Fluorinated 1,5-Dideoxy-1,5-iminoalditols: Synthesis of 1,5,6-Trideoxy-6-fluoro-1,5-imino-D-glucitol (1,6-Dideoxy-6-fluoronojirimycin) and 1,4,5-Trideoxy-4-fluoro-1,5-imino-D-ribitol (1,2,5-Trideoxy-2-fluoro-1,5-imino-L-ribitol)

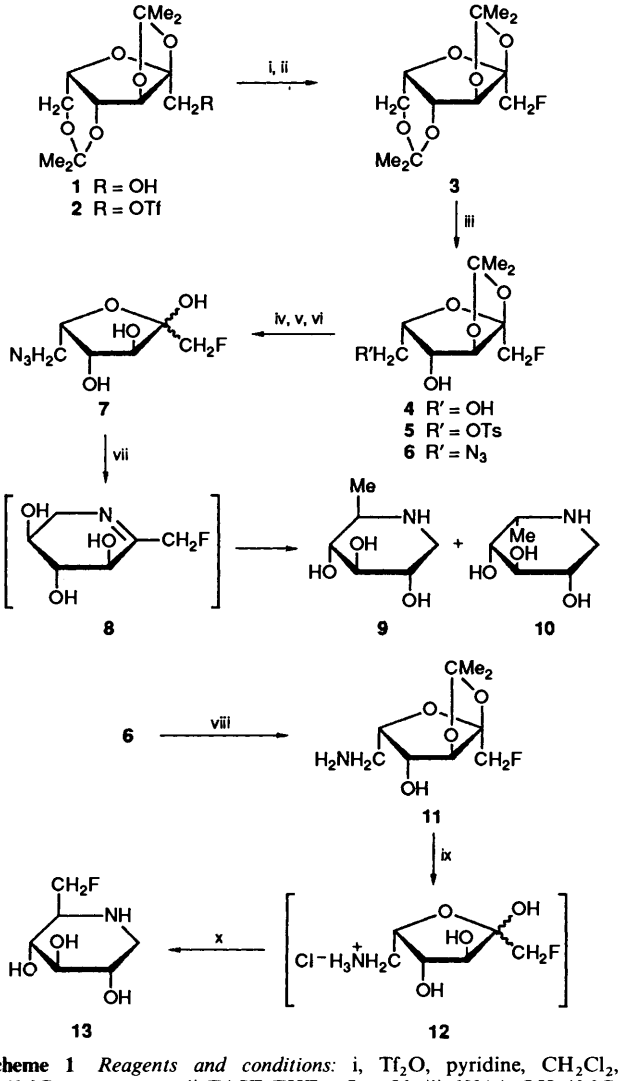
Jie Di, Bandaru Rajanikanth and Walter A. Szarek*
Department of Chemistry, Queen's University, Kingston, Ontario K7L 3N6, Canada

An efficient synthesis of 1,5,6-trideoxy-6-fluoro-1,5-imino-D-glucitol **13** from inexpensive L-sorbose by way of reductive amination of **12** is described. Synthesis of 1,4,5-trideoxy-4-fluoro-1,5-imino-D-ribitol (1,2,5-trideoxy-2-fluoro-1,5-imino-L-ribitol) **19** has been achieved also by a route which involves fluorination of **16** with retention of configuration at C-4.

