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SYNTHESIS AND ANTIVIRAL ACTIVITY OF NOVEL ISODIDEOXY NUCLEOSIDES WITH EXOCYCLIC METHYLENE

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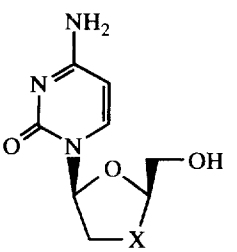
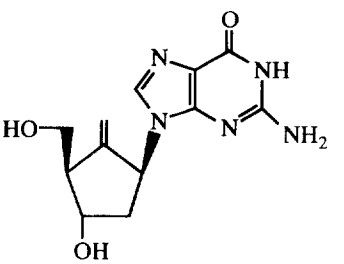
Abstract: Novel isodideoxy nucleosides with exocyclic methylene were synthesized starting from L-xylose utilizing anomeric demethoxylation, Wittig reaction and Mitsunobu reaction as key steps and evaluated for antiviral activity.

Much attentions have been paid to unusual nucleosides since 1,3-dioxolanyl and 1,3-oxathiolanyl nucleosides were reported to be the promising anti-human immunodeficiency virus (HIV) and anti-hepatitis B virus (HBV) agents.[1-4] Among these compounds, (-)-L-β-1,3-oxathiolanyl cytosine (**1a**, 3TC, Lamivudine) is being clinically used as anti-AIDS drugs and will be soon approved by Food and Drug Administration (FDA) for the treatment of HBV infected individuals as well.[2] (-)-L-β-1,3-Dioxolanyl cytosine (**1b**) also exhibited extremely potent anti-HIV and anti-HBV activities, but its cytotoxicity hindered it from being further developed as antiviral agent.[4]

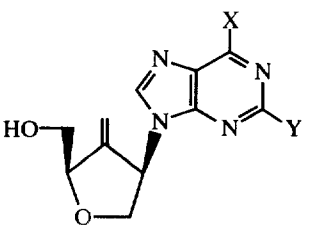
Recently, carbocyclic nucleoside **2** with an exocyclic methylene group in place of oxygen atom of the furanose ring was reported to show antiviral activity, especially anti-HBV activity.[5]



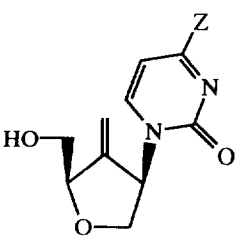
1a : X = S
1b : X = O



2



3a (X = NH_2, Y = H)
3b (X = OH, Y = H)
3c (X = OH, Y = NH_2)



4a (Z = OH)
4b (Z = NH_2)

