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Stereocontrolled Synthesis of Pyrimidine 2',3'-Dideoxy-β-nucleosides by Intramolecular Glycosylation

Keiko Sujino and Hideyuki Sugimura*

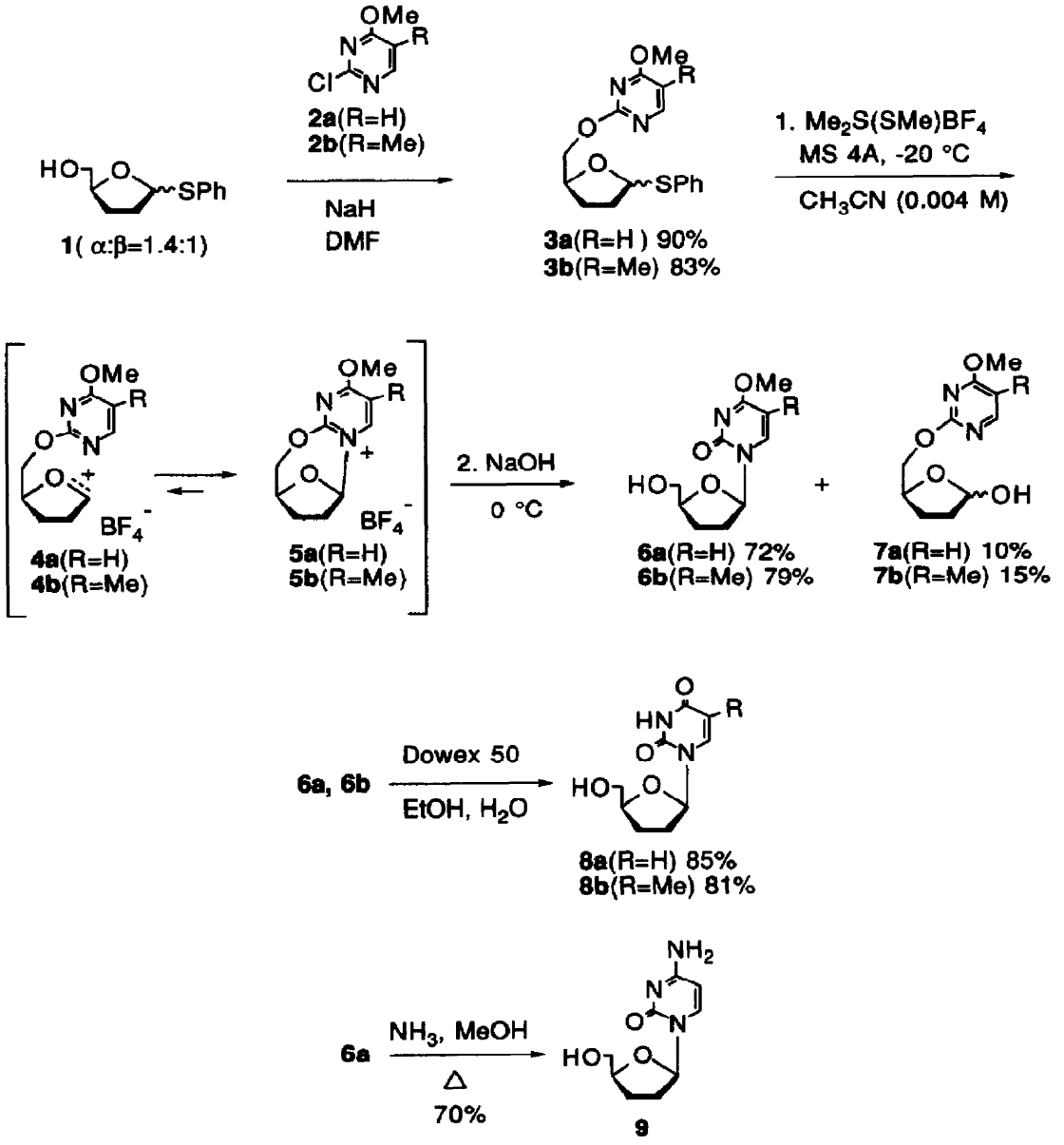
The Noguchi Institute, 1-8-1, Kaga, Itabashi-ku, Tokyo 173, Japan

