Tetrahedron Letters,Vol.30,No.24,pp 3171-3174,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

SYNTHESIS OF 9-(3-DEOXY- AND 2,3-DIDEOXY-3-FLUORO-β-D-XYLOFURANOSYL)GUANINES AS POTENTIAL ANTIVIRAL AGENTS

Frédéric PUECH, Gilles GOSSELIN and Jean-Louis IMBACH*
Université des Sciences et Techniques du Languedoc, Laboratoire de Chimie Bio-organique associé au CNRS, Place E. Bataillon, 34060 Montpellier, France.

Abstract : The first synthesis of the title compounds 8 and 10 was accomplished by a multi-step approach involving prior preparation of a suitably protected fluorosugar 6.

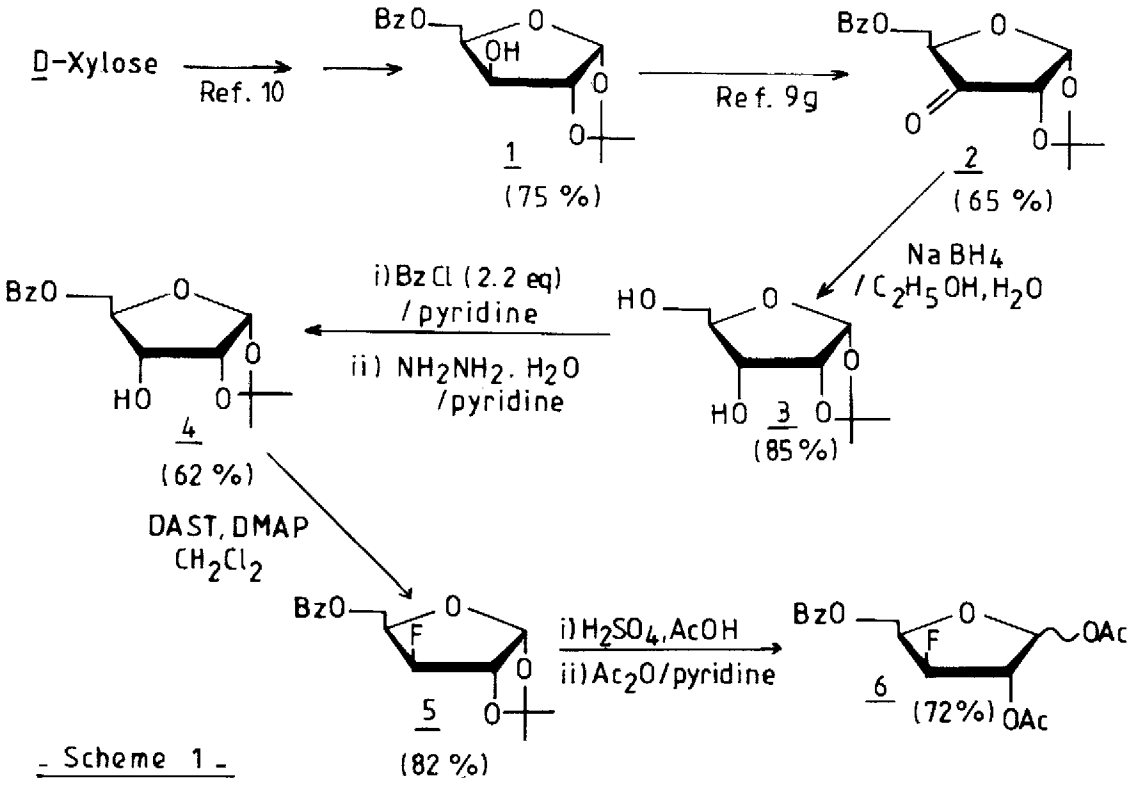
Nucleosides fluorinated at the 2'-position of the sugar moiety have been extensively investigated in the search for anti-viral agents, and some 2'-deoxy- and 2',3'-dideoxy-2'-*ara*-fluoro analogues actually display potent anti-herpes[1] and anti-human immunodeficiency virus[2] (anti-HIV) activities, respectively. In contrast, nucleosides fluorinated at their 3'-position have been less explored. For instance, among the analogues with 3'-*xylo*-fluoro configuration two derivatives (those of adenine[3] and cytosine[4]) in the 3'-deoxy series and only one (of adenine[5]) in the 2',3'-dideoxy series have been prepared previously. The recently mentioned inhibitory effects of the latter compound on the replication of HIV[6] prompted us to synthesize the hitherto unknown 9-(3-deoxy- and 2,3-dideoxy-3-fluoro-β-D-xylofuranosyl)guanine (8) and (10) in order to evaluate their antiviral activities.

