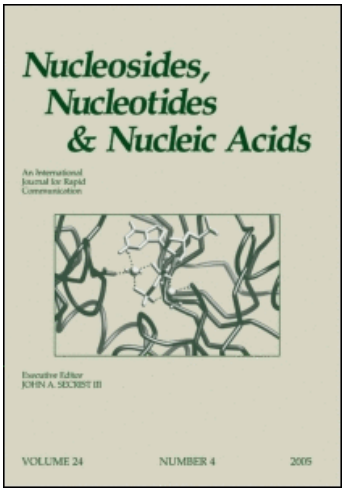

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RING-EXPANDED ANALOGUES OF NATURAL OXETANOCIN: (+) AND (−) HYDROXYMETHYL ISODIDEOXYADENOSINE

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▫ *New enantiomeric isonucleoside analogues related to natural oxetanocin have been synthesized from* D*-glucosamine and* D*-glucose. The structures of the target compounds were confirmed by NMR, HRMS, UV, single crystal X-ray, and optical rotation data. Stability studies with respect to purine nucleoside phosphorylase and adenosine deaminase show that these compounds are not substrates. Antiviral results are discussed.*

Keywords Oxetanocin, Isonucleoside, Chiral Synthesis, Antiviral

INTRODUCTION

The anti-HIV active compound, oxetanocin **1** (Figure 1), isolated from bacteria has a ring-contracted surrogate carbohydrate moiety.[1] In designing antiviral analogues of oxetanocin with a tetrahydrofuran ring in place of an oxetane, we combined some of the structural features of the surrogate carbohydrate moiety of oxetanocin with that of a potent antiviral compound, 4(*S*)-(adenin-9-yl)-2(*S*)-hydroxymethyltetrahydrofuran [(*S,S*)-isoddA] (**2**).[2–4] Compound **2** exhibits potent anti-HIV activity against HIV-1, HIV-2, and HIV-resistant strains. (*S,S*)-IsoddA triphosphate is among the strongest known inhibitors of HIV reverse transcriptase.[2] In addition, another isomeric nucleoside related to oxetanocin and bearing a tetrahydrofuranyl moiety shows antiviral activity against HSV-1 and HSV-2.[5] This paper reports on the chemistry and biology of the enantiomeric isonucleosides **3** and **4** (Figure 1).

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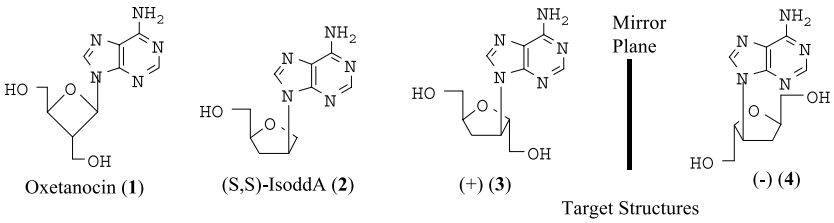


FIGURE 1 Structures of compounds 1, 2, 3 and 4.

RESULTS AND DISCUSSION

Retrosynthetic analysis revealed that the (+) enantiomer would be accessible through an epoxide[6–8] derived from D-glucosamine and the (−) enantiomer through an intermediate accessible through a rearrangement reaction[9,10] from D-glucose derivative (Figure 2).

The total synthesis of the (+) isomer is shown in Scheme 1.

Details of the synthesis of the (−) isomer are shown in Scheme 2.

The structures of the target compounds and intermediates were confirmed by NMR, HRMS, UV spectral data. Compounds **3** and **4** gave identical ^{1}H and ^{13}C NMR spectra except that compound **3** was dextrorotatory and compound **4** was levorotatory with approximately the same magnitude of optical rotation. Final confirmation of structure and stereochemistry came from the single crystal X-ray data for compound **4**.

Compounds **3** and **4** were not substrates for adenosine deaminase and purine nucleoside phosphorylase. Anti-HIV evaluations showed that these compounds were either devoid of anti-HIV activity or had low anti-HIV activity. Other antiviral studies are in progress.

