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Synthesis of L-β-3′-Deoxy-3′,3′-difluoro-4′-thionucleosides

Feng Zheng, Xiao-Hua Zhang, Xiao-Long Qiu, Xingang Zhang, and Feng-Ling Qing*

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

flq@mail.sioc.ac.cn

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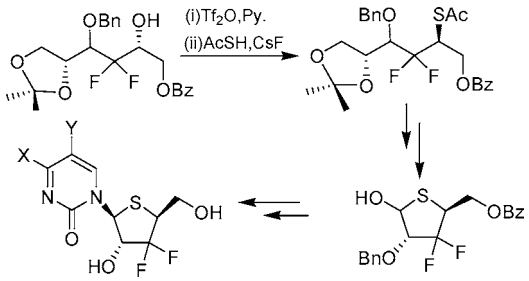
ABSTRACT



An efficient route to L-β-3′-deoxy-3′,3′-difluoro-4′-thionucleosides, thio-containing analogues of highly bioactive gemcitabine, is described. Our synthesis highlighted the installation of the thioacetyl group in high efficiency and construction of 3-deoxy-3,3-difluorothiofuranose skeleton in a novel method.

gem-Difluoromethylene (CF_2) has been suggested by Blackburn as an isopolar and isosteric substituent for oxygen.[1] Since then, the CF_2 group was extensively used to modify nucleoside analogues. For example, 2′-deoxy-2′,2′-difluorocytidine (gemcitabine **1**, Figure 1) has been approved as a drug for solid tumor treatment.[2] Unnatural L-configuration nucleosides have drawn considerable attention due to their lower host toxicity while maintaining good activity in comparison with their corresponding D-nucleosides.[3] 4′-Thionucleosides, in which the furanose ring oxygen is replaced by a sulfur atom, have been studied extensively over the past 10 years because of their potent biological activity.[4] Recently, a number of D-(L-)difluoromethylene-containing thionucleosides have been prepared, such as D-2′-deoxy-2′,2′-difluoro-4′-thiocytidine **2**,[5] L-2′-deoxy-2′,2′-difluoro-4′-thiocytidine **3**,[6] and D-2′,3′-dideoxy-3′,3′-difluoro-4′-thiocytidine **4**.[7] Based on the above considerations and our efforts to prepare the fluorinated sugar nucleosides,[8] we designed our target molecules L-3′-deoxy-3′,3′-difluoro-4′-thionucleosides

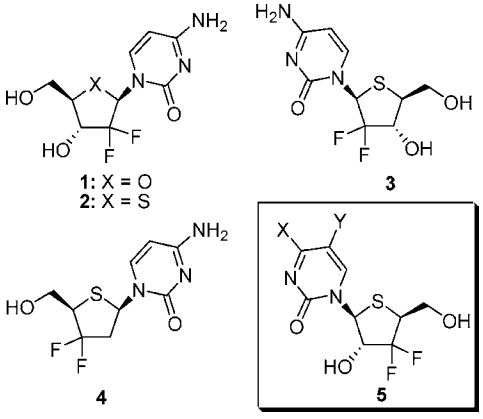


Figure 1. Rationale for the design of the target molecule **5**.

(1) Blackburn, C. M.; England, D. A.; Kolkmann, F. *J. Chem. Soc., Chem. Commun.* **1981**, 930.
(2) (a) Hertel, L. W.; Kroin, J. S.; Misner, J. W.; Tustin, J. M. *J. Org. Chem.* **1988**, *53*, 2406. (b) Hertel, L. W.; Boder, G. B.; Kroin, J. S.; Rinzel, S. M.; Poore, G. A.; Todd, G. C.; Grindey, G. B. *Cancer Res.* **1990**, *50*, 4417.
(3) For a minireview, see: Mathe, C.; Gosselin, G. *Antiviral Res.* **2006**, *71*, 276.
(4) For review; see: Yokoyama, M. *Synthesis* **2000**, 1637.

