphosphinoyl derivatives by the reaction of such ketones as (2) with the phosphite.

Experimental

The specimens for X-ray analysis were recrystallized from a mixed solution of ethyl acetate and hexane as colourless plates with developed faces {010} and elongated along *a*. Weissenberg photographs showed the systematic absences *h*00 for *h* odd, 0*k*0 for *k* odd and 00*l* for *l* odd, indicating the space group to be *P*2₁2₁2₁. A crystal of dimensions 0.50 × 0.23 × 0.25 mm was mounted on a Rigaku four-circle diffractometer with the *a* axis coincident with the ϕ axis of the goniostat. The diffractometer was equipped with a rotating anticathode, and operated at 40 kV and 200 mA. The intensity data were collected within the *hkl* and *hk \bar{l}* octants up to $2\theta = 120^\circ$, using Ni-filtered Cu radiation ($\lambda = 1.5418$ Å) and the ω - 2θ scan method (scan speed 4° min⁻¹ in 2θ ; scan range in 2θ : 1.2° + 0.15° tan θ). Background was measured for 5 s on either side of the peak. Three reference reflexions showed no significant intensity deterioration. The intensities were corrected for Lorentz and polarization factors, but not for absorption. In total 2877 independent reflexions were collected, of which 2834 with $|F_o| > 2\sigma(F)$ were used in the refinement.



Determination of the structure and the absolute configuration

At first the anomalous-dispersion effect was ignored, and 1656 reflexions of $F_o(+)$ with $h \geq 0$, $k \geq 0$ and $l \geq 0$ were used for the structure determination. The

structure was solved by *MULTAN* (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978), the positions of 22 non-H atoms including P being correctly determined. The remaining five atoms were located from a Fourier map. The parameters of the non-H atoms were refined to $R = 0.076$ by a block-diagonal least-squares method (Ashida, 1979).

Table 1. Final atomic parameters (positional $\times 10^4$, for H $\times 10^3$) with *e.s.d.*'s in parentheses

$$B_{eq} = \frac{4}{3} \sum_i \beta_{ii} / a_i^{*2}.$$

	x	y	z	B_{eq}/B_{iso} (\AA^2)
P	5791.8 (5)	1670.0 (4)	1461 (1)	5.08 (3)
O(1)	4282 (1)	3288 (1)	176 (3)	4.88 (9)
O(2)	3665 (1)	3475 (1)	4997 (3)	4.63 (8)
O(3)	3917 (1)	4193 (1)	2288 (3)	5.02 (9)
O(4)	3369 (1)	2090 (1)	1422 (3)	5.30 (9)
O(5)	4683 (2)	2005 (1)	-1769 (4)	6.75 (12)
O(6)	6342 (1)	2090 (1)	3090 (3)	5.51 (9)
O(7)	5149 (1)	1327 (1)	3028 (5)	6.94 (12)
O(8)	6265 (2)	1260 (1)	-11 (5)	7.29 (13)
C(1)	3616 (2)	3606 (1)	1293 (5)	4.55 (12)
C(2)	3354 (2)	3152 (1)	3137 (5)	4.43 (11)
C(3)	3849 (2)	2518 (1)	2761 (4)	4.22 (11)
C(4)	4624 (2)	2775 (1)	1496 (5)	4.31 (11)
C(5)	5098 (2)	2277 (1)	122 (5)	4.81 (13)
C(6)	5367 (3)	2458 (2)	-2056 (5)	6.78 (18)
C(7)	3714 (2)	4163 (1)	4542 (5)	4.75 (13)
C(8)	4439 (3)	4459 (2)	5810 (6)	7.00 (19)
C(9)	2869 (3)	4485 (2)	4970 (8)	7.34 (20)
C(10)	3010 (3)	1547 (2)	2425 (6)	7.06 (19)
C(11)	2520 (2)	1164 (1)	774 (5)	4.84 (13)
C(12)	1648 (2)	1082 (1)	990 (6)	5.57 (14)
C(13)	1184 (2)	749 (2)	-568 (8)	6.89 (18)
C(14)	1579 (2)	498 (2)	-2351 (6)	6.56 (17)
C(15)	2448 (3)	567 (1)	-2570 (6)	6.17 (16)
C(16)	2908 (2)	907 (1)	-1029 (6)	5.60 (15)
C(17)	7089 (2)	2430 (2)	2305 (6)	6.22 (16)
C(18)	5397 (3)	810 (2)	4526 (7)	6.83 (18)
H(1)	322 (2)	366 (2)	19 (5)	2.9 (6)
H(2)	273 (2)	307 (2)	313 (6)	3.6 (7)
H(3)	398 (2)	233 (2)	403 (5)	2.9 (6)
H(4)	505 (2)	299 (1)	256 (4)	1.8 (5)
H(6A)	519 (2)	286 (2)	-267 (6)	3.7 (7)
H(6B)	569 (3)	225 (3)	-260 (9)	10.5 (16)
H(8A)	431 (2)	439 (2)	728 (5)	3.4 (7)
H(8B)	458 (2)	494 (2)	546 (6)	3.7 (7)
H(8C)	504 (2)	415 (2)	561 (6)	4.7 (8)
H(9A)	295 (2)	484 (2)	486 (6)	4.3 (8)
H(9B)	250 (4)	440 (3)	661 (11)	10.6 (16)
H(9C)	249 (3)	441 (2)	414 (7)	6.8 (10)
H(10A)	341 (3)	131 (2)	299 (7)	5.9 (10)
H(10B)	265 (3)	160 (2)	377 (9)	7.6 (12)
H(12)	137 (3)	128 (2)	242 (7)	6.0 (10)
H(13)	64 (3)	74 (2)	-16 (7)	6.5 (10)
H(14)	129 (2)	23 (2)	-348 (7)	5.4 (9)
H(15)	270 (2)	43 (2)	-357 (7)	4.8 (9)
H(16)	350 (2)	101 (2)	-132 (7)	5.8 (9)
H(17A)	701 (3)	295 (3)	295 (10)	9.7 (15)
H(17B)	751 (4)	238 (3)	266 (9)	10.4 (16)
H(17C)	702 (3)	240 (3)	90 (10)	11.2 (17)
H(18A)	575 (3)	58 (3)	372 (9)	8.9 (13)
H(18B)	481 (3)	75 (2)	494 (7)	6.8 (11)
H(18C)	578 (3)	94 (2)	538 (7)	6.7 (11)

