COMMUNICATION

A highly efficient synthesis of L-β-2′-deoxy-4′-thio-1′-purine nucleosides as potential antiviral agents

Hea Ok Kim,[a] Lak Shin Jeong,*[b] Sun Nan Lee,[b] Soo Jeong Yoo,[b] Hyung Ryong Moon,[b] Kil Soo Kim[b] and Moon Woo Chun[c]

[a] *College of Medicine, Yonsei University, Seoul 120-752, Korea*
[b] *Laboratory of Medicinal Chemistry, College of Pharmacy, Ewha Womans University, Seoul 120-750, Korea*
[c] *College of Pharmacy, Seoul National University, Seoul 151-742, Korea*

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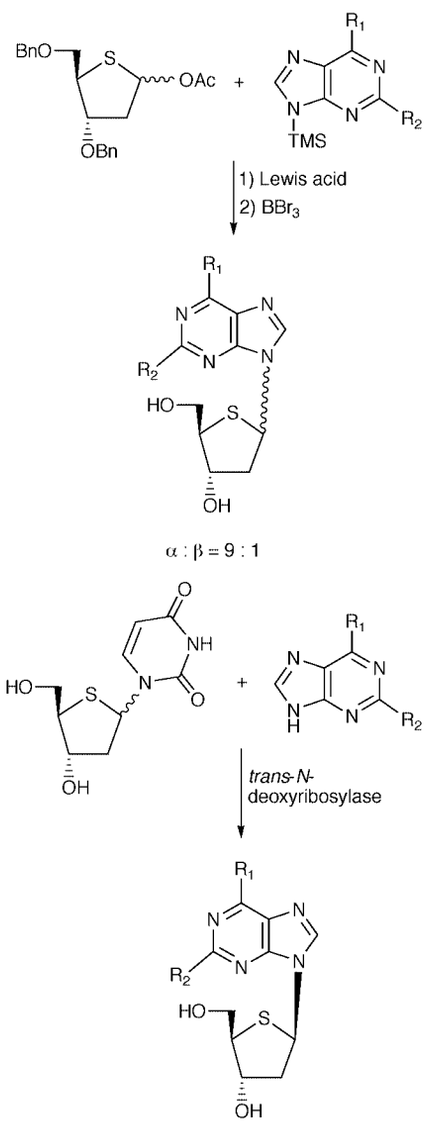
L-β-2′-Deoxy-4′-thio-1′-purine nucleosides were synthesized efficiently utilizing the neighboring group effect of the 2-benzoyl-4-thiosugar acetate.

D-4′-Thionucleosides in which the furanose oxygen is substituted by a sulfur atom exhibit interesting biological properties such as antibiotic,[1] antiviral[2] and antitumor[3] activities, and also have inherent advantages such as a more stable glycosidic linkage and increased metabolic stability.[4] Among these nucleosides, D-2′-deoxy-4′-thio-1′-pyrimidine nucleosides[5] show potent anti-HSV (herpes simplex virus) and antitumor activities, and D-β-2′-deoxy-4′-thio-1′-purine nucleosides exhibit potent anti-HBV (hepatitis B virus) and anti-HCMV (human cytomegalovirus) activity, but they were found to be highly nephrotoxic when tested *in vivo*.[6] Therefore, it was interesting to synthesize L-β-2′-deoxy-4′-thio-1′-purine nucleosides and to compare their biological activities to those of their corresponding D-nucleosides, since many L-nucleosides such as 3TC,[7] L-Fd4C,[8] and L-FMAU[9] exhibit more potent antiviral activities with much less cytotoxicity than their corresponding D counterparts.

However, although D-β-2′-deoxy-4′-thio-1′-purine nucleosides show interesting biological activity, the biological activity of β-2′-deoxy-4′-thio-1′-purine nucleosides has rarely been reported in the literature because of the synthetic difficulties in the 2-deoxy-4-thiosugar acetate, together with the unfavorable anomeric ratio produced during the condensation. For example, when a D-2-deoxy-4-thiosugar acetate was condensed with purine bases, the α-anomer was always formed predominantly over the β-anomer (α : β = 9 : 1).[10] Van Draanen and co-workers[6] obtained the desired β-anomer by a *trans* glycosylation method using *trans-N*-deoxyribosylase, but this method involved synthesis of an anomeric mixture of the D-2′-deoxy-4′-thio-1′-pyrimidine nucleoside followed by condensation with purine bases in the presence of the transfer enzyme (Scheme 1).

