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Reactions of trimethylsilyl fluorosulfonyldifluoroacetate with purine and pyrimidine nucleosides

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ABSTRACT

Difluorocarbene, generated from trimethylsilyl fluorosulfonyldifluoroacetate (TFDA), reacts with the uridine and adenosine substrates preferentially at the enolizable amide moiety of the uracil ring and the 6-amino group of the purine ring. 2′,3′-Di-*O*-benzoyl-3′-deoxy-3′-methyleneuridine reacts with TFDA to produce 4-*O*-difluoromethyl product derived from an insertion of difluorocarbene into the 4-hydroxyl group of the enolizable uracil ring. Reaction of the difluorocarbene with the adenosine substrates having the unprotected 6-amino group in the purine ring produced the 6-*N*-difluoromethyl derivative, while reaction with 6-*N*-benzoyl protected adenosine analogues gave the difluoromethyl ether product derived from the insertion of difluorocarbene into the *enol* form of the 6-benzamido group. Treatment of the 6-*N*-phthaloyl protected adenosine analogues with TFDA resulted in the unexpected one-pot conversion of the imidazole ring of the purine into the corresponding *N*-difluoromethylthiourea derivatives. Treatment of the suitably protected pyrimidine and purine nucleosides bearing an exomethylene group at carbons 2′, 3′ or 4′ of the sugar rings with TFDA afforded the corresponding spirodifluorocyclopropyl analogues but in low yields.

1. Introduction

Attachment of fluorine atoms on the sugar and heterocyclic moieties of nucleoside analogues can impart potent anticancer and antiviral activity [1,2]. The small size and powerful electronegativity of fluorine can cause significant effects on the metabolic pathway as compared to the natural nucleoside analogues. The best known examples are 5-fluorouracil (inhibitor of thymidylate synthase) [3], 2′-deoxy-2′-(fluoromethylene)cytidine [4] and 2′-deoxy-2′-difluorocytidine [5] [gemcitabine, inhibitors of ribonucleotide diphosphate reductase (RDPR)], and 4′,5′-unsaturated 5′-fluoroadenosine (inhibitor of the adenosylhomocysteine hydrolase) [6] among others [1,2]. Robins and co-workers [7a] and Czernecki et al. [7b] prepared 2′-deoxy-2′-spirocyclopropane nucleosides (e.g., **A**) as putative inhibitors of the RDPR (Fig. 1). Other fused- and spiro-cycloalkyl derivatives of naturally occurring carbohydrate and nucleoside analogues with restrictions in their conformational flexibility were also designed and synthesized [7–11]. Marquez and coworkers elegantly demonstrated that bicyclo[3.1.0]hexane scaffold of carbocyclic nucleosides can be used to differentiate the contrasting conformational preferences between kinases and polymerases [12].

It is well known that geminal fluorine substituents on cyclopropane give rise to a substantial increase in ring strain which leads to an increasing ease of cleavage [13]. The kinetic effect of the 9–10 kcal/mol of incremental strain is derived largely from a homolytic cleavage of the carbon–carbon bond which is *opposite* to the CF_2 group. We designed *gem*-difluoro substituted 2′-deoxyuridine 2′-spirocyclopropane **B** as a potential inhibitor of RDPR since the abstraction of H3′ by the radical initiator (Cys439) from C3′ of the 5′-diphosphate **C** and *distal* (to the fluorine substituents) ring opening of the spiro 2,2-difluorocyclopropylcarbinyl radical **D** would result in generation of the corresponding 2,2-difluoro-3-butenyl radical species **E** which might cause inactivation of RDPR. The calculated activation barrier of 1.9 kcal/mol and an estimated ring opening rate constant of $1.5 \times 10^{11}\ s^{-1}$ at 25 °C qualifies the difluorocyclopropylcarbinyl system [13b] as a "hypersensitive" probe of reactions involving radicals as intermediates.

Recently, Nowak and Robins reported meticulous studies on the addition of difluorocarbene [generated from either $Hg(CF_3)_2$ or $PhHgCF_3$ and NaI] to double bonds placed between carbons 3′-4′ and 4′-5′ in the ribose rings of nucleosides (all electron rich vinyl ethers) to give derivatives with the 3′,4′-fused and 4′-spiro difluorocyclopropane rings, respectively [11]. We now report studies on the reactions of difluorocarbene, generated from the

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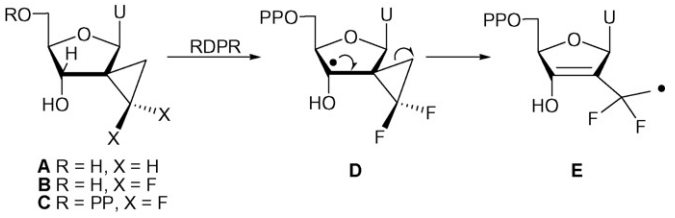


Fig. 1. Possible generation of the active intermediates from the spirodifluorocyclopropyl nucleoside analogues by the ribonucleoside diphosphate reductase.

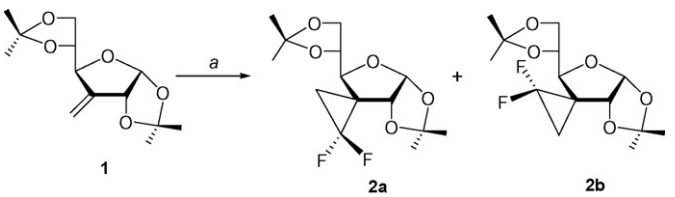
trimethylsilyl fluorosulfonyl-difluoroacetate (TFDA) [14], with the purine and pyrimidine nucleosides bearing a less reactive exomethylene double bond on the ribose ring. The TFDA reagent was selected because of (a) its lower toxicity as compared to the Hg-based reagents, (b) its capability of generating difluorocarbene at a lower temperature than is usually required for most reagents, and (c) the fact that all the products of the fluoride-catalyzed thermal decomposition of TFDA, other than $:CF_2$ and the recycled fluoride, are gases which are lost from the reaction mixture.

2. Results and discussion

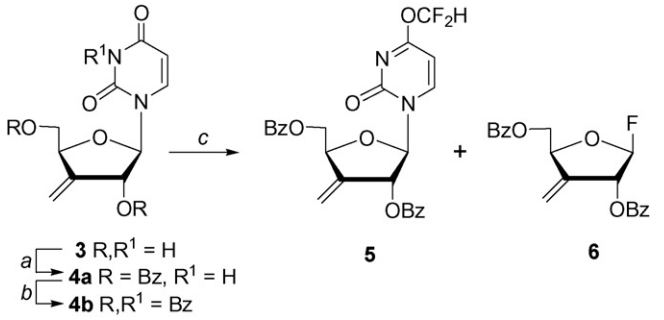
We chose diacetone 3-deoxy-3-methyleneglucose [15] **1** as a convenient substrate to study the feasibility of the addition of difluorocarbene to exomethylene double bonds of pentofuranose sugar rings that are not electron rich vinyl ethers. Treatment of **1** with difluorocarbene generated *in situ* from "acid free" trimethylsilyl fluorosulfonyldifluoroacetate (TFDA) [14] produced spirodifluorocyclopropane derivatives **2a** and **2b** (20%, 2:1; Scheme 1). The ^{19}F NMR signals for the geminal fluorine atoms in **2a** appeared at δ −128.83 (ddd, J = 4.3, 13.5, 165.6 Hz) and −134.56 (dd, J = 11.2, 165.0 Hz) whereas for **2b** they were located at δ −127.72 (ddt, J = 7.0, 13.8, 159.0 Hz) and −135.64 (dd, J = 11.3, 159.0 Hz). The values of the larger coupling constants observed for these two compounds are typical for AB couplings of unsymmetrical *gem*-difluorocyclopropanes. Attempted reaction of **1** with TFDA at a higher temperature (toluene/110 °C) produced only traces of **2a** and **2b**.

