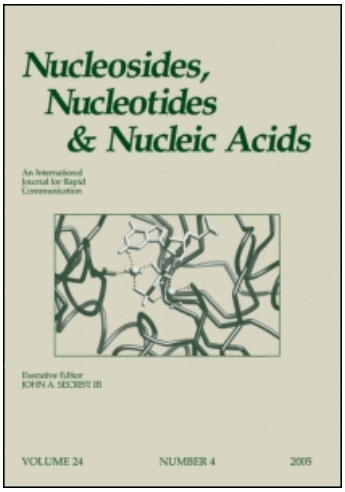


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Asymmetric Synthesis of Novel Apio Carbocyclic Nucleoside Analogues as Potential Antiviral and Antitumor Agent

Lak Shin Jeong[a]; Jeong A. Lee[a]; Hyung Ryong Moon[b]; Hea Ok Kim[a]; Kang Man Lee[a]; Hyun Joo Lee[a]; Moon Woo Chun[c]
[a] College of Pharmacy, Ewha Womans University, Seoul, Korea [b] College of Pharmacy and Research Institute for Drug Development, Pusan National University, Busan, Korea [c] College of Pharmacy, Seoul National University, Seoul, Korea

To cite this Article Jeong, Lak Shin , Lee, Jeong A. , Moon, Hyung Ryong , Kim, Hea Ok , Lee, Kang Man , Lee, Hyun Joo and Chun, Moon Woo(2007) 'Asymmetric Synthesis of Novel Apio Carbocyclic Nucleoside Analogues as Potential Antiviral and Antitumor Agent', Nucleosides, Nucleotides and Nucleic Acids, 26: 6, 721 — 724
To link to this Article: DOI: 10.1080/15257770701493237
URL: http://dx.doi.org/10.1080/15257770701493237

Nucleosides, Nucleotides, and Nucleic Acids, 26:721–724, 2007

ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770701493237

Taylor & Francis
Taylor & Francis Group

ASYMMETRIC SYNTHESIS OF NOVEL APIO CARBOCYCLIC NUCLEOSIDE ANALOGUES AS POTENTIAL ANTIVIRAL AND ANTITUMOR AGENT

Lak Shin Jeong and Jeong A. Lee □ *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*

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

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

□ *Novel apio carbocyclic nucleosides **18–21** were asymmetrically synthesized as potential antiviral and antitumor agent, starting from D-ribose employing aldol reaction, RCM reaction and Mitsunobu reaction as key reactions.*

Keywords Apio carbocyclic nucleoside; stereoselective hydroxymethylation; ring-closing metathesis; Mitsunobu condensation; asymmetric synthesis

INTRODUCTION

Neplanocin A (**1**)[1] and aristeromycin are the representatives of the carbocyclic nucleosides, which possess inherent stability of the glycosidic bond, and exhibit potent biological activity such as antiviral and antitumor activities. Their biological activity is known to result from inhibition of *S*-adenosylhomocysteine (AdoHcy) hydrolase.[2] However, compound **1** and aristeromycin could not be further developed as clinically useful drugs due to their high cytotoxicity. Fluoro-neplanocin A (**2**),[3] developed by our laboratory, also has shown significant antiviral activity with inhibition of AdoHcy hydrolase, but exhibited high cytotoxicity. These results seem to imply that *ribo*-cyclopentenyl structure is essential to potent biological

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

Address correspondence to Lak Shin Jeong, Department of Pharmacy, Ewha Womans University, Seoul 120-750, Korea. E-mail: lakjeong@ewha.ac.kr

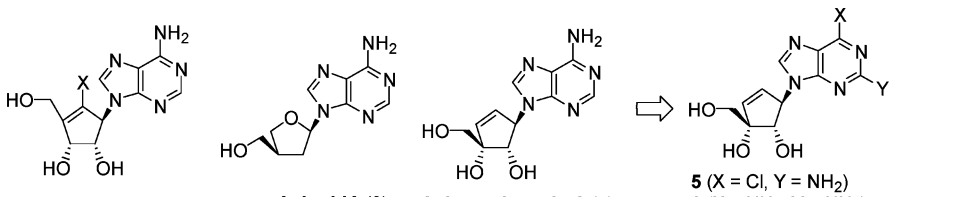


FIGURE 1 Rationale for the design of apio carbocylic purine nucleosides **5–8**.

