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Synthesis and Antiviral Activities of 1,3-Oxathiolanyl Nucleosides with 5-Hydroxymethyl Substituent

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SYNTHESIS AND ANTIVIRAL ACTIVITIES OF 1,3-OXATHIOLANYL NUCLEOSIDES WITH 5-HYDROXYMETHYL SUBSTITUENT

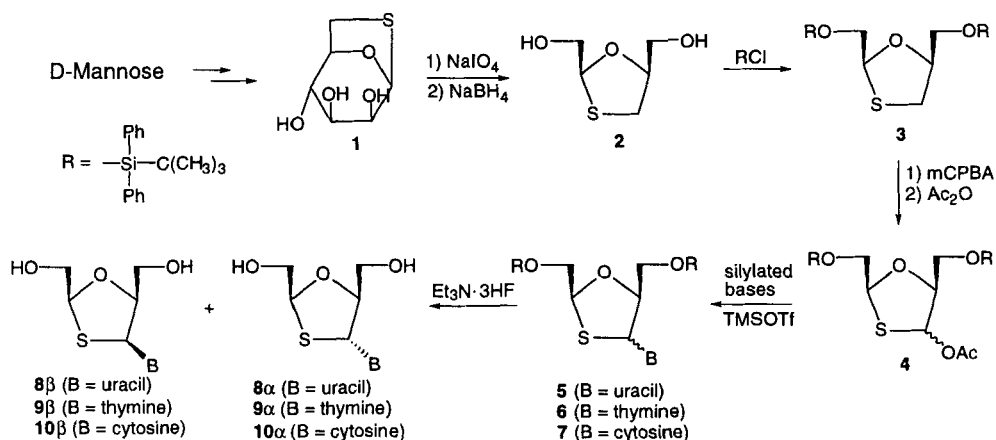
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Abstract: Novel 1,3-oxathiolanyl pyrimidine nucleosides with 5-hydroxymethyl substituent were synthesized starting from D-mannose and evaluated for antiviral activities against HIV-1, HSV type 1,2 and HCMV.

(-)-L-β-1,3-oxathiolanyl cytosine (3TC, Lamivudine) whose C3 methylene of the furanose was substituted by oxygen atom has shown potent anti-human immunodeficiency virus (HIV) and anti-hepatitis B virus (HBV) activities.¹⁻² Another class of nucleosides in which sulfur and oxygen of sugar moiety of 1,3-oxathiolanyl nucleosides were transposed were also reported to show potent antiviral activities.³ As a part of our ongoing effort to search for new antiviral agent, we decided to put hydroxymethyl substituent into sugar moiety of 1,3-oxathiolanyl nucleosides since ring-enlarged oxetanocin analogues exhibited good anti-HIV activity.⁴ Therefore, Novel 1,3-oxathiolanyl nucleosides with 5-hydroxymethyl substituent were synthesized starting from D-mannose and evaluated for antiviral activities against HIV-1, HSV-1,2 and HCMV. Our synthetic plan was to utilize the key intermediate, 1,6-thioanhydro-D-mannose (**1**)⁵ which could be easily prepared from D-mannose. Oxidative cleavage of the intermediate **1** with NaIO₄ followed by reduction with NaBH₄ gave the diol **2**. Two primary hydroxyl groups were protected with TBDPSCl to give **3**. Treatment of **3** with mCPBA followed by refluxing of the resulting sulfoxide with acetic anhydride afforded the acetate **4**. Condensation of the acetate **4** with silylated uracil, thymine and cytosine in the presence of TMSOTf in dichloroethane gave the uracil **5**, thymine **6** and cytosine **7** analogues, respectively. ¹H NMR indicated that the

Scheme 1



α isomer was formed as the major isomer during the condensation due to the steric effects of bulky TBDPS groups. Desilylation of **5-7** with $\text{NEt}_3 \cdot 3\text{HF}$ yielded the α nucleosides **8 α -10 α** and β nucleosides **8 β -10 β** , respectively (Scheme 1).

The antiviral assays of the final nucleosides **8-10** were performed against HIV-1, HSV-1,2, and HCMV. All synthesized compounds did not show significant antiviral activities.

Acknowledgment

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