Substitution of the ring oxygen of pyranoses and furanoses by nitrogen[1,2] leads to a class of specific glycosidase inhibitors[3] whose chemotherapeutic potential has been the subject of considerable recent research. 1,5-Dideoxy-1,5-imino-D-glucitol (1-deoxynojirimycin) is an important aza-sugar antibiotic, isolated from several natural sources,[4] having an array of interesting biological activities.[5] Fluorinated carbohydrates have been utilized widely in biochemical investigations of sugars.[6] Recently, syntheses of 1,5,6-trideoxy-6-fluoro-1,5-imino-D-glucitol **13**,[7a] other fluorinated analogues,[7b] and 6-deoxy-6-fluorocastanospermine[8] were reported. As a part of a programme concerned with the synthesis of modified 1,5-dideoxy-1,5-iminoalditols, we became interested in facile syntheses of fluorinated derivatives, compounds which might provide useful information about the active-site domains of endoglycosidases.[9] Here we report a facile synthesis of 1,6-dideoxy-6-fluoronojirimycin **13** and 1,4,5-trideoxy-4-fluoro-1,5-imino-D-ribitol **19** (1,2,5-trideoxy-2-fluoro-1,5-imino-L-ribitol).

The synthesis of **13** was achieved from 2,3:4,6-di-*O*-isopropylidene-α-L-sorbofuranose **1** in good yield (see Scheme 1). Fluorination of **1** using (diethylamino)sulfur trifluoride[10] (DAST) (6 equiv.) gave **3** in 30% yield. If 1 equiv. of DAST were employed the yield of **3** was <5%. However, tris(dimethylamino)sulfonium difluorotrimethylsilicate[11] (TASF) reacts with triflate **2** to afford **3** in good yield. Treatment of **1** in dichloromethane and pyridine with triflic anhydride in dichloromethane gave the triflate **2** {95%; m.p. 56 °C; $[\alpha]_D^{25}$ −10.0† (*c* 1.0, $CHCl_3$)}, which, on treatment with TASF in tetrahydrofuran at reflux temperature, furnished **3** {80%; $[\alpha]_D^{25}$ −7.6 (*c* 1.84, $CHCl_3$)}. Selective removal of the 4,6-*O*-isopropylidene group gave **4** {96.0%; m.p. 108 °C; $[\alpha]_D^{25}$ +10.0 (*c* 1.60, $CHCl_3$)}. Regioselective tosylation of the primary hydroxy group in **4** with toluene-*p*-sulfonyl chloride in dry pyridine and a catalytic amount of 4-(dimethylamino)pyridine provided **5** {85.0%; m.p. 106 °C; $[\alpha]_D^{25}$ +4.0 (*c* 1.0, $CHCl_3$)}. Treatment of **5** with sodium azide and urea in *N*,*N*-dimethylformamide furnished **6** {98.0%; m.p. 62 °C; $[\alpha]_D^{25}$ +21.8 (*c* 1.10, $CHCl_3$)}. Hydrolysis of **6** with 75% aqueous trifluoroacetic acid yielded **7** (84.5%) as a mixture of anomers.

Catalytic hydrogenation of **7** over 5% palladium-on-carbon in methanol (pH adjusted to 8.0 with triethylamine) did not yield the expected product **13**, but rather a 3:2 mixture of **9** and **10** (68%); the reaction in neutral or acidic medium also failed to yield **13**. The formation of **9** and **10** can be explained by reductive defluorination of the intermediate, activated fluoride **8**. Compound **13** was obtained as follows. Catalytic hydrogenation of **6** over 5% palladium-on-carbon in methanol gave the amine **11** {90.0%; m.p. 92 °C; $[\alpha]_D^{25}$ −2.72 (*c* 1.10, $CHCl_3$)}, which, on hydrolysis using conc. HCl in aqueous tetrahydrofuran (see ref. 12) and treatment of the resultant product (presumably **12**) with an excess of sodium cyanoborohydride in methanol, afforded, after silica gel, flash chromatography, **13** as

