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

Tony Bouisset, Gilles Gosselin, Ludovic Griffe, Jean-Christophe Meillon *, Richard Storer

Laboratoire de Chimie Médicinale Idenix, Cap Gamma, 1682 rue de la Valsière, BP 50001, Montpellier, F-34189 Cedex 4, France

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

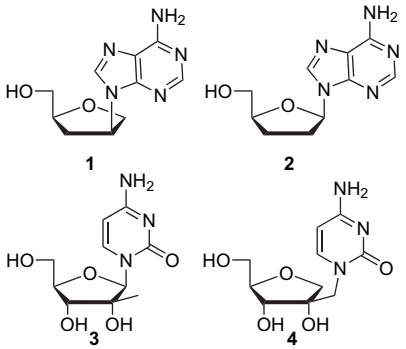


Figure 1.

* Corresponding author. Tel.: +33 4 67637320; fax: +33 4 67637326.
E-mail address: meillon.jean-christophe@idenix.com (J.-C. Meillon).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.05.022

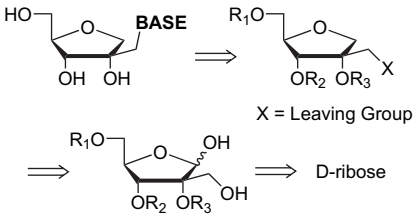
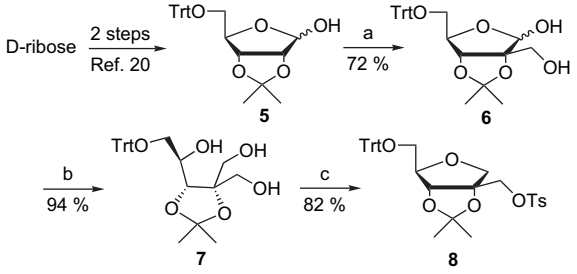


Figure 2. Retrosynthetic analysis.

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

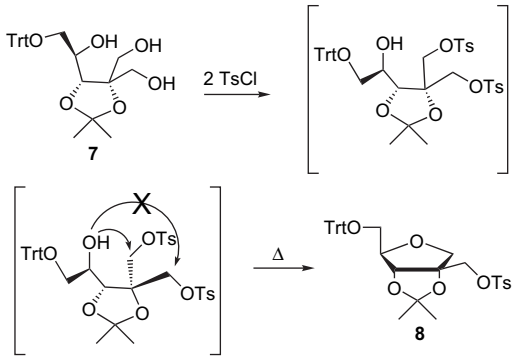
2.2. Preparation of key tosylate 8

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.

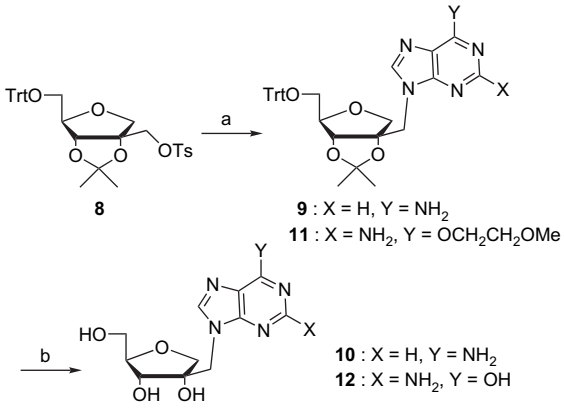
The second key step consisted of the preparation of tosylated furan derivative **8**. Hossain and Herdewijn reported a two-step one-pot cyclization of a protected ribitol using tosyl chloride.[24] We decided to try and adapt their conditions to triol **7**. When the latter was treated with 2.4 equiv 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**.

