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Tetrahedron
Tetrahedron 62 (2006) 10011–10017

Synthesis of 1′-fluorouracil nucleosides as potential antimetabolites☆

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Received 7 June 2006; accepted 27 July 2006
Available online 23 August 2006

Abstract—The first synthesis of 1′-fluoronucleosides, which has long been synthetic targets as the potential antimetabolites, was achieved. Electrophilic fluorination of the 1′-position occurred to form an anomeric mixture of 1′-fluorouridine derivatives, when the lithium enolate, prepared from 3′,5′-*O*-tetraisopropyldisiloxane-1,3-diyl (TIPDS)-protected 2′-ketouridine (**10**) and LiHMDS, was treated with an electrophilic fluorinating agent such as NFSI (**13**). Subsequent reduction of the 2′-keto-moiety of the resulting β-nucleoside gave the protected 1′-fluorouridine **16** and its arabino-type congener **17**. Alternatively, nucleophilic fluorination was also successful. Thus, treatment of 2′,3′,5′-tri-*O*-acetyl-1′-phenylselenouridine (**20**) with DAST/NBS produced the 1′-fluorouridine triacetate (**21**) and its α-anomer **22**.

1. Introduction

Antimetabolic nucleoside and nucleobase analogues are essential for anticancer and antiviral chemotherapies. More than 50 years ago, 5-fluorouracil (5-FU, **1**, Fig. 1) was found to be a very effective drug in cancer chemotherapy,[2] and 5-FU and its prodrugs[3] have become some of the most clinically important anticancer drugs to date. As a result, the introduction of fluorine atoms into nucleobases has been studied extensively. For example, arabinofuranosyl-2-fluoroadenine (**2**) was identified as a metabolically stable congener of the clinically useful antileukemic and antiviral agent arabinofuranosyladenine (ara A), which is readily inactivated by adenosine deaminase in vivo.[4]

In 1969, the naturally occurring 4′-fluoronucleoside, nucleocidine (**3**) was discovered, and its potent antitrypanosomal activity was reported.[5] This finding suggested that the introduction of a fluorine atom into a sugar moiety of a nucleoside could also be an effective strategy for the development of potent antimetabolites, leading to the synthetic studies of fluorosugar nucleosides. Consequently, various sugar-modified fluoronucleosides of biological importance were identified, e.g., fluorination at the 2′-position produced the anti-herpes

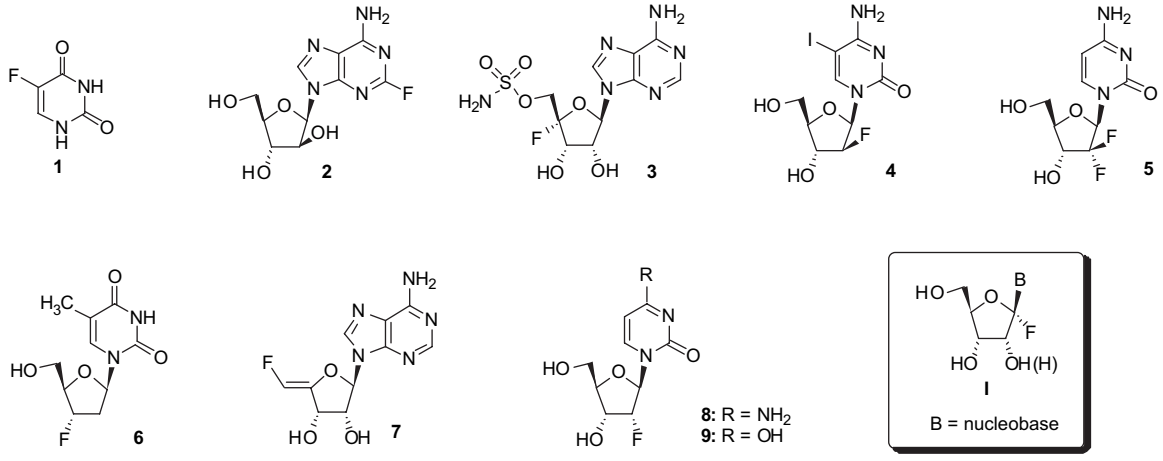

Figure 1. Fluoronucleobases and fluoronucleosides.

