

# Stereocontrolled Synthesis of $\alpha$ -2'-Deoxyribonucleosides

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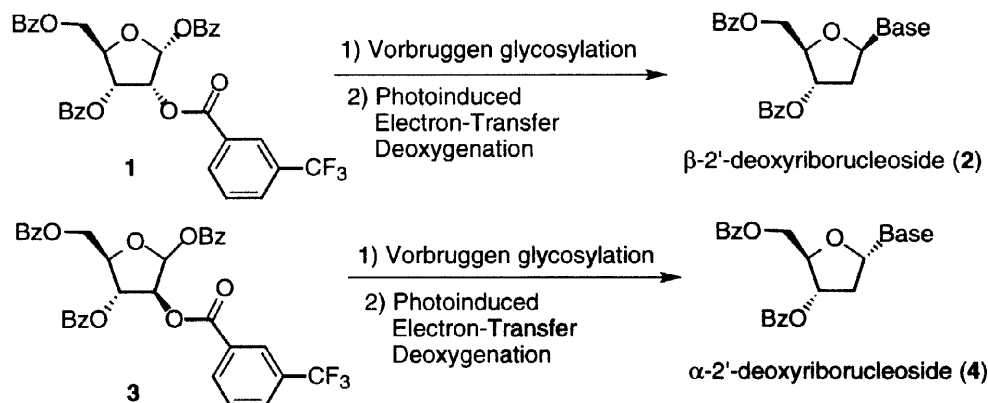
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**Abstract:** A stereocontrolled synthesis of  $\alpha$ -2'-deoxynucleosides has been achieved. Our synthetic strategy involves the use of a benzoyl group at the 2-position of arabinose as a directing group for Vorbrüggen glycosylation and a deoxygenation precursor. © 1997 Elsevier Science Ltd.

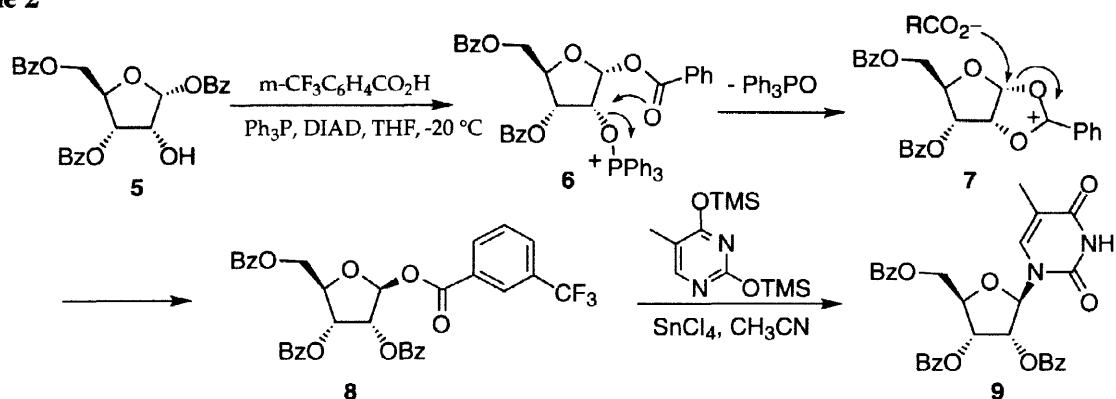
We have recently described an efficient stereocontrolled, de novo synthesis of  $\beta$ -2'-deoxyribonucleosides.<sup>1,2</sup> The key step in this work (Scheme 1) was the use of a *m*-trifluoromethylbenzoyl group at the 2-position of ribose (**1**) to direct the Vorbrüggen glycosylation.<sup>3</sup> After glycosylation, this group was selectively deoxygenated via a photoinduced electron-transfer (PET) mechanism to give the protected  $\beta$ -2'-deoxyribonucleoside (**2**); 9-methylcarbazole (MCZ) was used as the photosensitizer.<sup>4</sup> We now report the extension of this strategy to the stereocontrolled synthesis of  $\alpha$ -2'-deoxynucleosides.