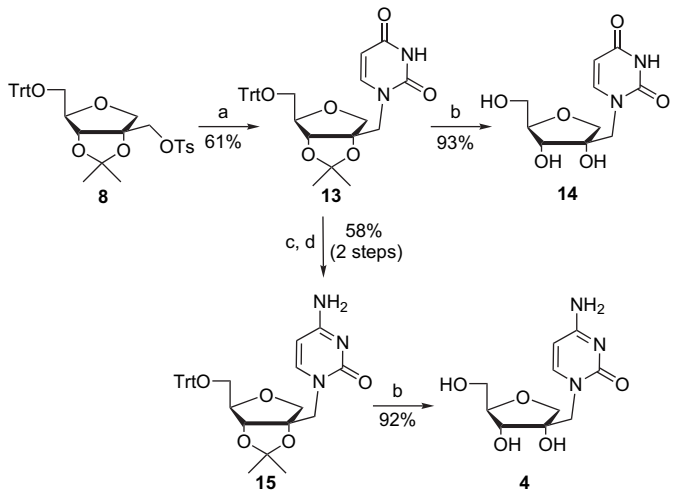
2.3. Synthesis of the isonucleosides

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



Scheme 4. Reagents and conditions: (a) uracil, NaH, DMF, 140 °C, 24 h; (b) 2 N HCl, 80 °C, 2 h; (c) *N*-methylpyrrolidine, trifluoroacetic anhydride then, *p*-nitrophenol, MeCN, 0 °C, 3.5 h; (d) NH_3-saturated MeOH, 100 °C, 5 h.

deprotection of the latter gave **4**, the regioisomer of the anti-hepatitis C drug **3**.

3. Conclusion

We have described a short and efficient synthesis of novel isonucleosides that could possibly mimic known anti-viral drugs. This approach could be easily applied to the preparation of molecules bearing non-natural nucleobases or targetting specific viruses by further simple modifications made to the furan ring.

Compounds **4**, **10**, **12**, and **14** were evaluated for anti-viral activity in cell culture experiments against the following viruses: Hepatitis C (HCV replicon system), Bovine Viral Diarrhea, Human Immunodeficiency, Dengue and West Nile. Neither activity nor cytotoxicity was found for any of these molecules at concentrations of up to 100 μM.

Two hypotheses one could advance to explain this lack of activity are the price paid in terms of entropy by the addition of rotational flexibility between the sugar and the nucleobase or the change in spatial distance between the base and the primary alcohol of the isonucleosides.

4. Experimental section

4.1. General

All ^{1}H chemical shifts are reported in δ relative to $CHCl_3$ (δ 7.26) or DMSO (δ 2.55). All ^{13}C chemical shifts are reported in δ relative to $CDCl_3$ (center of triplet, δ 77.2) or DMSO-d_6 (center of septet, δ 39.5). The spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet), m (multiplet), and br (broad). Reactions were monitored by thin-layer chromatography (TLC) using Merck silica gel 60-F_{254} precoated plates with visualization by irradiation with an UV lamp or by charring after immersion in a solution of $(NH_4)_2SO_4$ and H_2SO_4 in aqueous EtOH. TLC plates were developed with solvent systems (A) EtOAc/hexanes 1:3, (B) EtOAc/hexanes 1:1, (C) DCM/MeOH 9:1 or (D) DCM/MeOH 8:2. Column chromatographies were performed on either silica gel 60 (normal phase) or C_{18}-branched silica gel 40–63 μm (reverse phase) and eluted with the indicated solvent system. Yields refer to chromatographically and spectroscopically (NMR) homogeneous materials. The reactions were generally carried out in an argon atmosphere using Fluka dry solvents. 2-*C*-Hydroxymethyl-2,3-*O*-isopropylidene-5-*O*-triphenylmethyl-D-ribofuranose (**6**) was synthesized according to Ref. 22 and 2-amino-6-(methoxyethoxy)-purine was synthesized according to Ref. 25. All other chemicals were purchased from Sigma-Aldrich or Acros.