Abstract: *β-2',3'-Dideoxynucleosides and their 3'-azido and 3'-fluoro substituted derivatives were synthesized in a stereocontrolled manner by the dimethyl(methylthio)sulfonium tetrafluoroborate promoted intramolecular glycosylation of phenyl 2,3-dideoxy-5-O-(2-pyrimidyl)-1-thioglycosides followed by hydrolysis or ammonolysis.*

Since the discovery of the antiviral activity of 3'-azido-3'-deoxythymidine (AZT) against human immunodeficiency virus (HIV),[1] 2',3'-dideoxynucleosides have received much attention as potent therapeutic agents for the treatment of HIV infection diseases. Consequently, a number of studies have been reported on the synthesis of these compounds and their analogs.[2] Although the coupling of sugar moiety and a nucleoside base is one of the most simple and effective strategies for obtaining such nucleoside derivatives, the use of this strategy for their syntheses usually results in production of their anomeric mixture.[3] Hence, various approaches have been developed for the selective synthesis of their β anomers.[4-6] Recently we[7] and others[8] have independently reported a new methodology for the stereoselective formation of 2'-deoxy-β-D-ribonucleosides based on the intramolecular glycosylation concept.[9] In this letter, we report the stereocontrolled synthesis of pyrimidine 2',3'-dideoxy-β-nucleosides and their 3'-azido and 3'-fluoro derivatives from the corresponding phenyl 2,3-dideoxy-1-thiopentofuranosides utilizing this methodology.

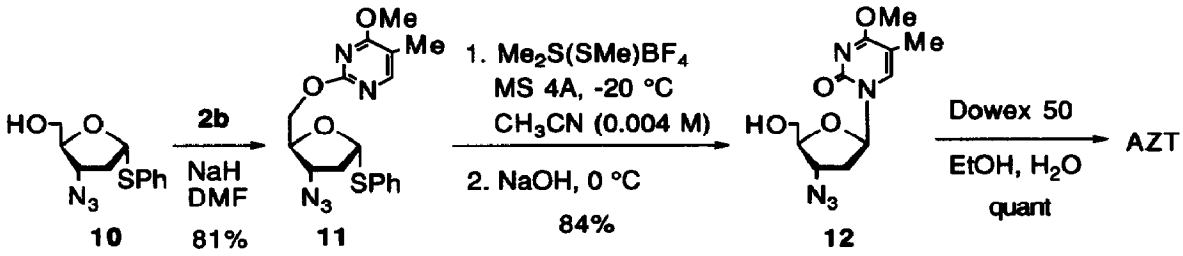
We initially explored the synthesis of 2',3'-dideoxyuridine (ddU) and 2',3'-dideoxycytidine (ddC) from thioglycoside **1**[5] and 2-chloro-4-methoxypyrimidine (**2a**) by an essentially similar procedure described previously[7] (Scheme 1). The introduction of the 2-pyrimidyl group at the 5-O position of thioglycoside **1** was achieved as follows; after treatment of **1** with 2.0 equiv. of sodium hydride in DMF at r.t. for 1h, the resulting sodium salt was allowed to react with 2.0 equiv. of **2a** at 0 °C to afford **3a** in 90% yield. Subsequently, **3a** was intramolecularly glycosylated by the treatment with 1.1 equiv. of dimethyl(methylthio)sulfonium tetrafluoroborate in acetonitrile (0.004 M) in the presence of MS 4A at -20 °C for 5 h, followed by basic hydrolysis (1 M NaOH, 0 °C, 2.5 h) to give β-nucleoside **6a** in 72% yield along with a 10% yield of **7a**, presumably resulting from direct hydrolysis of the oxonium intermediate **4a** existing in equilibrium with **5a**. We examined the suppression of hydrolysis at the C-1 position under several reaction conditions (activators, solvent, hydrolysis conditions, etc.) but none proved to be better than the above conditions. Conversion of **6a** into ddU (**8a**)[10] accomplished by acidic hydrolysis using an ion-exchange resin and into ddC (**9**)[10] by ammonolysis, respectively. Also, we examined the synthesis of 3'-deoxythymidine from thioglycoside **1** and

