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Asymmetric Synthesis of Novel Thioiso Dideoxynucleosides with Exocyclic Methylene as Potential Antiviral Agents

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Abstract: Novel thioiso pyrimidine and purine nucleosides substituted with exocyclic methylene have been synthesized, starting from D-xylose. The glycosyl donor **14** was synthesized from D-xylose, using cyclization of dimesylate **10** with sodium sulfide as a key step. Cyclization proceeded in pure S_N2 reaction without going through S_N1 reaction in the presence of an allylic functional group at low reaction temperature (0 °C) in polar solvent (DMF), affording compound **12** as a major product. At higher temperatures, S_N2' product **11** was almost exclusively obtained as a major product. On the other hand, glycosylation of **14** with 6-chloropurine under Mitsunobu conditions afforded the desired S_N2 product **26**, while palladium-catalyzed glycosylation resulted in the sole formation of S_N2' product **34**.

1,3-Dioxolanyl and 1,3-oxathiolanyl nucleosides, showing potent antiviral activity against human immunodeficiency virus (HIV) and hepatitis B virus (HBV), opened a new era in developing the area of antiviral nucleosides. Among them, (−)-L-β-1,3-oxathiolanyl cytosine (3TC, lamivudine)[1] is clinically used worldwide for HBV- and/or HIV-infected patients and (−)-L-β-1,3-oxathiolanyl 5-fluorocytosine (FTC, emtricitabine)[2] is also currently in phase III clinical trials for the treatment of HBV. (−)-L-β-1,3-Dioxolanyl cytosine (L-OddC, troxacitabine)[3] is undergoing phase II clinical trials as an anticancer drug and (+)-D-β-1,3-dioxolanyl 2,6-diaminopurine (DAPD, amdoxivir)[4] is also in phase II clinical trials for the treatment of HIV. The discovery of promising 1,3-dioxolanyl and 1,3-oxathiolanyl nucleosides proved that unusual sugar structures can provide very active compounds. Since then the nucleoside analogues with unusual ribose mimics have been considered as main stream in developing new antiviral agents.

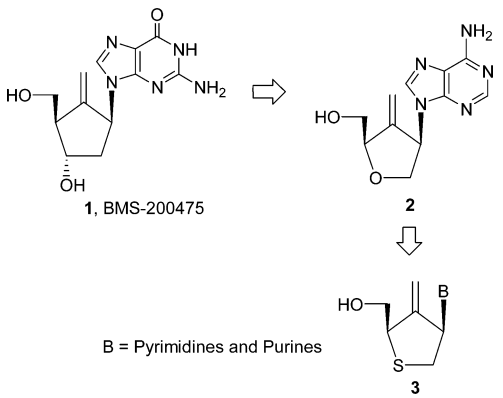

FIGURE 1. The rationale for the design of the target nucleosides.

BMS-200475 (**1**, entecavir),[5] showing potent anti-HBV activity, belongs to one of these aforementioned classes in that it possesses exocyclic methylene in place of oxygen of the furanose ring. It was 100 times more potent than lamivudine and is currently undergoing phase III clinical trials.

On the basis of these findings, we have designed and synthesized iso dideoxynucleosides with exocyclic methylene since C3′-OH of compound **1** might act as a bioisostere of oxygen, among which adenine analogue **2** exhibited potent anti-HBV activity.[6] Iso dideoxynucleosides also belong to unique nucleosides in that furanose oxygen moves to the C3 position. Among these, adenine analogue (iso-ddA) and guanine analogue (iso-ddG) showed not only potent anti-HIV activity comparable to 2′,3′-dideoxyadenosine (ddA) and 2′,3′-dideoxyguanosine (ddG), respectively, but also chemical and metabolic stability.[7]

On the basis of the potent anti-HBV activity of **2**, it was interesting to design and synthesize compound **3** because sulfur is well-known as a bioisostere of oxygen and to compare its anti-HBV activity with that of compound **2**. Here, we wish to report the asymmetric synthesis of novel thioiso dideoxynucleosides **3** with exocyclic methylene as potential antiviral agents and their related chemistry, in which the hitherto unknown S_N2' reaction is involved.

