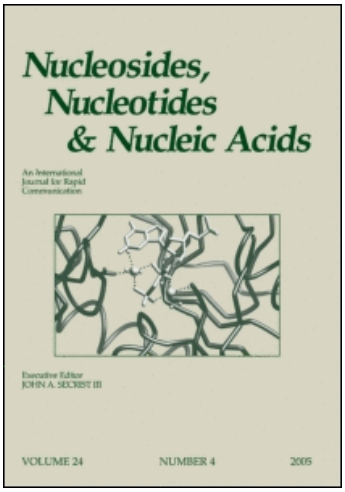


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Stereoselective Synthesis Of Homo-Apioneplanocin A As Potential Inhibitor Of S-Adenosylhomocysteine Hydrolase

Moon Woo Chun[a]; Hyuk Woo Lee[a]; Jin-Hee Kim[a]; Hea Ok Kim[b]; Kang Man Lee[b]; Shantanu Pal[b]; Hyung Ryong Moon[c]; Lak Shin Jeong[b]
[a] College of Pharmacy, Seoul National University, Seoul, Korea [b] College of Pharmacy, Ewha Womans University, Seoul, Korea [c] College of Pharmacy and Research Institute for Drug Development, Pusan National University, Busan, Korea

To cite this Article Chun, Moon Woo , Lee, Hyuk Woo , Kim, Jin-Hee , Kim, Hea Ok , Lee, Kang Man , Pal, Shantanu , Moon, Hyung Ryong and Jeong, Lak Shin(2007) 'Stereoselective Synthesis Of Homo-Apioneplanocin A As Potential Inhibitor Of S-Adenosylhomocysteine Hydrolase', Nucleosides, Nucleotides and Nucleic Acids, 26: 6, 729 — 732
To link to this Article: DOI: 10.1080/15257770701493559
URL: http://dx.doi.org/10.1080/15257770701493559

Nucleosides, Nucleotides, and Nucleic Acids, 26:729–732, 2007

ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770701493559

Taylor & Francis
Taylor & Francis Group

STEREOSELECTIVE SYNTHESIS OF HOMO-APIONEPLANOCIN A AS POTENTIAL INHIBITOR OF S-ADENOSYLHOMOCYSTEINE HYDROLASE

Moon Woo Chun, Hyuk Woo Lee, and Jin-Hee Kim □ *College of Pharmacy, Seoul National University, Seoul, Korea*

Hea Ok Kim, Kang Man Lee, and Shantanu Pal □ *College of Pharmacy, Ewha Womans University, Seoul, Korea*

Hyung Ryong Moon □ *College of Pharmacy and Research Institute for Drug Development, Pusan National University, Busan, Korea*

Lak Shin Jeong □ *College of Pharmacy, Ewha Womans University, Seoul, Korea*

□ *Homo-apioneplanocin A (**1**) as a potential inhibitor of* S*-adenosylhomocysteine hydrolase was synthesized from* D*-ribose, employing stereoselective hydroxymethylation, regioselective oxidation, and regio- and chemoselective hydroboration as key steps.*

Keywords Ring-closing metathesis; S-adenosylhomocysteine hydrolase; homo-apioneplanocin A

INTRODUCTION

Neplanocin A[1] and aristeromycin[2] (Figure 1) are representative of carbocyclic nucleosides and showed potent antitumor and antiviral activities by inhibiting *S*-adenosylhomocysteine (AdoHcy) hydrolase.[3] Inhibition of AdoHcy hydrolase induced inhibitory activity against methyltransferases, which are essential enzymes to formation of cap structure of viral mRNA. Therefore, inhibition of AdoHcy hydrolase results in antiviral activity by inhibiting the formation of viral mRNA cap structure. Neplanocin A has been known to be a potent inhibitor of AdoHcy hydrolase, but it was too cytotoxic to be developed as a clinically useful antiviral agent and was

This research was supported by a grant from the Korea Research Foundation (KRF-2005-005-J01502).

