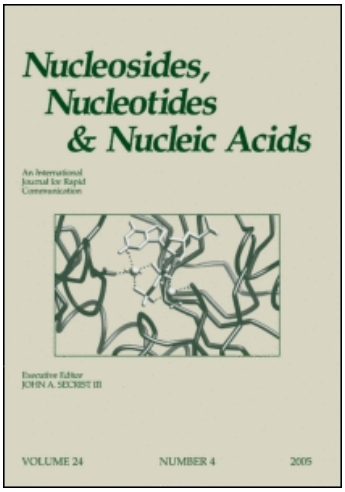

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis of 3'-Fluoro-3'-Deoxyribonucleosides; Anti-HIV-1 and Cytostatic Properties

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To cite this Article Van Aerschot, Arthur , Balzarini, Jan , De Clercq, Erik and Herdewijn, Piet(1989) 'Synthesis of 3'-Fluoro-3'-Deoxyribonucleosides; Anti-HIV-1 and Cytostatic Properties', Nucleosides, Nucleotides and Nucleic Acids, 8: 5, 1123 — 1124
To link to this Article: DOI: 10.1080/07328318908054305
URL: http://dx.doi.org/10.1080/07328318908054305

NUCLEOSIDES & NUCLEOTIDES, 8(5&6), 1123-1124 (1989)

SYNTHESIS OF 3'-FLUORO-3'-DEOXYRIBONUCLEOSIDES: ANTI-HIV-1 AND CYTOSTATIC PROPERTIES

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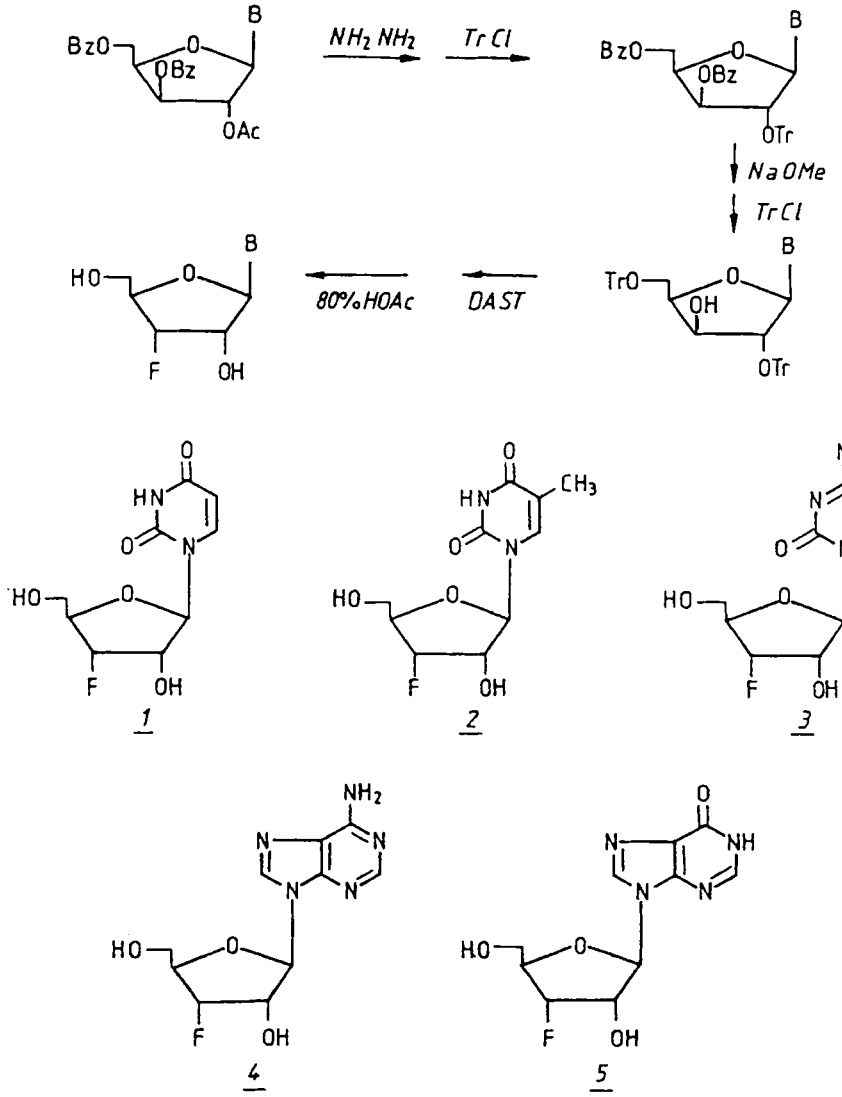
It has generally proven difficult to synthesize ribonucleosides with sugar modifications at the 3'-position. We now present a practical route for the synthesis of ribonucleosides with a 3'-fluorine substituent. Nucleosides with the xylo configuration were prepared by sugar-base condensation. Tritylation of the unprotected nucleosides gave a mixture of 2',5'- and 3',5'-bistritylated nucleosides which were difficult to characterize. Therefore the necessary precursors were synthesized in a stepwise fashion, starting with selective deprotection of the 2'-acyl group, followed by tritylation. This gave the 2',5'-tritylated xylonucleosides in good yield. Reaction with diethylaminosulfur trifluoride and deprotection with 80 % acetic acid provided the 3'-fluoro-3'-deoxyribonucleosides 1, 2 and 4. The cytidine derivative was synthesized from 1 by reaction with trifluoromethanesulfonic anhydride followed by ammonia. Treatment of 4 with adenosine deaminase yielded 5.

TABLE 1. ANTI-HIV-1 ACTIVITY IN MT-4 CELLS

Compound	ED_{50} (μM)	CD_{50} (μM)
1	> 20	38
2	> 500	> 500
3	> 20	43
4	2	1.6
5	> 500	> 500

ED_{50} : 50 % effective dose; CD_{50} : 50 % cytotoxic dose.



None of the compounds showed a selective activity against HIV-1 (Table 1), but 3'-fluoroadenosine (compound 4) proved markedly cytostatic for the host cells. The cytostatic potential of 4 was confirmed in different cell systems. The CD_{50} of 3'-fluoroadenosine was 3.1 μM for murine leukemia (L1210) cells, 23 μM for human B-lymphoblast (Raji) cells, 23 μM for human T-lymphocyte (H9) cells and 1.6 μM for human T4-lymphocyte (MT-4) cells.