☆ See Ref. 1.
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doi:10.1016/j.tet.2006.07.101

virus agent 2′-deoxy-2′-fluoroarabinosyl-5-iodocytosine (FIAC, **4**)[6] and the potent anticancer drug gemcitabine (**5**).[7] A potent anti-HIV agent 2′,3′-dideoxy-3′-fluorothymidine (**6**) also was developed,[8] in which a fluorine atom was introduced at the 3′-position of thymidine. The 5′-fluoro-4′,5′-dehydroadenosine derivative **7** was shown to be a potent mechanism-based inhibitor of adenosylhomocysteine hydrolase,[9] an effective target enzyme for antiviral and antimalarial chemotherapy. In recent years, the 2′-fluoro-2′-deoxynucleosides **8** and **9** have been recognized as useful nucleoside units for antisense and DNA/RNA aptamer studies,[10] for which their 5′-triphosphates are now commercially available.

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, and, as a consequence, the anomeric 1′-position remaining the only site in nucleosides not fluorinated. It is likely that, with the above success stories in mind, a number of medicinal chemists thought that the eventual compounds, namely the 1′-fluoronucleosides, would make good synthetic targets. However, they may have considered that the 1′-fluoronucleosides would be anticipated to be chemically unstable. As shown in Figure 2, the nucleosides might degrade; the electronically highly negative fluorine atom would make the 1′-carbon reactive to nucleophiles, and also the fluorine 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),[11] which has long been the synthetic target as potential antimetabolites.

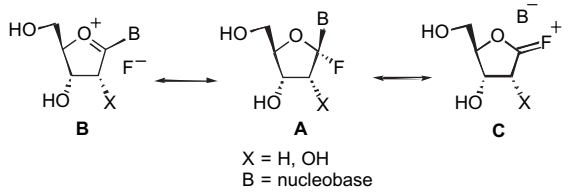


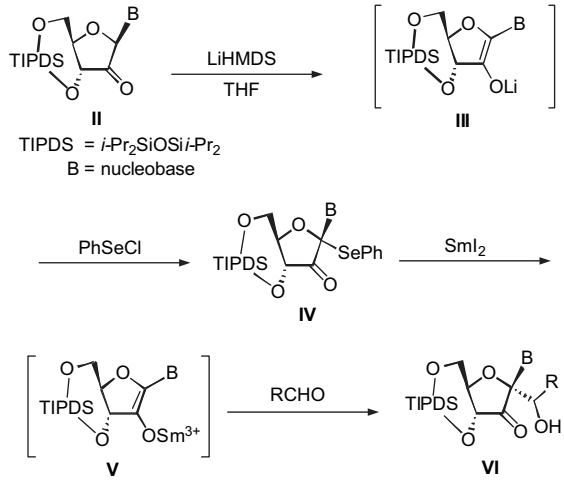
Figure 2. Possible resonance structures of 1′-fluoronucleosides.

2. Results and discussion

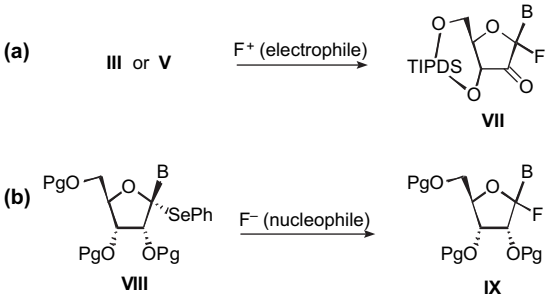
2.1. Synthetic plan

The synthesis of nucleoside analogues modified at the anomeric 1′-position[12,13] is not as common as that of nucleoside derivatives modified at the other positions in the sugar moiety, in spite of the biological importance of nucleoside analogues.[14] 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.[15] However, the synthesis of the 1′-fluoronucleosides via glycosidation between a nucleobase and a sugar having an anomeric fluoro substituent would seem improbable, since an anomeric fluoro group has been one of the most successful leaving groups in glycosidation reactions.[16] An anomeric fluoro substituent would easily eliminate under the usual Lewis acidic glycosidation conditions, and the proper glycosyl donor for the synthesis of 1′-fluoronucleosides would be unavailable. Consequently, we decided to examine the synthesis of the 1′-fluoronucleosides starting from natural nucleosides.[17]

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.[18,19] We found that the lithium enolate **III** was formed when the 2′-keto-nucleoside **II** was treated with 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 synthesis of the target 1′-fluoronucleosides via both electrophilic and nucleophilic approaches, as shown in Scheme 2. We devised a scheme to accomplish the fluorination at the 1′-position using the reaction of the enolate **III** or **V** with electrophilic fluorinating agents. Alternatively, using the 1′-phenylselenonucleoside **VIII** as the substrate, we also planned to examine nucleophilic fluorination via oxidative activation of the phenylseleno moiety.



