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Synthesis of New 2′,3′-Dideoxy-6′,6′-difluoro-3′-thionucleoside from *gem*-Difluorohomoallyl Alcohol

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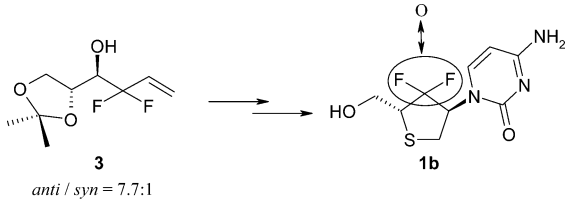
ABSTRACT



2′,3′-Dideoxy-6′,6′-difluoro-3′-thionucleoside 1b, an analogue of 3Tc that has high biological activities against HIV and HBV, has been synthesized from *gem*-difluorohomoallyl alcohol 3 in an efficient way. The key intermediate 4-amino-3,3-difluorotetrahydrothiophen-2-ylmethyl benzoate 15 was prepared from 2,2-difluoro-1-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]but-3-en-1-ol 3 in 11 steps. The construction of pyrimidine ring with the amino group of compound 15 gave the target compound 1.

Nucleoside analogues have drawn great attention due to their high antitumor and antiviral activities. Among these classes of modified nucleosides, the 2′,3′-dideoxynucleosides (ddNs) have proved to be the most effective therapeutic agents against human immunodeficiency virus (HIV) and hepatitis B virus (HBV).[1] However, the toxicities associated with certain nucleoside analogues and the emergence of resistant viral strains warrant the search for further novel and structurally diversified compounds with minimum overlapped resistance profiles and toxicities.[2] Sulfur-containing dideoxynucleosides, (−)-β-L-(2R,5S)-1,3-oxathiolanylcytosine (3TC)[3] and its 5-fluorocytosine analogue, (−)-FTC,[4] show higher biological activities against HIV-1, HIV-2, and HBV with lower toxicities than conventional ddNs. However, such ddNs have shown limited stability: the glycoside linkage of ddNs is susceptible to both acidic and enzymatic hydrolysis.[5] One important phenomenon has been observed: the replacement of the oxygen in the sugar portion of the nucleoside with a methylene (CH_2) unit results in carbocyclic nucleoside analogues that are highly resistant to the phosphorylases, which cleave the glycosidic bond of natural nucleosides.[6]

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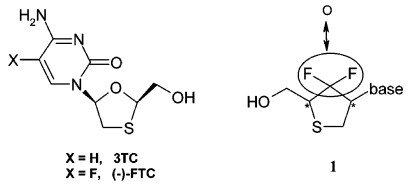
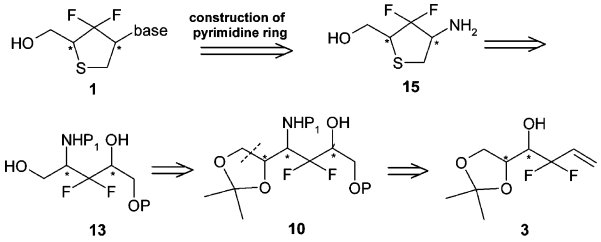


Figure 1. Rationale for the design of the target compound **1**.

Therefore, what interests us most is to synthesize a new type of 3TC analogue by replacing the oxygen with a difluoromethylene group (CF_2) on the basis of the bioisosteric rationale (Figure 1). This is because the carbocyclic nucleoside analogues have more stable glycosidic bonds, which can be of advantage to antiviral agents. Notably, the *gem*-difluoromethylene has been considered as an isopolar-isosteric substitute for oxygen.[7] Additionally, the introduction of fluorine atoms to a nucleoside may enhance its clinical efficacy by altering drug metabolism and lipophilicity.[8] However, as far as we know, the synthesis of 6′,6′-difluoronucleoside is extremely difficult, which has impeded the investigation of structure−activity relationships (SARs) and their development as clinical agents. Therefore, new and practical synthetic methods are needed. Herein, a route to synthesize 2′,3′-dideoxy-6′,6′-difluoro-3′-thionucleoside **1** is described.

Our retrosynthetic analysis (Scheme 1) was based on the idea that the target molecule **1** could be derived from the

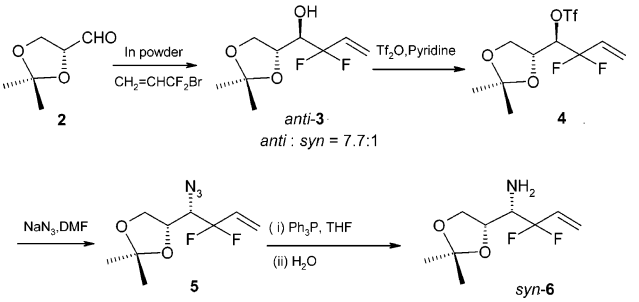
Scheme 1. Retrosynthetic Analysis of **1**



precursor of type **15** by building a base moiety at the C1 position through the procedure of Shaw and Warrener.[9] However, construction of the special backbone of **15**, especially the introduction of a *gem*-difluoromethylene group to the C4 position, is very difficult. Although the fluorination of carbonyl group with DAST is a common method for the introduction of a *gem*-difluoromethylene group, very few sterically hindered five-membered cyclic ketones have been difluorinated by DAST.[10] Recently, we have reported the preparation of 3-deoxy-3,3-difluoro-D-arabinofuranose from *gem*-difluorohomoallyl alcohol **3**.[11] We envisioned that the *gem*-difluoromethylenated diol **13** could be a suitable precursor for compound **15**. Compound **13** can be derived from the chiral *gem*-difluorohomoallyl alcohol **3** through dihydroxylation and followed by ring closure and opening. The absolute configuration of the target compound could be controlled by performing the synthesis in an enantioselective fashion.

