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Stereoselective Synthesis of a Novel Apio Analogue of Neplanocin A as Potential *S*-Adenosylhomocysteine Hydrolase Inhibitor

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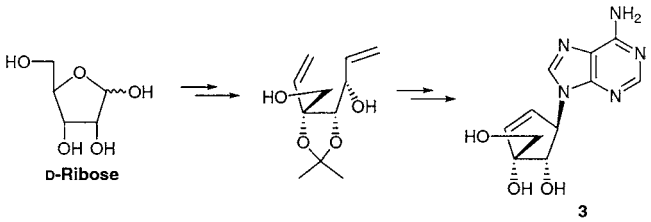
ABSTRACT



A total synthesis of apio-neplanocin A, which combines properties of apio nucleoside and neplanocin A and is a potential inhibitor of *S*-adenosylhomocysteine hydrolase, was accomplished starting from D-ribose via stereoselective hydroxymethylation and RCM reaction.

S-Adenosylhomocysteine hydrolase (SAH) catalyzes the interconversion of *S*-adenosylhomocysteine into adenosine and L-homocysteine.[1] Inhibition of this enzyme accumulates *S*-adenosylhomocysteine in the cell, which in turn inhibits *S*-adenosylmethionine-dependent transmethylation reaction.[1] Such transmethylation is essential for viral *m*RNA maturation and thus plays a crucial role in viral replication. Since a close correlation between SAH inhibitors and their antiviral activity has been found, SAH has been a promising target for the development of antiviral agents.[2−4] Neplanocin A (**1**)[5] is a natural carbocyclic nucleoside and one of the most potent inhibitors of SAH.[6] It belongs to the type-I mechanism-based inhibitors,[3] in which 3′-hydroxyl group of compound **1** is oxidized by NAD^+ to the 3′-keto derivative, resulting in the depletion of the cofactor NAD^+. In correlation with neplanocin A's strong inhibition of SAH, it also exhibits strong antiviral activity against DNA viruses as well as RNA viruses.[7]

Recently, the major trend in developing new antiviral agents has been shifted to the development of unique nucleosides with an unnatural sugar moiety. Discovery of L-β-1,3-oxathiolanyl cytosine (3TC, lamivudine)[8] as an anti-

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hepatitis B virus (HBV) drug gave an impetus to the research in this class of compounds. Apio nucleoside also belongs to this unique group, in that the 4′-hydroxymethyl group of the normal sugar is moved to the C3′-position.[9] One of them, apio-ddA (**2**) has been reported to show potent anti-HIV activity comparable to that of the parent 2′,3′-dideoxyadenosine (ddA) and better stability against glycosidic bond hydrolysis than that of ddA.[9]

On the basis of these findings, it was of great interest to synthesize novel apio-neplanocin A (**3**) and evaluate its inhibitory effect on SAH (Figure 1). This molecule combines

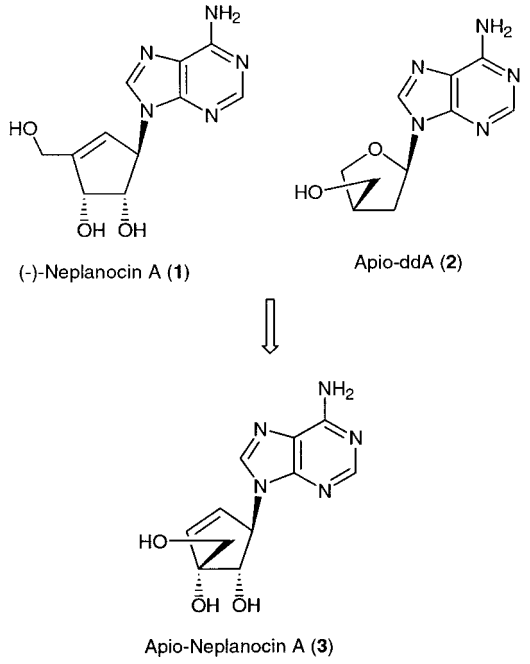
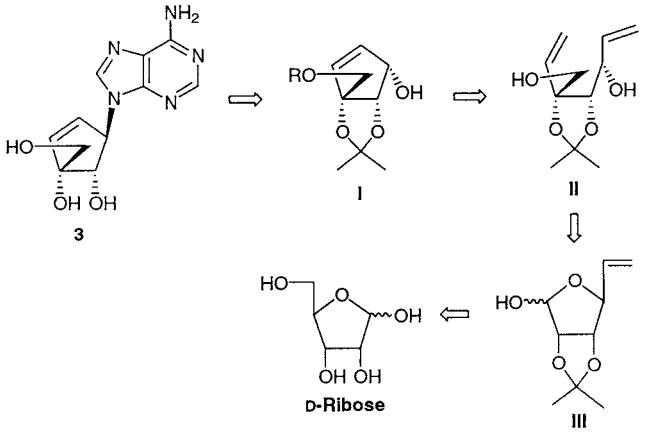


