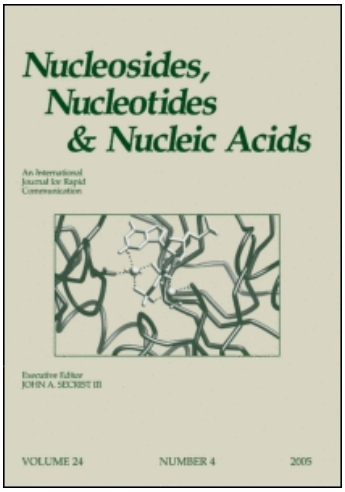


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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

Ingemar Kvarnström[a]; Lars Svansson[a]; Carina Svensson[a]; Stefan[a]; C. T. Svensson[a]; Björn Classon[b]; Bertil Samuelsson[bc]
[a] Department of Chemistry, Linköping University, Linköping, Sweden [b] Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, Stockholm, Sweden [c] Astra Hässle AB, Mölndal, Sweden

To cite this Article Kvarnström, Ingemar , Svansson, Lars , Svensson, Carina , Stefan, Svensson, C. T. , Classon, Björn and Samuelsson, Bertil(1992) 'Synthesis of 2',3'-Dideoxy-3'-C-Hydroxymethyl Nucleosides Having the L-Configuration as Potential Inhibitors of HIV', Nucleosides, Nucleotides and Nucleic Acids, 11: 7, 1367 — 1370
To link to this Article: DOI: 10.1080/07328319208021179
URL: http://dx.doi.org/10.1080/07328319208021179

NUCLEOSIDES & NUCLEOTIDES, 11(7), 1367-1370 (1992)

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

Ingemar Kvarnström, Lars Svansson, Carina Svensson and Stefan C. T. Svensson.

Department of Chemistry, Linköping University, S-581 83 Linköping, Sweden

Björn Classon and Bertil Samuelsson†*

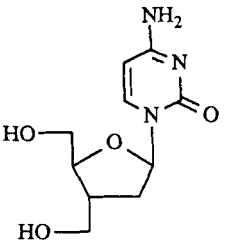
Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, S-106 91 Stockholm, Sweden

†*Address also: Astra Hässle AB, S-431 83 Mölndal, Sweden*

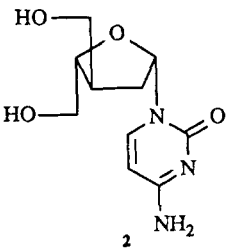
Abstract

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

Recently we published[1] the synthesis of some 2',3'-dideoxy-3'-*C*-hydroxymethyl nucleosides. One of the compounds in this series, 2',3'-dideoxy-3'-*C*-hydroxymethylcytidine **1**, was found to be a potent inhibitor of HIV activity *in vitro*.



