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Synthesis of pyrimidine 1′-fluoronucleosides☆

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Abstract—Treatment of the 1′-lithium enolate, prepared from a 2′-ketouridine derivative, with NFSI, followed by reduction of the 2′-keto-moiety gave the corresponding 1′-fluorouridine derivative and its arabino-type congener. Thus, the first synthesis of 1′-fluoronucleosides was achieved.

Since 5-fluorouracil (5-FU, **1**, Fig. 1) was found to be a very effective drug in cancer chemotherapy,[2] introduction of a fluorine atom into nucleobases or nucleosides has been studied extensively. Consequently, various fluoro-nucleobase and fluoro-nucleoside analogues of biological importance were reported. For example, anti-leukemic agent arabinofuranosyl-2-fluoroadenine (**2**),[3] anti-herpes virus agent 2′-deoxy-2′-fluoroarabinosyl-5-iodocytosine (FIAC, **3**),[4] anticancer drug gemcitabine (**4**),[5] and anti-HIV agent 2′, 3′-dideoxy-3′-fluorothymidine (**5**) have been developed.[6]

As a result, a large number of fluoronucleobase and -nucleoside analogues have been synthesized and biologically evaluated as potential antimetabolites. Thus, almost all of the hydrogens attached to carbons in natural nucleobases and nucleosides have been chemically replaced by fluorine atoms, with, as a consequence, the anomeric 1′-position remaining the only site in nucleosides not fluorinated. However, as shown in Figure 2, the 1′-fluoronucleosides might degrade; the electronically highly negative fluorine atom would make the 1′-carbon reactive to nucleophiles, and also the fluorine

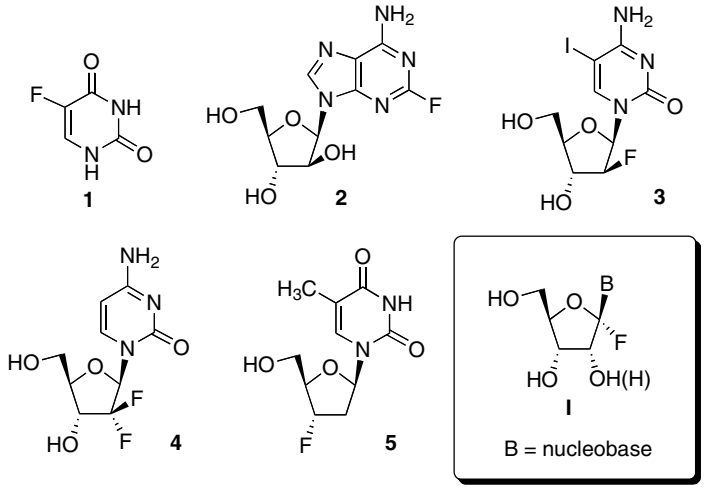

Figure 1. Fluoronucleobases and fluoronucleosides.

☆See Ref. 1.

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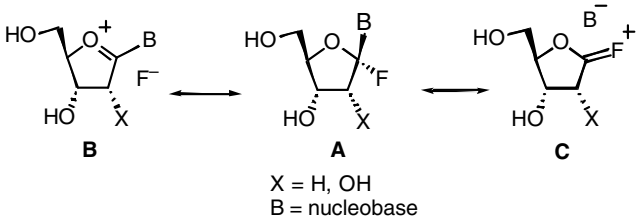
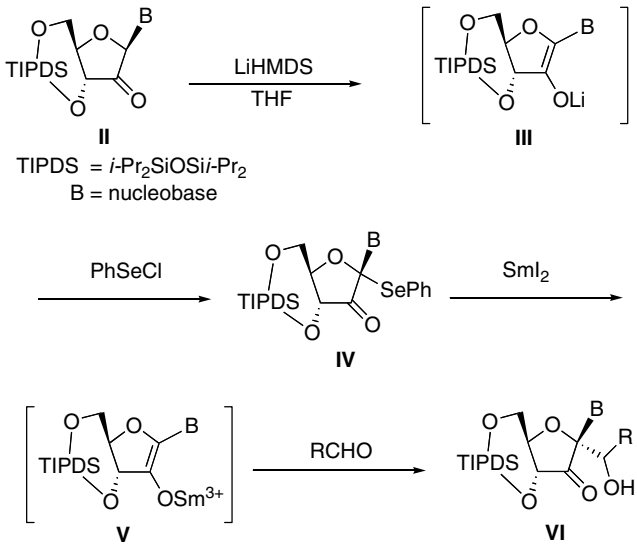