Figure 1. Rationale for the design of apio-neplanocin A (**3**).

the properties of **1** and **2**. To the best of our knowledge, compound **3** is the first example of an apio carbocyclic nucleoside with unnatural five-membered carbocycles. In this communication, we report the stereoselective synthesis of enantiomerically pure apio-neplanocin A (**3**), starting from D-ribose via ring-closing metathesis (RCM)[10] and stereoselective hydroxymethylation at the C3′-position and its inhibitory activity against SAH.

Retrosynthetic analysis (Scheme 1) shows that the desired nucleoside **3** can be synthesized from the glycosyl donor, cyclopentenol **I**, which is derived from RCM reaction of diene **II**. Compound **II** can be prepared from lactol **III** via

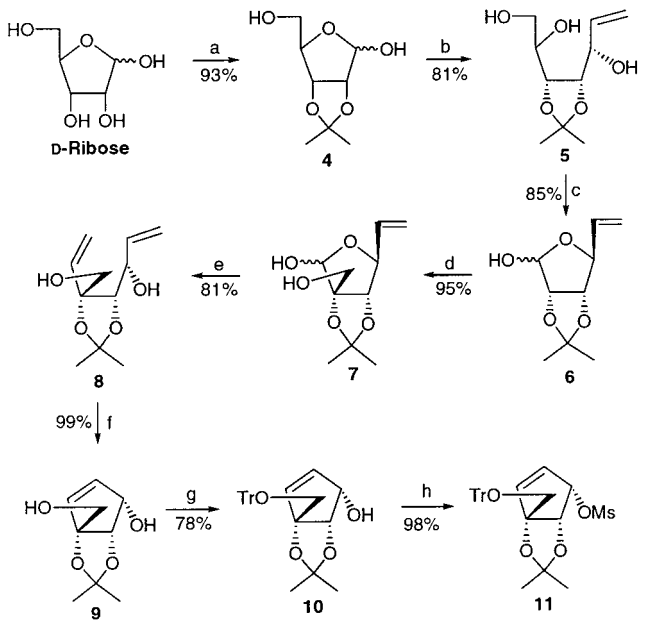
Scheme 1. Retrosynthetic Analysis of the Desired Nucleoside **3**



stereoselective hydroxymethylation and Wittig reaction. Lactol **III** can be derived from D-ribose using Grignard reaction and oxidative cleavage.

Synthesis of the glycosyl donor **11** is shown in Scheme 2. D-Ribose was reacted with acetone and catalytic amounts

Scheme 2[a]



[a] Reagents: (a) acetone, *c*-H_2SO_4, rt, 2.5 h; (b) CH_2═$CHMgBr$, THF, from −78 to 0 °C, 3 h; (c) $NaIO_4$, CH_2Cl_2, H_2O, from 0 °C to rt, 40 min; (d) K_2CO_3, 37% CH_2O, MeOH, 80 °C, 36 h; (e) Ph_3PCH_3Br, KO*t*-Bu, THF, rt, 15 h; (f) Grubbs catalyst (second generation), CH_2Cl_2, rt, 2 h; (g) TrCl, DMAP, pyridine, rt, 20 h; (h) MsCl, NEt_3, CH_2Cl_2, rt, 2 h.

of sulfuric acid to give 2,3-acetonide **4.** Treatment of **4** with vinylmagnesium bromide in THF afforded the triol **5** stereoselectively.[11] Oxidative cleavage of **5** with sodium metaperiodate gave the lactol **6** in excellent yield. Compound **6** was subjected to the aldol condensation[12] to give the

