Stereocontrolled de Novo Synthesis of β-2′-Deoxyribonucleosides

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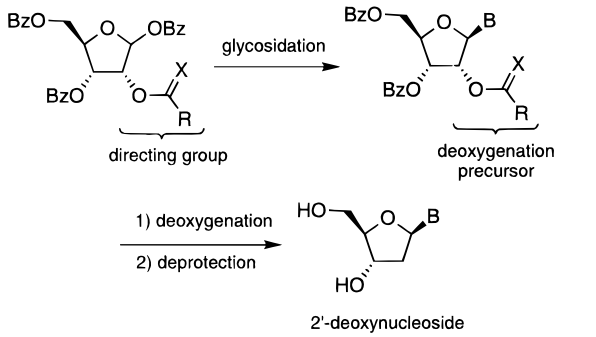
General and convenient methods for the synthesis of nucleosides are of obvious interest. Nucleosides and nucleoside analogs have long been an important class of medicinal agents, possessing anticancer and antiviral activity.[1] Recent interest in antiviral nucleosides has centered around the development of reverse transcriptase inhibitors as potential AIDS therapies.[2] Modified nucleosides have also played a central role in the development of genetic therapies such as triplex (antigene) and antisense strategies.[3]

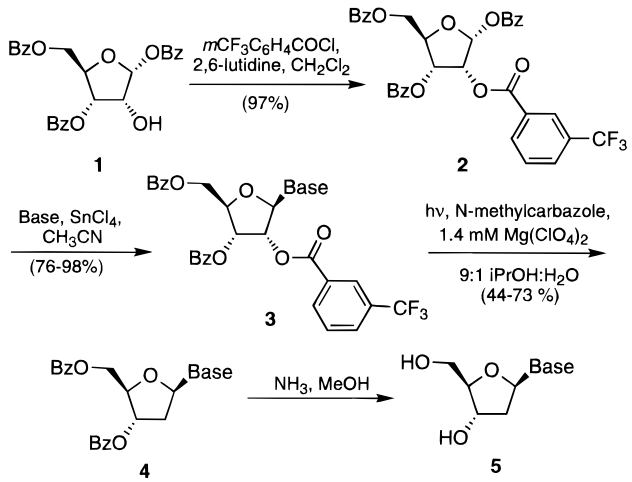
The Vorbrüggen glycosidation involving the reaction of ribose tetraacetate (or benzoate) with the appropriate silylated base under Lewis acid conditions has been used for the synthesis of nucleosides for over three decades.[4] Participation of the neighboring 2′-ester group directs the glycosidation exclusively from the desired β-face. In the absence of a directing 2′-group, mixtures of anomers result which are often difficult to separate.[2] If β-2′-deoxynucleosides are desired, the 2′-hydroxyl is selectively deoxygenated by simultaneous protection of the 5′- and 3′-hydroxyl groups with an expensive bifunctional silylating reagent, 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane.[5] Derivatization of the 2′-hydroxyl group, tin hydride mediated deoxygenation and deprotection, provides the desired 2′-deoxynucleoside.[6]

We are interested in developing more efficient methods for the deoxygenation of ribonucleosides which would involve minimum use of protecting groups, thus making the procedure simpler and more economical. This would provide a valuable method for the synthesis of natural and unnatural 2′-deoxynucleosides of biomedical interest. Our synthetic strategy for the de novo synthesis of 2′-deoxynucleosides is outlined in Scheme 1. We wished to prepare a glycosidation precursor in which the 2-*O*-ester of ribose is differentiated. The 2-*O*-ester group should be capable of directing the glycosidation reaction as well as be suitable as a precursor for deoxygenation. We utilized a *m*-trifluoromethylbenzoyl group as this directing/deoxygenation precursor. A similar strategy

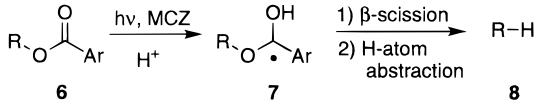
Scheme 1



Scheme 2



Scheme 3



was employed previously by Benner for the synthesis of potential antisense nucleosides with modified backbones.[7]

α-1,3,5-Tribenzoylribose (**1**) is an ideal starting material, since it is differentiated at the 2-position.[8] Reaction of commercially available **1** with *m*-trifluoromethylbenzoyl chloride and 2,6-lutidine gave the *m*-trifluoromethylbenzoate derivative **2** in 97% yield after recrystallization (Scheme 2).[9] The use of a hindered base is necessary to prevent migration of the benzoates in **1**, consistent with previous reports.[8b] We have studied the Vorbrüggen glycosidation of **2** with the five pyrimidine bases shown in Table 1. Entries a−d utilized silylated uracil derivatives, while entry e used a protected cytosine. In all cases, glycosidation gave only the desired β-anomer in greater than 90% yield using either tin tetrachloride or trimethylsilyl triflate in acetonitrile.

