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Unanticipated Retention of Configuration in the DAST Fluorination of Deoxy-4'-thiopyrimidine Nucleosides with "Up" Hydroxyl Groups.

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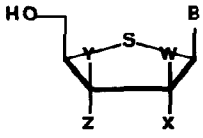
Abstract: Fluorination of 1-(5-*O*-trityl-3-deoxy-4-thio-β-D-*threo*-pentofuranosyl)uracil (**17**) and 1-(5-*O*-trityl-2-deoxy-4-thio-β-D-*threo*-pentofuranosyl)uracil (**20**) with DAST proceeded with exclusive retention of configuration. The structures of the products were confirmed by X-ray analysis.

Incorporation of fluorine into the sugar ring of dideoxynucleosides has a profound effect on the chemical stability and biological potency of the resulting modified analogues.[1,2] In view of the moderate anti-HIV activity displayed by 2',3'-dideoxy-4'-thiocytidine (**1b**),[3] we decided to synthesize 2'- and 3'-fluorinated analogues of **1b** carrying the fluorine substituent above and below the plane of the 4'-thioribofuranose ring. In this communication, we report the syntheses of the 2'- and 3'-"up" monofluoro 4'-thiouridine precursors (**2a** and **4a**) and their conversion to the 4'-thiocytidine targets **2b** and **4b**. Compounds **2a** and **4a** were obtained by a diethylaminosulfur trifluoride (DAST) fluorination reaction that proceeded with an unanticipated retention of configuration. The synthesis of the isomeric 2'- and 3'-"down" analogues is described in a separate communication immediately following this one.[4]



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

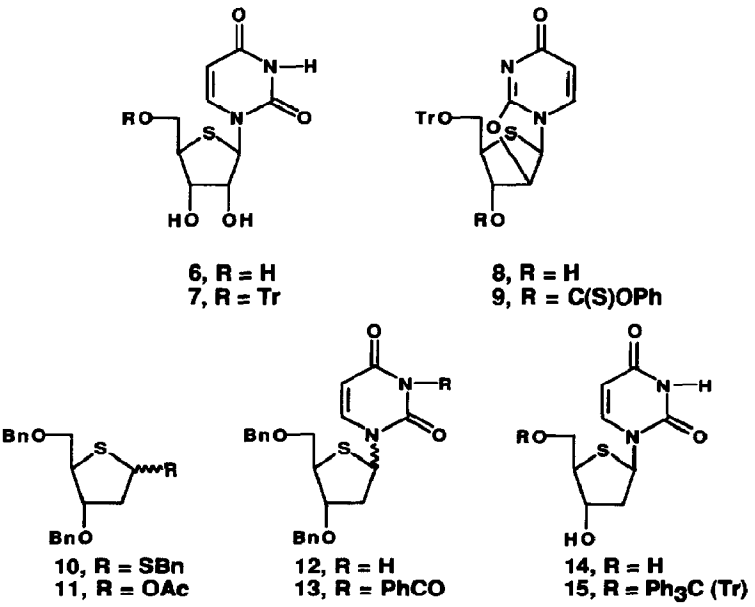
a series, B = uracil

b series, B = cytosine

For the 2'-substituted analogues (**2a** and **2b**), we started with 1-(4-thio-β-D-ribofuranosyl)uracil (**6**) which was prepared according to the method of Imbach et al.[5] Conversion of **6** to the 5'-*O*-trityl derivative **7** (60%) was followed by formation of the O^2,2'-anhydronucleoside **8** (80%) after treatment with 1,1'-thiocarbonyldiimidazole in refluxing toluene. Deoxygenation of the corresponding 2'-*O*-phenoxythiocarbonyl derivative **9** with tri-*n*-butyltin hydride in the presence of Et_3B proceeded in 92% yield to give the key anhydro intermediate **16** (Scheme).

For the 3'-substituted analogues (**4a** and **4b**), we synthesized benzyl 3,4-di-*O*-benzyl-2-deoxy-1,4-dithio-α,β-D-*erythro*-pentofuranoside (**10**) following the method of Walker et al.[6], and converted it to a 1:1 mixture of acetate anomers (**11**, 67%) after treatment with $Hg(OAc)_2$ in AcOH. Lewis acid-catalyzed