4.1.1. *(2R,3R)-1-Bis(hydroxymethyl)-1,2-O-isopropylidene-4-triphenylmethyloxy-butane-1,2,3-triol (**7**)*

To a solution of 2-*C*-hydroxymethyl-2,3-*O*-isopropylidene-5-*O*-triphenylmethyl-D-ribofuranose (**6**) (17.0 g, 36.8 mmol) in EtOH (200 mL) was slowly added a solution of $NaBH_4$ (2.7 g, 70.8 mmol) in EtOH (300 mL). The mixture was stirred for 2 h at room temperature. Then, solid NH_4Cl (17 g) was added and the suspension was stirred for 15 min. After filtration, EtOH was evaporated and the crude material was purified by chromatography (silica gel, DCM/MeOH 97:3) to afford **7** (16.0 g, 94%) as a white foam: TLC R_f=0.46 (C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.38 (s, 3H), 2.54 (br, 1H), 2.69 (t, 1H, J=6.6 Hz), 3.08 (d, 1H, J=3.9 Hz), 3.33 (dd, 1H, J=6.4, 9.6 Hz), 3.50 (dd, 1H, J=3.0, 9.6 Hz), 3.64 (dd, 1H, J=6.6, 11.7 Hz), 3.76–3.90 (m, 4H), 4.01 (d, 1H, J=9.3 Hz), 7.25–7.38 (m, 9H), 7.42–7.50 (m, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 26.5, 28.4, 62.1, 64.8, 65.4, 68.7, 78.6, 84.5, 87.1, 108.7, 127.2, 128.0, 128.6, 143.6; MS(ES) calcd $[M+Na]^+$ ($C_{28}H_{32}NaO_6$): 487, found: 487.

4.1.2. *(1R,2R,3R)-1-(Triphenylmethyloxymethyl)-2,3-O-isopropylidene-3-C-(p-toluenesulfonyloxymethyl)-furan-2,3-diol (**8**)*

To a solution of **7** (12.7 g, 27.3 mmol) in dry pyridine (125 mL) was added tosyl chloride (12.5 g, 65.8 mmol). The solution was stirred at room temperature for 3 h and then, at 60 °C for 15 h. The solvent was evaporated and the crude material was purified by chromatography (silica gel, hexanes/EtOAc 8:2) to afford **8** (13.4 g, 82%) as a white foam: TLC R_f=0.27 (A); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.50 (s, 3H), 2.44 (s, 3H), 3.17 (dd, 1H, J=5.0, 10.2 Hz), 3.24 (dd, 1H, J=4.7, 10.2 Hz), 3.91 (s, 2H), 4.07–4.23 (m, 3H), 4.42 (d, 1H, J=1.9 Hz), 7.25–7.36 (m, 11H), 7.38–7.49 (m, 6H), 7.70 (d, 2H, J=8.1 Hz); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 21.7, 27.5, 27.8, 63.5, 70.1, 75.0, 84.8, 84.9, 87.3, 90.5, 114.7, 127.2, 128.0, 128.7, 129.8, 132.6, 143.5, 144.9, 158.4; MS(ES) calcd $[M+Na]^+$ ($C_{35}H_{36}NaO_7S$): 623, found: 623.

4.1.3. *iso-2′-C-Methyl-2′,3′-O-isopropylidene-5′-O-triphenylmethyl-adenosine (**9**)*

To a stirred suspension of adenine (1.35 g, 9.92 mmol) in DMF (18 mL) was added NaH (60% oil dispersion) (0.33 g, 8.26 mmol) at room temperature. After the evolution of hydrogen had ceased, the creamy mixture was stirred at 80 °C for 20 min. Then, tosylate **8** (2.00 g, 3.33 mmol) dissolved in DMF (18 mL) was added via a syringe. The resulting suspension was stirred at 110 °C for 15 h and then, cooled down to room temperature. The solid was removed by filtration over Celite and rinsed with DCM. The filtrate was evaporated and the brown residue was taken up in DCM (50 mL). The resulting solution was extracted with 0.5 N HCl (50 mL), satd $NaHCO_3$ solution (50 mL), and H_2O (50 mL). After drying over Na_2SO_4, the organic phase was evaporated. The crude material was purified by chromatography (silica gel, DCM/MeOH 96:4) to afford **9** (1.41 g, 75%) as a white foam: TLC R_f=0.47 (C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (s, 3H), 1.50 (s, 3H), 3.29 (dd, 1H, J=5.2, 10.2 Hz), 3.38 (dd, 1H, J=4.7, 10.2 Hz), 3.96 (d, 1H, J=10.1 Hz), 4.13 (d, 1H, J=10.1 Hz), 4.24 (m, 1H), 4.43 (s, 2H), 4.65 (s, 1H), 5.87 (br, 2H), 7.25–7.38 (m, 9H), 7.42–7.50 (m, 6H), 7.85 (s, 1H), 8.25 (s, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 27.6, 27.7, 46.5, 64.1, 76.0, 85.1, 85.5, 87.5, 91.7, 114.2, 119.0, 127.2, 127.9, 128.8, 141.9, 143.6, 150.4, 153.1, 155.4; MS(ES) calcd $[M+H]^+$ ($C_{33}H_{34}N_5O_4$): 564, found: 564.

