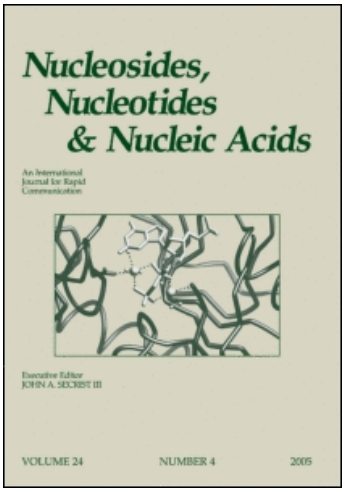


Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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

Lak Shin Jeong[a]; Prashantha Gunaga[a]; Hea Ok Kim[a]; Dilip K. Tosh[a]; Hyuk Woo Lee[a]; Seung Ah Choe[a]; Hyung Ryong Moon[b]; Zhan-Guo Gao[c]; Kenneth A. Jacobson[c]; Moon Woo Chun[d]

[a] College of Pharmacy, Ewha Womans University, Seoul, Korea [b] College of Pharmacy, Pusan National University, Busan, Korea [c] Laboratory of Bioorganic Chemistry, National Institute of Diabetes, and Digestive and Kidney Disease, NIH, Bethesda, Maryland, USA [d] College of Pharmacy, Seoul National University, Seoul, Korea

To cite this Article Jeong, Lak Shin , Gunaga, Prashantha , Kim, Hea Ok , Tosh, Dilip K. , Lee, Hyuk Woo , Choe, Seung Ah , Moon, Hyung Ryong , Gao, Zhan-Guo , Jacobson, Kenneth A. and Chun, Moon Woo(2007) 'Stereoselective Synthesis of 1'-Functionalized-4'-Thionucleosides', Nucleosides, Nucleotides and Nucleic Acids, 26: 8, 1011 — 1014

To link to this Article: DOI: 10.1080/15257770701508588

URL: http://dx.doi.org/10.1080/15257770701508588

Nucleosides, Nucleotides, and Nucleic Acids, 26:1011–1014, 2007

ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770701508588

Taylor & Francis
Taylor & Francis Group

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

Lak Shin Jeong, Prashantha Gunaga, Hea Ok Kim, Dilip K. Tosh, Hyuk Woo Lee, and Seung Ah Choe □ *College of Pharmacy, Ewha Womans University, Seoul, Korea*

Hyung Ryong Moon □ *College of Pharmacy, Pusan National University, Busan, Korea*

Zhan-Guo Gao and Kenneth A. Jacobson □ *Laboratory of Bioorganic Chemistry, National Institute of Diabetes, and Digestive and Kidney Disease, NIH, Bethesda, Maryland, USA*

Moon Woo Chun □ *College of Pharmacy, Seoul National University, Seoul, Korea*

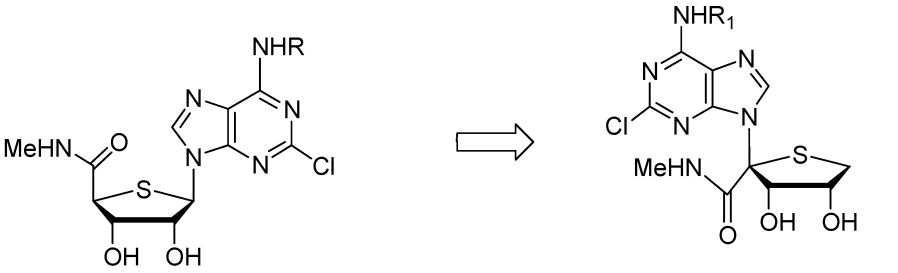
□ *Stereoselective functionalization of the 1′-position of 4′-thionucleosides was achieved using a stereoselective S_N2 reaction controlled by 5-membered ring coordination.*

Keywords 4′-Thionucleosides; S_N2 reaction; 5-membered ring coordination, A3 adenosine receptor antagonis

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

This work was supported by the grant of the Seoul R&BD Program (10541).
Address correspondence to Lak Shin Jeong, College of Pharmacy, Ewha Womans University, Seoul 120-750, Korea. E-mail: lakjeong@ewha.ac.kr



1a (R = 3-iodobenzyl, K_i = 0.38 nM for hA_3AR)
1b (R = methyl, K_i = 0.28 nM for hA_3AR)

2 (R = H, alkyl, or arylakyl)

FIGURE 1 Rationale for the design of the target nucleosides.