NOESY experiments supported the stereochemical assignment at C3 in **2a** as being 3*R* since correlations were observed between one of the cyclopropyl protons (H3′, δ 1.38) and H2 (δ 4.31–4.34) as well as between the other cyclopropyl proton (H3″, δ 1.84) and H5 (δ 3.80), whereas a weak correlation was noted between H3′ and H4 for **2b**(3*S*). The difluorocarbene appears to have added preferentially to the more hindered α-face to give **2a** as the major isomer. This is in contrast to the stereoselective β-face reduction that is observed for the $NaBH_4$ reduction of the 3-keto and 3-deoxy-3-methylene derivatives of diacetoneglucose [16].

The attempted difluorocyclopropanation reaction of closely related nucleoside analogue 3′-deoxy-3′-methyleneuridine **4a** produced instead 4-*O*-difluoromethyl product **5** (68%), derived from an insertion of difluorocarbene into the 4-hydroxyl group of the enolizable uracil ring (Scheme 2). The pair of doublet of doublets at δ −90.66 and −91.20 (J = 71.0, 176.0 Hz) in the



Scheme 1. (a) TFDA/NaF/benzene/3 h/Δ.



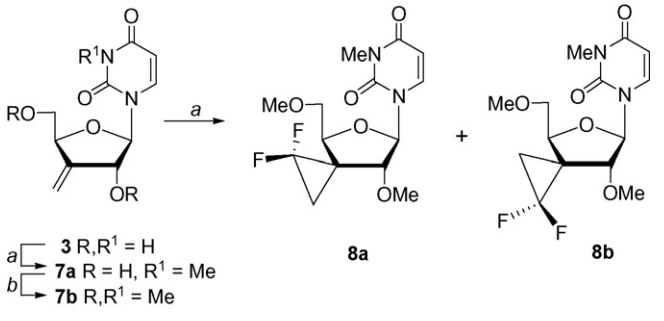
Scheme 2. (a) BzCl/pyridine, (b) BzCl/Et(i-Pr)$_2$N/pyridine, (c) TFDA/NaF/benzene/3 h/Δ.

product's ^{19}F NMR spectrum and the triplet at δ 7.41 (J = 71.0 Hz) in its ^1H NMR spectrum are characteristic of the diastereotopic fluorines of the OCF_2H group. In addition to **5**, a sugar byproduct whose structure was assigned as ribosyl fluoride [17] **6** (8%) was also isolated. A similar insertion of difluorocarbene, generated from Seyferth's phenyl(trifluoromethyl) mercury reagent, into the 4-hydroxyl group of a uracil ring has been observed [18]. When the reaction between **4a** and TFDA was carried out in toluene (110 °C) the ratio of products changed [**5** (30%) and **6** (23%)].

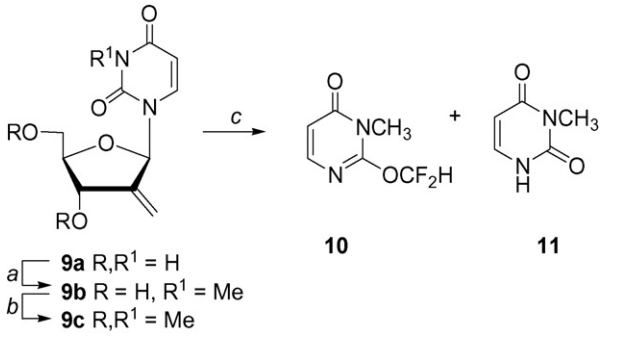
In an attempt to prevent difluorocarbene insertion into the 4-hydroxyl of the uracil ring the substrates **4b** and **7b** with unenolizable uracil rings protected with benzoyl and methyl groups at N3 were prepared. Unfortunately, treatment of **4b** with TFDA resulted mainly in removal of the *N*-benzoyl group from the uracil aglycone giving **4a** (70%) plus **5** (13%).

Difluorocyclopropanation of 3-*N*-2′,5′-*O*-trimethylated derivative **7b** did lead to formation in a low yield of the desired 3′-spirodifluorocyclopropyl uridine analogues **8a** and **8b** [10%, ~1:1, ^1H and ^{19}F NMR (crude reaction mixture)], but most of **7b** was recovered unchanged (Scheme 3). The stereochemical assignments for separated **8a**(3′*R*) and **8b**(3′*S*) were confirmed by NOESY experiments. Thus, the correlation between one of the cyclopropyl protons (H3′, δ 1.34) and H4′ (δ 4.26) was observed for isomer **8a** (β-face addition), whereas isomer **8b** (α-face addition) exhibited a correlation between H3′/3″ and H5′ and H2′. Attempts of difluorocyclopropanation in refluxing benzene or cyclohexanone resulted only in the recovery of substrate **7b**.

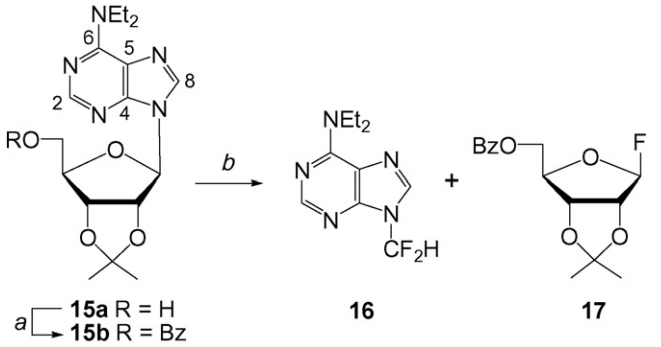
Based on the known greater reactivity of the 2′-deoxy-2′-methylene nucleosides than the corresponding 3′-methylene counterparts in 1,3-dipolar cycloaddition reactions with diazomethane [7c], we turned our attention to difluorocyclopropantion of the 2′-deoxy-2′-methyleneuridine derivatives. Unfortunately, reaction of the trimethylated **9c** with TFDA in benzene failed to give the corresponding 2′-spirodifluorocyclopropyl products. Use of higher temperatures (toluene) and extended reaction times



Scheme 3. (a) CH_2N_2/Et_2O/EtOH, (b) $(MeO)_2SO_2$/NaH/THF, (c) TFDA/NaF/toluene/6 h/Δ.



Scheme 4. (a) $CH_2N_2/Et_2O/EtOH$, (b) $(MeO)_2SO_2/NaH/THF$, (c) TFDA/NaF/toluene/Δ.



Scheme 6. (a) BzCl/pyridine, (b) TFDA/NaF/toluene/Δ.

(14 h) led to hydrolysis of the glycosylic bond and insertion of difluorocarbene at 2 position of the pyrimidine base to give 2-*O*-difluoromethyl-3-*N*-methyluracil **10** (17%) in addition to **11** (11%; Scheme 4). Traces of acid present in the TFDA reagent and the high temperature of these reactions presumably cause glycosylic bond cleavage, particularly for the less stable 2′-deoxy substrates.

The 5,6-double bond of the uracil ring of **7b** or **9c** was also unreactive to difluorocyclopropanation under these conditions, with no products containing a difluoro[4.1.0]bicyclic ring being observed. Additions of (di)halocarbenes generated from the corresponding di(or tri)haloacetic acid or acetates to uracil ring are known [19], although no example of such a difluorocarbene addition has been reported. It is also worth mentioning that an attempted cyclopropanation of the 3-*N*-benzoyl-3′,5′-di-*O*-benzoyl-2′-deoxy-2′-difluoromethyleneuridine [20] with diazomethane, followed by the photochemical extrusion of nitrogen as demonstrated by Robins and co-workers [7a] and Czernecki et al. [7b] for the synthesis of unfluorinated spirocyclopropyl derivatives, also failed to give the desired spirodifluorocyclopropyl analogues.

