Carbohydrate Research 346 (2011) 2011–2015

Contents lists available at ScienceDirect

Carbohydrate Research

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

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Keto-fluorothiopyranosyl nucleosides: a convenient synthesis of 2- and 4-keto-3-fluoro-5-thioxylopyranosyl thymine analogs

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ARTICLE INFO

Article history:
Received 21 January 2011
Received in revised form 9 May 2011
Accepted 12 May 2011
Available online 19 May 2011

Keywords:
Xylopyranonucleosides
Ketonucleosides
Fluoronucleosides
5-Thionucleosides

ABSTRACT

A novel series of fluorinated keto-β-D-5-thioxylopyranonucleosides bearing thymine as the heterocyclic base have been designed and synthesized. Deprotection of 3-deoxy-3-fluoro-5-*S*-acetyl-5-thio-D-xylofuranose (**1**) and selective acetalation gave the desired isopropylidene 5-thioxylopyranose precursor **3**. Acetylation and isopropylidene removal followed by benzoylation led to 3-deoxy-3-fluoro-1,2-di-O-benzoyl-4-*O*-acetyl-5′-thio-D-xylopyranose (**6**). This was condensed with silylated thymine and selectively deacetylated to afford 1-(2′-O-benzoyl-3′-deoxy-3′-fluoro-5′-thio-β-D-xylopyranosyl)thymine (**8**). Oxidation of the free hydroxyl group in the 4′-position of the sugar led to the formation of the target 4′-keto compound together with the concomitant displacement of the benzoyl group by an acetyl affording, 1-(2′-*O*-acetyl-3′-deoxy-3′-fluoro-β-D-xylopyranosyl-4′-ulose)thymine (**9**). Benzoylation of 3 and removal of the isopropylidene group followed by acetylation, furnished 3-deoxy-3-fluoro-1,2-di-O-acetyl-4-*O*-benzoyl-5′-thio-D-xylopyranose (**12**). Condensation of thiosugar **12** with silylated thymine followed by selective deacetylation led to the 1-(4′-O-benzoyl-3′-fluoro-5′-thio-β-D-xylopyranosyl)thymine (**14**). Oxidation of the free hydroxyl group in the 2′-position and concomitant displacement of the benzoyl group by an acetyl gave target 1-(4′-*O*-acetyl-3′-deoxy-3′-fluoro-β-D-xylopyranosyl-2′-ulose)thymine (**15**).

Nucleosides and their analogs have far been proven to take an important place in medicinal chemistry as the structural basis for the development of therapeutic agents.[1–3] In spite of the initial success obtained with modified nucleosides, both the undesirable side effects of certain nucleosides and the demand for new antiviral and antitumor agents have prompted the search for further novel nucleosides with improved biological and chemical properties.[4–6]

In seeking to investigate new biologically active agents, we have previously designed and synthesized fluorinated pyranonucleosides, evaluated their potential antiviral, antitumor,[7,8] and antioxidant[9] properties and their activity at molecular level.[10,11] More recently, in our attempts to arrive at new modified analogs, we have demonstrated that insertion of a keto group and removal of the primary hydroxymethyl function in the sugar moiety led to various uncommon nucleosides,[7,8,12–15] which showed promising antitumor and antiviral activities. It also appeared that these nucleosides represent novel types of prodrugs,[13] while they may act as acceptors in a Michael-addition mechanism.[12]

In the field of modified nucleosides, considerable interest has been drawn in the synthesis of thiosugars[16] and thionucleoside analogs[17–19] in which the ring oxygen atom is replaced by sulfur. The biological interest in thiosugars has expanded to studies on diabetes, enzyme inhibition, and antiviral and antitumor activities,[20] while thionucleosides have been recognized as a novel and important class of antiviral agents and promising antitumor candidates.[21] It is noteworthy that the replacement of the oxygen atom by sulfur in the sugar ring of the fluorinated analog of cytosine (FAC) led to an increase of its activity against various human tumor cell lines, while a new more biologically important compound was obtained.[22,23]

In view of the above observations and considering the utility of derivatives containing sulfur in the ring, as biologically important targets in medicinal chemistry, we found intriguing to further explore structure–activity relationships of fluorinated ketopyranonucleosides, by replacing the ring oxygen atom by sulfur. We thus present the synthesis of a novel class of xylopyranonucleosides of thymine, possessing a ring sulfur atom and a keto group in the 2′- or 4′-position of the sugar portion.

