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SYNTHESIS AND ANTIVIRAL ACTIVITY OF NOVEL ISODIDEOXY NUCLEOSIDES WITH EXOCYCLIC METHYLENE

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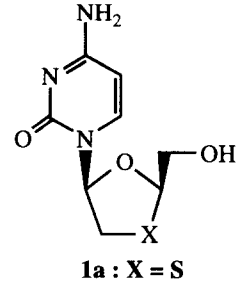
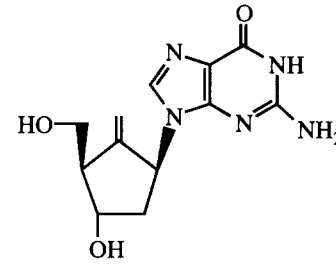
Abstract: Novel isodideoxy nucleosides with exocyclic methylene were synthesized starting from L-xylose utilizing anomeric demethoxylation, Wittig reaction and Mitsunobu reaction as key steps and evaluated for antiviral activity.

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]

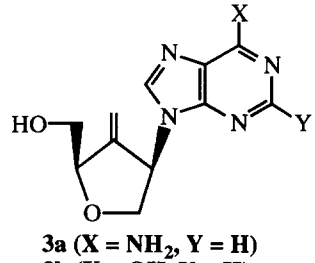
Recently, carbocyclic nucleoside **2** with an exocyclic methylene group in place of oxygen atom of the furanose ring was reported to show antiviral activity, especially anti-HBV activity.[5]



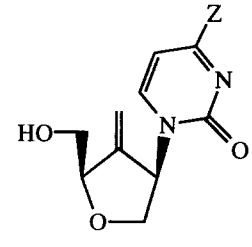
1a : X = S
1b : X = O



2



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

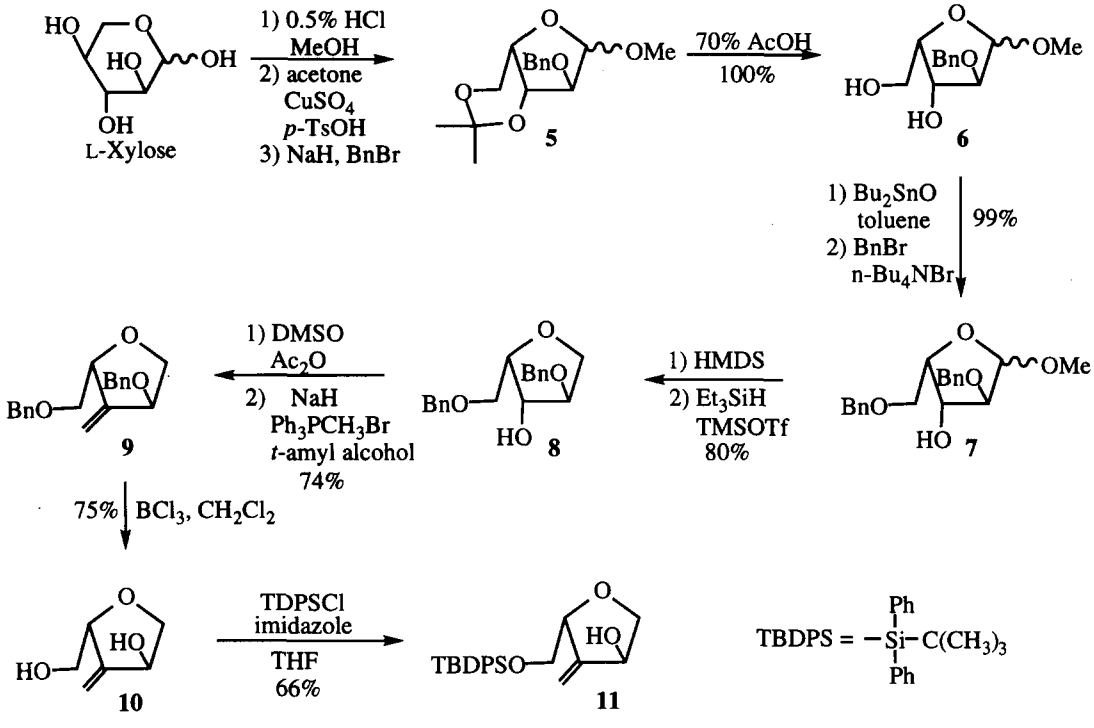


4a (Z = OH)
4b (Z = NH_2)

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.