Address correspondence to Moon Woo Chun, College of Pharmacy, Seoul National University, Seoul 151–742, Korea. E-mail: mwchun@snu.ac.kr

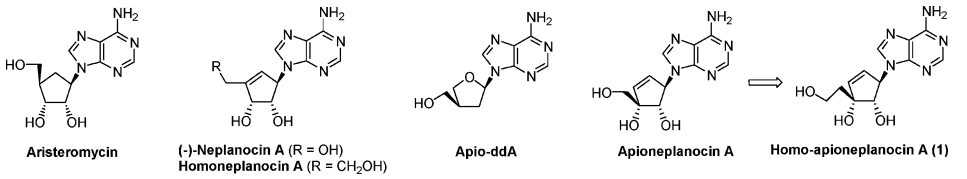


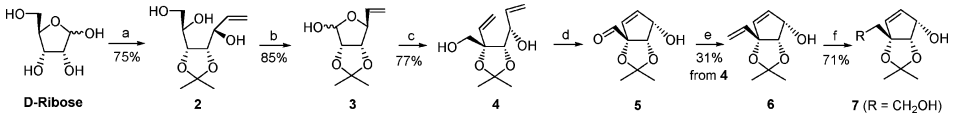
FIGURE 1 Rationale for the design of the desired nucleoside **1**.

also metabolized by adenosine deaminase (ADA) to the biologically inactive compound, the inosine analogue.[4]

Apio-ddA,[5] in which 4′-hydroxymethyl group of ddA is moved to C3′ position, was found to exhibit anti-HIV activity comparable to that of the parent nucleoside ddA and improved stability of glycosidic bond. From these findings, apio-neplanocin A[6] was designed and synthesized by our laboratory for the purpose of searching for more potent antiviral agent with benefits such as resistance to ADA and increasing stability of glycosidic bond, but it showed neither antiviral activity nor inhibitory activity against AdoHcy hydrolase. However, the fact that homo-neplanocin A,[7] another neplanocin A-modified nucleoside was reported to exhibit a significant inhibitory activity against AdoHcy hydrolase stimulated us to synthesize homo-apioneplanocin A (**1**). Here, we wish to report enantioselective synthesis of homo-apioneplanocin A (**1**) from D-ribose via regio- and chemoselective hydroboration and chemoselective oxidation as key steps.

RESULTS AND DISCUSSION

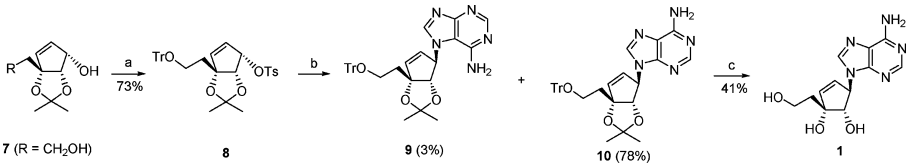
Synthesis of the key intermediate **7** for the synthesis of homo-apioneplanocin A (**1**) is shown in Scheme 1. Treatment of D-ribose with anhydrous acetone in the presence of *c*-H_2SO_4 gave 2,3-*O*-isopropylidene-D-ribose, which was reacted with vinylmagnesium bromide to give (*S*)-allylic alcohol **2** as a single stereoisomer. Oxidative diol cleavage of **2** gave lactol **3**, which was converted to diene **4** by stereoselective hydroxymethylation followed by Wittig reaction. Stereoselective hydroxymethylation was explained by an aldol-retroaldol reaction mechanism.[6] Chemoselective oxidation of **4** with TEMPO followed by ring-closing metathesis (RCM) with second



SCHEME 1 Reagents and conditions: a) i. acetone, c-H_2SO_4; ii. CH_2 =CHMgBr, THF; b) $NaIO_4$, CH_2Cl_2, H_2O; c) i. CH_2O, K_2CO_3, MeOH; ii. CH_3PPh_3Br, KO*t*-Bu, THF; d) i. TEMPO, TBACl, NCS, aqueous $NaHCO_3$ and K_2CO_3 (pH = 8.6). CH_2Cl_2; ii. Second generation Grubbs catalyst, CH_2Cl_2; e) CH_3Ph_3PBr, KO*t*-Bu, THF; f) i. Sia_2BH, THF; ii. $NaBO_3$, H_2O.

generation Grubbs catalyst afforded cyclopentenol **5**. However, reverse reaction sequence (RCM followed by chemoselective oxidation) failed to give the desired product **5**. Wittig reaction of **5** with methyltriphenylphosphonium bromide in the presence of potassium *tert*-butoxide smoothly generated olefin **6**, which was subjected to hydroboration and oxidation. Several hydroboration reagents (9-BBN in THF or catecholborane and Wilkinson catalyst, etc.) were attempted to achieve chemo- and regioselective hydroboration, but only Sia_2BH afforded the desired product **7** after oxidation with sodium perborate.

