

# Synthesis of 2',3'-Dideoxy-6',6'-difluorocarbocyclic Nucleosides

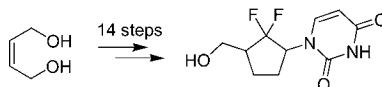
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## ABSTRACT



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.<sup>1,2</sup> Abacavir (Figure 1) has been used as an anti-HIV agent.<sup>3</sup> Entecavir, a carbocyclic nucleoside with an exocyclic double bond, is undergoing phase III clinical trials for the treatment of chronic hepatitis B virus infection.<sup>4</sup> 6'-Fluorocarbocyclic

nucleoside **1** exhibited moderate activities against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) in vitro.<sup>5</sup> The 2',3'-dideoxynucleosides (ddNs) have been proved to be the most effective therapeutic agents against human

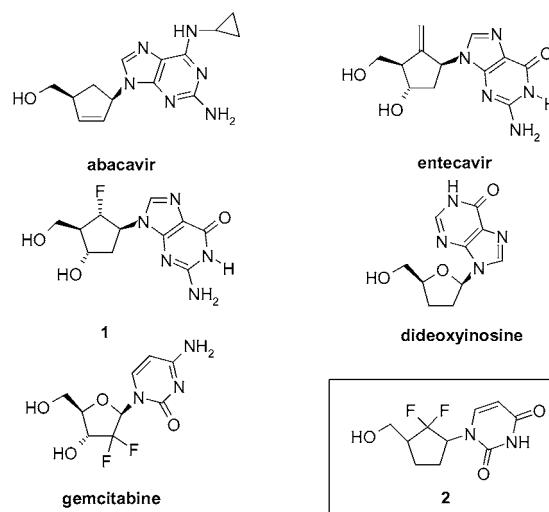


Figure 1. Rationale for the design of the target nucleosides **2**.

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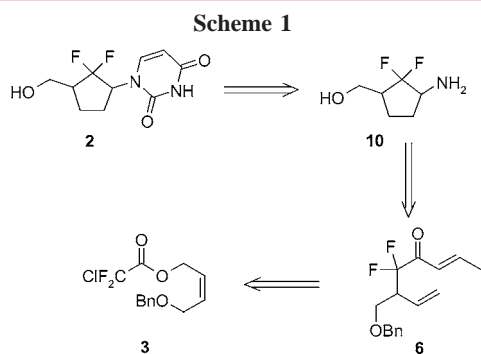
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immunodeficiency virus (HIV) and hepatitis B virus (HBV). Among them, dideoxyinosine (DDI) had been developed into an anti-HIV drug.<sup>6</sup> The *gem*-difluoromethylene (CF<sub>2</sub>) group has been suggested by Blackburn as an isopolar and isosteric substituent for oxygen.<sup>7</sup> Since then, the CF<sub>2</sub> 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.<sup>8</sup> 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<sub>2</sub>) 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



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.

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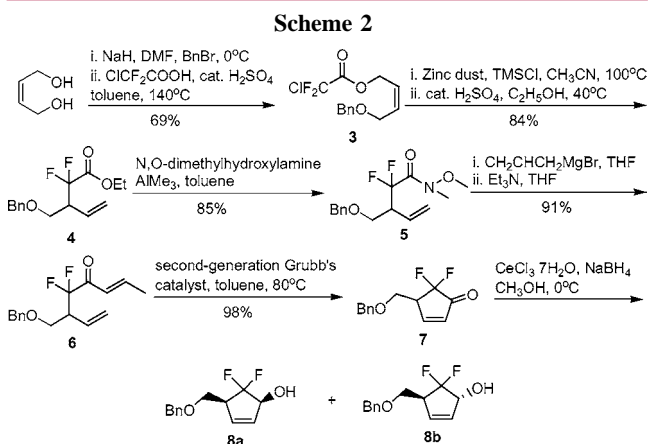
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The synthesis of the nucleosides **2** began with (*Z*)-2-butene-1,4-diol (Scheme 2). Protection of one of its hydroxy



groups, followed by esterification of another one with chlorodifluoroacetic acid catalyzed by sulfonic acid, gave **3** in multigram quantities.<sup>9,10</sup> Then, **3** underwent a silicon-induced Reformatskii–Claisen reaction<sup>11</sup> 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  $\beta,\gamma$ -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<sup>12</sup> 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<sup>13</sup> 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).<sup>14</sup> Treatment of alcohol **9a** with trifluoromethanesulfonic

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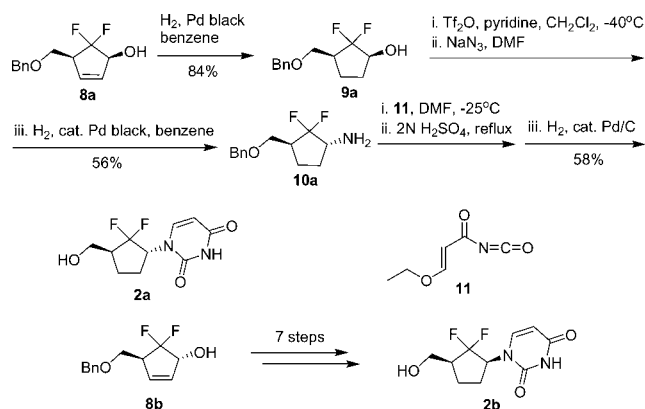
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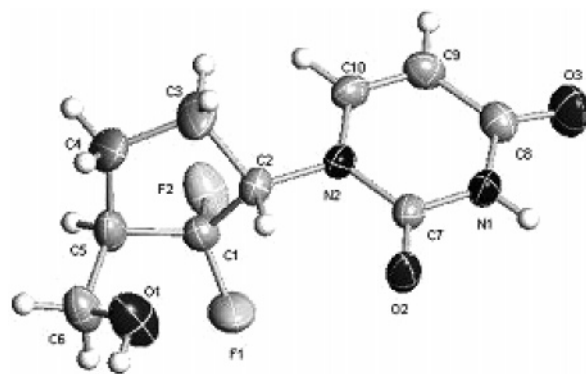
### Scheme 3



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.<sup>15</sup> Condensation of cyclic amine **10a** with 3-ethoxy-2-propenoyl isocyanate in DMF at  $-25^{\circ}\text{C}$  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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