

This article was downloaded by:

On: 25 January 2011

Access details: *Access Details: Free Access*

Publisher *Taylor & Francis*

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



## **Nucleosides, Nucleotides and Nucleic Acids**

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597286>

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

Vasu Nair<sup>a</sup>; Dorota G. Piotrowska<sup>a</sup>; Maurice Okello<sup>a</sup>; Jean Vadakkan<sup>a</sup>

<sup>a</sup> Center for Drug Discovery and the Department of Pharmaceutical and Biomedical Sciences, University of Georgia, Athens, Georgia, USA

**To cite this Article** Nair, Vasu , Piotrowska, Dorota G. , Okello, Maurice and Vadakkan, Jean(2007) 'Isonucleosides: Design and Synthesis of New Isomeric Nucleosides with Antiviral Potential', *Nucleosides, Nucleotides and Nucleic Acids*, 26: 6, 687 — 690

**To link to this Article:** DOI: 10.1080/15257770701490639

**URL:** <http://dx.doi.org/10.1080/15257770701490639>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

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

Vasu Nair, Dorota G. Piotrowska, Maurice Okello, and Jean Vadakkan □

Center for Drug Discovery and the Department of Pharmaceutical and Biomedical Sciences,  
University of Georgia, Athens, Georgia, USA

□ *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.<sup>[1]</sup> 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.<sup>[2,3]</sup> (*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.<sup>[4,5]</sup>

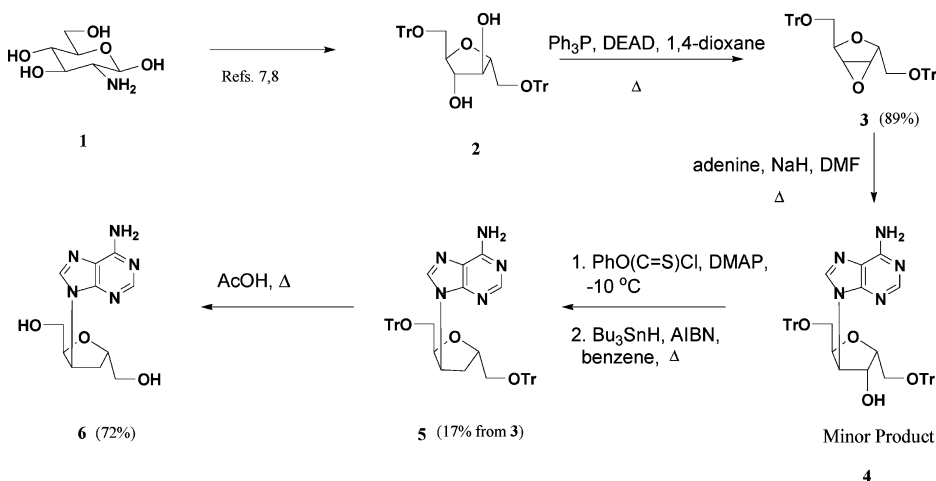
In the course of this work with isomeric nucleoside analogs of oxetanocin A, we discovered isonucleoside **6**, which exhibited interesting antiviral activity against HCV (Scheme 1).<sup>[6]</sup> In this report, we describe the design, stereochemical approaches and total synthesis of two new

This project was supported by the National Institutes of Health (NIAID). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

Dorota G. Piotrowska is on leave of absence from the Medical University of Łódź Poland

Address correspondence to Vasu Nair, Department of Pharmaceutical and Biomedical Sciences, University of Georgia, Athens, GA 30602-2352, USA. E-mail: vnair@rx.uga.edu

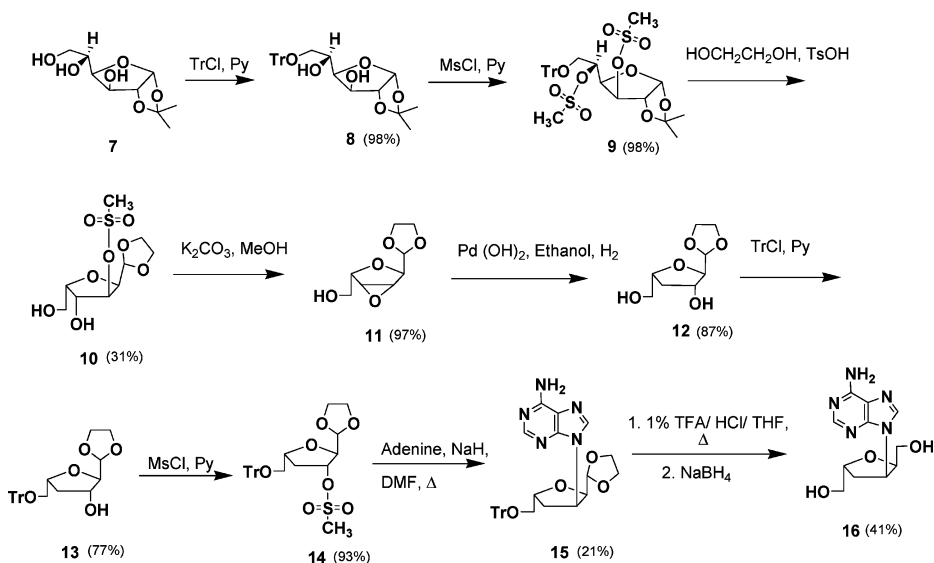
isonucleosides related to our anti-HCV compound. Preliminary antiviral information is mentioned.