The *gem*-difluorohomoallyl alcohol **3** was obtained through the coupling of *gem*-difluoroallylindium, generated from 3-bromo-3,3-difluoropropene and indium in DMF, with 1-(*R*)-glyceraldehyde acetonide **2** in 90% yield (Scheme 2).[12]

Scheme 2



The ratio of anti/syn compound **3** is 7.7:1 determined by ^{19}F NMR. The difluoromethylene group in *anti*-**3** appeared at a higher field than that in *syn*-**3** in ^{19}F NMR spectra. Notably, the *anti*-**3** isomer is our desired compound. Then, compound **3** was treated with trifluoromethanesulfonic anhydride in dichloromethane at −25 °C to afford the corresponding triflate **4**. Subsequent treatment of compound **4** with sodium azide in DMF at room temperature provided compound **5**. However, the reduction of the azide **5** was not easy to accomplish. Initial attempts to obtain the amide **7** through the reduction of compound **5** with $LiAlH_4$ and then direct protection of reduced product by *tert*-butoxycarbonyl group failed. Fortunately, by using Ph_3P as a reducing agent instead of $LiAlH_4$ in THF, our desired amine *syn*-**6** was obtained in 62% overall yield from alcohol **3**. The *syn*-**6** could be easily separated through column chromatography.

However, to our surprise, the protection of amine *syn*-**6** with di-*tert*-butyl dicarbonate (Boc_2O) in a common way afforded protected amide **7** in poor yield (16−29%, entries 1−3) together with byproduct **8** (Table 1). In addition, the more equivalents of Et_3N used, the lower the yield of product

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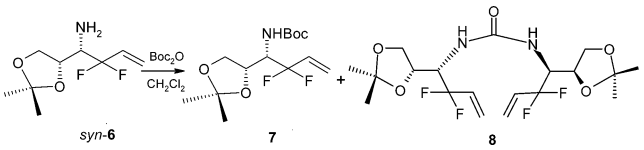
Table 1. Protection of Amine *syn*-**6** with Boc_2O



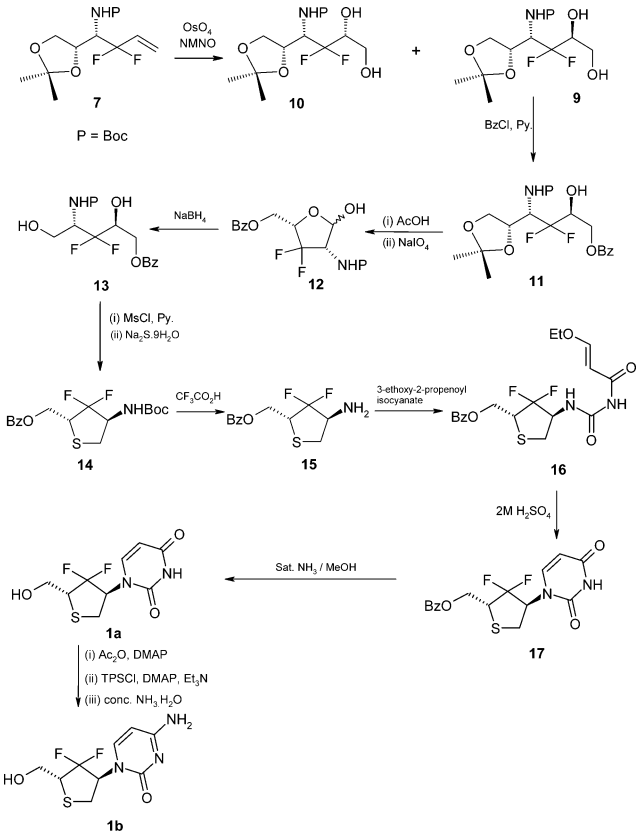
entry	Boc_2O (equiv)	*T* (°C)	base	time (h)	yield of **7** (%)	yield of **8** (%)
1[a]	1.5	rt		24	29	52
2[a]	1.5	rt	Et_3N (2 equiv)	24	20	58
3[a]	1.5	rt	Et_3N (4 equiv)	24	16	62
4[a]	3.0	−35		20	16	
5[b]	1.5	rt		12	25	
6[b]	1.5	rt		20	37	
7[b]	2.0	rt		24	54	
8[b]	5.0	rt		10	90	

[a] Common method: adding the solution of Boc_2O in CH_2Cl_2 to amine **6**. [b] Adding the solution of amine **6** in CH_2Cl_2 to Boc_2O.

