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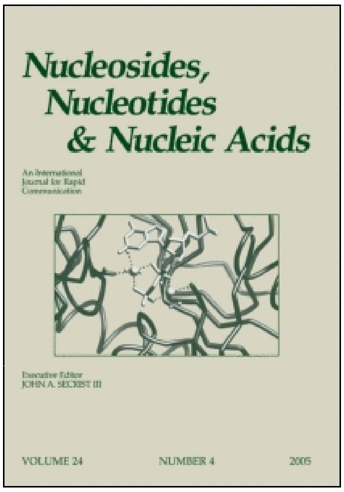

Nucleosides, Nucleotides and Nucleic Acids

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Synthesis And Anti-Hcv Activity Of 2''-β-Hydroxymethylated Nucleosides

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SYNTHESIS AND ANTI-HCV ACTIVITY OF 2′-β-HYDROXYMETHYLATED NUCLEOSIDES

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□ *Synthesis of 2′-β-hydroxymethyl nucleosides **3–6** was accomplished, using stereoselective hydroxymethylation as a key step. Adenine nucleoside **3** showed potent anti-HCV activity, implying that 2′-β-hydroxymethyl group has the appropriate electronic properties interfering with HCV polymerase.*

Keywords Stereoselective hydroxymethylation; anti-HCV activity; 2′-hydroxymethyl adenosine

INTRODUCTION

Hepatitis C virus (HCV) is known to be the most common blood-born infection and a major cause of hepatocellular carcinoma.[1] An estimated 170 million people worldwide are infected with HCV and more than 50% of patients with acute HCV infection progress to chronic hepatitis and eventually hepatocellular carcinoma.[2] However, ribavirin (**1**), which belongs to ribofuranosyl nucleoside is the only chemotherapeutic agent for the treatment of HCV infection in combination with interferon-α (Figure 1), which stimulated us to search for novel anti-HCV nucleosides.[3]

Recently, it was reported that 2′-β-methyladenosine (**2**) showed highly potent anti-HCV activity because 2′-β-methyl group prevented subsequent incorporation of incoming nucleosides triphosphate (NTP) into the viral RNA chain by NS5b RNA dependent RNA polymerase.[4] On the basis of these findings, we designed and synthesized β-2′-hydroxymethylnucleoside analogues because we expected β-2′-hydroxymethyl group might give the favorable electronic and steric effects on interfering with HCV RNA

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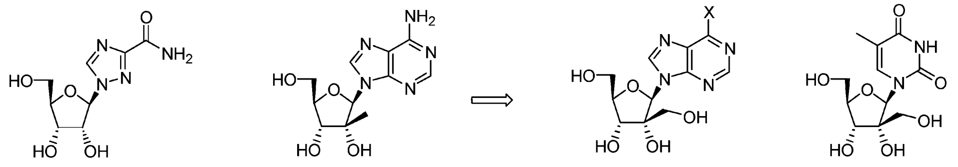


Ribavirin (1) **2** **3** (X = NH_2) **4** (X = NHMe) **5** (X = OH) **6**

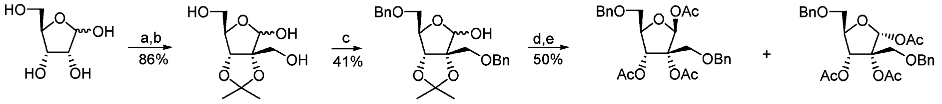
FIGURE 1 Rationale for the design of β-2′-hydroxymethyl pyrimidine and purine nucleosides, **3–6**.

polymerase. Herein, we report the synthesis of β-2′-hydroxymethyl pyrimidine and purine nucleosides **3–6** and their anti-HCV activity.

RESULTS AND DISCUSSION

Our synthetic strategy was first to synthesize the peracetylated glycosyl donors, **9a** and **9b**, and then condense with silylated nucleobases using a neighboring group effect by C2-α-acetoxy group to give β-2′-hydroxymethyl nucleosides **3–6** stereoselectively.