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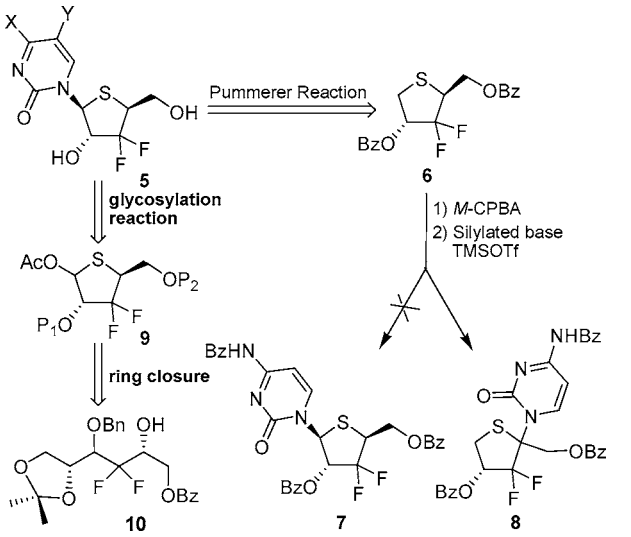
5 (Figure 1). The *gem*-difluoromethylene (CF_2) group was at the C3′ position of compounds **5**. Moreover, nucleosides **5** would combine the characteristics of compounds **1**−**4** based on the bioisosteric rationale (Figure 1).

Our previous attempt to prepare L-3′-deoxy-3′,3′-difluoro-4′-thiocytosine **5** via Pummerer reaction of compound **6** failed (Scheme 1).[9] The oxidation of **6** followed by the

Scheme 1

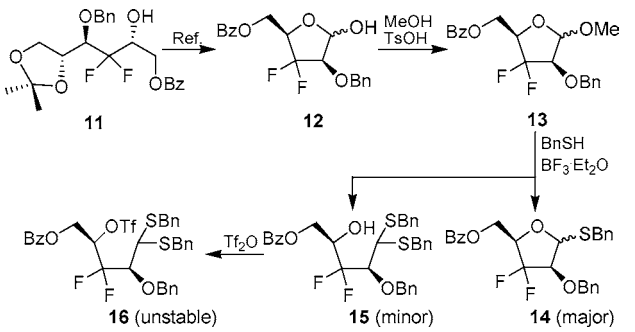


condensation with silyated N^4-benzoylcytosine (Pummerer recation) did not give our desired protected nucleoside **7**, but the regioisomer **8**. The regiochemistry of the Pummerer recation was determined by the kinetic acidity of the α-proton of 4′-thiofuranose **6**.

The new synthetic route was based on the supposition that the target molecules **5** could be derived from the precursor **9** by introduction a base moiety using the glycosylation reactions (Scheme 1). Intermediate **9** would be reached through ring closure of the our developed versatile *gem*-difluorinated synthon **10**, which was easily prepared according to our reported methodology.[8a,9]

The construction of the special skeleton **9** appeared to be a great challenge. Recently, Chu group reported the synthesis of thiosugar through the corresponding riboside,[7] which stimulated us to prepare the intermediate **9** using the same strategy. Thus, 3-deoxy-3,3-difluoro-D-arabinofuranose **12**, prepared from optically pure *gem*-difluorinated synthon **11** via our reported procedure,[9] was converted to compound **13** by treatment with TsOH/MeOH (Scheme 2). However, the

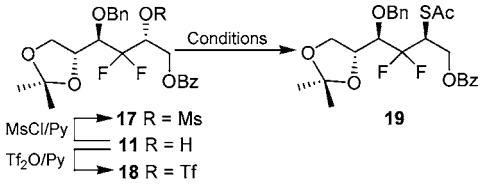
Scheme 2



ring opening of **13** with BnSH afforded the 1-thiofuranoside **14** as the main product, and our desired thioacetal **15** was provided only in very low yield. More unfortunately, the corresponding triflate **16**, obtained via *O*-triflation of **15**, decomposed very quickly at room temperature.

