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Note

Synthesis of 1,3-dideoxy-3-fluoronojirimycin *

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Since the discovery that several naturally occurring, mono- and bi-cyclic, polyhydroxylated alkaloids[1] are potent inhibitors of glycosidases[2], including those involved in the processing of glycoproteins[3], there has been considerable interest in analogues as potential therapeutic agents for the treatment of AIDS. We have reported the synthesis of potential intermediates for 1-deoxynojirimycin, castanospermine, and swainsonine from simple sugars[4,5], and now describe a synthesis of 1,3-dideoxy-3-fluoronojirimycin [(2*R*, 3*R*, 4*R*, 5*S*)-4-fluoro-3,5-dihydroxy-2-hydroxymethylpiperidine] (**1**) and its X-ray crystal structure.

Hydrogenation of 5-azido-6-*O*-benzoyl- (**2**) or -6-*O*-*tert*-butyldiphensylsilyl-3,5-dideoxy-3-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose[4] (**3**) gave the 5-amino-5-deoxy derivatives **4** and **5**, respectively. Debenzoylation (sodium methoxide) of **4**, or desilylation (tetrabutylammonium fluoride) of **5**, followed by deacetalation [Amberlite IR-120 (H^+) resin] and hydrogenation (Pd/C) gave **1**, but the yield was low. An improved procedure involved deacetalation of 5-azido-3,5-dideoxy-3-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose[4] (**6**), followed by hydrogenation.

The structure of **1** was confirmed by the ^1H, ^{13}C, and ^{19}F NMR spectra. The presence of a deoxy group at C-1 was reflected by the signals at δ 3.06 ($J_{1ax,1eq}$ 12.6, $J_{1eq,2}$ 5.0 Hz, H-1*eq*) and 2.40 ($J_{1ax,2}$ 11.0 Hz, H-1*ax*). The ^{19}F–^1H couplings of **1** were similar to those of 3-deoxy-3-fluoro-D-*gluco* compounds[6]. The $^4J_{F\text{-}3,H\text{-}1eq}$ value of 6.4 Hz accords with the known stereospecificity of such coupling[7].

The ^1H and ^{19}F NMR spectra of the triacetate (**7**) of **1** had $J_{F\text{-}3,H\text{-}2}$ and $J_{F\text{-}3,H\text{-}4}$ values of ~ 0 Hz, which indicated the dihedral angles H-2–F-3 and H-4–F-3 to be near to 90°. Molecular models showed that such dihedral angles are possible only when the ring N and C-1,2,4,5 are nearly coplanar. This distortion precludes $^4J_{F,H}$ coupling of the type observed for **1**.

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* 1,3-Dideoxy-3-fluoronojirimycin Derivatives, Part I.

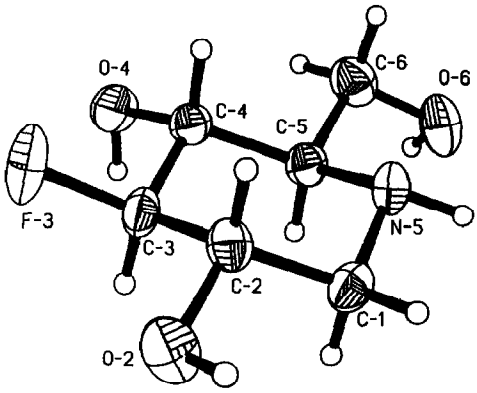
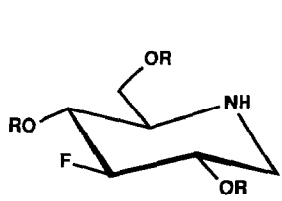


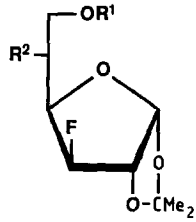
Fig. 1. XP plot[13] of 1,3-dideoxy-3-fluoronojirimycin (**1**) giving the numbering scheme.

