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Stereoselective Synthesis of 2′-*C*-Methyl-cyclopropyl-Fused Carbanucleosides as Potential Anti-HCV Agents

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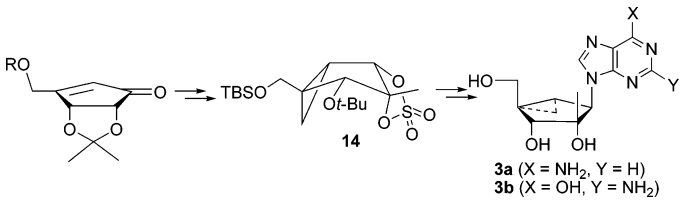
ABSTRACT



Stereoselective synthesis of 2′-*C*-methyl-cyclopropyl-fused carbanucleosides was accomplished via stereoselective cyclopropanation, regioselective cleavage of the isopropylidene group, stereoselective Grignard reaction, and cyclic sulfate chemistry.

The hepatitis C virus (HCV) is a lethal single-stranded RNA virus with which 170 million people are infected worldwide.[1] Its chronic infection is the cause of liver cirrhosis and hepatocellular carcinoma.[2] The only approved treatment of HCV infection is immunotherapy using recombinant interferon-α in combination with ribavirin.[3] Thus, it is highly desirable to develop effective chemotherapeutic agents for the treatment of HCV-infected patients.

Many nucleoside and nonnucleoside derivatives have been synthesized as anti-HCV agents.[4] Among these, 2′-*C*-methyladenosine (**1**) and 2′-*C*-methylguanosine (**2**) were discovered as potent HCV inhibitors (EC_{50} = 0.26 and 3.5 μM, respectively) in a cell-based HCV replicon assay (Figure 1).[5] These nucleosides exhibit their anti-HCV activity by RNA-chain termination because the 2′-methyl group of **1** and **2** prevents subsequent incorporation of an incoming natural substrate, the nucleoside triphosphate.[6]

Compounds **1** and **2** were reported to display a strong preference for a Northern C3′-*endo* conformation (pseudorotation angle $P = 15.6°$),[5] as shown in Figure 1. It has been known that the bicyclo[3.1.0]hexane carbocyclic nucleosides adapt an extreme Northern or Southern conformation because

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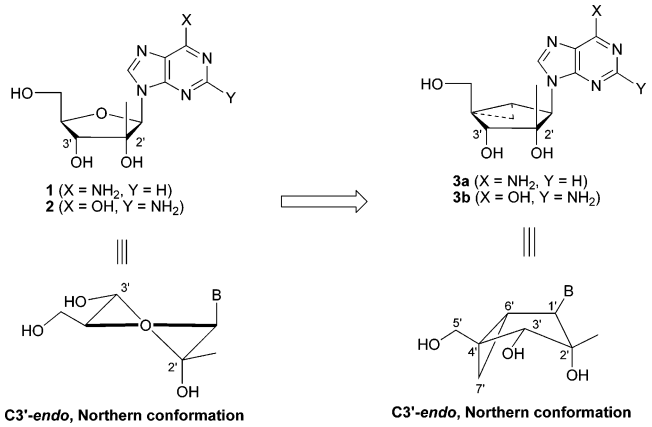
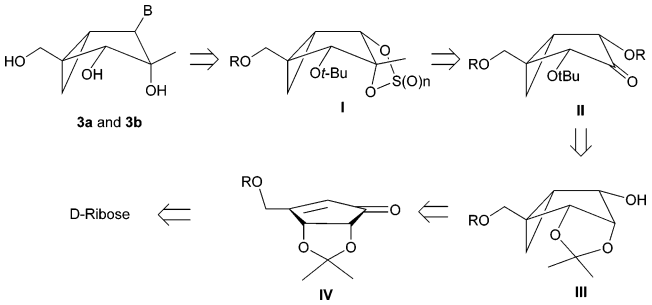


Figure 1. Rationale for the design of the target nucleosides.

of their rigid pseudoboat conformation.[7] For example, conformationally restricted nucleosides in which the cyclopropane ring is fused between C4′ and C6′ lock the positions of the carbasugars at the typical range of Northern C3′-*endo* conformers ($P = 0 \pm 18°$), and carbanucleosides in which the cyclopropane ring is fused between C1′ and C2′ take the typical Southern C3′-*exo* conformation. On the basis of this conformational information, we designed the cyclopropyl-fused analogues **3a** and **3b** because these compounds could take the Northern C3′-*endo* conformation similar to that for compounds **1** and **2** as demonstrated in Figure 1. Herein, we report the stereoselective synthesis of our designed 2′-*C*-methyl-cyclopropyl-fused carbocyclic nucleosides **3a** and **3b** as potential anti-HCV agents.

