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Facile Fluorination of Deoxy-4'-thiopyrimidine Nucleosides with "Down" Hydroxyl Groups. Retention of Configuration After Fluoride Opening of the Quaternized N^3-MEM Anhydronucleosides

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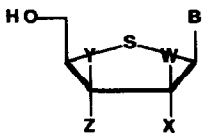
Abstract: Attempted fluorination of 1-(5-*O*-trityl-3-deoxy-4-thio-β-D-*erythro*-pentofuranosyl)-3-(2-methoxyethoxymethyl)uracil (**12**) and 1-(5-*O*-trityl-2-deoxy-4-thio-β-D-*erythro*-pentofuranosyl)-3-(2-methoxyethoxymethyl)uracil (**14**) with diethylaminosulfur trifluoride (DAST) produced very reactive N^3-MEM-O^2,2- and N^3-MEM-O^2,3-anhydronucleoside intermediates (**16**) that reacted with KF to give the desired fluorinated nucleosides with retention of configuration.

In the preceding communication,[1] we have described the synthesis of 2'- and 3'-"up" monofluoro 4'-thio-2',3'-dideoxypyrimidine nucleosides by way of a fluorination reaction with DAST that proceeded with retention of configuration at the hydroxyl-bearing carbon, by the unexpected participation of the 4'-thiofuranose sulfur during the reaction. Hence, a similar mechanism of fluorination to prepare the corresponding "down" isomers (**2a** and **3a**) dictated that the starting stereochemistries for the hydroxyl groups at 2' and 3' had to be "down" also. However, such a stereochemical disposition was expected to favor formation of anhydronucleosides which can be readily obtained through the action of DAST.[2,3] Indeed, sulfur participation as described above was not observed. Nonetheless, the desired stereochemical outcome of the fluorination was achieved through nucleophilic attack with fluoride of two very reactive N^3-alkyl-O^2,2'- and N^3-alkyl-O^2,3'-anhydronucleoside intermediates that were produced under DAST treatment. The intermediacy of these anhydrides insured overall retention of configuration.



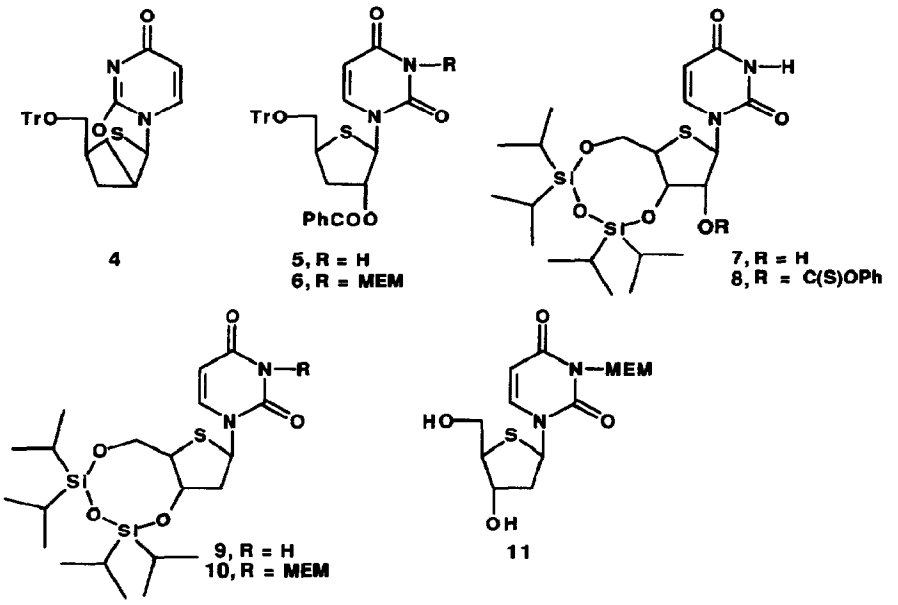
1a,b; W=X=Y=Z=H
2a,b; X=F, W=Y=Z=H
3a,b; Z=F, W=X=Y=H

a series, B = uracil

b series, B = cytosine

For the preparation of the 2'-substituted analogues (**2a** and **2b**), the anhydride **4** described in the antecedent communication served as the starting material.[1] Opening of the anhydro bridge in **4** with sodium benzoate/benzoic acid in DMF at 100 °C afforded compound **5** (60%). In an attempt to block anhydride formation and favor sulfur participation, the N^3 nitrogen of the uracil ring was protected with the MEM group. Reaction of **5** with 2-methoxyethoxymethyl chloride (Et_3N, THF, 80 °C) gave compound **6** in 80% yield and hydrolysis of the benzoate ester in **6** (NaOMe, MeOH, 98%) afforded the key intermediate **12** (Scheme).