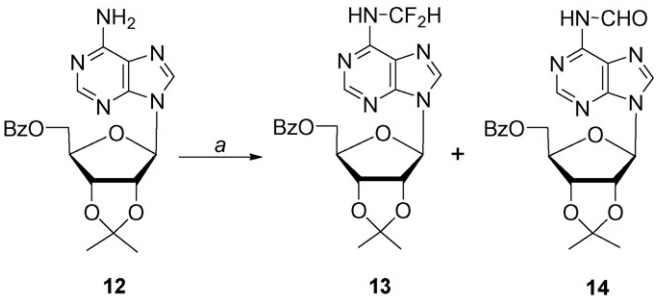
We also performed reactions of purine nucleosides with TFDA. To test the interaction of difluorocarbene with the unprotected exo amino group in the purine ring, we carried out reactions with 5′-*O*-benzoyl-2′,3′-*O*-isopropylideneadenosine **12**. Thus, treatment of **12** with TFDA in toluene led to the formation of 6-*N*-difluoromethyl derivative **13** (18%) and 6-*N*-formyladenosine analogue **14** (33%, Scheme 5). Although we did not investigate this reaction in details, based on the NMR and TLC analysis of the aliquots taken during the reaction, it appears that **13** is formed initially and then is slowly converted to **14**.

Treatment of the adenosine analogue **15b** with the exo amino group of the adenine ring protected with diethyl groups [21a] yielded 6-*N*,*N*-diethyl-9-difluoromethyladenine **16** (21%) in addition to the ribofuranosyl fluoride **17** (9%; Scheme 6). The position of difluoromethyl group at N9 in **16** was established based on the UV, ^{13}C and 2D NMR (HMBC) spectra in agreement with the literature value for the N7/N9 methylated adenosine and 6-*N*,*N*-dimethyladenine analogues. Thus, the chemical shifts for C4 and C5 in **16** are at δ 150.5 and 119.3, respectively, similar to the reported values for adenosine [δ 149.3 (C4) and 119.6 (C5)] rather than for the N7 isomer, e.g., 7-(β-D-ribofuranosyl)adenine [δ 160.7 (C4) and 110.3 (C5)] [21b].

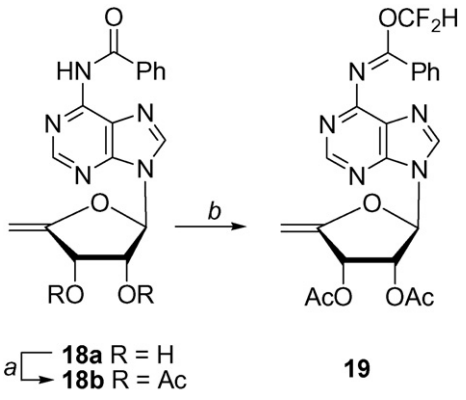
Moreover, the UV spectrum of **16** (λ_{max} 276 nm) is identical to those of **15a** (λ_{max} 277 nm) and 6-*N*,*N*-dimethylamino-9-methyladenine (λ_{max} 276 nm) while a bathochromic shift was observed for the 6-*N*,*N*-dimethylamino-7-methyladenine regioisomer (λ_{max} 291 nm) [21c].

Next, reactions of highly electrophilic difluorocarbene with nucleosides containing an electron rich vinyl ether unit were examined. However, treatment of 2′,3′-di-*O*-acetyl-6-*N*-benzoyl protected **18b** with TFDA produced the difluoromethyl ether **19** (68%), as a result of the insertion of difluorocarbene into the *enol* form of the 6-benzamido group, together with two minor byproducts containing fluorine (~10%, ^1H and ^{19}F NMR) which also had intact exomethylene units present (Scheme 7).

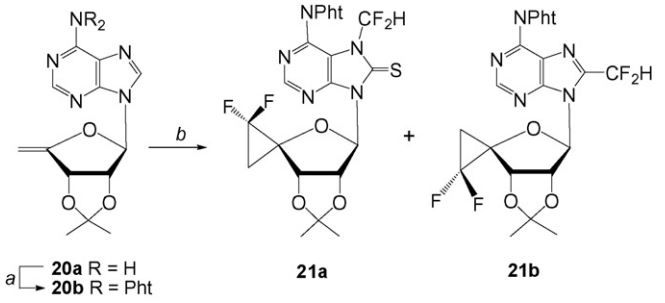
In order to eliminate the interaction of the difluorocarbene with the 6-*N*-benzoyl protecting group, we tested 6-*N*-phthaloyl protection [22] for the exo amino group in the adenine ring, since a phthaloyl strategy for the protection of an amino group had previously been used for the reaction with TFDA [14]. Thus, treatment of **20b** [prepared (76%) by reaction of 9-(2,3-*O*-isopropylidene-5-deoxy-β-D-*erythro*-pent-4-enofuranosyl) adenine [23] **20a** with phthaloyl dichloride in pyridine] with TFDA followed by column chromatography afforded **21a** and **21b** in 11% and 6% yield, respectively (Scheme 8). The ^{19}F NMR spectrum for each product showed two sets of signals, one from the spirodifluorocyclopropane ring and the second from a CF_2H unit. Slightly different ^1H NMR spectra for both products **21a**



Scheme 5. (a) TFDA/NaF/toluene/Δ.



Scheme 7. (a) Ac_2O/pyridine, (b) TFDA/NaF/benzene/Δ.

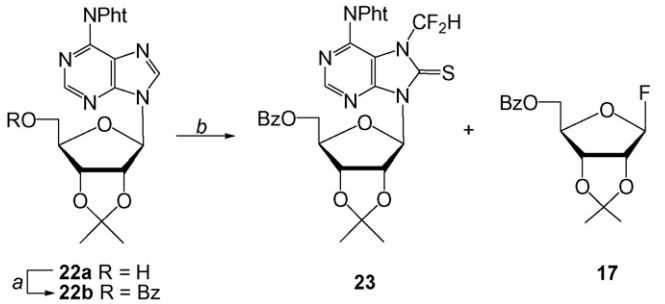


Scheme 8. (a) Phthaloyl dichloride/pyridine, (b) TFDA/NaF/toluene/Δ.

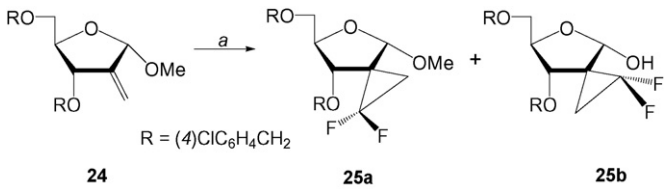
and **21b** showed only singlets for purine H2 proton and a characteristic triplet (J = 58 Hz) for the CF_2H groups. On the basis of the overall spectroscopic evidence and studies of the reaction of TFDA with model imidazole compounds, including an X-ray structure determination, a thiourea entity bearing a difluoromethyl group attached to N7 was proposed as the structure of **21a** [24]. A structure for the second product was tentatively assigned as **21b** based on: (i) the UV spectrum of **21b** (λ_{max} 278 nm) did not exhibit bathochromic shifts as observed for thione **21a** (λ_{max} 319 nm); and (ii) NOESY experiment showed correlations between H5′ and H3′ confirming the α-face addition of difluorocarbene to exomethylene double bond while such correlation was not observed for **21a**.

The formation of the *N*-difluoromethylthiourea-type product **23** (18%) was also observed in the reaction of the protected adenosine derivative **22b** with TFDA, although the 1-fluoro sugar byproduct **17** (32%) was a major product isolated from the reaction mixture (Scheme 9).

We also attempted difluorocyclopropanation of a ribose derivative having an exomethylene group at C2 next to the anomeric carbon. Thus, treatment of methyl-3,5-di-*O*-(4-chlorobenzyl)-2-deoxy-2-methylene-α-D-ribofuranoside **24** [25] with TFDA afforded methyl furanoside **25a**(2*R*) and furanose **25b**(2*S*) with a free hydroxyl group at C1 (35%, 7:1; Scheme 10). A NOESY experiment with **25a** showed a correlation between one of the protons from the cyclopropyl ring (H2′) and H1 and H3, while no such correlation was observed with **25b** confirming α-face and β-face addition of difluorocarbene.