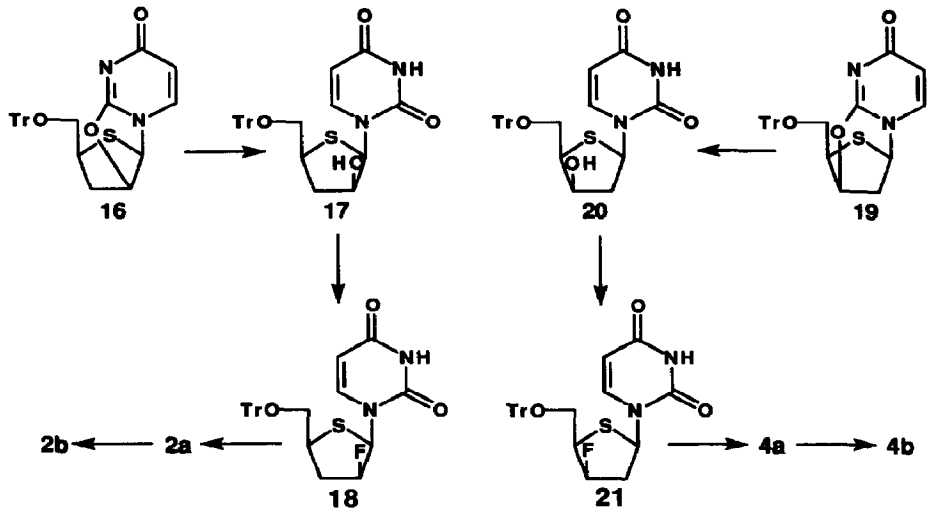
condensation ($CF_3SO_3SiMe_3$)[7] of this sugar with bis-silylated uracil in 1,2-dichloroethane at room temperature afforded a mixture of anomeric nucleosides (**12**, 82%). Separation of this mixture was achieved by silica gel chromatography (hexane/ethyl acetate, 3:1) of the N_3-benzoyl-4'-thiouridine nucleosides (**13**) obtained after treatment of **12** with benzoyl chloride in pyridine. The signal for the anomeric proton in the ^1H NMR spectrum of the desired β-isomer (**13β**, 40%) appeared as a triplet (δ 6.49, J = 6.9 Hz), while the equivalent signal for the α-isomer (**13α**, 50%) appeared as a doublet of doublets (δ 6.27, J = 7.6, 2.2 Hz). Simultaneous deblocking of both protecting groups was achieved for the desired β-isomer after treatment with BBr_3 in CH_2Cl_2 to give 1-(2-deoxy-4-thio-β-D-*erythro*-pentofuranosyl)uracil (**14**, 60%) which proved to be identical to the same material reported earlier by Secrist et al.[8] This compound was converted to the 5'-*O*-trityl derivative **15** (66%) which after treatment with DAST in CH_2Cl_2 at –78 °C afforded the expected[3,9] anhydride **19** (Scheme) in 66% yield.



The critical hydroxylated precursors **17** and **20** (Scheme) were obtained in excellent yield (ca. 90%) after opening the *O*2,2'- and *O*2,3'-anhydro bridges in compounds **16** and **19** with a mixture of 1N NaOH and 50% aq. ethanol at ambient temperature. Further treatment of **17** and **20** with DAST in CH_2Cl_2 at –78 °C for 15-30 min, and then at room temperature for 10-20 min, afforded the corresponding fluorinated nucleoside products **18** and **21** in 65% and 85% yield, respectively. Since it was assumed that DAST fluorination of **17** and **20** would proceed with the usual inversion of configuration[10] at C2' and C3', the structures of the deblocked nucleosides —produced after removal of the trityl group (80% AcOH, 100 °C, 70%)— were

expected to be equal to **3a** and **5a** (i.e., the corresponding epimers of **2a** and **4a**). However, X-ray analysis of the structures revealed, instead, that the fluorine stereochemistry was "up" in each case.[11] It appears, therefore, that participation of the 4'-thiofuranose sulfur during the DAST reaction is responsible for a double inversion mechanism that results in overall retention of configuration.