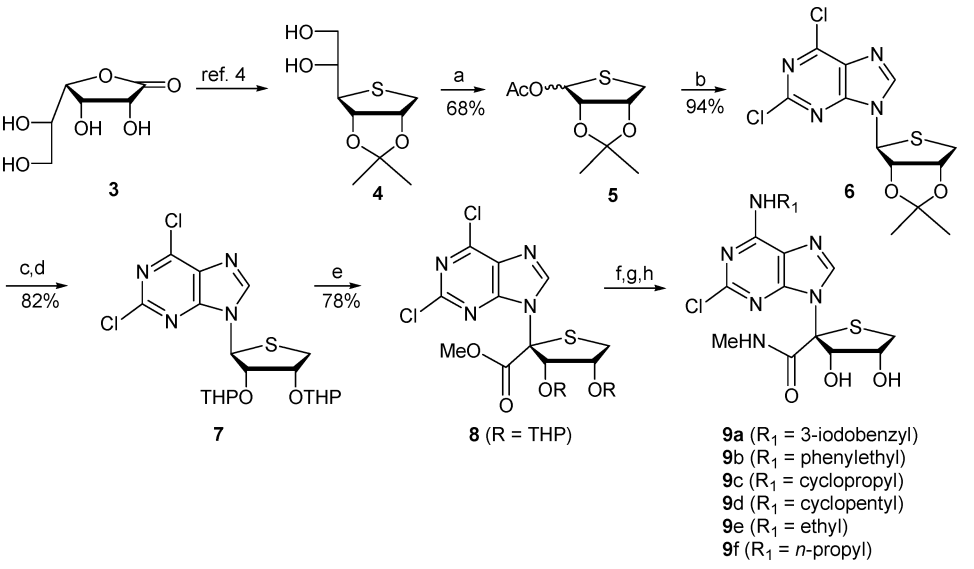
D-adenosine. In addition, the 5′-uronamide group of **1a** and **1b**, which is essential for an A_3AR agonistic activity through a hydrogen bonding[4] at the binding site of the A_3AR, was changed from β- to α-position to remove a hydrogen bonding with the receptor, and to induce favorable interaction for A_3AR 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 ^{1}H NOE experiment between H-8 and 3′-H. During the condensation, the initially formed N_3-isomer was smoothly rearranged to the desired $\mathbf{N}_9$-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°C; c) 2 M HCl, THF; d) 3,4-dihydro-2*H*-pryan, PPTS, CH_2Cl_2; e) LiHMDS, THF, ClCOOMe, −78°C ; f) R_1NH_2, THF-EtOH, rt, 2 hours; g) $MeNH_2$, THF, rt, 2 hours; h) p- TsOH, MeOH, CH_2CL_2.

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 A_3AR.

In summary, we have achieved stereoselective synthesis of 1′α-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.

REFERENCES

1. Baraldi, P.G.; Cacciari, B.; Romagnoli, R.; Merighi, S.; Varani, K.; Borea, P.A.; Spalluto, G. A_3 adenosine receptor ligands: History and perspectives. *Med. Res. Rev.* **2000**, 10, 103–128.
2. Gao, Z.-G.; Jeong, L.S.; Moon, H.R.; Kim, H.O.; Choi, W.J.; Shin, D.H.; Elhalem, E.; Comin, M.J.; Melaman, N.; Mamedova, L.; Gross, A.S.; Rodriguez, J.B.; Jacobson, K.A. Structural determinants of

efficacy at A_3 adenosine receptors: Modification of the ribose moiety. *Biochem. Pharmacol.* **2004**, 67, 893–901.
3. Gao, Z.-G.; Joshi, B.V.; Klutz, A.M.; Kim, S.-K.; Lee, H.W.; Kim, H.O.; Jeong, L.S.; Jacobson, K.A. Conversion of A_3 adenosine receptor agonists into selective antagonists by modification of the 5′-ribofuran-uronamide moiety. *Bioorg. Med. Chem. Lett.* **2006**, 16, 596–601.
4. Jeong, L.S.; Lee, H.W.; Jacobson, K.A.; Kim, H.O.; Shin, D.H.; Lee, J.A.; Gao, Z.-G.; Lu, C.; Duong, H.T.; Gunaga, P.; Lee, S.K.; Jin, D.Z.; Chun, M.W.; Moon, H.R. Structure-activity relationships of 2-Chloro-N^6-substituted-4′-thioadenosine-5′-uronamides as highly potent and selective agonists at the human A_3 adenosine receptor. *J. Med. Chem.* **2006**, 49, 273–281.
5. Kodama, T.; Shuto, S.; Nomura, M.; Matsuda, A. Synthesis of a 1′-α-phenylselenouridine derivative as a synthetic precursor for various 1′-modified nucleosides, via enolization at the 1′-position of 3′,5′-*O*-TIPDS-2′-ketouridine. *Tetrahedron Lett.* **2000**, 41, 3643–3646.