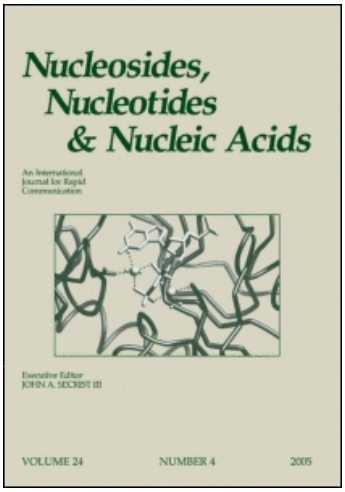


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis of Halogenated 9-(Dihydroxycyclopent-4'-enyl) Adenines and Their Inhibitory Activities Against *S*-Adenosylhomocysteine Hydrolase

Lak Shin Jeong[ab]; Jae Gyu Park[a]; Won Jun Choi[a]; Hyung Ryong Moon[a]; Kang Man Lee[a]; Hea Ok Kim[c]; Hee-Doo Kim[d]; Moon Woo Chun[e]; Hea-Young Park[a]; Kilhyoun Kim[a]; Yhun Y. Sheen[a]
[a] College of Pharmacy, Ewha Womans University, Seoul, Korea [b] College of Pharmacy, Ewha Womans University, Seoul, Daehyun-dong, South Korea [c] Division of Chemistry and Molecular Engineering, [d] College of Pharmacy, Sookmyung Women's University, Seoul, Korea [e] College of Pharmacy, Seoul National University, Seoul, Korea

Online publication date: 09 August 2003

To cite this Article Jeong, Lak Shin , Park, Jae Gyu , Choi, Won Jun , Moon, Hyung Ryong , Lee, Kang Man , Kim, Hea Ok , Kim, Hee-Doo , Chun, Moon Woo , Park, Hea-Young , Kim, Kilhyoun and Sheen, Yhun Y.(2003) 'Synthesis of Halogenated 9-(Dihydroxycyclopent-4'-enyl) Adenines and Their Inhibitory Activities Against *S*-Adenosylhomocysteine Hydrolase', Nucleosides, Nucleotides and Nucleic Acids, 22: 5, 919 — 921
To link to this Article: DOI: 10.1081/NCN-120022686
URL: http://dx.doi.org/10.1081/NCN-120022686

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS
Vol. 22, Nos. 5–8, pp. 919–921, 2003

Synthesis of Halogenated 9-(Dihydroxycyclopent-4′-enyl) Adenines and Their Inhibitory Activities Against *S*-Adenosylhomocysteine Hydrolase

Lak Shin Jeong,[1,*] Jae Gyu Park,[1] Won Jun Choi,[1] Hyung Ryong Moon,[1] Kang Man Lee,[1] Hea Ok Kim,[2] Hee-Doo Kim,[4] Moon Woo Chun,[3] Hea-Young Park,[1] Kilhyoun Kim,[1] and Yhun Y. Sheen[1]

[1]College of Pharmacy, Ewha Womans University, Seoul, Korea
[2]Division of Chemistry and Molecular Engineering and
[3]College of Pharmacy, Seoul National University, Seoul, Korea
[4]College of Pharmacy, Sookmyung Women's University, Seoul, Korea

ABSTRACT

Novel halovinyl analogues of neplanocin A without 4′-hydroxymethyl group were easily synthesized starting from D-ribose via cyclopentenone **5** as a key intermediate and their inhibitory activity against SAH hydrolase was assayed.

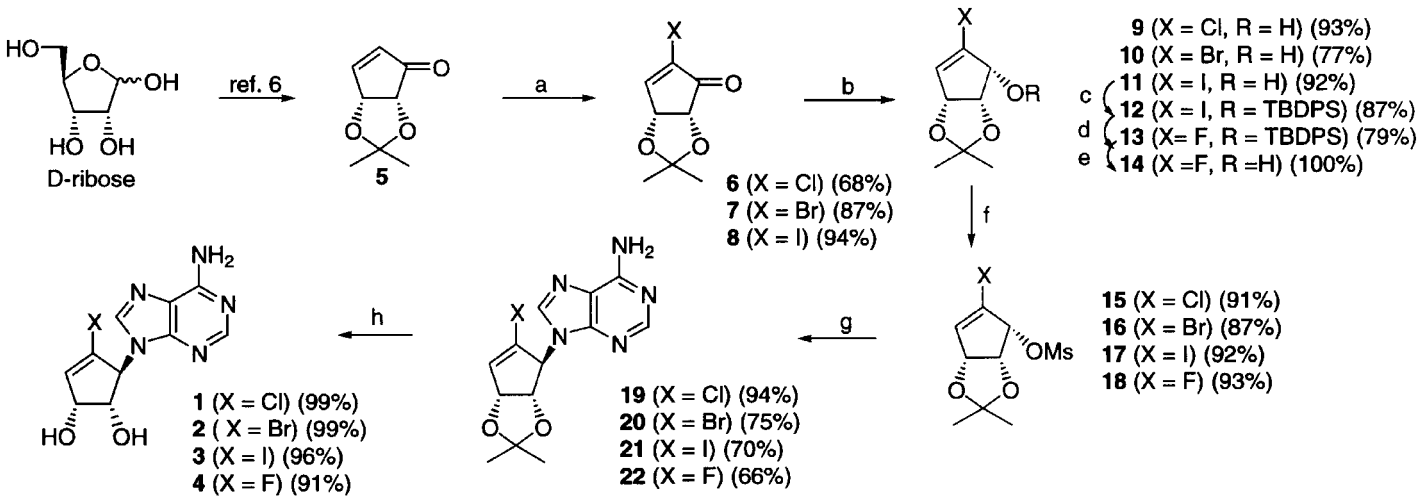
Key Words: S-Adenosylhomocysteine hydrolase; Halogenated 9-(dihydroxycyclopent-4′-enyl) adenines.

