

Stereocontrolled Synthesis of β -D-2'-Deoxyribonucleosides by Intramolecular Glycosylation

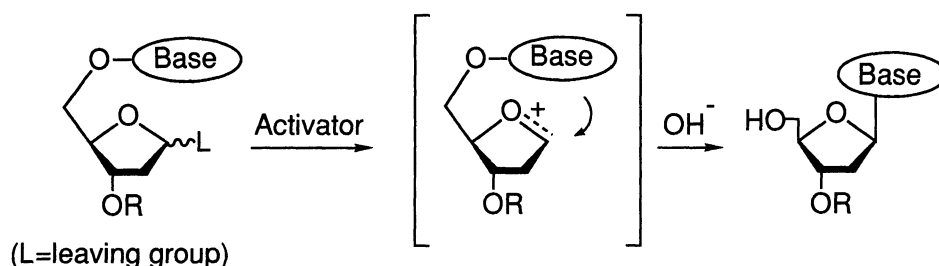
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Intramolecular glycosylation of phenyl 2-deoxy-5-*O*-(2-pyridyl)- and 2-deoxy-5-*O*-(4-methoxy-2-pyrimidyl)-1-thio-D-ribofuranoside by activation with dimethyl-(methylthio)sulfonium tetrafluoroborate followed by hydrolysis gave the corresponding β -2'-deoxyribonucleoside derivatives in good yields.

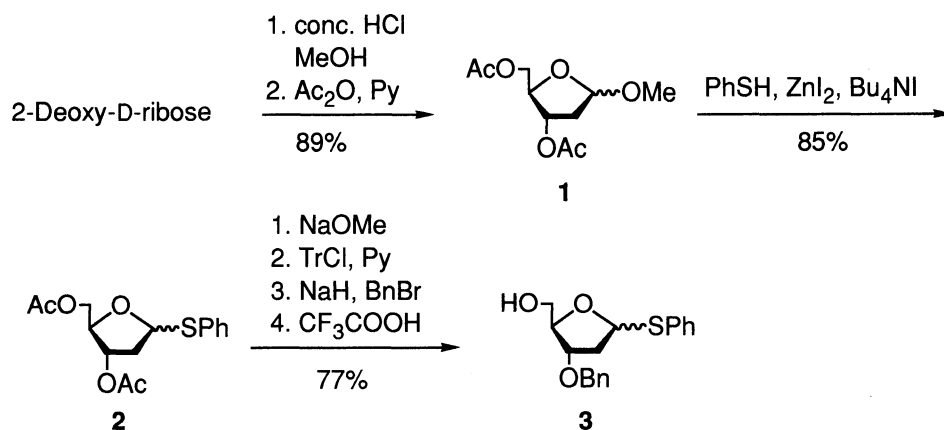
Since sugar modified β -2'-deoxyribonucleosides are expected to exhibit clinically important biological activities (e. g. 3'-azido-3'-deoxythymidine and 2',3'-dideoxy-3'-fluoro nucleosides),¹⁾ many efforts have been made on the development of synthetic methods for these derivatives. The condensation of a sugar moiety and a nucleoside base is one of the most simple ways to construct the skeleton of nucleoside derivatives. However, the Vorbrüggen reaction, most commonly used for coupling sugar and nucleoside base, employing 2-deoxy sugars usually results in the formation of both α and β anomers.²⁾ Although the S_N2 type reaction using 1-chloro-2-deoxy-3,5-di-*O*-toluoyl- α -D-ribofuranose provides a selective route to β -2'-deoxynucleosides,³⁾ the applicability of this procedure to other modified 2-deoxy sugars is limited because the corresponding α -chloro sugars are not always obtained selectively.

