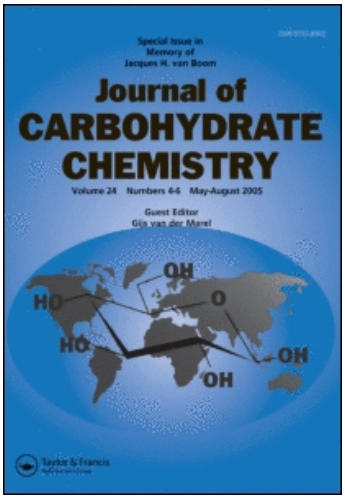

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Asymmetric Synthesis of 1,3,6-Trideoxy-3,6-difluoronojirimycin[1]

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ASYMMETRIC SYNTHESIS OF 1,3,6-TRIDEOXY-3,6-DIFLUORONOJIRIMYCIN[1]

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ABSTRACT

Reaction of 5-azido-3,5-dideoxy-3-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose (**1**) with trifluoromethanesulfonic anhydride followed by tris(dimethylamino)sulfonium difluorosilicate gave a 1:2 mixture of 5-azido-3,5,6-trideoxy-3-fluoro-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (**2**) and 5-azido-3,5,6-trideoxy-3,6-difluoro-α-D-glucofuranose (**3**) in 74% yield. When 5-azido-5-deoxy-1,2-*O*-isopropylidene-α-D-allofuranose (**7**) was similarly treated, it yielded instead, 5-azido-5-deoxy-3-*O*-trifluoromethanesulfonyl-1,2-*O*-isopropylidene-α-D-*ribo*-hex-5-enofuranose (**8**). Further treatment of **8** with TASF gave **2**. The 3-*O*-benzoate **4** also did not yield the expected product, but instead, gave 5-azido-6-*O*-benzoyl-3,5-dideoxy-3-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose (**5**). Deacetalation and hydrogenation of **3** gave 1,3,6-trideoxy-3,6-difluoronojirimycin [(2*S*,3*R*,4*R*,5*S*)-4-fluoro-3,5-dihydroxy-2-fluoromethylpiperidine] (**10**).

INTRODUCTION

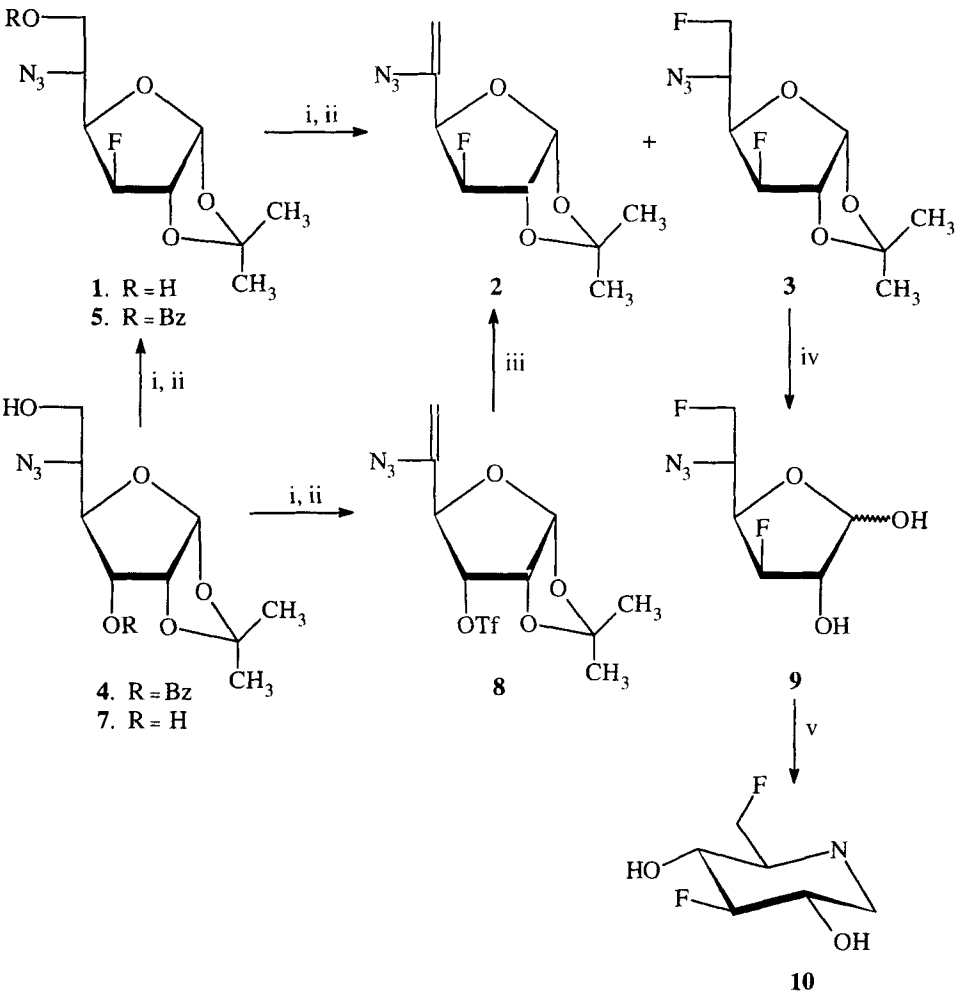
Several naturally occurring monocyclic[2] and bicyclic[3] polyhydroxylated alkaloids are known to be powerful inhibitors of glycosidases and enzymes responsible for glycoprotein processing, and some have shown anti-HIV activity.[2,4] Synthetic analogues of some of these have shown similar potent activities. Considerable attention has been focused on derivatives of 1-deoxynojirimycin, which were shown to interfere with HIV-induced syncytium formation and viral infectivity.[5] Fluorinated carbohydrates have been

