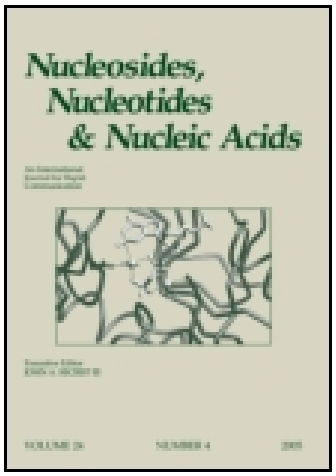

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SYNTHESIS AND ANTIVIRAL ACTIVITY OF D- AND L-2′-AZIDO-2′,3′-DIDEOXY-4′-THIOPYRIMIDINE AND PURINE NUCLEOSIDES

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ABSTRACT

Novel D- and L-2′-azido-2′,3′-dideoxy-4′-thionucleosides were synthesized starting from L- and D-xylose via D- and L-4-thioarabitol derivative as key intermediates and evaluated for antiviral activity, respectively. When the final nucleosides were tested against HIV-1, HSV-1, HSV-2, and HCMV, they were found to be only active against HCMV without cytotoxicity up to 100 μg/ml.

INTRODUCTION

Since 3′-azido-3′-deoxythymidine (AZT) has been discovered as anti-AIDS drug, a series of 2′,3′-dideoxynucleosides with azido substituent at 2′, 3′ or 4′ position of furanose moiety have been synthesized and many of them have shown potent antiviral activity (1). The 4′-thionucleosides have also shown promising biological activities such as antitumor and antiviral activities (2), but their structure-activity relationships have not been studied due to their synthetic difficulties. Recently, our laboratory developed very efficient synthetic procedure of 4-thioarabitol derivative which could be converted to the various 2′-substituted-4′-thionucleosides (3).

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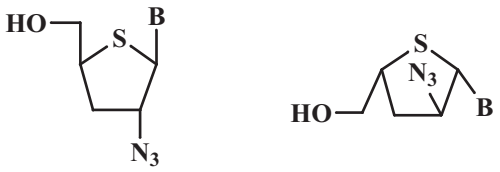


B = pyrimidines and purines

Figure 1.

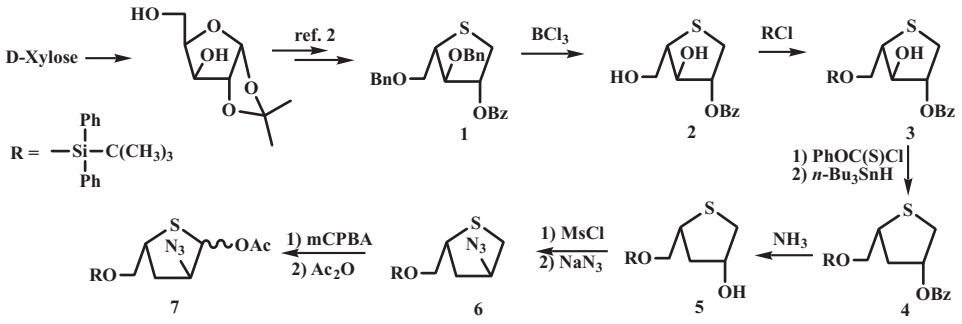
Utilizing this procedure, it was interesting to design and synthesize 2′-azido-2′,3′-dideoxy-4′-thionucleosides since the corresponding 2′-azido-2′,3′-dideoxynucleosides exhibited potent antiviral activity. In addition to D-nucleosides, we also wanted to synthesize the corresponding L-nucleosides because many L-nucleosides were found to be more potent than the corresponding D-nucleosides and to compare their antiviral activities.

Here, we wish to report the synthesis and antiviral activity of D- and L-2′-azido-2′,3′-dideoxy-4′-thionucleosides starting from L-xylose and D-xylose, respectively.

RESULTS AND DISCUSSION

For the synthesis of the desired azido substituted nucleosides, L-2-azido-4-thiosugar acetate **7** was first synthesized and then condensed with pyrimidine and purine bases. Synthesis of the key intermediate **7** is shown in Scheme 1.

D-Xylose was converted to the L-4-thioarabitol derivative **1** according to the very efficient method developed by our laboratory (2). Debenzylation (84%) of **1** with boron trichloride at −78°C gave diol **2** which was selectively silylated to give **3** in 76% yield. Barton's deoxygenation of **3** afforded deoxygenated material **4** (70%). Treatment of benzoate **4** with methanolic ammonia produced compound **5** (78%) which was converted to the azide **6** in two steps (84%). Oxidation of **6** with *m*CPBA (98%) followed by refluxing of the sulfoxide **6** with acetic anhydride gave the glycosyl donor **7**.



Scheme 1.