Then, another strategy to thiosugar, pioneered by Montgomery et al.,[10] was attempted. Their method highlighted the fact that reductive deprotection of SAc to SH with DIBAL-H and simultaneous reduction of the methyl ester to −CHO in the same molecule would give rise to thioactol formation via spontaneous cyclization. Thus, developing a practical route to thioacetate **19** starting from compound **11** was what should be first addressed (Table 1).

Table 1. Preparation of the Thioacetate **19**



entry	R	conditions	**19** (%)
1	Ms	AcSH (3 equiv)/CsF (3 equiv)/DMF/rt	NR[a]
2	Ms	AcSH (3 equiv)/CsF (3 equiv)/DMF/50 °C	defluorination[a]
3	Tf	KSAc (3 equiv)/DMF	defluorination[a]
4	Tf	AcSH (3 equiv)/CsF (3 equiv)/DMF/rt	72[b]
5	Tf	AcSH (5.4 equiv)/CsF (5.4 equiv)/DMF/rt	86[b]

[a] Determined by ^{19}F NMR spectra. [b] Yield was based on chromatography isolation over silica gel.

Otera and co-workers reported an efficient method of CsF/DMF-mediated nucleophilic inversion of secondary mesylates and tosylates.[11] Their strategy could be successfully ultilized with a variety of oxygen-, sulfur-, nitrogen- and carbo-nucleophiles. Thus, we think that thioacetate **19** could

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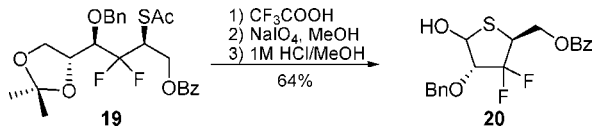
(10) Secrist, J. A., III; Riggs, R. M.; Tiwari, K. N.; Montgomery, J. A. *J. Med. Chem.* **1992**, *35*, 533.
(11) Otera, J.; Nakazawa, K.; Sekoguchi, K.; Orita, A. *Tetrahedron* **1997**, *53*, 13633.

be provided by treatment of the corresponding mesylate **17**, obtained via exposure of compound **11** to MsCl/pyridine, with AcSH under a CsF/DMF system. However, no reaction occurred when compound **17** was treated with AcSH (3 equiv)/CsF (3 equiv) in DMF at room temperature (Table 1, entry 1). When the reaction was performed at 50 °C, ^{19}F NMR of reaction mixture showed that the defluorination occurred (Table 1, entry 2). In our opinion, failure of above reactions was attributed to the facts that (1) a strong electron-withdrawing *gem*-difluoromethylenyl group (CF_2) could effectively stabilize the neighboring C−O bond, which made the mesyl group hard to remove, and (2) a strong electron-withdrawing CF_2 would enhance the acidity of 2-H in compound **17**, and thus, when reaction temperature was increased, the dehydrofluorination reaction and other side reactions occurred in the presence of Lewis base F^-. Taking the above analyses together, we envisioned that the trifloromethanesulfonyl as the leaving group should probably afford our desired compound. Thus, triflate **18** was first prepared in good yield via *O*-triflation of **11**. To our delight, although treatment of compound **18** under the normal conditions (KSAc/DMF) still resulted in dehydrofluorination (Table 1, entry 3), substitution of AcSH (3 equiv)/CsF (3 equiv) for KSAc smoothly furnished our desired thioacetate **19** in 72% yield (Table 1, entry 4), which could be further improved to 86% when 5.4 equiv of AcSH/CsF was used (Table 1, entry 5).