Table 2. Comparison of the observed and calculated structure factors for reflexions with significant anomalous-dispersion effects

<i>h k l</i>	$ F_o(+) $	$ F_o(-) $	$ F_c(+) $	$ F_c(-) $
1 6 1	27.8 (3)	29.6 (4)	29.9	31.5
1 18 1	10.8 (2)	9.8 (2)	10.8	10.0
5 3 1	31.7 (4)	33.7 (4)	31.6	32.7
6 2 1	5.5 (1)	4.0 (1)	5.0	3.4
9 1 1	14.6 (2)	16.2 (2)	14.7	15.7
1 1 2	46.9 (6)	49.9 (6)	46.6	48.5
2 4 2	17.0 (2)	19.9 (3)	17.3	18.9
5 11 2	23.3 (3)	25.0 (3)	23.7	24.6
3 4 3	12.6 (2)	14.3 (2)	11.8	13.3
6 7 3	12.7 (2)	14.1 (2)	12.1	13.2
2 5 4	21.3 (3)	22.8 (3)	21.7	22.5

Including all the H atoms, found on a difference Fourier map, subsequent refinement reduced the R to 0.046. The quantity minimized was $\sum w(|F_o| - |F_c|)^2$, with $w = 1.0$ for $|F_o| \leq 10.0$ and $(10.0/|F_o|)^2$ for $|F_o| > 10.0$.

The absolute configuration was determined by least-squares refinements based on 2834 reflexions: $F_o(-)$ with $h > 0$, $k > 0$, and $l < 0$ in addition to the $F_o(+)$. The anomalous-dispersion terms for P, O and C, and atomic scattering factors used were taken from *International Tables for X-ray Crystallography* (1974). The final R was 0.044. Atomic parameters are given in Table 1.*

For the reflexions with $\Delta F_o [= |F_o(+)| - |F_o(-)|] > 3\sigma(F)$, the signs of ΔF_o were the same as those of ΔF_c without exception (Table 2). The least-squares refinements assuming z parameters with inverted signs increased R to 0.050, and none of the ΔF_o signs coincided with those of ΔF_c .

The computations were carried out at the Crystallographic Research Center, Institute for Protein Research, Osaka University, and at the Okayama University Computer Center.

