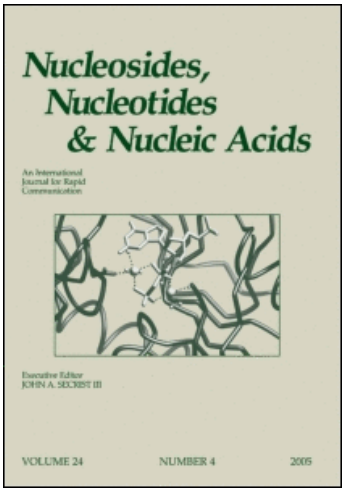

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Hiroki Kumamoto[a]; Kazuki Deguchi[a]; Nonoko Takahashi[a]; Hiromichi Tanaka[a]; Yukio Kitade[b]
[a] School of Pharmaceutical Sciences, Showa University, Tokyo, Japan [b] Department of Biomolecular Sciences, Faculty of Engineering, Gifu University, Gifu, Japan

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SYNTHESIS OF NOVEL 4′-MODIFIED NEPLANOCIN A ANALOGUES AND THEIR INHIBITORY ACTIVITY AGAINST *S*-ADENOSYL-L-I-HOMOCYSTEINE HYDROLASE

Hiroki Kumamoto, Kazuki Deguchi, Nonoko Takahashi, and Hiromichi Tanaka □ *School of Pharmaceutical Sciences, Showa University, Tokyo, Japan*

Yukio Kitade □ *Department of Biomolecular Sciences, Faculty of Engineering, Gifu University, Gifu, Japan*

□ *A new approach was developed for the synthesis of 4′-modified neplanocin A analogues, as potential inhibitors against S-adenosyl-L-homocysteine hydrolase. The vinylstannane* **13***, a key intermediate in the present approach, was prepared by radical-mediated sulfur-extrusive stannylation.*

Keywords Neplanocin A; sulfur-extrusive stannylation; SAHase

INTRODUCTION

The cellular enzyme *S*-adenosyl-L-homocysteine hydrolase (SAH hydrolase) effects hydrolytic cleavage of *S*-adenosyl-L-homocysteine (AdoHcy) to give adenosine and L-homocysteine. Inhibition of SAH hydrolase is an attractive strategy for the development of broad spectrum antiviral and anticancer agents.[1,2] Neplanocin A (**1**)[3] is one of the potent inhibitors of this enzyme. In order to reduce its cytotoxicity, a large number of modified neplanocin A analogues have been synthesized, especially those modified at the 4′-position of the carbocyclic unit.[4–6] In this study, we investigated the synthesis of novel 4′-modified neplanocin A analogues **2** using organostannane chemistry.

RESULTS AND DISCUSSION

To introduce several halogen or carbon functionalities at the 4'-position, we planned to employ the vinylstannane **9** (Table 1) as a key intermediate,

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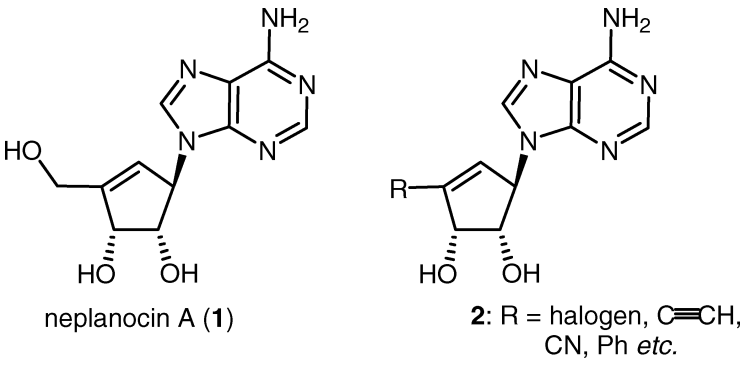
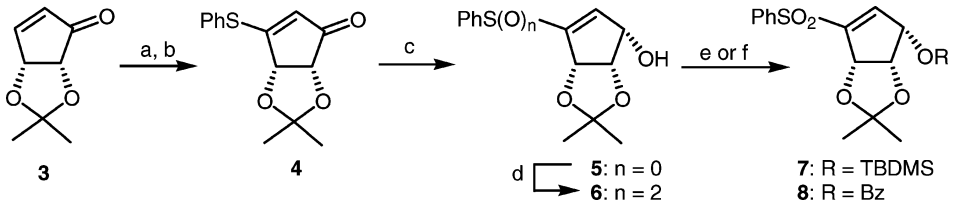
Address correspondence to Hiroki Kumamoto, School of Pharmaceutical Scienses, Showa University, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8555, Japan. E-mail: kumamoto@pharm.showa-u.ac.jp



