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# Stereoselective Functionalization of the 1′-Position of 4′-Thionucleosides

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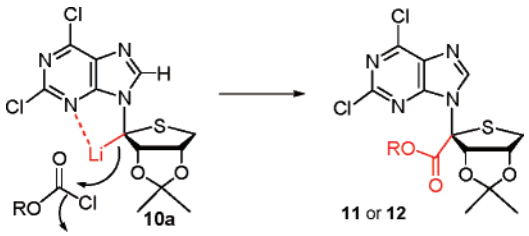
## ABSTRACT




**Stereoselective synthesis of novel 1′-α-substituted-4′-thionucleosides was achieved starting from D-gulonic acid γ-lactone via stereoselective nucleophilic substitution.**

Since $A_3$ adenosine receptor (AR) regulates many physiological functions using adenosine as a natural ligand,[1] it has been a promising target for the development of clinically useful agents.[2] For example, $A_3$AR agonists have been targeted as anti-cancer, cerebro- and cardioprotective agents,[3] while $A_3$AR antagonists have been developed for anti-asthma, anti-glaucoma, and anti-inflammatory agents.[4]

A number of adenosine derivatives have been synthesized as $A_3$AR agonists.[5,6] Modifications at the $N^6$ position and/or 4′-hydroxymethyl group of adenosine have been extensively explored, among which Cl−IB−MECA (**1a**)[7] showed a potent binding affinity to the human $A_3$AR ($K_i$ = 1.4 nM) with high selectivity to the human $A_1$ and $A_{2A}$ARs. Recently, we have reported the 4′-thio analogue (LJ-529, **1b**)[8] which is more potent than **1a** as an $A_3$AR agonist ($K_i$ = 0.38 nM) (Figure 1). Although a number of nucleoside derivatives have been discovered as potent and selective $A_3$AR agonists, very few examples of selective $A_3$AR antagonists with a nucleo-

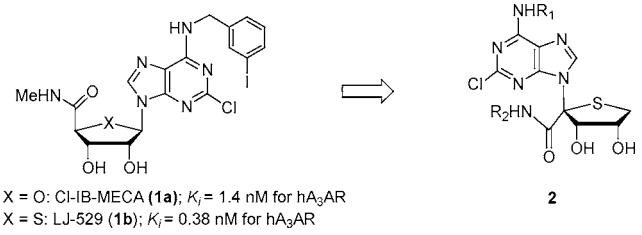



**Figure 1.** The rationale for the design of the target nucleoside (**2**).

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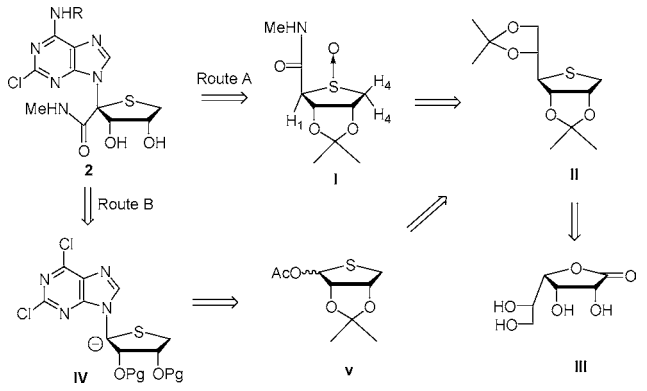
side skeleton have been reported. Since $A_3$AR antagonists with a nucleoside skeleton possess several advantages, including independence of species and increased water solubility to be developed as clinically useful agents,[9] it is desirable to discover nucleoside derivatives exhibiting $A_3$AR antagonism, compared to non-nucleoside $A_3$AR antagonists.

