COMMUNICATION

Participation of sulfur occurred during the Mitsunobu reaction: synthesis of novel isodideoxythionucleosides

Lak Shin Jeong,*[a] Su Jeong Yoo,[a] Hyung Ryong Moon,[a] Yun Ha Kim[a] and Moon Woo Chun[b]

[a] *Laboratory of Medicinal Chemistry, College of Pharmacy, Ewha Womans University, Seoul 120-750, Korea*
[b] *College of Pharmacy, Seoul National University, Seoul 151-742, Korea*

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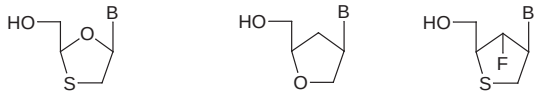
Novel isodideoxythionucleosides have been synthesized from our versatile intermediate, L-4-thioarabitol derivative 5 using the Mitsunobu reaction as a key step. It is found that the sulfur atom of the 4-thiofuranose derivative takes part in the Mitsunobu reaction.

Introduction

1,3-Oxathiolanyl pyrimidine and purine nucleosides (**1**) belong to an unusual class of nucleosides in that the C3 methylene is substituted by an oxygen atom.[1] Many of them have been found to show potent antiviral activities against the human immunodeficiency virus (HIV) and hepatitis B virus (HBV).[1] In particular, L-1,3-oxathiolanyl cytosine (3TC, lamivudine) is being clinically used for the treatment of AIDS patients[2] and L-1,3-oxathiolanyl 5-fluorocytosine (FTC) is now undergoing clinical trials as an anti-HBV agent.[3]

Isodideoxynucleosides in which the ring oxygen and 3′-carbon of 2′,3′-dideoxyribose unit are interchanged are also an unusual class of nucleosides developed since the discovery of 3TC.[4] Among these compounds, iso-ddA (**2a**) and iso-ddG (**2b**) have been reported to exhibit potent anti-HIV activity without apparent cytotoxicity.[4,5] These compounds possess enhanced chemical and enzymatic stability of the labile glycosidic bond when compared to 2′,3′-dideoxynucleosides.



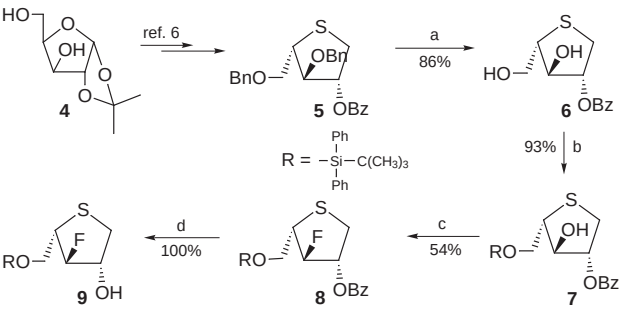
1 (B = pyrimidines and purines) **2a** (B = Adenine) **2b** (B = Guanine) **3a** (B = uracil) **3b** (B = adenine)

Chart 1

As a part of our ongoing efforts to develop new antiviral agents, it was interesting to design compound **3** because C–F can act as a bioisostere of oxygen and sulfur is also a bioisostere of oxygen. Thus, we synthesized the target nucleosides **3** utilizing a Mitsunobu reaction as a key step from the versatile intermediate, an L-4-thioarabitol derivative[6] developed by our laboratory. While preparing compound **3**, we discovered the sulfur participation of the 4-thiofuranose derivative in the Mitsunobu reaction. This contrasts with the results which Yoshimura and his co-workers had reported, that the sulfur atom of 4-thiofuranoses does not take part in the Mitsunobu reaction.[7] Here, we wish to report the sulfur chemistry related to the Mitsunobu reaction and the synthesis of novel fluoro substituted isodideoxythionucleosides.

