

Samuel Parker,^{a*} David Watkin,^a
 Benjamin Mayes,^b Richard
 Storer,^b Sarah Jenkinson^c and
 George Fleet^c

^aDepartment of Chemical Crystallography,
 Chemical Research Laboratory, Mansfield Road,
 Oxford OX1 3TA, England, ^bIdenix
 Pharmaceuticals, 60 Hampshire Street,
 Cambridge, MA 02139, USA, and ^cDepartment
 of Organic Chemistry, Chemical Research
 Laboratory, Mansfield Road, Oxford OX1 3TA,
 England

Correspondence e-mail:
 samuel.parker@magd.ox.ac.uk

Key indicators

Single-crystal X-ray study
 T = 150 K
 Mean $\sigma(\text{C}-\text{C}) = 0.002 \text{ \AA}$
 R factor = 0.030
 wR factor = 0.098
 Data-to-parameter ratio = 9.6

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

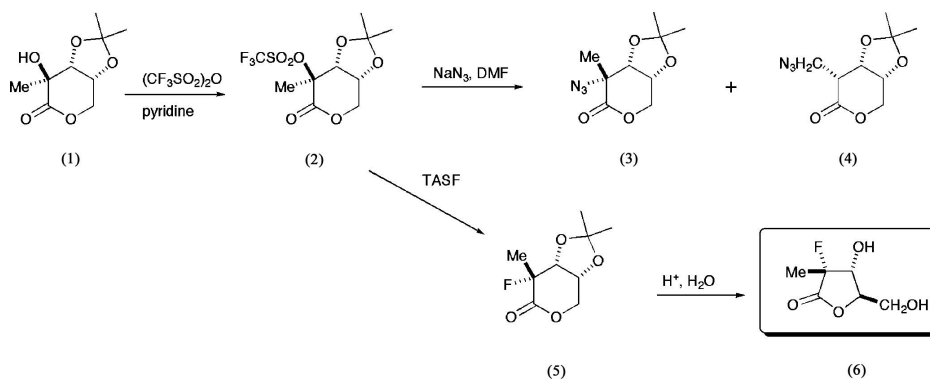
2-Deoxy-2-fluoro-2-C-methyl-D-ribo- 1,4-lactone (fluoromethylrib)

The relative stereochemistry of the fluoro substituent (as *ribo*) and the ring size of the lactone (as five) in the title compound, $\text{C}_6\text{H}_9\text{FO}_4$, have been established by X-ray crystallographic analysis.

Received 7 February 2006
 Accepted 20 February 2006

Comment

Until recently, carbohydrate building blocks with branched carbon chains have not been readily available in large quantities (Bols, 1996; Lichtenthaler & Peters, 2004). The Kiliani reaction of ketoses with cyanide, followed by acetonation (Hotchkiss *et al.*, 2004; Soengas *et al.*, 2005), provides access to a novel class of carbohydrate scaffold which contains a branched hydroxymethyl carbon chain. Branched sugars bearing a C-2 alkyl group are also available from the Kiliani reaction of cyanide with 1-deoxyketoses, themselves prepared by addition of organometallic reagents to sugar lactones. Thus, reaction of cyanide with a protected 1-deoxy-D-ribose afforded the isopropylidene derivative of arabinono-1,5-lactone (1) (Hotchkiss *et al.*, 2006), shown to crystallize in a boat conformation (Punzo, Watkin, Jenkinson & Fleet, 2005).



Protected sugar lactones such as (1) allow modification of the tertiary alcohol group to introduce other functional groups at the quaternary centre; hitherto, there have been very few strategies for the synthesis of branched carbohydrates with a non-oxygen functional group at a quaternary position. Esterification of the free hydroxyl group in (1) with triflic anhydride in pyridine afforded the trifluoromethanesulfonate (2). Reaction of (2) with sodium azide in dimethylformamide gave the *ribo*-azide (3) as the major product in good yield, even though the overall reaction is a nucleophilic displacement at a very hindered position; this reaction is very unlikely to be an $\text{S}_{\text{N}}2$ reaction, so the stereochemistry at C-2 of the azide (3) was established by X-ray crystallographic analysis (Punzo, Watkin, Jenkinson, Cruz & Fleet, 2005), showing that the reaction

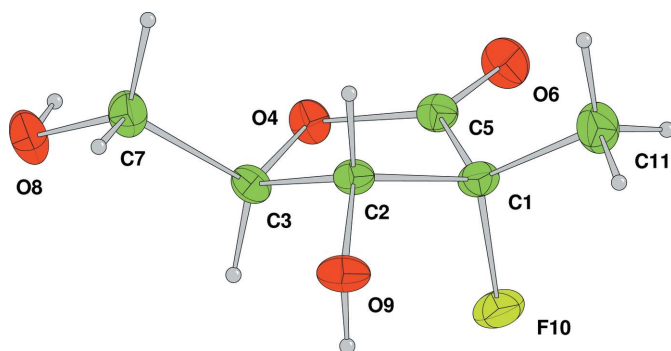


Figure 1
The molecular structure of the title compound, with displacement ellipsoids drawn at the 50% probability level. H atoms are shown as spheres of arbitrary radius.