utilized widely in biochemical investigations of sugars.[6,7] Fluorinated analogues of 1-deoxynojirimycin could be important because, like fluorosugars, they could show potential or enhanced inhibitory activity and, in addition, might provide useful information about the site domains of endoglycosidases.[8] Recently, synthesis of 1,2,5-trideoxy-2-fluoro-1,5-imino-L-ribitol,[9] 1,6-dideoxy-6-fluoro-[9,10] and 1,3-dideoxy-3-fluoro-nojirimycin,[11] 6-deoxy-6-fluoro-[12] and 1,7-dideoxy-7-fluorocastanospermine[13] were reported. We now report a facile asymmetric synthesis of 1,3,6-trideoxy-3,6-difluoronojirimycin [(2*S*,3*R*,4*R*,5*S*)-4-fluoro-3,5-dihydroxy-2-fluoromethylpiperidine] (**10**).

RESULTS AND DISCUSSION

A convenient synthesis of 1,3,6-trideoxy-3,6-difluoronojirimycin (**10**) was achieved from 5-azido-3,5-dideoxy-3-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose[14] (**1**) (Scheme 1). When **1** was reacted with trifluoromethanesulfonic anhydride, and then treated with tris(dimethylamino)sulfonium difluororsilicate[15] (TASF) in dichloromethane at -12 °C, a 1:2 mixture of 5-azido-3,5,6-trideoxy-3-fluoro-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (**2**) and 5-azido-3,5,6-trideoxy-3,6-difluoro-1,2-*O*-isopropylidene-α-D-glucofuranose (**3**) was obtained in 74% yield. When the reaction was carried out at higher temperatures or when acetonitrile was used as solvent, **2** was formed as the major product. Thus, in dichloromethane at -3 °C, the reaction gave a 8:1 mixture of **2** and **3** while in acetonitrile the ratio was 9:2. The structures of **2** and **3** were consistent with their ^{1}H, ^{13}C and ^{19}F NMR and mass spectra. The presence of a double bond at C-5,6 in **2** was indicated by the absence of an H-5 signal and large downfield shifts of the C-5,6 signals (Table 2). The presence of a fluorine substituent at C-6 in **3** was evident from the large deshielding of H-6a,6b (ca. 1.1 ppm). The *J* values ($J_{6a,F}$ 46.6, $J_{6b,F}$ 47.1) confirmed the location of the fluorine substituent.

