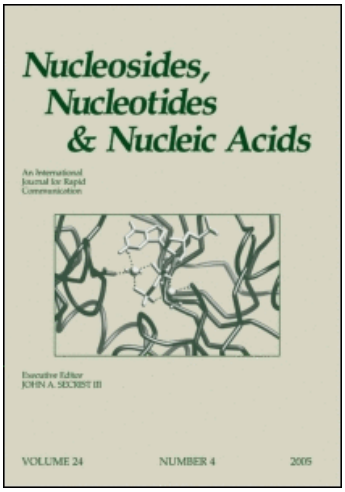



**Nucleosides, Nucleotides and Nucleic Acids**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

# Stereoselective Synthesis of Novel *Thioiso* Dideoxy Nucleosides with Exocyclic Methylene as Potential Antiviral Agents

Prashantha Gunaga[a]; Hea Ok Kim[a]; Hyun Ji Kim[a]; Moon Woo Chun[b]; Lak Shin Jeong[a]
[a] Laboratory of Medicinal Chemistry, College of Pharmacy, Ewha Womans University, Seoul, Korea [b] College of Pharmacy, Seoul National University, Seoul, Korea

**To cite this Article** Gunaga, Prashantha , Kim, Hea Ok , Kim, Hyun Ji , Chun, Moon Woo and Jeong, Lak Shin(2005) 'Stereoselective Synthesis of Novel *Thioiso* Dideoxy Nucleosides with Exocyclic Methylene as Potential Antiviral Agents', Nucleosides, Nucleotides and Nucleic Acids, 24: 5, 1115 — 1117
**To link to this Article: DOI:** 10.1081/NCN-200060072
**URL:** http://dx.doi.org/10.1081/NCN-200060072

*Nucleosides, Nucleotides, and Nucleic Acids,* 24 (5–7):1115–1117, (2005)

ISSN: 1525-7770 print/ 1532-2335 online
DOI: 10.1081/NCN-200060072

Taylor & Francis
Taylor & Francis Group

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

**Prashantha Gunaga, Hea Ok Kim, and Hyun Ji Kim** ▫ *Laboratory of Medicinal Chemistry, College of Pharmacy, Ewha Womans University, Seoul, Korea*

**Moon Woo Chun** ▫ *College of Pharmacy, Seoul National University, Seoul, Korea*

**Lak Shin Jeong** ▫ *Laboratory of Medicinal Chemistry, College of Pharmacy, Ewha Womans University, Seoul, Korea*



▫ *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),[1] 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[2] (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

Address correspondence to Lak Shin Jeong, Laboratory of Medicinal Chemistry, College of Pharmacy, Ewha Womans University, Seoul 120-750, Korea.

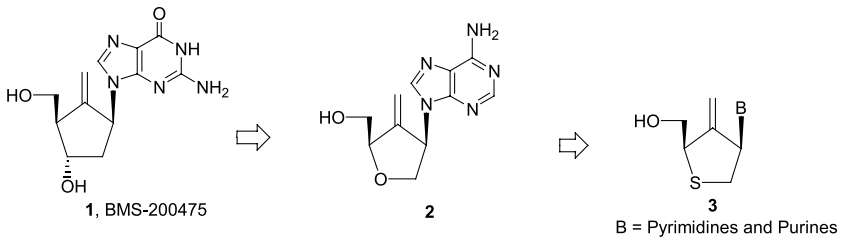
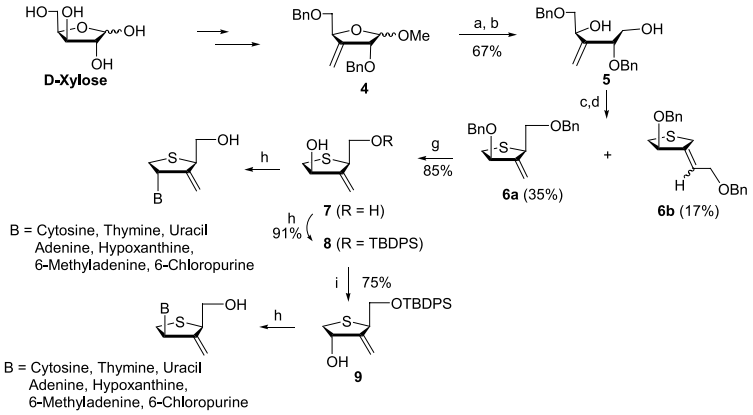



**FIGURE 1** The rationale for the design of the target nucleosides.

known procedures.[2–5] 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.[6]

For the synthesis of trans-purine nucleosides, glycosyl donor **8** was condensed with 6-chloropurine under the Mitsunobu conditions[6] 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) $LiBH_4$, THF; (c) MsCl, Pyridine, $CH_2Cl_2$; (d) $Na_2S$, DMF, 0°C; (e) $BCl_3$, $CH_2Cl_2$; (f) TBDPSCI, Imidazole, DMF; (g) BzOH, $PPh_3$, DEAD, THF then MeOH/$NH_3$; (h) Base, $PPh_3$, DEAD, 0°C.

**6a**, Mitsunobu condensation reaction proceeded in pure $S_N2$ fashion without the formation of $S_N2'$ 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 $S_N2$ cyclization reaction in the presence of allylic mesylate was obtained by stirring a solution of dimesylate in DMF at low temperature.

## REFERENCES

1. Genovesi, E.V.; Lamb, L.; Medina, I.; Tayler, D.; Seifer, M.; Innaimo, S.; Colonno, R.J.; Standring, D.N.; Clark, J.M. Efficacy of the carbocyclic 2′-deoxyguanosine nucleoside BMS-200475 in the woodchuck model of hepatitis B virus infection. Antimicrob. Agents Chemother. **1998**, *42*(12), 3209–3217.
2. Yoo, S.J.; Kim, H.O.; Lim, Y.; Kim, J.; Jeong, L.S. Synthesis of novel (2R,4R)- and (2S,4S)-iso dideoxynucleosides with exocyclic methylene as potential antiviral agents. Bioorg. Med. Chem. **2002**, *10*(1), 215–226.
3. Yoshimura, Y.; Kitano, K.; Yamada, K.; Satoh, H.; Watanabe, M.; Miura, S.; Sakata, S.; Sasaki, T.; Matsuda, A. A novel synthesis of 2′-modified 2′-deoxy-4′-thiocytidines from D-glucose. J. Org. Chem. **1997**, *62*(10), 3140–3152.
4. Jeong, L.S.; Moon, H.R.; Choi, Y.J.; Chun, M.W.; Kim, H.O. A short and efficient synthesis of L-thioarabinose derivative: a versatile synthon for the synthesis of L-2′-deoxy-2′,2′-disubstituted-4′-thionucleosides. J. Org. Chem. **1998**, *63*(14), 4821–4825.
5. Ma, T.; Pai, S.B.; Zhu, Y.L.; Lin, J.S.; Shanmuganathan, K.; Du, J.; Wang, C.; Kim, H.; Newton, M.G.; Cheng, Y.C.; Chu, C.K. Structure-activity relationships of 1-(2-deoxy-2-fluoro-beta-L-arabinofuranosyl)pyrimidine nucleosides as anti-hepatitis B virus agents. J. Med. Chem. **1996**, *39*(14), 2835–2843.
6. Jenny, T.F.; Horlacher, J.; Previsani, N.; Benner, S.A. Carbocyclic analogs of nucleosides. 2. Synthesis of 2′,3′-dideoxy-5′-homonucleoside analogs. Helv. Chim. Acta **1992**, *75*(6), 1944–1954.