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1-(2′,3′-Anhydro-5′-*O*-benzoyl-β-D-lyxofuransoyl)-5-fluorouracil

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Key indicators

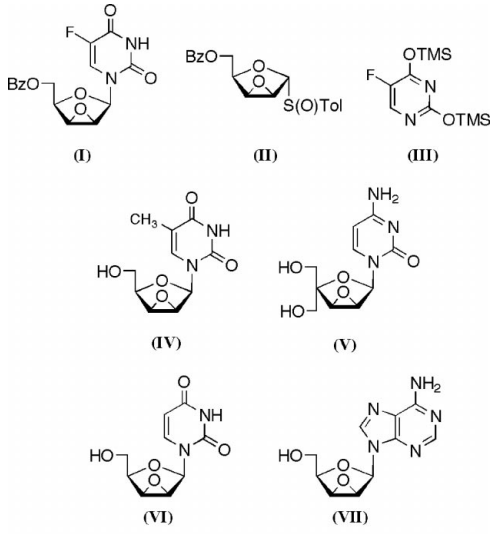
Single-crystal X-ray study
T = 298 K
Mean σ(C–C) = 0.010 Å
R factor = 0.052
wR factor = 0.151
Data-to-parameter ratio = 8.1

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

The crystal structure of the title compound, $C_{16}H_{13}FN_2O_6$, was determined in order to establish the relative stereochemistry between the nucleoside base and the epoxide ring oxygen. This analysis allowed us to establish that the relationship of these two groups is *cis*. The furanose ring adopts an envelope conformation in which the oxygen is displaced above the plane ($^\circ E$). The pseudorotational phase angle (P) is 88.5° and the puckering amplitude (τ_m) is 29.8°. The conformation about the C4—C5 bond is *gauche–trans* (*ap*) and the nucleoside base adopts the *anti* orientation.

Comment

2′,3′-Anhydro-β-D-lyxofuranosyl nucleosides are important intermediates in the synthesis of nucleoside derivatives. Modification of these structures can be readily performed through reactions involving the epoxide moiety (Huryn & Okabe, 1992; Roussev *et al.*, 1997; Miah *et al.*, 1998; Hirota *et al.*, 1999; Hirota *et al.*, 2000). Because nucleophilic opening of the epoxide ring in these compounds usually proceeds such that the nucleophile attacks regioselectively at C3′, they have found particular application in the synthesis of *β-arabino*-furanosyl nucleosides (Codington *et al.*, 1962; Hollenberg *et al.*, 1977). Some 2′,3′-anhydro-β-D-*lyxo*furanosyl nucleosides, or their corresponding 5′ triphosphates, have also been shown to possess antiviral activity (Krayevsky *et al.*, 1988; Dimoglo *et al.*, 1997; Webb *et al.*, 1988).



Bz = benzoyl
Tol = *p*-toluyl
TMS = trimethylsilyl

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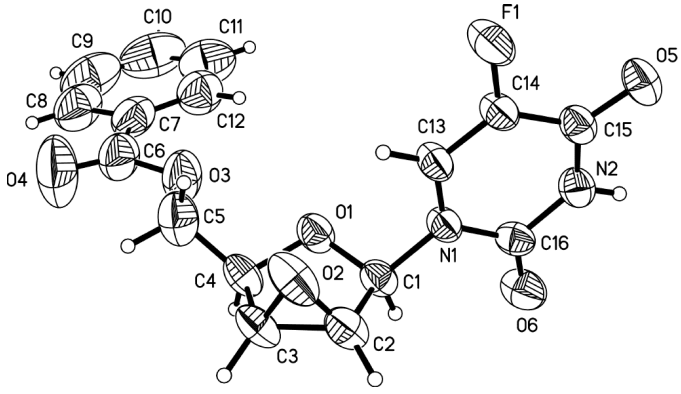

Figure 1
A plot of the molecular structure of (I), with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small circles of an arbitrary radius.

We have recently developed a highly convergent method for the synthesis of 2′,3′-anhydro-β-D-*lyxo*furanosyl nucleosides that proceeds *via* the coupling of glycosyl sulfoxide (II) and a silylated nucleoside base, *e.g.* (III), mediated by trifluoromethanesulfonic acid anhydride (Callam *et al.*, 2003). This approach is significantly more efficient than previously developed methods for the synthesis of compounds of this type, of which all have involved the installation of the epoxide ring on a preformed nucleoside. However, unambiguously determining the stereochemistry at the anomeric center in (I) was not possible using NMR spectroscopy and we therefore crystallized this compound so that the structure could be proven. The key issue was the relative stereochemistry between the epoxide oxygen and the nucleoside base.

The structure of (I) in the crystal is given in Fig. 1 and it is clear that there is a *cis* relationship between the nucleoside base and the epoxide oxygen. This is the relative stereochemistry that would have been predicted for a product formed by condensation of (II) and (III), given previous results on the glycosylation of alcohols by (II) (Gadikota *et al.*, 2003). Note also that the absolute configuration for the structure was assigned on the basis of the known configuration of (II), which was synthesized from D-arabinose (Gadikota *et al.*, 2003). The furanose ring in (I) adopts an envelope conformation, in which the ring oxygen is displaced above the plane ($^{\circ}E$). The pseudorotational phase angle (P) is 88.5° and the puckering amplitude (τ_m) is 29.8° (Altona & Sundaralingam, 1972). In this regard, the structure is similar to other 2′,3′-anhydro-β-D-lyxofuranosyl nucleotides for which crystal structures have been determined, *e.g.* (IV) and (V) (Gurskaya *et al.*, 1990, 1996) or for which molecular-mechanics calculations have been carried out, *e.g.* (IV), (VI) and (VII) (Koole *et al.*, 1991). In these compounds, the furanose and epoxide O atoms are on the same side of the furanose ring, resulting in a boat-like structure. In addition, the five-membered rings in these systems are generally less puckered than other nucleoside derivatives, which typically have τ_m magnitudes in the range 34–40° (Sanger, 1984). Similar structural features have been observed in *ab initio* and density functional theory calculations on 2,3-anhydro-D-*lyxo*furanosyl glycosides (Callam *et al.*, 2001) and in the crystal structure of a 2,3-anhydro-D-*lyxo*furanosyl thioglycoside (Gallucci *et al.*, 2000).