Figure 2. Possible resonance structures of 1′-fluoronucleosides.

atom might promote elimination of the nucleobase because of its conjugative electron-donating effect due to the unshared electrons on the fluorine atom. Therefore, one might speculate that the 1′-fluoronucleosides would be too unstable to be synthesized, or assuming they could be synthesized, that they would be too unstable to be isolated. In this report we describe the first synthesis of 1′-fluoronucleoside **I** (Fig. 1), which has long been the synthetic target as potential antimetabolites.

Most of the 1′-modified nucleosides have been synthesized via glycosidation reactions with sugars with a proper anomeric substituent, even though these routes were not stereoselective.[7] However, the synthesis of the 1′-fluoronucleosides via glycosidation between a nucleobase and a sugar having an anomeric fluoro substituent seems improbable, since an anomeric fluoro group has been one of the most successful leaving groups in glycosidation reactions.[8] Consequently, we decided to examine the synthesis of the 1′-fluoronucleosides starting from natural nucleosides.[9]

We recently developed an efficient method for functionalizing the 1′-position of nucleosides to synthesize several 1′-branched nucleoside analogues of biological interest, which is shown in Scheme 1.[10,11] We found that the 1′-lithium enolate **III** was formed when the 2′-ketonucleoside **II** was treated with lithium hexamethyldisilazide (LiHMDS), and that the enolate **III** was trapped effectively with PhSeCl to give stereoselectively the corresponding 1′-phenylselenenyl product **IV**. Further treatment of **IV** with SmI_2 produced the samarium enolate **V**, condensation of which with an aldehyde formed stereoselectively the corresponding 1′-branched aldol product **VI**. With these successful results in mind, we decided to investigate the fluorination at the 1′-position using the reaction of the enolate **III** or **V** with electrophilic fluorinating agents.



Scheme 1.

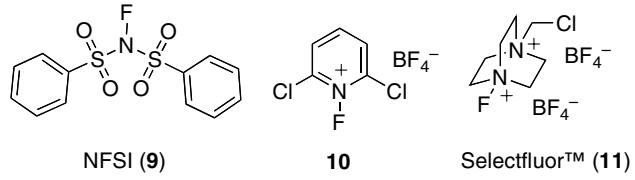


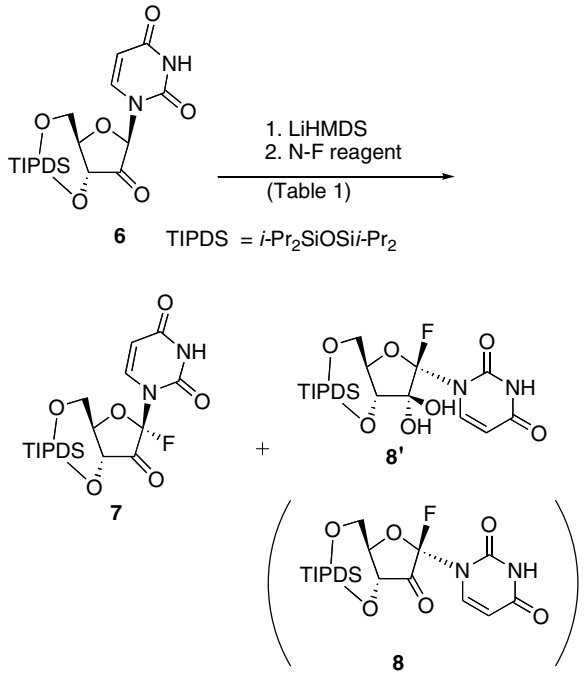
Figure 3. N–F fluorinating reagents.