As illustrated in Scheme 1, retrosynthetic analysis shows that the target nucleosides could be synthesized from the Mitsunobu condensation with the glycosyl donor **I**. The introduction of the exocyclic methylene group to get the key intermediate **I** can be visualized in two ways.

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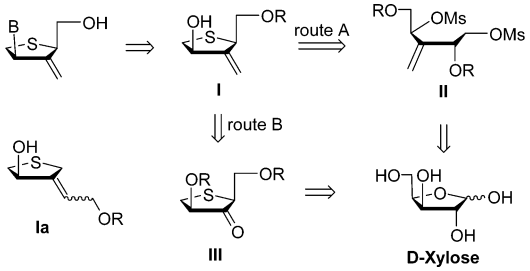
SCHEME 1. Retrosynthetic Analysis for the Synthesis of the Target Nucleosides



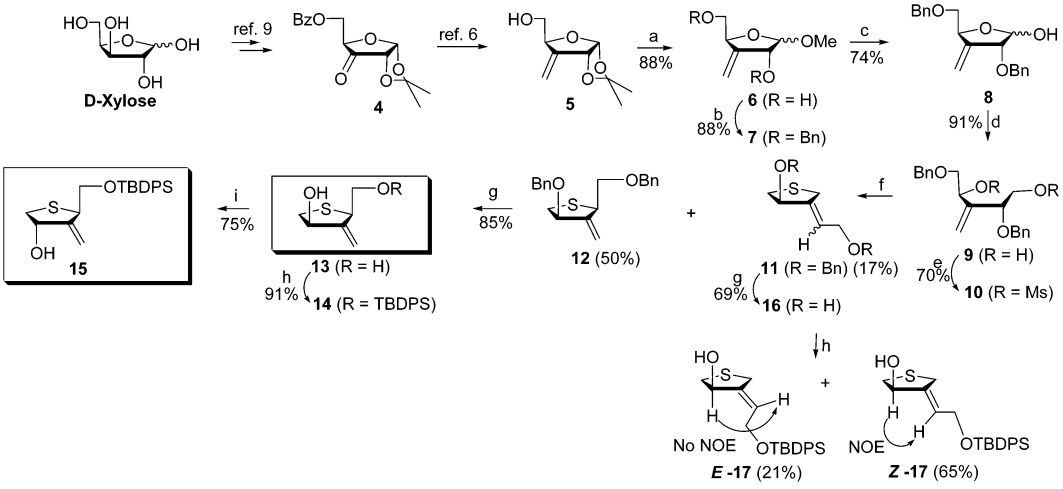
The Wittig reaction can be either carried out before the thiosugar formation (route A), as we have done ultimately, or it can be delayed until the formation of the thiosugar (route B), as was done in all the earlier cases[8] of synthesis of thionucleosides with an exocyclic double bond. However, both strategies are fraught with at least one likely complication. If we introduce the exocyclic double bond before the thiosugar formation, a diastereomeric thiosugar **Ia**, resulting from the double bond migration/OMs elimination associated with the S_N2' reaction, may be obtained along with the desired intermediate **I** during cyclization of **II**. On the other hand, Wittig reaction on thiosugar **III** is vulnerable to epimerization due to the presence of the acidic C4-H. After taking the pros and cons of the two respective routes mentioned above into consideration, we thought it was prudent to choose route A involving the early Wittig reaction. Moreover, it will give us an opportunity to probe the cyclization of 1,4-dimesylate **II** to get the thiosugar in the presence of the exocyclic double bond, as nobody has investigated this aspect so far. The intermediates **II** and **III** can be derived from D-xylose.

