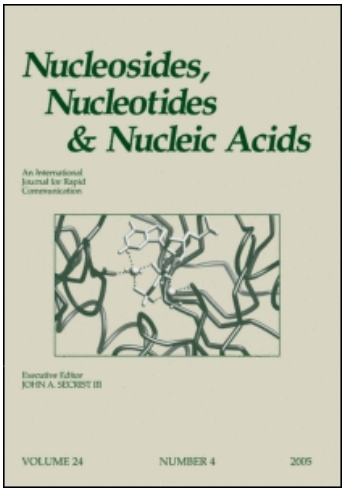

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Synthesis and Antiviral Activity of D- and L-Isodideoxy Nucleosides with Exocyclic Methylene

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

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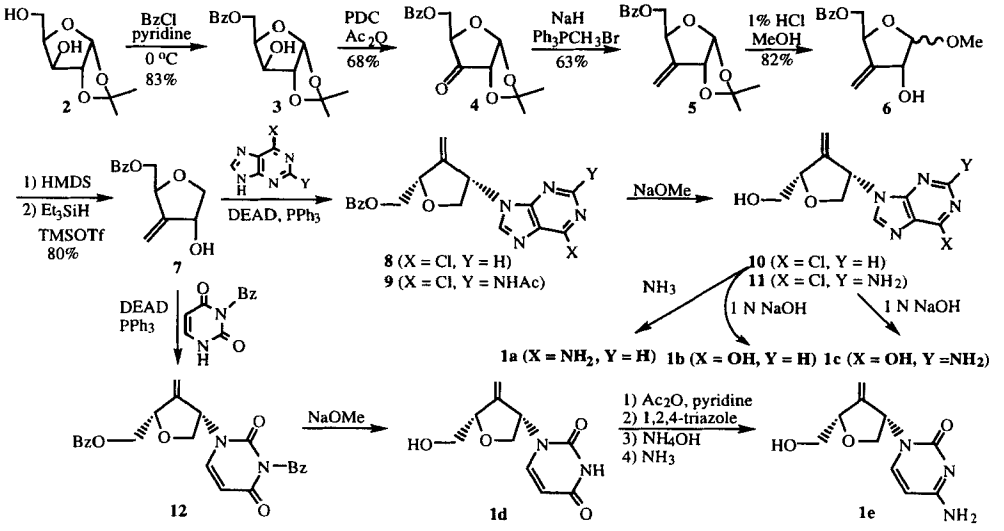
Abstract: Novel D- and L-isodideoxynucleosides were synthesized starting from D- and L-xylose and evaluated for antiviral activities against HIV-1, HSV-1, HSV-2, HBV and HCMV, respectively.

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.[1] 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.[2] 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,[3] 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-D-xylose (**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 2-acetamido-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 2-amino-6-chloropurine derivative **11** was also converted to the guanine derivative **1c**. Condensation of **7** with N^3-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_{50} = 3.5 μg/mL) without cytotoxicity upto 20 μg/mL.

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