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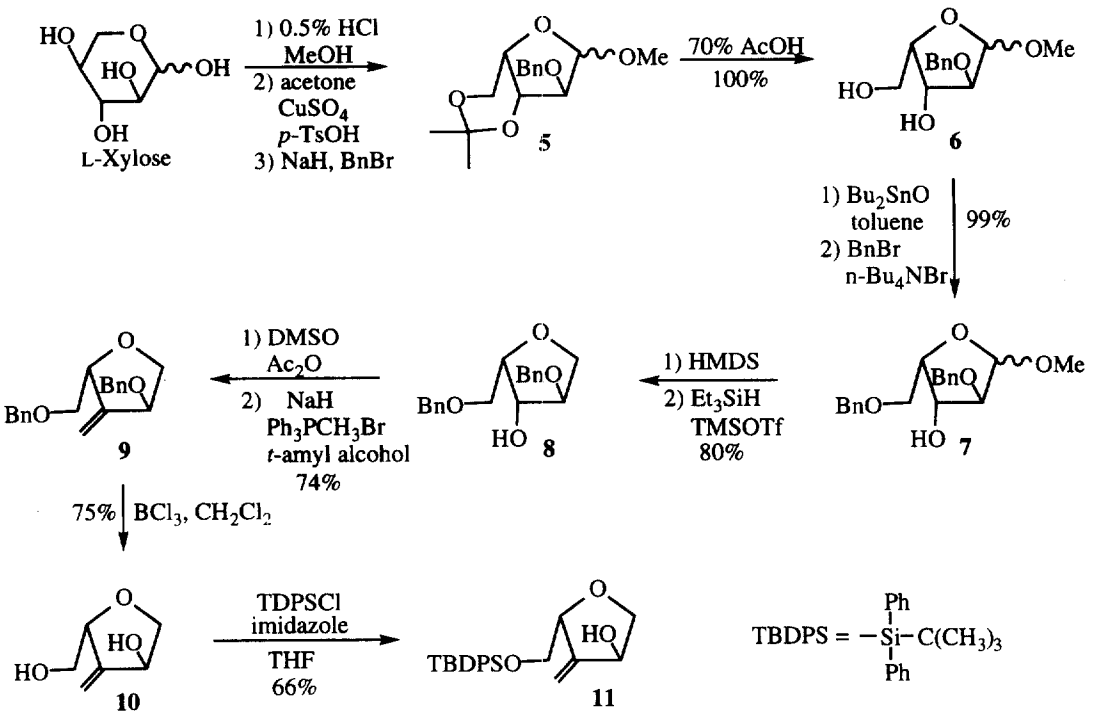
PII: S0960-894X(98)00122-X

Based on these findings, we wanted to synthesize the novel compounds **3**, which replace C-OH of the 3-position in compound **2** with bioisosteric oxygen atom,[4] that would combine the properties of L-dioxolanyl nucleosides and exocyclic methylene substituted nucleosides. Here, we report synthesis and antiviral activity of novel isodideoxynucleosides with an exocyclic methylene substituent starting from L-xylose.