Therefore, it was necessary to develop a new efficient synthetic method to obtain L-β-2′-deoxy-4′-thio-1′-purine nucleosides for the structure–activity relationship study, as well as for the purpose of reducing the toxicity of D-nucleosides. Our laboratory developed a very short and efficient route[11] to the L-4-thiosugar, in which the C2 position can be modified selectively. Since neighboring group participation by the C2 acyl group is a very efficient way to obtain the β-anomer selectively in synthesizing nucleosides, our key intermediate, an L-4-thioarabitol derivative, was thought to be an excellent synthon for the chemical synthesis of L-2′-deoxy-4′-thio-1′-purine nucleosides. Here, we report the highly efficient synthesis of L-β-2′-deoxy-4′-thio-1′-purine nucleosides, utilizing the anchimeric effect of the C2 benzoyl group of L-4-thiosugar.



Scheme 1

Results and discussion

The glycosyl donor, L-2-benzoyl-4-thiosugar acetate, was synthesized from the L-4-thioarabitol derivative **2**,[11] which could be easily synthesized from 1,2-*O*-isopropylidene-D-xylose in 50% overall yield (Scheme 2). The benzoyl group of **2** was

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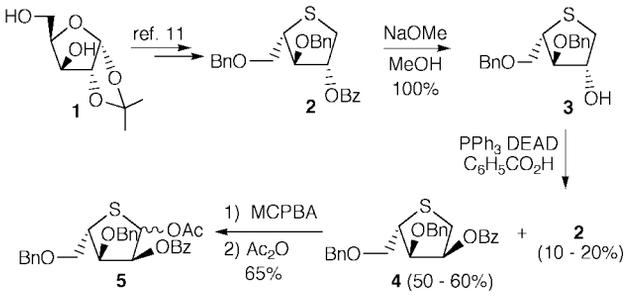
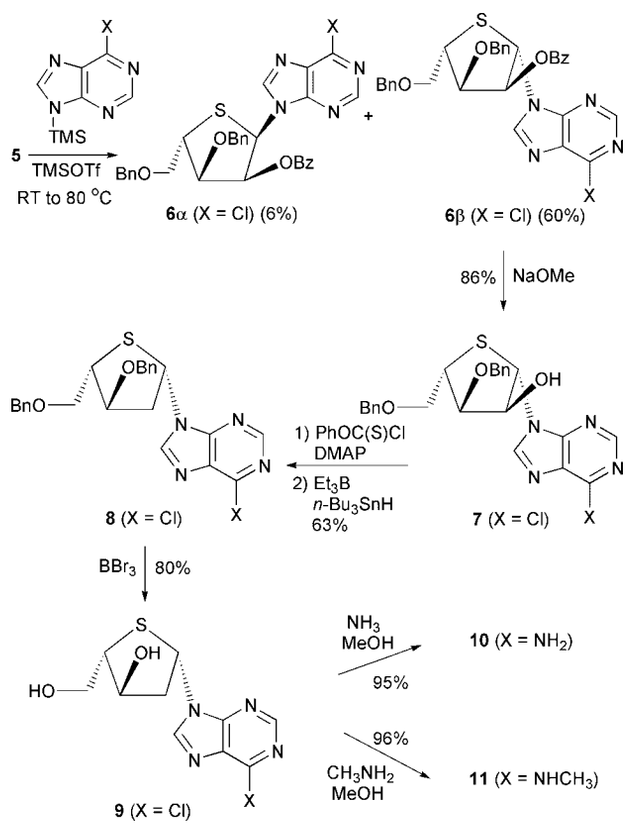


Scheme 2

removed by treatment with sodium methoxide in quantitative yield. To obtain the desired neighboring group effect during the condensation reaction with nucleosidic base, the stereochemistry of the C2 hydroxy group of **3** was inverted using Mitsunobu conditions (PPh_3, DEAD, benzoic acid, 60 °C) to give **4** (50%) with the concomitant formation of compound **2** (10–20%), which resulted from the participation of the sulfur atom of the 4-thiofuranose.[12] The acetoxy group at the anomeric position was introduced by Pummerer rearrangement by treating **4** with MCPBA, followed by refluxing with acetic anhydride to yield an acetate **5** (65%).

The synthesis of the target nucleosides **9**–**11** is shown in Scheme 3. Condensation of the acetate **5** with silylated 6-