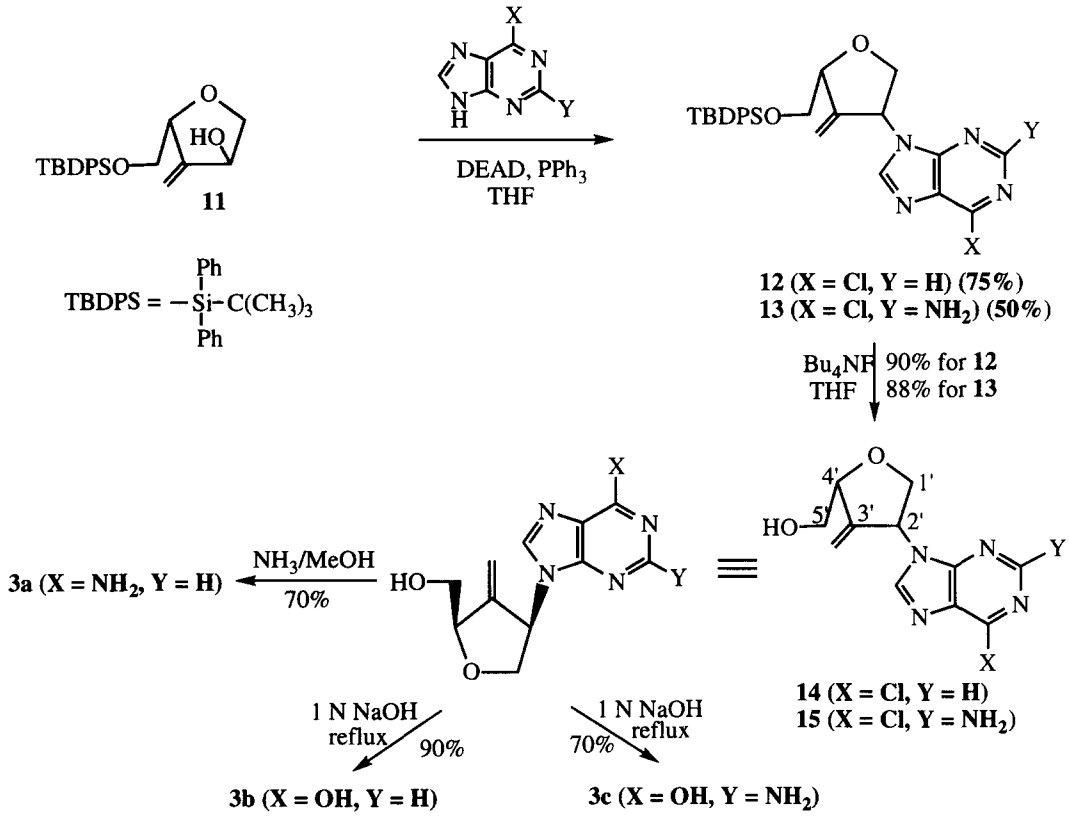
Scheme 1



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

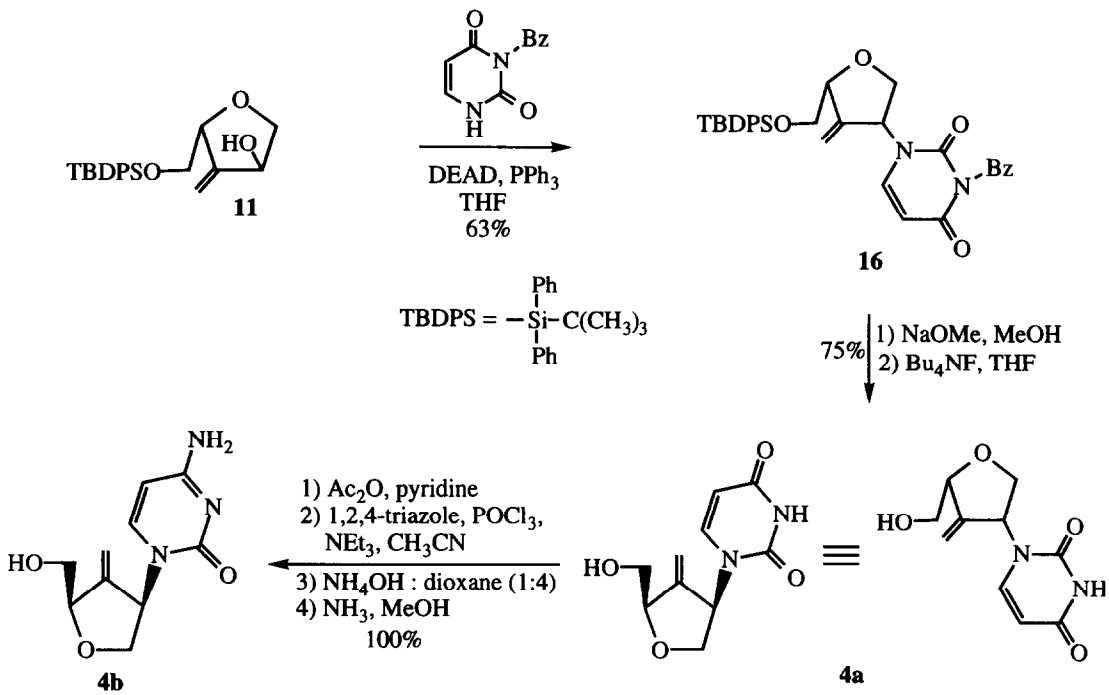
reaction of the ketone intermediate with BuLi and Ph_3PCH_3Br at 0 °C produced the olefin **9** in 30-40% yield, while use of t-amyl alcohol (rt, 0.5 h) and NaH[10] instead of BuLi afforded the same product **9** in 92% yield. Debenzylation of **9** with BCl_3 at -78 °C for 0.5 h gave the diol **9**, 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

Antiviral testing by Dr. Chong-Kyo Lee (Korea Research Institute of Chemical Technology) is greatly appreciated. Authors also thanks KOSEF for the financial support of this research.

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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