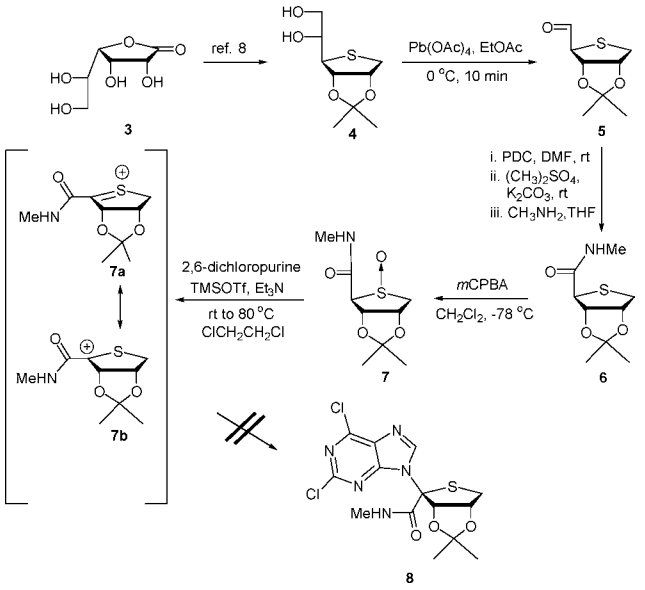
It is known that the activation of the $A_3$AR is highly dependent on the geometry and flexibility of hydrogen bonding groups of the ribose moiety.[9] In the target compound **2**, we have retained the same hydrogen bonding groups that occur in known potent agonist **1b**, a uronamide and two hydroxyl groups; however, they are arranged in a different geometry. Two structural changes of the thioribose moiety of **1b** have been made, that is, transformation of the natural D-type to an L-type nucleoside and movement of the 5′-uronamide from the $\beta$- to α-position (Figure 1). The hypothesis to be tested with these analogues is whether the newly arranged hydrogen bonding moieties allow the nucleoside to bind to the receptor but not undergo the required conformational change needed to activate the receptor. While synthesizing compound **2**, we discovered interesting chemistries, such as stereoselective alkylation of the 1′-position and one-step conversion of diol into acetate. Herein, we report the stereoselective synthesis of the target nucleoside **2** as a potential $A_3$AR antagonist.

Retrosynthetic analysis indicated that the target nucleosides **2** could be synthesized via two routes, as shown in Scheme 1. Route A utilizes an electrophilic addition of the purine base to the carbocation derived from the loss of the most acidic proton ($H_1$) of the key intermediate **I** under the Pummerer conditions, while route B uses the nucleophilic substitution of the carbanion **IV** formed under the basic conditions with alkyl chloroformate. The key intermediates **I** and **IV** are derived from the 4-thiosugar **II**, which is transformed from D-gulonic acid $\gamma$-lactone (**III**). We first attempted an electrophilic addition (route A) using the key intermediate **7** as an electrophilic synthon easily formed by a Pummerer rearrangement (Scheme 2).

**Scheme 1.** Retrosynthetic Analysis of the Desired Nucleoside **2**




**Scheme 2**




D-Gulonic acid $\gamma$-lactone (**3**) was converted to the diol **4** according to our reported procedure.[8] Oxidative cleavage of diol **4** with lead tetraacetate at 0 °C over a short period of time gave aldehyde **5**, which was transformed to the methylamide **6** in three steps (i.e., oxidation, methylation, and amination). Oxidation of **6** with *m*-CPBA afforded the glycosyl donor **7**. Electrophilic addition of **7** with 2,6-dichloropurine under the Pummerer reaction conditions failed to give the desired product **8** probably due to the destabilization of the carbocation **7a** or **7b** by the electron-withdrawing carbonyl group. Thus, we turned our attention to the direct nucleophilic substitution at the 1′-position utilizing carbanion chemistry (route B). There is a report that functionalizes the 1′-position of the 4′-oxonucleosides, utilizing the enolization of the 2′-ketouridine, but with low stereoselectivity.[10]