For the synthesis of the glycosyl donors, **14** and **15** (Scheme 2), D-xylose was converted to methylene derivative **5** according to the known procedure.[6,9] Acid-catalyzed methanolysis of **5** followed by benzyl protection of the resulting methyl furanoside **6** produced dibenzylate **7**. Hydrolysis of the anomeric methoxide **7** was carried out with a 1:1 mixture of 8 M HCl and 1,4-dioxane at room temperature to give lactol **8**, which was treated with $LiBH_4$ to give diol **9**. After treatment of **9** with mesyl chloride, the resulting dimesylate **10** was reacted with sodium sulfide in DMF to give the desired thiosugar **12** along with the S_N2' product **11** as a mixture of (*E*)- and (*Z*)-isomers.

Cyclization turned out to be controlled by reaction temperature and solvent. At higher temperature, S_N2' product **11** was almost exclusively formed as a major product, indicating compound **11** is a thermodynamic product, while use of a low temperature and polar solvent gave the S_N2 reaction product **12** as a desired kinetic product. The optimum yield of **12** was obtained on stirring in DMF at 0 °C for 4 h. It is interesting to note that formation of **12** proceeded in pure S_N2 reaction, not the S_N1 reaction in the presence of an allylic fuctional group. For the synthesis of trans nucleosides, compound **12** was debenzylated and the primary hydroxyl group of diol **13** was protected as TBDPS ether to give the glycosyl donor **14**. For the synthesis of cis nucleosides, the stereochemistry of the C3-hydroxyl group of **12** had to be inverted by using the Mitsunobu reaction[10] to give another glycosyl donor **15**. The inseparable (*E*)- and (*Z*)-mixture of S_N2' product **11** on treatment with BCl_3 still gave the (*E*)- and (*Z*)-mixture of **16** that could not be separated on silica gel. However, silyl protection of **16** afforded the separable mixture of (*E*)-**17** (21%) and (*Z*)-**17** (65%) after silica gel column chromatography. The stereochemistry of (*E*)-**17** and (*Z*)-**17** was confirmed by ^1H NOE experiment between the C3 proton and the vinyl proton as shown in Scheme 2.

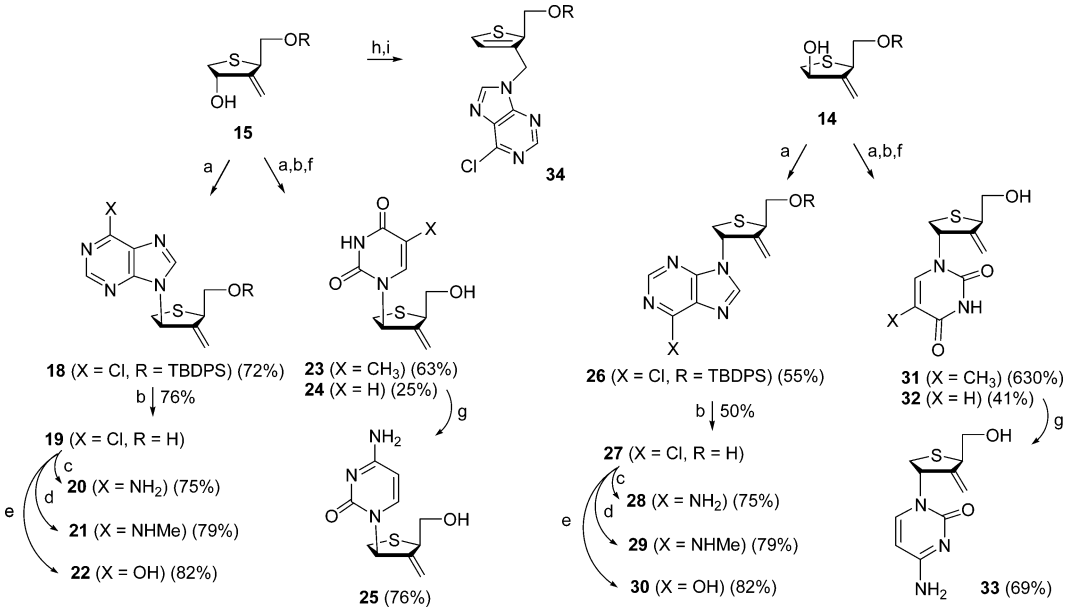
For the synthesis of cis and trans nucleoside derivatives from the glycosyl donors **15** and **14**, respectively, we employed two glycosylation methods (Mitsunobu condensation and palldium-catalyzed coupling), as shown in Scheme 3. Glycosyl donor **15** was first condensed with 6-chloropurine under the Mitsunobu conditions[10] to give the protected nucleoside **18**. Unlike cyclization, the Mitsunobu reaction proceeded as a pure S_N2 reaction without the formation of S_N2' product. After desilylation of **18**, the resulting 6-chloropurine analogue **19** was converted to adenine derivative **20**, N^6-methyladenine derivative **21**, and hypoxanthine derivative **22** by heating