4.1.4. *iso-2′-C-Methyl-adenosine (**10**)*

A suspension of **9** (1.20 g, 2.13 mmol) in 2 N HCl (50 mL) was heated at 80 °C for 2 h. The mixture was cooled down to room

temperature and extracted with DCM (2×50 mL). The aqueous phase was evaporated and the residue was taken up in H_2O (30 mL). The resulting solution was neutralized with Dowex® 1X8-200 resin (OH^- form) and filtered. The filtrate was evaporated and the crude material was purified by chromatography (reverse phase, H_2O/MeCN 98:2) to afford **10** (0.57 g, 95%) as a white solid: TLC R_f=0.10 (D); ^{1}H NMR (400 MHz, DMSO) δ 3.27–3.35 (d, 1H, J=9.6 Hz, under H_2O peak), 3.38–3.48 (m, 1H), 3.54–3.64 (m, 2H), 3.65–3.73 (m, 1H), 3.87 (d, 1H, J=9.6 Hz), 4.16 (d, 1H, J=14.1 Hz), 4.26 (d, 1H, J=14.1 Hz), 4.70 (t, 1H, J=5.5 Hz), 4.98 (s, 1H), 5.25 (d, 1H, J=6.5 Hz), 7.19 (br, 2H), 8.05 (s, 1H), 8.12 (s, 1H); ^{13}C NMR (100.5 MHz, DMSO) δ 48.5, 61.8, 73.0, 74.8, 78.2, 84.1, 118.7, 142.3, 150.3, 152.8, 156.4; MS(ES) calcd $[M+H]^+$ ($C_{11}H_{16}N_5O_4$): 282, found: 282, calcd $[M-H]^-$ ($C_{11}H_{14}N_5O_4$): 280, found: 280; HRMS(FAB) calcd $[M+H]^+$ ($C_{11}H_{16}N_5O_4$): 282.1202, found: 282.1205.

4.1.5. *iso-2′-C-Methyl-2′,3′-O-isopropylidene-5′-O-triphenylmethyl-6-O-(methoxyethyl)-guanosine (**11**)*

To a stirred suspension of 2-amino-6-(methoxyethoxy)-purine (2.08 g, 9.92 mmol) in DMF (18 mL) was added NaH (60% oil dispersion) (0.33 g, 8.26 mmol) at room temperature. After the evolution of hydrogen had ceased, the solution was stirred at 80 °C for 20 min. Then, tosylate **8** (2.00 g, 3.33 mmol) dissolved in DMF (18 mL) was added via a syringe. The solution was stirred at 120 °C for 15 h and then, cooled down to room temperature. The solvent was evaporated and the brown residue was taken up in DCM (50 mL). The resulting solution was extracted with 0.5 N HCl (50 mL), satd $NaHCO_3$ solution (50 mL), and H_2O (50 mL). After drying over Na_2SO_4, the organic phase was evaporated. The crude material was purified by chromatography (silica gel, DCM/MeOH 97:3) to afford **11** (1.34 g, 63%) as a white foam: TLC R_f=0.69 (C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 3H), 1.49 (s, 3H), 3.35 (d, 2H, J=4.5 Hz), 3.44 (s, 3H), 3.81 (t, 2H, J=4.9 Hz), 3.94 (d, 1H, J=10.0 Hz), 4.06 (d, 1H, J=10.0 Hz), 4.21–4.38 (m, 3H), 4.44 (s, 2H), 4.61–4.69 (m, 3H), 7.22–7.39 (m, 9H), 7.51–7.60 (m, 6H), 7.66 (s, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 27.6, 27.7, 46.1, 59.1, 64.0, 65.7, 70.5, 76.0, 85.0, 85.2, 87.4, 91.8, 114.3, 114.8, 127.2, 128.0, 128.8, 140.8, 143.8, 154.3, 159.2, 161.1; MS(ES) calcd $[M+H]^+$ ($C_{36}H_{40}N_5O_6$): 638, found: 638.