Results and discussion

Molecular structure

The molecular shape is illustrated in Fig. 1. Bond lengths and angles involving the non-H atoms are listed in Table 3, and the endocyclic torsion angles in Table 4.

The furanoid ring takes a C(4)-*exo* envelope conformation (E_4) with pseudorotation parameters P and τ_m (Altona & Sundaralingam, 1972) of 44.7 and 36.7° respectively. The C(4) atom deviates by 0.53 Å from the plane through the other four atoms of the ring. This

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36037 (16 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

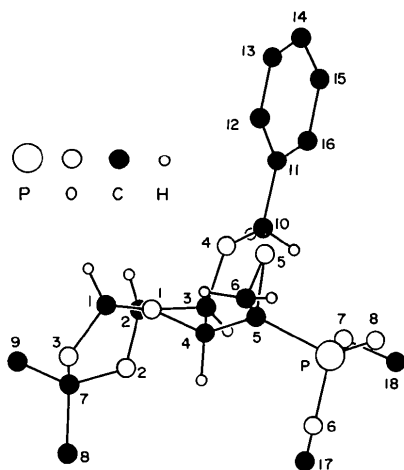


Fig. 1. Molecular structure viewed parallel to the plane through O(1), C(1), C(2) and C(3), and numbering of the non-H atoms. H atoms attached to the phenyl and methyl groups are omitted.

Table 3. Bond lengths (Å) and angles (°) with *e.s.d.*'s in parentheses

P—O(6)	1.575 (2)	O(7)—C(18)	1.449 (5)
P—O(7)	1.561 (3)	C(1)—C(2)	1.522 (4)
P—O(8)	1.437 (3)	C(2)—C(3)	1.513 (4)
P—C(5)	1.835 (3)	C(3)—C(4)	1.535 (4)
O(1)—C(1)	1.407 (4)	C(4)—C(5)	1.512 (4)
O(1)—C(4)	1.424 (4)	C(5)—C(6)	1.462 (5)
O(2)—C(2)	1.412 (4)	C(7)—C(8)	1.505 (5)
O(2)—C(7)	1.417 (4)	C(7)—C(9)	1.497 (6)
O(3)—C(1)	1.415 (4)	C(10)—C(11)	1.495 (5)
O(3)—C(7)	1.436 (4)	C(11)—C(12)	1.382 (5)
O(4)—C(3)	1.414 (4)	C(11)—C(16)	1.374 (5)
O(4)—C(10)	1.379 (4)	C(12)—C(13)	1.383 (6)
O(5)—C(5)	1.449 (4)	C(13)—C(14)	1.365 (6)
O(5)—C(6)	1.419 (5)	C(14)—C(15)	1.375 (6)
O(6)—C(17)	1.441 (4)	C(15)—C(16)	1.379 (6)
O(6)—P—O(7)	101.0 (1)	O(5)—C(5)—C(4)	119.2 (3)
O(6)—P—O(8)	115.8 (2)	C(4)—C(5)—C(6)	119.8 (3)
O(7)—P—O(8)	118.3 (2)	C(5)—O(5)—C(6)	61.3 (2)
C(5)—P—O(6)	104.8 (1)	O(5)—C(5)—C(6)	58.3 (2)
C(5)—P—O(7)	101.3 (2)	O(5)—C(6)—C(5)	60.4 (2)
C(5)—P—O(8)	113.6 (2)	P—C(5)—O(5)	112.3 (2)
C(1)—O(1)—C(4)	109.1 (2)	P—C(5)—C(4)	118.6 (2)
C(2)—O(2)—C(7)	107.9 (2)	P—C(5)—C(6)	114.5 (2)
C(1)—O(3)—C(7)	108.4 (2)	O(2)—C(7)—O(3)	104.3 (2)
C(3)—O(4)—C(10)	115.8 (3)	O(2)—C(7)—C(8)	108.9 (3)
P—O(6)—C(17)	118.9 (2)	O(2)—C(7)—C(9)	109.9 (3)
P—O(7)—C(18)	123.0 (3)	O(3)—C(7)—C(8)	109.0 (3)
O(1)—C(1)—O(3)	110.4 (2)	O(3)—C(7)—C(9)	110.5 (3)
O(1)—C(1)—C(2)	107.2 (2)	C(8)—C(7)—C(9)	113.7 (3)
O(3)—C(1)—C(2)	105.3 (2)	O(4)—C(10)—C(11)	108.1 (3)
O(2)—C(2)—C(1)	104.1 (2)	C(10)—C(11)—C(12)	120.2 (3)
O(2)—C(2)—C(3)	109.8 (2)	C(10)—C(11)—C(16)	121.7 (3)
C(1)—C(2)—C(3)	104.7 (2)	C(12)—C(11)—C(16)	118.1 (3)
O(4)—C(3)—C(2)	109.5 (2)	C(11)—C(12)—C(13)	120.6 (4)
O(4)—C(3)—C(4)	109.0 (2)	C(12)—C(13)—C(14)	120.6 (4)
C(2)—C(3)—C(4)	101.5 (2)	C(13)—C(14)—C(15)	119.4 (4)
O(1)—C(4)—C(3)	104.0 (2)	C(14)—C(15)—C(16)	119.9 (4)
O(1)—C(4)—C(5)	110.0 (2)	C(11)—C(16)—C(15)	121.4 (4)
C(3)—C(4)—C(5)	116.9 (3)		