Scheme 9. (a) BzCl/pyridine, (b) TFDA/NaF/toluene/Δ.



Scheme 10. (a) TFDA/NaF/benzene/5 h/Δ.

3. Conclusions

In summary, we have shown that difluorocarbene, generated from trimethylsilyl fluorosulfonyldifluoroacetate (TFDA), reacts with the uridine substrates to produce 4-*O*-difluoromethyl products derived from the insertion of difluorocarbene into the 4-hydroxyl group of the enolizable uracil ring. Similar reactions of difluorocarbene with adenosine substrates having unprotected 6-amino group of the purine ring produced a 6-*N*-difluoromethyl derivative, while reaction with 6-*N*-benzoyl protected substrates gave difluoromethyl ether products derived from the insertion of difluorocarbene into the *enol* form of the 6-benzamido group. Treatment of the 6-*N*-phthaloyl protected adenosine analogues with TFDA resulted in one-pot conversion of the imidazole ring of the purine into the corresponding *N*-difluoromethylthiourea derivatives. Treatment of suitably protected carbohydrates as well as pyrimidine and purine nucleosides bearing an exomethylene group at carbons 2′, 3′ or 4′ of the sugar rings with TFDA gave the corresponding spirodifluorocyclopropyl analogues, but in low yields.

4. Experimental section

^1H (Me_4Si) NMR spectra at 400 MHz, ^{13}C (Me_4Si) at 100.6 MHz and ^{19}F (CCl_3F) at 376.4 MHz were determined with solutions in $CDCl_3$ unless otherwise noted. The NOESY, HMQC and HMBC experiments were recorded at 600 MHz instruments. Mass spectra (MS) were obtained by atmospheric pressure chemical ionization (APCI) techniques and HRMS using FAB mode unless otherwise noted. Reagent grade chemicals were used and solvents were dried by reflux over and distillation from CaH_2, except toluene and benzene (sodium) and THF (potassium), under an argon atmosphere. TLC was performed on Merck Kieselgel 60-F_{254} with MeOH/$CHCl_3$ (1:9, 1:19), EtOAc/hexane (1:2) or EtOAc/*i*-PrOH/H_2O (4:1:2, upper layer; S1) as developing systems, and products were visualized under 254 nm light or with I_2. Merck Kieselgel 60 (230–400 mesh) was used for column chromatography. An "acid free" trimethylsilyl 2-fluorosulfonyl-2,2-difluoroacetate (TFDA) was prepared by treatment of the equimolar quantity of TFDA with triethylamine as reported [14]. The purity of TFDA was conveniently evaluated by ^{19}F NMR in $CDCl_3$ (dried over molecular sieves 4 Å) where TFDA shows peak at δ −103.20 while the signal from 2-fluorosulfonyl-2,2-difluoroacetic acid (FDA) appears at δ −103.91. TFDA and FDA were purchased from Aldrich Co. Sodium fluoride (NaF) was dried in the oven. Reactions with TFDA were carried out in 10 or 25 mL three-necked flasks equipped with a magnetic stirrer, a funnel with nitrogen (N_2) inlet and a water-cooled condenser with gas outlet. Carbohydrates and nucleosides substrates have to be well dried prior to use.

3-Deoxy-(R/S)-3,3-C-(1,1-difluoroethane-1,2-diyl)-1,2;5,6-di-O-isopropylidene-α-D-ribo-hexofuranose (**2a**/**2b**). A solution of **1** [15] (150 mg, 0.58 mmol) in anhydrous benzene (1.5 mL) containing dried NaF (1.4 mg, 0.03 mmol) was heated at 80 °C (oil bath) for 30 min. An "acid free" trimethylsilyl fluorosulfonyldifluoroacetate [14] (TFDA; 0.30 mL, 380 mg, 1.5 mmol) was then added dropwise via a Teflon needle at the rate of 0.15 mL/h (controlled by syringe pump). The solution was refluxed for 3 h and then cooled to ambient temperature and was evaporated to give crude mixture of **2a**/**2b** (~20%, 2:1; ^1H and ^{19}F NMR). The reaction mixture was partitioned ($NaHCO_3$/H_2O//$CHCl_3$) and the separated organic layer was washed (brine), dried (Na_2SO_4), evaporated and was carefully column chromatographed (0 → 20% EtOAc/hexane) to give **2a**(3*R*) (10 mg, 6%) and **2b**(3*S*) (5 mg, 3%) as slightly yellow oils and recovered **1** (102 mg, 68%). Compound **2a** [slightly more polar than **1** on TLC (EtOAc/hexane, 3:7)] had: ^1H NMR δ 1.23 (s, 3H), 1.27 (s, 3H), 1.30 (s, 3H), 1.38 (ddd, J = 8.1, 11.7, 13.5 Hz, 1H), 1.52 (s, 3H),

1.84 (ddd, J = 4.6, 8.1, 12.0 Hz, 1H), 3.80 (ddd, J = 4.8, 6.3, 7.7 Hz, 1H), 3.96 (dd, J = 4.9, 8.8 Hz, 1H), 4.02 (dd, J = 6.4, 8.8 Hz, 1H), 4.31–4.34 (m, 1H), 4.35 (d, J = 8.0 Hz, 1H), 5.89 (d, J = 3.6 Hz, 1H); ^{19}F NMR δ −128.83 (ddd, J = 4.3, 13.5, 165.6 Hz, 1F), −134.56 (dd, J = 11.2, 165.0 Hz, 1F); ^{13}C NMR δ 17.8 (t, J = 10.5 Hz), 25.3, 26.4, 26.9, 27.3, 37.7 (t, J = 11.0 Hz), 67.2, 76.0, 77.2, 77.9, 104.6, 110.0, 110.8 (t, J = 286.2 Hz), 113.3; HRMS calcd for $C_{14}H_{21}F_2O_5$ [M+H]$^+$: 307.1357; found: 307.1350. Compound **2b** [less polar than **1** on TLC (EtOAc/hexane, 3:7)] had: ^{1}H NMR δ 1.24 (s, 3H), 1.26 (s, 3H), 1.34 (s, 3H), 1.48 (s, 3H), 1.64 (ddd, J = 3.2, 8.3, 13.6 Hz, 1H), 1.74 (ddd, J = 6.5, 8.3, 11.4 Hz, 1H), 3.85 (ddd, J = 1.0, 5.1, 8.7 Hz, 1H), 4.00 (dd, J = 6.1, 8.6 Hz, 1H), 4.10–4.18 (m, 1H), 4.31 ("t", J = 7.7 Hz, 1H), 4.51 (d, J = 4.2 Hz, 1H), 5.78 (d, J = 4.1 Hz, 1H); ^{19}F NMR δ −127.72 (ddt, J = 7.0, 13.8, 159.0 Hz, 1F), −135.64 (dd, J = 11.3, 159.0 Hz, 1F); ^{13}C NMR δ 15.6 (t, J = 10.9 Hz), 25.5, 27.0, 27.1, 27.1, 37.6 (t, J = 8.3 Hz), 68.1 (d, J = 1.7 Hz), 74.2 (d, J = 3.7 Hz), 79.4, 81.1 (d, J = 4.8 Hz), 104.6 (d, J = 1.6 Hz), 110.0, 112.3, 113.7 (t, J = 286.0 Hz); HRMS calcd for $C_{14}H_{21}F_2O_5$ [M+H]$^+$: 307.1357; found: 307.1347.

