Synthesis of (±)-2′,3′-dideoxy-3′-fluoroapiosylpyrimidine nucleosides

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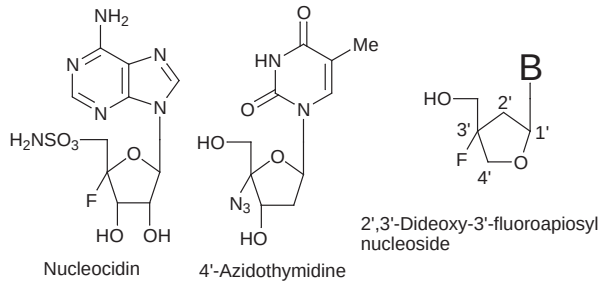
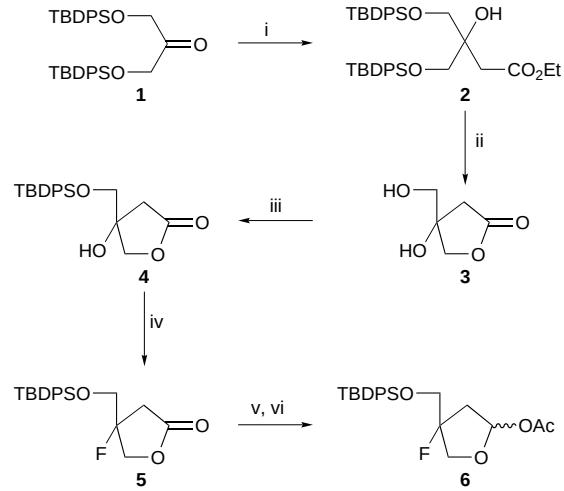
Various (±)-2′,3′-dideoxy-3′-fluoroapiosylpyrimidine nucleoside analogs have been prepared.

Since the discovery and synthesis of nucleocidin,[1] which has a unique 4′-fluorosugar, a number of 4′-substituted nucleosides[2] and 4′-substituted carbocyclic nucleosides[3] have been synthesized and their biological activities evaluated. Among them, 4′-azidothymidine exhibited potent anti-HIV activity.

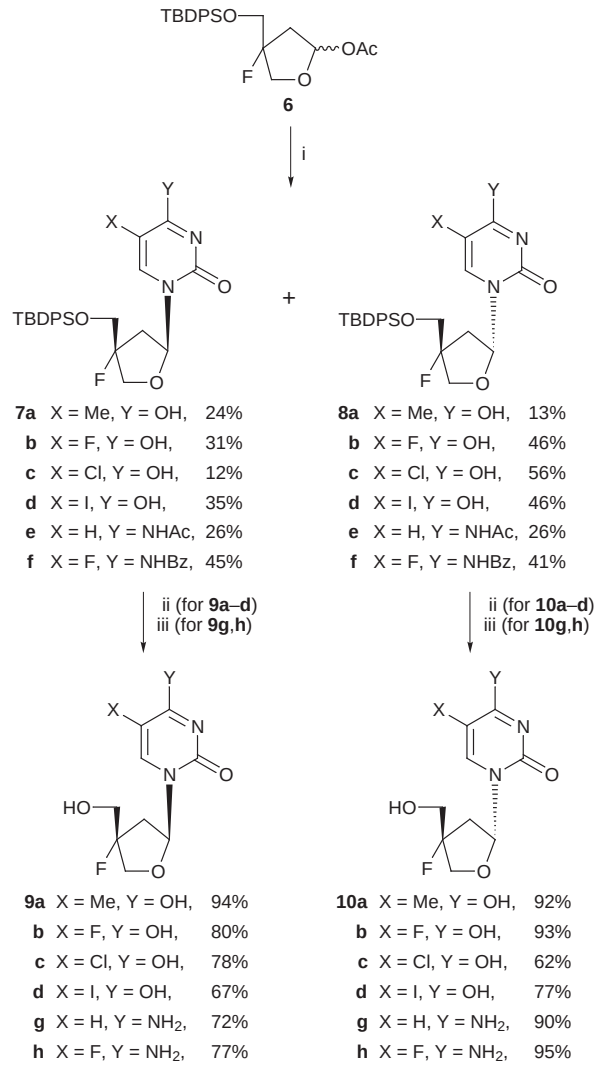


In our effort to synthesize novel 4′-substituted nucleoside derivatives with biological activity, we envisioned 2′,3′-dideoxy-3′-substituted apiosyl nucleosides to be one of these 4′-substituted nucleosides. While the synthesis and biological activities of a great many structurally modified nucleoside analogs have been reported, relatively little work has been done on the synthesis and biological activities of nucleoside analogs which contain apiose as the sugar moiety.[4] Here we report on the synthesis of (±)-2′,3′-dideoxy-3′-fluoroapiosylpyrimidine nucleosides.