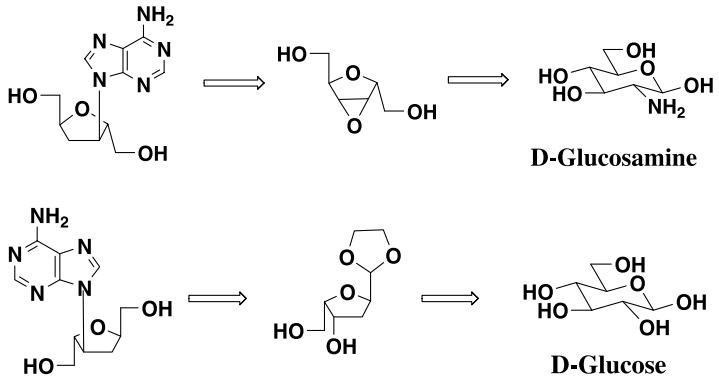
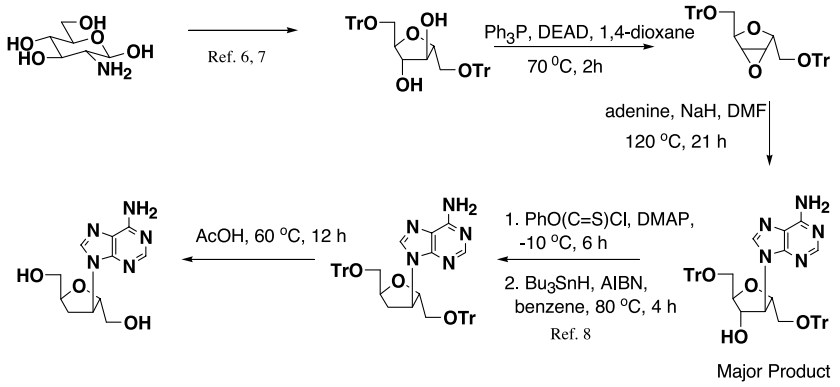
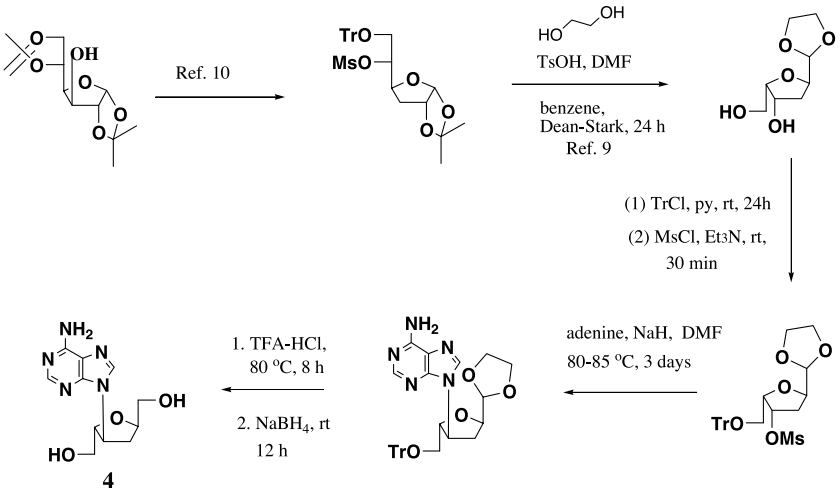


FIGURE 2 Retrosynthetic analysis.



SCHEME 1 Synthesis of compound 3.



SCHEME 2 Synthesis of compound 4.

REFERENCES

1. Hoshino, H.; Shimizu, N.; Shimada, N.; Takita, T.; Takeuchi, T.J. Inhibition of infectivity of human immunodeficiency virus by oxetanocin. Antibiotics **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. Nair, V. Antiviral isonucleosides: discovery, chemistry and chemical biology. In *Recent Advances in Nucleosides: Chemistry and Chemotherapy*; Chu, C.K., Ed.; Elsevier Science: Amsterdam, Netherlands, 2002; 149–166.
5. 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.

6. 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.
7. 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.
8. Nair, V.; Buenger, G.S. Novel, stable congeners of the antiretroviral compound, 2′,3′-diedoxyadenosine. J. Am. Chem. Soc. **1989**, *111*, 8502–8504.
9. Defaye, J.; Horton, D.; Musser, M. Methanolysis of 1,2-O-isopropylidene-5-O-p-toluenesulfonylpentofuranoses: influence of steric factors on the formation of 2,5-anhydropentose dimethyl acetals. Carbohydr. Res. **1971**, *20*, 305–318.
10. Bolon, P.J.; Jahnke, T.S.; Nair, V. Homologues of anti-HIV active isodideoxynucleosides. Tetrahedron **1995**, *51*, 10443–10452.