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Stereoselective Synthesis of 1'-Functionalized-4'-Thionucleosides

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STEREOSELECTIVE SYNTHESIS OF 1'-FUNCTIONALIZED-4'-THIONUCLEOSIDES

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 \Box Stereoselective functionalization of the 1'-position of 4'-thionucleosides was achieved using a stereoselective $S_N 2$ reaction controlled by 5-membered ring coordination.

 $\label{eq:second} \begin{array}{ll} \mbox{Keywords} & 4'\mbox{-Thionucleosides}; S_N 2\ reaction; 5\mbox{-membered ring coordination}, A3\ adenosine\ receptor\ antagonis \end{array}$

INTRODUCTION

It has been known to be difficult to discover A_3AR antagonists with a nucleoside skeleton due to the structural resemblance to a natural ligand, adenosine. Thus, nonnucleoside derivatives with a heterocyclic skeleton have been reported as potent and selective A_3AR antagonists,^[1,2] but they had several drawbacks such as dependence of species and low water solubility.^[3] Therefore, it is very interesting to discover novel A_3AR antagonists with a nucleoside skeleton to overcome the disadvantages of nonnucleoside A_3AR antagonists. To achieve this goal, the potent and pure human A_3AR agonists^[4] compounds **1a** and **1b** were first transformed to L-type nucleosides **2** since D-type nucleosides were thought to possess the intrinsic agonistic activity due to the structural resemblance with a natural ligand

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FIGURE 1 Rationale for the design of the target nucleosides.

D-adenosine. In addition, the 5'-uronamide group of **1a** and **1b**, which is essential for an A₃AR agonistic activity through a hydrogen bonding^[4] at the binding site of the A₃AR, was changed from β - to α -position to remove a hydrogen bonding with the receptor, and to induce favorable interaction for A₃AR antagonism (Figure 1).

Herein, we report the synthesis of the target nucleoside **2** using the stereoselective functionalization of 4'-thionucleosides and their binding affinities to adenosine receptors.

RESULTS AND DISCUSSION

In general, the stereoselective introduction of the functional groups at the 1'-position of 4'-oxonucleosides was to utilize the enolization of the 2'-ketouridine followed by treating with an electrophile like PhSeCl to give 1'- α -branched derivative and 1'- β -branched derivative in low stereoselectivity (1.2~2.9:1).^[5] Thus, we decided to functionalize directly the 1'-position of the 4'-thionucleosides, utilizing the acidic character of the α -proton to the sulfur atom, as shown in Scheme 1.

D-Gulonic γ -lactone (**3**) was converted to the diol **4** according to our previously reported procedure.^[4] Treatment of diol **4** with one equivalent of lead tetraacetate at 0°C produced the aldehyde, but use of excess lead tetraacetate at room temperature gave the acetate **5** (68%) as a major product. Condensation of the glycosyl donor **5** with 2,6-dichloropurine using TMSOTf as a Lewis acid catalyst gave the β -anomer **6** as a single stereoisomer in high yield, whose configuration was confirmed by ¹H NOE experiment between H-8 and 3'-H. During the condensation, the initially formed N_3 isomer was smoothly rearranged to the desired **N**₉-isomer upon heating.^[4] Compound **6** was transformed to di-*O*-THP ether **7** easily removable under very mild acidic conditions to prevent deglycosylation, which may happen during the deprotection of the isopropylidene group due to the presence of the electron-withdrawing 1'-methylamide group at the final step. Lithiation



SCHEME 1 Regents and cnditions: a) $Pb(OA)_4$, EtOAC, rt; b) silylated 2.6-dichloropurine, TMSOTf, DCE, $70^{\circ}C$; c) 2 M HCl, THF; d) 3,4-dihydro-2*H*-pryan, PPTS, CH₂Cl₂; e) LiHMDS, THF, ClCOOMe, $-78^{\circ}C$; f) R₁NH₂, THF-EtOH, rt, 2 hours; g) MeNH₂, THF, rt, 2 hours; h) p-TsOH, MeOH, CH₂CL₂.

of **7** with LiHMDS at the most acidic 1'-position followed by treatment of methyl chloroformate gave the 1'- α carbonate **8** as a single stereoisomer. Stereoselective formation of **8** might be explained with stable 5-membered ring coordination between N_3 atom and 1'-lithium, which allowed an electrophile (alkyl chloroformate) to approach only from the α -side. Selective N^6 -amination of **8** with various amines at room temperature followed by conversion of methyl ester into methyl amide afforded the corresponding N^6 substituted derivatives, whose THP groups were deprotected with *p*-TsOH in MeOH to give **9a–f**. Binding affinity of the final 4'-thionucleosides **9a–f** were measured using radioligand binding assays.^[2] All final nucleosides did not show any significant binding affinity to human A₃AR.

In summary, we have achieved stereoselective synthesis of $1'\alpha$ -substituted-4'-thionucleosides using stereoselective nucleophilic substitution with 100% retention of stereochemistry. To our best knowledge, it is the first example to functionalize 1'-position of 4'-thionucleosides in stereoselective manner.

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