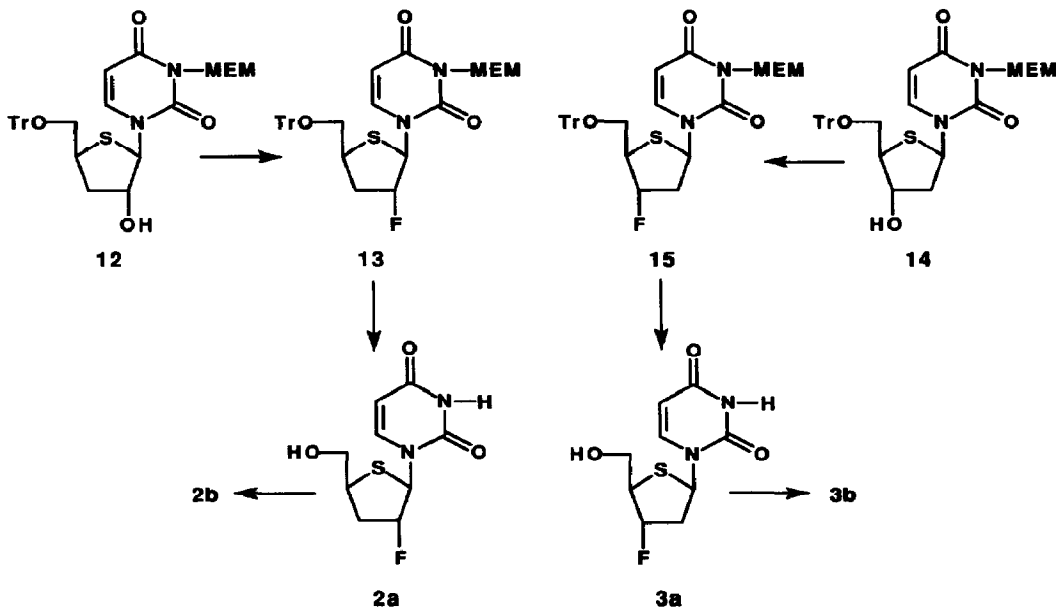
For the 3'-substituted analogues (**3a** and **3b**), the already described 1-(4-thio-β-D-ribofuranosyl)uracil served as the starting material.[1] Simultaneous protection of 3'- and 5'-hydroxyl groups by means of the TIPSi protecting group (TIPSiCl, pyridine, rt, 61%) produced compound **7**. The 2'-hydroxyl group in **7** was then converted to the desired thionocarbonate **8** (PhOC(S)Cl, DMAP, rt), which was immediately reduced to the corresponding 2'-deoxy analogue **9** with Bu_3SnH in the presence of Et_3B (79% yield in 2 steps). Formation of the MEM-protected intermediate **10** (78%), under the identical conditions used for **6**, set the stage for the removal of the TIPSi group (*n*-Bu_4F, THF, rt, 63%) to give **11**, followed by the selective protection of the 5'-hydroxyl group as the 5'-*O*-trityl ether (TrCl, pyridine, 100 °C, 79%) to give the other key intermediate **14** (Scheme).



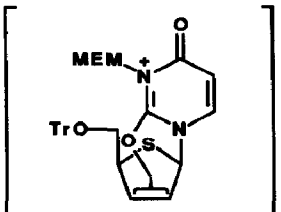
When either **12** or **14** was reacted with DAST (CH_2Cl_2, –78 °C, 15 min), the starting materials quickly disappeared giving rise to very polar compounds which remained at the origin of the tlc plate. During workup, these polar materials were easily hydrolyzed to non-fluorinated compounds identified as the 2'- and 3'-epimers of **12** and **14**, respectively. Taking advantage of what we anticipated to be the formation of very reactive anhydro intermediates (structure **16**), both reaction mixtures were treated immediately with KF (CH_2Cl_2, rt, 5h) to give, respectively, the corresponding fluorinated products **13** (96%) and **15** (90%). MEM group deblocking proved to be a challenge, resisting most conventional methods of removal.[4] Treatment with $BF_3 \cdot Et_2O$/LiBr in acetic anhydride at rt for 48 h, finally afforded the corresponding diacetates which were converted to **2a** and **3a**, respectively, in 60% and 76% yields (2 steps). Compounds

