Synthesis of Pyrimidine Analog of Fluoroneplanocin A as Potential Anti-HCV Agent

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ABSTRACT

N-Hydroxycytosine nucleoside 3 was synthesized as potential anti-HCV agent, starting from d-ribose using an iodine-fluorine exchange reaction by a help of BuLi, a RCM reaction, a stereoselective reduction and a Mitsunobu reaction as the key steps.

INTRODUCTION

Over several decades, a number of nucleoside derivatives modified in the sugar moiety have been designed, synthesized and evaluated against a variety of viruses and cancer cell lines with the hope of finding novel antiviral and antitumor agents. As the results, cytarabine¹ and gemcitabine² were launched as a drug of anticancer, and AZT, ddf, ddC, d4T, 3TC and abacavir were found to be good anti-HIV agents. As d-N⁴-hydroxycytidine (1)³ has shown potent anti-HCV activity and compound 2 has exhibited potent anticancer activity, it was of interest to combine the two functionalities into one molecule.

![Scheme 1](https://academic.oup.com/nass/article-abstract/52/1/607/1108576)

Figure 1.

The fact that compound 2⁴ had anticancer activity implicates it could be phosphorylated converting to its triphosphate. Usually, phosphorylation of nucleoside is a prerequisite for showing antiviral activity. The sugar of compound 2 would be an appropriate template for being phosphorylated. Therefore, compound 3 which mimicked N-hydroxycytosine from 1 and the sugar template from 2, respectively, was designed and synthesized. Herein, we wish to report the synthesis of 3 bearing hydroxycytosine as a nucleobase on the fluorocyclopentene template.

RESULTS AND DISCUSSION

It was envisioned that cyclopentenone 9 could be an appropriate intermediate for the synthesis of fluorine-substituted sugar template. The synthetic method reported by Jeong and coworkers⁵ was employed for the synthesis of glycosyl donor 11. Treatment of d-ribose with acetone under acidic conditions gave acetone 4, which was subjected to Wittig reaction followed by organocatalyzed benzylolation⁶ for the regioselective protection to give secondary alcohol 5. Swern oxidation of hydroxyl group and Grignard reaction with vinylmagnesium bromide afforded tert-allylic alcohol 6, as an inseparable mixture, which was treated with Grubbs catalyst⁷ to give tert-cyclopentenone 7 and 8 as an easily distereomic mixture. β-Cyclopentenone 7 underwent oxidative rearrangement on the treatment with PDC⁸,⁹ in DMF to generate cyclopentenone 9, whereas α-cyclopentenone 8 was unreactive in the same reaction conditions. Iodination at α-vinyl position with I₂ and pyridine, stereoselective reduction of ketone with NaBH₄ in the presence of CeCl₃ and protection of the resulting hydroxy group as a TBDPS ether gave the starting material 10 for an iodine-fluorine exchange reaction. Reaction of 10 with BuLi generated vinyl lithium anion, which reacted with NFSI (N-fluorobenzenesulfonylimidate)¹⁰ to afford fluorinated compound 11 after desilylation.
Condensation of 11 with N²-benzoyluracil under Mitsunobu conditions gave 12, which was deprotected leading to 14. The uracil nucleoside 14 was converted to N-hydroxycytosine nucleoside 3 by treating with i) Ac₂O, ii) TIPSCI, iii) NH₂OH, and iv) NH₃.

Scheme 2. Reagents and conditions: (a) N²-benzoyluracil, PPh₃, DEAD, THF; (b) i) NH₂/MeOH; (c) BB₃, CH₂Cl₂ then MeOH; (d) Ac₂O, pyridine; (e) i) TIPSCI, Et₃N, DMAP, CH₃CN; ii) NH₂OH; iii) NH₂/MeOH.

CONCLUSION

Structural characteristics of d-N⁴-hydroxycytidine (1) and fluoroneplanocin A were combined giving the target molecule 3 as potential anti-HCV agent. Iodine-fluorine exchange reaction, RCM, stereoselective reduction of ketone and a Mitsunobu reaction were employed for the synthesis of the target compound.

REFERENCES


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