Thus, we decided to generate the carbanion directly at the 1′-position of 4′-thionucleoside since the 1′-position is highly acidic due to the sulfur atom and electron-withdrawing purine base and then to treat with electrophile for the stereoselective functionalization at the 1′-position. To achieve this goal, we synthesized the appropriate 4′-thionucleoside **10**, as shown in Scheme 3. Treatment of diol **4** with excess lead tetraacetate at room temperature over a longer period of reaction time yielded the acetate **9**, surprisingly instead of forming the aldehyde **5**, indicating that oxidative cleavage of diol,

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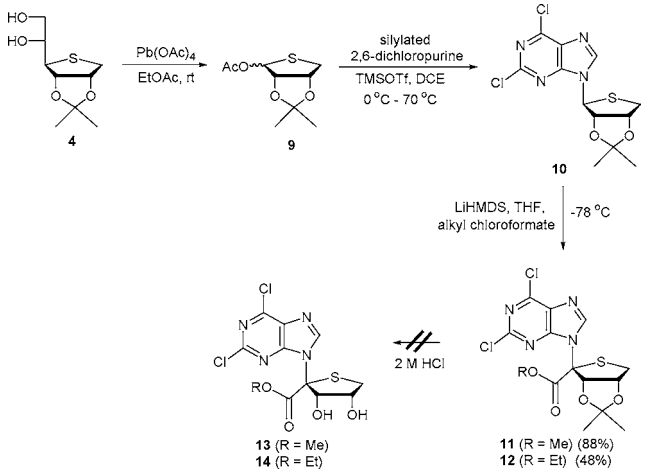
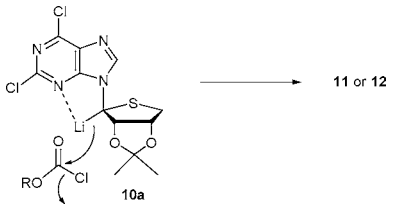
**Scheme 3**




oxidation of the resulting aldehyde to the acid, and oxidative decarboxylation of the acid occurred simultaneously under these reaction conditions. Since oxidation of the aldehyde to the corresponding acid with lead tetraacetate is generally difficult, it is under investigation whether this oxidation is only limited to 4-thiosugar or whether lead tetraacetate can be also applied to the oxidation of the primary or the secondary alcohol of 4-thiosugar.

Condensation of the glycosyl donor **9** with 2,6-dichloropurine in the presence of TMSOTf gave the $\beta$-anomer **10** exclusively. During the condensation, the initially formed $N^3$ isomer was smoothly rearranged to the desired $N^9$ isomer upon heating.[8] The anomeric configuration was confirmed by $^1$H NOE experiment in which a NOE between H-8 and 3′-H was observed. Treatment of **10** with LiHMDS produced the corresponding lithiate at the most acidic 1′-position, which was reacted with alkyl chloroformate to give the 1′-α carbonate **11** or **12** as a single stereoisomer. Methyl chloroformate turned out to be superior to ethyl chloroformate probably due to steric reasons. Stereoselective formation of **11** or **12** might be explained by the reaction intermediate shown in Scheme 4.

