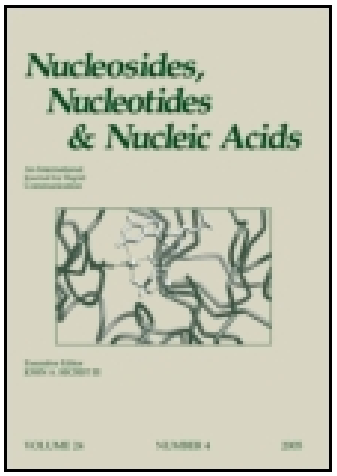

Nucleosides, Nucleotides and Nucleic Acids

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Isonucleosides: Design and Synthesis of New Isomeric Nucleosides with Antiviral Potential

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ISONUCLEOSIDES: DESIGN AND SYNTHESIS OF NEW ISOMERIC NUCLEOSIDES WITH ANTIVIRAL POTENTIAL

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□ *Isonucleosides discovered in our laboratory have been found to have interesting antiviral activity. The design, development of methodology, and stereochemical synthesis of new isonucleosides of anti-HCV interest are described. Antiviral results are cited.*

Keywords Isonucleosides; stereochemical synthesis; antiviral activity

INTRODUCTION

Oxetanocin, a natural nucleoside with a surrogate carbohydrate moiety isolated from bacterial sources, exhibits, anti-HIV activity.[1] In designing ring-expanded analogues of oxetanocin that would have the potential for antiviral activity, we focused on a combination of the structural features of the surrogate carbohydrate moiety of oxetanocin with the sugar component of another antiviral compound, 4(*S*)-(adenin-9-yl)-2(*S*)-hydroxymethyltetrahydrofuran [(*S*, *S*)-isoddA]. The isomeric nucleoside, (*S*, *S*)-isoddA, exhibits potent anti-HIV activity against HIV-1, HIV-2, and HIV- resistant strains.[2,3] (*S*,*S*)-IsoddATP is among the strongest known inhibitors of HIV reverse transcriptase. (*S*, *S*)-IsoddA also showed in vitro anti-HBV activity. Isonucleosides also have been discovered that show anti-HSV activity.[4,5]

In the course of this work with isomeric nucleoside analogs of oxetanocin A, we discovered isonucleoside **6**, which exhibited interesting antiviral activity against HCV (Scheme 1).[6] In this report, we describe the design, stereochemical approaches and total synthesis of two new

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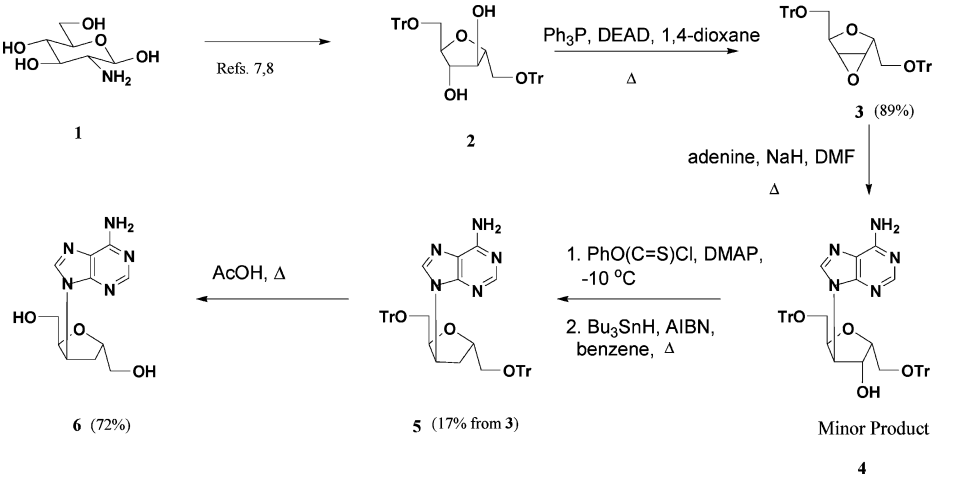
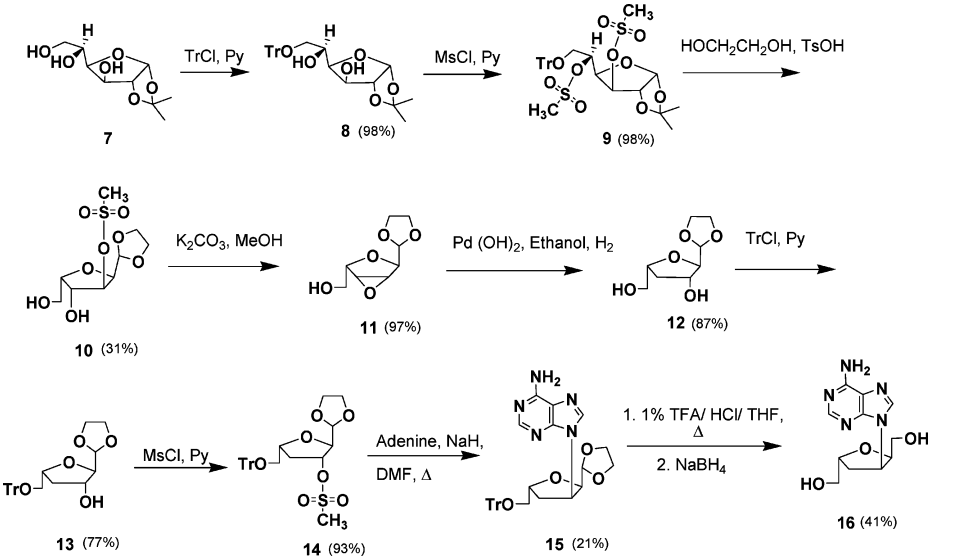
isonucleosides related to our anti-HCV compound. Preliminary antiviral information is mentioned.