Fluorination appears to occur less readily at C-6 than at C-3. Thus, the reaction of the triflate of 5-azido-3-*O*-benzoyl-5-deoxy-1,2-*O*-isopropylidene-α-D-allofuranose[16] (**4**) with TASF did not yield the expected 6-fluoride, but gave instead, 5-azido-6-*O*-benzoyl-3,5-dideoxy-3-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose (**5**), presumably by neighbouring group participation of the C-3 benzoyloxy substituent to give the α-triflic acetal (**6a**) and/or the benzoxonium ion (**6b**) prior to fluorination[17] (Scheme 1). Treatment of the triflate of 5-azido-5-deoxy-1,2-*O*-isopropylidene-α-D-allofuranose (**7**) with TASF also did not yield the expected difluoro derivative **2.** The initial product formed was 5-azido-5,6-dideoxy-3-*O*-trifluoromethanesulfonyl-1,2-*O*-isopropylidene-α-D-*ribo*-hex-5-enofuranose (**8**) (86%). Further treatment of **8** then gave the corresponding



Scheme 1. *Reagents and conditions*: i. Tf_2O, pyridine, CH_2Cl_2, -18 °C; ii. TASF, CH_2Cl_2, -12 °C, 1.25 h; iii. TBAF, CH_3CN, room temp., 4 h.; iv. Amberlite IR 120 (H^+) resin, 40 °C; v. H_2, 20% $Pd(OH)_2/C$, 6 h, room temp.

3-deoxyfluoro-5-enofuranose derivative **2** in 79% yield. The large $J_{2,3}$ and $J_{3,4}$ values (4.8 and 8.3 Hz) for **8** were consistent with the *ribo* configuration.[14,18]

Deacetalation of **3** [Amberlite IR 120 (H^+) resin] (**9**), followed by catalytic hydrogenation over 20% palladium hydroxide-on-carbon in aqueous ethanol gave 1,3,6-trideoxy-3,6-difluoronojirimycin (**10**) in 86% yield. The structure of **10** was confirmed by its ^1H, ^{13}C and ^{19}F NMR spectra. The presence of a deoxy group at C-1 was reflected by the signals at δ 3.19 ($J_{lax,leq}$ 12.2, $J_{leq,2}$ 5.6 Hz, H-1eq) and 2.79 ($J_{lax,2}$ 11.8 Hz). The large $J_{2,3}$ and $J_{3,4}$ (8.6 and 9.4 Hz) clearly indicated the *gluco* configuration. Furthermore, the

TABLE 1. ^{1}H NMR (300 MHz) data[a] ($CDCl_3$)

Compound	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	CMe_2
2	6.03(d)	4.71(dd)	4.93(dd)	4.51(dd)		4.94(dd)	5.24(t)	1.34, 1.50(2s)
3	5.96(d)	4.72(dd)	5.06(dd)	4.08(ddd)	3.8-3.9(m)	4.60(ddd)	4.79(ddd)	1.33, 1.48(2s)
4	5.84(d)	4.62dd)	4.61(dd)	4.40(dd)	--------4.1-4.2(m)--------		3.96(dd)	1.31, 1.50(2s)
7[b]	5.84(d)	4.65(dd)	4.16(td)	4.02(dd)	3.96(dd)	--------3.7-3.9(m)-------		1.38, 1.58(2s)
8	5.87(d)	4.74(t)	4.87(dd)	4.54(d)		5.05(d)	5.27(d)	
10	H-1a: 2.43(t) H-1e: 3.06(td)	3.7-3.9(m)	4.21(tt)	3.56(tt)	2.66(dd)	4.53(dd)	4.57(dd)	

Compound	$J_{1a,1e}$	$J_{1a,2}$	$J_{1e,2}$	$J_{1,2}$	$J_{2,3}$	$J_{2,F}$	$J_{3,4}$	$J_{3,F}$	$J_{4,5}$	$J_{4,F}$	$J_{5,6a}$	$J_{5,6b}$	$J_{5,F}$	$J_{6a,6b}$	$J_{6a,F}$	$J_{6b,F}$
2				3.7	0	9.8	2.3	49.7		28.8				1.9	1.1	1.7
3				3.7	0	10.5	2.1	49.9	10.0	27.4	6.5	2.4		9.9	47.1	46.6
4				3.8	4.5		11.8		8.6			3.9		8.6		
7[b]				3.7	5.0		8.5		3.1		8.5					
8				3.7	4.8		8.3							2.5		
10	12.0	12.0	5.6		8.6	9.4	53.5	9.7	13.2		4.2	27.6	10.2	47.1	47.1	