The synthesis of the key intermediate, 2,3-dideoxy-3-fluoroapiofuranosyl acetate **6**, is shown in Scheme 1. Reformatsky reaction[5] of bis-silyl protected dihydroxyacetone **1**[6] with ethyl bromoacetate in the presence of activated zinc gave a β-hydroxy ester **2**. This was then treated with a 12% methanolic HCl solution at room temperature to afford hydroxy lactone **3** in 77% yield over two steps. The primary hydroxy group of **3** was selectively protected with a *tert*-butyldiphenylsilyl group to give **4** in 93% yield.[7] Fluorination of the tertiary alcohol of **4** with DAST in CH_2Cl_2 at room temperature gave fluoro lactone **5** in 32% yield. In this reaction the α,β-unsaturated lactone was obtained by elimination reaction in 27% yield. Reduction of fluoro lactone **5** to lactol with DIBAL-H at −78 °C followed by acetylation with Ac_2O gave the key intermediate, 2,3-dideoxy-3-fluoroapiofuranosyl acetate **6**, in 70% yield over two steps.



Scheme 1 *Reagents and conditions*: i, $BrCH_2CO_2Et$, activated Zn, benzene–toluene (2 : 1), reflux, 4 h; ii, 12% HCl in MeOH, room temp., 20 h, 77% (2 steps); iii, TBDPSCl, DMAP, Et_3N, CH_2Cl_2, room temp. overnight, 93%; iv, DAST, CH_2Cl_2, room temp. 1 h, 32%; v, DIBAL-H, CH_2Cl_2, −78 °C, 0.5 h; vi, Ac_2O, Et_3N, DMAP, CH_2Cl_2, room temp. 0.5 h, 70% (2 steps)



Scheme 2 *Reagents and conditions*: i, bis-silylated base, TMSOTf, $ClCH_2CH_2Cl$, 0 °C, 0.5 h; ii, TBAF, THF, room temp.; iii, methanolic NH_3, room temp. then TBAF, THF, room temp.

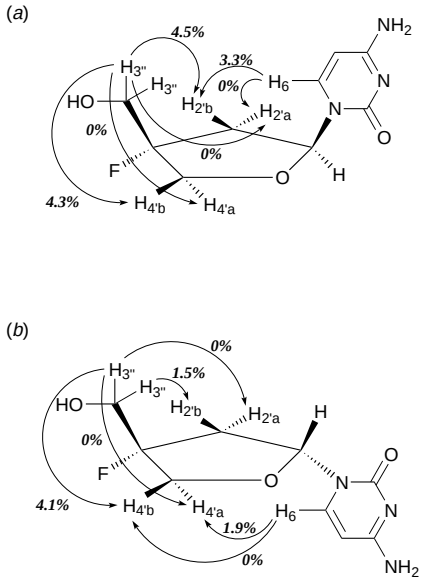


Fig. 1 NOE experiments of compounds (*a*) **9g** and (*b*) **10g**

The coupling of acetate **6** with bis-silylated pyrimidine derivatives under Vorbrüggen conditions is depicted in Scheme 2.[8] Bis-silylated pyrimidine derivatives were condensed with fluorosugar **6** in the presence of TMSOTf in 1,2-dichloroethane to give an α:β mixture of **7** and **8** in moderate yield. The mixtures were separated by silica gel column chromatography to give the individual isomers **7** and **8**. Deprotection of **7** and **8** afforded the pyrimidine nucleosides **9** and **10**, respectively.‡

