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Synthesis and Antiviral Activity of L-2'-Deoxy-2'-up-fluoro-4'-thionucleosides

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SYNTHESIS AND ANTIVIRAL ACTIVITY OF L-2'-DEOXY-2'-UP-FLUORO-4'-THIONUCLEOSIDES

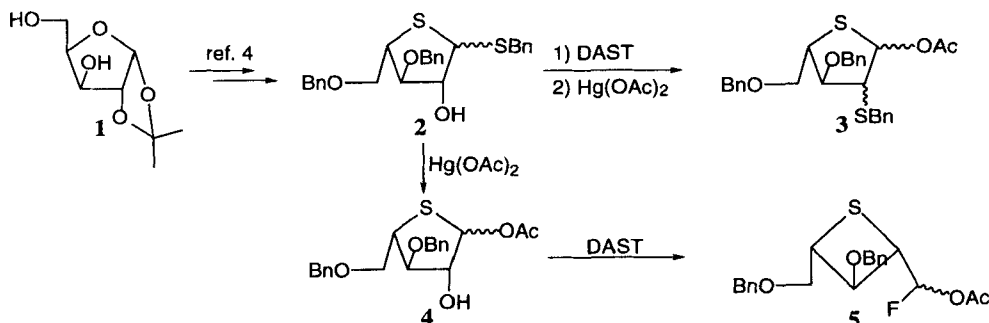
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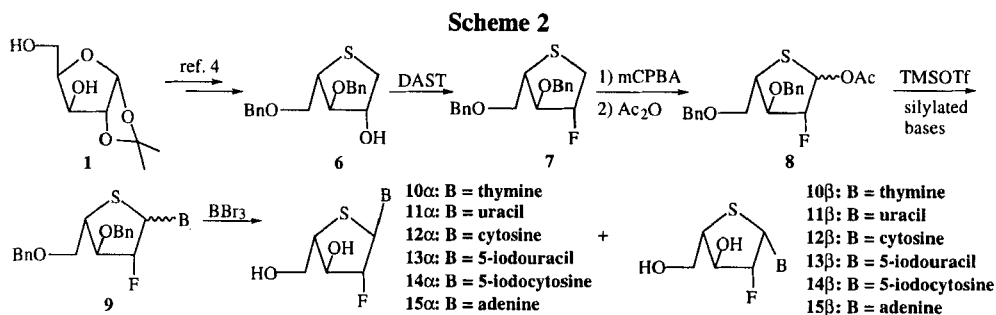
Abstract: L-2'-Deoxy-2'-up-fluoro-4'-thionucleosides were efficiently synthesized from D-xylose via L-4-thioarabitol derivative as a key intermediate and evaluated for antiviral activities against HIV-1, HSV-1,2 and HBV.

Since the discovery of (-)-L-β-1,3-oxathiolanyl cytosine (3TC, Lamivudine)¹ as potent antiviral agent, a number of L-nucleosides have been synthesized and evaluated for antiviral activity. Among these compounds, 2'-deoxy-2'-fluoro-5-methyl-β-L-arabino-furanosyluracil (L-FMAU) has been reported to exhibit potent anti-hepatitis B virus (HBV) and anti-Epstein-Barr virus (EBV) activities with a favorable toxicity profile.² In an effort to discover analogues to L-FMAU based on a "bioisosteric replacement rationale", we synthesized the 4'-thio congener (L-SFMAU) of L-FMAU and compared its antiviral activity with the parent L-FMAU.³ We also carried out structure-activity relationship study of L-2'-deoxy-2'-up-fluoro-4'-thionucleosides in order to search for new antiviral agents.

Scheme 1



The key intermediate **2** was synthesized from 1,2-isopropylidene-D-xylose (**1**) by the efficient procedure developed by our laboratory.⁴ Reaction of **2** with DAST followed by treatment with $\text{Hg}(\text{OAc})_2$ did not give the 2-fluoro-4-thiosugar, but yielded a rearranged product **3** by the participation of the anomeric thiobenzyl group. In order to prevent participation from the anomeric center, the thiobenzyl group was converted to an acetate to give **4**. However, treatment of **4** with DAST did not give the rearranged product, but gave the ring-contracted product **5** (Scheme 1).



To prevent the rearrangement or ring contraction, the substituent at the anomeric center was removed as shown in Scheme 2. Treatment of **6** with DAST gave the 2-fluoro-4-thiosugar **7** with retention of configuration. Compound **7** was converted to the acetate **8** by treating with mCPBA followed by refluxing with acetic anhydride. Condensation of **8** with silylated pyrimidine and purine bases gave the protected nucleosides **9** which were treated with boron tribromide to yield the final nucleosides **10** α –**15** α and **10** β –**15** β , respectively. The final nucleosides were assayed against HIV-1, HSV-1, HSV-2, and HBV. The thymine analogue **10** β only exhibited moderate activity against both HSV-1 and HSV-2 and all synthesized compounds were found to be inactive against HIV-1.

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This research was supported by the grant from the STEPI (97-N6-01-01-A-18).

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