The structure of **1** was further confirmed by X-ray crystallography (see Fig. 1). The structure and numbering systems are shown in Fig. 1. The unit cell contained discrete molecules of **1** (Fig. 2), a single molecule comprising the asymmetric unit. Bond lengths and angles are within the normal ranges; average bond lengths, C–C = 1.518 Å, C–N = 1.468 Å, and C–O = 1.425 Å. The C–F bond length (1.401 Å) is comparable to those found for fluorinated monosaccharides (1.397–1.410 Å)[8]. The six-membered ring has the chair conformation. The Cremer and Pople ring-puckering parameters[9], Q = 47.1°, θ = 16.4°, and ϕ = 47.1°, indicated a moderate distortion of the $^4C_1$ chair conformation towards the $^NH_5$ form. The C-1–N-5–C-5 bond angle (112.0°) is much closer to the nearly tetrahedral C–N–C angle (108°) of trimethylamine than those found in 2,2,6,6-tetramethyl-4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)piperidine (126°)[10] or the free nitroxide (134°)[11]. The torsion angle C-4–C-5–C-6–O-6 (−171.2°) corresponded to the usual more



1 R = H

7 R = Ac



2 R^1 = Bz, R^2 = N_3

3 R^1 = ^{t}BuPh$_2$Si, R^2 = N_3

4 R^1 = Bz, R^2 = NH_2

5 R^1 = ^{t}BuPh$_2$Si, R^2 = N_3

6 R^1 = H, R^2 = N_3

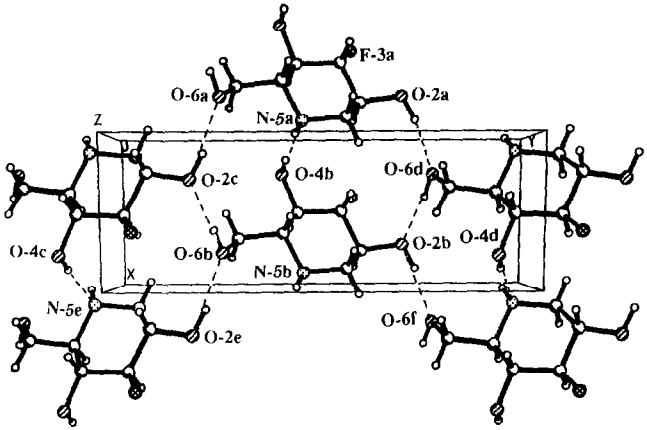


Fig. 2. Molecular packing of the crystal of **1** viewed along the *c* axis.

stable conformation of the hydroxymethyl group, in which O-6 is *gauche* to O-5 and *trans* to C-4, also designated[12] *gt* [N-5–C-5–C-6–O-5 (68°) and C-4–C-5–C-6–O-6 (−171.2)], and HO-6 is both a receiver and donor of hydrogen bonds from and to HO-2 of two adjacent molecules. A third intermolecular hydrogen bond holding the molecules together in the crystal is that between the ring nitrogen and O-4 (Fig. 2, Table III). The fluorine substituent is not involved in hydrogen bonding.

EXPERIMENTAL

Optical rotations were determined at 22–25 °C in a 1-dm tube with a Perkin–Elmer 141 polarimeter. The ^{1}H, ^{13}C, and ^{19}F NMR spectra (internal Me_4Si) were recorded with a Bruker ACS-300 (300 MHz) or AMX-500 (MHz) spectrometer. EI-mass spectra (70 eV) were determined with a Micromass VG 7035 spectrometer. Melting points were determined using a Büchi 512 melting-point apparatus and are uncorrected. Microanalyses were carried out using a Perkin–Elmer 2400 Elemental Analyser. Reactions were monitored by TLC on Silica Gel 60 F_{254} (Merck) with detection by charring with H_2SO_4. 1-Deoxynojirimycin derivatives were detected with ninhydrin. Flash-column chromatography was performed on Kieselgel 60 (Merck 230–400 mesh) at 5–10 psi.

*5-Amino-6-*O*-benzoyl-3,5-dideoxy-3-fluoro-1,2-*O*-isopropylidene-α-*D*-glucofuranose* (**4**).—A suspension of $Pd(OH)_2$ (20%) on activated charcoal (80 mg) in EtOH (20 mL) and tetrahydrofuran (10 mL) was shaken under H_2 (50 psi) for 2 h. Compound **2** (ref. 4, 95.5 mg) was then added and hydrogenated (50 psi) for 4 h at room temperature. TLC (3:5 EtOAc—hexane) then revealed only one slow-moving spot. The solution was filtered and concentrated, and a solution of the residue in EtOAc was washed (thrice) with aq 10% NaOH, dried (MgSO4), filtered, and concentrated to give **4** (84.3 mg, 94.9%); mp 110–111°C (from EtOAc–hexane);

