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Synthesis of 2′,3′-Dideoxy-6′,6′-difluorocarbocyclic Nucleosides

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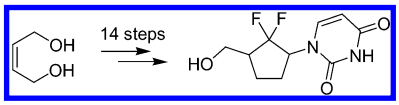
ABSTRACT



2′,3′-Dideoxy-6′,6′-difluorouracils, a novel series of *gem*-difluoromethylenated carbocyclic nucleosides, were synthesized from (*Z*)-but-2-ene-1,4-diol in 14 steps. A notable step was the construction of the carbocyclic ring via ring-closing metathesis and the incorporation of *gem*-difluoromethylene group by way of silicon-induced Reformatskii–Claisen reaction of chlorodifluoroacetic ester 3.

In recent years, attention has been increasingly focused on structural modifications of carbocyclic nucleosides. Due to the absence of a glycosidic linkage, carbocyclic nucleosides are chemically more stable and not subject to the phosphorylases that cleave the N-glycosidic linkage in conventional nucleosides. Many carbocyclic nucleosides have now been identified to exhibit antiviral and antitumor activities.[1,2] Abacavir (Figure 1) has been used as an anti-HIV agent.[3] Entecavir, a carbocyclic nucleoside with an exocyclic double bond, is undergoing phase III clinical trials for the treatment of chronic hepatitis B virus infection.[4] 6′-Fluorocarbocyclic nucleoside **1** exhibited moderate activities against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) in vitro.[5] The 2′,3′-dideoxynucleosides (ddNs) have been proved to be the most effective therapeutic agents against human

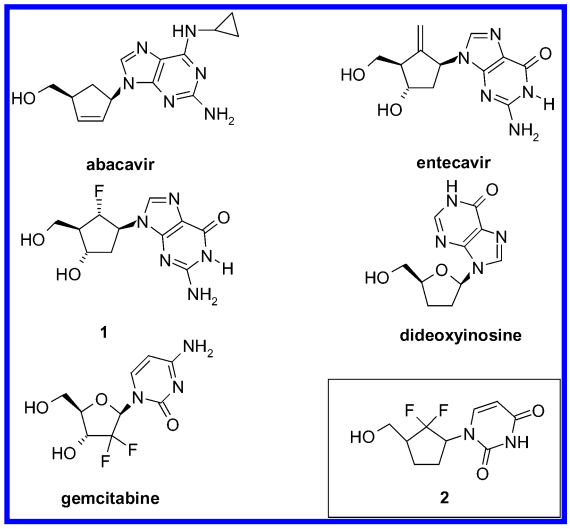


Figure 1. Rationale for the design of the target nucleosides **2**.

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(2) For some recent examples, see: (a) Choi, W. J.; Moon, H. R.; Kim, H. O.; Yoo, B. N.; Lee, J. A.; Shin, D. H.; Jeong, L. S. *J. Org. Chem.* **2004**, *69*, 2634. (b) Yang, M.; Ye, W.; Schneller, S. W. *J. Org. Chem.* **2004**, *69*, 3993. (c) Fang, Z.; Hong, J. H. *Org. Lett.* **2004**, *6*, 993. (d) Roy, A.; Schneller, S. W. *J. Org. Chem.* **2003**, *68*, 9269. (e) Jin, Y. H.; Liu, P.; Wang, J.; Baker, R.; Huggins, J.; Chu, C. K. *J. Org. Chem.* **2003**, *68*, 9012. (f) Kim, H. S.; Jacobson, K. A. *Org. Lett.* **2003**, *65*, 1665. (g) Ludek, O. R.; Meier, C. *Synthesis* **2003**, 2101.

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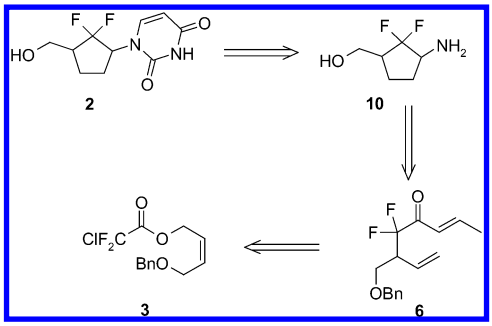
immunodeficiency virus (HIV) and hepatitis B virus (HBV). Among them, dideoxyinosine (DDI) had been developed into an anti-HIV drug.[6] The *gem*-difluoromethylene (CF_2) group has been suggested by Blackburn as an isopolar and isosteric substituent for oxygen.[7] Since then, the CF_2 group was used extensively to modify nucleoside analogues. For example, 2′-deoxy-2′,2′-difluorocytidine (gemcitabine) has been approved as a drug for solid tumor treatment.[8] On the basis of the above consideration and our ongoing efforts to develop new antiviral and anticancer agents, we designed the 2′,3′-dideoxycarbocyclic nucleosides **2** (Figure 1), a new type of analogue of DDI, by replacing the oxygen with difluoromethylene group (CF_2) based on the bioisosteric rationale. Herein, an efficient route to synthesize 2′,3′-dideoxycarbocyclic nucleosides **2** is described.

