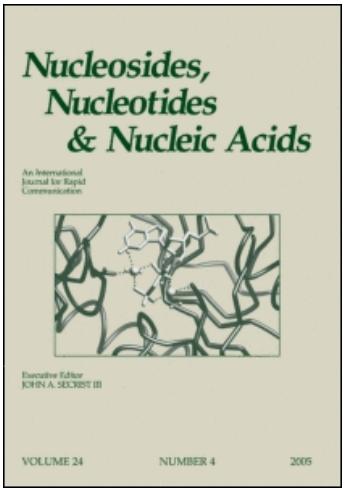

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Design, Synthesis, and In Vitro Evaluation of APIO Analogue of Neplanocin A

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ABSTRACT

A novel apio analogue of neplanocin A was efficiently synthesized from D-ribose via stereoselective aldol-retroaldol reaction for introducing hydroxymethyl group and RCM reaction for synthesizing carbocycle, and its inhibitory activity against SAH hydrolase was assayed.

Key Words: Neplanocin A; Apio nucleosides; *S*-Adenosylhomocysteine hydrolase.

S-adenosylhomocysteine (SAH) hydrolase catalyzes the hydrolysis of *S*-adenosylhomocysteine to adenosine and homocysteine.[1] Inhibition of SAH hydrolase accumulates *S*-adenosylhomocysteine in cell, which in turn interrupts the

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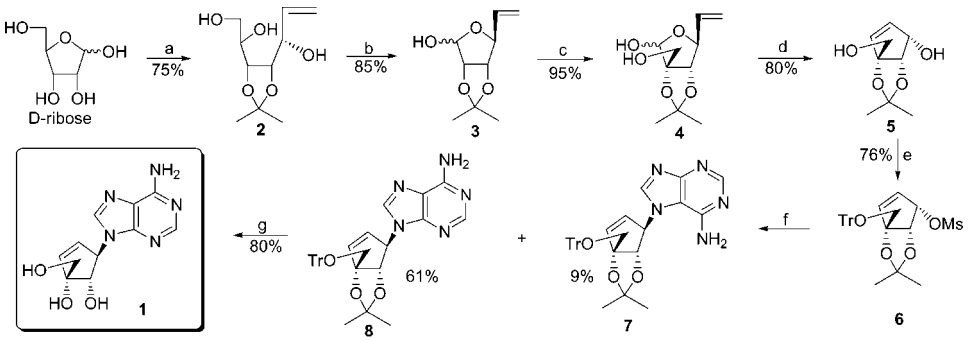

Scheme 1. Reagents[a]: a) i) acetone, *c*-H_2SO_4, ii) $CH_2CHMgBr$; b) $NaIO_4$; c) CH_2O, K_2CO_3; d) i) Ph_3PCH_3Br, KO*t*-Bu, ii) Grubbs catalyst (2nd Generation); e) i) TrCl, Pyridine, DMAP. ii) MsCl, Et_3N; f) adenine, K_2CO_3, 18-crown-6; g) 66% aqueous CF_3CO_2H.

transmethylation of viral *m*RNA via inhibition of SAM (*S*-adenosylmethionine) methyltransferase, resulting in antiviral activities.[1] Nucleosides in which the furanose ring oxygen and C2′-methylene are transposed are called apio nucleosides. Apio-ddA was reported to have anti-HIV activity comparable to that of the parent ddA. On the basis of these findings, we report the synthesis and biological activity of apio derivative of neplanocin A, which is one of potent inhibitors of SAH hydrolase, expecting it to exhibit the inhibition of SAH hydrolase by tightly binding to the enzyme.

D-Ribose was converted to the 2,3-acetonide under acidic condition, which was treated with vinylmagnesium bromide to afford the allylic alcohol **2** stereoselectively (Sch. 1).[2] Oxidative cleavage of the vicinal diol of allylic alcohol **2** using $NaIO_4$ gave lactol **3**, which was reacted with formaldehyde and potassium carbonate to give **4** via recurrent aldol-retroaldol reaction, stereoselectively.[3] Wittig reaction of **4** using triphenylphosphonium methyl ylide followed by RCM (ring-closing metathesis)[4] of the resulting diene employing Grubbs catalyst (second generation) produced cyclopentenol **5** in excellent yield. Protection of primary hydroxyl group of **5** as a trityl ether and then mesylation of secondary hydroxyl group gave glycosyl donor **6**. Coupling of **6** with adenine in the presence of K_2CO_3 afforded the desired N9 isomer **8** (61%) as a major product with concomitant formation of minor isomer **7** (9%). Assignments of isomers of N7 product and N9 product were accomplished by comparison of UV data.[5] The final product **1** was obtained after concomitant deprotection of trityl and isopropylidene groups of **8** under 66% aqueous trifluoroacetic acid.

The final product **7** didn't show significant inhibition against SAH hydrolase, maybe due to being impossible not only to bind to the enzyme tightly, but also for NAD^+ to oxidize the tertiary hydroxyl group at C3′-position.

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