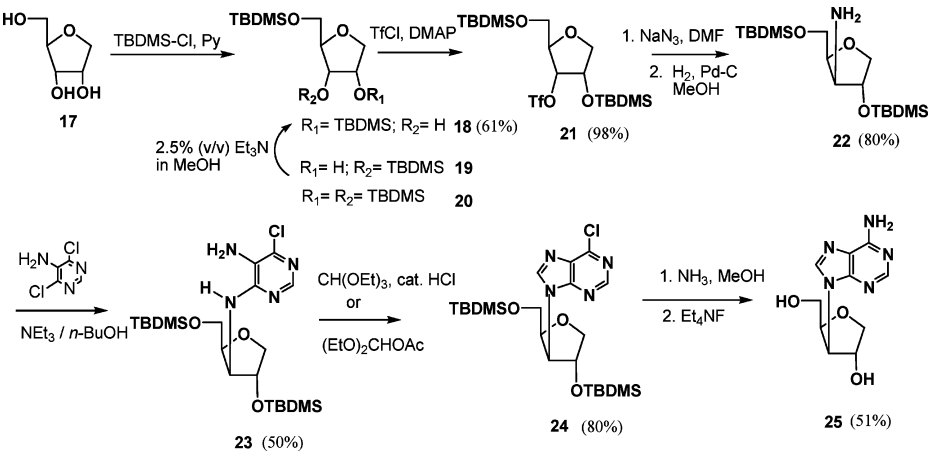
SCHEME 1 Synthesis of an anti-HCV compound (**6**).

RESULTS AND DISCUSSION

The enantiomer of the anti-HCV compound, **6**, was a logical extension of our work. Synthesis of this enantiomer is presented in Scheme 2. The starting material was 1,2-O-isopropylidene-α-D-glucofuranose (**7**), which



SCHEME 2 Methodology for synthesis of the enantiomer of the anti-HCV compound **6**.



SCHEME 3 Synthesis of a 3'-isonucleoside analogue of compound **6.**

was tritylated at the primary hydroxyl group and then mesylated at both secondary hydroxyl groups to give **9**. Acid-catalyzed rearrangement of **9** to **10** followed by an intramolecular S_N2 reaction led to the epoxide **11**. Cleavage of the epoxide under hydrogenation conditions, protection of the primary hydroxyl group by tritylation, and mesylation of the secondary hydroxyl functionality produced the key intermediate **14**. Coupling of **14** with sodium adenine and deprotection gave the target enantiomeric compound **16**, which was purified by reversed-phase HPLC. Structures of this and other target molecules described in this paper were established by HRMS, UV and multinuclear NMR data including COSY and HMBC data.

The second synthesis involved an analogue with an α-hydroxyl group at the position adjacent to the base moiety. This synthesis commenced with ribitol (**17**),[9] which was treated with TBDMS-Cl in pyridine to give a mixture of **18**, **19,** and **20**. Compound **19** could be converted to the desired intermediate **18** by a base-catalyzed rearrangement. The free hydroxyl group was esterified with triflic chloride and DMAP, and the adenine base was constructed using standard methodology as illustrated in Scheme 3. The target molecule was purified by reversed-phase HPLC.

Finally, it should be stated that while compound **6** exhibited in vitro anti-HCV activity, its enantiomer, **16,** was inactive. Compound **25** also did not show anti-HCV activity. Other analogues of compound **6** are currently under investigation.

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