Scheme 1.



Scheme 2.

2.2. Electrophilic fluorination

In recent years, a variety of N–F fluorination reagents, some of which are shown in Figure 3, have been developed.[20–23] These reagents are rather stable, easy to handle and have been shown to be very effective in electrophilic fluorination of various compounds. We examined fluorination of the lithium or samarium enolate of 3′,5′-*O*-tetraisopropyldisiloxane-1,3-diyl (TIPDS)-protected 2′-ketouridine (**10**), using these N–F reagents (Scheme 3). The results are summarized in Table 1.

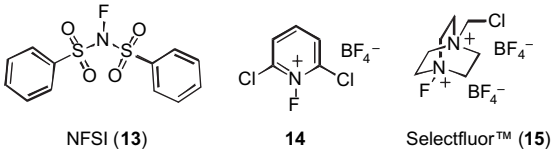
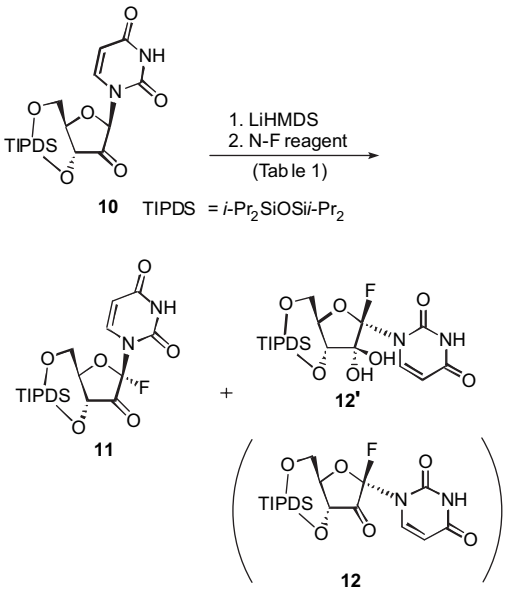


Figure 3. N–F fluorinating reagents.



Scheme 3.

The lithium enolate of **10**, prepared by treating **10** with lithium hexamethyldisilazide (LiHMDS),[19] was first treated with a well-known N–F reagent, *N*-fluorobenzenesulfonimide (NFSI, **13**),[21] 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 **11** and **12** (entry 1, β/α=1:2.4). The α-nucleoside **12** was obtained mainly as the corresponding 2′-hydrate **12′** after purification by silica gel column chromatography. When potassium hexamethyldisilazide (KHMDS) was used as a base instead of LiHMDS, the percentage of the α-nucleoside **12** (**12′**) increased (entry 2, β/α=1:6.2). The effect of 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 and 4). Therefore we examined the reaction using $MgBr_2$, $Yb(OTf)_3$, or SmI_3, which have been known to be effective chelating agents, as additives. However, fluorination did not proceed in the presence of these additives (data not shown). 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%, β/α=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%, β/α=1.4:1). We next examined other N–F fluorinating agents. Thus, the lithium enolate was treated with *N*-fluoro-2,6-dichloropyridinium tetrafluoroborate (**14**)[22] 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, β/α=1.9:1). The desired β-selective result (β/α=2.0:1) was observed when 1-chloromethyl-4-fluoro-1,4-diazabicyclo[2.2.2]octane bis(tetrafluoroborate) (F–TEDA–BF_4, **15**)[23] 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 **15** performed in DMF/THF (9:1) at −40 °C resulted in further improvement of the β-selectivity (entry 10, 57%, β/α=3.3:1).

Table 1. Fluorination of **10** at the 1′-position via its enolate[a]