$[\alpha]_D$ +10° (*c* 1.0, MeOH), NMR data (CD_3COCD_3): ^1H, δ 7.4–8.2 (m, 5 H, Ph), 6.04 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 4.86 (dd, 1 H, $J_{3,4}$ 1.9, $J_{3,F}$ 50.15 Hz, H-3), 4.75 (dd, 1 H, $J_{2,F}$ 10.9 Hz, H-2), 4.67 (dd, 1 H, $J_{5,6a}$ 2.7, $J_{6a,6b}$ 10.8 Hz, H-6a), 4.54 (ddd, 1 H, $J_{4,5}$ 9.6, $J_{4,F}$ 29.8 Hz, H-4), 4.39 (m, 1 H, H-6b), 4.20 (td, 1 H, H-5), 1.31 and 1.47 (2 s, 6 H, CMe_2); ^{13}C, δ 112.8 (s, CMe_2), 106.1 (s, C-1), 95.2 (d, $J_{3,F}$ 182.8 Hz, C-3), 83.0 (d, $J_{2,F}$ 32.8 Hz, C-2), 80.4 (d, $J_{4,F}$ 19.5 Hz, C-4), 66.8 (d, $J_{5,F}$ 5.5 Hz, C-5), 58.1 (s, C-6), 26.5 and 26.9 [2 s, $C(CH_3)_2$]; ^{19}F, δ −133.5. Anal. Calcd for $C_{16}H_{20}FNO_5$: C, 59.07; H, 6.20; F, 5.84; N, 4.31. Found: C, 58.85; H, 5.78; F, 5.53; N, 4.04.

*5-Amino-6-*O*-*tert*-butyldiphenylsilyl-3,5-dideoxy-3-fluoro-1,2-*O*-isopropylidene-α-*D*-glucofuranose* (**5**).—Compound **3** (ref. 4, 0.54 g) was treated with $Pd(OH)_2$ (20%) on activated charcoal (0.35 g), as described for **2**, to give syrupy **5** (0.41, 80%); $[\alpha]_D$ −23° (*c* 1.0, $CHCl_3$). NMR data ($CDCl_3$): ^1H, δ 7.2–7.7 (m, 10 H, 2 Ph), 5.95 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 5.13 (dd, 1 H, $J_{3,4}$ 2.1, $J_{3,F}$ 50.1 Hz, H-3), 4.68 (dd, 1 H, $J_{2,F}$ 10.9 Hz, H-2), 4.23 (ddd, 1 H, $J_{4,5}$ 9.2, $J_{4,F}$ 30.6 Hz, H-4), 3.86 (dd, 1 H, $J_{5,6a}$ 3.4, $J_{6a,6b}$ 10.1 Hz, H-6a), 3.82 (dd, 1 H, $J_{5,6b}$ 5.0 Hz, H-6b), 3.23 (td, 1 H, H-5), 2.70 (s, 2 H, N–H), 1.26 and 1.46 (2 s, 6 H, CMe_2), 1.07 (s, 9 H, ^{t}Bu); ^{13}C, δ 111.1 (s, CMe_2), 104.0 (s, C-1), 93.6 (d, $J_{3,F}$ 183.3 Hz, C-3), 81.5 (d, $J_{2,F}$ 32.5 Hz, C-2), 79.1 (d, $J_{4,F}$ 18.7 Hz, C-4), 64.6 (s, C-5), 49.9 (s, C-6), 29.3 [2 s, $C(CH_3)_2$], 18.3 [s, $C(CH_3)_3$]; ^{19}F, δ −130.35. Anal. Calcd for $C_{25}H_{34}FNO_4Si$: C, 65.34; H, 7.46; F, 4.13; N, 3.05. Found: C, 65.66; H, 7.83; F, 3.94; N, 2.84.

1,3-Dideoxy-3-fluoronojirimycin (**1**).—A solution of **6** (ref. 4, 1.33 g) in water (14 mL) was treated with Amberlite- 120 (H^+) resin (2.2 g) for 20 h at 40°C, then filtered, and concentrated at room temperature. The residue was hydrogenated (50 psi) in the presence of $Pd(OH)_2$ (20%) on activated charcoal (~ 1 g) in EtOH (45 mL), as described for **4**, to give, after flash-column chromatography (9 : 1 EtOAc–MeOH), **1** (0.45 g, 62.7%); mp 161–162 °C (from EtOH–ether); $[\alpha]_D$ +39° (*c* 0.2,

TABLE I

Atomic coordinates (×10⁴) and equivalent isotropic displacement coefficients U_{eq} [a] (Å² × 10³) [b]