Results and discussion

Synthesis of the precursor **9** for the Mitsunobu reaction is shown in Scheme 1. 1,2-*O*-Isopropylidene-D-xylose was converted to L-thioarabitol derivative **5** according to the short and



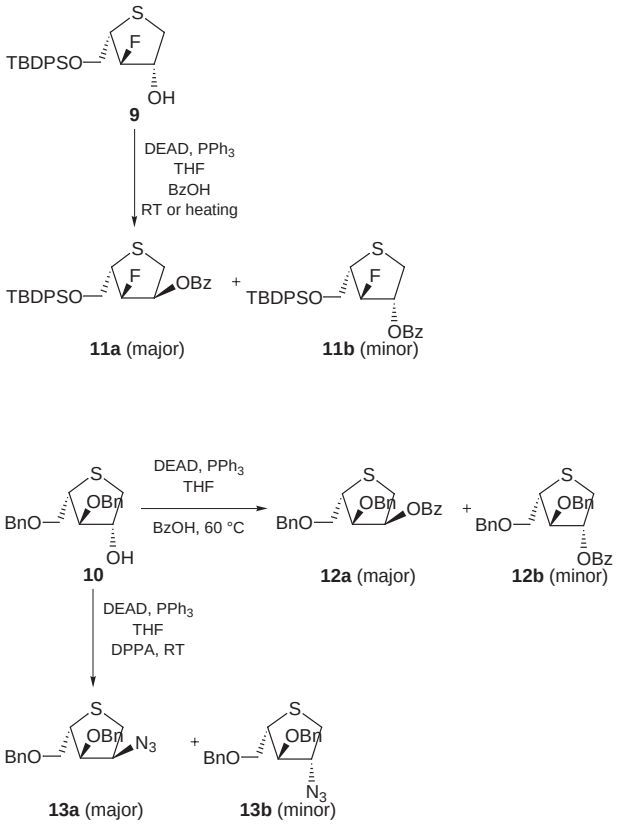
Scheme 1 *Reagents and conditions*: (a) BCl_3, CH_2Cl_2, −78 °C, 0.5 h; (b) RCl, imidazole, DMF, 0 °C, 1 h; (c) DAST, CH_2Cl_2, −4 °C, 10 min; (d) NaOMe, MeOH, CH_2Cl_2, 0 °C, 2 h.

efficient procedure developed by our laboratory.[6] The benzyl protecting groups of **5** were removed by boron trichloride at −78 °C to give the diols **6**. Treatment of diols **6** with *tert*-butyldiphenylsilyl chloride at 0 °C gave silyl ether **7** in 93% yield. Treatment of **7** with DAST (diethylaminosulfur trifluoride) at −4 °C yielded the fluoro compound **8** with complete retention of stereochemistry.[7–9] The benzoyl group of **8** was removed with NaOMe to give **9** in quantitative yield.

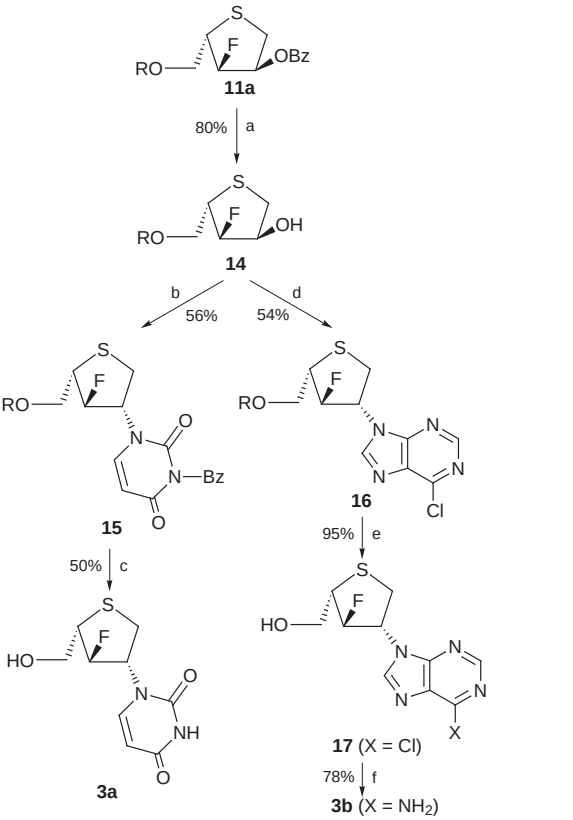
Since the stereochemistry of the hydroxy group at C2 had to be inverted to synthesize the desired β nucleosides, we employed the Mitsunobu reaction as shown in Scheme 2. Mitsunobu reaction of compound **9** under standard conditions (Ph_3P, DEAD, $C_6H_5CO_2H$, THF, RT or 60 °C) always afforded the desired **11a** as the major product, but these conditions also gave **11b** as a minor product (3–10% isolated yield) which was formed by the participation of the sulfur atom of the 4-thiofuranose.[10] In order to confirm the participation of sulfur, we tried other Mitsunobu reactions using benzoic acid or diphenylphosphoryl azide (DPPA) as incoming nucleophiles. Thus, Mitsunobu reactions of **10** (benzoic acid, 60 °C, 48 h; DPPA, RT, 2 h)[7] afforded **12b** and **13b** (3–15% isolated yield) as minor products, respectively.

