

**(E)-1-(2'-Deoxy- β -D-ribofuranosyl)-
2,4-difluoro-5-(2-iodovinyl)benzene**Brian L. Mark,^{a†} Jonathan C. Parrish,^{a†} Zhi-Xian Wang,^b
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Received 21 January 2001

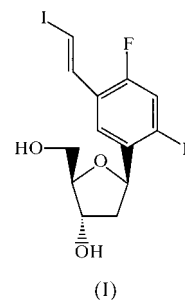
Accepted 20 March 2001

This analysis of the title compound, C₁₃H₁₃F₂IO₃, establishes the orientation of (*E*)-5-(CH=CH—I) as antiperiplanar (*ap*) to the C—C bond (5–6 position) of the 2,4-difluorophenyl ring system, with the (*E*)-5-(CH=CH—I) H atom located in close proximity (2.17 Å) to the F4 atom of the 2,4-difluorophenyl moiety.

Comment

The development of 2'-deoxyuridine derivatives possessing novel 2-carbon substituents at the C-5 position, which are potent and selective antiviral agents, represents an important area of antiviral drug design. Accordingly, (*E*)-5-(2-iodovinyl)-2'-deoxyuridine (IVDU) was identified as a highly specific inhibitor of herpes virus replication due to its specific phosphorylation by virus-encoded thymidine kinase (TK) in virus-infected, but not in uninfected, host cells (De Clercq, 1983). 2,4-Difluoro-5-methyl-1-(2'-deoxy- β -D-ribofuranosyl)-benzene (DFT) was designed as a non-polar hydrophobic unnatural thymidine mimic that retains a close structural, steric and isoelectronic relationship to natural thymidine (T) (Schweitzer & Kool, 1994). DFT was envisaged to be a valuable model compound to determine the importance of hydrogen bonding and base stacking in the formation of stable DNA duplex structures. The 2,4-difluoro-5-methylphenyl moiety of DFT is isosteric with the thymine (5-methyluracil) base moiety of thymidine, where F is the isosteric replacement for O, CH replaces NH, and the thymine N1 is replaced by an *sp*²-hybridized C atom. Although aromatic substituted F atoms can participate in weak intramolecular hydrogen bonds (Jones & Watkinson, 1964), NMR titration experiments using 2,4-difluorotoluene (the aryl moiety of DFT) did not show any evidence of hydrogen bonding with potential complementary partners (Schweitzer & Kool, 1995). Nonetheless, the 5'-tri-

phosphate of DFT (DFTTP) is a good substrate for the Klenow fragment (KF, *exo*-mutant) of *E. coli* DNA polymerase 1 and is inserted into replicating DNA strands. Steady-state measurements indicated that DFTTP was inserted into a template opposite adenine (A) with an efficacy (V_{\max}/K_m) only 40-fold lower than that for the 5'-triphosphate of thymidine. Furthermore, DFTTP was inserted opposite A, relative to cytidine (C), guanidine (G) or thymidine (T), with a selectivity (fidelity) nearly as high as that for the 5'-triphosphate of thymidine (Moran *et al.*, 1997).



We now describe the X-ray analysis of 2,4-difluoro-5-methyl-1-(2'-deoxy- β -D-ribofuranosyl)benzene, (I), to determine the orientation of the (*E*)-5-(2-iodovinyl) substituent, and whether a potential intramolecular hydrogen-bonding interaction between the (*E*)-CH=CH—I moiety and the F4 substituent exists. The title compound, which is an unnatural mimic of (*E*)-5-(2-iodovinyl)-2'-deoxyuridine, warrants evaluation as an antiviral agent.

The overall conformation of the title compound is similar to that found in other nucleosides. The glycosidic torsion angle χ (O4'—C1'—C1—C6) is 18.5 (7)° (*anti* conformation), and the sugar ring adopts a C2'-*endo* conformation, with a displacement of C2' by 0.60 (2) Å from the least-squares plane through the other four ring atoms, given by the equation $0.7607x + 0.6453y - 0.0707z = -5.5105$.