2′,5′-Di-O-benzoyl-3′-deoxy-3′-methyleneuridine (**4a**). BzCl (217 μL, 263 mg, 1.87 mmol) was added to a stirred solution of 3′-deoxy-3′-methyleneuridine [26] (**3**; 150 mg, 0.62 mmol) in pyridine (3 mL) at 0 °C (ice-bath) and the resulting mixture was stirred overnight at ambient temperature. Volatiles were evaporated in *high-vacuum* (<5 °C) and the residue was partitioned (1N $HCl/H_2O//CHCl_3$). The separated organic layer was washed with $NaHCO_3/H_2O$, brine, dried (Na_2SO_4), evaporated and column chromatographed (EtOAc/hexane, 2:1) to give **4a** (230 mg, 82%) as a white powder: ^{1}H NMR δ 4.62 (dd, J = 4.8, 12.2 Hz, 1H), 4.73 (dd, J = 3.0, 12.3 Hz, 1H), 5.10–5.14 (m, 1H), 5.47–5.49 (m, 1H), 5.61–5.64 (m, 2H), 5.93–5.97 (m, 1H), 6.23 (d, J = 4.8 Hz, 1H), 7.42–7.49 (m, 5H), 7.60 ("q", J = 7.4 Hz, 2H), 8.02–8.07 (m, 4H), 9.57 (br s, 1, NH); MS m/z 449 (MH$^+$). Anal. calcd for $C_{24}H_{20}N_2O_7$ (448.43): C, 64.28; H, 4.50; N, 6.25. Found: C, 64.53; H, 4.82; N, 6.37.

3-N-Benzoyl-2′,5′-di-O-benzoyl-3′-deoxy-3′-methyleneuridine (**4b**). BzCl (166 μL, 201 mg, 1.43 mmol) was added to a stirred solution of **4a** (428 mg, 0.95 mmol) in pyridine (8 mL) containing ethyldiisopropylamine (830 μL, 615 mg, 4.76 mmol) at 0 °C (ice-bath). After 16 h, volatiles were evaporated and the residue was partitioned (1N $HCl/H_2O//CHCl_3$). The separated organic layer was washed with $NaHCO_3/H_2O$, brine, dried (Na_2SO_4), evaporated and column chromatographed (EtOAc/hexane, 1:1) to give **4b** (442 mg, 84%) as a slightly yellow foam: ^{1}H NMR δ 4.62 (dd, J = 4.6, 12.3 Hz, 1H), 4.78 (dd, J = 2.7, 12.8 Hz, 1H), 5.13–5.17 (m, 1H), 5.48–5.51 (m, 1H), 5.64–5.67 (m, 1H), 5.77 (d, J = 8.2 Hz, 1H), 5.94–5.98 (m, 1H), 6.18 (d, J = 5.2 Hz, 1H), 7.42–7.53 (m, 6H), 7.57–7.67 (m, 4H), 7.97 (d, J = 7.5 Hz, 2H), 8.02 (d, J = 7.4 Hz, 2H), 8.08 (d, J = 7.4 Hz, 2H); MS m/z 553 (MH$^+$). Anal. calcd for $C_{31}H_{24}N_2O_8$ (552.53): C, 67.39; H, 4.38; N, 5.07. Found: C, 67.04; H, 4.67; N, 5.17.

2′,5′-Di-O-benzoyl-3′-deoxy-4-O-difluorometyl-3′-methyleneuridine (**5**). A solution of **4a** (65 mg, 0.14 mmol) in anhydrous benzene (1.5 mL) containing NaF (1.4 mg, 0.03 mmol) was heated at 80 °C (oil bath) for 30 min. TFDA (0.25 mL, 320 mg, 1.28 mmol) was added dropwise via a Teflon needle at the rate of 0.15 mL/h (controlled by syringe pump). The solution was refluxed for 3 h and then was cooled to ambient temperature. The reaction mixture was partitioned ($NaHCO_3/H_2O//CHCl_3$) and the separated organic layer was washed (brine), dried (Na_2SO_4), evaporated and column chromatographed (20 → 40% EtOAc/hexane) to give **5** (49 mg, 68%) as an oil: ^{1}H NMR δ 4.62 (dd, J = 4.9, 12.2 Hz, 1H), 4.67 (dd, J = 3.0, 12.4 Hz, 1H), 5.11–5.14 (m, 1H), 5.40 (s, 1H), 5.60 (s, 1H), 5.82 (d, J = 7.3 Hz, 1H), 5.87–5.91 (m, 1H), 6.20 (d, J = 3.9 Hz, 1H), 7.36–7.43 (m, 4H), 7.41 (t, J = 71.0 Hz, 1H), 7.49–7.57 (m, 2H), 7.92–8.00 (m, 4H), 7.99 (d, J = 7.3 Hz, 1H); ^{19}F NMR δ −90.66 (dd, J = 71.0, 176.0 Hz, 1F), −91.20 (dd, J = 71.0, 176.0 Hz, 1F); ^{13}C NMR δ 65.2, 78.0, 79.8, 90.1, 95.2, 113.1 (t, J = 259.9 Hz), 114.9, 128.9, 129.0, 129.3, 129.7, 129.9, 130.3, 133.9, 134.0, 141.5, 145.6, 154.4, 166.0, 166.5, 168.1 (t, J = 3.9 Hz); HRMS calcd for $C_{25}H_{21}F_2N_2O_7$ [M+H]$^+$: 499.1317; found: 499.1316.

Also isolated was sugar byproduct whose structure was tentatively assigned as 2,5-di-*O*-benzoyl-3-deoxy-3-methylene-β-D-*erythro*-pentofuranosyl fluoride [**6**; 4 mg, 8%; less polar on TLC (EtOAc/hexane, 1:1) than **5** and **4a**]: ^{1}H NMR δ 4.40 (dd, J = 6.8, 12.0 Hz, 1H), 4.56 (dd, J = 3.7, 12.0 Hz, 1H), 5.15–5.20 (m, 1H), 5.53 (br s, 1H), 5.78 (d, J = 5.1 Hz, 1H), 5.82 (d, J = 2.5 Hz, 1H), 5.88 (d, J = 60.8 Hz, 1H), 7.39 (t, J = 7.7 Hz, 4H), 7.48–7.55 (m, 2H), 7.96 (d, J = 8.3 Hz, 2H), 8.03 (d, J = 8.3 Hz, 2H); ^{19}F NMR δ −116.66 (dt, J = 5.0 Hz, 60.9 Hz, 1F); ^{13}C NMR δ 67.2, 78.1 (d, J = 40.4 Hz), 81.0 (d, J = 2.5 Hz), 112.5 (d, J = 225.3 Hz), 118.0 (d, J = 3.8 Hz), 128.8, 128.9, 129.5, 130.0, 130.1, 130.2, 133.6, 134.0, 141.7, 165.7, 166.7; MS m/z 357 (M+H$^+$); HRMS calcd for $C_{20}H_{17}FLiO_5$ [M+Li]$^+$: 363.1220; found: 363.1219.

Treatment of **4a** (65 mg, 0.14 mmol) with TFDA (0.25 mL, 320 mg, 1.28 mmol) in toluene [1.5 mL; 110 °C (oil bath)/3 h] instead of benzene gave **5** (22 mg, 30%) and **6** (12 mg, 23%).

Analogous treatment of **4b** (150 mg, 0.27 mmol) with TFDA (toluene, 3 h) gave **5** (18 mg, 13%), **4a** (85 mg, 70%) and unchanged **4b** (10 mg, 7%).