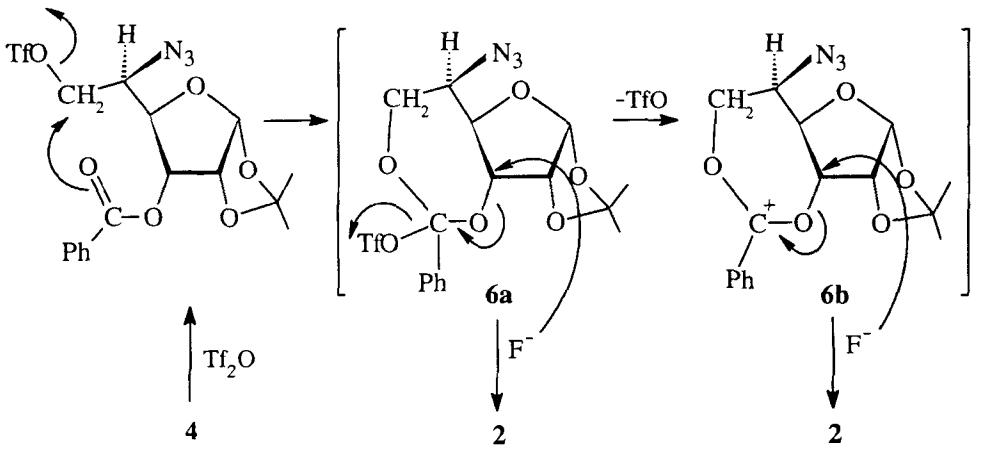
a. Chemical shifts in ppm, *J* in Hz. b. D_2O exchange

TABLE 2. ^{13}C NMR chemical shifts[a] ($CDCl_3$)

Compound	C-1	C-2	C-3	C-4	C-5	C-6	CMe_2	CMe_2	C=O	CF
2	103.8(s)	81.3(d)	92.2(d)	78.0(d)	138.6(s)	99.0(s)	111.6(s)	25.2, 25.7(2s)		
3	104.2(s)	81.1(d)	92.7(d)	78.0(d)	57.8(dd)	82.5(d)	112.80(s)	25.2, 25.7(2s)		
4	104.0(s)	79.5(s)	71.7(s)	78.9(s)	61.4(s)	63.9(s)	113.1(s)	26.6(2s)	166.1	
7	103.8(s)	81.1(s)	70.6(s)	79.05(s)	61.8(s)	63.0(s)	113.2(s)	26.4, 26.6(2s)		
8	103.1/ 103.2(s)	76.0(s)	81.8(s)	76.0(s)	139.7(s)	103.2/ 103.1(s)	113.6(s)	25.5, 25.6(2s)		117.4
10[b]	50.3(d)	71.4(d)	101.1(d)	70.8(d)	61.3(d)	85.0(d)				

Compound	$J_{1,F}$	$J_{2,F}$	$J_{3,F}$	$J_{4,F-3}$	$J_{4,F-6}$	$J_{5,F-3}$	$J_{5,F-6}$	$J_{6,F-6}$
2		32.2	187.8	19.7	0			
3		32.4	185.5	19.7	0	7.2	18.4	173.3
10[b]	7.4	180.0	12.6	16.9	5.8	7.1	18.0	165.9

a. Chemical shifts in ppm, *J* in Hz, downfield from Me_4Si. At 500 MHz. b. In D_2O.



Scheme 2

^{19}F-^{1}H couplings were similar to those of 3-deoxy-3-fluoro-D-*gluco* compounds[19] and the $^{4}J_{F\text{-}3,H\text{-}1eq}$ value of 6.4 Hz is consistent with known values[7] for similar compounds and with values reported for 1,3-dideoxy-3-fluoronojirimycin.[10]

EXPERIMENTAL

Optical rotations were determined at 22-25 °C in a 1-dm tube using a Perkin-Elmer 141 Polarimeter. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded with a Bruker ACS 300 (300 MHz) or AMX-500 (500 MHz) spectrometer for solutions in $CDCl_3$, unless otherwise stated, with Me_4Si (for ^{1}H and ^{13}C NMR) and CF_3CO_2H (for ^{19}F NMR) as the internal standards. 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. Microanalysis 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 sulfuric acid. 1-Deoxynojirimycin derivatives were detected with ninhydrin. Flash column chromatography were monitored by TLC on Silica Gel 60 F_{254} (Merck) with detection by charring with sulfuric acid. 1-Deoxynojirimycin derivatives were detected with ninhydrin. Flash column chromatography was performed on Kieselgel 60 (Merck 230-400 mesh) at 5-10 psi. Chromatographic solvents were designated as volume-to-volume ratios. Organic solutions were concentrated at 40-45 °C under reduced pressure.