Nucleosides and nucleoside analogs are an important class of anticancer and antiviral agents.<sup>5</sup> Modified nucleosides have also played a central role in the development of genetic therapies such as triplex (antigene) and antisense strategies. Vorbrüggen glycosylation of ribose tetrabenzoate leads nearly exclusively to ribonucleosides possessing the natural  $\beta$ -anomeric stereochemistry. It was observed that oligo- $\alpha$ -2'-deoxynucleotides hybridize with a complementary oligo- $\beta$ -2'-deoxynucleotide to form a parallel B-like helix.<sup>6</sup> Of particular note, the unnatural oligo- $\alpha$ -2'-deoxynucleotides were resistant to enzymatic degradation making them of interest as potential antisense agents.<sup>7</sup>

Scheme 1



## Scheme 2



$\alpha$ -2'-Deoxynucleosides have been prepared via non-stereoselective glycosylation of 2-deoxyribose chloride derivatives or by anomerization of the  $\beta$ -2'-deoxyribonucleosides followed by separation of anomers.<sup>5,8</sup> It is documented that Vorbrüggen glycosylation of arabinose tetraesters (Scheme 1, **3**) selectively gives the  $\alpha$ -anomeric stereochemistry.<sup>9</sup> Our plan was to invert the C-2 stereochemistry of **5** to give the desired arabinose derivative however, Mitsunobu reaction of **5** with *m*-trifluoromethylbenzoic acid followed an unexpected course.<sup>10</sup> Instead of the product derived from inversion of the C-2 hydroxyl group, we observed suprafacial migration of the C1-benzoyl group to C2 to give **8**.<sup>10b</sup> We propose an S<sub>N</sub>1-like mechanism involving neighboring group participation of the C1-benzoate as shown in Scheme 2. Glycosylation of **8** with bis-trimethylsilylthymine under standard Vorbrüggen conditions gave **9** lacking a trifluoromethylbenzoyl group. The structure and stereochemistry of **9** was ultimately confirmed by independent synthesis.

A suitable glycosylation precursor was prepared by Scheme 3. It is reported that the C2 benzoate of **10** could be selectively hydrolyzed<sup>11</sup> however, in our hands this was only a minor product with the major product being hydrolysis at C3 to give **11**. We have recently discovered that 3,6-dimethyl-9-ethylcarbazole<sup>12</sup> could efficiently deoxygenate benzoates, thus the C2-benzoyl group of **11** could be used as the deoxygenation precursor instead of the more expensive *m*-trifluoromethylbenzoate.<sup>13</sup> Conversion of the anomeric methoxy group to an acetyl occurred with concomitant acetylation of the C3 hydroxyl to give **12** as a mixture of anomers. Vorbrüggen glycosylation of **12** (silylated nucleoside base, CH<sub>3</sub>CN, SnCl<sub>4</sub>) proceeded in 51-97% yield to give **13** exclusively as the  $\alpha$ -anomer. PET deoxygenation provided **14** which can be deprotected to give the  $\alpha$ -2'-deoxyribonucleoside.<sup>14</sup> The sequence required seven steps from arabinose but only three steps from common intermediate **12**.

## Scheme 3

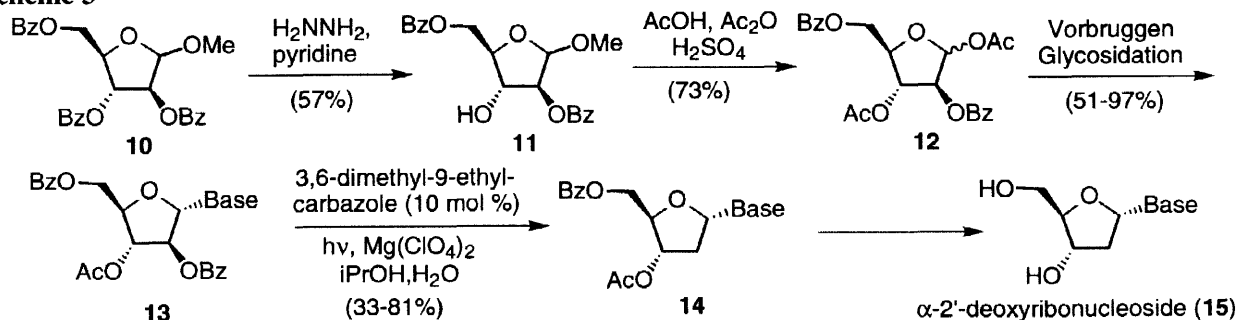
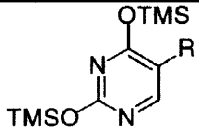
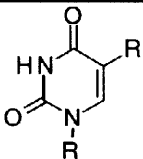
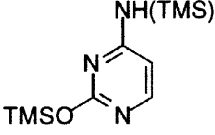
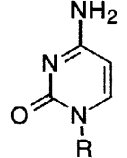
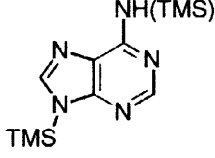
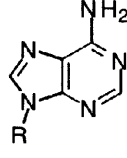
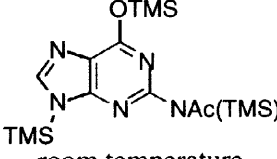
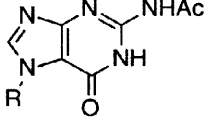
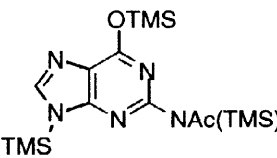
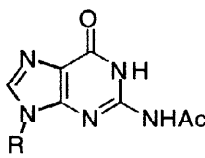


