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(2*S*)-2-[1-(2,4-Difluoro-5-iodophenyl)-2-deoxy-β-D-ribofuranos-5-yloxy]-8-methyl-4*H*-1,3,2-benzodioxaphosphole 2-oxide

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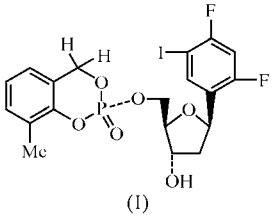
The title compound, $C_{19}H_{18}F_2IO_6P$, prepared as a potential antiviral and anticancer agent from 3-methylsalicylchlorophosphane and 1-(2,4-difluoro-5-iodophenyl)-2-deoxy-β-D-ribofuranose, is one of a 1:1 mixture of two diastereomers. The diastereomers differ in their configuration, *S* or *R*, at the asymmetric phosphorus center. X-Ray crystallographic analysis of the title compound has determined the absolute configuration at the asymmetric P center to be *S*.

Comment

A group of synthetic 3-substituted (H, Me or OMe) cyclosaligenyl derivatives of 1-(2-deoxy-β-D-ribofuranosyl)-2,4-difluoro-5-iodo(or trifluoromethyl)benzene, previously evaluated as antiviral and anticancer agents (Wang *et al.*, 2001), have been synthesized. These cyclosaligenyl derivatives were designed to act as thymidine kinase-bypass pronucleotides that would give rise to the intracellular release of the monophosphate derivative of 1-(2-deoxy-β-D-ribofuranosyl)-2,4-difluoro-5-iodo(or trifluoromethyl)benzene (Meier, De Clercq & Balzarini, 1998; Meier *et al.*, 1999). The configuration of the phosphorus center in cyclosaligenyl phosphate has so



(I)

far been assigned only by comparison with the known stereochemistry of the model compound using CD (circular dichroism) spectroscopy (Meier, Lorey *et al.*, 1998). We now report the results of the X-ray crystal structure analysis for the title compound, (I), one of the two diastereomers of iodinated cyclosaligenyl phosphate produced in the reaction, in order to establish the absolute configuration at the asymmetric P center.

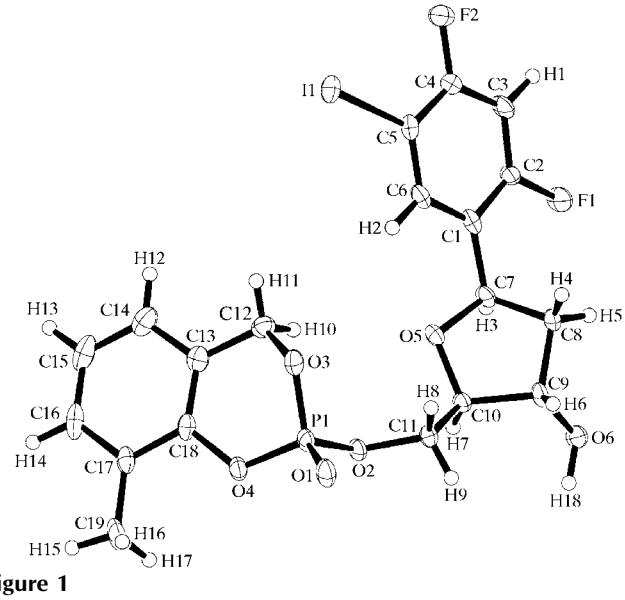


Figure 1
A view of the molecule of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 35% probability level and H atoms are shown as small spheres of arbitrary radii.

Compound (I) was synthesized by the oxidation reaction of the coupled product of 1-(2-deoxy-β-D-ribofuranosyl)-2,4-difluoro-5-iodobenzene with 3-methylsaligenylchlorophosphane. Removal of the solvent *in vacuo* gave a residue which was purified by flash silica-gel column chromatography using CH_2Cl_2–EtOAc (1:1 *v*/*v*) as eluant, to give a 1:1 mixture of the respective *S* and *R* diastereomeric products. Single crystals of optically pure (I) suitable for X-ray crystallographic analysis were obtained by fractional crystallization of an ether solution of the diastereomeric mixture, according to the following procedure. Subsequent flash silica-gel column chromatography of the 1:1 mixture of *S* [title compound (I)] and *R* diastereomeric isomers with CH_2Cl_2–EtOAc (3:2 *v*/*v*) as

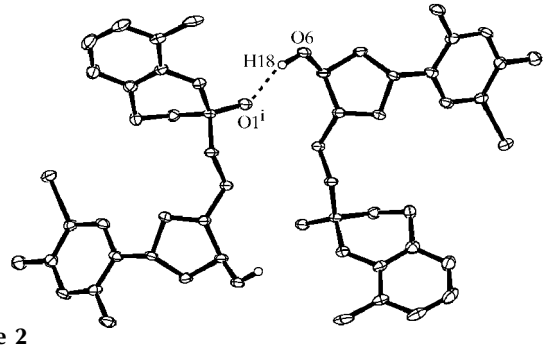


Figure 2
A molecular view of (I), showing the hydrogen-bonding pattern (dashed line). The two molecules are related by the crystallographic 2_1 screw axis, with atom O6 of the left-hand molecule hydrogen bonding to atom O1 of a molecule related to the right-hand molecule by a translation along the *b* axis, leading to the formation of an infinite spiral arrangement along the twofold screw axis. The symmetry code is the same as in Table 2.

