



SYNTHESIS AND ANTIVIRAL ACTIVITY OF 2-DEOXY-1,5-ANHYDRO-D-MANNITOL NUCLEOSIDES CONTAINING A PYRIMIDINE BASE MOIETY

María-Jesús Pérez-Pérez, Erik De Clercq and Piet Herdewijn*

Rega Institute for Medical Research, K.U.Leuven, B-3000 Leuven, Belgium.

Fax: +32 16 33.73.87, E-mail : Piet.Herdewijn@Rega.KULeuven.ac.be

Abstract : Nucleoside analogues containing a 2-deoxy-1,5-anhydro-D-mannitol and a pyrimidine base moiety were synthesized starting from D-glucose via a nucleophilic opening of an epoxide with the heterocyclic base and an inversion of configuration at the 3'-position. Study of the conformation of these molecules, that show some activity against herpesviruses (HSV, VZV, CMV) should increase our understanding of the structural requirements of hexitol nucleosides for antiviral activity. Copyright © 1996 Elsevier Science Ltd

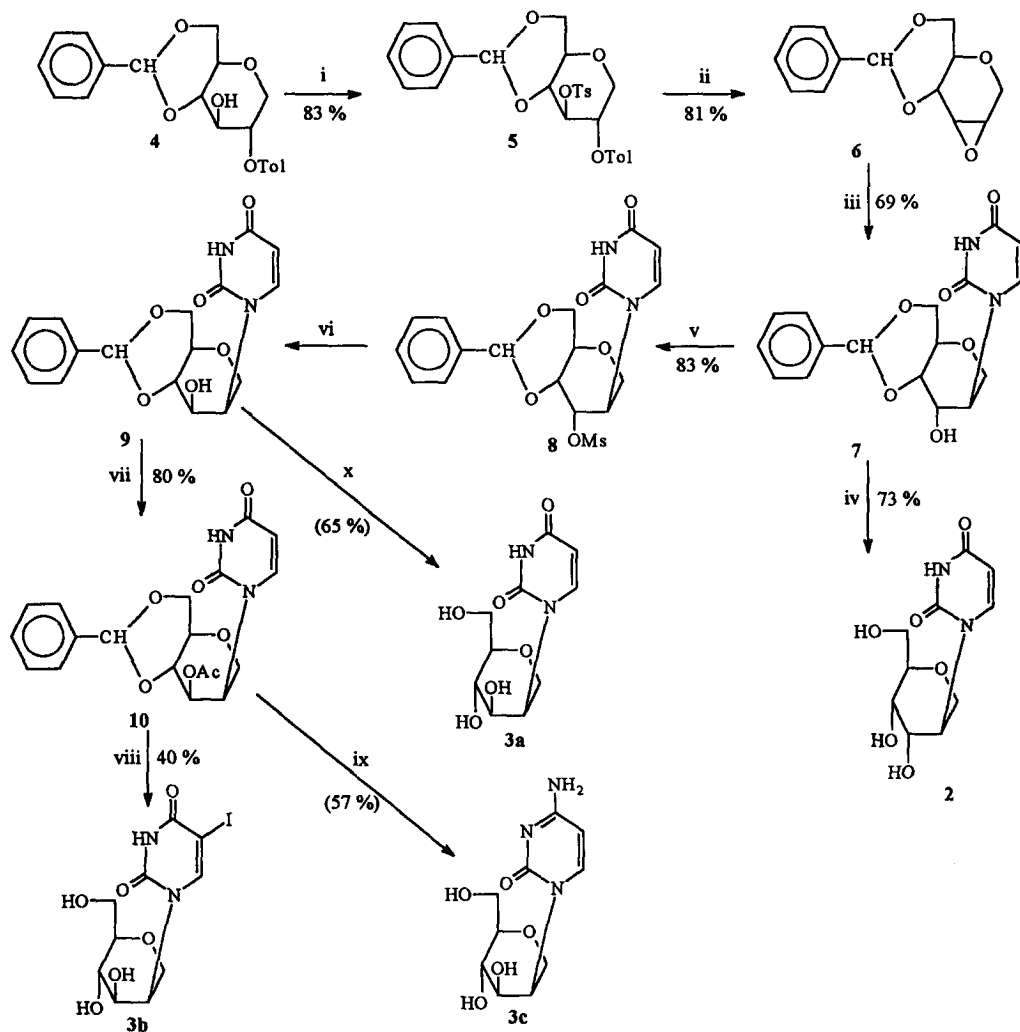
Nucleosides with a 1,5-anhydro-D-*arabino*-hexitol structure, represented by the 5-iodouracil congener **1**, possess selective antiherpes activity^{1,2}. This observation is unique as no other nucleoside with a six membered "pyranose-like structure" with antiviral properties is known. This observation raises questions as to the structural and conformational requirements of "pyranosyl-like" nucleosides necessary for biological activity. Generally, nucleobases in pyranosyl nucleosides are preferentially positioned equatorially even at the expense of axial orientation of one, two or three other substituents³⁻¹⁰ although exceptions to this general rule exist as demonstrated by 2',3'-dideoxy-3'-C-hydroxymethyl-β-D-*erythro*-pentopyranosyl adenine⁹. This conformational preference can be explained by the influence of steric and stereoelectronic factors⁷⁻¹⁰. The situation, however, is different when considering anhydrohexitol nucleosides. These nucleoside analogues do not have an anomeric center. All 1,5-anhydro-D-*arabino*-hexitol nucleosides, represented by formula **1**, have an axial oriented base moiety,^{1,2} which may be explained primarily by the influence of steric factors (see further).

