Tetrahedron 64 (2008) 6657–6661

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of 2′-*C*-methyl-branched isonucleosides

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ARTICLE INFO

Article history:
Received 8 April 2008
Accepted 7 May 2008
Available online 11 May 2008

Keywords:
Nucleoside analogues
Isonucleosides
Valopicitabine
Hepatitis C
Anti-virals

ABSTRACT

Novel regioisomers of 2′-methyl-branched nucleosides were designed and synthesized to mimic potent anti-viral drugs like Valopicitabine. The short and efficient synthesis of the targets involves a one-pot tosylation/cyclization step that leads to an activated furan scaffold on which the isonucleosides were built.

1. Introduction

In the course of our ongoing research program aiming at the discovery of potential new anti-viral agents, we became interested in regioisomeric nucleoside analogues ('isonucleosides') in which the nucleobase is attached to a position other than C-1 of the sugar. Indeed, these molecules are likely to exhibit better stability and resistance toward enzymatic degradation than natural nucleosides. Moreover, they increase the chemical diversity at the disposition of medicinal chemists involved in the preparation of modified nucleosides.

In recent years, isonucleosides have attracted the attention of many groups[1–7] and some of the compounds showed significant activity against human immunodeficiency (HIV) or herpes simplex viruses.[8–13] For instance, *iso*-ddA (**1**) displays good anti-HIV activity and compares favorably to ddA (**2**), its regioisomer with a nature-like structure (Fig. 1).[14] Hence, it appeared relevant to consider the preparation of isonucleoside analogues of other anti-virals, aimed at increasing their activity and specificity or reducing their toxicity.

2. Results and discussion

2.1. General strategy

Our initial targets were 2′-β-methyl-branched nucleosides. This class of molecules display potent anti-hepatitis C virus (HCV) properties.[15–18] For instance, Valopicitabine the valinyl ester prodrug of 2′-*C*-methyl-cytidine (**3**) reached phase IIb in clinical trials.[19] Its regioisomer **4** was designed by simple transposition of the aglycon from C-1 of the ribose moiety to the methyl branching in C-2. Thus, one might expect that the base in **4** could occupy a position in space similar to that of **3**. In this communication, we present the synthesis of isonucleoside **4** along with its analogues built from other natural bases. All the synthetic routes proceed via a common activated furan intermediate, which is the product of a stereocontrolled ring-closing reaction carried out on a modified ribitol.

The retrosynthetic plan (Fig. 2) shows that we have chosen to introduce the nucleobase in the late stages of the synthesis by an S_N2 reaction. Thus, the route was made more convergent and adaptable to any base. In the first instance, the hemiacetal function of the sugar would have been reduced to a methylene; the preparation

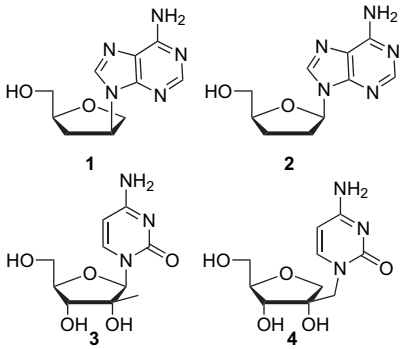

Figure 1.

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doi:10.1016/j.tet.2008.05.022

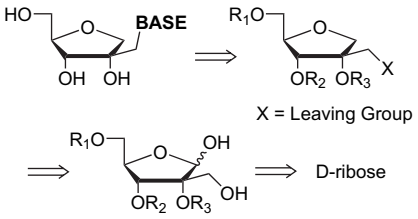
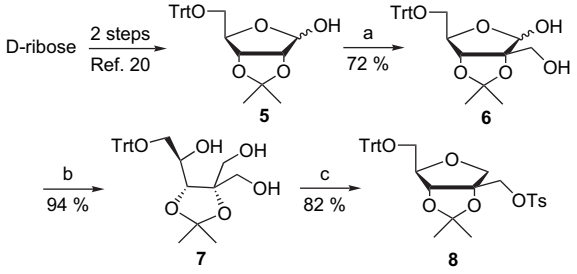


Figure 2. Retrosynthetic analysis.

beginning with a stereoselective β-hydroxymethylation of the starting material D-ribose.

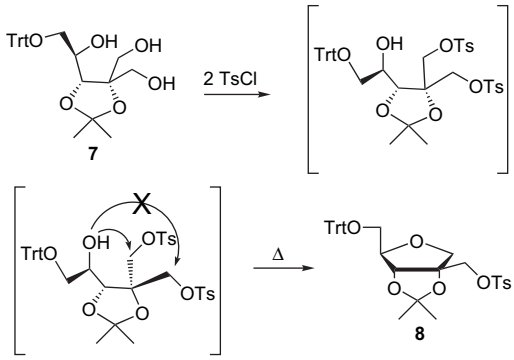
2.2. Preparation of key tosylate 8

Following well established procedures,[20,21] D-ribose was protected by a trityl and an acetonide in two steps to give sugar **5** (Scheme 1). The first important step of the synthesis comprised the selective hydroxymethylation of the protected sugar.[22] When **5** was reacted with paraformaldehyde in the presence of potassium carbonate, only the β-hydroxymethylated sugar was produced. The stereochemical outcome of this thermodynamically controlled reaction is directed by the acetonide protecting group on the vicinal diols. Indeed, the attack of formaldehyde on the α-face of the enolate would result in the formation of a *trans* junction between two fused five-membered rings, which is virtually impossible when a *cis* junction is available.[23] Therefore, the hydroxymethylated sugar **6** was obtained as the sole product of the reaction (as a mixture of α/β anomers). Subsequently, **6** was reduced with sodium borohydride in almost quantitative yield to give ribitol derivative **7**.



