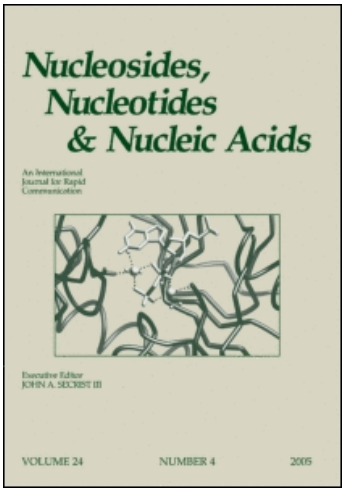

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ASYMMETRIC SYNTHESIS OF APIO FLUORONEPLANOCIN A ANALOGS AS POTENTIAL AdoHcy HYDROLASE INHIBITOR

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□ *Apio fluoroneplanocin A (apio F-NPA,* **3***) and its uracil analogue* **4** *have been designed and asymmetrically synthesized starting from* D*-ribose. Introduction of fluoro group into vinylic position of* **5** *was accomplished successfully over 5 steps employing key reactions such as iodination according to an addition-elimination reaction mechanism, stereo- and regioselective reduction of* α,β*-unsaturated ketone, and electrophilic fluorination. This methodology can be adapted to the synthesis of fluoro compounds extensively.*

Keywords Apio fluoroneplanocin A; D-ribose; fluoro compounds; electrophilic fluorination

INTRODUCTION

Carbocyclic nucleosides are biologically interesting compounds that exhibit antitumor or antiviral activities.[1,2] Due to the lack of a true glycosidic bond, carbocyclic nucleosides are resistant to the chemical and enzymatic conditions.[3] The higher lipophilicity of carbocyclic nucleosides than conventional nucleosides is potentially beneficial for oral availability and cell membrane penetration. (-)-Neplanocin A (NPA, **1**)[4] and aristeromycin are representatives of naturally occurring carbocyclic nucleosides which exhibit interesting biological activity (Figure 1). NPA (**1**), originally isolated from the culture of the soil fungus *Ampullariella regularis*, is one of the most potent inhibitors of *S*-adenosylhomocysteine (AdoHcy) hydrolase,[5] which catalyzes the hydrolysis of AdoHcy into homocysteine and adenosine. Methyltransferases are known to play a crucial role in the viral life

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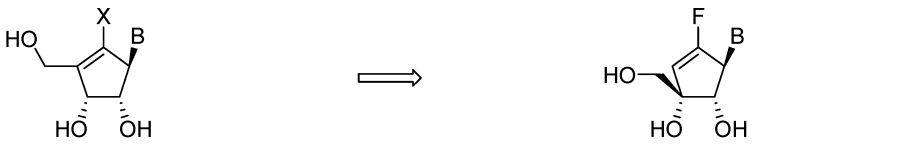


Neplanocin A (**1**, X = H, B = adenine)
F-Neplanocin A (**2**, X = F, B = adenine)

3 (Apio F-Neplanocin A, B = adenine)
4 (B = uracil)

FIGURE 1 The rationale for the design of the desired apio fluoroneplanocin A analogs.

cycle involved with viral m-RNA metabolism. Inhibition of AdoHcy hydrolase causes the accumulation of AdoHcy in cells, which in turn inhibits methyltransferases in a negative feedback manner. Therefore, antiviral activity of NPA (**1**) and aristeromycin results from the inhibition of AdoHcy hydrolase. Although NPA (**1**) and aristeromycin act as potent inhibitors of AdoHcy hydrolase, their high cytotoxicity hindered them from being further developed as clinically useful antiviral agents.

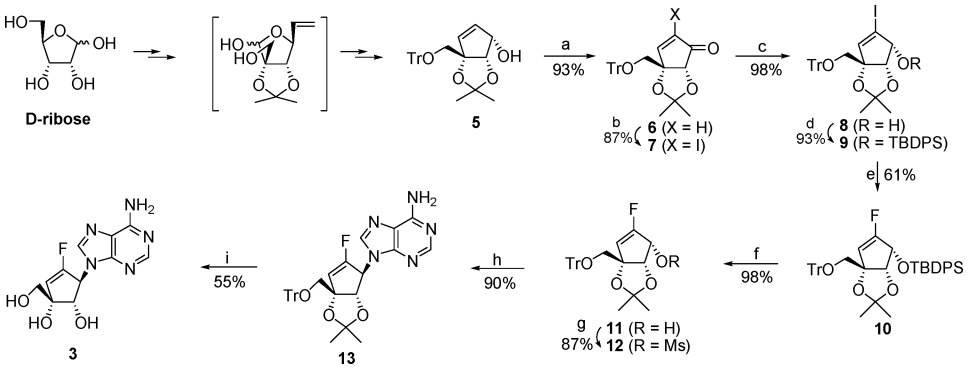
Fluoroneplanocin A (**2**, F-NPA),[6] which was developed in our laboratory exhibited more potent inhibition of AdoHcy hydrolase than NPA (**1**) and a significant antiviral activity, but also exhibited high cytotoxicity to the cells. Cytotoxicity of NPA (**1**) and F-NPA (**2**) seems to be derived from the inhibition of cellular polymerases by their 5′-triphosphate metabolites. On the other hand, it has been known that the inhibitory ability of AdoHcy hydrolase is derived from nucleosides by themselves such as NPA (**1**) and F-NPA (**2**), not their triphosphates. Therefore, nucleosides, which show potent inhibitory ability against AdoHcy hydrolase but which cannot be phosphorylated by kinases have been considered as a promising target for the development of new antiviral agents.