The structural assignment of the uracil and cytosine analogs was made on the basis of ^{1}H NMR studies. For example, upon irradiation of the H-3″ protons in compound **9g**, nuclear Overhauser effects (NOEs) were observed for the H-2′$_b$ (4.5%) and H-4′$_b$ (4.3%) protons, while no NOEs were detected for the H-2′$_a$ and H-4′$_a$ protons. Irradiation of the H-6 proton resulted in an NOE for the H-2′$_b$ (3.3%) proton, while no NOE was observed for the H-2′$_a$ proton. In compound **10g**, upon irradiation of the H-3″ proton, NOEs were detected for the H-2′$_b$ (1.5%) and H-4′$_b$ (4.1%) protons, while no NOEs were observed for the H-2′$_a$ and H-4′$_a$ protons. Irradiation of the H-6 proton resulted in an NOE for the H-4′$_a$ (1.9%) proton, while no NOE was detected for the H-4′$_b$ proton (Fig. 1). The above results showed **9g** was the β-isomer and **10g** was the α-isomer. The relative configuration of the rest of the compounds in this report was assigned using the results of the same NOE experiments. The β-configuration of cytosine analog **9g** was determined conclusively on the basis of X-ray crystallography (Fig. 2).§ Compound **9g** assumes the 4′-*endo* conformation, in which the fluorine at C-4′ is approximately in a *gauche* disposition relative to the furan oxygen.

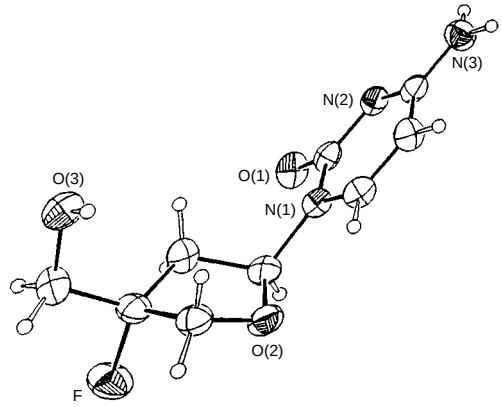


Fig. 2 ORTEP drawing of (±)-1-(2,3-dideoxy-3-fluoroapio-β-furanosyl)cytosine **9g**

Evaluation of antiviral activities and asymmetric synthesis of 2′,3′-dideoxy-3′-fluoroapiosyl nucleosides are in progress.

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Notes and References

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‡ All new compounds gave satisfactory analytical and spectral data. *Selected data* for **9g**: mp 179–181 °C; δ_H([^{2}H$_6$]DMSO)2.21 (ddd, $J_{2'b,F}$ 35.5 $J_{2'b,2'a}$ 14.6, $J_{2'b,1'}$ 7.7, 1 H, H$_b$-2′), 2.44 (m, 1 H, H$_a$-2′), 3.66 (m, 2 H, H-3″), 3.94 (dd, $J_{4'a,F}$ 21.5, $J_{4'a,4'b}$10.8, 1 H, H$_a$-4′), 4.19 (dd, $J_{4'b,F}$ 35.1, $J_{4'b,4'a}$ 10.8, 1 H, H$_b$-4′), 6.10 (dd, $J_{1',2'b}$ 7.7, $J_{1',2'a}$ 6.6, 1 H, H-1′);δ_C(CD$_3$OD) 166.78, 157.14, 141.54, 105.40, 103.62, 95.14, 88.68, 75.33, 75.07, 63.00, 62.73, 40.67, 40.44; λ_{max}(H$_2$O)/nm 269.4, 229.0 (sh) (pH 7), 278.0, 209.3 (sh) (pH 2), 268.0 (pH 11) (Calc. for C$_9$H$_{12}$N$_3$O$_3$F; C, 47.16; H, 5.28; N, 18.33. Found: C, 47.21; H, 5.36; N, 18.22%). For **10g**: mp 219–220 °C; δ_H([^{2}H$_6$]DMSO) 2.08 (dddd, $J_{2'a,F}$ 21.9, $J_{2'a,2'b}$ 15.2, $J_{2'a,1}$ 2.5, $J_{2'a,4'b}$ 1.5, 1 H, H$_a$-2′), 2.56 (ddd, $J_{2'b,F}$ 35.7, $J_{2'b,2'a}$ 15.2, $J_{2'b,1'}$ 7.6,1 H, H$_b$-2′), 3.59 (dd, $J_{3'',F}$ 20.7, $J_{3'',3''}$ 12.1, 1 H, H-3″), 3.65(dd, $J_{3'',F}$ 16.7, $J_{3'',3''}$ 12.1, 1 H, H-3″), 3.96 (dd, $J_{4'b,F}$ 34.5, $J_{4'b,4'a}$ 10.9, 1 H, H$_b$-4′), 4.26 (ddd, $J_{4'a,F}$ 20.5, $J_{4'a4'b}$ 10.9, $J_{4'a,2'a}$ 1.5, 1 H, H$_a$-4′), 6.02 (dd, $J_{1',2'b}$ 7.6, $J_{1',2'a}$ 2.5, 1 H, H-1′), 7.54 (d, $J_{6,5}$ 7.4, 1 H, H-6); δ_C(CD$_3$OD) 166.81, 157.20, 141.15, 141.10, 104.64, 102.87, 94.45, 87.87, 76.15, 75.91, 62.81, 62.53, 40.93, 40.71; λ_{max}(H$_2$O)/nm 269.8, 229.2 (sh) (pH 7), 278.6, 219.6 (sh) (pH 2), 270.2 (pH 11) (Calc. for C$_9$H$_{12}$N$_3$O$_3$F; C, 47.16; H, 5.28; N, 18.33. Found: C, 47.09; H, 5.18; N, 18.48%).

