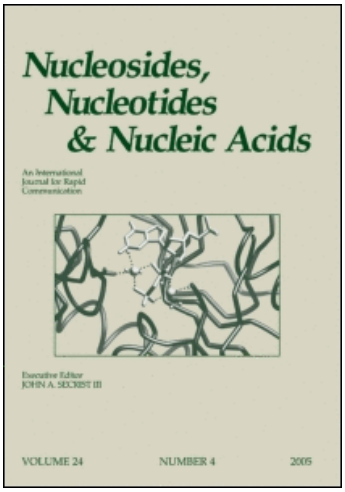

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Asymmetric Synthesis of Cyclopropyl-fused 2'-C-Methylcarbanucleosides as Potential Anti-HCV Agents

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ASYMMETRIC SYNTHESIS OF CYCLOPROPYL-FUSED 2′-*C*-METHYLCARBANUCLEOSIDES AS POTENTIAL ANTI-HCV AGENTS

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□ *Novel 2′-C-methyl-cyclopropyl-fused carbocyclic nucleosides as potential anti-HCV agents were stereoselectively synthesized, utilizing regioselective cleavage of the isopropylidene group and cyclic sulfate chemistry as key steps.*

Keywords anti-HCV agents; hepatitis C virus; cyclic sulfate chemistry; regioselective opening

INTRODUCTION

About 170 million people are infected with hepatitis C virus (HCV) worldwide and its chronic infection causes liver cirrhosis and hepatocellular carcinoma.[1,2] Thus, worldwide efforts to search for effective chemotherapeutic agents have been made, but ribavirin in combination with α-interferon is the only approved for the treatment of HCV-infected patients.[3]

2′-*C*-methyladenosine (**1a**) and 2′-*C*-methylguanosine (**1b**) showed potent anti-HCV activity in a cell-based HCV replicon assay, in which 2′-methyl group prevents the incorporation of incoming nucleosides

