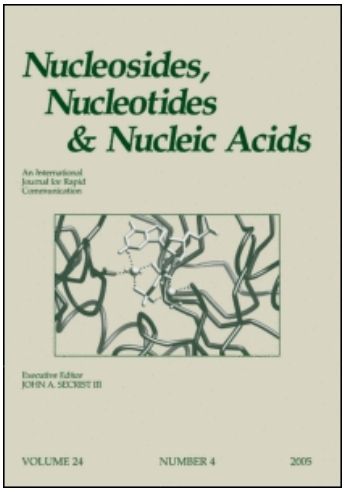

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SYNTHESIS AND BIOLOGICAL EVALUATION OF DIDEOXUNUCLEOSIDES CONTAINING A DIFLUOROMETHYLENE UNIT

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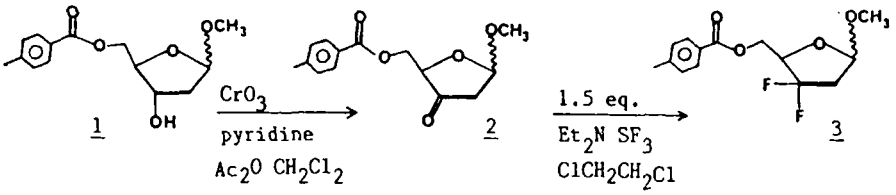
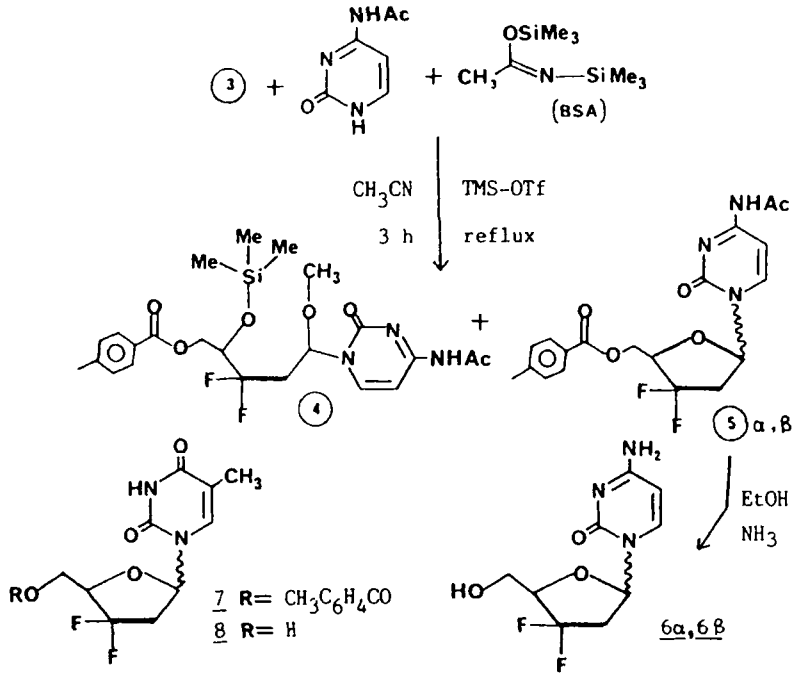
Abstract: 2'-difluoro and 3'-difluoro dideoxynucleosides containing thymine and cytosine as the base were synthesized. These compounds inhibited HeLa cell growth and Moloney leukemia virus to a modest degree.

Recent interest in the synthesis of fluorinated dideoxynucleosides[1,2] has prompted us to report our syntheses of nucleosides 6,8,14 and 15 in this class. Bergstrom et al. reported one dideoxynucleoside, but no biological data was presented.[2] Fluorine in the 3'-position has produced anti-tumor activity[3] and recently 3'-fluorothymidine triphosphate has been shown to inhibit HIV-reverse transcriptase.[12] Fluorines in the 2'-position are expected to stabilize the glycosidic bond. The enzyme targets for the title compounds are viral reverse transcriptase and mammalian DNA-polymerase alpha.

The synthesis of the 3'-difluoronucleosides was developed independently from that of Bergstrom et al., but used the same fluorinating agent. First, the readily available[4] deoxyribose derivative 1 was oxidized using Samuelsson's[5] procedure, affording 2 in 67% yield (and 23% recovery of 1).

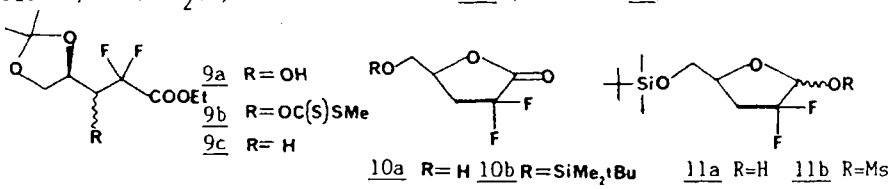


The ketone 2 was insensitive to DAST at room temperature, but after 3 days at 55°C in 1,2-dichloroethane a 34% yield of 3 was obtained. Following the example of Dyatkina et al.[6], the methyl acetal 3 was directly coupled with the pyrimidine base. The undesired ring opened product 4 (24% yield, R_f^7 = 0.40) and desired 5 (26% yield, 1:1 alpha-beta) were obtained. Isomer 5β (R_f^7 = 0.24) was converted to 6β (mp 170-172) and isomer 5α (R_f^7 = 0.31) to 6α (an oil).[8]