The most appropriate synthetic plan to reach 8 and 10 appeared to first prepare a suitably fluorodeoxy sugar like 6 and to condense it with N^2-acetylguanine. After condensation and selective 2'-deacetylation the resulting key nucleoside intermediate 7 could be fully deprotected, either directly or after 2'-deoxygenation *via* a Barton-type reaction,[7] to give 8 and 10, respectively.

To date there have been two indirect approaches to the synthesis of 3-deoxy-3-fluoro-β-D-xylofuranosyl sugars, involving nucleophilic displacement of the sulfonate group from 1,2:5,6-di-O-isopropylidene-3-O-toluene-*p*-sulfonyl-α-D-allofuranose[8] and action of potassium hydrogen fluoride on methyl 2,3-anhydro-5-O-benzyl-β-D-ribofuranoside .[3a] In order to make these fluoro sugars more accessible we have synthesized 1,2-di-O-acetyl-5-O-benzoyl-3-deoxy-3-fluoro-D-xylofuranose (6) from D-xylose.

Thus, D-xylose was first conveniently converted on a large scale into 5-O-benzoyl-1,2-O-isopropylidene-α-D-*erythro*-pentofuranose-3-ulose (2)[9] according to the most effective published procedure.[10,9g] The reduction of 2 with sodium borohydride in aqueous ethanol gave exclusively 1,2-O-isopropylidene-α-

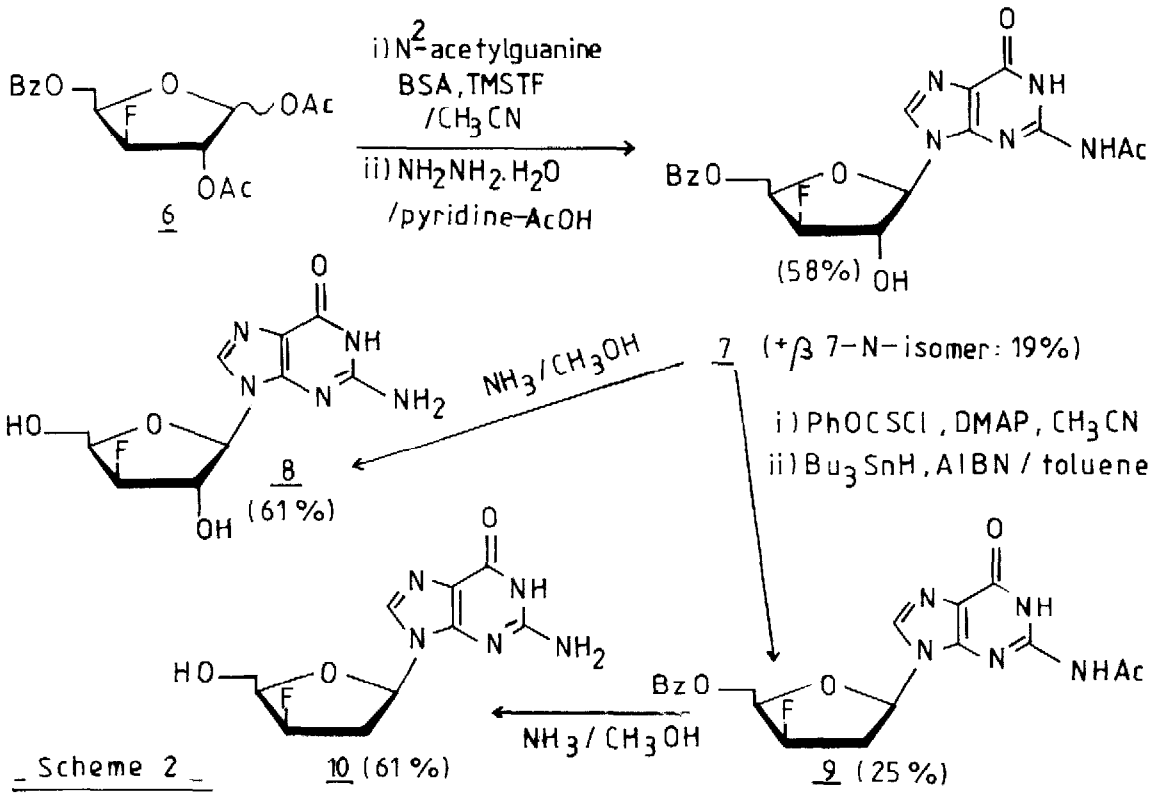
-D-ribofuranose (3)[9e,11] which on reaction with an excess of benzoyl chloride and subsequent treatment with hydrazine hydrate afforded 5-O-benzoyl-1,2-O--isopropylidene-α-D-ribofuranose (4).[12] Substitution with inversion of configuration of the 3'-hydroxy group of 4 by a fluorine atom was performed using diethylaminosulfur trifluoride (DAST). Fluorination of 4 under conditions usual in the hexose series,[13] afforded 5-O-benzoyl-1,2-O-isopropylidene-3--deoxy-3-fluoro-α-D-xylofuranose (5) in good yield. After selective removal of the 1,2-O-isopropylidene group from 5 and acetylation, the required sugar 6 was obtained (Scheme 1).