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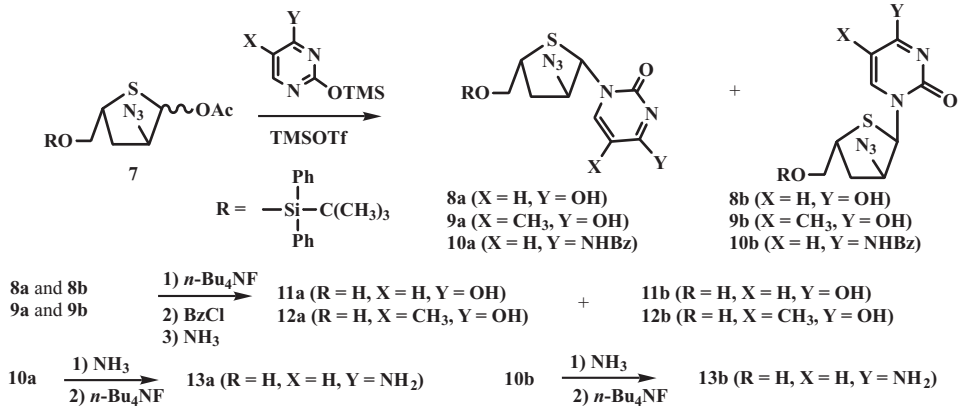
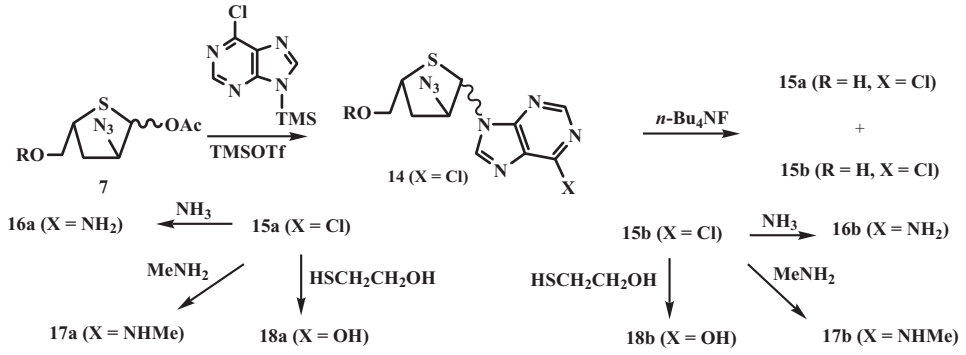


Scheme 2.

Synthesis of the desired pyrimidine nucleosides is depicted in Scheme 2. The glycosyl donor **7** was condensed with silylated uracil, thymine and N^4-benzoylcytosine in the presence of TMSOTf to give the inseparable anomeric mixture of protected nucleosides **8a/8b** (87%) and **9a/9b** (61%) and separable mixture of **10a** (30%) and **10b** (31%) after silica gel column chromatography, respectively.

Desilylation of **8a/8b** and **9a/9b** with tetra-*n*-butylammonium fluoride also afforded the inseparable mixture of the final nucleosides, respectively, which for the separation of anomers, were benzoylated at 70°C to give the *O*,*N*-dibenzoates. Dibenzoates were easily separated by silica gel column chromatography whose each anomers were treated with methanolic ammonia to yield the L-uracil derivative **11a** and **11b** and the L-thymine derivative **12a** and **12b**, respectively. The cytosine derivatives **10a** and **10b** were each deprotected to give the L-cytosine nucleosides **13a** (75%) and **13b** (70%).

Synthesis of the purine nucleosides is shown in Scheme 3. Condensation of **7** with silylated 6-chloropurine gave the inseparable mixture of protected nucleosides



Scheme 3.

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14 (71%) which was deprotected to give β-L-anomer **15a** (55%) and α-L-anomer **15b** (34%). Each L-anomer was converted to the L-adenine (**16a**, **16b**), L-N^6-methyladenine (**17a**, **17b**), and L-hypoxanthine (**18a**, **18b**) derivatives, respectively. The corresponding D-nucleosides (**ent-11a, ent-11b, ent-12a, ent-12b, ent-13a, ent-13b, ent-15a, ent-15b, ent-16a, ent-16b, ent-17a, ent-17b, ent-18a, and ent-18b**) were synthesized starting from L-xylose using the same method used in the preparation of L-nucleosides.

Antiviral assays against HIV-1, HSV-1, HSV-2, and HCMV were performed on the D- and L-final nucleosides (4). All compounds did not exhibit any significant antiviral activity except anti-HCMV activity. D-purine analogues exhibited significant anti-HCMV activity among which N^6-methyladenine derivatives (**ent-17a** and **ent-17b**) were found to be the most potent, while L-derivatives did not show anti-HCMV activity.

ACKNOWLEDGMENTS

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