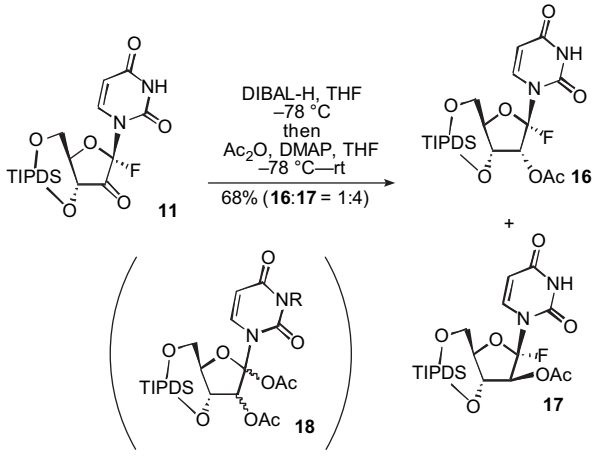
Entry	N–F reagent	Temp (°C)	Solvent	Yield (**11**+**12** (**12′**))[b] (%)	Ratio (β:α)
1	**13**	−78	THF	87	1:2.4
2[c]	**13**	−78	THF	72	1:6.2
3	**13**	−78	Toluene–THF (4:1)	77	1:1.4
4	**13**	−78	Et_2O–THF (4:1)	85	1:1.5
5	**13**	−78	DMA–THF (1:2)	88	1:2.7
6	**13**	−78	DMF–THF (1:2)	57	1:1.0
7	**13**	−40	DMF–THF (4:1)	58	1.4:1
8	**14**	rt[d]	DMF–THF (4:1)	52	1.9:1
9	**15**	−40	DMF–THF (4:1)	69	2.0:1
10	**15**	−40	DMF–THF (9:1)	57	3.3:1

[a] To a solution of the enolate, prepared by treating **10** 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.

Fluorination of the corresponding samarium enolate, prepared from the 1′-phenylseleno-2′-ketouridine derivative and SmI_2,[18] was examined with NFSI (**13**) as the fluorinating electrophilic reagent in THF. Although the 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,[18] none of the fluorinated products was obtained in this case.

As described, the first fluorination at the 1′-position of nucleosides was accomplished. We next tried the reduction of the 2′-carbonyl moiety of the 1′-fluoro-2′-ketouridine derivative **11**. After investigating various hydride reducing agents, for example, $NaBH_4$, $NaBH_4$–$CeCl_3$, DIBAL-H, and selectride, we realized that reduction only proceeded successfully when the β-nucleoside **11** 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 **11** was treated with DIBAL-H at −78 °C and 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 4). The ratio of the '*ribo*'-type **16** to the '*arabino*'-type **17** was 1:4.[24]



Scheme 4.

The stereochemistry of the compounds was confirmed from NOE experiments of **17** (Fig. 4a). 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%).

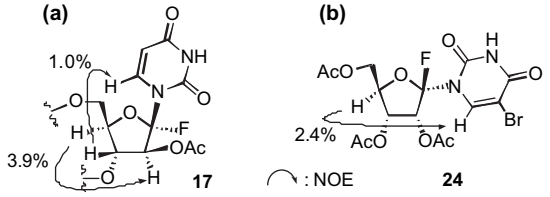
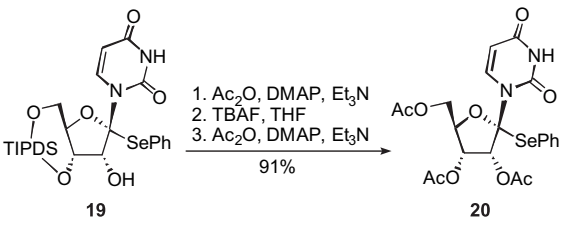


Figure 4. NOE data of **17** (a) and **24** (b).

2.3. Nucleophilic fluorination

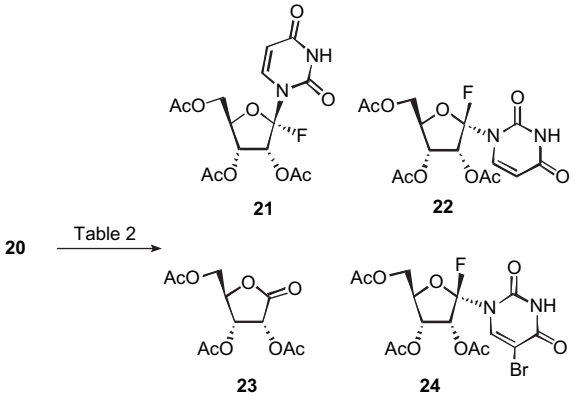
We next tried nucleophilic fluorination at the 1′-position using the 1′-phenylselenouridine derivative **20** as a substrate. Since 1-phenylselenosugars have been effectively used as glycosyl donors under oxidative conditions, we expected that the 1′-fluorination might occur by treating 1′-phenylselenonucleosides with a fluoro nucleophile under oxidative conditions, such as DAST/NBS. The substrate **20** was readily prepared from the 1′-phenylselenouridine derivative **19**, which was obtained from uridine by the previously reported method (Scheme 5).[18]