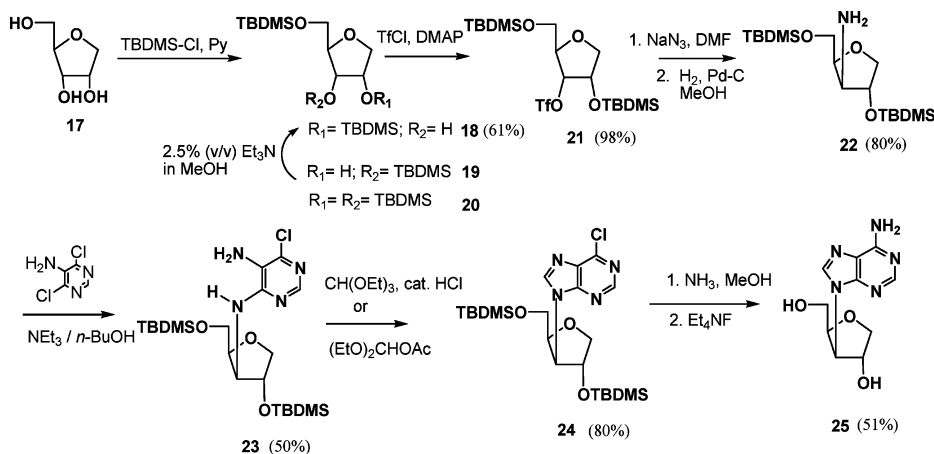
**SCHEME 1** Synthesis of an anti-HCV compound (**6**).

## 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- $\alpha$ -D-glucofuranose (**7**), which



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



SCHEME 3 Synthesis of a 3'-isomeric nucleoside 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<sub>N</sub>2 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  $\alpha$ -hydroxyl group at the position adjacent to the base moiety. This synthesis commenced with ribitol (**17**),<sup>[9]</sup> 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.

## REFERENCES

1. Hoshino, H.; Shimizu, N.; Shimada, N.; Takita, T.; Takeuchi, T. Inhibition of infectivity of human immunodeficiency virus by oxetanocin. *J. Antibiot.* **1987**, 40, 1077–1078.

2. Nair, V.; St. Clair, M.; Reardon, J.E.; Krasny, H.C.; Hazen, R.J.; Paff, M.T.; Boone, L.R.; Tisdale, M.; Najera, I.; Dornsife, R.E.; Everett, D.R.; Borroto-Esoda, K.; Yale, J.L.; Zimmerman, T.P.; Rideout, J.L. Antiviral, metabolic and pharmacokinetic studies on the isomeric dideoxynucleoside, 4(S)-(6-amino-9H-purin-9-tetrahydro-2(S)-furanmethanol. *Antimicrob. Agents Chemother.* **1995**, 39, 1993–1999.
3. Nair, V.; Jahnke, T.S. Antiviral activity of isomeric dideoxynucleosides of D- and L- related stereochemistry. *Antimicrob. Agents Chemother.* **1995**, 39, 1017–1029.
4. Tino, J.A.; Clark, J.M.; Field, A.K.; Jacobs, G.A.; Lis, K.A.; Michalik, T.L.; McGeever-Rubin, B.; Slusarchyk, W.A.; Spergel, S.H.; Sundeen, J.E.; Tuomari, A.V.; Weaver, E.R.; Young, M.G.; Zahler, R. Synthesis and antiviral activity of novel isonucleoside analogs. *J. Med. Chem.* **1993**, 36, 1221–1229.
5. Guenther, S.; Balzarini, J.; De Clercq, E.; Nair, V. A thymidine phosphorylase-stable analog of BVDU with significant antiviral activity. *J. Med. Chem.* **2002**, 45, 5426–5428.
6. Nair, V.; Chun, B.-K.; Vadakkan, J.J. Ring-expanded analogues of natural oxetanocin. *Tetrahedron* **2004**, 60, 10261–10268.
7. Horton, D.; Philips, K.D. The nitrous acid deamination of glycosides and acetates of 2-amino-2-deoxy-D-glucose. *Carbohydr. Res.* **1973**, 30, 367–374.
8. Guthrie, R.-D.; Jenkins, I.-D.; Walter, J.J.; Wright, M.W.; Yamasaki, R. Synthesis of some derivatives of 2,5-anhydro-D-mannitol. *Aust. J. Chem.* **1982**, 35, 2169–2173.
9. Nair, V.; Nuesca, Z.M. Isodideoxynucleosides: a conceptually new class of nucleoside antiviral agents. *J. Am. Chem. Soc.* **1992**, 114, 7951–7953.