5-Azido-3,5,6-trideoxy-3-fluoro-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (2) and 5-azido-3,5,6-trideoxy-3,6-difluoro-1,2-*O*-isopropylidene-α-D-glucofuranose (3). A stirred solution of **1** (0.93 g) in dry dichloromethane (110 mL) and pyridine (1.5 mL) was treated with trifluoromethanesulfonic anhydride (1.47 mL) during 10 min at -60 °C and allowed to slowly rise to room temperature. After 1.25 h, TLC (ethyl acetate- hexane, 1:2) showed only a faster moving spot. The solution was washed with ice-cold dilute aq hydrochloric acid, saturated aq sodium chloride solution, dried (Mg_2SO_4), filtered and concentrated at 30 °C.

Without further purification, the syrupy residue was dissolved in dry dichloromethane (110 mL) and treated with TASF (4.25 g) under N_2 for 6 h at -12 °C when TLC (ethyl acetate-hexane, 2:1) showed two faster moving compounds with very similar mobility. The reaction was washed with cold saturated aq sodium chloride, dried (Mg_2SO_4) and concentrated. Flash column chromatography (1:10, ethyl acetate-hexane) of the residue, gave, first, 5-azido-3,5,6-trideoxy-3-fluoro-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (**2**) (0.21 g, 24.7%), $[\alpha]_D$ - 47.3° (*c* 1.02, chloroform). ^{19}F NMR: δ_F -129.1 (F-3). EI-MS: 214 (5, $[M - 15]^+$), 209 (39), 167 (25), 149 (57), 105 (47), 91 (41), 43 (100).

Anal. Calcd for $C_9H_{12}FN_3O_3$: C, 47.14; H, 5.28; F, 8.29; N, 18.34. Found: C, 46.98; H, 4.97; F, 8.61; N, 18.04.

Eluted next was 5-azido-3,5,6-trideoxy-3,6-difluoro-1,2-*O*-isopropylidene-α-D-glucofuranose (**3**) (0.46 g, 49.4%), $[\alpha]_D$ -15.3° (*c* 1.0, chloroform). ^{19}F NMR: δ_F -131.9 (F-3), +82.9 (F-6). EI-MS: 234 (11, $[M - 15]^+$), 209 (47), 161 (52), 118 (14), 107 (34), 105 (65) 43 (100).

Anal. Calcd for $C_9H_{13}F_2N_3O_3$: C, 43.36; H, 5.26; F, 15.25;N, 16.86. Found: C, 43.55; H, 5.12; F, 15.67; N, 17.01.

When the reaction was carried out (i) in dichloromethane at -3 °C for 1.5 h, a 8:1 mixture of **2** and **3** was obtained in 50% yield, and (ii) in acetonitrile at -20 °C for 1 h and then at room temperature for 2 h, a 9:2 mixture of **2** and **3** was obtained in 55% yield.

5-Azido-3-*O*-benzoyl-5-deoxy-1,2-*O*-isopropylidene-α-D-allofuranose (4). A stirred solution of 5-azido-3-*O*-benzoyl-5-deoxy-1,2-*O*-isopropylidene-6-*O*-*tert*-butyldiphenylsilyl-α-D-allofuranose[14] (0.92 g) in dry tetrahydrofuran (75 mL) was treated with tetra-*n*-butylammonium fluoride (0.38 g) for 4 h at room temperature. The solution was concentrated and a solution of the residue in dichloromethane was washed with water, dried (Na_2SO_4), filtered and the solvent was evaporated. Flash column chromatography (5:1, hexane-ethyl acetate) of the residue gave **4** (0.25 g, 78.4%), mp 105-107 °C (ether-hexane), $[\alpha]_D$ +47.9 (*c* 1.0, chloroform). EI-MS: 334 (3 $[M - 15]^+$), 205 (13), 159 (16), 122 (30), 105 (100), 77 (33).

Anal. Calcd for $C_{16}H_{19}N_3O_6$: C, 55.01; H, 5.48; N, 12.03. Found: C, 49.89; H, 5.57; N, 11.88.