which would be prepared from the vinyl sulfide **5** or the vinyl sulfones **6-8** via radical-mediated sulfur-extrusive stannylation.[7–8] Compounds **5–8** were prepared from the cyclopentenone **4** derived from **3**[9,10] by 1,4-addition of PhSH followed by NCS oxidation (Scheme 1). After 1,2-reduction of **4**, the vinyl sulfide **5** was obtained in quantitative yield. Oxidation of **5** with *m*-CPBA gave the vinyl sulfone **6**. Compounds **7** and **8** were also prepared from **6** by a conventional silylation or benzoylation procedure.

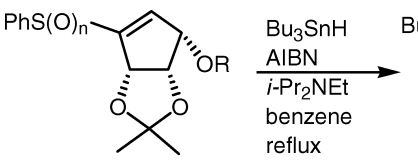
Sulfur-extrusive stannylation of **5–8** were then examined (Table 1). When reacted with Bu_3SnH in the presence of a catalytic amount of AIBN in refluxing benzene, **8** gave the best result forming the vinylstannane **11** in 94% yield (entry 4). Compound **9** was obtained in 90% yield after debenzoylation (NaOMe in MeOH) of **11**.

Introduction of 6-chloropurine to **9** was carried out under the Mitsunobu conditions.[11] The resulting **12** was converted to the adenine derivative **13** by ammonolysis. Halogenation of **13** gave the 4′-halogenated products **14**, **15**, and **16**. The Pd-catalyzed Stille reaction of **13** proceeded to yield the 4′-phenyl derivative **17** (51%). The Stille reaction between **14** and $RSnBu_3$ (R=CN, C≡CH or C≡CMe) gave the cyanide **18** (73%), and the ethynyl derivatives **19** (83%) and **20** (100%). The desired 4′-modified neplanocin A analogues (**2a–g**) were obtained in high yields simply by treatment of **14–20** with 50% HCO_2H.



SCHEME 1 Reagents and Conditions: a) PhSH, Et_3N, CH_2 (81%), b) NCS, CH_2Cl_2 (94%), c) $NaBH_4$, $CeCl_3$-$7H_2O$, MeOH (100%), d) *m*-CPBA, CH_2Cl_2 (100%), e) (for **7**), TBDMSCL, imidazole, MeCN (57%), f) (for **8**), BzCl, DMAP, *i*-Pr_2NEt, MeCN (93%)

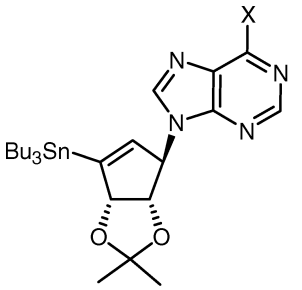
TABLE 1 Radical-mediated sulfur-extrusive stannylation of **5–8**



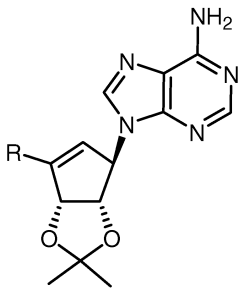
5-8

9: R = H
10: R = TBDMS
11: R = Bz

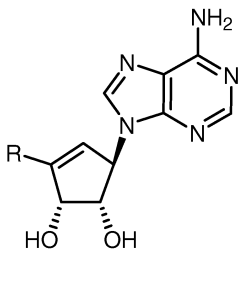
Entry	Substrate	Product	Yield (%)
1	5	9	2
2	6	9	52
3	7	10	79
4	8	11	94



12: X = Cl
13: X = NH_2



14: R = I **17**: R = Ph
15: R = Br **18**: R = CN
16: R = Cl **19**: R = C≡CH
20: R = C≡CMe



2a: R = I **2d**: R = Ph
2b: R = Br **2e**: R = CN
2c: R = Cl **2f** : R = C≡CH
2g: R = C≡CMe

Inhibitory activity of compounds **2** against SAH hydrolase was briefly evaluated. Compounds **2d** and **2g** showed weak inhibition against SAH hydrolase of malaria (64% inhibition by 100 μM of **2d** and 81% inhibition by 10 μM of **2g**). Further conversion of **13** to other analogues and evaluation of their biological activities are under investigation.

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