The results of the fluorination of **20** with nucleophilic fluorinating agents are shown in Scheme 6 and Table 2. The substrate **20** was first subjected to the reaction with DAST/NBS conditions. Treatment of **20** with DAST (2 equiv) and NBS (2 equiv) in CH_2Cl_2 at room temperature resulted in the expected 1′-fluorination. However, bromination at the pyrimidine 5-position occurred concomitantly to give



Scheme 5.

the 5-bromo-1′-fluoro-α-nucleoside **24** in 37% yield, where the desired 1′-β-nucleosidic product **21** was obtained in only 2% yield along with the corresponding α-nucleoside **22** in 5% yield. Ribonolactone tri-*O*-acetate (**23**) was produced during this reaction, which was also produced in all of the entries summarized in Table 2. When the reaction with DAST/NBS was performed at lower temperature (−40 °C), the bromination was avoided thereby increasing the 1′-fluoro-products **21** and **22**, where the 1′-α-nucleoside was obtained predominantly (**21**, 14% and **22**, 56%, entry 2). A similar reaction using EtCN as the solvent improved the yield of the 1′β-product (**21**, 29% and **22**, 25%, entry 3).



Scheme 6.

The fluorination of **20** was next examined with AgF (entries 4 and 5). In these reactions, although the fluorination proceeded, the undesired α-nucleoside **22** was formed predominantly. Treatment of **20** with XeF_2 gave the desired β-nucleoside **21** as the major product in 29% yield.

The stereochemistries of these products were confirmed by NOE experiments as follows. In the experiments with **21** or **22**, none of the NOE confirming the stereochemistry was observed. However, as shown in Figure 4b, when the

Table 2. Fluorination of **20** at the 1′-position

Entry	Reagents (equiv)	Solvent	Temp	Yield[a]			
				21 (%)	**22** (%)	**23** (%)	**24** (%)
1	DAST (2), NBS (2)	CH_2Cl_2	rt	2	5	36	37
2	DAST (2), NBS (2)	CH_2Cl_2	−40 °C	14	56	15	—
3	DAST (2), NBS (2)	EtCN	−40 °C	29	25	32	—
4[b]	AgF (2)	CH_2Cl_2	rt	7	41	10	—
5	AgF (4)	CH_2Cl_2	rt	9	59	22	—
6	XeF_2 (1.2)	CH_2Cl_2	rt	29	14	26	—

[a] Isolated yield.
[b] The substrate **20** was recovered in 41% yield.

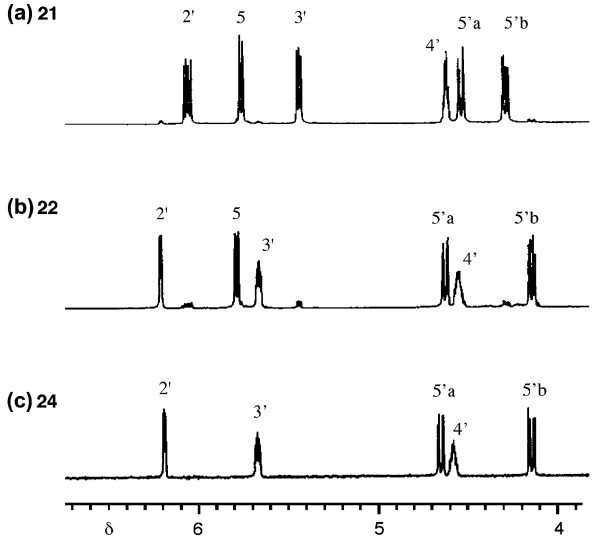


Figure 5. ^{1}H NMR spectra of **21**, **22**, and **24**.

H-4′ of the 5-bromo-product **24** was irradiated, an NOE was observed at the H-6 of the pyrimidine moiety to show its α-nucleosidic structure. By comparing the ^{1}H NMR spectra of **21**, **22**, and **24**, as shown in Figure 5, **21** and **22** were assigned as the β- and α-nucleosides, respectively, since signals of the sugar moiety of **22** were superimposable onto those of the α-nucleoside **24**.

In conclusion, the first synthesis of 1′-fluoronucleosides as potential antimetabolites was achieved.[25]

3. Experimental

3.1. General

NMR chemical shifts are reported in parts per million downfield from tetramethylsilane and *J* values are given in hertz. The ^{1}H NMR assignments reported for key compounds are in agreement with 2D NMR spectra. Thin layer chromatography was done on Merck coated plates $60F_{254}$. Silica gel chromatography was done on Merck silica gel 5715 or Kanto Chemical silica gel 60 N (neutral). Reactions were carried out under an argon atmosphere.