We examined fluorination of the lithium or samarium enolate of 3′,5′-*O*-tetraisopropyldisiloxane-1,3-diyl (TIPDS)-protected 2′-ketouridine (**6**), using N–F reagents (Fig. 3), which have been shown to be effective in electrophilic fluorination of various compounds.[12–15] The results are summarized in Table 1 and Scheme 2.

Table 1. Fluorination of **6** at the 1′-position via its 1′-enolate[a]

Entry	N–F reagent	Temp (°C)	Solvent	Yield (**7** + **8** (**8′**))[b] (%)	Ratio (β:α)
1	**9**	−78	THF	87	1:2.4
2[c]	**9**	−78	THF	72	1:6.2
3	**9**	−78	Toluene–THF (4:1)	77	1:1.4
4	**9**	−78	Et_2O–THF (4:1)	85	1:1.5
5	**9**	−78	DMA–THF (1:2)	88	1:2.7
6	**9**	−78	DMF–THF (1:2)	57	1:1.0
7	**9**	−40	DMF–THF (4:1)	58	1.4:1
8	**10**	rt[d]	DMF–THF (4:1)	52	1.9:1
9	**11**	−40	DMF–THF (4:1)	69	2.0:1
10	**11**	−40	DMF–THF (9:1)	57	3.3:1

[a] To a solution of the 1′-enolate, prepared by treating **6** with LiHMDS (2.1 equiv) at −78 °C, was slowly added a solution of a N–F reagent in the indicated solvent.
[b] The α (α-nucleoside)/β (β-nucleoside) ratio was based on the isolated yields.
[c] KHMDS was used instead of LiHMDS.
[d] The reaction did not proceed at −40 °C.



Scheme 2.

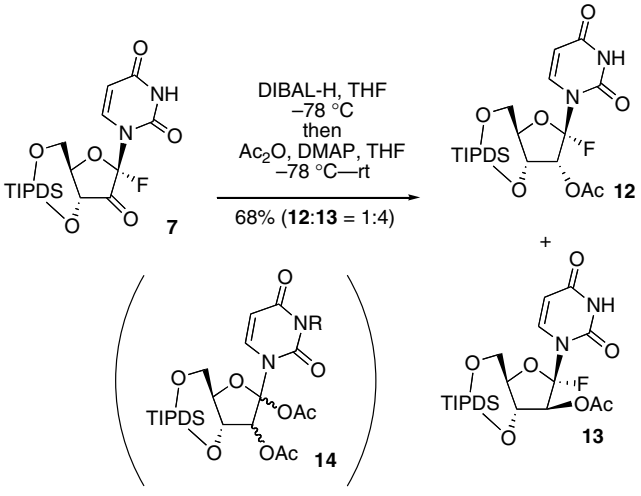
The lithium enolate of **6**, prepared by treating **6** with lithium LiHMDS,[11] was first treated with a well-known N–F reagent, *N*-fluorobenzenesulfonimide (NFSI, **9**),[13] as the electrophile at −78 °C in THF. The reaction successfully produced the expected 1′-fluorinated 2′-ketouridine derivatives in 87% yield as an anomeric mixture of **7** and **8** (entry 1, $\beta/\alpha = 1{:}2.4$). The α-nucleoside **8** was obtained mainly as the corresponding 2′-hydrate **8′** after purification by silica gel column chromatography. When potassium hexamethyldisilazide (KHMDS) was used as a base instead of LiHMDS, the α-nucleoside **8** (**8′**) increased (entry 2, $\beta/\alpha = 1{:}6.2$). The effect of the solvent on the reaction was next investigated. The use of the relatively non-polar toluene or Et_2O, compared with THF, as a co-reaction solvent somewhat increased the yield of the desired β-anomer (entries 3–4). We next examined the use of polar reaction solvents. *N*,*N*-Dimethylacetamide (DMA) was not as effective as a co-solvent, where the undesired α-nucleoside was the major product (entry 5). When DMF was used as a co-solvent, the ratio of the β-isomer increased (entry 6, 57%, $\beta/\alpha = 1{:}1.0$), while an unidentified non-fluorinated product was generated to decrease the total yield of the 1′-fluorinated products. The β-isomer was formed in preference to the α-isomer, when the fluorination reaction was performed in a DMF–THF (4:1) solvent (entry 7, 58%, $\beta/\alpha = 1.4{:}1$). We next examined other N–F fluorinating agents. Thus, the lithium enolate was treated with *N*-fluoro-2,6-dichloropyridinium tetrafluoroborate (**10**)[14] in DMF–THF. Although no fluorination proceeded at −40 °C, the reaction at room temperature gave the 1′-fluorinated products in 52% yield (entry 8, $\beta/\alpha = 1.9{:}1$). The desired β-selective result ($\beta/\alpha = 2.0{:}1$) was observed when 1-chloromethyl-4-fluoro-1,4-diazabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA-BF_4, **11**)[15] was used as the electrophile in DMF–THF (4:1) at −40 °C to afford the 1′-fluorinated products in 69% yield (entry 9). A similar reaction with **11** performed in DMF–THF (9:1) at −40 °C resulted in further improvement of the β-selectivity (entry 10, 57%, $\beta/\alpha = 3.3{:}1$).