Retrosynthetic analysis suggested that 2′-keto- and 4′-keto-thionucleosides could be obtained by utilizing the available 5-thioxylopyranosyl nucleoside of thymine **I** and its corresponding fully unprotected analog **II**, respectively (Scheme 1). However, neither selective deacetylation[24,25] of thio-analog **I**, nor specific benzoylation,[26] pivaloylation,[27] or silyl protection[28] of 5-thioxylopyranonucleoside **II** led to the desirable partially protected precursors, but only to the corresponding deacetylated derivative **II**, along with the fully protected analogs **III**, respectively.

Since all attempts to selectively deprotect or protect the 5-thioxylopyranosyl analogs of thymine were unsuccessful, we altered the retrosynthetic routes for the synthesis of the desirable

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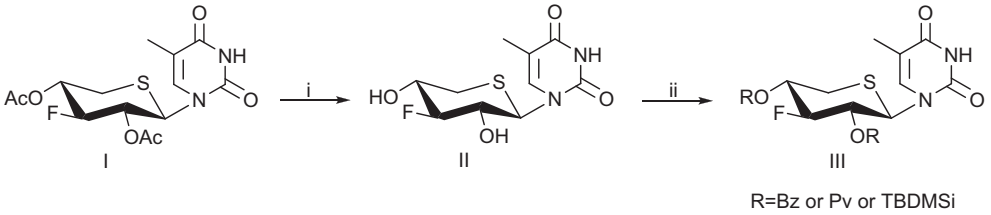
doi:10.1016/j.carres.2011.05.013

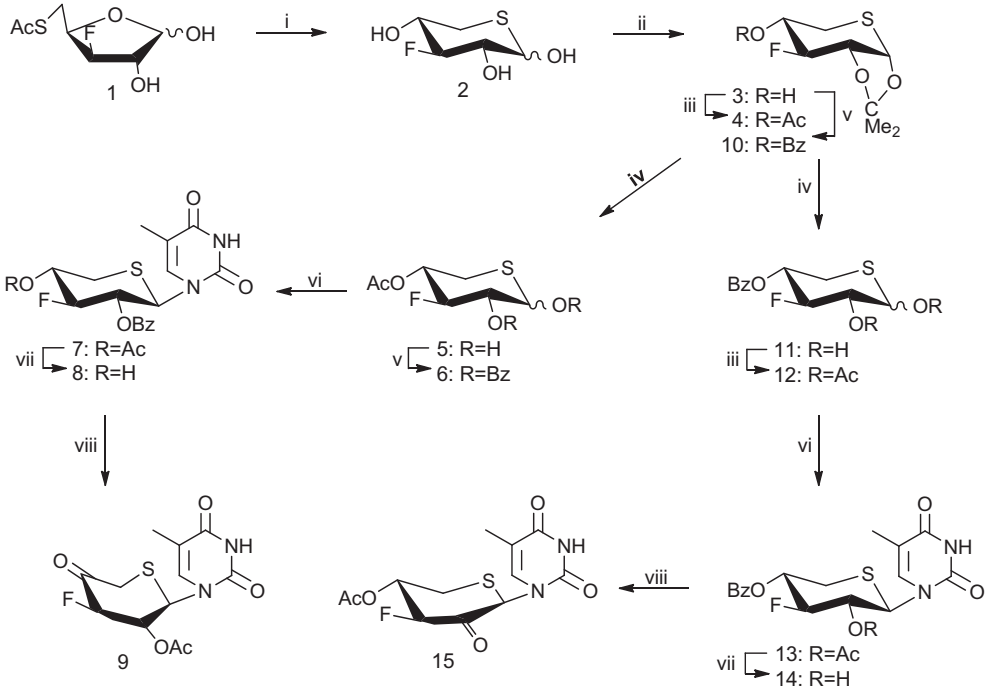


Scheme 1. Reagents: (i) (a) NaOH/EtOH/pyridine or (b) $HONH_2$·HCl/NaOAc/pyridine; (ii) (a) BzCl/pyridine or (b) PvCl/pyridine or (c) TBDMSCl/pyridine.

