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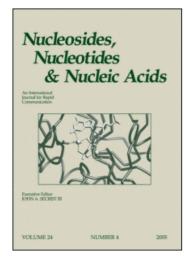
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Nucleosides, Nucleotides and Nucleic Acids

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Synthesis of 2',3'-Dideoxy-3'-C-Hydroxymethyl Nucleosides Having the L-Configuration as Potential Inhibitors of HIV

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SYNTHESIS OF 2',3'DIDEOXY-3'-C-HYDROXYMETHYL NUCLEOSIDES HAVING THE L-CONFIGURATION AS POTENTIAL INHIBITORS OF HIV

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Abstract

Synthesis of 2',3'-Dideoxy-3'-C-(hydroxymethyl)- α - and β -L-erythro-pento-furanosyl nucleosides of thymine, cytosine and adenine is reported.

Recently we published¹ the synthesis of some 2',3'-dideoxy-3'-C-hydroxy-methyl nucleosides. One of the compounds in this series, 2',3'-dideoxy-3'-C-hydroxy-methylcytidine 1, was found to be a potent inhibitor of HIV activity *in vitro*.

HO HO HO NH2

$$N = 0$$
 $N = 0$
 $N = 0$

The synthetic route that was developed for 1¹ provides an easy access to the enantiomers of these 3'-C-hydroxymethyl nucleosides. Since enantiomers of biologically active compounds often differ in both potency and selectivity, we decided to synthesize 2 which is the enantiomer of 1 along with the adenosine and thymidine

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Scheme Ia

analogues and to evaluate their anti-HIV activity *in vitro*. An attempt to explore the chiral origin of recognition was recently explored in the synthesis of L-3'-azido--3'-deoxythymidine. The described anti-HIV activity of this compound was however very low.²

As starting material for the synthesis of 2, the chiral epoxide 3 was used in place of epoxide 4, both readily available using the Sharpless epoxidation procedure.³

The L-furanoside 8 thus obtained was condensed with silylated thymine, cytosine and 6-chloropurine respectively according to the Vorbrüggen procedure⁴ to give a mixture of α - and β -nucleoside derivatives. These intermediates were processed further as previously described¹ to give compounds 2 and 9-13. The optical rotations of the nucleosides 2 and 9-13 differ in absolute value from the enantiomeric nucleosides,

 ⁽a) AllylMgBr, diethyl ether, -50 °C;
 (b) BzCl, pyridine;
 (c) OsO₄, N-methylmorpholine N- oxide, THF-H₂O;
 (d) NaIO₄, THF-H₂O;
 (e) HCl, MeOH;
 (f) Na, NH₃;
 (g) Silylated thymine, TBDMSOTf, CH₂Cl₂;
 (h) Silylated cytosine, TBDMSOTf, CH₂Cl₂;
 (i) Silylated 6-Cl-purine, TBDMSOTf, CH₂Cl₂;
 (j) NH₃, MeOH.

which most likely reflex a difference in water content. Compounds 2 and 9-13 were tested for inhibition of HIV multiplication in H-9⁵ cells but were all found to be inactive.

Experimental

General methods were the same as those previously described.¹ All substances were prepared and analysed following the same procedure as for the preparation of the enantiomerical compound.¹ The NMR spectra were identical with those for the enantiomerical compound.

(2R,3S)-1-
$$O$$
-(p -Bromobenzyl)-3-(2'-propenyl)-1,2,4-butanetriol (5). Yield 71%. [α]²²D -1.4° (c 1.00, CHCl₃).

(2R,3S)-4-*O*-Benzoyl-1-*O*-(*p*-bromobenzyl)-3-(2'-propenyl)-1,2,4-butanetriol (6). Yield 78%. [
$$\alpha$$
]²²_D -9.9° (*c* 1.06, CHCl₃).

Methyl 3-C-[(Benzoyloxy)methyl]-5-O-(p-bromobenzyl)-2,3-dideoxy- α - and β -L--erythro-pentofuranoside (7).

Yield 81%.

Methyl 5-O-Benzoyl-3-C-[(benzoyloxy)methyl]-2,3-dideoxy- α - and β -L-erythro-pentofuranoside (8).

Yield 94%.

1-[2',3'-Dideoxy-3'-C-(hydroxymethyl)- α - and β -L-erythro-pentofuranosyl]-thymine (9 and 10).

9: Yield 36%. [α]²²_D +8.3⁰ (c 0.48, H₂O); UV (H₂O) λ_{max} 268 nm (ϵ 7976). **10**: Yield 41%. [α]²²_D -21.2⁰ (c 0.32, H₂O); UV (H₂O) λ_{max} 268 nm (ϵ 8123).

1-[2',3'-Dideoxy-3'-C-(hydroxymethyl)- α - and β -L-erythro-pentofuranosyl]-cytosine (11 and 2).

11: Yield 24%. [α]²²_D +57.3⁰ (c 0.61, H₂O); UV (H₂O) λ_{max} 272 nm (ϵ 7647). 2: Yield 20%. [α]²²_D -76.3⁰ (c 1.14, H₂O); UV (H₂O) λ_{max} 272 nm (ϵ 5333).

9-[2',3'-Dideoxy-3'-C-(hydroxymethyl)- α - and β -L-*erythtro*-pentofuranosyl]-adenine (12 and 13).

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12: Yield 14%. $[\alpha]^{22}_D$ -45.2° (c 0.37, H₂O); UV (H₂O) λ_{max} 260 nm (ϵ 10987). 13: Yield 21%. $[\alpha]^{22}_D$ +22.5° (c 0.44, H₂O); UV (H₂O) λ_{max} 260 nm (ϵ 11482).

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