4.1.6. *iso-2′-C-Methyl-guanosine (**12**)*

A suspension of **11** (1.10 g, 1.73 mmol) in 3 N HCl (50 mL) was heated at 80 °C for 3 h. The mixture was cooled down to room temperature and extracted with DCM (2×50 mL). The aqueous phase was evaporated and the residue was taken up in H_2O (30 mL). The resulting solution was neutralized with Dowex® 1X8-200 resin (OH^- form) and filtered. The filtrate was evaporated and the crude material was purified by chromatography (reverse phase, H_2O/MeCN 98:2) to afford **12** (0.36 g, 70%) as a white solid: ^{1}H NMR (400 MHz, DMSO) δ 3.26–3.36 (m, 1H, under H_2O peak), 3.37–3.46 (m, 1H), 3.54–3.67 (m, 3H), 3.87 (d, 1H, J=9.7 Hz), 4.00 (m, 2H), 4.66 (t, 1H, J=5.6 Hz), 4.93 (s, 1H), 5.21 (d, 1H, J=6.0 Hz), 6.45 (br, 2H), 7.62 (s, 1H), 10.59 (br, 1H); ^{13}C NMR (100.5 MHz, DMSO) δ 48.3, 61.6, 73.0, 74.9, 78.1, 83.6, 116.5, 138.9, 151.9, 154.0, 157.4; MS(ES) calcd $[M+H]^+$ ($C_{11}H_{16}N_5O_5$): 298, found: 298, calcd $[M-H]^-$ ($C_{11}H_{14}N_5O_5$): 296, found: 296; HRMS(FAB) calcd $[M+H]^+$ ($C_{11}H_{16}N_5O_5$): 298.1151, found: 298.1146.

4.1.7. *iso-2′-C-Methyl-2′,3′-O-isopropylidene-5′-O-triphenylmethyl-uridine (**13**)*

To a stirred suspension of uracil (4.46 g, 39.87 mmol) in DMF (65 mL) was added NaH (60% oil dispersion) (1.32 g, 33.19 mmol) at room temperature. After the evolution of hydrogen had ceased, the mixture was stirred at 80 °C for 20 min. Then, tosylate **8** (8.00 g, 13.29 mmol) dissolved in DMF (65 mL) was added via a syringe. The resulting suspension was stirred at 140 °C for 24 h and then, cooled down to room temperature. The solvent was evaporated and the brown residue was taken up in DCM (200 mL). The resulting solution was extracted with 0.5 N HCl (200 mL), satd $NaHCO_3$ solution (200 mL), and H_2O (200 mL). After drying over Na_2SO_4, the organic phase was evaporated. The crude material was purified by chromatography (silica gel, DCM/MeOH 98:2) to afford **13** (4.39 g, 61%) as a white foam: TLC R_f=0.64 (C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.52 (s, 3H), 3.21 (dd, 1H, J=5.1, 10.2 Hz), 3.34 (dd, 1H, J=4.9, 10.2 Hz), 3.96 (d, 1H, J=10.2 Hz), 3.97 (s, 2H), 4.04 (d, 1H, J=10.2 Hz), 4.22 (td, 1H, J=1.6, 4.9 Hz), 4.55 (d, 1H, J=1.6 Hz), 5.66 (dd, 1H, J=2.2, 8.0 Hz), 7.21–7.35 (m, 10H), 7.45–7.50 (m, 6H), 8.92 (br, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 27.6, 28.1, 50.5, 63.8, 75.8, 85.0, 85.7, 87.4, 92.0, 101.6, 114.2, 127.1, 127.9, 128.8, 143.5, 146.1, 150.8, 163.5; MS(ES) calcd $[M+Na]^+$ ($C_{32}H_{32}NaN_2O_6$): 563, found: 563, calcd $[M-H]^-$ ($C_{32}H_{31}N_2O_6$): 539, found: 539.

