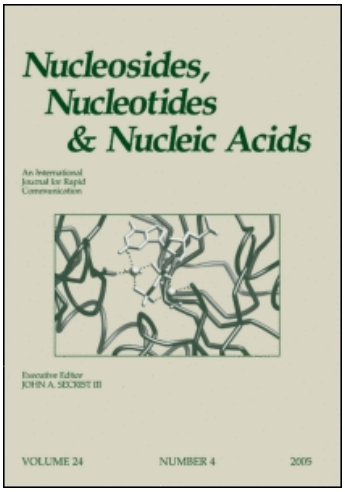

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF SUGAR-FLUORINATED 2′,3′-DIDEOXY-4′-THIORIBOFURANOSYL NUCLEOSIDES

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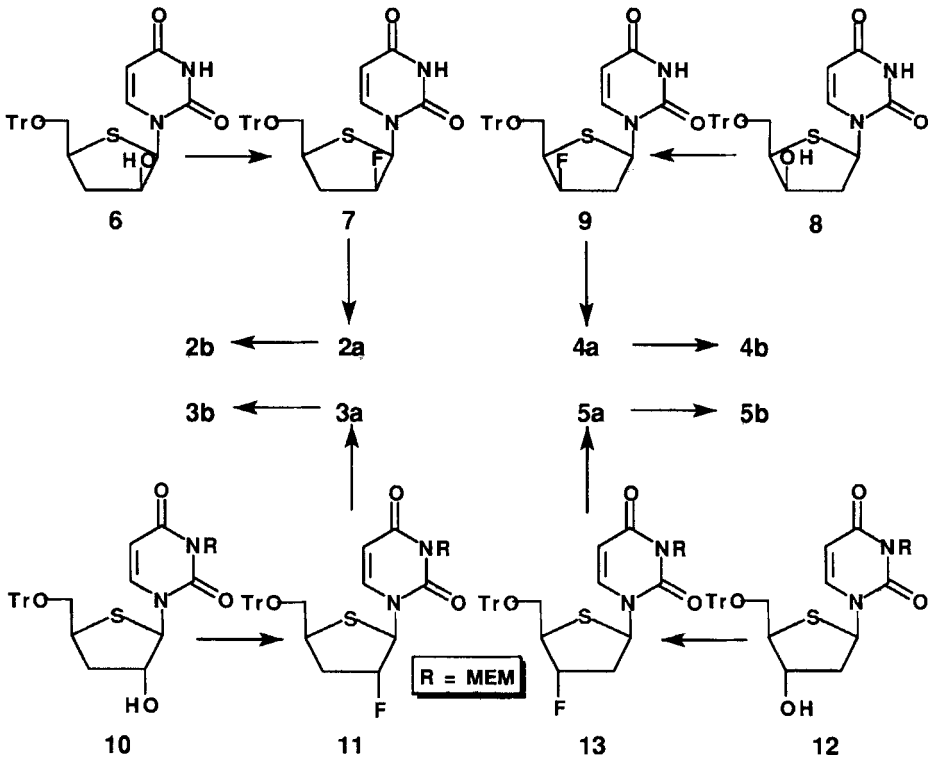
Abstract: The efficient DAST fluorination of deoxy-4′-thiopyrimidine nucleosides is reported. The cytidine analogue **3b** was marginally effective against HIV.

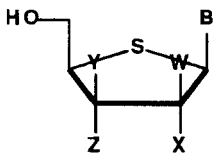
In monofluorodideoxynucleosides, fluorine substitution at positions 3′-"down" or 2′-"up" is associated with compounds having good to excellent anti-HIV activity.[1] On the other hand, inversion of the fluorine stereochemistry at the same positions produces virtually inactive compounds.[1] In all these compounds, the fluorine forces the sugar moiety into a specific form of puckering due to the attractive interaction between the ribose oxygen and fluorine (*gauche* effect).[2] Since the same kind of *gauche* interaction between fluorine and sulfur was expected to be weaker (less attractive) than that between fluorine and oxygen,[3] we sought to investigate the changes in conformation and anti-HIV activity incurred by transforming the dideoxyribose moiety into a dideoxy-4′-thioribose moiety. The aglycone bases chosen for this study were uracil and cytosine. This selection was made in view of the moderate anti-HIV activity displayed by 2′,3′-dideoxy-4′-thiocytidine (**1b**).[4]

For the synthesis of compounds having a fluorine atom above the plane of the ring (compounds **2a,b** and **4a,b**), the corresponding 1-(5-*O*-trityl-3-deoxy-4-thio-β-D-*threo*-pentofuranosyl)uracil (**6**) and 1-(5-*O*-trityl-2-deoxy-4-thio-β-D-*threo*-pentofuranosyl)uracil (**8**) were synthesized by procedures adapted from methods reported in the literature.[5-7] Treatment of these compounds with diethylaminosulfur trifluoride (DAST) at –78 °C for 15-30 min, and then at room temperature for 10-20 min, afforded