3′-Deoxy-3-N-methyl-2′,5′-di-O-methyl-3′-methyleneuridine (**7b**). *Step a.* An ethereal solution of the excess diazomethane [generated from (*N*-methyl-*N*-nitroso)-*p*-toluenesulfonamide (DIAZALD; 0.55 g, 2.6 mmol)] was added to a stirred solution of 3′-deoxy-3′-methyleneuridine [26] (**3**; 184 mg, 0.77 mmol) in EtOH (2 mL). After 1 h, the volatiles were evaporated to give 3′-deoxy-3-*N*-methyl-3′-methyleneuridine (**7a**; 195 mg, 100%) which was directly used in next step: ^{1}H NMR δ 3.29 (s, 3H), 3.65–3.75 (m, 2H), 3.85–3.95 (m, 1H), 4.66–4.74 (m, 1H), 5.19 (s, 1H), 5.39 (s, 1H), 5.69 (d, J = 5.6 Hz, 1H), 5.74 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H); MS m/z 255 (MH$^+$). *Step b.* NaH (123 mg, 3.1 mmol, 60% dispersion in oil) and dimethyl sulfate (146 μL, 193 mg, 1.53 mmol) were added to a stirred solution of **7a** (195 mg, 0.77 mmol) in THF (8 mL) at ambient temperature. After 14 h, glacial AcOH was added to neutralize reaction mixture to pH ∼6 and then volatiles were evaporated. The residue was partitioned ($NaHCO_3/H_2O//CHCl_3$) and the organic layer was washed (brine), dried (Na_2SO_4), evaporated and chromatographed (20 → 50% EtOAc/hexane) to give **7b** (174 mg, 80%) as a transparent oil: ^{1}H NMR δ 3.23 (s, 3H), 3.32 (s, 3H), 3.33 (s, 3H), 3.56 (dd, J = 3.6, 10.9 Hz, 1H), 3.71 (dd, J = 2.9, 10.9 Hz, 1H), 4.06–4.09 (m, 1H), 4.65–4.69 (m, 1H), 5.21 (t, J = 1.6 Hz, 1H), 5.33 (t, J = 1.6 Hz, 1H), 5.65 (d, J = 8.1 Hz, 1H), 5.96 (d, J = 2.9 Hz, 1H), 7.63 (d, J = 8.1 Hz, 1H); ^{13}C NMR δ 27.6, 56.8, 59.4, 73.0, 79.9, 85.7, 88.7, 101.7, 112.3, 138.1, 142.9, 151.1, 162.8; HRMS calcd for $C_{13}H_{19}N_2O_5$ [M+H]$^+$: 283.1294; found: 283.1297.

3-N-Methyl-1-[3-deoxy-(R/S)-3,3-C-(1,1-difluoroethane-1,2-diyl)-2,5-di-O-methyl-β-D-erythro-pentofuranosyl]uracil (**8a**/**8b**). A solution of **7b** (70 mg, 0.25 mmol) in anhydrous toluene (1.0 mL) containing NaF (1.4 mg, 0.03 mmol) was refluxed for 15 min. TFDA (0.10 mL, 127 mg, 0.51 mmol) was then added dropwise via a Teflon needle at the rate of 0.15 mL/h (controlled by syringe pump). The solution was refluxed for 6 h and then was cooled to ambient temperature and was evaporated to give mainly unchanged substrate **7b** in addition to two minor less polar products **8a** and **8b** (TLC, ^{19}F NMR). The reaction mixture was partitioned ($NaHCO_3/H_2O//CHCl_3$) and the separated organic layer was washed (brine), dried (Na_2SO_4), evaporated and column chromatographed (20 → 50% EtOAc/hexane) to give in order of elution **8a**(3′*R*) (2 mg, 2.5%), **8b**(3′*S*) (2 mg, 2.5%) and **7b** (29 mg, 41%) as slightly yellow oils. Compound **8a** had: ^{1}H NMR δ 1.34 (ddd, J = 4.6, 8.4, 13.3 Hz, 1H), 1.91 (ddd, J = 5.2, 8.4, 13.2 Hz, 1H), 3.28 (s, 3H), 3.32 (s, 3H), 3.38 (s, 3H), 3.47 (ddd, J = 2.2, 3.7, 10.6 Hz, 1H), 3.52 (ddd, J = 1.5, 2.6, 10.8 Hz, 1H), 3.83 (d, J = 4.6 Hz, 1H), 4.26

("dt", J = 3.1, 5.3 Hz, 1H), 5.78 (d, J = 8.1 Hz, 1H), 6.07 (d, J = 4.7 Hz, 1H), 7.63 (d, J = 8.1 Hz, 1H); ^{19}F NMR δ −132.06 (ddt, J = 4.8, 12.8, 164.1 Hz, 1F), −134.83 (ddd, J = 4.5, 13.4, 164.3 Hz, 1F); ^{13}C NMR (150.9 MHz) δ 16.3 (t, J = 10.9 Hz), 27.8, 34.0 (t, J = 10.7 Hz), 58.9, 59.2, 72.1, 81.1, 82.6, 88.4, 102.5, 111.7 (t, J = 288.1 Hz), 137.5, 151.2, 162.6; HRMS (FAB) calcd for $C_{14}H_{19}F_2N_2O_5$ [M+H]$^+$: 333.1257; found: 333.1260. Compound **8b** had: ^{1}H NMR δ 1.30 (ddd, J = 4.2, 8.5, 12.8 Hz, 1H), 2.01 (ddd, J = 4.4, 8.5, 13.0 Hz, 1H), 3.26 (s, 3H), 3.32 (s, 3H), 3.46 ("dt", J = 1.7, 11.7 Hz, 1H), 3.50 (br s, 1H), 3.53 (s, 3H), 3.77 (dd, J = 2.9, 11.7 Hz, 1H), 4.59–4.62 (m, 1H), 5.67 (d, J = 8.1 Hz, 1H), 5.92 (s, 1H), 8.13 (d, J = 8.1 Hz, 1H); ^{19}F NMR δ −131.59 (ddd, J = 3.8, 13.0, 171.0 Hz, 1F), −137.64 (ddd, J = 3.5, 12.6, 170.9 Hz, 1F); ^{13}C NMR δ 20.4 (t, J = 10.6 Hz), 27.4, 34.5 (t, J = 10.7 Hz), 58.1, 59.3, 69.9 (d, J = 3.6 Hz), 78.6, 89.1, 90.1, 100.8, 111.2 (t, J = 288.6 Hz,), 137.6, 151.0, 162.9; HRMS (FAB) calcd for $C_{14}H_{19}F_2N_2O_5$ [M+H]$^+$: 333.1257; found: 333.1261.

2′-Deoxy-3-N-methyl-3′,5′-di-O-methyl-2′-methyleneuridine (**9c**). *Step a.* An ethereal solution of the excess of diazomethane [generated as described for **7b** (*step a)*] was added to a stirred solution of 2′-deoxy-2′-methyleneuridine [26] (**9a**; 411 mg, 1.71 mmol) in EtOH (5 mL). After 1 h, the volatiles were evaporated to give 2′-deoxy-3-*N*-methyl-2′-methyleneuridine (**9b**; 435 mg, 100%) which was directly used in next step: ^{1}H NMR δ 3.23 (s, 3H), 3.75 (dd, J = 3.2, 12.9 Hz, 1H), 3.83–3.91 (m, 2H), 4.73 (d, J = 7.0 Hz, 1H), 5.35 (s, 1H), 5.43 (s, 1H), 5.66 (d, J = 8.1 Hz, 1H), 6.52 (s, 1H), 7.70 (d, J = 8.1 Hz, 1H); MS m/z 255 (MH$^+$). *Step b.* NaH (356 mg, 8.9 mmol, 60% dispersion in oil) and dimethyl sulfate (0.42 mL, 564 mg, 4.47 mmol) was added to a stirred solution of **9b** (435 mg, 1.71 mmol) in THF (5 mL) at ambient temperature. After 14 h, glacial AcOH was added to neutralize reaction mixture to pH ∼6 and then the volatiles were evaporated. The residue was partitioned ($NaHCO_3/H_2O//CHCl_3$) and the organic layer was washed (brine), dried (Na_2SO_4), evaporated and chromatographed (20 → 40% EtOAc/hexane) to give **9c** (383 mg, 79%) as a white solid: ^{1}H NMR δ 3.26 (s, 3H), 3.33 (s, 3H), 3.36 (s, 3H), 3.54 (dd, J = 3.3, 10.7 Hz, 1H), 3.58 (dd, J = 3.0, 10.7 Hz, 1H), 4.06 ("q", J = 3.3 Hz, 1H), 4.21–4.25 (m, 1H), 5.18 ("t", J = 1.6 Hz, 1H), 5.46 ("t", J = 1.6 Hz, 1H), 5.72 (d, J = 8.1 Hz, 1H), 6.65–6.67 (m, 1H), 7.43 (d, J = 8.1 Hz, 1H); ^{13}C NMR δ 27.9, 56.7, 59.4, 73.1, 81.1, 82.6, 85.5, 102.3, 114.9, 139.1, 145.1, 151.8, 162.9; HRMS calcd for $C_{13}H_{19}N_2O_5$ [M+H]$^+$: 283.1294; found: 283.1299.