As illustrated in Scheme 1, retrosynthetic analysis showed that the target nucleosides could be synthesized from cyclic

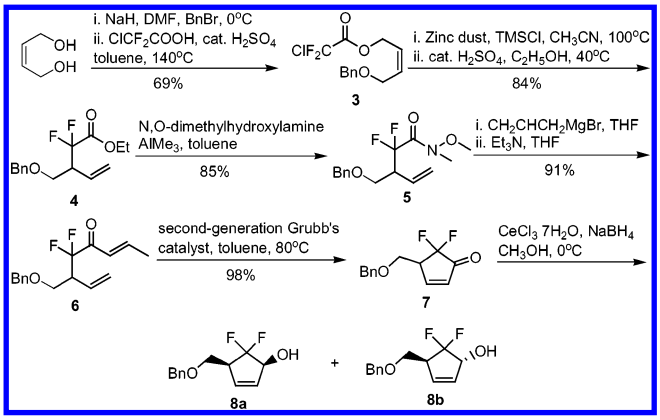
Scheme 1



amine **10**, which could be used to introduce a base moiety at the C1 position using a well-known procedure. However, construction of the special backbone of **10**, especially introduction of *gem*-difluoromethylene to the C4 position of **10**, is very difficult. Although DAST appears to be the most common reagent for introduction of a *gem*-difluoromethylene group, very few sterically hindered five-membered cyclic ketones have been difluorinated by DAST. We envisioned that compound **6** could be converted into **10** via ring-closing metathesis. Compound **6** can be derived from chlorodifluoroacetic ester **3** through Reformatskii−Claisen reaction.

The synthesis of the nucleosides **2** began with (*Z*)-2-butene-1,4-diol (Scheme 2). Protection of one of its hydroxy

Scheme 2



groups, follwed by esterification of another one with chlorodifluoroacetic acid catalyzed by sulfonic acid, gave **3** in multigram quantities.[9,10] Then, **3** underwent a silicon-induced Reformatskii−Claisen reaction[11] when a mixture of **3**, chlorotrimethylsilane, and freshly activated zinc dust was heated for 20 h in dry acetonitrile at 100 °C. The resulting crude product was esterified with ethanol to give **4** in 84% yield (two steps). Ester **4** was then transformed into Weinreb amide **5** in 85% yield. Treatment of **5** with allylmagnesium bromide resulted in successful conversion into the corresponding β,γ-unsaturated ketone, which was transformed to **6** in 91% yield (two steps) by double-bond isomerization. With compound **6** in hand, we turned our attention to the ring-closing metathesis (RCM) of compound **6**. Initially, the RCM of **6** was carried out in the presence of the first-generation Grubbs' catalyst, and the reaction did not occur. Fortunately, when compound **6** was subjected to the second-generation Grubbs'catalyst[12] in refluxing toluene, the reaction resulted in complete conversion and compound **7** was isolated in 98% yield. Ketone **7** was transformed to alcohols **8a** and **8b** via Luche reduction[13] in a 2.9:1 cis/trans ratio, which can be separated easily through column chromatography. The relative configuration of **8a** was confirmed by the structure of **2a**, which was identified by X-ray analysis.

Hydrogenation of **8a** with the catalyst of Pd/C in benzene for 24 h gave compound **9a** in 84% yield (Scheme 3).[14] Treatment of alcohol **9a** with trifluoromethanesulfonic

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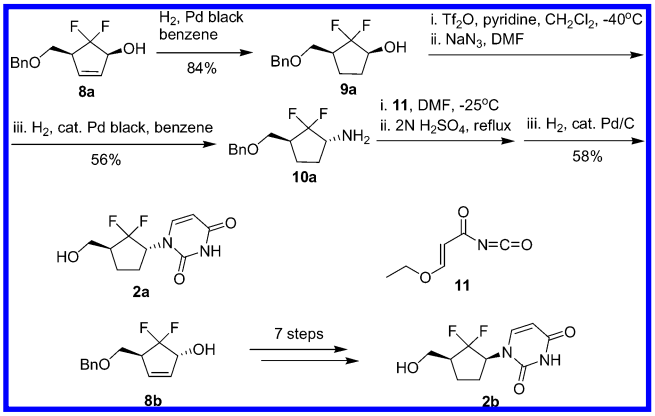
Scheme 3



anhydride and pyridine followed by substitution reaction with sodium azide in DMF gave the azide compound, which was directly reduced by hydrogenation to give cyclic amine **10a** in 56% yield (three steps). The construction of pyrimidine was followed by the reported procedure.[15] Condensation of cyclic amine **10a** with 3-ethoxy-2-propenoyl isocyanate in DMF at −25 °C followed by ring closure with 2 N sulfuric acid in dioxane successfully produced the nucleoside. Removal of the benzyl group by hydrogenation gave the target molecule **2a** in 58% yield (three steps). The relative configuration of racemic **2a** was determined by X-ray crystal structure (Figure 2). With the same synthetic route, isomer **2b** was prepared from **8b**.

In conclusion, we have completed a 14-step synthesis of racemic 2′,3′-dideoxy-6′,6′-difluorocarbocyclic nucleoside **2a** in 7.6% overall yield and **2b** in 1.5% overall yield.

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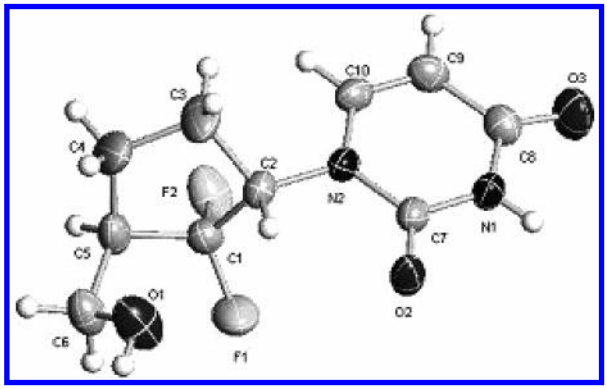

Figure 2. ORTEP drawing of the X-ray crystallographic structure of **2a**.

Reformatskii−Claisen rearrangement and ring-closing metathesis are the key steps of the synthesis. The flexibility in our approach to access these novel nucleosides is noteworthy, and we are currently investigating enantioselective synthesis of 2′,3′-dideoxy-6′,6′-difluoro-carbocyclic nucleosides.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds and crystallographic data for compound **2a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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