4.1.8. *iso-2′-C-Methyl-uridine (**14**)*

A suspension of **13** (1.20 g, 2.22 mmol) in 2 N HCl (50 mL) was heated at 80 °C for 2 h. The mixture was cooled down to room temperature and extracted with DCM (2×50 mL). The aqueous phase was evaporated and the residue was taken up in H_2O (30 mL). The resulting solution was neutralized with Dowex® 1X8-200 resin (OH^- form) and filtered. The filtrate was evaporated and the crude material was purified by chromatography (reverse phase, H_2O/MeCN 95:5) to afford **14** (0.53 g, 93%) as a white solid: TLC R_f=0.26 (D); ^{1}H NMR (400 MHz, DMSO) δ 3.35–3.48 (m, 2H), 3.52–3.72 (m, 4H), 3.79 (d, 1H, J=9.6 Hz), 3.86 (d, 1H, J=14.1 Hz), 4.63 (t, 1H, J=5.6 Hz), 4.78 (s, 1H), 5.16 (d, 1H, J=6.1 Hz), 5.51 (d, 1H, J=7.9 Hz), 7.55 (d, 1H, J=7.9 Hz), 11.19 (br, 1H); ^{13}C NMR (100.5 MHz, DMSO) δ 51.9, 61.8, 73.1, 74.8, 78.6, 83.4, 100.6, 147.4, 152.0, 164.2; MS(ES) calcd $[M-H]^-$ ($C_{10}H_{13}N_2O_6$): 257, found: 257; HRMS(FAB) calcd $[M+H]^+$ ($C_{10}H_{15}N_2O_6$): 259.0930, found: 259.0940.

4.1.9. *iso-2′-C-Methyl-2′,3′-O-isopropylidene-5′-O-triphenylmethyl-cytidine (**15**)*

To a solution of **13** (1.62 g, 3.00 mmol) in MeCN (30 mL) at 0 °C were added *N*-methylpyrrolidine (3.40 mL) and trifluoroacetic anhydride (1.28 mL, 9.13 mmol). The yellow solution was stirred for 30 min then, *p*-nitrophenol (1.68 g, 12.16 mmol) was added and the resulting solution was stirred at 0 °C for 3 h. The reaction was quenched by addition of H_2O (5 mL) and DCM (100 mL) was added. The solution was extracted with satd $NaHCO_3$ solution (3×100 mL) and H_2O (100 mL). After drying over Na_2SO_4, the organic phase was evaporated. The yellow residue was taken up in NH_3-saturated MeOH (50 mL) and heated up at 100 °C under pressure for 5 h. The reaction was cooled down to room temperature and MeOH was evaporated. The crude material was purified by chromatography (silica gel, DCM/MeOH 95:5) to afford **15** (0.94 g, 58%) as a yellow foam: TLC R_f=0.34 (C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 3H), 1.50 (s, 3H), 3.27 (d, 2H, J=5.5 Hz), 3.87–4.08 (m, 4H), 4.20 (m, 1H), 4.58 (d, 1H, J=1.6 Hz), 5.59 (d, 1H, J=7.2 Hz), 7.18–7.38 (m, 10H), 7.44–7.54 (m, 6H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 27.7, 28.0, 51.5, 63.4, 75.7, 85.0, 85.5, 87.1, 92.3, 93.7, 113.8, 127.0, 127.9, 128.8, 143.7, 147.2, 156.6, 165.8; MS(ES) calcd $[M-H]^-$ ($C_{32}H_{32}N_3O_5$): 538, found: 538.