Our synthetic strategy to the target nucleosides is illustrated in Scheme 1. The final nucleosides **3a** and **3b** might be

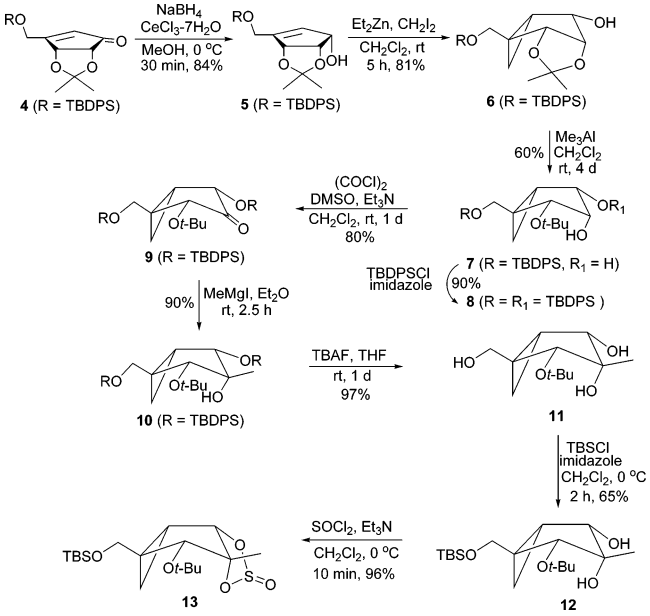
Scheme 1. Retrosynthetic Analysis of the Desired Nucleosides **3a** and **3b**



derived from a common precursor, cyclic sulfite ($n = 1$) or cyclic sulfate ($n = 2$) **I**, by condensation with a nucleobase. Cyclic sulfite or cyclic sulfate **I** could be prepared from ketone **II** via stereoselective methyl addition as a key step. Ketone **II** might be derived from isopropylidene derivative **III** using regioselective cleavage of the isopropylidene group as a key step. It was further thought that compound **III** would be easily synthesized from cyclopentenone derivative **IV** which could be derived from D-ribose.

Our synthesis began by preparing the known cyclopentenone **4** from D-ribose, according to our previously reported procedure.[8] The obtained enone **4** was stereoselectively reduced to allylic alcohol **5** by treating with $NaBH_4$ in the presence of ceric chloride (Scheme 2).[9] The hydroxyl-

Scheme 2. Synthesis of the Glycosyl Donor **13**



directed Simmons−Smith cyclopropanation[10] of **5** using diethyl zinc and methylene diiodide afforded cyclopropane derivative **6** as a single stereoisomer. Regioselective cleavage of the isopropylidene group was achieved by treating **6** with trimethylaluminum at room temperature to give **7**.[11] Selective protection of diol **7** with a bulky silyl group could be accomplished at the pseudoequatorial positioned secondary hydroxyl group to give the desired alcohol **8** in excellent yield. Swern oxidation of the remaining secondary alcohol of **8** gave the ketone **9** which was subjected to the Grignard reaction using methylmagnesium iodide to afford the tertiary alcohol **10** as a single stereoisomer. This stereochemical outcome can be explained by considering the attack of the Grignard reagent from the less-hindered convex side. For