Therefore, it is concluded that sulfur takes some participation in the Mitsunobu reaction, leading to the formation of products with retention of stereochemistry, whose yields were increased by the use of more Mitsunobu reagents at higher temperatures.

Compound **11a** was treated with methanolic ammonia to give **14** which serves as a versatile intermediate for the synthesis of the desired nucleosides (Scheme 3). Condensation of **14** with N^3-benzoyluracil under the Mitsunobu conditions gave the protected nucleoside **15** in 56% yield.[11] Deprotection of the benzoyl group (NH_3, MeOH) and *tert*-butyldiphenylsilyl group (*n*-Bu_4NF, THF) afforded the final uracil derivative **3a**. The intermediate **14** was also condensed with 6-chloropurine under the same conditions used in the preparation of **15** to give compound **16**[11] which was treated with tetra-*n*-butylammonium fluoride to yield 6-chloropurine derivative **17**. Treatment of **17** with methanolic ammonia at 100 °C afforded the final adenine



Scheme 2



Scheme 3 *Reagents and conditions*: (a) NH_3, RT, 2 h; (b) N^3-benzoyluracil, DEAD, PPh_3, THF, 0 °C to RT, 15 h; (c) NH_3, MeOH, RT, 2 h, then n-Bu_4NF, THF, RT, 1 h; (d) 6-chloropurine, DEAD, PPh_3, THF, 0 °C to RT, 15 h; (e) n-Bu_4NF, THF, RT, 1 h; (f) NH_3, MeOH, 100 °C, 48 h.

derivative **3b**. The structure of compound **3b** was confirmed by NOESY and HMQC NMR experiments.

In summary, we have completed the synthesis of novel isodideoxythionucleosides from the versatile intermediate, L-4-thioarabitol derivative in which we discovered the participation of the sulfur during the Mitsunobu reaction as in the DAST fluorination. It is a new finding in sulfur chemistry since it had been reported that sulfur did not participate in the Mitsunobu reaction.

Acknowledgements

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10 To a solution of triphenylphosphine (1.5 mol) in dry THF was added dropwise diethyl azodicarboxylate (DEAD, 1.5 mol) at 0 °C and the reaction mixture was stirred at room temperature for 2 h. To this mixture was added a solution of benzoic acid (1.5 mol) in THF followed by a solution of **9** (1.0 mol) in dry THF and the reaction mixture was stirred at 60 °C for 8 h. More triphenylphosphine (1.5 mol), DEAD (1.5 mol) and benzoic acid (1.5 mol) were added to the mixture at room temperature and the mixture was stirred at 60 °C for 15 h. Since starting material **9** still remained on TLC, more triphenylphosphine (1.5 mol), DEAD (1.5 mol) and benzoic acid (1.5 mol) were again added to the mixture at room temperature and the mixture was further stirred at 60 °C for 6 h. The mixture was evaporated and the residue was purified by silica gel column chromatography (hexanes–ethyl acetate 15 : 1) to give **11a** (85%) and **11b** (15%).

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