4′-keto- and 2′-keto-3′-fluoro-5-thioxylopyranosyl nucleosides, **9** and **15**, respectively. In both routes, the suitable key precursor is the newly synthesized 1,2-*O*-isopropylidene analog of 5-thioxylopyranose **3**.

3′-Deoxy-3′-fluoro-4′-keto-5-thio-β-D-xylopyranonucleoside (**9**) was prepared according to the synthetic route outlined in Scheme 2. Deprotection of 3-deoxy-3-fluoro-5-*S*-acetyl-5-thio-D-xylofuranose (**1**) in methanolic ammonia[29] gave the glycosyl donor, 5-thioxylopyranose **2**. Specific acetalation of the free hydroxyl groups in the 1,2-position of the sugar moiety of **2** with 2,2-dimethoxypropane [$(CH_3)_2C(OCH_3)_2$], in the presence of *p*-toluenesulfonic acid (*p*-TsOH) in *N*,*N*-dimethylformamide (DMF),[30] afforded the desired isopropylidene 5-thioxylopyranose **3**, in 70% yield. Acetylation of the free hydroxyl group in the 4-position of the thiosugar **3** with Ac_2O/pyridine furnished the acetylated derivative **4**. The isopropylidene group of compound **4** was removed under acidic conditions and the resulting compound **5** was reacted with benzoyl chloride (BzCl) and pyridine to give the 1,2-di-*O*-benzoyl derivative **6**. Compound **6** was readily converted into the 1-(2′-*O*-benzoyl-4′-*O*-acetyl-3′-deoxy-3′-fluoro-5′-thio-β-D-xylopyranosyl)thymine (**7**), in 68% yield, upon reaction with silyl-protected thymine in the presence of tin chloride (IV) as catalyst.[31] The participation of 2′-benzoyloxy group led to the exclusive formation of the β-anomer **7**. As expected, the ^{1}H NMR spectrum of **7** showed a large coupling between protons H-1′ and H-2′ (J = 10.6 Hz), indicating an axial orientation of both protons and an equatorially oriented thymine ring. When selective deprotection of the fully protected thionucleoside **7** with NaOH–ethanol–pyridine[24] was employed, partially benzoyl analog of thymine **8** was formed. The crucial step of this synthetic pathway proved to be the oxidation of the suitably protected precursor **8**. However, the target ketone **9** was obtained, only when the oxidation reaction was performed by pyridinium dichromate (PDC)/Ac_2O at 60 °C for 15 min, while surprisingly, a simultaneous replacement of the benzoyl group by an acetyl was observed. The IR spectrum measured immediately after completion of the reaction workup revealed a characteristic absorption of a carbonyl group at 1712 cm^{-1}, confirming the presence of the desired ketonucleoside **9**. It is of interest to mention that when the duration of the aforementioned oxidation reaction was extended, a mixture of untreatable products was obtained. Furthermore, when oxidation of **8** was performed by a modified Albright–Goldman reaction, using the DMSO/EtOAc/Ac_2O system,[32] Pfitzner–Moffatt,[33] Garegg–Samuelsson,[34] Swern,[35] Dess–Martin,[36] and pyridinium dichromate (PDC)/3E molecular sieves[37] methods, resulted in a mixture of intractable and unseparable materials. The IR spectra of the crude reaction mixtures exhibited characteristic absorptions of S=O and O=S=O groups at 1055 and 1140 cm^{-1}, respectively, convincing the instability of sulfur versus oxidative step.

For the synthesis of the 3′-deoxy-3′-fluoro-2′-keto-5-thio-β-D-xylopyranonucleoside (**15**), a synthetic route starting from the isopropylidene 5-thioxylopyranose **3** was devised (Scheme 2).



Scheme 2. Reagents: (i) Ammonia/MeOH; (ii) $(CH_3)_2C(OCH_3)_2$/*p*-TsOH/DMF; (iii) Ac_2O/pyridine; (iv) 90% TFA; (v) BzCl/pyridine; (vi) silylated thymine/$SnCl_4$/CH_3CN; (vii) NaOH/EtOH/pyridine; (viii) PDC/Ac_2O/60 °C/15 min.