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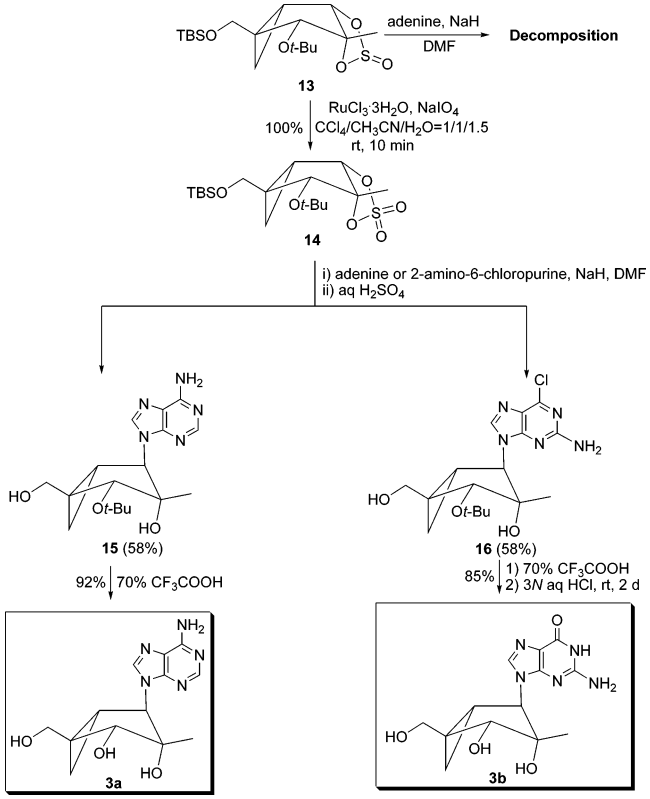
the synthesis of the glycosyl donor, TBDPS groups of **10** were removed to give the triol **11**, whose primary alcohol was selectively protected as TBS ether to give **12**. Treatment of diol **12** with thionyl chloride gave the cyclic sulfite **13** which is ready for the condensation with nucleobases.[12]

Condensation of cyclic sulfite **13** with an adenine anion in DMF at high temperature resulted in decomposition instead of giving the desired condensed product (Scheme 3).[13] Thus, we turned our attention to the more reactive cyclic sulfate[12] for the condensation. Cyclic sulfite **13** was oxidized to cyclic sulfate **14** by treating with ruthenium chloride and sodium metaperiodate in a mixture of CCl_4, CH_3CN, and H_2O.[14] To our delight, the regioselective nucleophilic substitution of cyclic sulfate **14** with an adenine anion led, after hydrolysis of the resulting sulfate ester intermediate with aqueous sulfuric acid, to the formation of the desired N_9-isomer **15** (58%) without forming the N_7-isomer.[15] However, condensation with a 2-amino-6-chloropurine anion yielded the desired N_9-isomer **16** (58%) with concomitant formation of the corresponding N_7-isomer (14%). The structural assignment of the N_9-isomer and the N_7-isomer was accomplished by the comparison of UV and ^{13}C NMR data reported in the literature.[16] Removal of the *tert*-butyl group of **15** using 70% trifluoroacetic acid afforded the adenosine derivative **3a**. Similarly, removal of the *tert*-butyl group of **16** under the same conditions followed by treatment of the resulting 6-chloro derivative with 3 N HCl gave the guanosine derivative **3b**.

Scheme 3. Synthesis of the Final Nucleosides **3a** and **3b**



Antiviral activity of **3a** and **3b** against HCV was measured, but these compounds did not show any significant anti-HCV activity in a cell-based HCV replicon assay, indicating that cellular kinases might prefer the Southern conformation to the Northern conformation for the phosphorylations.[7]

In summary, on the basis of potent anti-HCV activity of 2′-*C*-methyladenosine (**1**) and 2′-*C*-methylguanosine (**2**), we have designed the conformationally restricted 2′-*C*-methyladenosine and -guanosine derivatives. For the efficient synthesis of the desired nucleosides, stereoselective cyclopropanation, regioselective cleavage of the isopropylidene group, stereoselective Grignard reaction, and cyclic sulfate chemistry for the condensation were utilized as key steps. Although we did not discover potent anti-HCV compounds, all chemistries employed in this study will greatly contribute to the development of new carbasugar templates by organic and medicinal chemists.

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Supporting Information Available: Complete experimental procedure for all compounds described herein and ^1H and ^{13}C NMR copies of **7**, **10**, **3a**, and **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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