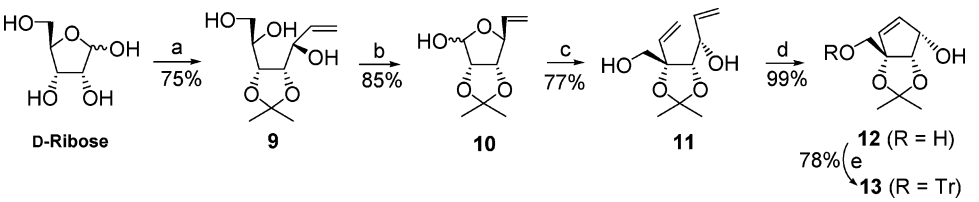
activity. On the other hand, a number of apio nucleosides,[4,5] in which 4′-hydroxymethyl group are shifted to C3′ position have been designed and synthesized in order to search for novel antiviral agent. Apio-ddA (**3**), mimicking the parent compound ddA, exhibited comparable anti-HIV activity to ddA. On the basis of these findings, apio-neplanocin A (**4**) was synthesized by our laboratory, but unlike compounds **1** and **2**, it did not show inhibitory activity against AdoHcy hydrolase (Figure 1).[6]

Here, we report the synthesis of purine base modified analogues **5–8** of compound **4** to study structure-activity relationship (SAR) of apiocarbocyclic nucleosides.

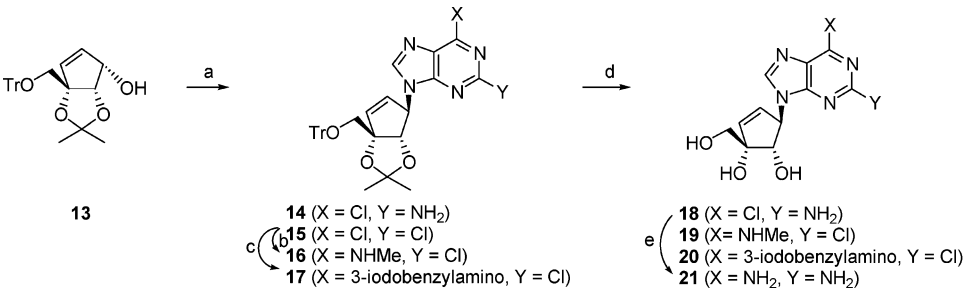
RESULT AND DISCUSSION

It was envisioned that cyclopentenyl alcohol **13** could be an appropriate glycosyl donor for the condensation with a variety of nucleobases. Synthesis of glycosyl donor, cyclopentenyl alcohol **13** is described in Scheme 1.

Triol **9** was easily synthesized from D-ribose using subsequent two reaction steps. Treatment of D-ribose with anhydrous acetone under acidic conditions afforded the corresponding 2,3-acetonide in 93% yield, which was subjected to Grigard reaction with excess vinylmagnesium bromide. Oxidative C-C cleavage of vicinal diol **9** through two-phase reaction gave lactol **10**. Stereoselective introduction of hydroxymethyl group at C3′ position was accomplished by treatment with formaldehyde and K_2CO_3 in methanol.[6] After hydroxymethylation, Wittig reaction with methyltriphenylphosphonium



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) second generation Grubbs catalyst, CH_2Cl_2; e) TrCl, DMAP, pyridine.