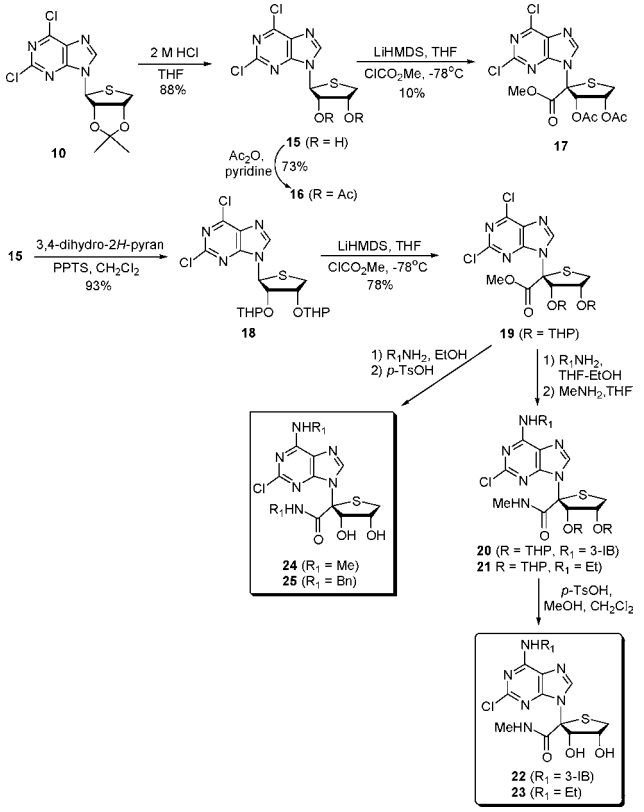
**Scheme 4**




The lithiate **10a** formed by treating **10** with LiHMDS is stabilized by five-membered ring coordination, as shown in Scheme 4, allowing the electrophile (alkyl chloroformate) to approach only from the α-side of **10a**, which resulted in the sole formation of **11** or **12**. Stereochemistry of **11** or **12** was confirmed by $^1$H NOE experiment as in the case of **10**. To our best knowledge, it is the first example of functionalizing the 1′-position of 4′-thionucleosides in 100% pure stereoselectivity.

However, removal of the isopropylidene group of **11** or **12** under acidic conditions resulted in the deglycosylation due to the electron-withdrawing carbonyl and 2,6-dichloropurine, requiring a protecting group removable under very mild conditions. Thus, we first tried an acyl protecting group, which could be removed under basic conditions, as shown in Scheme 5. Treatment of **10** with 2 M HCl in THF yielded

**Scheme 5**




diol **15**, which was protected as diacetate **16**. Stereoselective formation of 1′-α carbonate **17** was achieved under the same reaction conditions described in Scheme 3, but the yield was very low. Hence, we were forced to use a protecting group, such as tetrahydropyran (THP), which could be removed under mild acidic conditions (Scheme 5). Compound **15** was protected as di-*O*-THP ether **18**, and then it was converted to the 1′-α carbonate **19** in very good yield as a sole stereoisomer. Selective $N^6$ amination of **19** with 3-iodobenzylamine and ethylamine at room temperature for 2 h followed by conversion of the methyl ester into a methyl amide afforded $N^6$-3-iodobenzyl derivative **20** and $N^6$-ethyl derivative **21**, respectively. Removal of the THP protecting groups in **20** and **21** yielded the final nucleosides, **22** and **23**, respectively. Treatment of **19** with 3-iodobenzylamine and methylamine in ethanol at room temperature for 24 h

gave other final nucleosides **24** and **25**, in which the $N^6$ substituent and amide possessed the same group.

Binding affinity of the synthesized nucleosides **22**−**25** at the adenosine receptors was measured using radioligand binding assays.[11] All tested compounds were devoid of binding affinities to all subtypes of adenosine receptors, indicating that the 1′-uronamide group might form strong intramolecular hydrogen bonding with the 2′-hydroxyl group, hindering proper binding interaction of the synthesized molecule with the binding site of the receptor.

In summary, stereoselective synthesis of novel 1′-α-substituted-4′-thionucleosides was achieved starting from D-gulonic acid γ-lactone via stereoselective nucleophilic substitution as a key step. During nucleophilic substitution, 100% retention of stereochemistry control was observed regardless which protecting groups were used. It is the first example to functionalize the 1′-position of 4′-thionucleosides in a stereoselective manner. One-step conversion of diol **4** into acetate **9** using lead tetraacetate was also discovered, which may be extended to the oxidation of the primary or the secondary alcohol of 4-thiosugar.

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**Supporting Information Available:** Complete experimental procedures and $^1$H and $^{13}$NMR copies of compounds **11**, **22**, and **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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