Table 1

Entry	Silylated Base	Yield of <b>13</b>	Protected $\alpha$ -Nucleoside	Yield of <b>14</b>
a b c		94% 97% 91%		69% 73% trace
d		93%		33%
e		61%		76%
f	 room temperature	92%		78%
g	 reflux for 3h	51%		81%

We found that silylated N<sup>4</sup>-isobutrylcytosine and N<sup>6</sup>-benzoyladenine undergoes glycosylation to give the corresponding  $\alpha$ -arabinonucleosides in high yield. Unfortunately, attempted PET deoxygenation with these base protected intermediates gave decomposition; related difficulties were reported by Benner.<sup>1b</sup> Saito showed that PET deoxygenation of a trifluoromethylbenzoyl derivative of adenosine could be achieved when N<sup>6</sup> was not protected.<sup>4</sup> Glycosylation of **12** with silylated cytosine and adenine gave the corresponding  $\alpha$ -arabinonucleosides in 97 and 61% yield respectively (entries d and e). Gratifyingly, deoxygenation of the arabinoadenine derivative proceeded smoothly to give the  $\alpha$ -2'-deoxynucleoside in 76% yield (entry c). The cytosine case proved more difficult (entry d). PET deoxygenation proceeded to give the desired product however, the product appeared to decompose under the photochemical conditions. The best yield of  $\alpha$ -2'-deoxycytidine was obtained when the deoxygenation was conducted at 40°C for 1 h to give the desired product in 33% yield along with about 35% recovery of starting material.

Glycosylation of **12** with silylated N-acetylguanine at room temperature gave exclusively the N7 product (entries f). The structure of this compound was unambiguously assigned by 2-D NMR using long-range <sup>1</sup>H-<sup>13</sup>C heteronuclear correlation (HMBC). When the glycosylation was performed at reflux for 3h, the N9-isomer was obtained in 51% yield along with 8% of the N7-product (entry g). These results are analogous

to those reported in the ribose series with guanine.<sup>15,16</sup> Both the  $\alpha$ -N7 and  $\alpha$ -N9-guanosine derivatives were deoxygenated to give the corresponding  $\alpha$ -2'-deoxynucleoside in excellent yield.

In conclusion, we have developed a relatively short, stereocontrolled *de novo* synthesis of  $\alpha$ -2'-deoxyribonucleosides. Oligo- $\alpha$ -nucleotides have shown interesting hybridization properties and the efficient synthesis described here should provide quantities of  $\alpha$ -ribonucleosides for further physical study.

**Acknowledgments:** This work was supported by Grant #DHP-172 from the American Cancer Society. C.J.R. thanks the American Cancer Society for a Junior Faculty Research Award. We are grateful to Markus Voehler for obtaining <sup>1</sup>H-<sup>13</sup>C heteronuclear correlated 2-D NMR spectra on compound **13f**.

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- Typical procedure for the PET deoxygenation: In a custom made Pyrex reaction vessel equipped with a cold-finger, a solution of **13b** (35 mg, 0.069 mM), magnesium perchlorate hydrate (15 mg, 0.45 mM) and 3,6-dimethyl-9-ethylcarbazole (1.5 mg, 0.007 mM) in 30 mL of 10% deionized water/isopropanol was degassed by bubbling UHP argon through the solution from 30 min. The reaction was irradiated with a Hanovia 450W medium-pressure Hg lamp while maintaining the temperature at 23 °C with a circulating temperature bath. After 2 h, the reaction was evaporated to remove the isopropanol and the aqueous residue extracted three times with ethyl acetate. The organic phases were washed with saturated brine, dried over magnesium sulfate, filter and evaporated. Purification by flash chromatography on silica gave **14b** as a white solid (19 mg, 73% yield). All new compounds have been characterized by <sup>1</sup>H and <sup>13</sup>C NMR.
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