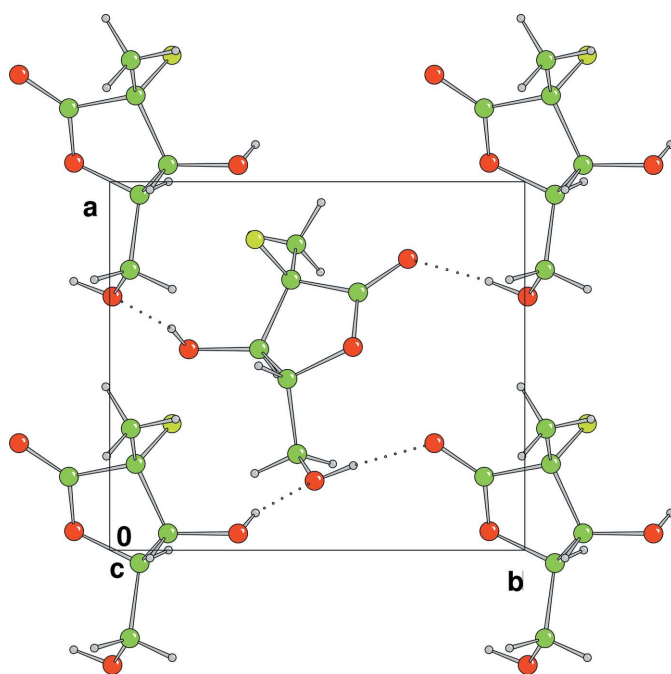


Figure 2
A *c*-axis projection. The molecules are linked by hydrogen bonds (dashed lines) into pleated sheets perpendicular to *c*.

proceeded with inversion of configuration to give the ribonolactone (3) in a boat conformation with the C-2 methyl group in a hindered flagpole position. A minor product was also formed during the azide displacement reaction and was proven by X-ray analysis to have the *ribo*-configuration (4) (Punzo *et al.*, 2006). It is noteworthy that the 1,5-lactones (1), (3) and (4) all adopt a boat conformation in the solid state.

When the trifluoromethanesulfonate (2) was treated with tris(dimethylamino)sulfur trimethylsilyl difluoride – an excellent source of nucleophilic fluoride – fluorolactone (5) was isolated as the major product. Removal of the isopropylidene protecting group by treatment with aqueous acid gave the title unprotected fluorolactone, (6). The crystal structure reported in this paper (Fig. 1) establishes the relative *ribo*-stereochemistry in both (5) and (6), and also shows that deprotection of the ketal (5) is accompanied by contraction of

the six-ring lactone in (5) to give a five-ring lactone in (6). The quaternary fluoride (6) is likely to be a powerful intermediate for the synthesis of a novel class of carbohydrate in which a F atom is attached to a quaternary centre. The absolute configuration of (6) was established by the use of D-erythrulactone as the starting material for the preparation of (1).

The crystal structure consists of pleated sheets lying perpendicular to *c*, with molecules linked by hydrogen bonds (Fig. 2). There is a short contact between adjacent sheets [2.86 \AA for $\text{O9} \cdots \text{C5}(\frac{1}{2} + x, \frac{1}{2} - y, 1 - z)$].

Experimental

The fluorolactone (6) (Mayes *et al.*, 2006) was crystallized from ethyl acetate:heptane (8:1), m.p. 415–416 K; $[\alpha]_{20}^D +129.3^\circ$ ($c = 0.9$ in CH_3CN).