- Scheme 1 -

Condensation of 6 with silylated N^2-acetylguanine, separation of the resulting β 9-N,7-N isomers and full deacylation to give ultimately the desired fluoronucleoside 8 were effected under conditions similar to those used for the synthesis of β-D-xylofuranosylguanine in our earlier paper.[14] The isolated intermediate 7 on reductive 2'-deoxygenation[7] followed by a deacylation afforded the second desired nucleoside 10 (Scheme 2).

Structural assignments for the compounds 1-10 were based on their physicochemical properties.[15] Unfortunately, the title compounds 8 and 10 were shown to be uneffective against various DNA and RNA viruses in primary rabbit kidney, Hela and Vero cell cultures. They were also not active against HIV-1 in MT4 cell cultures.



Scheme 2

Further data and studies on the use of the fluorodeoxy sugar 6 in the synthesis of other nucleoside analogues will be reported in a full paper.

Acknowledgments : The authors gratefully acknowledge financial support from INSERM (PNR-SIDA) and Prof. E. De Clercq for the biological results.

References and Notes.

1. J.J. Fox, K.A. Watanabe, T.C. Chou, R.F. Schinazi, K.F. Soike, I. Fourel, G. Hantz and C. Trepo In *Fluorinated Carbohydrates, Chemical and Biochemical Aspects*, N.F. Taylor Ed., ACS Symposium Series 374: Washington, 1988, pp. 176-190.
2. V.E. Marquez, C.K.-H. Tseng, J.A. Kelley, H. Mitsuya, S. Broder, J.S. Roth and J.S. Driscoll, *Biochem, Pharmacol.* **1987**, *36*, 2719.
3. **a)** J.A. Wright and N.F. Taylor, *Carbohyd. Res.* **1968**, *6*, 347; **b)** M.J. Robins, Y. Fouron and R. Mengel, *J. Org. Chem.* **1974**, *39*, 1564; **c)** M. Auer, P. Rösch and R.S. Goody, Presented at the 8th International Round Table on "Nucleosides, Nucleotides and Their Biological Applications", 2-5 October 1988, Orange Beach, Alabama, USA (To be published in *Nucleosides Nucleotides*).
4. J.A. Wright, D.P. Wilson and J.J. Fox, *J. Med. Chem.* **1970**, *13*, 269.