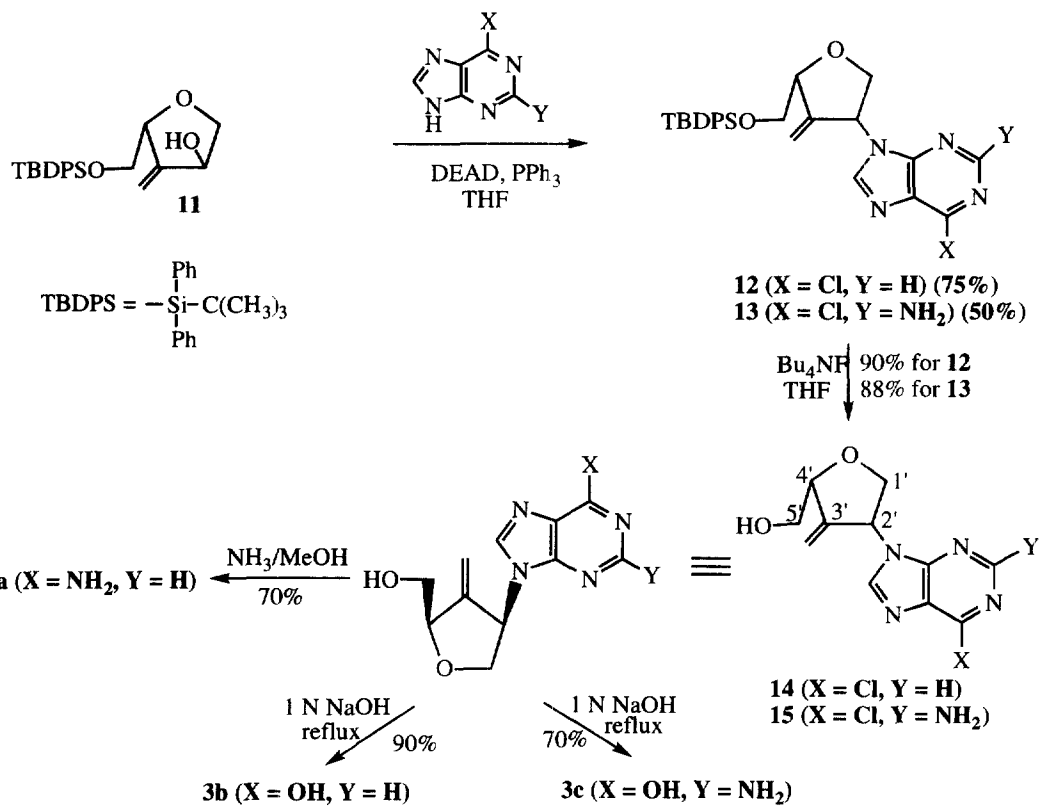
Scheme 1



Synthesis of the key intermediate **11** for the synthesis of isodideoxy nucleosides with exocyclic methylene is illustrated in Scheme 1. L-Xylose was converted to compound **5** according to the known method.[6] Isopropylidene group of **5** was removed using 70% acetic acid (50 °C, 1 h) to give the diol **6**. The selective protection of primary hydroxyl group was achieved by dibutyltin oxide method.[7] Treatment of compound **6** with dibutyltin oxide in refluxing toluene for 5 h followed by addition of benzyl bromide and *n*-tetrabutylammonium bromide (100 °C, 15 h) afforded dibenzyl derivative **7** in almost quantitative yield. Next step was the removal of anomeric methoxy group. We first benzoylated secondary hydroxyl group in compound **7** and then treated with triethylsilane and TMSOTf in CH_2Cl_2 to give the demethoxylated compound,[8] but this method needed extra debenzoylation step to prepare the desired compound **8** (61% from **7**). To eliminate extra benzoylation and debenzoylation steps, we used *in situ* silylation method.[9] Refluxing **7** with hexamethyldisilazane (HMDS) followed by treatment with triethylsilane and TMSOTf in CH_2Cl_2 at room temperature for 2 h gave the demethoxylated compound **7** in 80% yield directly. The secondary hydroxyl group of **8** was oxidized with DMSO and acetic anhydride (rt, 18 h) to the ketone (80%). Wittig

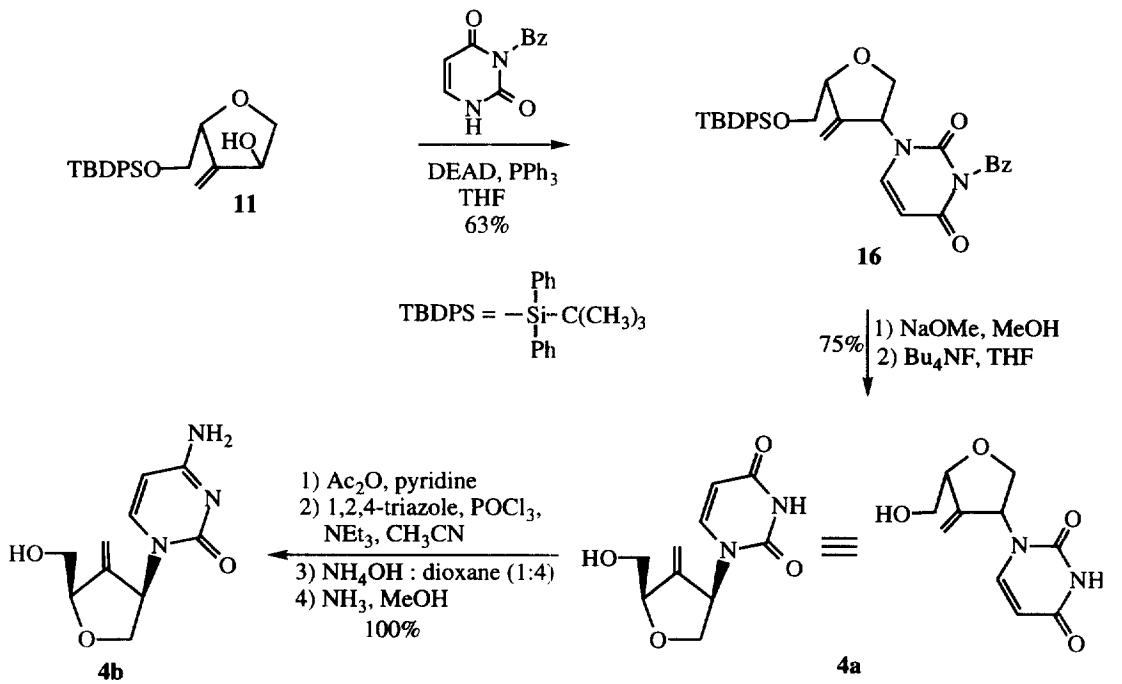
reaction of the ketone intermediate with BuLi and Ph_3PCH_3Br at 0 °C produced the olefin **9** in 30-40% yield, while use of t-amyl alcohol (rt, 0.5 h) and NaH[10] instead of BuLi afforded the same product **9** in 92% yield. Debenzylation of **9** with BCl_3 at -78 °C for 0.5 h gave the diol **9**, whose primary hydroxyl group was selectively protected with *t*-butyldiphenylsilyl (TBDPS) group to yield **11**,[11] which acts as the key intermediate for the desired isodideoxy purine and pyrimidine nucleosides.