7 obtained and, at the same time, the more byproduct **8** (52−62%) produced (entries 1−3). On the basis of the thought that the formation of byproduct **8** was possibly due to the coupling between the protected amide **7** and amine **6**, the reaction was cooled to −35 °C in order to lower the reactivity of amine **6** (entry 4). As expected, no byproduct **8** was produced; however, the yield of our desired compound **7** was not satisfactory (16%). When the addition sequence of reactants was changed by adding the amine **6** to Boc_2O, only product **7** was obtained with no trace of byproduct **8** (entries 5−7). What excited us most was that, when 5.0 equiv of Boc_2O was used, product **7** was obtained in 90% yield (entry 8).

With the difluorohomoallyl amide **7** in hand, we turned our attention to the synthesis of key intermediate **15**. The Os-catalyzed dihydroxylation of compound **7** gave a mixture of compound **9** and **10** in 90% yield (**9**/**10** ≈ 1:1, Scheme 3). Meanwhile, the catalytic asymmetric dihydroxylation (AD) of compound **7** by the procedure of Sharpless also gave a mixture of compound **9** and **10** in a ratio of 1:1. Luckily, compounds **9** and **10** were easily separated by column chromatography and the absolute configurations of these two compounds were determined by the X-ray crystal structure of compound **9** (Figure 2). Selective benzoylation at the primary hydroxyl group of the resulting diol **9** at −78 °C gave benzoate **11** in 84% yield. The conversion of benzoate **11** to the difluoromethylenated furanose **12** was achieved by the following two steps: (1) the acidic hydrolysis of the isopropylidene group by treatment with 75% acetic acid at 50 °C and (2) the oxidative scission of the resulting diol with sodium periodate and subsequent cyclization to compound **12**. Without further purification, the difluorinated furanose **12** was directly reduced by sodium borohydride in methanol to give the diol **13** in 80% overall yield from **11** (three steps). Mesylation at C1 and C4 positions of **13**, followed by treatment with sodium sulfide in DMF, resulted in a ring closure to give thiofuranose **14** as a single stereoisomer in 45% yield. The absolute configuration of compound **14** was determined by X-ray crystal structure (Figure 3). Deprotection of compound **14** with trifluoroacetic acid in CH_2Cl_2 gave the key intermediate **15** in 85% yield. At this stage, a novel and efficient method to prepare the difluoromethylenated compound **15** was successfully developed in our laboratory. The construction of pyrimidine was followed by the procedure reported by Shaw and Warrener.[9] Condensation of amine **15** with 3-ethoxy-2-propenoyl isocyanate in DMF at −25 °C gave compound **16** followed by ring closure with 2 M sulfuric acid in dioxane successfully to afford compound **17**. Deprotection of compound **17** was

Scheme 3



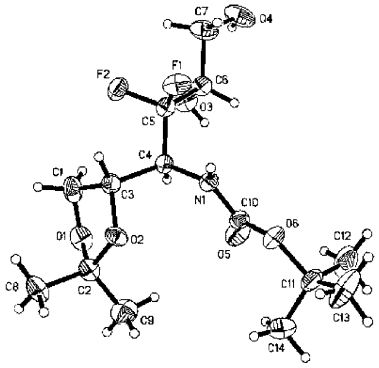


Figure 2. ORTEP drawing of the X-ray crystallographic structure of compound **9**.

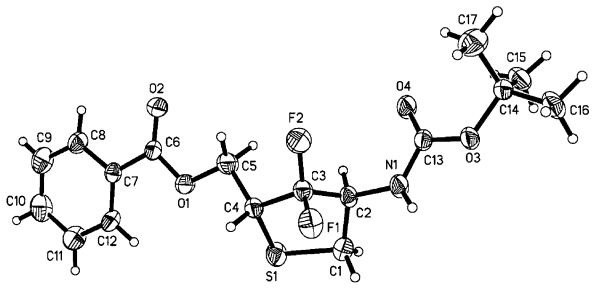


Figure 3. ORTEP drawing of the X-ray crystallographic structure of **14**.

accomplished by ammonolysis to give the target molecule 2′,3′-dideoxy-6′,6′-difluoro-3′-thiouridine **1a** (55% yield, three steps). Compound **1a** was also converted into the cytosine derivative **1b** by triisopropylbenzene-sulfonylation of the O^4-position of **1a**, followed by treatment with concentrated $NH_3 \cdot H_2O$.

The absolute configuration of the target molecule **1b** was made on the basis of the X-ray crystal structure of compound **14** (Figure 3).

In summary, on the basis of bioisosteric rationale, we have synthesized 2′,3′-dideoxy-6′,6′-difluoro-3′-thionucleoside **1**, an analogue of 3TC, in 16 steps and developed a novel method to synthesize 6′,6′-difluoronucleosides. Now, the enantioselective synthesis of D/L-2′,3′-dideoxy-6′,6′-difluoro-3′-thionucleosides and the evaluation of these nucleoside analogues are in progress.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds and crystallographic data for compounds **9** and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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