Atom	*x*	*y*	*z*	U_{eq}
C-1	8707(5)	5592(3)	4648(5)	29(1)
C-2	7574(5)	5958(3)	1973(5)	27(1)
C-3	4869(5)	5485(3)	1204(5)	28(1)
C-4	4691(5)	4401(2)	1318(5	26(1)
C-5	6321(5)	4065(2)	3977(5)	27(1)
C-6	6694(6)	2982(3)	4093(6)	38(1)
N-5	8966(4)	4544	4570(4)	29(1)
O-2	7164(4)	6971(2)	1943(4)	39(1)
O-4	2324(3)	4004(2)	667(4)	37(1)
O-6	7575(4)	2667(2)	6662(4)	44(1)
F-3	3849(3)	5761(2)	−1310(3)	48(1)

[a] Equivalent isotropic *U* defined as one third of the trace of the orthogonalized U_{ij} tensor. [b] Standard deviation in parentheses.

H_2O). NMR data (D_2O): ^1H, δ 4.18 (tt, 1 H, $J_{3,4}$ 8.9, $J_{3,F}$ 53.5 Hz, H-3), 3.73 (q, 1 H, $J_{5,6a}$ 2.9, $J_{6a,6b}$ 11.8 Hz, H-6a), 3.68 (qq, 1 H, $J_{1ax,2}$ 11.0, $J_{1eq,2}$ 5.0, $J_{2,3}$ 8.9, $J_{2,F}$ 14.4 Hz, H-2), 3.58 (q, 1 H, $J_{5,6b}$ 5.6 Hz, H-6b), 3.45 (ddd, 1 H, $J_{4,5}$ 10.1 $J_{4,F}$ 13.3 Hz, H-4), 3.06 (td, 1 H, $J_{1ax,1eq}$ 12.6, $J_{1eq,2}$ 5.0, $J_{1eq,F}$ 6.4 Hz, H-1*eq*), 2.49 (m 1 H, H-5), 2.40 (ddd, 1 H, $J_{1ax,2}$ 11.0 Hz, H-1*ax*); ^{13}C, δ 101.7 (d, $J_{3,F}$ 179.2 Hz, C-3), 72.3 (d, $J_{2,F}$ 16.8 Hz, C-2), 71.9 (d, $J_{4,F}$ 16.6 Hz, C-4), 63.5 (s, C-6), 62.5 (d, $J_{1,F}$ 6.0 Hz, C-1), 50.4 (d, $J_{5,F}$ 7.7 Hz, C-5); ^{19}F, δ −116.8. Anal. Calcd for $C_6H_{12}FNO_3$: C, 43.63; H, 7.32; F, 11.50; N, 8.48. Found: C, 43.92; H, 7.56; F, 11.89; N, 8.56.

N-*Acetyl-2,4,6-tri*-O-*acetyl-1,3-dideoxy-3-fluoronojirimycin* (**7**).—Conventional treatment of **1** in pyridine and acetic anhydride gave, after flash-column chromatography (2:1 EtOAc–hexane), **7** (35.3%); $[\alpha]_D$ −18.3° (*c* 1.0 $CHCl_3$). NMR data ($CDCl_3$): ^1H, δ 4.8–5.2 (m, 3 H, H-2,4,5), 4.6–4.8 (m, H-3), 4.3–4.6 (m, 2 H, H-6a,6b), 4.16 (dd, $J_{1ax,1eq}$ 11.6, $J_{1eq,2}$ 5.1 Hz, H-1*eq*), 3.7–3.9 (m, 1 H, H-1*ax*), 2.06, 2.09, 2.10, 2.12 (4 s, 12 H, 4 Ac); ^{13}C, δ 84.2 (d, $J_{3,F}$ 177.6 Hz, C-3), 67.25 (d, $J_{2,F}$ 26.4 Hz, C-2), 65.3 (d, $J_{4,F}$ 27.65 Hz, C-4), 59.2 (s, C-6), 54.4 (s, C-1), 49.5 (s, C-5), 21.7 (s, NCH_3), 20.3 (s, 3 C, 3 CH_3CO); ^{19}F, δ −117.3 ($J_{H\text{-}3,F}$ 43.9, $J_{H\text{-}2,F} = J_{H\text{-}4,F} = 0$ Hz). *Anal.* Calcd for $C_{14}H_{20}FNO_7$: C, 50.45; H, 6.05; F, 5.70; N, 4.20. Found: C, 50.02; H, 6.23; F, 5.43; N, 3.89.