Crystal data

$\text{C}_6\text{H}_9\text{FO}_4$
 $M_r = 164.13$
 Orthorhombic, $P2_12_12_1$
 $a = 7.3570$ (2) \AA
 $b = 8.2864$ (2) \AA
 $c = 11.7886$ (3) \AA
 $V = 718.67$ (3) \AA^3
 $Z = 4$
 $D_x = 1.517 \text{ Mg m}^{-3}$

Mo $K\alpha$ radiation
 Cell parameters from 900 reflections
 $\theta = 1\text{--}27^\circ$
 $\mu = 0.14 \text{ mm}^{-1}$
 $T = 150 \text{ K}$
 Block, colourless
 $0.60 \times 0.40 \times 0.40 \text{ mm}$

Data collection

Nonius KappaCCD diffractometer
 ω scans
 Absorption correction: multi-scan
 (DENZO/SCALEPACK;
 Otwinowski & Minor, 1997)
 $T_{\min} = 0.64$, $T_{\max} = 0.94$
 1612 measured reflections

964 independent reflections
 958 reflections with $I > -3\sigma(I)$
 $R_{\text{int}} = 0.008$
 $\theta_{\max} = 27.5^\circ$
 $h = -9 \rightarrow 9$
 $k = -10 \rightarrow 10$
 $l = -14 \rightarrow 14$

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.030$
 $wR(F^2) = 0.098$
 $S = 0.91$
 958 reflections
 100 parameters

H-atom parameters constrained
 $w = 1/[\sigma^2(F^2) + (0.1P)^2]$
 where $P = [\text{max}(F_o^2, 0) + 2F_c^2]/3$
 $(\Delta/\sigma)_{\max} < 0.001$
 $\Delta\rho_{\max} = 0.22 \text{ e \AA}^{-3}$
 $\Delta\rho_{\min} = -0.18 \text{ e \AA}^{-3}$

Table 1

Hydrogen-bond geometry (\AA , $^\circ$).

$D\text{--}H \cdots A$	$D\text{--}H$	$H \cdots A$	$D \cdots A$	$D\text{--}H \cdots A$
$\text{O9--H6} \cdots \text{O8}^i$	0.82	1.90	2.701 (2)	165
$\text{O8--H7} \cdots \text{O6}^i$	0.84	2.01	2.804 (2)	157

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

The H atoms were all located in a difference map, but those attached to C atoms were repositioned geometrically. The H atoms were initially refined with soft restraints on the bond lengths and angles to regularize their geometry (C–H in the range 0.93–0.98, O–H = 0.82 \AA) and $U_{\text{iso}}(\text{H})$ (in the range 1.2–1.5 times U_{eq} of the parent atom), after which the positions were refined with riding constraints.

Data collection: COLLECT (Nonius, 2001); cell refinement: DENZO/SCALEPACK (Otwinowski & Minor, 1997); data reduction: DENZO/SCALEPACK; program(s) used to solve structure:

SIR92 (Altomare *et al.*, 1994); program(s) used to refine structure: CRYSTALS (Betteridge *et al.*, 2003); molecular graphics: CAMERON (Watkin *et al.*, 1996); software used to prepare material for publication: CRYSTALS.

References

- Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435.
- Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, K. & Watkin, D. J. (2003). *J. Appl. Cryst.* **36**, 1487.
- Bols, M. (1996). *Carbohydrate Building Blocks*. New York: Wiley.
- Hotchkiss, D. J., Jenkinson, S. F., Storer, R., Heinz, T. & Fleet, G. W. J. (2006). *Tetrahedron Lett.* **47**, 315–318.
- Hotchkiss, D., Soengas, R., Simone, M. I., van Ameijde, J., Hunter, S., Cowley, A. R. & Fleet, G. W. J. (2004). *Tetrahedron Lett.* **45**, 9461–9464.
- Lichtenthaler, F. W. & Peters, S. (2004). *C. R. Chim.* **7**, 65–90.
- Mayer, B. A., Storer, R., Watkin, D. J., Jenkinson, S. F. & Fleet, G. W. J. (2006). In preparation.
- Nonius (2001). COLLECT. Nonius BV, Delft, The Netherlands.
- Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.
- Punzo, F., Watkin, D. J., Jenkinson, S. F., Cruz, F. P. & Fleet, G. W. J. (2005). *Acta Cryst.* **E61**, o511–o512.
- Punzo, F., Watkin, D. J., Jenkinson, S. F., Cruz, F. P. & Fleet, G. W. J. (2006). *Acta Cryst.* **E62**, o321–o323.
- Punzo, F., Watkin, D. J., Jenkinson, S. F. & Fleet, G. W. J. (2005). *Acta Cryst.* **E61**, o127–129.
- Soengas, R., Izumori, K., Simone, M. I., Watkin, D. J., Skytte, U. P., Soetaert, W. & Fleet, G. W. J. (2005). *Tetrahedron Lett.* **46**, 5755–5759.
- Watkin, D. J., Prout, C. K. & Pearce, L. J. (1996). CAMERON. Chemical Crystallography Laboratory, Oxford, England.