Table 4. Endocyclic torsion angles (°)

Furanoid ring		Isopropylidene ring	
C(4)—O(1)—C(1)—C(2)	-16.7 (3)	C(7)—O(3)—C(1)—C(2)	-9.9 (3)
O(1)—C(1)—C(2)—C(3)	-7.4 (3)	O(3)—C(1)—C(2)—O(2)	-9.7 (3)
C(1)—C(2)—C(3)—C(4)	26.1 (3)	C(1)—C(2)—O(2)—C(7)	26.2 (3)
C(2)—C(3)—C(4)—O(1)	36.4 (3)	C(2)—O(2)—C(7)—O(3)	-32.6 (3)
C(3)—C(4)—O(1)—C(1)	33.7 (3)	O(2)—C(7)—O(3)—C(1)	25.9 (3)

conformation may reduce the steric strain [C(3)—C(4)—C(5) 116.9 (3)°] caused by the interactions O(4)···C(5) 2.850 (4) Å and P···C(3) 3.581 (3) Å. O(4) and C(5) are related by the torsion angle τ [O(4)—C(3)—C(4)—C(5)] -42.4 (3)°. The O(1)—C(1) bond is significantly shorter than the O(1)—C(4) bond, and the C(3)—C(4) bond is longer than the other C—C bonds in the ring, as found in some 1,2-*O*-isopropylidene-3,4-disubstituted furanoid rings (Rettig & Trotter, 1977; Phillips & Trotter, 1977). The configurations at C(1), C(2), C(3) and C(4) are *R*, *R*, *S* and *S*, respectively, as expected from the native origin of the furanoid ring.

The isopropylidene ring has a slightly twisted C(7)-*exo* envelope conformation. C(7) deviates by 0.42 Å from the plane through the other four atoms. Bond lengths and angles in the ring are in agreement with those found for isopropylidene rings fused to sugar rings (Riche & Pascard-Billy, 1975). A short non-bonding contact of 3.015 (6) Å is found between C(2) and C(9). This may cause the larger exocyclic angles of O(2)—C(7)—C(9) and O(3)—C(7)—C(9) compared to the angles involving the C(7)—C(8) bond.

The Newman projections viewed down the bonds C(4)—C(5), C(5)—P and C(5)—C(6) are shown in Fig. 2. The C(4)—C(5)—P—O(8) side chain extends equatorially, with τ [O(1)—C(4)—C(5)—P] 166.9 (2)° and τ [C(4)—C(5)—P—O(8)] -175.0 (2)°. The configuration of C(5) is *R* as seen from Fig. 2(c). This fact and the *trans* conformation of O(1)—C(4)—C(5)—P indicate that (1) is presumably formed by attack of the phosphite anion on the carbonyl group of (2) from the *trans* side of the O(1)—C(4) bond of the furanoid ring.