Scheme 2



Synthesis of the purine nucleosides having adenine, hypoxanthine and guanine was accomplished using the Mitsunobu reaction (Scheme 2).[12] Treatment of **11** with DEAD and PPh_3 in THF at 0 °C for 1 h produced the N-9 derivative **12** in 80% yield without the formation of N-7 isomer. The N-9 isomer of the coupling was confirmed by UV spectral data [λ_{max} (MeOH) 264 nm].[12a] Desilylation (Bu_4NF, THF, 0 °C, 0.5 h) of **12** followed by amination with methanolic ammonia (100 °C, 15 h) afforded the adenine derivative **3a**.[13] Compound **14** was converted to hypoxanthine derivative **3b** by refluxing with 1 N NaOH. For the synthesis of guanine analogue, compound **11** was reacted with 2-amino-6-chloropurine using the same Mitsunobu conditions to give **13** (50%) with concomminant formation of the N-7 substituted product (5%). Compound **13** was successively treated with Bu_4NF and 1 N NaOH to afford the guanine analogue **3c**. The regioisomers were also confirmed by comparison of the UV data of N-9 (252 nm) and N-7 (248 nm) guanine analogues.[14]

Scheme 3



Isodideoxy pyrimidine nucleosides (**4a** and **4b**) were also synthesized utilizing the Mitsunobu reaction (Scheme 3). The key intermediate **11** was condensed with N^3-benzoyluracil under the standard Mitsunobu conditions[12] to give the desired N-alkylated product **16** (63%) with concomminant formation of O-alkylated compound (10%). The regioisomers were easily confirmed by comparison of the UV literature data.[12a] Protecting groups of **16** were removed by treating successively with Bu_4NF and NaOMe successively to yield uracil derivative **4a**.[15] Finally, the stereochemistry of the C2-position in compound **4a** was decided by NOSEY experiment, indicating the Mitsunobu reaction of the allylic alcohol **11** was proceeded in pure S_N2 type reaction, not in S_N1 or S_N2' type reaction.[16] Uracil analogue **4a** was converted to the cytosine derivative **4b** according to the conventional method.

The antiviral assays against human immunodeficiency virus 1 (HIV-1), herpes simplex virus-1,2 (HSV-1,2) and human cytomegalovirus (HCMV) were performed and the results are shown in Table 1. As shown in Table 1, all synthesized compounds did show neither anti-HIV activity nor cytotoxicity. Any compounds did not show antiviral activity against HSV-1,2 except hypoxanthine derivative **3b** which exhibited very weak anti-HSV-1 activity. However, the uracil analogue **4a** was found to show significant anti-HCMV activity and the adenine derivative **3a** also exhibited weak anti-HCMV activity.