The orientation about the C4—C5 bond in (I) is *gauche–trans* (*ap*) (Sanger, 1984). This bond adopts the same orientation in the crystal structure of (IV) and in low-energy geometries obtained from molecular mechanics calculations of (IV), (VI) and (VII), thus indicating that the presence of the benzoate ester on O3 in (I) does not alter the favored rotamer around the C4—C5 bond, as compared to the unprotected nucleosides. In the crystal structure of (V), however, the orientation of this bond differs from that in (I), (IV), (VI) and (VII), which is likely due to the presence of the additional hydroxymethyl group substituent at C4. Finally, in (I) the nucleoside base adopts the *anti*-conformation, which is the same as in compounds (IV)–(VII).

Experimental

Sulfoxide (II) (0.5 mmol), 2,6-di-*tert*-butyl-4-methyl pyridine (2.5 mmol), and 4 Å molecular sieves (0.1 g) were dried for 3 h under vacuum in the presence of P_2O_5. To this mixture was added CH_2Cl_2 (10 ml) and the reaction mixture was cooled to 195 K. Triflic anhydride (0.6 mmol) was added and the mixture was stirred for 10 min before a solution of the persilylated nucleoside [(III), 0.6 mmol; Nishimura & Iwai, 1964] in CH_2Cl_2 (1.0 ml) was added dropwise by syringe over 2 min. After 15 min, the reaction mixture turned dark brown–green and a saturated aqueous solution of $NaHCO_3$ was added, before the solution was allowed to warm to room temperature. The resulting solution was filtered through Celite, dried, filtered, and concentrated, to yield a crude oil that was purified by chromatography (2:1, hexanes/EtOAc), yielding (I) (0.35 mmol, 70%) as an oil. The product was recrystallized from 10:1 dichloromethane–hexane (m.p.: 366–367 K).

Crystal data

$C_{16}H_{13}FN_2O_6$
M_r = 348.28
Monoclinic, $P2_1$
a = 7.3537 (8) Å
b = 5.5149 (8) Å
c = 19.290 (2) Å
β = 100.928 (9)°
V = 768.13 (17) Å^3
Z = 2
D_x = 1.506 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 96 reflections
θ = 2.8–25.3°
μ = 0.12 mm^{-1}
T = 298 (2) K
Plate, colorless
0.32 × 0.20 × 0.07 mm

Data collection

Bruker $P4$ diffractometer
$\theta/2\theta$ scans
Absorption correction: ψ scan (*XPREP*; Bruker, 2001)
T_{min} = 0.834, T_{max} = 0.981
3910 measured reflections
1839 independent reflections
980 reflections with $I > 2\sigma(I)$
R_{int} = 0.048
θ_{max} = 27.5°
$h = -9 \rightarrow 9$
$k = -7 \rightarrow 7$
$l = -25 \rightarrow 25$
3 standard reflections
every 97 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.052
$wR(F^2)$ = 0.151
S = 1.05
1839 reflections
227 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0707P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.27 e Å^{-3}
$\Delta\rho_{min}$ = −0.27 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.039 (8)

Table 1
Selected geometric parameters (Å, °).

O1—C1	1.404 (5)	N1—C1	1.453 (6)
O1—C4	1.450 (6)	C1—C2	1.507 (7)
O2—C3	1.441 (6)	C2—C3	1.457 (7)
O2—C2	1.452 (7)	C3—C4	1.506 (8)
O3—C5	1.445 (8)	C4—C5	1.469 (7)
C1—O1—C4	109.0 (3)	O2—C2—C3	59.4 (3)
C3—O2—C2	60.5 (3)	C3—C2—C1	105.2 (4)
O1—C1—N1	108.3 (3)	O2—C3—C2	60.1 (4)
O1—C1—C2	105.7 (4)	C2—C3—C4	108.3 (4)
N1—C1—C2	115.2 (4)	O1—C4—C3	102.8 (4)
C4—O1—C1—C2	−30.4 (5)	C1—O1—C4—C3	29.2 (5)
C13—N1—C1—O1	57.7 (5)	C2—C3—C4—O1	−16.5 (5)
C16—N1—C1—O1	−126.0 (5)	O1—C4—C5—O3	58.9 (6)
O1—C1—C2—C3	18.6 (5)	C3—C4—C5—O3	174.1 (5)
C1—C2—C3—C4	−0.8 (6)		

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N2—H2···O5^{i}	0.86	2.01	2.846 (5)	165

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

All H atoms were refined using a riding model, with bond lengths of 0.86 (N—H), 0.93 (aryl H), 0.97 (CH_2), and 0.98 Å (epoxide ring H). For all H atoms, $U_{iso}(H) = 1.2U_{eq}$(parent). Friedel pair reflections were merged prior to final refinement, as the refined Flack (1983) parameter was meaningless.

Data collection: *XSCANS* (Bruker, 1996); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *XP* (Bruker, 2001); software used to prepare material for publication: *SHELXL*97.

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