The introduction of a supplementary hydroxyl group in the 3'-position leads to D-altritol **2** (3'-OH in α-position) and D-mannitol **3** (3'-OH in β-position) nucleosides. The introduction of this hydroxyl group may have a further stabilization effect on the aforementioned conformation because of the presence of an additional gauche effect (O3'-C3'-C4'-O4') in both examples. However, only in the case of the D-mannitol nucleosides **3** a second gauche effect (O3'-C3'-C2'-N) is present, while an unfavorable steric effect is created by introduction of the 3'-hydroxyl group in an α-position (D-altritol **2**). Therefore it should be expected that D-mannitol nucleosides **3** adopt the same conformation as D-*arabino*-hexitol nucleosides **1** while the situation is less clear when D-altritol nucleosides are considered. These considerations, together with interests in the structure-antiviral activity relationship, prompted us to undertake the synthesis of the D-mannitol nucleosides **3**. The same synthetic scheme may also lead to the preparation of D-altritol congeners **2**.

The precursor **6** is synthesized from **4**¹ using a tosylation (**5**), epoxidation step. Nucleophilic opening of the epoxide by uracil (NaH, DMF, 120°C)^{11,12} afforded the *altro*-hexitol derivative **7** in 69 % yield. Removal of the benzylidene moiety in 80 % AcOH at 80°C afforded the deprotected uracil derivative **2** (73 % yield). To obtain the mannohexitol nucleosides, the configuration of the 3'-position in **7** was inverted by mesylation and treatment in basic aqueous conditions leading to O²,3'-anhydro formation and "in situ" opening¹³, to afford **9** that was characterized after deprotection of the benzylidene moiety (**3a**, 65 % yield). Compound **9** was acetylated (**10**) before conversion to the cytosine and 5-iodouracil derivatives. Reaction of **10** with POCl₃ and 1,2,4-triazole in Et₃N and acetonitrile¹⁴ afforded the 1,2,4-triazol-1-yl intermediate that was treated with NH₄OH in dioxane to yield the 3'-OH cytosine derivative. Treatment of this derivative with 80 % AcOH at 80°C afforded the fully deprotected cytosine derivative (**3c**, 57 % from **10**). On the other hand, **10** reacted with iodine monochloride in refluxing CH₂Cl₂ to yield the 5-iodouracil derivative, that was characterized after deprotection of the sugar

^(c) Minimum cytotoxic concentration required to cause a microscopically detectable alteration of normal cell morphology : > 400 µg/ml. The concentration required to reduce cell growth by 50 % was > 50 µg/ml^(d) and 30 µg/ml^(e)

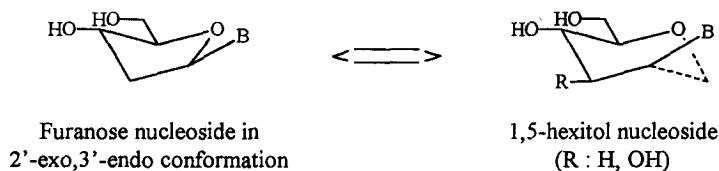
Scheme 1



i : Tosyl chloride, DMAP, Et₃N, CH₂Cl₂, R.T.; ii : NaOMe, MeOH, dioxane, 50°C; iii : uracil, NaH, DMF, 120 °C; iv : HOAc 80 %, 80°C; v : Mesyl chloride, DMAP, pyr, R.T.; vi : NaOH, EtOH, 60 °C; vii : Ac₂O, pyr, R.T. (yield for two steps : vi and vii); viii : ICl, CH₂Cl₂, reflux and HOAc 80 %, 80°C; ix : 1,2,4-triazole, POCl₃, CH₃CN, Et₃N and NH₃, dioxane and HOAc 80 %, x : HOAc 80 %, 80°C (yield for two steps : v and x).

The antiherpes activity of the 2-deoxy-1,5-anhydro-D-mannitol nucleosides is presented in Table 1. Although the antiviral activity is not very high, the compounds clearly show activity, which is in contrast to all pyranose nucleosides with an equatorial base moiety that have been synthesized till now. These results point to the importance of the orientation of the base moiety in hexitol nucleosides. Indeed, a better fit can be found between the hexitol structures as depicted in Figure 2 and furanose nucleosides in their 2'-exo,3'-endo conformation, than between these furanose nucleosides and the hexitol nucleosides in the inverted conformation. That hexitol nucleosides are very good mimics of natural nucleosides in the 2'-exo,3'-endo conformation has also been confirmed when using hexitol nucleosides as building blocks in oligonucleotide synthesis. These oligonucleotides fit very well for A-RNA¹⁵.

Figure 2



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