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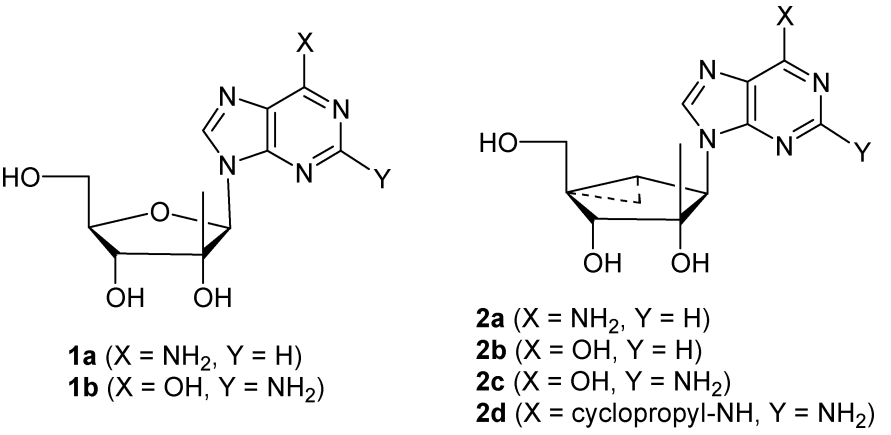
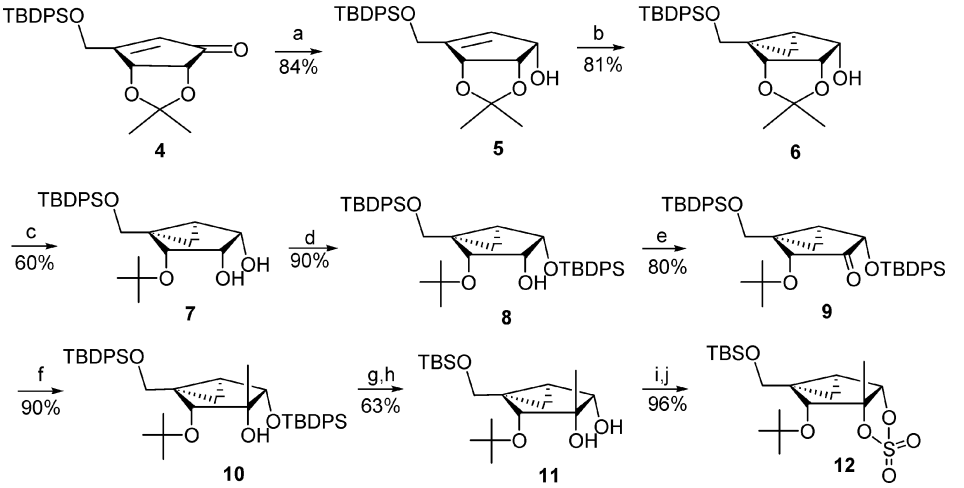
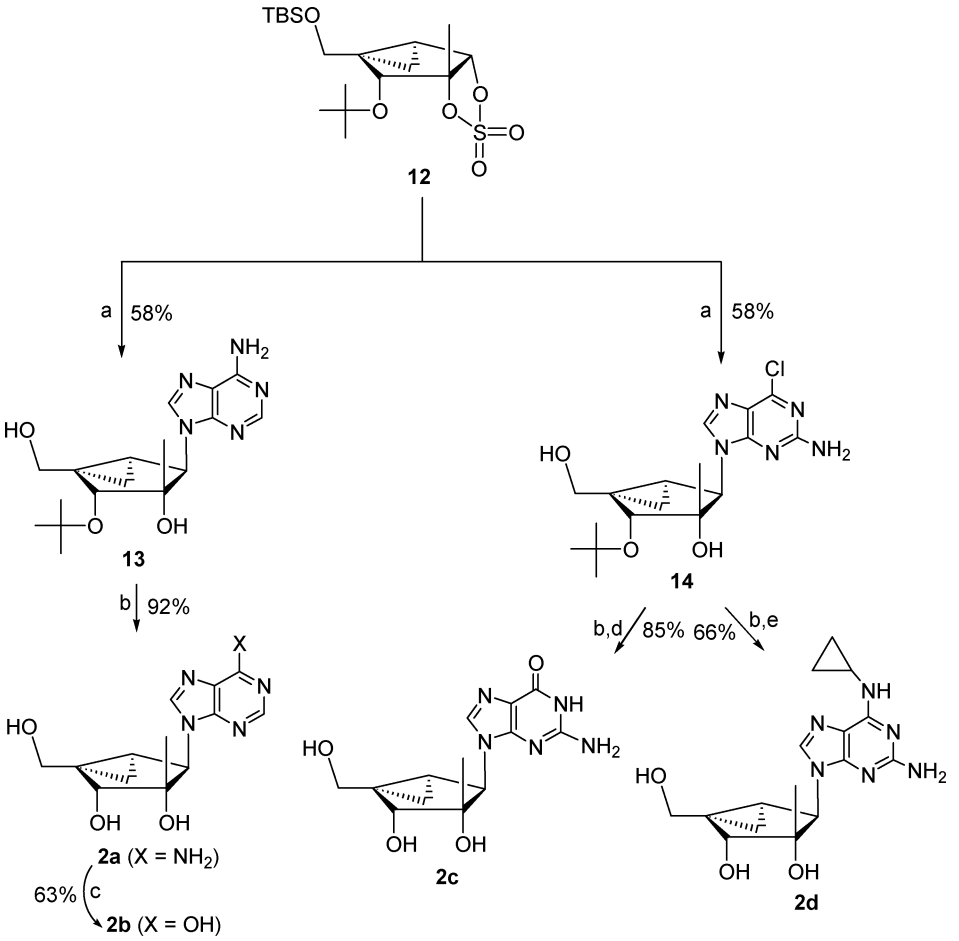


FIGURE 1 Design of the target nucleosides **2** based on the conformational similarity between**1** and **2**.

triphosphates.[4] These nucleosides were reported to adopt a Northern C3′-*endo* conformation (pseudorotation angle $P = 15.6°$).[4] Carbocyclic nucleosides in which the cyclopropane ring is fused between C4′ and C6′ also fix the conformation of the carbasugars to a Northern C3′-*endo* conformation ($P = 0 \pm 18°$).[5] Thus, this conformational information prompted us to design the cyclopropyl-fused-carbanucleosides **2a-d**, as demonstrated in Figure 1. Herein, we report the stereoselective synthesis of conformationally restricted carbocyclic nucleosides **2a-d** and their anti-HCV activity.