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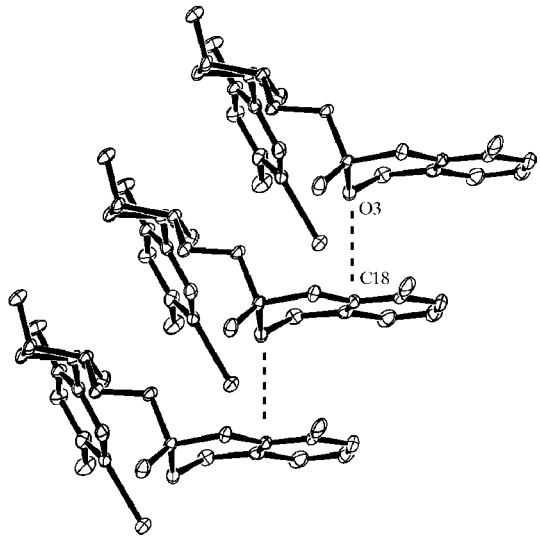

Figure 3
A packing diagram for (I), showing the π–π interactions between atoms O3 and C18 (dashed lines). The molecules shown are related by translations along the *b* axis.

eluant gave the fast-eluting isomer, (I), and the slow-eluting isomer, respectively. The fast-eluting isomer, (I), was recrystallized from ether to afford optically pure crystals. Characterization of (I) by ^{1}H and ^{31}P NMR spectroscopy showed that the ^{31}P resonance was more shielded (higher field), but in the ^{1}H NMR spectra, the benzyl-CH_2 H atoms were less shielded than those of the slow-eluting isomer. Thus, the less polar diastereisomer, (I), was successfully crystallized from ether as colorless needles, which were subsequently subjected to X-ray crystallographic analysis. The crystallographic analysis afforded the assignment of the absolute configuration of the compound at the asymmetric P center in the cyclosaligenyl ring as *S*.

The molecular structure of (I) is shown in Fig. 1 and selected geometric parameters are listed in Table 1. The P1═O1 bond [1.454 (4) Å] indicates double-bond character and is shorter than P1—O2, P1—O3 and P1—O4 [1.565 (4), 1.557 (4) and 1.565 (4) Å, respectively]. The torsion angles at the phosphate, O1—P1—O2—C11, O1—P1—O3—C12 and O1—P1—O4—C18, are −48.3 (3), −170.6 (3) and 136.5 (4)°, respectively. The absolute stereochemistry is confirmed by the value of the Flack (1983) parameter [0.02 (2)].

Our labeling of the deoxyribose ring differs from the standard labeling and in our description of its conformation we therefore use standard labels for the atoms followed by our labeling in parentheses. The O4′(O5)-*endo* conformation of the deoxyribose ring present in (I) is different from the C2′-*endo* conformation found in the structurally related compounds (*E*)-1-(2-deoxy-β-D-ribofuranosyl)-2,4-difluoro-5-(2-iodovinyl)benzene (Mark *et al.*, 2001) and 1-(2-deoxy-β-D-ribofuranosyl)-2,4-difluoro-5-methylbenzene (Guckian & Kool, 1997). This O4′(O5)-*endo* conformation is consistent with the larger C3′—C4′—O4′—C1′(C9—C10—O5—C7) torsion angle of 32.4 (5)° relative to the smaller C1′—C2′—C3′—C4′(C7—C8—C9—C10) torsion angle of −13.3 (5)°. The 2,4-difluoro-5-iodobenzene ring in (I) is *anti* with respect to the deoxyribose moiety, as measured by the O4′—C1′—C1—C2(O5—C7—C1—C2) torsion angle of −171.2 (5)°.

Inspection of the packing structure of (I) reveals that intermolecular interactions are formed through hydrogen bonding between a hydroxyl group (O6—H18) of the sugar ring and a phosphate O atom (P1═O1) (Fig. 2 and Table 2), and also through π–π interactions between the methylsaligenyl aromatic ring, represented by the short intermolecular distance [3.011 (8) Å] between atoms O3 and C18 of the cyclosaligenyl rings and the molecules related by unit-cell translations along the crystallographic *b* axis (Fig. 3). Intermolecular C—H···F—C hydrogen-bonding interactions have been observed in the crystal structure of 1-deoxy-1-(2,4-difluorophenyl)-β-D-ribofuranose (Bats *et al.*, 2000). The crystal structure of (I), however, shows no intermolecular hydrogen bonding involving the F atoms of the aryl ring.