For the epoxide ring, the conformations of C(5)—C(6) and C(5)—O(5) bonds around the C(4)—C(5) bond are *gauche* (Fig. 2a): τ [C(3)—C(4)—C(5)—C(6)] 136.3 (3), τ [C(3)—C(4)—C(5)—O(5)] 68.2 (4)°. The C—C bond in the ring is slightly longer than the C—O bonds. The

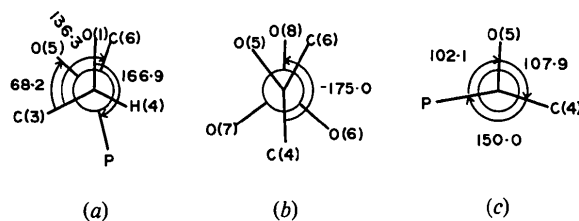


Fig. 2. Newman projections viewed down along the bonds (a) C(4)—C(5), (b) C(5)—P, and (c) C(5)—C(6). The *e.s.d.*'s of the torsion angles (°) are 0.2–0.4°.

endocyclic and exocyclic bond angles are in agreement with those recently found in other epoxides: humulene triepoxide (Murray-Rust & Murray-Rust, 1977) and toxisterol₂-D epoxide (Lindley & Mahmoud, 1978).

The P—O(8) bond is situated at the *syn* position to the epoxide ring. Its length is shorter than the 1.47 Å found in organic phosphates (Gałdecki & Głowka, 1977), and 1.48 Å in the phenylphosphinoyl group (Luger, Yamashita & Inokawa, 1980). The other bond lengths and angles in the dimethoxyphosphinoyl group are in agreement with the corresponding values in the phosphates.

The benzyloxy side chain extends axially with a *gauche-trans-gauche* conformation: $\tau[C(2)-C(3)-O(4)-C(10)] -106.9$ (3), $\tau[C(3)-O(4)-C(10)-C(11)] 179.0$ (2), and $\tau[O(4)-C(10)-C(11)-C(12)] -118.0$ (3) $^\circ$. The side chain takes an *anti* orientation with respect to the isopropylidene ring: $\tau[O(2)-C(2)-C(3)-O(4)] 159.7$ (2).

Molecular packing

The crystal structure viewed along *c* is shown in Fig. 3. Molecules are packed with van der Waals interactions. Intimate contacts are found between the molecules related by a 2₁ axis along *a*, C(17ⁱ)...O(4^{iv})

3.210 (4), C(17ⁱ)...C(11^{iv}) 3.484 (5) Å. Many contacts also exist between the molecules related by a *c* translation, although the distances are rather long, the shortest being 3.784 (6) Å between C(10ⁱ) and C(15^{vi}). The molecular sheets are thus formed in the planes parallel to (010), and stacked along *b* by weak interactions [C(9ⁱ)...C(9ⁱⁱ) 3.908 (10) Å, O(3ⁱ)...C(18ⁱⁱⁱ) 3.612 (4) Å], consistent with the morphology of the crystals. The benzene rings (i) and (v) have contacts C(11)...C(15) 3.638 (5) Å and C(16)...C(15) 3.708 (6) Å. The dihedral angle of 58.2 $^\circ$ between the rings is close to those found frequently in more simple benzene derivatives (Haisa, Kashino, Ueno, Shinozaki & Matsuzaki, 1980).

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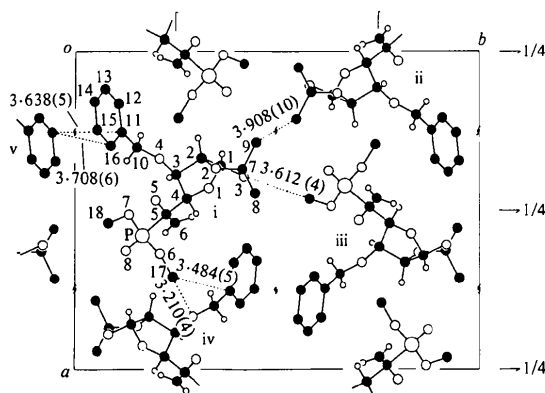


Fig. 3. Projection of the crystal structure viewed down *c*. H atoms attached to the phenyl and methyl groups are omitted. Dotted lines indicate intermolecular contacts. Symmetry code: (i) x, y, z ; (ii) $\frac{1}{2} - x, 1 - y, \frac{1}{2} + z$; (iii) $1 - x, \frac{1}{2} + y, \frac{1}{2} - z$; (iv) $\frac{1}{2} + x, \frac{1}{2} - y, -z$; (v) $\frac{1}{2} - x, -y, \frac{1}{2} + z$; (vi) $x, y, 1 + z$. Distances are in Å.