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# Nucleosides, Nucleotides and Nucleic Acids

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# STEREOSELECTIVE SYNTHESIS OF NOVEL THIOISO DIDEOXY NUCLEOSIDES WITH EXOCYCLIC METHYLENE AS POTENTIAL ANTIVIRAL AGENTS

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## STEREOSELECTIVE SYNTHESIS OF NOVEL *THIOISO* DIDEOXY NUCLEOSIDES WITH EXOCYCLIC METHYLENE AS POTENTIAL ANTIVIRAL AGENTS

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• Novel thioiso pyrimidine and purine nucleosides substituted with exocyclic methylene have been synthesized, starting from D-xylose. Cyclization of the dimesylate to the 4-thiosugar 6a proceeded in pure  $S_N2$  reaction in the presence of allylic functional group.

### INTRODUCTION

BMS-200475 (1, entecavir),<sup>[1]</sup> has shown potent anti-HBV activity and was found to be 100 times more potent than lamivudine and is in phase III clinical trials. On the basis of the chemical structure of 1, we have designed and synthesized iso dideoxynucleosides among which adenine analogue 2 exhibited potent anti-HBV activity<sup>[2]</sup> (Figure 1).

Based on the potent anti-HBV activity of 2, and the principle of bioisosterism, we designed the target nucleoside 3 to compare its anti-HBV activity with that of compound 2. Here, we wish to report the stereoselective synthesis of novel thioiso dideoxynucleosides 3 with exocyclic methylene as potential antiviral agents and their related chemistry.

### **RESULTS AND DISCUSSION**

Synthesis of the glycosyl donors, **10** and **11**, starting from D-xylose is shown in Scheme 1. D-Xylose was converted to methylene derivative **4** according to the

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FIGURE 1 The rationale for the design of the target nucleosides.

known procedures.<sup>[2–5]</sup> Hydrolysis of **4** under acidic conditions followed by reduction of the lactol with lithium borohydride gave diol **5**. Treatment of **5** with mesyl chloride followed by treating with sodium sulfide in DMF afforded the desired thiosugar **6a** along with  $S_N2'$  product **6b** as a mixture of (*E*)- and (*Z*)- isomers. The optimum yield of **6a** was obtained on stirring in DMF at 0°C for 4 h. It is interesting to note that cyclization proceeded in pure  $S_N2$  reaction, not  $S_N1$  reaction in the presence of allylic fuctional group. Thiosugar **6** was debenzylated and slectively protected with TBDPS group to give the glycosyl donor **8**. For the synthesis of cis-nucleosides, another glycosyl donor **9** was obtained by the inversion of the stereochemistry of C3-hydroxyl group using Mitsunobu reaction.<sup>[6]</sup>

For the synthesis of trans-purine nucleosides, glycosyl donor **8** was condensed with 6-chloropurine under the Mitsunobu conditions<sup>[6]</sup> to give the protected nucleoside which in turn was desilylated and converted to adenine derivative,  $N^6$ methyladenine derivative, and hypoxanthine derivative. Condensation of **8** with  $N^3$ -benzoylthymine and  $N^3$ -benzoyluracil under the standard Mitsunobu conditions followed by removal of the protecting groups also yielded cis-pyrimidine nucleosides, thymine, and uracil derivatives. Unlike cyclization to get 4-thiosugar



**SCHEME 1** Reagents: (a) HCl/Dioxane; (b) LiBH<sub>4</sub>, THF; (c) MsCl, Pyridine,  $CH_2Cl_2$ ; (d) Na<sub>2</sub>S, DMF, 0°C; (e) BCl<sub>3</sub>,  $CH_2Cl_2$ ; (f) TBDPSCI, Imidazole, DMF; (g) BzOH, PPh<sub>3</sub>, DEAD, THF then MeOH/NH<sub>3</sub>; (h) Base, PPh<sub>3</sub>, DEAD, 0°C.

**6a**, Mitsunobu condensation reaction proceeded in pure  $S_N^2$  fashion without the formation of  $S_N^2$  product. Cis-uracil derivative was converted to the cis-cytosine derivative according to the conventional method. Similarly, another glycosyl donor **9** was converted to the trans-purine and pyrimidine nucleosides.

All synthesized final nucleosides were tested against several viruses such as HIV-1, HBV, HCV, and HCMV. The 6-chloropurine derivatives only exhibited very weak anti-HCV activity.

In summary, we have accomplished the asymmetric synthesis of novel thioiso nucleosides with exocyclic methylene, starting from D-xylose. The pure  $S_N^2$  cyclization reaction in the presence of allylic mesylate was obtained by stirring a solution of dimesylate in DMF at low temperature.

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