Fluorination of the corresponding 1′-samarium enolate, prepared from the 1′-phenylseleno-2′-ketouridine derivative and SmI_2,[10] was examined with NFSI (**9**) as the fluorinating electrophilic reagent in THF. Although the 1′-samarium enolate was more effective than the lithium enolate in the previous aldol-type condensation reaction with aldehydes as electrophiles in terms of both yield and stereoselectivity,[10] none of the fluorinated products was obtained in this case.

We next tried the reduction of the 2′-carbonyl moiety of the 1′-fluoro-2′-ketouridine derivative **7**. After investigating various hydride reducing agents, for example $NaBH_4$, $NaBH_4$–$CeCl_3$, DIBAL–H and Selectride, we recognized that reduction only proceeded successfully when the β-nucleoside **7** was treated with DIBAL–H. However, the reduction products could not be isolated probably owing to their instability. Instead, uracil was quantitatively isolated after silica gel column chromatography. Therefore, the hydroxyl group resulting from the reduction products was immediately protected without purification. When **7** was treated with DIBAL–H at −78 °C and then an excess of Ac_2O and DMAP in THF, the expected 1′-fluoro-2′-O-acetylated products were obtained in 68% yield as a diastereomeric mixture at the 2′-position (Scheme 3). The ratio of the 'ribo'-type **12** to the 'arabino'-type **13** was 1:4.[16]

The stereochemistry of the compounds was confirmed from NOE experiments of **13** (Fig. 4). When the H-3′ was irradiated, an NOE was observed at the 6-H (1.0%), to indicate its β-nucleoside structure. The 2′-'arabino'-type configuration was determined by irradiation of the H-2′ to show an NOE at the H-4′ (3.9%).

In conclusion, the first synthesis of 1′-fluoronucleosides, which have long been synthetic targets as potential



Scheme 3.

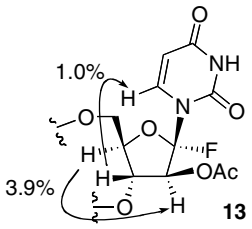


Figure 4. NOE data of **13**.

antimetabolites, was achieved. Deprotection of these 1′-fluoronucleosides are now under investigation.

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16. In this reaction, the 1′-acetoxyluridine derivative **14** (Scheme 3) was sometimes obtained.