SCHEME

the corresponding fluorinated products **7** and **9** in 65% and 85% yield, respectively (Scheme). Removal of the trityl group was initially anticipated to give compounds with fluorine atoms below the plane of the ring since it was assumed that DAST fluorination would proceed with the usual inversion of configuration.[8] However, X-ray analysis of the structures revealed, instead, that the fluorine stereochemistry was "up" in each case.[9] These results can be explained if one invokes initial sulfur participation to give a transient episulfonium ion which is further opened by fluoride to complete a second Walden inversion. Both compounds **2a** and **4a** were converted to the corresponding cytidine analogues **2b** and **4b** using known procedures.[10]



1a,b; W=X=Y=Z=H
2a,b; W=F, X=Y=Z=H
3a,b; X=F, W=Y=Z=H
4a,b; Y=F, W=X=Z=H
5a,b; Z=F, W=X=Y=H

a series, B = uracil

b series, B = cytosine

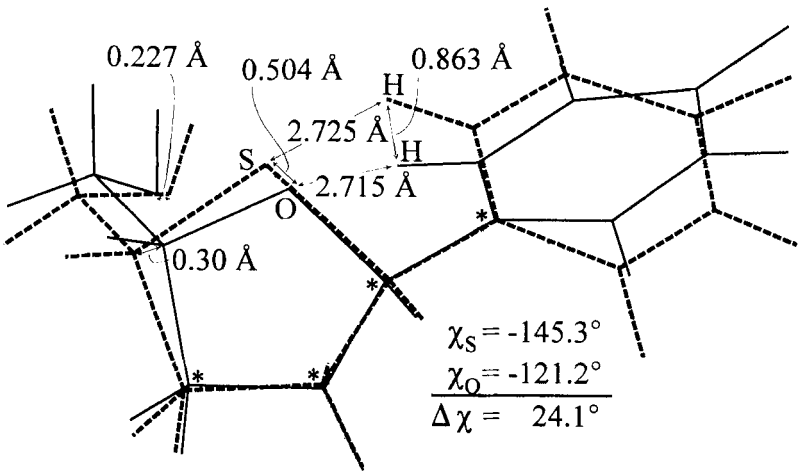


FIGURE. Superposition (on "*") of X-ray structures of FddUrd (—) and **5a** (---)

For the synthesis of compounds having a fluorine atom below the plane of the ring (compounds **3a,b** and **5a,b**), a similar mechanism of sulfur participation dictated that the starting stereochemistries for the hydroxyl groups had to be "down" also. However, DAST reactions with uracil nucleosides having "down" hydroxyl groups overwhelmingly favor formation of the corresponding anhydronucleosides. In an effort to block anhydride formation and favor sulfur participation, the N^3- nitrogen of the uracil ring was protected with the methoxyethoxymethyl (MEM) group and hence the corresponding *erythro* isomers **10** and **12** were synthesized by procedures adapted from the literature.[5-7] Treatment of **10** and **12** with DAST, under the same conditions as above, did not provide any evidence of sulfur participation. Instead, very reactive anhydro intermediates were formed which reacted *under extremely mild conditions* (KF, CH_2Cl_2, rt, 5 h) to give the corresponding fluorinated products **11** and **13** (90-96%) with the expected retention of configuration. Removal of the MEM group (BF_3•Et_2O/LiBr, Ac_2O) gave the corresponding intermediate acetates which were then hydrolyzed to the final products **3a** and **5a**. The stereochemical assignments for **3a** and **5a** were also corroborated by X-ray analysis.[11] As before, the uracil moiety was converted to the cytosine moiety to give compounds **3b** and **5b**.

Anti-HIV evaluation of these compounds in ATH8 cells revealed that only the cytidine analogues with fluorine substitution below the plane of the dideoxy-4'-

thioribofuranose ring (**3b** and **5b**) provided a weak level of protection against viral infection. No cytotoxicity was evidenced in the 5 -80 μM range.

FddUrd [1-(3-fluoro-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)uracil] is a fairly potent anti-HIV compound,[12] and it represents the only pattern equivalent to one of our series whose crystal structure is known.[13] A comparison of the X-ray structures (FIGURE) of FddUrd (P_O = 165.2°, ν_{max} = 34.9°) and **5a** (P_S = 192.2°, ν_{max} = 43.9°) revealed a similar form of ring puckering in the S-hemisphere. Atoms C3′, C2′, C1′ and N1 are in nearly equivalent positions (rms = 0.066 Å) and both 5′-OH groups are only 0.227 Å apart. The significance of the differences in the values of P and χ in relation to the observed anti-HIV activity is not clearly understood.

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