SCHEME 2[a]



[a] Reagents and conditions: (a) MeOH, AcCl, rt, 6 h; (b) BnBr, NaH, TBAI, THF; (c) HCl/dioxane; (d) $LiBH_4$, THF; (e) MsCl, pyridine, CH_2Cl_2; (f) Na_2S, DMF, 0 °C; (g) BCl_3, CH_2Cl_2; (h) TBDPSCl, imidazole, DMF; (i) BzOH, PPh_3, DEAD, THF then MeOH/NH_3.

SCHEME 3[a]



[a] Reagents and conditions: (a) 6-chloropurine, N^3-Bz-uracil, or N^3-Bz-thymine, PPh_3, DEAD, THF, 0 °C, 1 h; (b) TBAF, THF, 0 °C, 15 min; (c) NH_3/MeOH, 80 °C; (d) CH_3NH_2, MeOH, 80 °C; (e) 2-mercaptoethanol, NaOMe, MeOH; (f) NH_3/MeOH, rt; (g) (i) Ac_2O, pyridine, (ii) 1,2,4-triazole, $POCl_3$, (iii) NH_4OH, 1,4-dioxane, (iv) NH_3, MeOH; (h) Ac_2O, pyridine, rt; (i) NaH, $Pd(PPh_3)_4$, DMF, 40 °C.

with methanolic ammonia, methanolic methylamine, and finally 2-mercaptoethanol and sodium methoxide, respectively. On the other hand, condensation of **15** with N^3-benzoylthymine and N^3-benzoyluracil under the same Mitsunobu conditions[10] followed by deprotection of TBDPS and benzoyl groups yielded *cis*-thymine derivative **23** and *cis*-uracil derivative **24**, respectively, along with a small amount of respective *O*-glycosylated products.[11] The *cis*-uracil derivative **24** was converted to the *cis*-cytosine derivative **25** according to the conventional method. Another glycosyl donor **14** was similarly converted to the final *trans*-purine nucleosides **27**−**30** and *trans*-pyrimidine nucleosides **31**−**33**. However, when glycosyl donor **15** was coupled with 6-chloropurine after being converted to its acetate in the presence of NaH and $Pd(PPh_3)_4$ in DMF, there was sole formation of the S_N2' product **34** (31%), instead of giving the S_N1' product or the desired S_N2 product **26**. It is attributed to glycosylation occurring at the least hindered site.

All synthesized final nucleosides were tested against several viruses such as HIV-1, HBV, HCV, and HCMV. Among compounds tested, only 6-chloropurine derivative **19** showed weak anti-hepatitis C virus (HCV) activity.

In summary, we have accomplished the asymmetric synthesis of novel thioiso nucleosides with exocyclic methylene, starting from D-xylose. We have developed an efficient procedure to synthesize thiosugar **12** in the presence of the allyl group by controlling the temperature and the solvent, without epimerizaion via the allylic cation. Although our efforts were not translated into the discovery of highly active antiviral nucleosides, it is sure that the novel thiosugar **12** developed in this work has the potential to serve as a new template for the design of new antiviral nucleosides.

