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Synthesis of 2',3'-Cyclohexene Bicyclic Nucleoside Analogues as Antiviral Compounds

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ABSTRACT

Chiral syntheses of a series of hexahydroisobenzofuran (HIBF) nucleosides have been accomplished via glycosylation of a stereo-defined (*syn*-isomer) sugar motif with the appropriate silylated bases. All nucleoside analogues were obtained in 52-71% yield as a mixture of α- and β-anomeric products increasing the breadth of the novel nucleosides available for screening. Nucleoside derivatives were tested as inhibitor of HIV-1 in human peripheral blood mononuclear (PBM) cells.

INTRODUCTION

Nucleoside analogues are a promising class of compounds in drug development for the treatment of diseases like cancer, fungal, bacterial and viral infections.[1] Consequently, extensive changes have been made to both the heterocyclic base and the sugar moiety to design novel nucleoside analogues with remarkable antiviral and antitumor activities. The anti-HIV studies with various carbohydrate-modified nucleosides have culminated in various structural attributes that contribute to the observed activity. For example, the placement of a 2',3'-double bond in the structures of d4T (**1**, Figure 1), abacavir, reverset (D-d4FC, **2**) and elvucitabine (L-d4TC) is essential to their anti-HIV-1 activity.[2] The acid labile nature of the 2',3'-dideoxypurine analogues can be overcome by introducing a fluorine atom or other hydrophobic groups at the 2' or 3'-positions (structure **3**) of the carbohydrate moiety.[3] Such groups improve the stability of these compounds at a lower pH and increase their lipophilicity for uptake, both essential features for oral delivery of drugs. Also, nucleoside analogues with a variety of conformational restrictions imposed on the sugar ring have resulted in modulation of the enzyme-substrate recognition.[4] In this case the planar pseudo-sugar ring systems are usually preferred. This concept has led to the synthesis of several bicyclic nucleoside analogues with some exhibiting *N*-type (2'-*exo*/3'-*endo*) sugar conformation and antiviral activity.[5]

Based on our ongoing interest[6] in the design of conformationally restricted nucleoside analogues for various drug-discovery approaches, we decided to explore the possibility of introducing foregoing attributes to one molecule and ultimately discover new compounds with antiviral activity. More specifically, we envisioned that a hexahydroisobenzofuran (HIBF) nucleoside, represented by structure **4** (Figure 1), could contain all characteristics discussed above.

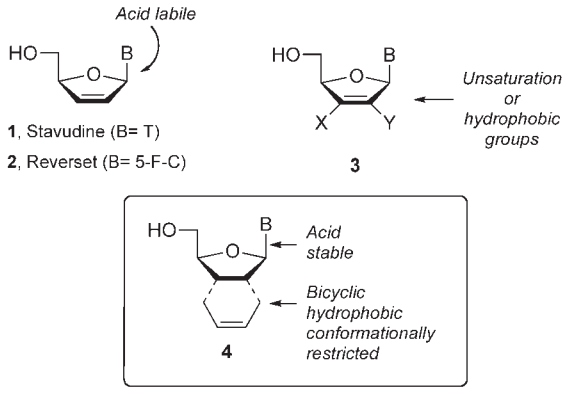
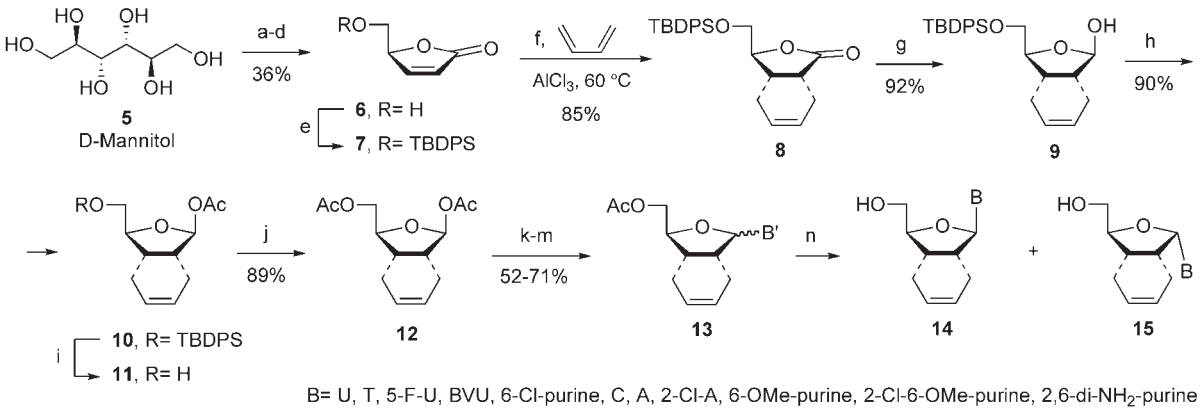