In summary, we completed the synthesis of bioisosteric compounds (**3a, 3b, 3c, 4a,** and **4b**) of potent antiviral agent **2**, starting from L-xylose utilizing demethoxylation, Wittig reaction and Mitsunobu reaction as key steps. The hypoxanthine derivative **3b** exhibited weak anti-HSV-1 activity and the uracil derivative **4a** exhibited significant anti-HCMV activity.

Acknowledgment

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Table 1. The antiviral activities of the synthesized compounds.

Activity / Compounds	HIV-1 EC_{50} (μg/ml)	HSV-1 EC_{50} (μg/ml)	HSV-2 EC_{50} (μg/ml)	HCMV EC_{50} (μg/ml)	cytotoxicity IC_{50} (μg/ml)
3a	> 100	> 100	> 100	33.3	> 100
3b	> 100	35	> 100	> 100	> 100
3c	> 100	> 100	> 100	> 100	> 100
4a	> 100	> 100	> 100	10.6	> 100
4b	> 100	> 100	> 100	> 100	> 100
AZT	0.00132	ND	ND	ND	1.0
Acyclovir	ND	1.0539	5.1165	ND	250
Ganciclovir	ND	ND	ND	0.74	> 10

ND : Not Determined

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11. Compound **11**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.70–7.25 (m, 10 H, Ph x 2), 5.36 (t, 1 H, J = 2.0 Hz, vinyl), 5.11 (t, 1 H, J = 1.9 Hz, vinyl), 4.70-4.60 (m, 2 H, 2-H and 4-H), 4.13 (dd, 1 H, J = 5.4, 9.3 Hz, 1-H_a), 3.80-3.40 (m, 3 H, 1-H_b and 5-H), 1.04 (s, 9 H, *t*-butyl).
Anal. Calcd for $C_{22}H_{28}O_3Si$: C, 71.74; H, 7.61. Found: C, 71.75; H, 7.66.
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13. Compound **3a**: UV (MeOH) λ_{max} 259 nm; ^{1}H NMR (CD_3OD, 300 MHz) δ 8.31 (s, 1 H, H-8), 8.22 (s, 1 H, H-2), 5.66 (m, 1 H, 2'-H), 5.36 (m, 2 H, vinyl), 4.54 (m, 1 H, 4'-H), 4.22 (pseudo t, 2 H, J = 3.9, 9.5 Hz, 1'-H), 3.95 (dd, 1 H, J = 3.2, 12.2 Hz, 5'-H_a), 3.87 (dd, 1 H, J = 4.1, 12.2 Hz, 5'-H_b). Anal. Calcd for $C_{11}H_{13}O_2N_5$: C, 53.44; H, 5.30; N, 28.34. Found: C, 53.75; H, 5.60; N, 28.02.
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15. Compound **4a**: UV (MeOH) λ_{max} 265 nm; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 11.42 (br s, 1 H, NH), 7.73 (d, 1 H, J = 8.1 Hz, H-6), 5.67 (d, 1 H, J = 8.1 Hz, H-5), 5.54 (m, 1 H, 2'-H), 5.38 (m, 2 H, vinyl), 5.12 (t, 1 H, J = 5.5 Hz, OH, exchangeable with D_2O), 4.42 (m, 1 H, 4'-H), 4.08 (dd, 1 H, J = 6.8, 9.8 Hz, 1'-H_a), 3.97 (dd, 1 H, J = 4.4, 9.8 Hz, 1'-H_b), 3.82 (m, 2 H, 5'-H).
Anal. Calcd for $C_{10}H_{12}O_4N_2$: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.65; H, 5.66; N, 12.29.
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