As part of our continuing efforts to develop a general method for β -selective formation of 2'-deoxynucleosides,⁴⁾ we planned the glycosylation of the nucleoside base utilizing the C-4 configuration of the glycosyl donor. Scheme 1 illustrates our intramolecular glycosylation strategy, which originated from a recently introduced concept for stereocontrolled glycosylation by several research groups.⁵⁾ Namely, the nucleoside base is initially introduced at the 5-position of the glycosyl donor. After activation of the anomeric position, the nucleoside base will be delivered to the resulting oxonium ion from the β -face to produce the β -*N*-glycoside solely. Although there have been some reports concerning the intramolecular *N*-glycosylation reaction,⁶⁾ they seem not to be suitable for the direct synthesis of β -D-2'-deoxyribonucleosides. A recent publication regarding a similar approach by Jung and Castro⁷⁾ prompted us to report our preliminary findings.

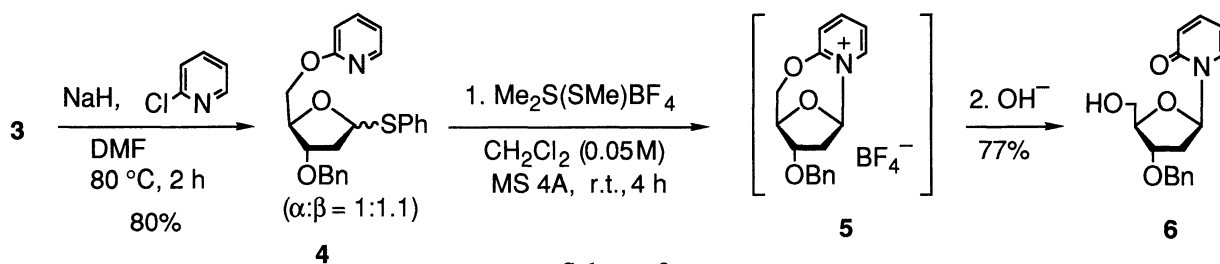


Scheme 1.

We have already revealed that thioglycosides are efficient glycosyl donors in several situations of nucleoside synthesis.^{4, 8)} In addition, they are easily prepared from the corresponding methyl glycosides, stable under a variety of protection and deprotection conditions, and capable of selective activation at the anomeric carbon under mild conditions. Therefore, we chose thioglycoside **3** as a substrate of the intramolecular glycosylation and prepared it as follows (Scheme 2). 2-Deoxy-D-ribose was transformed to the methyl glycoside **1** in good yield in the usual manner. Then the phenylthio group was introduced at the anomeric position by a modification of Hanessian's method.⁹⁾ After deacetylation of **2**, the hydroxy group at C-3 was selectively benzylated in three steps to afford **3** in totally good yield.