Crystal data for **1**.—$C_6H_{12}FNO_3$, M_r 165.2, $a = 5.007(1)$, $b = 13.87(33)$, $c =$ 5,265(1) Å, $\beta = 98.35(3)°$, monoclinic space group $P2_1$, $V = 361.8$ Å^3, $Z = 2$, $D_x = 1.516$, $\mu = 0.135$ mm^{-1}, and $F(000) = 176$. A single crystal of approximate size 0.4 × 0.35 × 0.2 mm was studied, using a Siemens R3m/v diffractometer, with Mo radiation (graphite monochromator). The cell parameters were determined from 25 reflections by a least squares procedure. Intensity data were collected in the range $\theta = 7–45°$ ($h = 0–5$, $k = 0–16$, $l = -6–6$). Three standard reflections were measured every 100 reflections. A total of 734 reflections was measured and 611 with $I > 4\sigma(I)$ were used in subsequent calculations.

TABLE II

Selected torsion angles (°) [a]

C-1–C-2–C-3–C-4	−55.3(.3)	C-1–C-2–C-3–F-3	−176.4(.3)
C-2–C-3–C-4–C-5	55.2(.3)	C-2–C-3–C-4–O-4	176.7(2)
C-2–C-1–N-5–C-5	−65.0(.3)	C-3–C-4–C-5–C-6	−174.6(.2)
C-3–C-4–C-5–N-5	−53.3(.3)	C-4–C-5–C-6–O-6	−171.2(.2)
C-4–C-5–N-5–C-1	61.0(.3)	C-6–C-5–N-5–C-1	−176.3(.2)
F-3–C-3–C-4–C-5	174.6(.2)	F-3–C-3–C-4–O-4	−60.9(.3)
F-3–C-3–C-4–H-4	56.9(.2)	H-1*eq*–C-1–C-2–H-2	60.9(.1)
H-1*ax*–C-1–C-2–H-2	179.9(.1)	H-1*eq*–C-1–N-5–H-N	51.4(.1)
H-1*ax*–C-1–N-5–H-N	−67.7(.1)	H-2–C-2–C-3–H-3	−175.2(0)
H-3–C-3–C-4–H-4	174.6(0)	H-4–C-4–C-5–H-5	−177.5(0)
H-5–C-5–C-6–H-6a	69.2(.1)	H-5–C-5–C-6–H-6b	−172.6(0)
H-5–C-5–N-5–H-N	60.1(0)	N-5–C-1–C-2–C-3	59.2(.2)
N-5–C-1–C-2–O-2	177.5(.2)	N-5–C-5–C-6–O-6	68.0(.3)
O-2–C-2–C-3–C-4	−176.2(.2)	O-2–C-2–C-3–F-3	62.7(.3)
O-4–C-4–C-5–C-6	61.7(.2)	O-4–C-4–C-5–N-5	−177.0(.2)

[a] Standard deviation in parentheses.

TABLE III

Hydrogen bond characteristics [a,b]

A-H···B	Symmetry operation on A	A···B (Å)	A–H (Å)	H···B (Å)	A-H···B (°)
O-4–H-4···N-5	$-1+x, y, z$	2.935(3)	0.91(2)	2.04(2)	169(2)
O-2–H-2···O-6	$2-x, 0.5+y, 1-z$	2.802(4)	0.91(2)	1.91(2)	166(2)
O-6–H-6···O-2	$1-x, -0.5+y, 1-z$	2.758(4)	0.89(2)	1.88(2)	169(2)

[a] A, Donor atom; B, acceptor atom. [b] Standard deviations in parentheses.

Determination of structure and refinement *.—The structure was determined by the direct method and refined by a full matrix least-squares procedure, using SHELXTL PLUS[13] on a Micro Vax 2000 computer. The carbon, fluorine, nitrogen, and oxygen atoms were then refined anisotropically. The hydrogen atoms were included with isotropic temperature factors in the final R calculations, but their positions were not refined. The final refinement gave $R = 0.28$, $wR = 0.039$, max $\Delta/\sigma = 0$ with a goodness-of-fit of 1.64, and the largest difference peak of 0.15 eÅ^{-3}. The weighting scheme was $w^{-1} = \sigma^2(F) + 0.0003F^2$.

The atomic coordinates and equivalent isotropic displacements coefficients, and torsion angles are given in Tables I and II, respectively, and the hydrogen bond characteristics are given in Table III.

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* Lists of bond lengths, bond angles, final atomic parameters, anisotropic thermal parameters, hydrogen positions and F_0/F_c are deposited with, and can be obtained from, Elsevier Science Publishers B.V., BBA Data Deposition, P.O. Box 1527, Amsterdam, The Netherlands. Reference should be made to No. BBA/DD/516/*Carbohydr. Res.*, 239 (1993) 309–315.

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