Scheme 3

chloropurine in the presence of TMSOTf in 1,2-dichloroethane gave the desired β-anomer **6β** as the predominant product (60%), which could be formed by the neighboring group effect of the C2 benzoyl group, and also the α-anomer **6α** as the minor product (6%) after purification by silica gel column chromatography.[13] The assignments of the anomeric configurations of **6α** and **6β** were based on NOE experiments. When each 4′-H peak of **6α** and **6β** was irradiated, enhancement of the 1′-H peak of **6β** was observed, suggesting the *cis* orientation, while no enhancement of the 1′-H peak of **6α** was observed, indicating the *trans* configuration. Additionally, the NOE effect (1.5%) between 1′-H and 2′-H of **6β** was smaller than that of **6α** (5.3%). It is of interest to note that the N-3 isomer [$R_f = 0.32$, UV (MeOH) λ_{max} 271 nm] was initially formed during the condensation, and smoothly rearranged to the N-9 isomer [$R_f = 0.62$, UV (MeOH) λ_{max} 265 nm] on refluxing, as reported by Chu and co-workers.[14] Besides the UV data of **6β**, the assignment of N-9 regiochemistry was further confirmed by the UV spectral data of the adenine analog **9** [UV (MeOH) λ_{max} 260 nm] and *N*-methyladenine analog **10** [UV (MeOH) λ_{max} 266 nm]. Treatment of **6β** with sodium methoxide afforded **7**, which was deoxygenated using modified Barton's conditions to give the 2′-deoxy nucleoside **8**. Treatment of 2′-deoxy derivative **8** with boron trichloride produced the 6-chloropurine derivative **9** in low yield because of the partial deprotection of the benzyl group. However, use of an excess of boron tribromide gave the desired **9** in 80% yield. Compound **9** was easily converted to the adenine derivative **10** (95%) by treatment with methanolic ammonia at 80 °C. The *N*-methyladenine analog **11** was obtained by heating with 40% methylamine in methanol at 80 °C (96%). The antiviral assay of the final nucleosides **9**–**11** is in progress and will be reported in due course.

In summary, we accomplished an efficient synthesis of L-β-2′-deoxy-4′-thio-1′-purine nucleosides through neighboring group participation of the C2 benzoyl group of the L-2-benzoyl-4-thiosugar. This synthetic method illustrates the general procedure for the predominant synthesis of β-2′-deoxy-4′-thio-1′-purine nucleosides from our versatile intermediate, 1,4-anhydro-2-benzoyl-3,5-dibenzyl-L-4-thioarabitol.

Acknowledgements

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13 A solution of the acetate **5** (984 mg, 1.99 mmol) in 1,2-dichloroethane (5 mL) was added to a solution of silylated 6-chloropurine (462 mg, 2.99 mmol) in 1,2-dichloroethane (2 mL) followed by the dropwise

addition of trimethylsilyl trifluoromethanesulfonate (0.43 mL, 2.39 mmol) at 0 °C. The mixture was stirred at RT for 24 h. TLC gave a slower moving spot due to the N-3 isomer (major product) which was almost completely converted to the N-9 isomer (faster moving spot) on refluxing for another 24 h. The usual work-up and successive purification by silica gel chromatography (hexanes–ethyl acetate = 4 : 1 to 3 : 1) gave **6**β (R_f = 0.62, 703.8 mg, 60%) and **6**α (R_f = 0.55, 70.1 mg, 6%). Compound **6**β: ^{1}H NMR δ 3.82–3.89 (m, 2 H, 5′-H), 3.91–3.93 (m, 1 H, 4′-H), 4.50–4.68 (m, 5 H, 3′-H and 2 × CH_2C$_6$H$_5$), 6.04 (dd, 1 H, J = 3.7 and 5.2 Hz, 2′-H), 6.45 (d, 1 H, J = 5.2 Hz, 1′-H), 7.22–8.07 (m, 15 H, 3 × C$_6H_5$), 8.76 (s, 1 H, H-8), 8.77 (s, 1 H, H-2). Calcd for $C_{31}H_{27}ClN_4O_4S$: C, 63.42; H, 4.64; N, 9.54. Found: C, 63.65; H, 4.54; N, 9.23%. Compound **6**α: ^{1}H NMR δ 3.60 (dd, 1 H, J = 6.0 and 10.0 Hz, 5′-H$_a$), 3.65 (dd, 1 H, J = 6.3 and 10.0 Hz, 5′-H$_b$), 4.06–4.11 (dt, 1 H, J = 3.2 and 6.0 Hz, 4′-H), 4.43 (t, 1 H, J = 3.8 Hz, 3′-H), 4.58 (s, 2 H, CH_2C$_6$H$_5$), 4.59 (s, 2 H, CH_2C$_6$H$_5$), 5.90 (dd, 1 H, J = 3.8 and 6.1 Hz, 2′-H), 6.57 (d, 1 H, J = 6.1 Hz, 1′-H), 7.18–7.58 (m, 15 H, 3 × C$_6H_5$), 8.51 (s, 1 H, H-8), 8.83 (s, 1 H, H-2). Calcd for $C_{31}H_{27}ClN_4O_4S$: C, 63.42; H, 4.64; N, 9.54. Found: C, 63.33; H, 4.76; N, 9.14%.

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