The root-mean-square deviation of the four atoms in this plane is 0.015 Å, with a maximum deviation of 0.018 Å. The orientation of the C5'—O5' bond is *trans* to C4'—O4' and *gauche* to C3'—C4'. This *trans-gauche* orientation of the C5'—O5' bond and C2'-*endo* conformation of the sugar ring is most similar to the crystal structure of 2'-deoxyuridine (Rahman & Wilson, 1972) and differs from the C3'-*exo* conformation seen in the crystal structure of (*E*)-5-(2-bromovinyl)-2'-deoxyuridine (Párkányi *et al.*, 1983).

Bond lengths for the 2,4-difluoro-(*E*)-5-(2-iodovinyl)-benzene base mimic are nearly identical with analogous bond lengths for the thymine base (Young *et al.*, 1969) and a 2,4-difluorotoluene base mimic from a deoxynucleoside analogue recently described by Guckian & Kool (1997). Aside from the 5-(2-iodovinyl) substituent, all bond lengths within the base mimic of the title compound are within 0.07 Å of the analogous bond lengths for the thymine base and the 2,4-difluorotoluene base mimic. However, as observed in the crystal structure of the 2,4-difluorotoluene deoxynucleoside (Guckian & Kool, 1997), the F—C bond lengths of the 2,4-difluorotoluene base mimic (both 1.37 Å) and the analogous

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bond lengths in the title compound (both 1.36 Å) differ substantially from the C=O bond lengths of thymine (1.23 and 1.21 Å).

The 2-iodovinyl group of the title compound is anti-periplanar (*ap*) to the C5–C6 bond of the 2,4-difluorobenzene ring. The least-squares plane of the 2-iodovinyl group makes an angle of 5.3 (8)° with the least-squares plane of the 2,4-difluorobenzene ring. The X-ray crystal structure for (*E*)-5-(2-bromovinyl)-2'-deoxyuridine has a similar conformational feature; the best plane of the 2-bromovinyl moiety is at an angle of 6° with respect to the plane of the uracil ring. In contrast with the *ap* conformation seen for the 2-bromo and 2-iodovinyl substituents of the compounds described above, the X-ray crystal structure for 5-vinyl-2'-deoxyuridine showed the unsubstituted vinyl group to be synperiplanar (*sp*) to the 5,6-olefinic bond and inclined at an angle of 12° to the best plane of the uracil ring (Hamor *et al.*, 1978).

The X-ray crystal structure of (*E*)-5-(2-bromovinyl)-2'-deoxyuridine indicates that H8 of the (*E*)-5-(C7H=C8H–Br) substituent donates an intramolecular hydrogen bond to the uracil O4 atom (Párkányi *et al.*, 1983). A similar hydrogen-bonding interaction is observed in the title compound, as evidenced by the intramolecular distance observed between H8 and F4 of 2.17 Å (Fig. 1).

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) and related fluorobenzene crystal structures (Thalladi *et al.*, 1998). The crystal structure of the title compound contains no intermolecular hydrogen bonds involving F atoms of the aryl ring. The only intermolecular hydrogen-bonding interactions formed in the crystal structure are between the 3'- and 5'-hydroxyl groups of the sugar rings. Intermolecular interac-

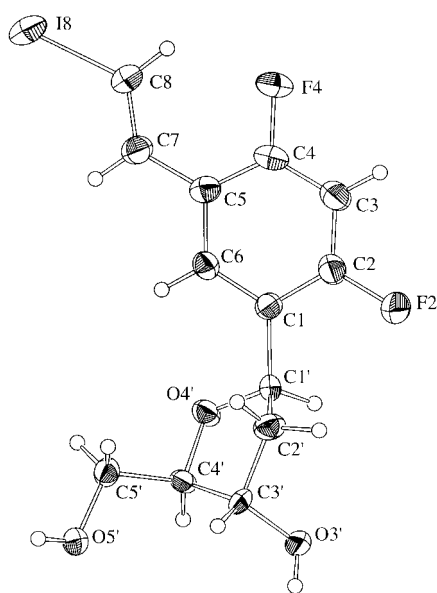


Figure 1
ZORTEP (Zsolnai & Huttner, 1994) diagram of the title compound showing the atom-labelling scheme. Displacement ellipsoids are at the 50% probability level.

tions of the 5-(2-iodovinyl)-2,4-difluorobenzene base mimic of the title compound appear to be limited to non-polar van der Waals contacts. A similar hydrogen-bonding network is observed in the crystal structure of the 2,4-difluorotoluene deoxynucleoside analogue, where only the sugar-ring hydroxyl groups are involved in intermolecular hydrogen-bonding interactions (Guckian & Kool, 1997).