Experimental Section

(*R*)-3-Benzyloxy-4-(2-benzyloxyethylidene)tetrahydrothiophene (*E*,*Z*-11) and (2*R*,4*R*)-4-Benzyloxy-2-benzyloxymethyl-3-methylenetetrahydrothiophene (12). To a solution of **10** (8 g, 16.5 mmol) in DMF (35 mL) was added Na_2S (1.93 g, 24.8 mmol) and the mixture was stirred at 0 °C under nitrogen atmosphere for 4 h. The reaction was quenched by adding water and was extracted with an excess of diethyl ether. The organic layer was washed with water, dried, and evaporated. The residue was purified by flash silica gel column chromatography (hexane/EtOAc = 10:1) to give **12** (2.7 g, 50%) and an inseparable mixture of *E*- and *Z*-**11** (0.9 g, 17%).

Compound **12**: $[\alpha]^{25}_D$ −25.47 (*c* 1.37, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.88 (dd, J = 4.4, 11.6 Hz, 1 H), 3.03 (dd, J = 5.2, 11.6 Hz, 1 H), 3.57 (dd, J = 6.2, 9.2 Hz, 1 H), 3.75 (dd, J = 7.4, 9.2 Hz, 1 H), 3.98 (t, J = 7.4 Hz, 1 H), 4.36 (t, J = 4.4 Hz, 1 H), 4.54 (m, 4 H), 5.27 (d, J = 1.2 Hz, 2 H), 7.32 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 35.2, 47.9, 70.4, 73.4, 75.3, 113.5, 127.8, 127.9, 128.6, 138.1, 138.4, 147.9. Anal. Calcd for $C_{20}H_{22}O_2S$: C, 73.58; H, 6.79; O, 9.80; S, 9.82. Found: C, 73.84; H, 7.10.

A Typical Experimental Procedure for the Mitsunobu Condensation. To a stirred solution of **15** (460 mg, 1.2 mmol), 6-chloropurine (463 mg, 2.99 mmol), and triphenyl phosphine (943 mg, 3.6 mmol) in dry THF (15 mL) was added diethyl azodicarboxylate (0.56 mL) dropwise at −10 °C under nitrogen. The reaction mixture was stirred for 1 h at −10 °C under nitrogen. The solvent was evaporated and the residue was purified by flash silica gel column chromatography (1:3 = EtOAc/hexane) to give (3*R*,5*R*)-9-[5-(*tert*-butyldiphenylsilyloxy)methyl)-4-methylenetetrahydrothiophen-3-yl]-6-chloro-9*H*-purine (**18**) (454 mg, 72%) as a colorless viscous liquid: UV ($CHCl_3$) λ_{max} 265.5 nm (pH 7); ^{1}H NMR ($CDCl_3$) δ 1.11 (s, 9 H), 3.29 (d, J = 7.6 Hz,

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2 H), 3.93 (m, 2 H), 4.11 (m, 1 H), 4.90 (s, 1 H), 5.30 (s, 1 H), 5.83 (t, J = 7.6 Hz, 1 H), 7.41 (m, 6 H), 7.67 (m, 4 H), 8.21 (s, 1 H), 8.71(s, 1 H); ^{13}C NMR ($CHCl_3$) δ 19.5, 27.1, 34.8, 50.7, 61.2, 67.6, 113.5, 128.0, 128.1, 130.2, 131.8, 133.2, 133.3, 135.8, 144.1, 147.1, 151.5, 151.9, 152.2. Anal. Calcd for $C_{27}H_{29}ClN_4OSSi$: C, 62.23; H, 5.61; Cl, 6.80; N, 10.75; O, 3.07; S, 6.15; Si, 5.39. Found: C, 62.20; H, 5.57; N, 10.91.

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Supporting Information Available: Full experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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