SCHEME 1 Reagents and conditions: a) $NaBH_4$, $CeCI_3$ $7H_2O$, MeOH, 0°C, 30 minutes; b) Et_2Zn, CH_2I_2, CH_2Cl_2, rt, 5 hours; c) Me_3AI, CH_2Cl_2, rt, 4 days; d) TBDPSCl, imidazole, CH_2Cl_2, rt, 20 minutes; e) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, rt, 1 days; f) MeMgl, Et_2O, rt, 2.5 hours; g) TBAF, THF, rt, 1 days; h) TBDMSCI, imidazole, CH_2Cl_2, 0°C, 2 hours; i) $SOCl_2$, TEA, CH_2Cl_2, 0°C, 10 minutes; j) $RuCl_3$-$3H_2O$, $NaIO_4$, CCl_4:CH_3CN:H_2O = 1:1:1.5, rt, 10 minutes.



SCHEME 2 Reagents and conditions: a) i) adenine or 2-amino-6-chloropurine, NaH, DMF, ii) 20% aq H_2SO_4; b) 70% CF_3COOH, rt, 50 minutes; c) $NaNO_2$, AcOH, rt, 3 hours; d) 3N aq HCl, rt, 2 days; e) cyclopropylamine, ethanol, rt, 1 day.

RESULTS AND DISCUSSION

Our synthetic strategy was to utilize the cyclic sulfate **12** as a glycosyl donor as illustrated in Scheme 1.

The cyclopentenone **4**, which was efficiently synthesized from D-ribose according to the procedure[6] developed by our laboratory, was stereoselectivity reduced to α-allylic alcohol **5**. Modified Simmons-Smith cyclopropanation of **5** using diethyl zinc and methylene iodide gave bicyclo[3.1.0]hexane derivative **6** as a single stereoisomer. Regioselective cleavage of the isopropylidene group was achieved using trimethylaluminum[7] in CH_2Cl_2 to give the *tert*-butoxy diol **7**. Selective protection of the least hindered alcohol in diol **7** with a TBDPS group followed by Swern oxidation of the remaining

alcohol afforded the ketone **9**. Stereoselective Grignard reaction on **9** with methylmagnesium iodide was achieved by the attack of methyl nucleophile from less hindered convex side. For the synthesis of cyclic sulfate **12**, both silyl protecting groups were removed to give the diol, whose primary alcohol was selectively protected as TBS ether **11**. Diol **11** was treated with $SOCl_2$ in presence of triethyl amine and oxidation of the resulting cyclic sulfite, with sodium periodate in presence of $RuCl_3$-$3H_2O$ to give the glycosyl donor **12**, which is ready for the condensation with a nucleobase.

Condensation of cyclic sulfate **12** with adenine and 2-amino-6-chloropurine anions followed by acid hydrolysis gave the *tert*-butoxy derivatives **13** and **14**, respectively (Scheme 2). Removal of *tert*-butyl group of **13** under acidic conditions afforded the adenine derivative **2a**, which was converted to the hypoxanthine derivative **2b** by diazotization method. In a similar manner, deprotection of *tert*-butyl group of **14** followed by conversion of 6-chloro group to 6-keto group and 6-cyclopropylamino group gave guanine derivative **2c** and 2-amino-6-cyclopropylamino purine derivative **2d**, respectively. Antiviral assay of **2a-d** against HCV was performed, but these compounds did not show any significant anti-HCV activity in a cell-based HCV replicon assay.

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