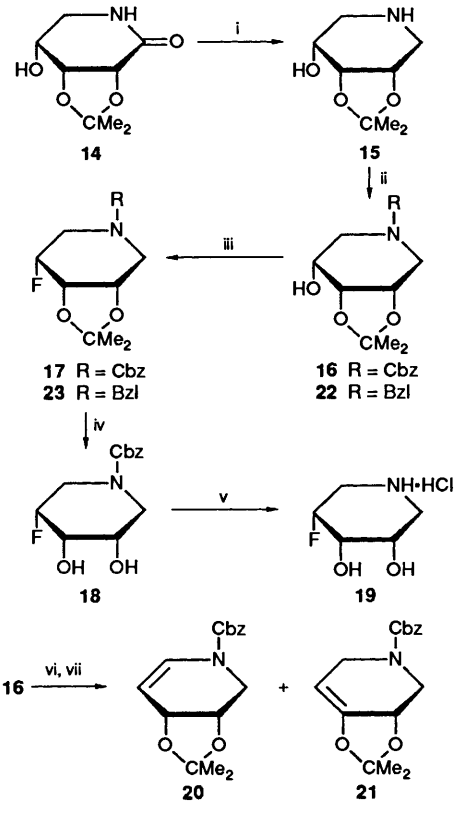


Scheme 1 *Reagents and conditions:* i, Tf_2O, pyridine, CH_2Cl_2, −60 °C→room temp.; ii, TASF, THF, reflux, 5 h; iii, 60% AcOH, 40 °C, 6 h; iv, *p*-TsCl, pyridine, DMAP, −60 °C→room temp., 6 h; v, NaN_3, urea, DMF, 100 °C, 6 h; vi, 75% CF_3CO_2H, room temp.; vii, H_2, 5% Pd/C, Et_3N, MeOH; viii, H_2, 5% Pd/C, MeOH; ix, 10% aqueous THF, conc. HCl; x, $NaCNBH_4$, MeOH, room temp., 12 h

† $[\alpha]_D$ Values are recorded in units of 10^{-1} deg cm^2 g^{-1}.

a white crystalline powder {72.0%; m.p. 153–154 °C; $[\alpha]_D^{25}$ +33.6 (*c* 1.07, H_2O); lit.,[7a] m.p. 149–153 °C; $[\alpha]_D^{25}$ +33.8 (*c* 0.52, MeOH)}. The NMR spectral data of **13** were in agreement with those reporte

The synthesis of 1,4,5-trideoxy-4-fluoro-1,5-imino-D-ribitol **19** was achieved from readily available[13] 5-amino-5-deoxy-2,3-*O*-isopropylidene-D-ribonolactam **14** (see Scheme 2). Treatment



Scheme 2 *Reagents and conditions:* i, $LiAlH_4$, THF, reflux; ii, for **16**, CbzCl, $NaHCO_3$, H_2O, 0 °C→room temp.; for **22**, benzyl bromide, K_2CO_3, DMF, 0 °C; iii, DAST, CH_2Cl_2, −40 °C→room temp.; iv, I_2, MeOH, reflux; v, H_2, Pd/C, MeOH, then 2 mol dm^{-3} HCl; vi, Tf_2O, pyridine, CH_2Cl_2, −20 °C→0 °C; vii, TASF, CH_2Cl_2, 0 °C→room temp.

of **14** with an excess of lithium aluminium hydride at reflux temperature gave **15** {88%; m.p. 95–97 °C; $[\alpha]_D^{25}$ +16 (*c* 0.1, $CHCl_3$)}. Protection of the amino group in **15** using benzyloxycarbonyl chloride in the presence of sodium hydrogen carbonate gave **16** as a syrup {75%; $[\alpha]_D^{25}$ +0.45 (*c* 2.2, $CHCl_3$)}. Fluorination of **16** with DAST gave **17**, with retention of configuration C-4, as a syrup {66%; $[\alpha]_D^{25}$ −6.9 (*c* 0.53, $CHCl_3$)}. Removal of the isopropylidene group in **17** using iodine in methanol[14] gave **18** {88%; m.p. 150–150.5 °C; $[\alpha]_D^{25}$ −8.9 (*c* 0.19, Me_2CO)}. Hydrogenolysis of **18** over 5% palladium-on-carbon in methanol gave a white solid which was converted into **19** as a white crystalline salt {m.p. >250 °C (decomp.); $[\alpha]_D^{25}$ +1.9 (*c* 0.21, H_2O)}.