Experimental

The title compound (Wang *et al.*, 1999) was dissolved in a minimum amount of methylene chloride and then diluted with an equal volume of hexanes. Slow evaporation of the methylene chloride from this solution resulted in recrystallization of the title compound. Yellow crystals of appropriate size were obtained after 1–2 d.

Crystal data

$C_{13}H_{13}F_2IO_3$	$D_x = 1.911 \text{ Mg m}^{-3}$
$M_r = 382.13$	Mo $K\alpha$ radiation
Monoclinic, $P2_1$	Cell parameters from 4139 reflections
$a = 9.2884 (8) \text{ \AA}$	$\theta = 1.9\text{--}25.7^\circ$
$b = 6.7527 (6) \text{ \AA}$	$\mu = 2.44 \text{ mm}^{-1}$
$c = 10.6582 (9) \text{ \AA}$	$T = 193 (2) \text{ K}$
$\beta = 96.5141 (14)^\circ$	Plate, clear pale yellow
$V = 664.19 (10) \text{ \AA}^3$	$0.23 \times 0.18 \times 0.04 \text{ mm}$
$Z = 2$	

Data collection

Bruker SMART CCD diffractometer	2464 independent reflections
φ and ω scans	2334 reflections with $I > 2\sigma(I)$
Absorption correction: multi-scan (SADABS; Sheldrick, 1997a)	$R_{\text{int}} = 0.025$
$T_{\text{min}} = 0.560$, $T_{\text{max}} = 0.862$	$\theta_{\text{max}} = 25.7^\circ$
4141 measured reflections	$h = -11 \rightarrow 11$
	$k = -8 \rightarrow 8$
	$l = -12 \rightarrow 12$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.069P)^2]$
$R[F^2 > 2\sigma(F^2)] = 0.037$	where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.095$	$(\Delta/\sigma)_{\text{max}} < 0.001$
$S = 1.02$	$\Delta\rho_{\text{max}} = 0.97 \text{ e \AA}^{-3}$
2464 reflections	$\Delta\rho_{\text{min}} = -0.31 \text{ e \AA}^{-3}$
174 parameters	Absolute structure: Flack (1983)
H-atom parameters constrained	Flack parameter = $-0.04 (3)$

Table 1

Selected geometric parameters (Å, °).

C1–C2	1.379 (8)	C1–C1'	1.518 (7)
C2–C3	1.373 (8)	C2–F2	1.363 (7)
C3–C4	1.378 (8)	C4–F4	1.355 (6)
C4–C5	1.391 (8)	C5–C7	1.471 (8)
C5–C6	1.409 (7)	C7–C8	1.318 (8)
C6–C1	1.382 (7)	C8–I8	2.064 (6)
C1–C2–F2	118.6 (5)	C4–C5–C7	124.9 (5)
C3–C2–F2	117.6 (5)	C6–C5–C7	118.9 (5)
C3–C4–F4	116.6 (5)	C5–C7–C8	127.9 (6)
C5–C4–F4	119.7 (5)	C7–C8–I8	123.7 (5)
O4'–C1'–C2'–C3'	37.3 (5)	C2'–C1'–C1–C2	78.4 (6)
C1'–C2'–C3'–C4'	–37.8 (5)	O4'–C1'–C1–C2	–164.2 (5)
C2'–C3'–C4'–O4'	25.9 (6)	C2'–C1'–C1–C6	–98.9 (6)
C3'–C4'–O4'–C1'	–3.2 (5)	O4'–C1'–C1–C6	18.5 (7)
C4'–O4'–C1'–C2'	–21.3 (5)	C4–C5–C7–C8	2.8 (10)
O4'–C4'–C5'–O5'	160.8 (4)	C6–C5–C7–C8	–174.8 (6)
C3'–C4'–C5'–O5'	–80.4 (5)	C5–C7–C8–I8	177.9 (5)

All H-atoms were refined as riding with C—H distances in the range 0.95–1.00 Å and an O—H distance of 0.84 Å.