SCHEME 2 Reagents and conditions: a) 2-amino-6-chloropurine or 2,6-dichloropurine, DEAD, Ph_3P, THF, 78% for **14** and **15**; b) 40% CH_3NH_2, EtOH, 98%; c) 3-iodobenzylamine hydrochloride, EtOH, Et_3N, 98%; d) 3 M HCl, THF, 37% from **13** for **18**, 19% to **19**, 21%, 21% to **20**; e) NH_3, MeOH, 36%.

bromide in the presence of potassium carbonate generated diene **11** in 77% from **10**. Ring-closing metathesis (RCM)[7,8] of diene **11** with second generation Grubbs catalyst formed cyclopentene ring, giving **12** in a quantitative yield. Regioselective protection at the primary hydroxyl group of **12** was achieved by bulky trityl chloride in 78% yield, affording cyclopentenyl alcohol **13**, which played a role as glycosyl donor for the condensation with various nucleobases.

Synthesis of purine nucleoside derivatives **18–21** from cyclopentenyl alcohol **13** is depicted in Scheme 2.

Condensation of **13** with 2-amino-6-chloropurine and 2,6-dichloropurine under general Mitsunobu conditions afforded **14** and **15** (78%), respectively. 2,6-Dichloropurine nucleoside **15** was converted to 6-methylamino- and 6-iodobenzylaminopurine nucleosides **16** (98%) and **17** (98%), using 40% methylamine and 3-iodobenzylamine hydrochloride and Et_3N, respectively. Treatment of **14**, **16**, and **17** with 3 M HCl to remove trityl and isopropylidene group generated **18**, **19,** and **20**. However, all the deprotecting steps gave less than 40%, maybe due to existence of *tert*-allylic ether. Finally, diaminopurine nucleoside **21** was obtained from **19** by treating with methanolic ammonia.

Biological assay of all the final compounds **18–21** are in progress to study SAR of apio carbocyclic nucleosides. In conclusion, synthesis of apio carbocyclic 2,6-disubstituted purine nucleosides **18–21** was efficiently accomplished as potential antiviral and antitumor agent starting from D-ribose using RCM reaction, stereoselective hydroxymethylation and Mitsunobu reaction. All the final compounds **18–21** will be used for the SAR study of apio 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. Wolfe, M.S.; Borchardt, R.T. *S*-adenosyl-L-homocysteine hydrolase as a target for antiviral chemotherapy. *J. Med. Chem.* **1991**, 34, 1521–1530.
3. Jeong, L.S.; Yoo, S.J.; Lee, K.M.; Koo, M.J.; Choi, W.J.; Kim, H.O.; Moon, H.R.; Lee, M.Y.; Park, J.G.; Lee, S.K.; Chun, M.W. Design, synthesis, and biological evaluation of fluoroneplanocin a as the novel mechanism-based inhibitor of *S*-adenosylhomocysteine hydrolase. *J. Med. Chem.* **2003**, 46, 201–203.
4. (a) nair, V.; Jahnke, T.S. Antiviral activities of isomeric dideoxynucleosides of D- and L-related stereochemistry. *Antimicrob. Agents Chemother.* **1995**, 39, 1017–1029. (b) Sells, T.B.; Nair, V. Synthetic approaches to novel cis and trans dideoxynucleosides of the apiose family. *Tetrahedron* **1994**, 50, 117–138.
5. Jeong, L.S.; Kim, H.O.; Moon, H.R.; Hong, J.H.; Yoo, S.J.; Choi, W.J.; Chun, M.W.; Lee, C.-K. Synthesis and structure-activity relationships of novel apio and thioapio dideoxydidehydronucleosides as anti-HCMV agents. *J. Med. Chem.* **2001**, 44, 806–813.
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 inhibitor. *Organic Lett.* **2002**, 4, 3501–3503.
7. Grubbs, R.H.; Chang, S. Recent advances in olefin metathesis and its application in organic synthesis. *Tetrahedron* **1998**, 54, 4413–4450.
8. Grubbs, R.H. Olefin metathesis. *Tetrahedron* **2004**, 60, 7117–7140.