4.1.10. *iso-2′-C-Methyl-cytidine (**4**)*

A suspension of **15** (900 mg, 1.67 mmol) in 2 N HCl (40 mL) was heated at 80 °C for 2 h. The mixture was cooled down to room temperature and extracted with DCM (2×50 mL). The aqueous phase was evaporated and the residue was taken up in H_2O (30 mL). The resulting solution was neutralized with Dowex® 1X8-200 resin (OH^- form) and filtered. The filtrate was evaporated and the crude material was purified by chromatography (reverse phase, H_2O/MeCN 98:2) to afford **4** (395 mg, 92%) as a white solid: ^{1}H NMR (400 MHz, DMSO) δ 3.33–3.44 (m, 2H), 3.52–3.68 (m, 4H), 3.82 (d, 1H, J=9.7 Hz), 3.91 (d, 1H, J=13.8 Hz), 4.63 (t, 1H, J=5.6 Hz), 4.93 (s, 1H), 5.05 (d, 1H, J=6.0 Hz), 5.62 (d, 1H, J=7.2 Hz), 6.88–7.17 (br, 2H),

7.53 (d, 1H, J=7.2 Hz); ^{13}C NMR (100.5 MHz, DMSO) δ 53.2, 61.8, 73.1, 74.7, 78.9, 83.4, 93.5, 147.7, 157.3, 166.4; MS(ES) calcd $[M+H]^+$ ($C_{10}H_{16}N_3O_5$): 258, found: 258, calcd $[M-H]^-$ ($C_{10}H_{14}N_3O_5$): 256, found: 256; HRMS(FAB) calcd $[M+H]^+$ ($C_{10}H_{16}N_3O_5$): 258.1090, found: 258.1098.

Acknowledgements

We wish to thank Dr. M. Liuzzi of Idenix Pharmaceuticals, Cagliari, Italy and Dr. V. Bichko of Idenix Pharmaceuticals, Cambridge, MA, USA for anti-viral testing.

Supplementary data

^{1}H and ^{13}C NMR spectra for compounds **4** and **7**–**15**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.05.022.