Protection of the primary hydroxyl group of **7** as trityl ether followed by conversion of the remaining secondary hydroxyl group into the tosylate gave **8**, which could be an appropriate glycosyl donor for the synthesis of **1**, as shown in Scheme 2. Condensation of **8** with adenine base in the presence of potassium carbonate and 18-Crown-6 in DMF at 80°C gave two separable regioisomers, *N*-7 isomer **9** (3%) and *N*-9 isomer **10** (78%). Anomeric assignments of regioisomers **9** and **10** were easily determined by comparison of their UV data with UV literature data.[8] Removal of trityl and isopropylidene groups of **10** with 1% aqueous HCl in methanol affrded the final homo-apioneplanocin A (**1**).



SCHEME 2 Reagents and conditions: a) i. TrCl, pyridine, DMAP; ii. TsCl, DMAP, CH_2Cl_2; b) adenine, K_2CO_3, 18-Crown-6, DMF, 80°C; c) 1% HCl, MeOH.

Unfortunately, compound **1** did not show significant inhibition of AdoHcy hydrolase, maybe due to the inability of hydroxyethyl group to induce the favorable binding to AdoHcy hydrolase and/or the presence of tertiary hydroxyl group, which cannot be oxidized by cofactor-bound NAD^+.

In conclusion, enantioselective synthesis of homo-apioneplanocin A (**1**) as potential AdoHcy hydrolase inhibitor was accomplished from D-ribose, using stereoselective hydroxymethylation, regioselective oxidation, and regio- and chemoselective hydroboration as key steps. Although the final compound **1** did not exhibit significant inhibitory activity against AdoHcy hydrolase, all chemistries employed here will contribute to the discovery of new carbocyclic nucleosides.

REFERENCES

1. Yaginuma, S.; Muto, N.; Tsujino, M.; Sudate, Y.; Hayashi, M.; Otani, M. Studies on neplanocin A, new antitumor antibiotic. I. Producing organism, isolation and characterization. *J. Antibiot.* **1981**, 34, 359–366.

2. Kishi, T.; Muroi, M.; Kusaka, T.; Nishikawa, M.; Kamiya, K.; Mizuno, K. *Chem. Pharm. Bull.* **1972,** 20, 940.
3. Borchardt, R.T.; Keller, B.T.; Patel-Thombre, U. Neplanocin A. A potent Inhibitor of S-adenosylhomocysteine hydrolase and of vaccinia virus multiplication in mouse L929 cells. *J. Biol. Chem.* **1984**, 259, 4353–4358.
4. Shuto, S.; Obara, T.; Toriya, M.; Hosoya, M.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. New Neplanocin Analogs. 1. Synthesis of 6′-modified neplanocin A derivatives as broad-spectrum antiviral agents. *J. Med. Chem.* **1992**, 35, 324–331.
5. Terao, Y.; Akamatsu, M.; Achiwa, K. Synthesis of chiral 3-substituted gamma-lactones and 9-furanosyladenine from (R)-2-(2,2-diethoxyethyl)-1,3-propanediol monoacetate prepared by lipase-catalyzed reaction. *Chem. Pharm. Bull.* **1991**, 39, 823–825.
6. Moon, H.R.; Kim, H.O.; Lee, K.M.; Chun, M.W.; Kim, J.H.; Jeong, L.S. Stereoselective synthesis of a novel apio analogue of neplanocin A as potential *S*-adenosylhomocysteine hydrolase iinhibitor. *Org. Lett.* **2002**, 4, 3501–3503.
7. Shuto, S.; Obara, T.; Saito, Y.; Andrei, G.; Snoeck, R.; De Clercq, E.; Matsuda, A. New neplanocin analogues. 6. Synthesis and potent antiviral acitivity of 6′-homoneplanocin A. *J. Med. Chem.* **1996**, 39, 2392–2399.
8. Naka, T.; Minakawa, N.; Abe, H.; Kaga, D.; Matsuda, A. The stereoselective synthesis of 4′-β-thioribonucleosides via the Pummerer reaction. *J. Am. Chem. Soc.* **2000**, 122, 7233–7243.