Saito showed that benzoyl and *m*-trifluoromethylbenzoyl derivatives of secondary alcohols undergo photosensitized electron-transfer deoxygenation with *N*-methylcarbazole (MCZ) as the photosensitizer.[10] This processes

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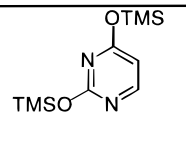
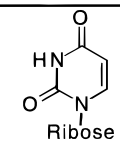
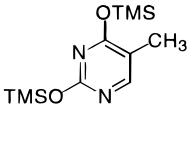
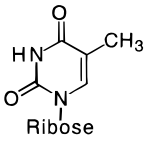
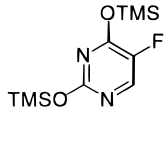
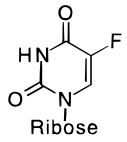
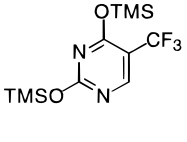
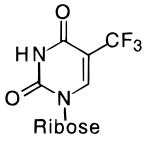
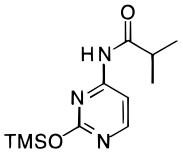
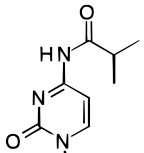
Table 1. Yields for the Gycosidation of 2 and Deoxygenation of 3

Entry	Pyrimidine Base	Yield of **3**	Protected Nucleoside	Yield of **4**
a		95		70
b		98		73
c		91		53
d		97		44
e		91		62

involves an electron transfer from the excited state of MCZ to the *m*-trifluoromethylbenzoate (Scheme 3). Protonation of the radical anion gives radical **7**, which undergoes fragmentation and hydrogen atom abstraction to give the deoxygenated product. Our examples (**3**) possess a benzoate and *m*-trifluoromethylbenzoate which are both secondary; while to our knowledge this is the first example of a direct competition between the two groups, it has been previously demonstrated that *m*-trifluoromethylbenzoates are deoxygenated faster under these conditions.[10] The photolysis of **3** was carried out through Pyrex using a 450-W medium-pressure mercury lamp in degassed 9:1 2-propanol/water at 25 °C with 1.4 mM magnesium perchlorate and 1 equiv of photosensitizer. The deoxygenated products **4a**−**e** were isolated in 44−73% yield.[10] Of particular interest are entries c and d which resulted in stereocontrolled syntheses of the anticancer nucleosides 5-fluoro-2′-deoxyuridine and 5-trifluoromethyl-2′-deoxyuridine (trifluridine).[1b] The structures of protected 2′-deoxynucleosides **4a**−**e** were confirmed by comparison to authentic samples prepared via benzoylation of commercially available 2′-deoxynucleosides; deprotection of these compounds to the parent nucleosides is well established.

In conclusion, we have developed a short, de novo synthesis of 2′-deoxynucleosides. The stereochemistry of the Vorbrüggen glycosidation is controlled by a 2-*O*-*m*-trifluoromethylbenzoyl directing group on the ribose unit **2**. After the stereocontrolled glycosidation, the *m*-trifluoromethylbenzoyl group is selectively deoxygenated via a photosensitized, electron-transfer mechanism. The overall sequence required just four steps from a commercially available starting material (**1**) and proceeded in high overall yield. An advantage of the photodeoxygenation over traditional tin hydride based radical deoxygenations is that toxic tin reagents and byproducts are avoided.

While pyrimidines undergo stereocontrolled Vorbrüggen glycosidation to give a single product, it is well-known that purines give regioisomers resulting from gycosidation at N-7 and N-9, the ratio of which is highly dependent upon the reaction conditions.[11] We are currently investigating the applicability of our sequence to the synthesis of β-2′-deoxypurines with particular attention to improving the regiochemistry of Vorbrüggen glycosidation of **2**. We are also interested in synthesizing unnatural 2′-deoxynucleosides of clinical interest as well as potential antisense nucleosides. A full account of this work will be reported in due time.

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Supporting Information Available: Typical experimental procedures for the preparation of **2**−**4** and copies of their ^{1}H and ^{13}C NMR spectra (25 pages).

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