Apio nucleosides have a unique sugar moiety in that the 4′-hydroxymethyl group of the sugar is shifted to the C′3-position. It might seldom occur for apio nucleosides to be phosphorylated by cellular kinases due to migration of 4′-hydroxymethyl group, indicating that apio nucleosides are one of the most promising candidates for antiviral agents with no cytotoxicity.

On the basis of these findings, apio fluoroneplanocin A (apio F-NPA, **3**) and its uracil analog **4** were designed, and asymmetrically synthesized as a potential AdoHcy hydrolase inhibitor.

CHEMISTRY

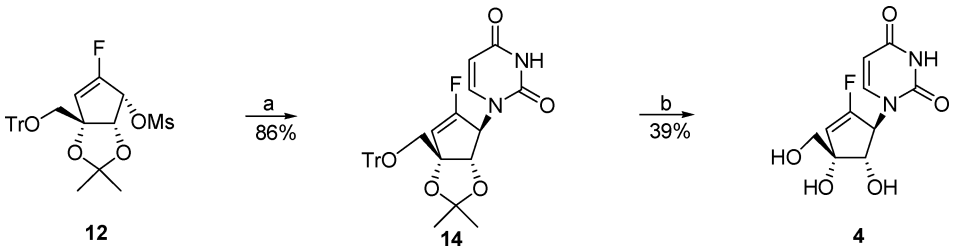
It was envisioned that apio carbocyclic template **5**, recently developed in our laboratory[7] could be an appropriate glycosyl donor for the synthesis of apio F-NPA (**3**). Conversion of **5** to apio F-NPA (**3**) is illustrated in Scheme 1. Cyclopentenol **5** was oxidized to α,β-unsaturated ketone **6** by treating with catalytic amount of TPAP (tetrapropylammonium perruthenate)[8] in the



SCHEME 1 Reagents and conditions: (a) TPAP, NMO, molecular sieve, CH_2Cl_2, rt, 1 hour; (b) I_2, pyridine, CCl_4, rt, 6 hours; (c) $NaBH_4$, $CeCl_3$, MeOH, CH_2Cl_2, −40°C, 40 minutes; (d) TBDPSCl, imidazole, DMF, 45°C, overmight; (e) *N*-fluorobenzenesulfonimide, *n*-BuLi, THF, −78°C, 30 minutes; (f) TBAF, THF, rt, 3 hours; (g) MsCl, Et_3N, CH_2Cl_2, 0°C, 20 minutes; (h) adenine, K_2CO_3, 18-Crown-6, DMF; (i) HCO_2H:H_2O (3:1), rt, 7 days.

presence of molecular sieve and 1.5 eq. of NMO (4-methylmorpholine *N*-oxide) in anhydrous methylene chloride. Introduction of iodo group into α position of ketone was successfully accomplished by treatment of the oxidized α,β-unsaturated ketone **6** with pyridine and I_2 in CCl_4[9] to give vinylic iodide **7**. The reaction might be explained as an addition-elimination mechanism. Pyridine might attack β position of α,β-unsaturated ketone to give pyridinium enolate, which might smoothly react with iodine molecule to afford pyridinium α-iodo ketone. Removal of α hydrogen by pyridine or iodide anion might induce elimination of pyridinium group at β position, resulting in giving α-iodocyclopentenone **7**. Compound **7** was stereo- and regioselectively reduced by sodium borohydride in the presence of cerium (III) chloride to give α-allylic alcohol **8**. After protection of hydroxyl group of **8** as the TBDPS ether, halogen exchange (I to F) reaction with **9** was accomplished via metal-halogen exchange reaction. Treatment of **9** with *n*-BuLi might produce lithiated vinylic anion through lithium-iodine exchange reaction and the anion might react with electrophilic fluorination agent, *N*-fluorobenzenesulfonimide[10] to give fluorinated compound **10** in 61% yield. Desilylation of **10** with tetrabutylammonium fluoride (TBAF) gave apio fluoro-cyclopentenol **11**, which was used as a glycosyl donor after mesylation for the synthesis of apio F-NPA (**3**). Treatment of mesylate **12** with adenine base in the presence of K_2CO_3, 18-Crown-6, and DMF at 80°C afforded protected adenine nucleoside **13** in 90% yield. Finally, hydrolysis of **13** with formic acid and water (3:1) for 7 days gave apio F-NPA (**3**).

Synthesis of uracil analog **4** is shown in Scheme 2. Coupling of mesylate **12** with uracil base in the presence of K_2CO_3 and DMSO at 90°C produced protected uracil nucleoside **14**, which was hydrolyzed by formic acid and water (3:1) to give uracil analogue **4**.



SCHEME 2 Reagents and conditions: (a) uracil, K_2CO_3, DMSO, 90°C, 6 hours; (b) HCO_2H:H_2O (3:1), THF, rt, 10 days.

Inhibitory activity against AdoHcy hydrolase and antiviral assay of the final nucleosides **3** and **4** are in progress and will be reported in due course.

CONCLUSION

Apio F-NPA (**3**) and its uracil analogue **4** were designed and asymmetrically synthesized to search for the first nontoxic and potent antiviral agent. Introduction of fluoro group into vinylic position of **5** was accomplished over five steps employing key reactions such as iodination according to an addition-elimination reaction mechanism, stereo- and regioselective reduction of α,β-unsaturated ketone, and electrophilic fluorination through metal-halogen exchange reaction. Apio fluorocyclopentenol **11** was converted to apio F-NPA (**3**) and its uracil analogue **4** through mesylation followed by S_N2 reaction with adenine and uracil bases, respectively, in the presence of K_2CO_3.

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