Data collection: *SMART* (Siemens, 1996); cell refinement: *SMART*; data reduction: *SHELXTL* (Sheldrick, 1996); program(s) used to solve structure: *DIRDIF99* (Beurskens *et al.*, 1998); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997b); molecular graphics: *ZORTEP* (Zsolnai & Huttner, 1994); software used to prepare material for publication: *SHELXL97*.

The authors thank Robert MacDonald in the Department of Chemistry (University of Alberta), and the reviewers for valuable suggestions. This work was supported by the Canadian Institutes of Health Research through grants to LIW, EEK (MT-14480) and MNGJ (CIHR Group in Protein Structure and Function). We are grateful to the Alberta Heritage Foundation for Medical Research for fellowships to ZX and BLM. BLM is also the recipient of an MRC doctoral research fellowship.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: DA1180). Services for accessing these data are described at the back of the journal.

References

- Bats, J. W., Parsch, J. & Engels, J. W. (2000). *Acta Cryst.* **C56**, 201–205.
- Beurskens, P. T., Beurskens, G., de Gelder, R., Garcia-Granda, S., Gould, R. O., Israel, R. & Smits, J. M. M. (1998). *The DIRDIF99 Program System*. Crystallography Laboratory, University of Nijmegen, The Netherlands.
- De Clercq, E. (1983). *Pure Appl. Chem.* **55**, 623–626.
- Flack, H. D. (1983). *Acta Cryst.* **A39**, 876–881.
- Guckian, K. M. & Kool, E. T. (1997). *Angew. Chem. Int. Ed. Engl.* **36**, 2825–2828.
- Hamor, T. A., O'Leary, M. K. & Walker, R. T. (1978). *Acta Cryst.* **B34**, 1627–1630.
- Jones, D. & Watkinson, J. (1964). *J. Chem. Soc.* pp. 2366–2370.
- Moran, S., Ren, R. & Kool, E. T. (1997). *Proc. Natl Acad. Sci. USA*, **94**, 10506–10511.
- Párkányi, L., Kálmán, A., Kovács, T., Szabolcs, A. & Ötvös, L. (1983). *Nucleic Acids Res.* **11**, 7999–8005.
- Rahman, A. & Wilson, H. R. (1972). *Acta Cryst.* **B28**, 2260–2270.
- Schweitzer, B. A. & Kool, E. T. (1994). *J. Org. Chem.* **59**, 7238–7242.
- Schweitzer, B. A. & Kool, E. T. (1995). *J. Am. Chem. Soc.* **117**, 1863–1872.
- Sheldrick, G. M. (1996). *SHELXTL96*. Version 5.04. University of Göttingen, Germany.
- Sheldrick, G. M. (1997a). *SADABS*. University of Göttingen, Germany.
- Sheldrick, G. M. (1997b). *SHELXL97*. University of Göttingen, Germany.
- Siemens (1996). *SMART*. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
- Thalladi, V. R., Weiss, H.-C., Blaser, D., Boese, R., Nahgia, A. & Desiraju, G. R. (1998). *J. Am. Chem. Soc.* **120**, 8702–8710.
- Wang, Z.-X., Knaus, E. E. & Wiebe, L. I. (1999). 82nd Canadian Society for Chemistry Conference, Toronto, Canada, May 30–June 2, Abstract p. 1019.
- Young, D. W., Tollin, P. & Wilson, H. R. (1969). *Acta Cryst.* **B25**, 1423–1432.
- Zsolnai, L. & Huttner, G. (1994). *ZORTEP*. University of Heidelberg, Germany.