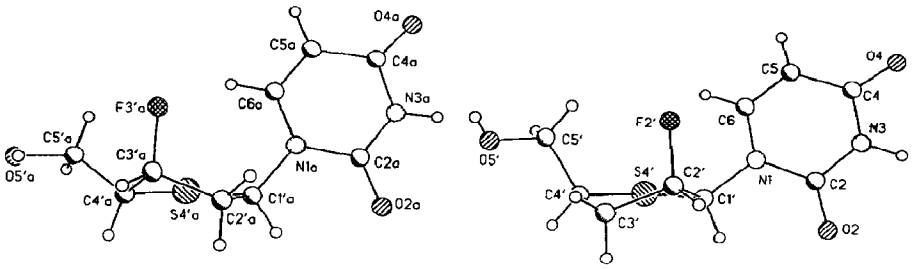
Scheme



The X-ray derived structures of **2a** and **4a** show that the disposition of the fluorine is pseudoaxial and in a *gauche* orientation relative to the sulfur. This is interesting in view of the fact that it has been argued that the *gauche* effect between fluorine and sulfur is expected to be weaker (less attractive) than that between fluorine and oxygen.[12,13] Compound **2a** crystallized singly in an almost pure South-type puckered conformation with a pseudorotation phase angle (P) of 179.18°, while compound **4a** crystallized as two independent molecules (*a* and *b*). Both *a* and *b* forms of **4a** are found in the North-type puckered conformation with P values of 10.24° for molecule *a* and 10.73° for molecule *b*. The maximum puckering amplitude (ν_{max}) is very similar: 45.40° for **2a** and 42.02° and 44.21°, respectively, for molecules *a* and *b* in **4a**. The bond lengths C1'—S4' and C4'—S4' are also similar in each case to the bond lengths reported for 4'-thiothymidine (ca. 1.82 Å),[14] and the disposition of the base in both molecules appears in the *anti* range with glycosidic torsion angles χ (S4'-C1'-N1-C2) equal to −140.4° in compound **2a** and −135.5° and −156.6°, respectively, for molecules *a* and *b* in **4a**. The C4'-C5' bond γ is found in the *-sc* orientation with torsion angles (O5'-C5'-C4'-C3') of −62.90° in **2a**, and −66.16° and −75.22°, respectively, for molecules *a* and *b* in **4a**. Both compounds **2a** and **4a** were converted to the corresponding cytidine analogues **2b** and **4b** by conventional chemistry.[15]

Anti-HIV evaluation in ATH8 cells revealed a complete lack of protection against viral infection for these compounds (**2a,b** and **4a,b**) that bear a fluorine substituent above the plane of the 4'-thioribofuranose ring.

Figure. X-ray crystal structures of dideoxymonofluoro 4'-thiouridines **2a** and **4a** (molecule *a*).



4a **2a**

References and Notes

1. Balzarini, J.; Baba, M.; Pauwels, R.; Herdewijn, P.; De Clercq, E. *Biochem. Pharmacol.* **1988**, *37*, 2847.
2. Marquez, V. E.; Tseng, C. K. H.; Mitsuya, H.; Aoki, S.; Kelley, J. A.; Ford, Jr. H.; Roth, J. S.; Broder, S.; Johns, D. G.; Driscoll, J. S. *J. Med. Chem.* **1990**, *33*, 978.
3. Secrist III, J. A.; Riggs, R. M.; Tiwari, K. N.; Montgomery, J. A. *J. Med. Chem.* **1992**, *35*, 533.
4. Jeong, L. S.; Nicklaus, M. C.; George, C.; Marquez, V. E. *Tetrahedron Lett.* following communication.
5. Bellon, L; Barascut, J.-L.; Imbach, J.-L. *Nucleosides Nucleotides* **1992**, *11*, 1467.
6. Dyson, M. R.; Coe, P. L; Walker, R. T. *Carbohydr. Res.* **1991**, *216*, 237.
7. Vorbrüggen, H.; Kroliekiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234.
8. Secrist III, J. A.; Tiwari, K. N.; Riordan, J. M.; Montgomery, J. A. *J. Med. Chem.* **1991**, *34*, 2361.
9. Agyei-Aye, K.; Yan, S.; Hebbler, A. K.; Baker, D. C. *Nucleosides Nucleotides* **1989**, *8*, 327.
10. Leroy, J.; Herbert, E.; Wakselman, C. *J. Org. Chem.* **1979**, *20*, 1823.
11. Crystal data of **2a**: $C_9H_{11}FN_2O_3S$, F. W. = 246.26, mp 210 °C. Monoclinic, $P2_1$, a=7.013(1), b=6.466(1), c=11.386(2) Å, β=97.05(1)°, V=512.4(1) Å^3, Z=2, D_c=1.596 g cm^{-3}. Crystal structural analysis of **4a** was performed by Crystalytics Co., P. O. Box 82286, Lincoln, Nebraska 68501, USA: $C_9H_{11}FN_2O_3S$, F. W. = 246.26, mp 196-198 °C, Monoclinic, $P2_1$–C_2^2(No.4), a=10.164(2), b=6.222(1), c=16.852(3) Å, β=99.12(2)°, V=1052.2(4) Å^3, Z=4, D_c=1.555 g cm^{-3}.
12. Koole, L. H.; Plavec, J.; Liu, H.; Vincent, B. R.; Dyson, M. R.; Coe, P. L.; Walker, R. T.; Hardy, G. W.; Rahim, S. G.; Chattopadhyaya, J. *J. Am. Chem. Soc.* **1992**, *114*, 9936.
13. Zefirov, N. S.; Gurvich, L. G.; Shashkov, A. S.; Krimer, M. Z.; Vorob'eva, E. A. *Tetrahedron* **1976**, *3 2* , 1211.
14. Uenishi, J.; Takahashi, K.; Motoyama, M.; Akashi, H. *Chem. Lett.* **1993**, 255.
15. Divakar, K. J.; Reese, C. B. *J. Chem. Soc. Perkin Trans 1*, **1982**, 1171.

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