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A Concise Synthesis of 4′-Fluoro Nucleosides

Seongmin Lee, Chayasith Uttamapinant, and Gregory L. Verdine*

Department of Chemistry and Chemical Biology, Harvard University,
Cambridge, Massachusetts 02138

gregory_verdine@harvard.edu

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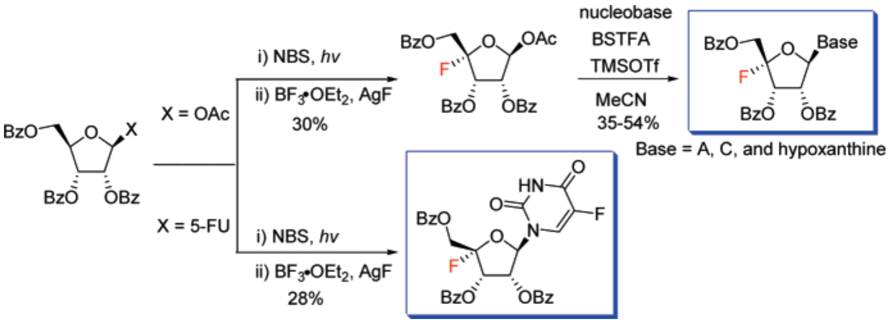
ABSTRACT



Various 4′-F nucleosides have been prepared in only two to three steps via sequential bromination and fluorination of ribofuranoses or nucleosides.

Nucleoside analogues are frequently used to inhibit DNA biosynthesis, a process that is essential for cell growth and viral replication.[1] Substitution of hydrogen atoms for fluorine has been extensively employed in the design of such analogues, as this can dramatically affect the electronic structure of a nucleoside without significantly altering its size and shape.[2] One such class of analogues that has received attention of late is 4′-fluoro nucleosides. Nucleocidin,[3] 5′-deoxy-4′,5-difluorouridine,[4] 4′-fluoroadenosine,[5] and 2′-deoxy-4′-fluorothimidine[6] have been synthesized and tested for biological activity. Access to a broader repertoire of 4′-fluoronucleosides has been significantly hampered by the lengthy synthetic routes (8 to 10 steps) employed to obtain these derivatives, and also by the low overall yields of product. Improved synthetic pathways would thus improve access to the potentially important 4′-F nucleoside class for biological studies. Herein, we describe two new and highly efficient synthetic routes for 4′-F nucleosides, with sequential bromination and fluorination being used as key reactions in both processes.

Previous synthesis of 4′-F nucleosides[3−5] employed iodofluorination of a nucleoside 4′-exo-olefin followed by hydroxide ion displacement of the iodine, which produces mixtures of 4′-epimers that can be difficult to separate. Our synthetic strategy avoids this problem by taking advantage of bromination and fluorination on nucleosides or 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose (Scheme 1).

Sequential photobromination and fluorination has been used to prepare fluorinated carbohydrate derivatives,[7] but the

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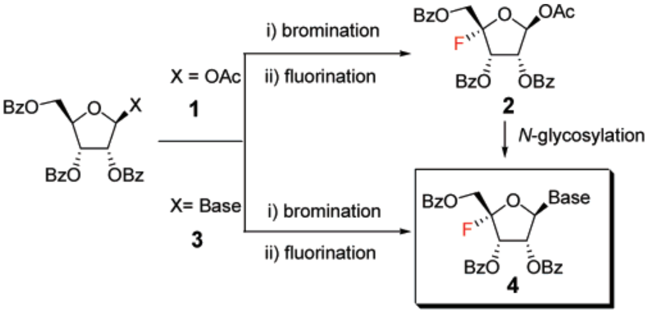
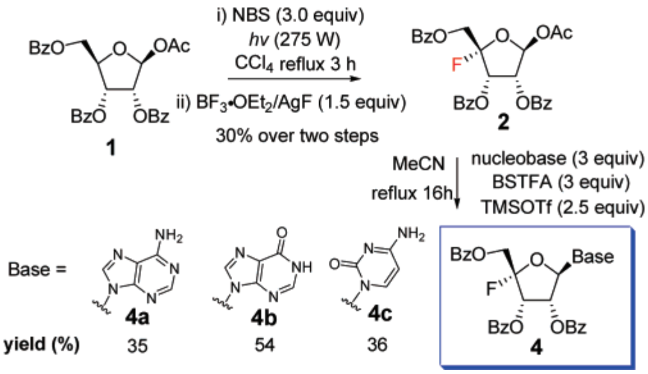
Scheme 1