Neplanocin A[1] and aristeromycin,[2] both natural products, are potent inhibitors of *S*-adenosylhomocysteine (SAH) hydrolase, which inhibit SAM (*S*-adenosylmethionine) methyltransferase[3] and exhibit interesting antiviral activities.[4] The analogue of neplanocin A, being devoid of the 4′-hydroxymethyl group, has also

*Correspondence: Lak Shin Jeong, College of Pharmacy, Ewha Womans University, 11-1 Seodaemun-gu, Daehyun-dong, 120-750 Seoul, South Korea; Fax: +82 23 277 2851; E-mail: lakjeong@ewha.ac.kr.

DOI: 10.1081/NCN-120022686
1525-7770 (Print); 1532-2335 (Online)
www.dekker.com

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016



Scheme 1. Reagents: a) Cl_2/pyridine, Br_2/Et_3N, or I_2/pyridine; b) $NaBH_4$, $CeCl_3$; c) TBDPSCl; d) *n*-BuLi, *N*-fluorobenzenesulfonimide; e) *n*-Bu_4NF; f) MsCl; g) adenine, 18-crown-8, K_2CO_3; h) 10–30% aqueous CF_3CO_2H.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

been discovered as a potent SAH hydrolase inhibitor.[5] If the 3′-hydroxyl group of the halovinyl nucleosides **1–4** would be oxidized by NAD^+ like in neplanocin A, the oxidized products, keto derivatives, might be able to act as good Michael acceptors, resulting in formation of a covalent bond between the inhibitors and SAH hydrolase via elimination of halogen after Michael addition reaction. Irreversible inhibition of SAH hydrolase has been expected to exhibit potent antiviral activities. Based on these findings and hypothesis, we report the syntheses of halovinyl nucleosides **1–4** and their inhibitory activity against SAH hydrolase.

Cyclopentenone **5** was efficiently synthesized from D-ribose according to the method developed in our laboratory. As shown in Sch. 1, introduction of halogens at vinyl position of **5** was accomplished by treatment with Cl_2/pyridine, Br_2/triethyl amine, or I_2/pyridine in 68–94% yield. Treatment of halovinyl compounds **6–8** with sodium borohydride in the presence of $CeCl_3$ afforded stereoselectively and regioselectively the reduced congeners **9–11**, respectively. Protection of **11** as a TBDPS ether followed by fluorination via metal-halogen exchange using *n*-BuLi and *N*-fluorobenzenesulfonimide and desilylation afforded fluoro cyclopentenol **14** in 69% yield. Mesylation of compounds **9–11** and **14** followed by coupling of the resulting mesylates with adenine in the presence of NaH or K_2CO_3 and 18-crown-6 afforded the protected nucleosides **19–22**, respectively. The final products **1–4** were obtained by treatment with 10–30% aqueous CF_3CO_2H.

All synthesized compounds were assayed for SAH hydrolase inhibition. Among them, fluoro compound **4** exhibited the most potent SAH hydrolase inhibition ($IC_{50} = 7.67\,\mu M$). The larger the halo substituent, the poorer proved the SAH hydrolase inhibition.

ACKNOWLEDGMENT

This work was supported by Korea Research Foundation (KRF-2001-005-F00022).

REFERENCES

1. Hayashi, M.; Yaginuma, S.; Yoshioka, H.; Nakatsu, K. J. Antibiot. (Tokyo) **1981,** *34*, 675.
2. Kishi, T.; Muroi, M.; Kusaka, T.; Nishikawa, M.; Kamiya, K.; Mizuno, K. Chem. Pharm. Bull. **1972**, *20*, 940.
3. a) Borchardt, R.T.; Keller, B.T.; Patel-Thrombre, U. J. Biol. Chem. **1984**, *259*, 4353; b) Cools, M.; De Clerq, E. Biochem. Pharmacol. **1989,** *38*, 1061.
4. De Clerq, E. Biochem. Pharmacol. **1987**, *36*, 2567.
5. Patil, S.D.; Schneller, S.W.; Hosoya, M.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clerq, E. J. Med. Chem. **1992**, *35*, 3372.
6. Moon, H.R.; Choi, W.J.; Kim, H.O.; Jeong, L.S. Tetrahedron: Asymmetry **2002**, *13*, 1189.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016