Figure 1. Designed features of modified nucleosides.

With this in mind, we embarked on the synthesis of bicyclic pyrimidine and purine nucleoside derivatives having a cyclohexene ring in the 2',3'-positions of the sugar moiety as a conformationally restricted compounds.

RESULTS AND DISCUSSION

The commercially available D-mannitol (**5**, Scheme 1) was transformed into butenolide **7** via a sequence of steps that includes: (a) acetonide protection of the 1,2 and 5,6 diol; (b) oxidative cleavage of the 3,4 diol; (c) Wittig olefination of the resulting aldehyde; (d) acid-catalyzed acetonide deprotection and lactonization of the resulting hydroxy ester; and (e) silylation of the hydroxyl group.[7] Next, the cyclohexene moiety was introduced via Diels-Alder reaction in 85% yield to furnish **12** after reduction and acylation steps. The target nucleosides **14-15** were prepared under Hilbert-Johnson conditions[8] (silylated base, DBU, TMSOTf) by condensation of the acetate **12** with various purine and pyrimidine bases. This procedure



Scheme 1. Reagents: (a) $SnCl_2$, 2,2-dimethoxypropane/DME; (b) $NaIO_4$, sat. aq. $NaHCO_3/CH_2Cl_2$; (c) $Ph_3P{=}CHCO_2Me$, MeOH; (d) conc. H_2SO_4/MeOH; (e) TBDPSCl, NH_4NO_3, DMF; (f) $AlCl_3$, CH_2Cl_2; (g) DIBAL-H, CH_2Cl_2; (h) Ac_2O, Py; (i) TBAF, THF; (j) Ac_2O, Py; (k) B-H, BSA; (l) DBU; (m) TMSOTf; (n) NH_3/MeOH.

affords a mixture of α- and β- nucleosides **13** in 52-71% overall yield. NOESY measurements confirmed that the β-anomer was the major compound. The nucleosides were deprotected with NH_3/MeOH as shown in Scheme 1.[9]

Additionally, we have studied and demonstrated greater chemical stability of the purine nucleoside **14** (B= A) in acidic media compared to the traditional dideoxynucleosides such as ddA.

These nucleoside analogues were tested against HIV-1 (strain LAI) and compared to those of 3'-azido-3'-deoxythymidine (AZT, zidovudine) in an assay with human peripheral blood mononuclear (PBM) cells. In general, the purine nucleosides were found to be more potent than the corresponding pyrimidine nucleosides, with the exception of β-5-(2-bromovinyl)uridine HIBF derivative. The structural resemblance of the ddI and HIBF inosine analogue is remarkable and warrants further studies with the HIBF series of purine nucleosides.

CONCLUSION

In summary, the present study provides for the first time a direct access to a variety of novel bicyclic nucleoside analogues starting with D-mannitol. The anti-HIV-1 activity exhibited by purine analogues is of particular interest because of the close resemblance with the US FDA approved anti-HIV-1 drug ddI.

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