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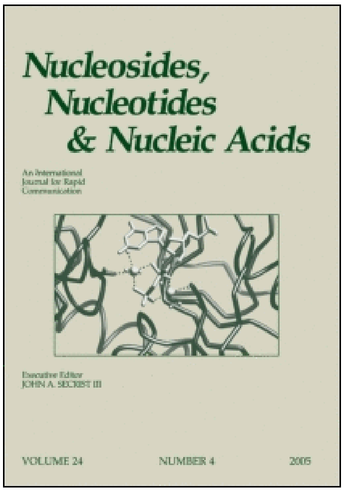

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SYNTHESIS AND ANTITUMOR ACTIVITY OF FLUOROCYCLOPENTENYL-PYRIMIDINES

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□ *Synthesis of fluorocyclopentenyl pyrimidine nucleosides* **6**–**9** *was enantiopurely accomplished employing oxidative rearrangement, RCM reaction and electrophilic fluorination starting from* D-*ribose. Cytosine analog* **8** *was found to exhibit significant anticancer activity in various human tumor cell lines.*

Keywords Electrophilic fluorination; ring-closing metathesis; oxidative rearrangement; Mitsubobu condensation; antitumor

INTRODUCTION

Aristeromycin (**1**) and neplanocin A (**2**)[1,2] are representatives of the carbocyclic nucleosides with potent antiviral and antitumor activities (Figure 1). They act by the inhibition of *S*-adenosylhomocysteine (AdoHcy) hydrolase, an enzyme which catalyzes hydrolysis of AdoHcy into adenosine and L-homocysteine. AdoHcy hydrolase is considered a promising target in the development of new antiviral agents because inhibition of AdoHcy hydrolase induces the inhibition of methyltransferases, an enzyme necessary to process viral *m*-RNA.

On the other hand, cytidine analog **3** constructed on the basis of cyclopentenyl sugar ring of neplanocin A (**2**) has been reported to show

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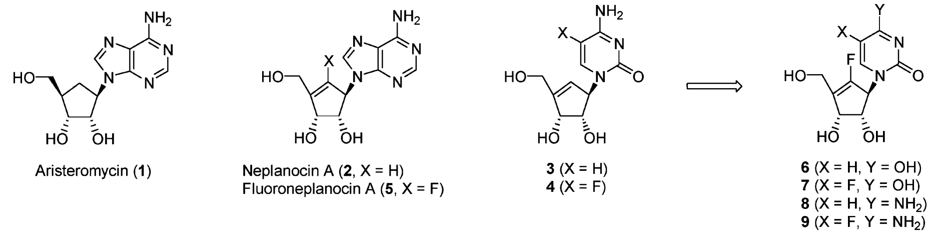


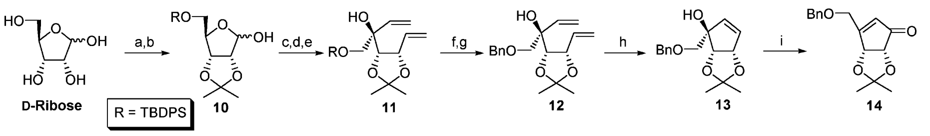
FIGURE 1 Rationale for the design of fluorocyclopentenyl pyrimidine nucleosides, **6–9**.

potent antitumor activity by Marquez et al.[3] Recently, 5-fluorocytosine derivative **4** was reported to exhibit potent anti-West-Nile virus activity by Chu and coworkers.[4] More recently, fluoroneplanocin A (**5**),[5] designed and synthesized by us as an irreversible AdoHcy hydrolase inhibitor, has shown potent antiviral activity.

The above finding prompted us to synthesize a series of new fluoroneplanocin A (**5**) derivatives. In the present communication, we report a synthetic method for fluorocyclopentenyl pyrimidines **6–9** and their cytostatic activity in a variety of human tumor cells.

RESULTS AND DISCUSSION

The key intermediate **16** has been obtained from cyclopentenone **14**[6,7] starting from D-ribose (Scheme 1). Briefly, treatment of D-ribose with anhydrous acetone in the presence of concentrated sulfuric acid followed by reaction with TBDPSCl gave 2,3-isopropylidene-5-TBDPS-D-ribose (**10**). Wittig reaction of compound **10** with methylenephosphorane followed by Swern oxidation with oxalyl chloride and DMSO afforded ketone, which was subjected to a Grignard reaction with vinylmagnesium bromide to give diene **11** as a single diastereomer. Before ring-closing metathesis (RCM) reaction[8] of **11**, TBDPS group was replaced with benzyl group compatible with further synthetic procedures. TBDPS group of **11** was removed with TBAF and then one of hydroxyl functions in resulting diol system was regioselectively protected with benzyl group, after hydroxyl activation with dibutyltin oxide,