With the thioacetate **19** in hand, we then focused on the construction of the thiofuranose **9**. Fortunately, we were delighted to find that the thiofuranose **20** could be provided in 64% overall yield (Scheme 3) when the resultant aldehyde,

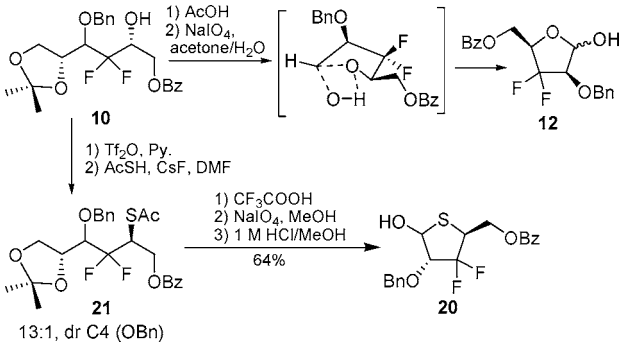
Scheme 3



in situ obtained via hydrolysis of the thioacetate **19** with TFA and oxidation of the resulting diols with $NaIO_4$, was treated with acidic methanol (1 M HCl) at room temperature for 12 h. The isomers of compound **20** could not be separated on silica gel chromatography.

During the synthesis of N^1-(3-deoxy-3,3-difluoro-D-arabinofuranosyl)cytosine,[9] we accidently found that the C3 (−OBn) configuration in compound **10** was stereospecifically transformed into a single arabino configuration in **12** (Scheme 4). As shown in Scheme 4, the hydrogen-bond-mediated four-membered ring may play an important role in the favorite transition state of the cyclization to form compound **12**. We were interested in investigating whether this stereospecifical transformation also occurred in the cyclization of the thioacetate. Thus, compound **21** (a mixture of C3 epimers) was first prepared starting from compound **10** using the aforementioned starategy. Then, compound **21** was subjected to the same conditions as described above for

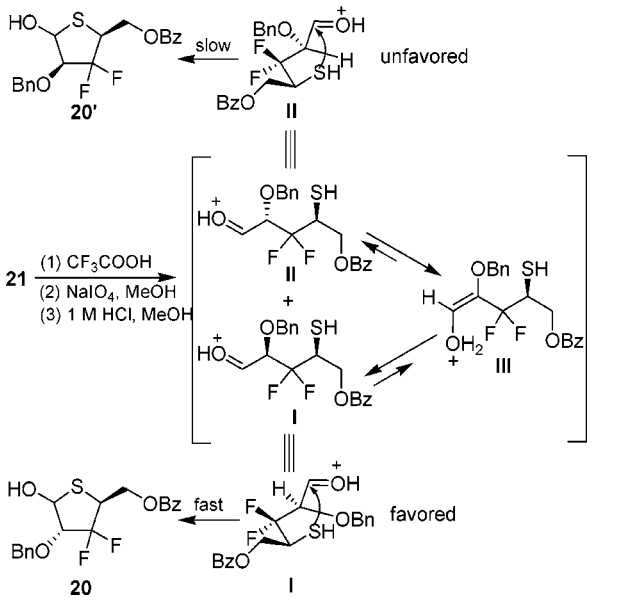
Scheme 4



preparing the thiofuranose **20** from **19**. What surprised us was that only compound **20** was isolated, which showed that the stereospecific transformation of the C3 (−OBn) configuration in compound **21** also happened. It was noteworthy that the C3 (−OBn) configuration of compound **20** was contrary to that of compound **12**.