§ *Crystal data* for **9g**: C$_9$H$_{12}$FN$_3$O$_3$, M = 229.22, monoclinic, space group $P2_1/c$ (No. 14), unit cell dimensions a = 5.1519 (10), b = 10.7326 (13), c = 17.756 (2) Å, β = 92.39 (2)°, V 981.0 (3) Å^3, T = 293 (2) K, Z = 4, μ = 0.130 mm^{-1}, F(000) = 480, 1580 reflections were measured and 1409 independent reflections were used for the structure solution. Final R values are as follows: $wR2$ = 0.0970 {R_1 = 0.0373 [I = 2σ(I)]}. CCDC 182/821.

1 I. D. Jenkins, J. P. H. Verheyden and J. G. Moffatt, *J. Am. Chem. Soc.*, 1976, **98**, 3346.
2 J. P. H. Verheyden and J. G. Moffatt, *J. Am. Chem. Soc.*, 1975, **97**, 4386; G. R. Owen, J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, 1976, **41**, 3010; C. O. Yang, W. Kurz, E. M. Eugui, M. J. McRoberts, J. P. H. Verheyden, L. J. Kurz and K. A. M. Walker, *Tetrahedron Lett.*, 1992, **33**, 41; B. H. Lipshutz, S. Sharma, S. H. Dimock and J. R. Behling, *Synthesis*, 1992, 191; H. Maag, R. M. Rydzewski, M. J. McRoberts, D. Crawford-Ruth, J. P. H. Verheyden and E. J. Prisbe, *J. Med. Chem.*, 1992, **35**, 1440.
3 J. Beres, G. Sagi, E. Baitz-Gacs, I. Tomoskozi, L. Gruber and L. Otvos, *Tetrahedron*, 1989, **45**, 6271; K. Biggadike and A. D. Borthwick, *J. Chem. Soc., Chem. Commun.*, 1990, 1380; H. Maag and R. M. Rydzewski, *J. Org. Chem.*, 1992, **57**, 5823.
4 F. Perini, F. A. Carey and L. Jr. Long, *Carbohydr. Res.*, 1969, **11**, 159; J. M. J. Tronchet and J. Tronchet, *Carbohydr. Res.*, 1974, **34**, 263; J. M. J. Tronchet, J. Tronchet and R. Graf, *J. Med. Chem.*, 1974, **17**, 1055; D. K. Parikh and R. R. Watson, *J. Med. Chem.*, 1978, **21**, 706; M. J. Bamford, D. C. Humber and R. Storer, *Tetrahedron Lett.*, 1991, **32**, 271; Y. Terao, M. Akamatsu and K. Achiwa, *Chem. Pharm. Bull.*, 1991, **39**, 823; T. B. Sells and V. Nair, *Tetrahedron*, 1994, **50**, 117; F. Hammerschmidt, E. Öhler, J. Polsterer, E. Zbiral, J. Balzarini and E. DeClercq, *Liebigs Ann.*, 1995, 551; F. Hammerschmidt, J. Polsterer and E. Zbiral, *Synthesis*, 1995, 415.
5 M. W. Rathke, *Org. React.*, 1975, **22**, 423.
6 R. Sharma, J. Lee, S. Wang, G. W. A. Milne, N. E. Lewin, P. M. Blumberg and V. E. Marquez, *J. Med. Chem.*, 1996, **39**, 19.
7 S. K. Chaudhary and O. Hernandez, *Tetrahedron Lett.*, 1979, 99.
8 H. Vorbrüggen, K. Krolikiewicz and B. Bennua, *Chem. Ber.*, 1981, **114**, 1234.

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