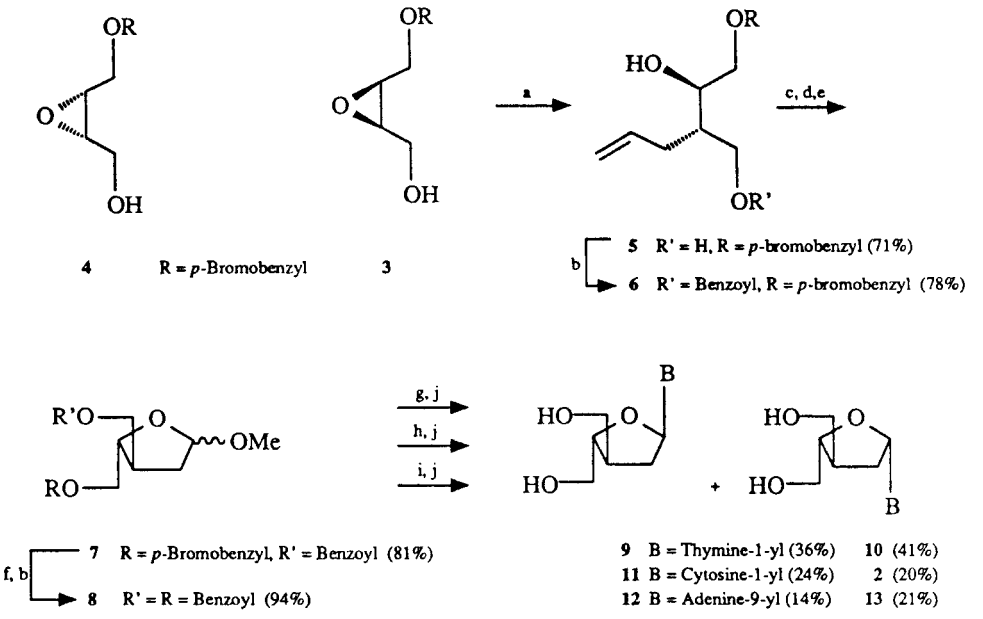
1



2

The synthetic route that was developed for **1**[1] 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

Scheme I[a]



[a] (a) AllylMgBr, diethyl ether, -50 °C; (b) BzCl, pyridine; (c) OsO_4, *N*-methylmorpholine *N*- oxide, THF-H_2O; (d) $NaIO_4$, THF-H_2O; (e) HCl, MeOH; (f) Na, NH_3; (g) Silylated thymine, TBDMSOTf, CH_2Cl_2; (h) Silylated cytosine, TBDMSOTf, CH_2Cl_2; (i) Silylated 6-Cl-purine, TBDMSOTf, CH_2Cl_2; (j) NH_3, MeOH.

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 procedure[4] to give a mixture of α- and β-nucleoside derivatives. These intermediates were processed further as previously described[1] 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,

which most likely reflex a difference in water content. Compounds **2** and **9-13** were tested for inhibition of HIV multiplication in H-9[5] 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%. $[\alpha]^{22}_D$ -1.4° (*c* 1.00, $CHCl_3$).

(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, $CHCl_3$).

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%. $[\alpha]^{22}_D$ +8.3^0 (*c* 0.48, H_2O); UV (H_2O) λ_{max} 268 nm (ϵ 7976). **10**: Yield 41%. $[\alpha]^{22}_D$ -21.2^0 (*c* 0.32, H_2O); UV (H_2O) 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%. $[\alpha]^{22}_D$ +57.3^0 (*c* 0.61, H_2O); UV (H_2O) λ_{max} 272 nm (ϵ 7647). **2**: Yield 20%. $[\alpha]^{22}_D$ -76.3^0 (*c* 1.14, H_2O); UV (H_2O) λ_{max} 272 nm (ϵ 5333).

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

12: Yield 14%. $[\alpha]^{22}_D$ -45.2^0 (*c* 0.37, H_2O); UV (H_2O) λ_{max} 260 nm (ϵ 10987).
13: Yield 21%. $[\alpha]^{22}_D$ +22.5^0 (*c* 0.44, H_2O); UV (H_2O) λ_{max} 260 nm (ϵ 11482).

Acknowledgement. We thank the Swedish National Board of Industrial Technical Development and Medivir AB for financial support, and Medivir AB for carrying out the biological testing.

REFERENCES

(1) Svansson, L.; Kvarnström, I.; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1991**, *56*, 2993.
(2) Wengel, J.; Lau, J.; Pedersen, E. B.; Nielsen; C. M. *J. Org. Chem.* **1991**, *56*, 3591.
(3) Chong, J. M.; Wong, S. *J. Org. Chem.* **1987**, *52*, 2596.
(4) Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234.
(5) Vial, J-M.; Johansson, N. G.; Vrang, L.; Chattopadhyaya, J. *Antiviral Chem. and Chemotheraphy*. **1990**, *1*, 183

Received 12/17/91
Accepted 4/21/92