References and notes

1. Alvarez de Cienfuegos, L.; Mota, A. J.; Robles, R. *Org. Lett.* **2005**, *7*, 2161.
2. Mereyala, H. B.; Mamidyala, S. K. *Tetrahedron Lett.* **2004**, *45*, 2965.
3. Aragonès, S.; Bravo, F.; Díaz, Y.; Matheu, I.; Castillón, S. *Tetrahedron Lett.* **2003**, *44*, 3771.
4. Bera, S.; Nair, V. *Tetrahedron Lett.* **2001**, *42*, 5813.
5. Taktakishvili, M.; Neamati, N.; Pommier, Y.; Pal, S.; Nair, V. *J. Am. Chem. Soc.* **2000**, *122*, 5671.
6. Díaz, Y.; Bravo, F.; Castillón, S. *J. Org. Chem.* **1999**, *64*, 6508.
7. Jung, M. E.; Nichols, C. J. *J. Org. Chem.* **1998**, *63*, 347.
8. Wang, J.-F.; Yang, X.-D.; Zhang, L.-R.; Yang, Z.-J.; Zhang, L.-H. *Tetrahedron* **2004**, *60*, 8535.
9. Yu, H.-W.; Zhang, L.-R.; Zhou, J.-C.; Ma, L.-T.; Zhang, L.-H. *Bioorg. Med. Chem.* **1996**, *4*, 609.
10. Nair, V.; St. Clair, M. H.; 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. *Antimicrob. Agents Chemother.* **1995**, *39*, 1993.
11. Verheggen, I.; Van Aerschot, A.; Van Meervelt, L.; Rozenski, J.; Wiebe, L.; Snoeck, R.; Andrei, G.; Balzarini, J.; Claes, P.; De Clercq, E.; Herdewijn, P. *J. Med. Chem.* **1995**, *38*, 826.
12. Kakefuda, A.; Shuto, S.; Nagahata, T.; Seki, J.; Sasaki, T.; Matsuda, A. *Tetrahedron* **1994**, *50*, 10167.
13. Huryn, D. M.; Sluboski, B. C.; Tam, S. Y.; Weigele, M.; Sim, I.; Anderson, B. D.; Mitsuya, H.; Broder, S. *J. Med. Chem.* **1992**, *35*, 2347.
14. Bravo, F.; Díaz, Y.; Castillón, S. *Tetrahedron: Asymmetry* **2001**, *12*, 1635.
15. Sommadossi, J.-P.; La Colla, P. WO 2001090121; *CAN* **2001**, *136*, 6296.
16. Benzaria, S.; Bardiot, D.; Bouisset, T.; Counor, C.; Rabeson, C.; Pierra, C.; Storer, R.; Loi, A.-G.; Cadeddu, A.; Mura, M.; Musiu, C.; Liuzzi, M.; Loddo, R.; Bergelson, S.; Bichko, V.; Bridges, E. G.; Cretton-Scott, E.; Mao, J.; Sommadossi, J.-P.; Seifer, M.; Standring, D. N.; Tausek, M.; Gosselin, G.; La Colla, P. *Antiviral Chem. Chemother.* **2007**, *18*, 225.
17. Eldrup, A. B.; Prhavc, M.; Brooks, J.; Bhat, B.; Prakash, T. P.; Song, Q.; Bera, S.; Bhat, N.; Dande, P.; Dan Cook, P.; Bennet, C. F.; Carroll, S. S.; Ball, R. G.; Bosserman, M.; Burlein, C.; Colwell, L. F.; Fay, J. F.; Flores, O. A.; Getty, K.; LaFemina, R.; Leone, J.; MacCoss, M.; McMasters, D. R.; Tomassini, J. E.; Von Lagen, D.; Wolanski, B.; Olsen, D. B. *J. Med. Chem.* **2004**, *47*, 5284.
18. Eldrup, A. B.; Allerson, C. R.; Bennet, C. F.; Bera, S.; Bhat, B.; Bhat, N.; Bosserman, M. R.; Brooks, J.; Burlein, C.; Carroll, S. S.; Dan Cook, P.; Getty, K. L.; MacCoss, M.; McMasters, D. R.; Olsen, D. B.; Prakash, T. P.; Prhavc, M.; Song, Q.; Tomassini, J. E.; Xia, J. *J. Med. Chem.* **2004**, *47*, 2283.
19. Pierra, C.; Amador, A.; Benzaria, S.; Cretton-Scott, E.; D'Amours, M.; Mao, J.; Mathieu, S.; Moussa, A.; Bridges, E. G.; Standring, D. N.; Sommadossi, J.-P.; Storer, R.; Gosselin, G. *J. Med. Chem.* **2006**, *49*, 6614.
20. Kiso, M.; Hasegawa, A. *Carbohydr. Res.* **1976**, *52*, 95.
21. Ohrui, H.; Fox, J. J. *Tetrahedron Lett.* **1973**, *14*, 1951.
22. Beigelman, L. N.; Ermolinsky, B. S.; Gurskaya, G. V.; Tsapkina, E. N.; Karpeisky, M. Y.; Mikhailov, S. N. *Carbohydr. Res.* **1987**, *166*, 219.
23. The ring strain energy difference between *cis*- and *trans*-bicyclo[3.3.0]-octane is 6.4 kcal/mol: Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 3rd ed.; Plenum: New York, NY, 1990; Vol. A, pp 157–158.
24. Hossain, N.; Herdewijn, P. *Nucleosides Nucleotides* **1998**, *17*, 1781.
25. Kjellberg, J.; Johansson, N. G. *Nucleosides Nucleotides* **1989**, *8*, 225.
26. Gosselin, G.; Griffe, L.; Meillon, J.-C.; Storer, R. *Tetrahedron* **2006**, *62*, 906.
27. Biggadike, K.; Borthwick, A. D.; Exall, A. M.; Kirk, B. E.; Roberts, S. M.; Youds, P. *J. Chem. Soc., Chem. Commun.* **1987**, 1083.
28. Miah, A.; Reese, C. B.; Song, Q.; Sturdy, Z.; Neidle, S.; Simpson, I. J.; Read, M.; Rayner, E. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3277.