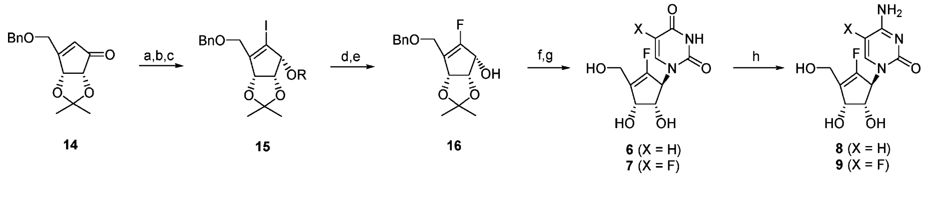


SCHEME 1 Reagents and conditions: a) acetone, c-H_2SO_4, 93%; b) TBDPSCl, imidazole, CH_2Cl_2, 99%; c) Ph_3PCH_3Br, KO*t*/-Bu, THF, 93%; d) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, 1 hour, then Et_3N, rt, 1 hour, 98%; e) CH_2 =CHMgBr, THF, 84%; f) *n*-Bu_4NF, THF, 99%; g) $Bu_2Sn(O)$, toluene, 15 hours, then TBAI, BnBr, 75°C, 16 hour, 87%; hour) second generation Grubbs catalyst, CH_2Cl_2, 88%; i) PDC, 4 A MS, DMF, rt, 18 hour, 59%.

giving **12**. RCM reaction of diene **12** with second generation Grubbs catalyst followed by oxidative rearrangement of the resulting *tert*-allylic alcohol **13** with PDC in DMF gave the desired cyclopentenone **14**, which was a substrate for the synthesis of fluorocyclopentenol **16**.

Synthesis of fluorocyclopentenol **16** and the final pyrimidine nucleosides **6-9** is shown in Scheme 2. First, compound**14** was converted to glycosyl donor, fluorocyclopentenol **16** in a five-step reaction procedure. These included: iodination of **14** using I_2 and pyridine; stereo- and regioselective reduction of α,β-unsaturated ketone with $NaBH_4$ in the presence of cerium (III) ion; and protection of the resulting hydroxyl group with TBDPS, providing **15**. Electrophilic fluorination at vinyl position via metal-halogen exchange was accomplished by treating of compound **15** with *N*-fluorobenzenesulfonimide and *n*-BuLi to give fluorocyclopentenol **16** after desilylation with TBAF. Coupling of **16** with N^3-benzoyluracil and N^3-benzoyl-5-fluorouracil under Mitsunobu conditions followed by removal of benzoyl group with methanolic ammonia and benzyl group with BCl_3, provided uracil nucleoside **6** and 5-fluorouracil nucleoside **7**, respectively. Compound **6** and **7** were converted to cytosine nucleosides **8** and **9** according to the conventional method: i. Ac_2O, pyridine; ii. $POCl_3$, Et_3N, 1,2,4-triazole; iii. NH_4OH, 1,4-dioxane; iv. NH_3/MeOH.

The growth inhibition activity of all synthesized final nucleosides **6-9** in various human tumor cell lines was evaluated using the Sulforhodamine B method.[9] Among the tested compounds, cytosine analog **8** was the most active in a range of tumor cell lines. IC_{50} (μM) of **8** against human cancer cell lines are as follows: 0.34 in MCF-7 (breast, hormone-dependent), 0.18 in MDA-MB-231 (breast), 1.35 in HeLa (cervix), 0.80 in human OVCAR-3 (ovary), 2.67 in LNCap (prostate), 0.79 in HepG2 (liver), 0.50 in A549 (lung), 0.25 in NCI-H226 (lung), 0.28 in HT-29 (colon), 0.19 in HCT116 (colon), 1.38 in SK-MEL-28 (melanoma), 0.62 in PANC-1 (pancreas), 0.63 in PC (prostate), 0.83 in U251 (brain), 0.34 in MKN-45 (stomach), and 0.83 in UMRC2 (kidney).



SCHEME 2 Reagents and conditions: a) I_2, pyridine, CCl_4, 55%; b) $NaBH_4$, $CeCl_3$, 93%; c) TBDPSCl, imidazole, DMF, 97%; d) *N*-fluorobenzene-sulfonimide, *n*-BuLi, THF, - 78°C, 80%; e) *n*-Bu_4NF, THF, 80%; f) N^3-benzoyluracil or N^3-benzoyl-5-fluorouracil, DEAD, Ph_3P, THF, then NH_3/MeOH, 81%; g) BCl_3, CH_2Cl_2, 60%; hour) i. $Ac_2.O$, pyridine; ii. $POCl_3$, Et_3N, 1,2,4-triazole; iii. NH_4OH, 1,4-dioxane; iv. NH_3/MeOH, 40%.

In conclusion, fluorocyclopentenyl pyrimidine nucleosides **6–9** were designed and synthesized starting from D-ribose using stereoselective Grignard reaction, oxidative rearrangement, and electrophilic fluorination. Among the obtained compounds, cytidine analog **8** has shown the most potent cytostatic activity in variety of human cancer cell lines.

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