Experimental

The title compound was prepared from the coupling reaction of methylsalicylchlorophosphane and 1-(2,4-difluoro-5-iodophenyl)-2-deoxy-β-D-ribofuranose, followed by oxidation using *tert*-butyl hydroperoxide (Sun *et al.*, 2003) (m.p. 408–409 K; yield 20%). ^{1}H NMR ($CDCl_3$, p.p.m.): 7.86 (*t*, *J* = 7.6 Hz, 1H, difluorophenyl H), 7.19 (*d*, *J* = 6.9 Hz, 1H, saligenyl H4), 7.05 (*dd*, *J* = 7.3 and 6.9 Hz, 1H, saligenyl H5), 6.94 (*d*, *J* = 7.3 Hz, 1H, saligenyl H6), 6.82 (*dd*, *J* = 9.8 and 7.6 Hz, 1H, difluorophenyl H), 5.38 (*d*, *J* = 16.5 Hz, 2H, benzyl-CH_2), 5.33 (*dd*, *J* = 10.4 and 6.1 Hz, 1H, H1′), 4.51 (*ddd*, *J* = 6.5, 3.4 and 3.1 Hz, 1H, H3′), 4.26–4.47 (*m*, 2H, H5′), 4.10–4.18 (*m*, 1H, H4′), 2.40 (*ddt*, *J* = 12.8, 5.8 and 1.8 Hz, 1H, H2′α), 2.30 (*s*, 3H, CH_3), 1.89–2.00 (*m*, 1H, H2′β), 1.82 (*br* s, 1H, OH); ^{31}P NMR ($CDCl_3$, p.p.m.): −8.69.

Crystal data

$C_{19}H_{18}F_2IO_6P$
M_r = 538.22
Monoclinic, $P2_1$
a = 14.552 (5) Å
b = 4.610 (2) Å
c = 15.989 (5) Å
β = 109.86 (3)°
V = 1008.9 (6) Å^3
Z = 2
D_x = 1.772 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 9501 reflections
θ = 3.3–27.5°
μ = 1.72 mm^{-1}
T = 123.1 K
Needle, colorless
0.10 × 0.10 × 0.05 mm

Data collection

Rigaku R-AXIS RAPID diffractometer
ω scans
Absorption correction: numerical (*ABSCOR*; Higashi, 1999)
T_{min} = 0.641, T_{max} = 0.800
9720 measured reflections
4063 independent reflections
3621 reflections with $F^2 > 2\sigma(F^2)$
R_{int} = 0.053
θ_{max} = 27.5°
h = −18 → 18
k = −5 → 5
l = −20 → 20

Refinement

Refinement on F^2
$R(F)$ = 0.037
$wR(F^2)$ = 0.096
S = 1.06
4063 reflections
282 parameters
H-atom parameters constrained
$w = 1/[0.0002F_o^2 + 0.6\sigma(F_o^2)]/(4F_o^2)$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 2.12 e Å^{-3}
$\Delta\rho_{min}$ = −2.03 e Å^{-3}
Extinction correction: Larson (1970), equation 22
Extinction coefficient: 61 (6)
Absolute structure: Flack (1983), with 1493 Friedel pairs
Flack parameter = 0.02 (2)

H atoms were treated as riding, with C—H = 0.95 Å and O—H = 0.93 Å, and with U_{iso}(H) = 1.3U_{eq}(C,O).

Table 1
Selected geometric parameters (Å, °).

I1—C5	2.088 (5)	P1—O3	1.557 (4)
P1—O1	1.454 (4)	P1—O4	1.565 (4)
P1—O2	1.565 (4)	O4—C18	1.410 (5)
O2—P1—O1	114.1 (2)	O3—P1—O2	106.9 (2)
O4—P1—O1	113.0 (2)	O4—P1—O3	105.3 (2)
C10—O5—C7—C8	−40.8 (5)	C7—C8—C9—C10	−13.3 (5)
C7—O5—C10—C9	32.4 (5)	O6—C9—C10—C11	110.6 (5)
C2—C1—C7—O5	−171.2 (5)	C8—C9—C10—O5	−10.7 (5)
O5—C7—C8—C9	33.1 (5)	C9—C10—C11—O2	−172.1 (3)

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O6—H18···O1^{i}	0.93	1.87	2.719 (5)	150

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

Data collection: *PROCESS-AUTO* (Rigaku, 1998); cell refinement: *PROCESS-AUTO*; data reduction: *CrystalStructure* (Rigaku/MSC, 2004); program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Watkin *et al.*, 1996); molecular graphics: *ORTEP*II (Johnson, 1976); software used to prepare material for publication: *CrystalStructure*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SX1133). Services for accessing these data are described at the back of the journal.

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