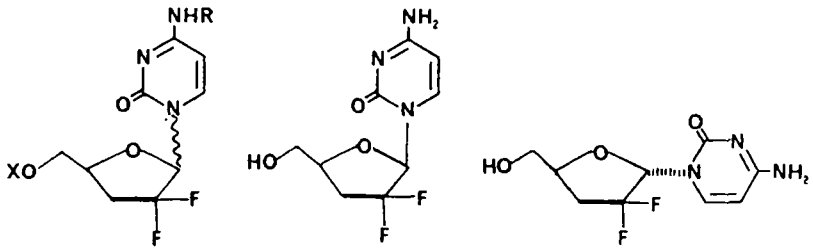


Similarly, thymine was coupled to 3, giving products analogous to 4 and 5. The intermediate 7 (31%, inseparable anomers) was deprotected (NH_3,EtOH) to give 8 as a 1:1 mixture of anomers (R_f^7 =0.55 and 0.50).[9]

The 2'-difluoronucleosides were synthesized starting with 9a, used previously for the synthesis of 2'-difluoro-2'deoxycytidine.[10] Intermediate 9b (85%,from 9a using CS_2,MeI,NaH) was deoxygenated (nBu_3SnH,toluene,70%) to 9c.[11] Ester 9c was hydrolyzed (80% TFA-H_2O) to the lactone 10a, which was silylated (pyridine, $tBuSiMe_2Cl$) to afford lactone 10b (92% from 9c).



DIBAL (toluene) converted 10b to lactol 11a (86%) and mesylation (MsCl, Et_3N in CH_2Cl_2) afforded 11b (96%) as a 1:1 mixture of anomers. Coupling of 11b with N-acetylcytosine (BSA, TMS-OTf,$ClCH_2CH_2Cl$ reflux, 4 h) gave a 1:1 mixture of nucleosides 12 (44%, foam). It is interesting to note that the analogous mesylate with a 3'-silyloxy substituent (also a 1:1 mixture of anomers) gave an 80:20 mixture,respectively, of alpha and beta nucleosides.[10] Ammonia (in EtOH) treatment yielded nucleosides 13 as a solid (100%). Finally, treatment with 80% TFA-H_2O (2.5 h) afforded the desired difluoronucleosides 14 and 15.[13]



12 X=SiMe$_2$tBu R=Ac

13 X=SiMe$_2$tBu R=H

14

15

Biological results are shown in the table below.

NUCLEOSIDE	IC_{50} HeLa cell growth [a]	IC_{50} for MoLV [a,b]
6β	34μg/ml	8μg/ml
6α	34μg/ml	> 5μg/ml[c]
8	>100μg/ml	>10μg/ml
14[d]	>100μg/ml	4.3μg/ml
15[d]	>100μg/ml	>10μg/ml

a) a number such as >5 means no activity was found up to that concentration

b) see note 14 c) toxic to host cells at 5μg/ml d) IC_{50} for HSV-1 10μg/ml

As can be seen from the table, modest antiproliferative and antiviral activity was found. This data will help complete the picture on the biological activity of fluorinated dideoxynucleosides.

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b. The triphosphate of the beta anomer of 8 is mentioned as 3'-E_2dTTP (apparently a typo) in a recent paper: Y.-C. Cheng, G.E. Dutschman, K.E. Bastow, M.G. Sarngadharan and R.Y.C. Ting, J. Biol. Chem. 262,2187-2189 (1987)

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7. TLC done on silicagel with EtOAc.

8. Irradiation of H-1' on 6β produced an NOE on H-4'. With 6α no NOE was observed between those protons.

9. The higher R_f isomer was isolated as an oil for spectroscopy only.

10. a. UK Patent Appl. G B 2 136425A (Chem. Abstr. 102, P 113894n).The chemistry is described there in detail. b. Chem. Abstr. 105, 91327n c. Chem. Abstr. 107, 134630s d. L.W. Hertel, J.S. Kroin, J.W. Misner, J.M. Tustin J.Org.Chem.1988,2406

11. Intermediates 9a to 12b were oils.

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13. These were purified by reverse phase HPLC (3% CH_3CN, H_2O). The slower moving 14 (a glass, 26% yield from 13) was identified by NMR (δ, DMSO-d_6; 5.78,d, H-5; 7.80,d, H-6; 6.10,dd, H-1') as the beta-anomer by comparison to 2'-difluoro-2'-deoxycytidine[10].Similarly, the faster moving isomer 15 (foam, 17%) was identified by its NMR (δ,DMSO-d_6; 5.76,d,H-5; 7.53,d,H-6; 6.25,dd,H-1') as the alpha anomer (by comparison to the alpha anomer of 2'-difluoro-2'-deoxycytidine).

14. Antiviral activity was determined in the XC-plaque assay against Moloney murine leukemia virus (MoLV) as described previously: Bowlin, T.L. and Proffitt. M.R, J.Interferon Res. 3, 19-31 (1983).