The proposed mechanism of this stereospecific transformation is outlined in Scheme 5. The aldehyde intermediates

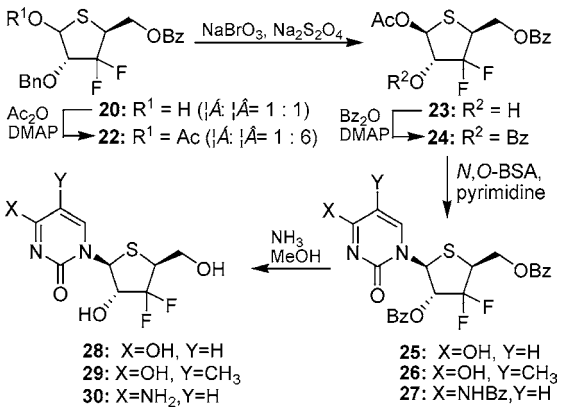
Scheme 5



I and **II** could be formed from compound **21** and were in tautomeric equilibrium through the intemediate **III**. The stereospecific formation of compound **20** from intermediate **I** with the *S* configuration at the C2 position was thought to be faster than the formation of compound **20′** because a huge gauche between the BnO group and the $BzOCH_2$ group in intermediate **II** existed. In addition, the attack of the free hydroxyl group of **I** on the carbonyl group from both the *re* and *si* faces of the aldehyde moiety resulted in a 1/1 mixture of α/β anomers of **20**.

The acetylation of **20** with acetic anhydride in CH_2Cl_2 afforded the β anomer **22** as the main product (α/β = 1/6)

Scheme 6



(Scheme 6), which resulted from the assistance of neighboring large group participation (Scheme 6).[12] In view of the fact that the glycosylation of furanose possessing an acyloxy group in C-2′ position would involve the oxonium intermediate, which might induce the attack of the silylated base from the contrary face of C-2′ acyloxy group[13] to give the β anomer nucleosides as main product and for the conveniency of the following removal of the protecting groups, we decided to replace the benzyloxy group in compound **22** with a benzoyloxy group. Thus, treatment of the acetate **22** with $NaBrO_3/Na_2S_2O_4$[14] smoothly provided the alcohol **23** in 87% yield, which was then benzoylated with $Bz_2O/DMAP/Et_3N$ to produce the key intermediate **24** in 92% yield. Then, coupling of compound **24** with various persilylated pyrimidines were performed in refluxed acetonitrile under Vorbrüggen conditions.[15] As expected, all the reactions gave the β anomers as the main products. Trace of the α anomers was detected by ^{19}F NMR spectra of the crude reaction mixture, but was not isolated by flash chromatography. Finally, removal of the benzoyl groups in compounds **25**−**27** with saturated methanolic ammonia smoothly produced the desired free nucleosides **28**−**30**.

The stereochemistry of compound **26** has been established by 2D NMR NOESY experiments. As shown in Figure 2,

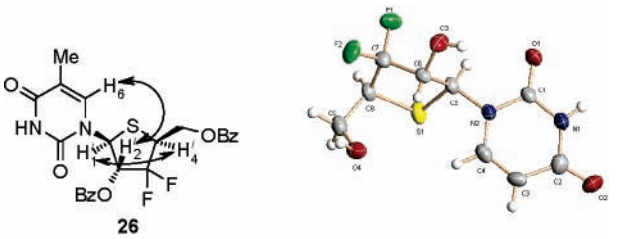


Figure 2. NOE correlation of compound **26** and X-ray structure of compound **28**.

correlation between H_1' and H_4' was clearly observed in this compounds. In addition, the H_2' proton strongly correlated with H6 protons of base. All of these showed that the nucleoside derivative **26** is β anomer. Furthermore, the structure of compound **28** was confirmed by X-ray crystal analysis (Figure 2).

In conclusion, we have designed and synthesized the new L-3′-dideoxy-3′,3′-difluoro-4′-thionucleosides **28**−**30** based on our versatile *gem*-difluorinated synthon. Our synthesis highlighted the installation of thioacetyl group in high efficiency and construction of thiofuranose skeleton in a novel method. Antiviral and cytotoxicity evaluations of herein synthesized L-3′-deoxy-3′,3′-difluoro-4′-thionucleosides are currently in progress and will be reported elsewhere.

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Supporting Information Available: Detailed experimental procedures and analytical data for all new compounds and crystallographic data for compound **28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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