2-O-Difluoromethyl-3-N-methyluracil (**10**). A solution of **9c** (70 mg, 0.25 mmol) in dry toluene (1.5 mL) containing NaF (1.4 mg, 0.03 mmol) was heated at 110 °C for 30 min. TFDA (0.10 mL, 127 mg, 0.51 mmol) was added dropwise via a Teflon needle at the rate of 0.05 mL/h (controlled by syringe pump). The resulting solution was refluxed overnight and then was cooled to ambient temperature. The reaction mixture was partitioned ($NaHCO_3/H_2O//CHCl_3$) and the separated organic layer was washed (brine), dried (Na_2SO_4), evaporated and column chromatographed (30 → 50% EtOAc/hexane) to give **10** [18] (7.5 mg, 17%): ^{1}H NMR δ 3.35 (s, 3H), 5.98 (d, J = 8.2 Hz, 1H), 7.43 (d, J = 8.2 Hz, 1H), 7.46 (t, J = 59.7 Hz, 1H); ^{19}F NMR δ −102.38 (d, J = 56.5 Hz, 2F); HRMS calcd for $C_6H_7F_2N_2O_2$ [M+H]$^+$: 177.0476; found: 177.0471.

Further elution yielded 3-*N*-methyluracil (**11**; 4 mg, 11%) with data identical to commercial sample [^{1}H NMR (CD_3OD) δ 3.35 (s, 3H), 5.96 (d, J = 8.3 Hz, 1H), 7.48 (d, J = 8.3 Hz, 1H); MS m/z 127 (MH$^+$)].

5′-O-Benzoyl-6-N-difluoromethyl-2′,3′-O-isopropylideneadenosine (**13**) *and 5′-O-benzoyl-6-N-formyl-2′,3′-O-isopropylideneadenosine* (**14**). Treatment [toluene (1.5 mL), NaF (1.4 mg, 0.03 mmol), 120 °C (oil bath), 5.5 h] of 5′-*O*-benzoyl-2′,3′-*O*-isopropylideneadenosine [27] (12; 40 mg, 0.10 mmol) with TFDA (0.25 mL, 320 mg, 1.28 mmol, adding with the rate of 0.10 mL/h), as described for **8a**/**8b** (column chromatography: 20 → 50% EtOAc/hexane), gave **13** (8 mg, 18%) and slightly more polar **14** (14 mg, 33%). Compound **13** had: ^{1}H NMR δ 1.39 (s, 3H), 1.61 (s, 3H), 4.47 (dd, J = 4.8, 11.8 Hz, 1H), 4.61 (q, J = 3.7 Hz, 1H), 7.66 (dd, J = 3.9, 11.8 Hz, 1H), 5.06 (dd, J = 3.4, 6.3 Hz, 1H), 5.33 (dd, J = 6.3, 2.4 Hz, 1H), 5.99 (d, J = 2.4 Hz, 1H), 7.41 (t, J = 7.4 Hz, 2H), 7.56 (t, J = 7.5 Hz, 1H), 7.71 (s, 1H), 7.83 (s, 1H), 7.93 (d, J = 7.1 Hz, 2H), 7.94 (t, J = 59.9 Hz, 1H); ^{19}F NMR δ −101.53 (dd, J = 59.7, 228.3 Hz, 1F), −102.35 (dd, J = 59.7, 228.3 Hz, 1F); ^{13}C NMR δ 25.7, 27.5, 64.3, 81.6, 85.0, 85.1, 91.7, 107.9 (t, J = 252.8 Hz), 115.3, 124.1, 128.7, 129.6, 129.9, 133.8, 138.2, 140.1, 141.4 (t, J = 5.1 Hz), 152.9, 166.3; MS m/z 462 (MH$^+$); HRMS calcd for $C_{21}H_{21}F_2N_5LiO_5$ [M+Li]$^+$: 468.1671; found: 468.1670. Compound **14** had: ^{1}H NMR δ 1.37 (s, 3H), 1.60 (s, 3H), 4.47 (dd, J = 4.7, 11.5 Hz, 1H), 4.67 (dd, J = 3.9, 11.5 Hz, 1H), 4.70 ("dd", J = 3.9, 7.1 Hz, 1H), 5.17 (dd, J = 2.9, 6.2 Hz, 1H), 5.63 (dd, J = 6.3, 2.1 Hz, 1H), 6.19 (d, J = 2.1 Hz, 1H), 7.36 (t, J = 7.5 Hz, 2H), 7.45 (t, J = 7.4 Hz, 1H), 7.82 (d, J = 7.1 Hz, 2H), 8.36 (s, 1H), 8.62 (s, 1H), 9.89 (d, J = 10.3 Hz, 1H), 9.95 (br d, J = 10.3 Hz, 1H); ^{13}C NMR δ 25.8, 27.5, 64.6, 82.0, 84.6, 85.6, 92.2, 115.2, 121.7, 128.6, 129.6, 129.8, 133.6, 143.4, 149.5, 151.4, 152.9, 163.2, 166.3; HRMS calcd for $C_{21}H_{22}N_5O_6$ [M+H]$^+$: 440.1570; found: 440.1563.

Notes: ^{19}F NMR of the crude reaction mixture showed formation of other byproducts having CF_2H group as judged by their characteristic splitting pattern. Reaction of **12** with TFDA (3 h, 120 °C, oil bath) gave recovered **12** (20 mg, 50%) and **13** (10 mg, 22%).

5′-O-Benzoyl-6-N,N-diethyl-2′,3′-O-isopropylideneadenosine (**15b**). Treatment of 6-*N*,*N*-diethyl-2′,3′-*O*-isopropylideneadenosine [21] [**15a**; 235 mg, 0.65 mmol; UV (MeOH) λ_{max} 277 nm] with BzCl (113 μL, 136 mg, 0.97 mmol), as described for **4a** (column chromatography: 40 → 60% EtOAc/hexane), gave **15b** (250 mg, 83%) as a white foam: ^{1}H NMR δ 1.23 (t, J = 7.0 Hz, 6H), 1.37 (s, 3H), 1.60 (s, 3H), 3.90 (br s, 4H), 4.47 (dd, J = 6.7, 12.9 Hz, 1H), 4.57–4.62 (m, 2H), 5.16 (dd, J = 3.1, 6.3 Hz, 1H), 5.57 (dd, J = 2.0, 6.3 Hz, 1H), 6.08 (d, J = 2.0 Hz, 1H), 7.32 (t, J = 8.0 Hz, 2H), 7.47 (t, J = 7.4 Hz, 1H), 7.80 (s, 1H), 7.87 (d, J = 8.2 Hz, 2H), 8.28 (s, 1, H); ^{13}C NMR δ 13.7 (br s), 25.6, 27.4, 43.3 (br s), 64.8, 82.0, 84.5, 85.2, 91.6, 114.6, 120.5, 128.5, 129.6, 129.8, 133.3, 137.5, 149.9, 152.9, 153.9, 166.2; MS m/z 468 (MH$^+$). Anal. calcd for $C_{24}H_{29}N_5O_5$ (467.52): C, 61.66; H, 6.25; N, 14.98. Found: C, 61.46; H, 6.62; N, 14.61.