The introduction of fluorine at C-4 in **17** with retention of configuration is noteworthy; the assignment of configuration at C-4 was based on geminal and vicinal ^{13}C–^{19}F (see ref. 15) and ^1H–^1H coupling constants in the spectra of **19**: ^{13}C NMR (D_2O), $^2J_{3,F}$ 16.5 Hz, $^3J_{2,F}$ 0 Hz; ^1H NMR (D_2O), $J_{3,4} = J_{3,2}$ 3.3 Hz. In an attempt to obtain the C-4 epimer of **17**, the triflate of **16** was treated with TASF; however, **20** and **21** (3.25:1.0) were obtained predominantly. The possibility of 1,3-neighbouring group participation by the benzyloxycarbonyl group in **16** during fluorination with DAST was eliminated, since the *N*-benzyl derivative **22** also yielded fluorinated compound **23** with retention of configuration at C-4.

The target compounds **13** and **19** have been characterized by IR and ^1H, ^{13}C and ^{19}F NMR spectroscopy, by mass spectrometry and by elemental analysis. Biological properties of **13** and **19** are currently being investigated.

References

1 H. Paulsen and K. Todt, *Adv. Carbohydr. Chem. Biochem.*, 1968, **23**, 115.
2 L. E. Fellows, *Chem. Br.*, 1987, 842.
3 G. Legler, *Adv. Carbohydr. Chem. Biochem.*, 1990, **48**, 319.
4 L. E. Fellows and G. W. J. Fleet, in *Natural Products Isolation*, ed. G. H. Wagman and R. Cooper, Elsevier, Amsterdam, 1989, ch. 13.
5 A. Karpas, G. W. J. Fleet, R. A. Dwek, S. Petursson, S. K. Namgoong, N. G. Ramsden, G. S. Jacob and T. W. Rademacher, *Proc. Natl. Acad. Sci. USA*, 1988, **85**, 9229.
6 See, *Fluorinated Carbohydrates: Chemical and Biochemical Aspects*, ed. N. F. Taylor, ACS Symposium Series 374, American Chemical Society, Washington, DC, 1988.
7 (*a*) K. Dax, V. Grassberger and A. E. Stütz, *J. Carbohydr. Chem.*, 1990, **9**, 903; (*b*) D. Getman, G. DeCrescenzo, R. Heintz, K. Houseman and R. Mueller, *Abstr. Pap. Am. Chem. Soc. Meet.*, 201 (1991) CARB-72.
8 J.-L. Reymond and P. Vogel, *J. Chem. Soc., Chem. Commun.*, 1990, 1070.
9 L. J. Liotta, J. Lee and B. Ganem, *Tetrahedron*, 1991, **47**, 2433.
10 P. J. Card, *J. Org. Chem.*, 1983, **48**, 393; P. J. Card and G. S. Reddy, *J. Org. Chem.*, 1983, **48**, 4734.
11 W. A. Szarek, G. W. Hay and B. Doboszewski, *J. Chem. Soc., Chem. Commun.*, 1985, 663; B. Doboszewski, G. W. Hay and W. A. Szarek, *Can. J. Chem.*, 1987, **65**, 412.
12 See, J. Stoltefuss, USP 4 220 782/1980.
13 S. Hanessian, *J. Org. Chem.*, 1969, **34**, 675.
14 W. A. Szarek, A. Zamojski, K. N. Tiwari and E. R. Ison, *Tetrahedron Lett.*, 1986, **27**, 3827.
15 V. Wray, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1598; P. Sarda, F. C. Escribano, R. J. Alves, A. Olesker and G. Lukacs, *J. Carbohydr. Chem.*, 1989, **8**, 115.

Paper 2/03193K
Received 17*th June* 1992
Accepted 7*th July* 1992