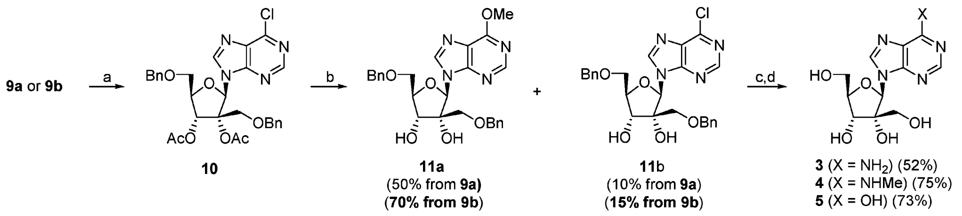
As shown in Scheme 1, D-ribose was treated with acetone under acidic conditions to give 2,3-*O*-isopropylidene-D-ribose, which was subjected to stereoselective hydroxymethylation using aldol-retroaldol reaction (35% CH_2O and K_2CO_3 in methanol under reflux) to give β-hydroxymethyl compound **7** as a single stereoisomer.[5] Two primary hydroxyl groups of **7** were selectively protected with benzyl group using organotin chemistry (i. Bu_2SnO, toluene, reflux; ii. BnBr, Bu_4NI, 100°C),[6] to give the dibenzylate **8**. Since the use of a neighboring group effect by C2-α-acetoxy group is a good method to obtain the desired β-selectivity during condensation with nucleobases, the isopropylidene lactol **8** was transformed to two separable anomeric acetates, **9a** and **9b**, which were used as glycosyl donors for the synthesis of the final products **3–6**.



D-Ribose **7** **8** **9a** (40%) **9b** (55%)

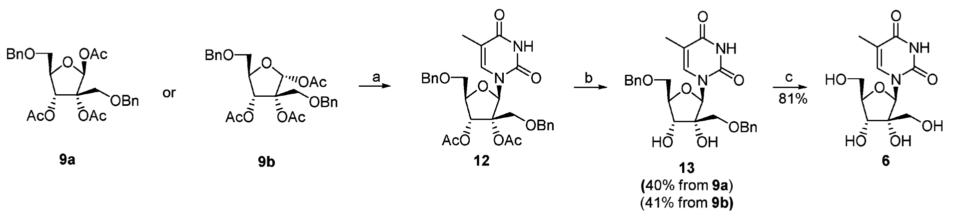
SCHEME 1 Reagents and conditions: a) acetone, *c*-H_2SO_4, rt, 2.5 hours; b) CH_2O, K_2CO_3, MeOH, reflux, 4 days; c) i. *n*-$Bu_2Sn(O)$, toluene, reflux, 15 hours, ii. BnBr, *n*-Bu_4NI, 100°C, 15 hours; d) 3 M HCl:THF (1:1), rt, 1 day; e) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt, 3 hours.

Condensation of the glycosyl donor, **9a** or **9b** with silylated 6-chloropurine in the presence of TMSOTf gave the β-nucleoside **10** as a single stereoisomer, as expected (Scheme 2). Treatment of **10** with 1 M NaOMe afforded the desired 6-chloropurine derivative **11b** with concomitant minor formation of 6-methoxypurine derivative **11a**. Compound **11b** was routinely



SCHEME 2 Reagents and conditions: a) i. 6-chloropurine, $(NH_4)_2SO_4$, HMDS, 160°C, overnight; ii. TMSOTf, $ClCH_2CH_2Cl$, rt, 4 hours from **9a**, 50°C, 2 hours from **9b**; b) NaOMe, MeOH, 1 hour; c) NH_3/MeOH, 80°C, 1 day, 40% CH_3NH_2 in H_2O, MeOH, 80°C, 1 hour, or 2-mercaptoethanol, NaOMe, MeOH, 20 hours; d) Pd/black, 50% HCO_2H in MeOH, 50°C, 5 hours.

converted to adenine derivative **3**, N^6-methyladenine derivative **4**, and hypoxanthine derivative **5**.



SCHEME 3 Reagents and conditions: a) i. thymine, $(NH_4)_2SO_4$, HMDS, 160°C, overnight; ii. TMSOTf, $ClCH_2CH_2Cl$, rt, overnight from **9a**, 50°C, 3 hours from **9b**; b) NaOMe, MeOH, 1 hour; c) Pd/C, H_2, MeOH, 60°C, 2 hours.

Synthesis of thymine derivative **6** is depicted in Scheme 3. Condensation of **9a** or **9b** with silylated thymine followed by treating the protected nucleoside **12** with NaOMe yielded deacetylated compound **13**. Catalytic hydrogenation of **13** using Pd/C in the presence of H_2 at 60°C afforded the final nucleoside **6**.

All synthesized compounds **3–6** were evaluated for anti-HCV activity in vitro. Among these, adenine nucleoside **3** only inhibited the replication of the replicon NK-R2AN in Huh-7 cells by 2% at 1 μM.

In conclusion, β-2′-hydroxymethyl nucleosides **3–6** were stereoselectively synthesized from D-ribose, using neighboring group effect. Among the synthesized nucleosides, adenine nucleoside **3** showed potent anti-HCV activity, indicating that 2′-hydroxymethyl group might interfere with RNA chain elongation by HCV polymerase.

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