3.2. General procedure for the fluorination of 10 forming 1′-fluorouracil nucleosides 11 and 12′ (Table 1)

A mixture of **10** (48 mg, 0.10 mmol) and LiHMDS (1.0 M solution in THF, 210 μL, 0.21 mmol) in a solvent (2.0 mL) was stirred at −78 °C for 1 h. To the mixture, a solution of an N–F fluorinating reagent (0.12 mmol) in the indicated solvent (1.5 mL) was added at the indicated temperature, and the resulting mixture was stirred at the indicated temperature for 3 h. After neutralization with AcOH, the mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, 25%, 33%, and 66% AcOEt in hexane) to give **11** as a white foam and **12′** as a colorless oil. **11**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.55 (br s, 1H), 7.52 (d, 1H, *J*=8.3), 5.83 (dd, 1H, *J*=8.3), 5.22 (dd, 1H, *J*=8.7, 2.7), 4.23 (m, 1H), 4.19–4.14 (m, 2H), 1.14–1.01 (m, 28H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.38 (d, *J*=25), 162.11, 148.9 (d, *J*=ca. 0), 137.65 (d, *J*=13), 107.8 (d, *J*=244), 103.4, 80.9, 71.0, 61.4, 17.4, 17.2, 17.2, 16.8, 16.8, 16.8, 16.7, 13.4, 13.0, 12.5, 12.4; FABHRMS calcd for $C_{21}H_{36}FN_2O_7Si_2$ 503.2045, found 503.2039 (MH^+). **12′**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.81 (br s, 1H), 7.74 (d, 1H, *J*=8.3), 6.38 (s, 1H), 5.77 (dd, 1H, *J*=8.3, 1.9), 4.51 (dd, 1H, *J*=6.9, 1.5), 4.11–4.01 (m, 3H), 3.95 (d, 1H), 1.13–0.98 (m, 28H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.9, 151.5, 139.0, 116.0 (d, *J*=253), 102.5, 98.3 (d, *J*=33), 83.5, 75.5, 62.9, 17.4, 17.3, 17.2, 17.0, 17.0, 16.7, 16.7, 13.3, 13.1, 12.7, 12.5; FABHRMS calcd for $C_{21}H_{38}FN_2O_8Si_2$ 521.2151, found 521.2134 (MH^+), calcd for $C_{21}H_{36}FN_2O_7Si_2$ 503.2045, found 503.2060 (MH^+-H_2O).

3.3. 2-*O*-Acetyl-1α-fluoro-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-*ribo*-pentofuranosyl]uracil (16) and 1-[2-*O*-acetyl-1α-fluoro-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-*arabino*-pentofuranosyl]-uracil (17)