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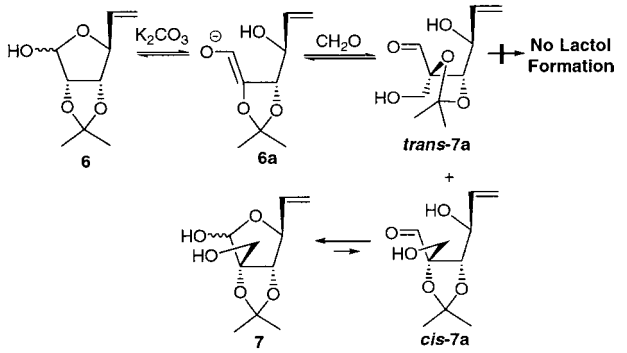
hydroxymethyl derivative **7** (95%) stereoselectively. The stereoselective formation of **7** in the mixed aldol condensation may be mechanistically explained as illustrated in Scheme 3. Treatment of **6** with K_2CO_3 followed by the

Scheme 3

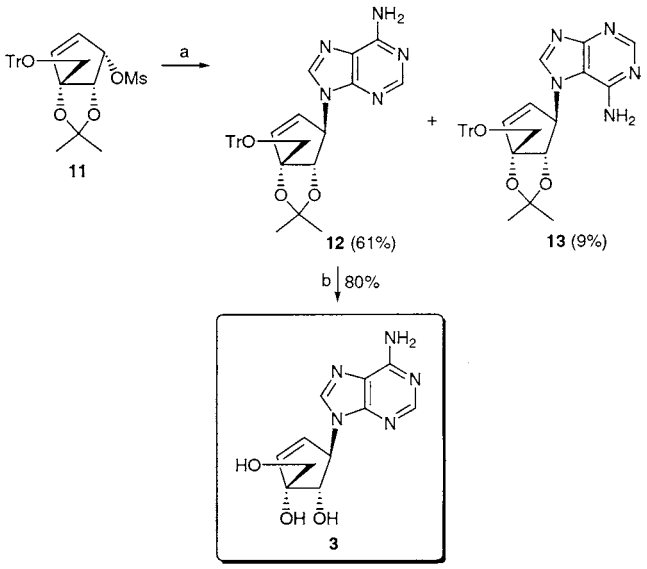


addition of 37% formaldehyde might produce two possible adducts, *trans*-**7a** and *cis*-**7a**, via the resulting enolate **6a**. Under equilibrium, *trans*-**7a** was not converted to a lactol due to high ring strain but underwent the reverse aldol reaction, going back to the enolate **6a**, while *cis*-**7a** was smoothly cyclized to form the thermodynamically stable lactol **7**. Thus, under the reaction conditions, compound **7** was formed as the sole product.

Wittig reaction of **7** with methyl triphenylphosphonium ylide gave the diene **8** as a single stereoisomer, which was ready for RCM.[10] Diene **8** was treated with second generation Grubbs catalyst in methylene chloride to give the cyclopentenol **9** with desired stereochemistry in almost exclusive yield. The primary hydroxyl group of **9** was selectively protected with a trityl group to give **10**, which was converted to the mesylate **11** for use in condensation reaction.

Synthesis of the desired nucleoside **3** is illustrated in Scheme 4. Condensation of **11** with adenine anion in the presence of 18-crown-6 afforded the desired N-9 isomer **12** (61%) as a major product with concomitant minor formation of N-7 isomer **13** (9%). Regioisomers N-9 [UV (MeOH) λ_{max} 260 nm] and N-7 [UV (MeOH) λ_{max} 279 nm] were easily differentiated by comparison of literature UV data.[13] The desired isomer **12** was treated with 66% aqueous trifluoroacetic acid to give the final nucleoside **3**.

Scheme 4[a]



[a] Reagents: (a) adenine, K_2CO_3, 18-crown-6, DMF, 80 °C, 12 h; (b) 66% aqueous CF_3CO_2H, THF, rt, 3 days.

The inhibitory activity of the final nucleoside **3** against human recombinant SAH was measured. Unlike neplanocin A, compound **3** did not exhibit significant inhibitory activity against SAH, although we expected tight binding of **3** to SAH. This lack of enzyme inhibitory activity might be due to the presence of the tertiary hydroxyl group at the C3′-position, which cannot be oxidized by cofactor-bound NAD^+. Antiviral assays against DNA and RNA viruses and structure−activity relationship studies are in progress in our laboratory and will be reported in due course.

In summary, a novel apio analogue **3** of neplanocin A, combining the structural characteristics of apio nucleoside and neplanocin A, was synthesized starting from D-ribose. The synthetic procedure is highlighted by stereoselective hydroxymethylation and RCM reaction. Apio-neplanocin A (**3**) is believed to be the first example of a carba nucleoside with an unnatural apio carbocycle.

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Supporting Information Available: Complete experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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