2-chloro-4-methoxy-5-methylpyrimidine[9] (**2b**). In this case, the substitution reaction of **2b** with the sodium salt of **1** must be carried out at -50 °C to prevent substitution at the 4-position on the pyrimidine ring. The intramolecular glycosylation of **3b** proceeded smoothly to give **6b** in 79% yield along with **7b** (15% yield). Acidic hydrolysis of **6b** led to 3'-deoxythymidine (**8b**) in 81% yield.

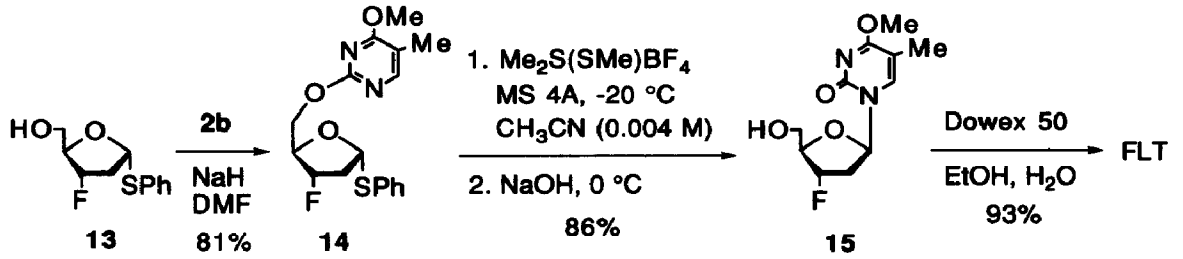


Scheme 1

We next turned our attention to the application of this intramolecular glycosylation strategy to the synthesis of AZT and 3'-deoxy-3'-fluorothymidine (FLT) as shown in Scheme 2 and Scheme 3. The starting thioglycosides **10** and **13** were prepared according to the method reported previously.[11] These thioglycosides failed to give useful yields in the reaction with **2b** under the conditions similar to those described above because elimination of the azido and the fluoro groups occurred in the desired products to produce a 2,3-didehydro derivative (maximum 40% yield). However, this problem was overcome by treatment of the thioglycosides with 1.3 equiv. of sodium hydride at -20 °C and then with **2b** at -50 °C to provide acceptable yields of **11** and **14**. The intramolecular glycosylation of **11** and **14** afforded **12** and **15** in good yields, respectively. It is noted that in these reactions C-1 hydrolyzed products such as **7** could not be detected in any of the chromatographic fractions. Moreover, in the previous study on the intramolecular glycosylation using a 3-*O*-benzyl-2-deoxy-D-ribofuranose derivative we have obtained the desired β-2'-deoxynucleoside in 82% yield accompanied by only small amounts (4%) of the C-1 hydrolyzed product.[7] These observations suggest that the substituents at the C-3 of the sugar moiety play an important role in suppressing the production of this type of byproduct. Further investigation for excluding the formation of C-1 hydrolyzed products in this glycosylation process is in progress. AZT [12] and FLT [13] were obtained in high yields by acidic hydrolysis of **12** and **15**, respectively.



Scheme 2



Scheme 3

In conclusion, clinically important β-2',3'-dideoxy pyrimidine nucleosides including AZT and FLT were synthesized utilizing the dimethyl(methylthio)sulfoniun tetrafluoroborate promoted intramolecular glycosylation as a key reaction. The outstanding characteristic of this method is the sole preparation of β-nucleosides by delivery of the nucleoside base from the β-face utilizing the configuration at the C-4 in 2,3-dideoxy sugars.

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