5. P. Herdewijn, R. Pauwels, M. Baba, J. Balzarini and E. De Clercq, *J. Med. Chem.* **1987**, *30*, 2131.
6. R. Pauwels, M. Baba, J. Balzarini, P. Herdewijn, J. Desmyter, M.J. Robins, R. Zou, D. Madej and E. De Clercq, *Biochem. Pharmacol.* **1988**, *37*, 1317.
7. See, for example: M.J. Robins, D. Madej, F. Hansske, J.S. Wilson, G. Gosselin, M-C. Bergogne, J-L. Imbach, J. Balzarini and E. De Clercq, *Can. J. Chem.* **1988**, *66*, 1258.
8. A.B. Foster, R. Hems and J.M. Webber, *Carbohyd. Res.* **1967**, *5*, 292.
9. **a)** G.L. Tong, W.W. Lee and L. Goodman, *J. Org. Chem.* **1967**, *32*, 1984; **b)** R.F. Nutt, M.J. Dickinson, F.W Holly and E. Walton, *J. Org. Chem.* **1968**, *33*, 1789; **c)** H. Yanagisawa, M. Kinoshita, S. Nakada and S. Umezawa, *Bull. Chem. Soc. Jpn.* **1970**, *43*, 246; **d)** A.N. Fujiwara, E.M. Acton and L. Goodman, *J. Heterocyclic Chem.* **1970**, *7*, 891; **e)** G.O. Aspinall and R.R. King, *Can. J. Chem.* **1973**, *51*, 394; **f)** B. Flaherty, S. Nahar, W.G. Overend and N.R. Williams, *J. Chem. Soc. Perkin I.* **1973**, 632; **g)** D.H. Hollenberg, R.S. Klein and J.J. Fox, *Carbohyd. Res.* **1978**, *67*, 491; **h)** O. Okruszek and J.G. Verkade, *J. Med. Chem.* **1979**, *22*, 882.
10. P.A. Levene and A.L. Raymond, *J. Biol. Chem.* **1933**, *102*, 317.
11. N.A. Hughes and P.R.H. Speakman, *Carbohyd. Res.* **1965**, *1*, 171.
12. Y. Ishido, N. Sakairi, M. Sekiya and N. Nakazaki, *Carbohyd. Res.* **1981**, *97*, 51.
13. **a)** T.J. Tewson and M.J. Welch, *J. Org. Chem.* **1978**, *43*, 1090; **b)** S.G. Withers, D.J. MacLennan and I.P. Street, *Carbohyd. Res.* **1986**, *154*, 127.
14. G. Gosselin, M-C. Bergogne, J. De Rudder, E. De Clercq and J.L. Imbach, *J. Med. Chem.* **1987**, *30*, 983.
15. For previously described compounds **1**-**4** our data were in accord with literature values. Hitherto unknown compounds **5**-**10** were characterized by ^{1}H and ^{19}F n.m.r, u.v., and mass spectrometry. *Selected spectroscopic data*; For **8**: ^{1}H n.m.r (Me_2SO-d_6) δ (relative to Me_2SO-d_5 set at 2.51 ppm) 10.7 (1H, br s, NH-1), 7.63 (1H, s, H-8), 6.6 (2H, br s, NH_2), 6.2 (1H, br s, OH-2'), 5.72 (1H, d, H-1'; J= 2.1 Hz), 5.05 (1H, d, H-3'; $J_{3',F}$= 51.7 Hz), 5.03 (1H, t, OH-5'), 4.60 (1H, dm, H-2'; $J_{2',F}$= 15.8 Hz), 4.23 (1H, m, H-4'; $J_{4',F}$= 26.0 Hz), 3.70 (2H, m, H-5',5"); ^{19}F n.m.r. (Me_2SO-d_6) δ (relative to $CFCl_3$) -200.16 (ddd, F-3'; $J_{F,3'}$= 52.0 Hz, $J_{F,2'}$= 16.0 Hz, $J_{F,4'}$= 29.0 Hz); *m/z* (f.a.b. > 0) (glycerol) 152 (BH_2), 286 (M+H), 378 (M+G+H), 571 (2M+H); For **10**: ^{1}H n.m.r (Me_2SO-d_6) δ 10.64 (1H, s, NH-1), 7.64 (1H, s, H-8), 6.5 (2H, br s, NH_2), 6.14 (1H, dd, H-1'; $J_{1',2"}$= 7.5 Hz, $J_{1',2'}$= 2.0 Hz), 5.36 (1H, ddd, H-3'; $J_{3',F}$= 53.2 Hz, $J_{3',2'}$= 4 Hz, $J_{3',4'}$= 2.7 Hz), 4.98 (1H, t, OH-5'; J= 5.6 Hz), 5.05 (1H, ddt, H-4'; $J_{4',F}$= 29.9 Hz, $J_{4',(5',5")}$= 6.3 Hz, $J_{4',3'}$= 2.5 Hz), 3.8-3.6 (2H, m, H-5',5"), 2.84 (1H, dddd, H-2", $J_{2",F}$= 42.3 Hz, $J_{2",2'}$= 15.8 Hz, $J_{2",1'}$= 7.5 Hz, $J_{2",3'}$= 4.5 Hz), 2.58 (1H, ddd, H-2'; $J_{2',F}$= 25.1 Hz, $J_{2',2"}$= 16 Hz, $J_{2',1'}$= 2 Hz); ^{19}F n.m.r. (Me_2SO-d_6) δ -191.48 (dddd, F-3'; $J_{F,3'}$= 54.0 Hz, $J_{F,2"}$= 42.5 Hz, $J_{F,4'}$= 30.0 Hz, $J_{F,2'}$= 23.8 Hz); *m/z* (f.a.b.>0) (glycerol) 152 (BH_2), 270 (M+H).

(Received in France 7 March 1989)