Scheme 1. Reagents and conditions: (a) $(CH_2O)_n$, K_2CO_3, MeOH, reflux, 24 h; (b) $NaBH_4$, EtOH, rt, 2 h; (c) TsCl (2.4 equiv), pyridine, rt then 60 °C, 15 h.

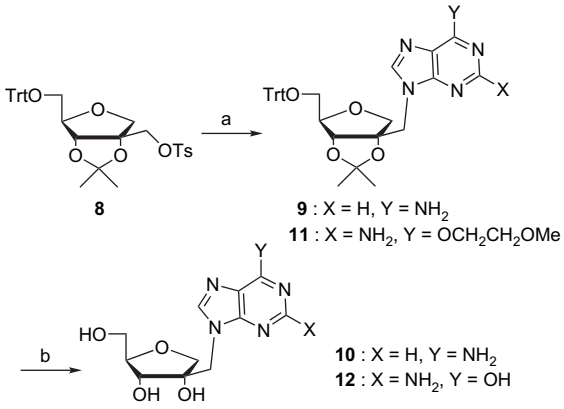
The second key step consisted of the preparation of tosylated furan derivative **8**. Hossain and Herdewijn reported a two-step one-pot cyclization of a protected ribitol using tosyl chloride.[24] We decided to try and adapt their conditions to triol **7**. When the latter was treated with 2.4 equiv of tosyl chloride in pyridine at room temperature, the two primary alcohols reacted readily to provide the ditosylated species shown in Scheme 2. This intermediate was not isolated but instead, forced to cyclize to produce compound **8**. Under the reaction conditions, the secondary alcohol remained available and could react with the tosylates. By just raising up the temperature to 60 °C, the tosylate-promoted cyclization occurred cleanly to give **8** in high yield. Yet again, the isopropylidene protection allowed a perfect regiochemical control of the process for the reasons disclosed earlier.[23] One of the tosylates remained out of the reach of the secondary alcohol during the reaction that only produced the *cis*-[3.3.0] bicyclic **8**. The quaternary carbon formed in the reaction recovered its chirality that was lost after the reduction step. The key tosylated furan derivative **8** was synthesized in 5 steps and 42% yield from D-ribose.



Scheme 2. Regioselective cyclization of ribitol derivative **7**.

2.3. Synthesis of the isonucleosides

With **8** in hand, everything was in place for the introduction of the bases of our isonucleosides. In the first instance, tosylate **8** was treated with the sodium salt of adenine in DMF at 110 °C. The protected isonucleoside **9** was obtained in good yield and eventually lead to the fully deprotected adenosine analogue **10** upon treatment with hot acid. The preparation of its guanine analogue followed a similar pathway: the only difference residing in the use of 2-amino-6-(methoxyethoxy)-purine[25] instead of guanine itself. Indeed, in a previous work,[26] it was observed that this protected purine gives much better results in nucleophilic substitution reactions than free guanine. The condensation step gave slightly lower yields for **11** than for **9** but the synthesis of **12** was still completed in two steps since the triple final deprotection was carried out in one pot using 3 N HCl at 80 °C (Scheme 3).



Scheme 3. Reagents and conditions: (a) for **9**, adenine, NaH, DMF, 110 °C, 15 h, 75%; for **11**, 2-amino-6-(methoxyethoxy)-purine, NaH, DMF, 120 °C, 15 h, 63%; (b) for **10**, 2 N HCl, 80 °C, 2 h, 95%; for **12**, 3 N HCl, 80 °C, 3 h, 70%.

The same approach was applied to pyrimidines. Although uracil is known as a somewhat weaker nucleophile than adenine or other protected purines,[27] we managed to get satisfying results with conditions similar to those previously described for purines (Scheme 4). Tosylate **8** was substituted with the sodium salt of uracil in 24 h in refluxing DMF. Isonucleoside **13**, which was obtained in good yield, was the key intermediate for the preparation of our two pyrimidine targets. When the classical double deprotection conditions in aqueous HCl were applied to **13**, uridine analogue **14** was isolated in almost quantitative yield. On the other hand, **13** could be used in the cytosine base elaboration process described by Miah et al.[28] After activation with trifluoroacetic anhydride and *p*-nitrophenol, **13** was treated with ammonia to give the protected cytidine analogue **15** in moderate yield. The straightforward final