To a solution of **11** (75 mg, 0.15 mmol) in THF (3.0 mL) was added a solution of DIBAL-H (1.0 M in hexane, 360 μL, 0.36 mmol) at the −78 °C, and the mixture was stirred at the same temperature for 10 min. After addition of a THF solution (0.3 mL) containing Ac_2O (2.0 M, 0.6 mmol) and DMAP (0.2 M, 0.06 mmol), the resulting mixture was warmed to room temperature and then partitioned between AcOEt and H_2O, and the aqueous layer was extracted with $CHCl_3$. The organic layers combined were dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (Si_2O, 20%, 25%, and 33% AcOEt in hexane) to give a mixture of **16** and **17** (54 mg, 68%) as a pale yellow solid. The diastereomers **16** (1.4 mg) and **17** (29 mg) were obtained in a pure form from the mixture (45 mg) by preparative HPLC separation (YMC D-ODS-5-A, 250 mm× 20 mm; 80% aqueous MeCN, 25 mL/min; 260 nm), followed by column chromatography (neutral SiO_2, 33% AcOEt in hexane). **16**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.04 (br s, 1H, NH-3), 7.77 (d, 1H, H-6, *J*=8.6), 5.95 (dd, 1H, H-2′, *J*=5.7, 1.6), 5.72 (d, 1H, H-5, *J*=8.6), 4.48 (dd, 1H, H-3′, *J*=8.9, 5.7), 4.30 (ddd, H-4′, 1H, *J*=8.9, 2.4, 2.4), 4.18 (dd, 1H, H-5′a, *J*=13.5, 2.4), 4.02 (dd, 1H, H-5′b, *J*=13.5, 2.4), 2.20 (s, 3H, 2′-*O*-Ac), 1.09–0.94 (m, 28H, TIPDS); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.7, 162.2, 148.6, 138.2 (d, *J*=3.3), 115.5 (d, *J*=248), 102.3, 83.6, 72.9 (d, *J*=20), 67.6, 59.3, 20.5, 17.4, 17.2, 17.2, 16.9, 16.9, 16.8, 13.4, 13.0, 12.7, 12.7; FABHRMS calcd for $C_{23}H_{39}FN_2O_8Si_2Na$ 569.2127, found 569.2132 (MNa^+). **17**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.15 (br s, 1H, NH-3), 7.68 (d, 1H, H-6, *J*=8.3), 5.88 (m, 1H, H-2′), 5.71 (dd, 1H, H-5, *J*=8.3, 2.4), 4.51 (m, 1H, H-3′), 4.28 (m, 1H, H-4′), 4.13 (dd, 1H, H-5′a, *J*=12.3, 3.6), 4.01 (dd, 1H, H-5′b, *J*=12.3, 9.7), 2.03 (s, 3H, 2′-*O*-Ac), 1.08–0.98 (m, 28H, TIPDS); NOE (400 MHz, $CDCl_3$): irradiated H-4′ observed H-2′ (3.9%), irradiated H-3′ observed H-6 (1.0%); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.3, 162.8, 148.0, 138.8 (d, *J*=1.7), 116.7 (d, *J*=249), 101.9, 83.7, 81.0 (d, *J*=46), 75.6, 61.7, 20.6, 17.6, 17.5, 17.4, 17.4, 17.0, 16.9, 16.9, 13.5, 13.3, 13.0, 12.5; FABHRMS calcd for $C_{23}H_{39}FN_2O_8Si_2Na$ 569.2127, found 569.2133 (MNa^+).

3.4. 1-[(1*S*)-2,3,5-Tri-*O*-acetyl-1α-phenylseleno-β-D-*ribo*-pentofuranosyl]uracil (20)

A solution of **19**[18] (1.93 g, 3.00 mmol), Ac_2O (0.85 mL, 9.0 mmol), Et_3N (1.25 mL, 9.00 mmol), and DMAP (73 mg, 0.60 mmol) in MeCN (28 mL) was stirred at room temperature for 1 h. The resulting mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with aqueous saturated $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated. To a solution of the residue in THF (30 mL) was added a mixture of TBAF (1.0 M in THF, 6.0 mL, 6.0 mmol) and AcOH (45 μL) at 0 °C, and the resulting mixture was stirred at the same temperature for 1 h and then evaporated. The residue was purified by column chromatography (neutral SiO_2, 5% MeOH in $CHCl_3$) to give the desilylated product as a yellow solid. A solution of the obtained solid, Ac_2O (0.88 mL, 9.3 mmol), Et_3N (1.3 mL, 9.3 mmol), and DMAP (75 mg, 0.60 mmol) in MeCN (30 mL) was stirred at room temperature for 30 min. The resulting mixture was partitioned between AcOEt and H_2O, the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (neutral SiO_2, 50% AcOEt in hexane) to give **20** (1.44 g, 91%) as a white foam: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.48 (br s, 1H, NH-3), 7.51–7.26 (m, 5H, PhSe), 6.93 (d, 1H, H-6, *J*=8.5), 5.98 (d, 1H, H-2′, *J*=6.8), 5.24 (dd, 1H, H-3′, *J*=8.0, 6.8), 5.20 (dd, 1H, H-5, *J*=8.5, 2.1), 4.66 (ddd, 1H, H-4′, *J*=8.0, 4.5, 2.6), 4.42 (dd, 1H, H-5′a, *J*=12.7, 2.6), 4.28 (dd, 1H, H-5′b, *J*=12.7, 4.5), 2.27, 2.09, 2.05 (each s, each 3H, each Ac); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2, 169.2, 168.3, 162.3, 148.2, 138.7, 130.1, 129.1, 124.9, 101.8, 100.2, 78.1, 75.1, 68.1, 61.3, 20.7, 20.4, 20.2; FABHRMS calcd for $C_{21}H_{23}N_2O_9Se$ 527.0569, found 527.0568 (MH^+).