5-Azido-6-*O*-benzoy-l-3,5-dideoxy-3-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose (5). When a solution of **4** (0.17 g) in dry dichloromethane (15 mL) and pyridine (0.2 mL) was treated with trifluoromethanesulfonic anhydride (0.33 mL) during 3 min at -19 °C and then with TASF (0.55 g) in dry dichloromethane (15 mL) for 2 h at -9 °C, as above, it gave **5** (0.13 g, 73.7%), which was identical to an authentic sample.[14,18]

5-Azido-5-deoxy-1,2-*O*-isopropylidene-α-D-allofuranose (7). Treatment of a solution of 5-azido-6-*O*-*tert*-butyldiphenylsilyl-5-deoxy-1,2-*O*-isopropylidene-α-D-allofuranose[14] (2.37 g) in dry tetrahydrofuran (150 mL) with tetra-*n*-butylammonium fluoride (2.0 g), as for **4**, gave crystalline **7** (1.03 g, 85.4%), mp 82-83 °C, $[\alpha]_D$ +47.6° (*c* 1.0, chloroform). EI-MS: 230 (3, [M - 15]$^+$), 199 (16), 155 (17), 143 (11), 127 (3), 59 (88), 43 (100).

Anal. Calcd for $C_9H_{15}N_3O_5$: C, 44.08; H, 6.17; N, 17.13. Found: C, 43.89; H, 6.12; N, 17.45.

5-Azido-3,5,6-trideoxy-1,2-*O*-isopropylidene-3-*O*-trifluoromethanesulfonyl-α-D-*xylo*-hex-5-enofuranose (8). Reaction of a solution of **7** (100 mg) with trifluoromethanesulfonic anhydride and TASF as above, gave crystalline **8** (54 mg, 86%), mp 80-82 °C, $[\alpha]_D$ +69.1° (*c* 1.0, chloroform). ^{19}F NMR: δ_F 1.04. EI-MS: 344 (9, [M - 15]$^+$), 316 (6), 291 (21), 233 (16), 96 (6), 43 (100)

Anal. Calcd for $C_{10}H_{12}F_3N_3O_6S$: C, 33.43; H, 3.37; F, 15.86; S, 8.90. Found: C, 33.12; H, 3.67; F, 15.57; S, 9.01.

5-Azido-3,5,6-trideoxy-3-fluoro-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (2). Treatment of a solution of **8** (61 mg) in dry acetonitrile (10 mL) with tetra-*n*-butylammonium fluoride for 30 h at room temperature, as for **4**, gave **2** (31 mg, 79.4%), identical to that obtained above.

1,3,5-Trideoxy-3,6-difluoronojirimycin [(2*R*,3*R*,4*R*,5*S*)-4-fluoro-3,5-dihydroxy-2-fluoromethylpiperidine] (10). A solution of **3** (0.6 g) in water (8 mL) was stirred with Amberlite IR-120 (H$^+$) resin (1 g) for 2 days at 40 °C, then concentrated at room temperature. The residue was hydrogenated (50 psi) in the presence of 20% palladium hydroxide-on-carbon (0.7 g) in aq ethanol (25 mL) for 6 h at room temperature. The solution was filtered and concentrated. Short column chromatography (20:3 ethyl acetate-methanol) of the syrupy residue gave **10** (0.29 g, 72.1%), mp 95 °C (from ethanol), $[\alpha]_D$ +32.4° (*c* 0.98, water). ^{19}F NMR: δ_F -115 (F-3), 79.5 (F-6). EI-MS: 167 (0.5, M$^+$), 147 (5, [M - HF]$^+$), 134 (12), 75 (100).

Anal. Calcd for $C_6H_{11}F_2NO_2$: C, 43.11; H, 6.63; F, 22.73; N, 8.38. Found: C, 43.12; H, 6.62; F, 23.02; N, 8.15.

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16. The structure of **4** is consistent with its ^{1}H NMR data. The H-3,5,6a,6b resonances were identified by spin-decoupling experiments (Table 1). When trichloroacetyl

isocyanate was added to the solution of **4,** the NMR spectrum showed the presence of only one NH singlet at δ 8.72, due to the resulting monocarbamate. The H-6a and H-6b signals were strongly deshielded and shifted downfield (δ 4.68 and 4.37 respectively) by ~0.7 and 0.2 ppm, respectively, but H-2 and H-3 were also deshielded (~0.3 ppm). The NOE difference spectrum showed a large enhancement of the OH peak (δ 2.56) on irradiation of H-6a and H-6b but no detectable enhancement on irradiation of H-3. This is clearly indicative of the presence of a hydroxyl group at C-6. Further confirmation was obtained from a COSY spectrum of **4**, which showed H-6a,6b, OH couplings. There was no coupling between H-3 and the OH peak.

17. A seven-membered orthoester-type imtermediate has been proposed by Hanessian [*J. Org. Chem.*, **34**, 2163 (1969)] in an acetal migration.
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