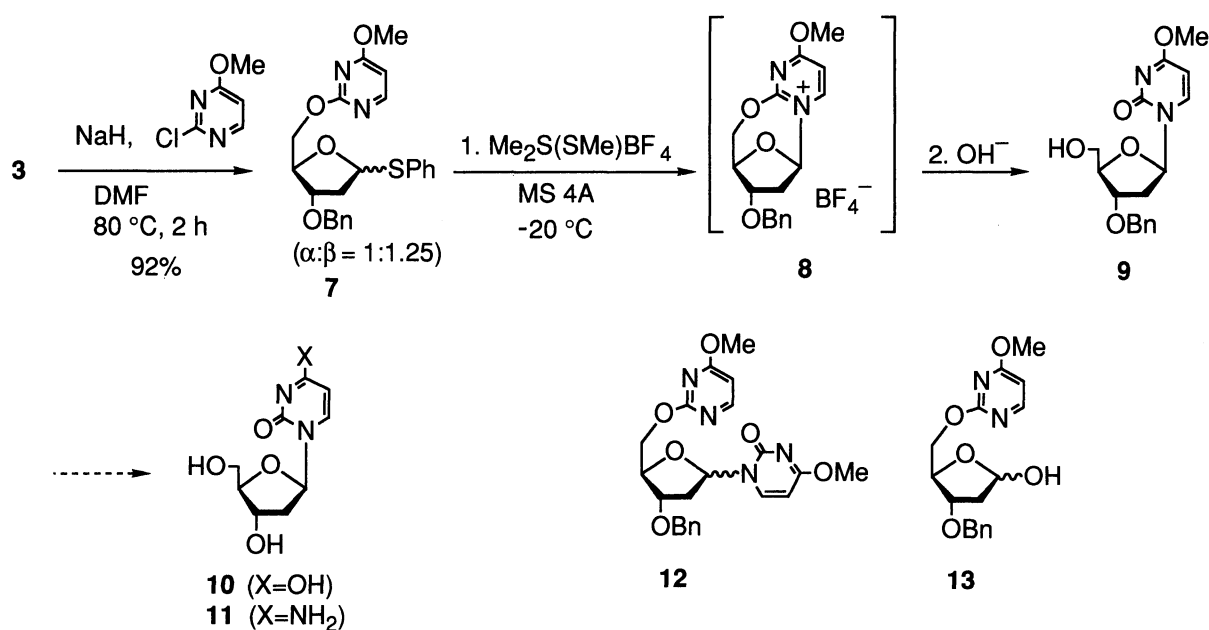


Intramolecular *N*-glycosylation was initially investigated using 2-chloropyridine as a model reaction (Scheme 3). The introduction of the 2-pyridyl group at the 5-position of thioglycoside **3** was achieved using sodium hydride and 2-chloropyridine in DMF to give **4** in 80% yield. Activation of **4** with 1.1 equiv. of *N*-bromosuccinimide at -20 °C to r.t. in dichloromethane followed by basic hydrolysis led to formation of many unidentified products. A solution to this problem was found by using sulfonium ion as the activator. When **4** was treated with 1.1 equiv. of dimethyl(methylthio)sulfonium tetrafluoroborate in dichloromethane at r.t. in the presence of MS 4A, a fine precipitate, probably the pyridinium salt **5**, was observed. After stirring for 4 h, a saturated aqueous solution of sodium carbonate was added to the reaction mixture and stirring was continued overnight to provide β -*N*-glycoside **6**¹⁰⁾ in 77% yield.



Next, we applied this methodology to the synthesis of pyrimidine nucleosides (Scheme 4). 2-Chloro-4-methoxypyrimidine, which was prepared from 2, 4-dichloropyrimidine by a reported procedure¹¹⁾ in 90% yield, was allowed to react with **3** in the same manner as described above, affording **7** in 92% yield. Then **7**

was treated with 1.1 equiv of dimethyl(methylthio)sulfonium tetrafluoroborate under several reaction conditions as summarized in Table 1. Under conditions similar to those described in the reaction of **4**, the desired β -nucleoside **9**¹²⁾ was obtained in only moderate yield due to by-products **12** and **13** (entry 1). Although the formation of **12** was suppressed by lowering the concentration, the yield of **13** was increased (entry 2). This problem was overcome by the use of acetonitrile as solvent instead of dichloromethane. Furthermore, by performing the hydrolysis with 1M NaOH the yield of **9** was improved to 82% (entry 4). Product **9** can be easily transformed to the 2'-deoxyuridine **10** or 2'-deoxycytidine **11** by removal of the 3'-O-benzyl group and hydrolysis or ammonolysis of the 4-methoxy group respectively.¹²⁾



Scheme 4.

Table 1. Synthesis of **9** from **7**

Entry	Reaction Conditions		Hydrolysis Conditions	Yields/%		
	Solvent (Concentration/M)	Time		9	12	13
1	CH ₂ Cl ₂ (0.05)	195 min	sat. Na ₂ CO ₃ , r.t., overnight	47	13	15
2	CH ₂ Cl ₂ (0.004)	5 h	sat. Na ₂ CO ₃ , r.t., overnight	48	trace	33
3	CH ₃ CN (0.004)	5 h	sat. Na ₂ CO ₃ , r.t., overnight	71	trace	5
4	CH ₃ CN (0.004)	5 h	1M NaOH, 0 °C, 2.5 h	82	trace	4

M=mol·dm⁻³

In conclusion, an efficient method for the stereocontrolled synthesis of β -2'-deoxyribonucleosides derivatives utilizing intramolecular *N*-glycosylation reaction was described. The application of this methodology to the synthesis of β -2', 3'-dideoxynucleosides and some base modified β -2'-deoxynucleosides are now in progress in our laboratory and will be published in due course.

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