3.5. General procedure for the fluorination of 20 giving 1′-fluorouridines 21 and 22 (Table 2)

A mixture of **20** (53 mg, 0.10 mmol) and reagent(s) (0.20 mmol) in CH_2Cl_2 or EtCN (2 mL) was stirred at the indicated temperature until **20** was disappeared on TLC. The mixture was poured into TEAB buffer (0.1 M, pH 8.0) at 0 °C, and the whole was extracted with $CHCl_3$. The extract was washed with H_2O, dried (Na_2SO_4), and evaporated, and the residue was purified by column chromatography (neutral SiO_2, 40%, 45%, 50%, and 55% AcOEt in hexane) to give **21**, **22**, and **23** (and **24** in entry 1). **21** (colorless solid): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.97 (br s, 1H, NH-3), 7.54 (d, 1H, H-6, *J*=8.5), 6.05 (dd, 1H, H-2′, *J*=12.4, 7.0), 5.76 (d, 1H, H-5, *J*=8.5), 5.43 (dd, 1H, H-3′, *J*=6.9, 4.7), 4.61 (m, 1H, H-4′), 4.52 (dd, 1H, H-5′a, *J*=12.4, 3.5), 4.28 (dd, 1H, H-5′b, *J*=12.4, 5.3), 2.14, 2.14, 2.11 (each s, each 3H, each Ac); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.4, 169.6, 169.1, 162.7, 148.7 (d, *J*=2.2), 138.3 (d, *J*=13), 116.9 (d, *J*=252), 102.8, 82.0, 70.8 (d, *J*=21), 69.2, 62.1, 20.7, 20.4, 20.2; UV λ_{max} 248.6 nm (THF); FABHRMS calcd for $C_{15}H_{17}FN_2NaO_9$ 411.0816, found 411.0801 (MNa^+). **22**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.52 (br s, 1H, NH-3), 7.79 (d, 1H, H-6, *J*=8.3), 6.21 (dd, 1H, H-2′, *J*=4.5, 1.1), 5.78 (d, 1H, H-5, *J*=8.3), 5.66 (ddd, 1H, H-3′, *J*=8.5, 4.4, 2.8), 4.62 (dd, 1H, H-5′a, *J*=12.7, 2.8), 4.54 (m, 1H, H-4′), 4.13 (dd, 1H, H-5′b, *J*=12.7, 4.9), 2.12, 2.07, 2.05 (each s, each 3H, each Ac); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.4, 168.9, 167.9, 162.1, 148.1, 138.7 (d, *J*=2.2), 117.1 (d, *J*=248), 102.5, 80.2, 73.1 (d, *J*=46), 68.7, 61.8, 20.6, 20.3, 20.2; UV λ_{max} 247.7 nm (THF); FABHRMS calcd for $C_{15}H_{17}FN_2NaO_9$ 411.0816, found 411.0812 (MNa^+). **23**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.72 (d, 1H, H-3, *J*=6.1), 5.45 (d, 1H, H-2, *J*=6.1), 4.73 (t, 1H, H-4, *J*=3.1), 4.40 (dd, 1H, H-5a, *J*=12.7, 3.1), 4.34 (dd, 1H, H-5′b, *J*=12.7, 3.1), 2.17 (s, 3H, Ac), 2.14 (s, 6H, Acx2). **24**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.86 (br s, 1H, NH-3), 8.10 (s, 1H, H-6), 6.19 (dd, 1H, H-2′, *J*=4.5, 1.5), 5.66 (ddd, 1H, H-3′, *J*=8.5, 4.5, 2.7), 4.65 (dd, 1H, H-5′a, *J*=12.8, 2.8), 4.57 (m, 1H, H-4′), 4.14 (dd, 1H, H-5′b, *J*=12.8, 4.6), 2.14, 2.08, 2.05 (each s, each 3H, each Ac); NOE (400 MHz, $CDCl_3$): irradiated H-4′ observed H-6 (2.4%); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.4, 168.9, 167.8, 158.0, 147.2, 138.0 (d, *J*=3), 116.9 (d, *J*=250), 97.5 (d, *J*=2), 80.5, 73.0 (d, *J*=45), 68.5 (d, *J*=2), 61.6, 20.6, 20.2, 20.2; FABHRMS calcd for $C_{15}H_{17}FBrN_2O_9$ 467.0102, found 467.0101 (MH^+).

Acknowledgements

This investigation was supported by a Grant-in-Aid for Creative Scientific Research (13NP0401) from the Japan Society for Promotion of Science. We are also grateful to the Japan Society for Promotion of Sciences for support of T.K. and to Ms. H. Matsumoto, A. Maeda, and S. Oka (Center for Instrumental Analysis, Hokkaido University) for technical assistance with NMR, MS, and elemental analyses.

References and notes

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