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# Nucleosides and Nucleotides

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## Synthesis and Antiviral Activity of D- and L-Isodideoxy Nucleosides with Exocyclic Methylene

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#### SYNTHESIS AND ANTIVIRAL ACTIVITY OF D- AND L-ISODIDEOXY NUCLEOSIDES WITH EXOCYCLIC METHYLENE

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**Abstract**: Novel D- and L-isodideoxynucleosides were synthesized starting from D- and L-xylose and evaluated for antiviral activities against HIV-1, HSV-1, HSV-2, HBV and HCMV, respectively.

D- and L-1,3-Dioxolanyl nucleosides where C3 methylene was substituted by oxygen atom exhibited diverse biological activities such as antiviral and antitumor activities.<sup>1</sup> Among these compounds, L-1,3-dioxolanyl cytosine is being developed as anticancer agent and D-1,3-dioxolanyl diaminopurine (DAPD) is under development as anti-HIV and anti-HBV agent. BMS-200475 with an exocyclic double bond in place of oxygen atom of the furanose ring, was found to exhibit potent anti-HBV activity without cytotoxicity.<sup>2</sup> This compound is undergoing clinical trials for the development of anti-HBV agent.

Since we have reported synthesis and antiviral activities of the novel D-compounds combining the properties of two classes of the above compounds,<sup>3</sup> where C-OH of the BMS-200475 are substituted by oxygen, the corresponding L-nucleosides (1a-1e) were synthesized and evaluated for antiviral activities.

The target L-nucleosides **1a-1e** were synthesized starting from 1,2-isopropylidene-Dxylose (2) via allylic alcohol **7** as a key intermediate (Scheme 1). The primary hydroxyl group of 1,2-isopropylidene-D-xylose (2) was selectively benzoylated at 0 °C to give the monobenzoate **3** and the remaining hydroxyl group was oxidized to the ketone **4** by the treatment with PDC and acetic anhydride. Wittig reaction of compound **4** afforded the exocyclic methylene **5**. Treatment of **5** with 1% HCl in methanol produced the methoxide **6** which was converted to the key intermediate **7** by treating with HMDS followed by the

#### Scheme 1



addition of TMSOTf and triethylsilane. Condensation of 7 with 6-chloropurine and 2acetamido-6-chloropurine under the standard Mitsunobu conditions gave the protected nucleosides 8 and 9, which was deprotected with sodium methoxide to yield 10 and 11. The 6-chloropurine derivative 10 was converted to the adenine derivative 1a and hypoxanthine derivative 1b by treating with ammonia and 1 N NaOH, respectively. The 2amino-6-chloropurine derivative 11 was also converted to the guanine derivative 1c. Condensation of 7 with N<sup>3</sup>-benzoyluracil followed by deprotection gave the uracil derivative 1d which was converted to the cytosine analogue 1e.

The antiviral assays of the final nucleosides (**1a-1e**) were performed against HIV-1, HSV-1,2, HCMV, and HBV. All synthesized compounds did not show significant antiviral activities, while the corresponding D-uracil analogue exhibited weak anti-HCMV activity and D-adenine analogue showed significant anti-HBV activity (EC<sub>50</sub> =  $3.5 \mu g/mL$ ) without cytotoxicity upto 20 µg/mL.

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