2a and **3a** were efficiently converted to the corresponding cytidine analogues **2b** and **3b** by conventional methods.[5]

Scheme



This enhanced electrophilicity of the N^3-MEM anhydrides (**16**) under very mild conditions is in line with the recent observations by Saha et al.,[6] who showed that N^3-alkylation of O^2,3'-cyclothymidine with methyl triflate activated nucleophilic opening at the 3'-position. The conditions described here for the removal of the MEM group, plus the ease of forming the N^3-alkylated product and the *in situ* formation of the anhydride, should make this approach even more attractive.[7]



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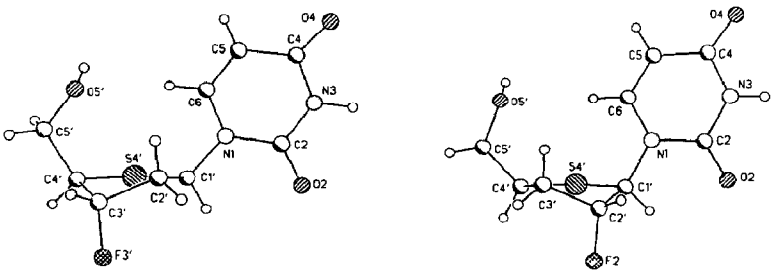
The X-ray structures of **2a** and **3a** confirmed the assigned stereochemistries and show that the disposition of the fluorine in both molecules is pseudoaxial (Figure).[8] Compound **2a** crystallized in a North-type puckered conformation with a pseudorotation phase angle (P) of –9.14°, while compound **3a** crystallized in an extreme South-type puckered conformation with a P value of 192.23°. The maximum puckering amplitudes (ν_{max}) are very similar: 43.87° and 43.95° for **2a** and **3a**, respectively. The disposition of the base in both molecules is in the *anti* range with glycosidic torsion angles χ equal to –154.9° in compound **2a** and –145.3° in **3a**. The C4'-C5' bond γ is found in the *+sc* orientation with torsion angles of 47.0° and 57.2° for **2a** and **3a**, respectively.

Sulfur participation[1] during the DAST fluorination of **12** and **14** is not a viable mechanism due to the more favorable formation of the anhydrides. Moreover, the competing participation of sulfur from the "up" side of the 4'-thioribofuranose ring might be prevented by a transition-state envisioned to bring the base and the CH_2OTr groups closer into steric contact. On the other hand, a similar back-side attack of the sulfur from the "down" side of the ring when the hydroxyl groups are "up", as reported in the previous communication,[1] appears more feasible in that case since there is no competing anhydride formation and because during the transition-state both the base and the CH_2OTr are moved away from each other.

Anti-HIV evaluation in ATH8 cells revealed that only the cytosine analogues (**2b** and **3b**) provided a weak level of protection against viral infection.

Figure. X-ray crystal structure of monofluoro 4'-thio-2',3'-dideoxyuridines **2a** and **3a**



3a **2a**

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6. Saha, A. K.; Schairer, W.; Upson, D. A. *Tetrahedron Lett.* **1993**, *34*, 8411.
7. Hydrofluorination of anhydropyrimidine nucleosides is not a facile process (see Green K.; Blum, D. M. *Tetrahedron Lett.* **1991**, *32*, 2901) and DAST fluorinations of glycofuranosyl pyrimidines do not go beyond the anhydride stage (see Leclerq, F.; Antonakis, C. *Carbohydrate Res.* **1991**, *222*, 2770).
8. Crystal data of **2a**: $C_9H_{11}FN_2O_3S$, F. W. = 246.26, mp 228-229 °C, orthorhombic, $P2_12_12_1$, a=7.440(1), b=9.744(1), c=14.538(2) Å, β=90°, V=1053.9(2) Å^3, Z=4, D_c=1.552 g cm^{-3}. Crystal data of **3a**: $C_9H_{11}FN_2O_3S$, F. W. = 246.26, mp 228-229 °C, orthorhombic, $P2_12_12_1$, a=6.861(1), b=9.778(2), c=15.468(2) Å, β=90°, V=1037.7(3) Å^3, Z=4, D_c=1.576 g cm^{-3}.

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