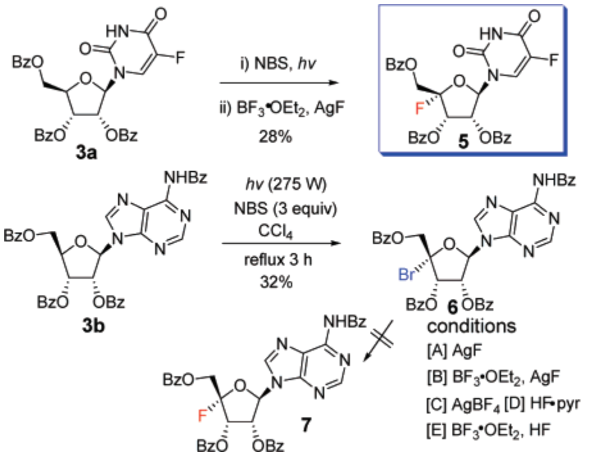
application of this strategy to nucleoside analogue synthesis has not been reported so far. Our 4′-F nucleoside synthesis started with preparation of a known 4-fluoro-β-D-ribofuranose **2** from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose **1** (Scheme 2).[7c] Treatment of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose **1** with *N*-bromosuccinimide under a sun lamp (275 W) afforded a mixture of 4-bromo-β-D-ribofuranose and 4-bromo-α-L-lyxofuranose (C4 epimer, not shown). The crude reaction mixture, without purification, was directly subjected to fluorination by using silver tetrafluoroborate generated in situ from borontrifluoride-etherate and silver fluoride. The reaction provided 4-fluoro-β-D-ribofuranose **2** in 30% yield, together with an almost equal amount of 4-fluoro-α-L-lyxofuranose. Modified Hilbert−Johnson *N*-glycosylation[8] of 4-fluoro-β-D-ribo furanose **2** with *N*,*O*-bis-(trimethylsilyl) trifluoro acetamide (BSTFA) and TMSOTf gave 4′-fluoroadenosine (**4a**), inosine (**4b**), and cytidine (**4c**) (Scheme 2). It is noteworthy that the *N*-glycosylation takes place slowly (~16 h) compared to that of nonfluorinated substrate (~3 h). This presumably results from retardation of oxocarbenium ion formation, which is required for *N*-glycosylation, by the inductive effect of the 4′-F substituent.[9]

Scheme 2



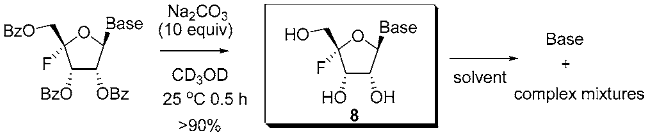
An alternative approach to 4′-F nucleoside synthesis via bromination and fluorination of a nucleobase-protected nucleoside was also investigated (Scheme 3). NBS-mediated bromination of 5-fluorouracil (FU) ribofuranose **3a** followed by fluorination furnished 4′-fluoro-5-FU nucleoside **5**. In the case of protected adenosine **3b**, although the photobromination readily afforded 4′-bromoadenosine **6**, various attempts to convert bromine to fluorine at 4′ were unsuccessful, generating a complex mixture of nonfluorinated compounds.

Scheme 3



The final stage of 4′-F nucleoside synthesis involved the removal of the benzoyl protecting groups on the sugar moiety (Table 1). This was readily effected by treatment with methanolic sodium carbonate to provide the target 4′-F nucleosides **8**. During the course of our investigation, we observed that 4′-F nucleosides (**8a**−**d**) were stable in CD_3OD but rapidly decomposed in D_2O. Fortunately, 4′-F nucleosides were considerably more stable in 10 mM sodium phosphate buffer at pH 7.4.[5]

Table 1. Stability Studies[a]



	bases **8a**−**d**			
solvent	**8a** (adenine)	**8b** (HX)	**8c** (cytosine)	**8d** (5-FU)
CD_3OD	no dec 1 d	no dec	no dec	no dec
D_2O	80% dec 1 d	100% dec 1 d	50% dec 3 h; 100% 16 h	50% dec 3 h
phosphate buffer (pH 7.4)	5% dec 4 d	10% dec 4 d	NA	NA

[a] dec: decomposition. NA: not available. d: day. h: hour.

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In summary, we have developed efficient synthetic pathways for 4′-fluoro nucleosides wherein sequential bromination and fluorination of nucleosides or ribofuranose are used as key reactions. Biological and biochemical assays on the nucleoside analogues thus obtained are in progress and results will be reported in due course. We expect 4′-F nucleosides and their derivatives will be of significant value in a variety of biologic and biochemical studies.

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Supporting Information Available: Experimental procedures and NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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