6-N,N-Diethyl-9-N-difluoromethyladenine (**16**). Treatment [toluene (1.5 mL), NaF (1.4 mg, 0.03 mmol), 120 °C (oil bath), 5.5 h] of **15b** (55 mg, 0.12 mmol) with TFDA (0.18 mL, 229 mg, 0.91 mmol; adding at the rate of 0.10 mL/h) as described for **8a**/**8b** (column chromatography: 20 → 80% AcOEt/hexane) gave recovered **15b** (30 mg, 55%) and **16** (6 mg, 21%) and **17** (3 mg, 9%). Compound **16** had: UV (MeOH) λ_{max} 276 nm; ^{1}H NMR δ 1.23 (t, J = 7.0 Hz, 6H), 3.87 (br s, 4H), 7.44 (t, J = 60.0 Hz, 1H), 7.88 (s, 1H), 8.24 (s, 1H); ^{19}F NMR δ −95.45 (d, J = 59.8 Hz, 2F); ^{13}C NMR δ 13.1 (br s), 43.6 (br s), 106.9 (t, J = 249.5 Hz), 119.3 (C5), 133.4 (C8), 150.0 (C4), 153.4 (C2), 153.5 (C6); MS m/z 242 (MH$^+$); HRMS (FAB) calcd for $C_{10}H_{13}F_2LiN_5$ [M+Li]$^+$: 248.1299; found: 248.1297.

The 5-*O*-benzoyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl fluoride **17** had: ^{1}H NMR δ 1.34 (s, 3H), 1.48 (s, 3H), 4.36 (dd, J = 6.9, 11.7 Hz, 1H), 4.42 (dd, J = 5.8, 11.8 Hz, 1H), 4.68 (ddt, J = 3.1, 5.9, 6.2 Hz, 1H), 4.83–4.87 (m, 2H), 5.83 (d, J = 61.7 Hz, 1H), 7.45 (t, J = 7.9 Hz, 2H), 7.57 (t, J = 7.6 Hz, 1H), 8.07 (d, J = 8.2 Hz, 2H); ^{19}F NMR δ −115.85 ("d quintet", J = 4.0, 61.6 Hz,); ^{13}C NMR δ 25.1, 26.5, 64.8, 81.2, 85.2 (d, J = 40.6 Hz), 86.6 (d, J = 2.8 Hz), 113.4, 115.5 (d, J = 223.1 Hz), 128.7, 129.7, 130.0, 133.5, 166.3; MS m/z 297 (MH$^+$); HRMS (FAB) calcd for $C_{15}H_{17}FLiO_5$ [M+Li]$^+$: 303.1220; found: 303.1220.

9-(2,3-Di-O-acetyl-5-deoxy-β-D-erythro-pent-4-enofuranosyl)-6-N-benzoyladenine (**18b**). Ac_2O (28 μL, 31 mg, 0.3 mmol) was added to solution of 6-*N*-benzoyl-9-(5-deoxy-β-D-erythro-pent-4-enofuranosyl)adenine [28] (**18a**, 35 mg, 0.1 mmol) in pyridine (2 mL) at 0 °C (ice-bath) and the resulting mixture was stirred overnight at ambient temperature. Volatiles were evaporated in *high-vacuum*

(<5 °C) and the residue was partitioned (1N HCl/H_2O//$CHCl_3$). The separated organic layer was washed with $NaHCO_3$/H_2O, brine, dried (Na_2SO_4), evaporated and column chromatographed (40 → 60% EtOAc/hexane) to give **18b** (37 mg, 85%): ^{1}H NMR δ 2.06 (s, 3H), 2.16 (s, 3H), 4.51 (d, J = 2.9 Hz, 1H), 4.70 (d, J = 2.9 Hz, 1H), 6.04 (t, J = 5.6 Hz, 1H), 6.14 (d, J = 5.6 Hz, 1H), 6.44 (d, J = 5.6 Hz, 1H), 7.48 (t, J = 7.7 Hz, 2H), 7.58 (t, J = 7.7 Hz, 1H), 8.00 (d, J = 7.3 Hz, 2H), 8.16 (s, 1H), 8.76 (s, 1H), 9.32 (s, 1, NH); HRMS calcd for $C_{21}H_{22}N_5O_6$ $[M+H]^+$: 438.1414; found: 438.1422.

9-(2,3-Di-O-acetyl-5-deoxy-β-D-erythro-pent-4-enofuranosyl)-6-N-[(α-difluorometoxy)benzylidene]adenine (**19**). Treatment of **18b** (65 mg, 0.15 mmol) with TFDA (60 μL, 76 mg, 0.30 mmol) as described for **2a**/**2b** [column chromatography (20 → 60% EtOAc/hexane)] gave **19** (49 mg, 68%) as slightly yellow oil: ^{1}H NMR δ 2.09 (s, 3H), 2.17 (s, 3H), 4.53 (d, J = 2.8 Hz, 1H), 4.71 (d, J = 2.7 Hz, 1H), 5.81 (t, J = 5.6 Hz, 1H), 6.03 (d, J = 5.5 Hz, 1H), 6.23 (d, J = 5.7 Hz, 1H), 7.43–7.48 (t, J = 7.8 Hz, 2H), 7.53–7.57 (m, 1H), 7.77 (s, 1H), 8.00 (t, J = 59.4 Hz, 1H), 8.10 (d, J = 7.8 Hz, 2H), 8.24 (s, 1H); ^{19}F NMR δ −101.75 (d, J = 60.0 Hz, 1F), −101.80 (d, J = 60.0 Hz, 1F); ^{13}C NMR δ 20.6, 21.0, 69.6, 72.8, 86.8, 90.5, 108.6 (t, J = 249.6 Hz, 1H), 122.5, 128.7, 130.0, 133.1, 134.7, 139.1, 141.8 (t, J = 3.6 Hz), 144.1, 144.3, 156.1, 169.5, 169.8, 177.1; HRMS calcd for $C_{22}H_{20}F_2N_5O_6$ $[M+H]^+$: 488.1380; found: 488.1380.

Notes: Analogous treatment of **18b** (0.15 mmol) with TFDA in toluene also gave **19** (65%).

9-(5-Deoxy-2,3-O-isopropylidene-β-D-erythro-pent-4-enofuranosyl)-6-N-phthaloyladenine (**20b**). Phthaloyl dichloride (75 μL, 105 mg, 0.52 mmol) was added to a stirred solution of 9-(5-deoxy-2,3-*O*-isopropylidene-β-D-*erythro*-pent-4-enofuranosyl) adenine [23] (**20a**; 75 mg, 0.26 mmol) in pyridine (1.0 mL). After 2 h, the volatiles were evaporated under oil-pump *vacuum* and the residue was partitioned (1% CH_3CO_2H/H_2O//$CHCl_3$). The organic layer was washed ($NaHCO_3$/H_2O//brine), dried (Na_2SO_4), evaporated and chromatographed (0 → 5% MeOH/$CHCl_3$) to give **20b** [24] (82 mg, 76%): UV (MeOH) λ_{max} 276 nm, λ_{min} 245 nm; ^{1}H NMR δ 1.46 (s, 3H), 1.62 (s, 3H), 4.65 (d, J = 2.6 Hz, 1H), 4.69 (d, J = 1.9 Hz, 1H), 5.38 (d, J = 6.0 Hz, 1H), 5.61 (d, J = 6.0 Hz, 1H), 6.37 (s, 1H), 7.81–7.83 (m, 2H), 7.99–8.02 (m, 2H), 8.20 (s, 1H), 9.00 (s, 1H); ^{13}C NMR δ 25.9, 27.0, 79.8, 82.9, 89.6, 91.1, 114.7, 124.7, 130.2, 132.1, 135.2, 144.7, 144.9, 153.1, 153.2, 161.6, 165.7; MS m/z 420 (MH^+); HRMS (ESI) calcd for $C_{21}H_{17}LiN_5O_5$ $[M+Li]^+$: 426.1386; found: 426.1384.

9-[(S)-4,4-C-(1,1-Difluoroethane-1,2-diyl)-2,3-O-isopropylidene-β-D-erythrofuranosyl]-7-difluoromethyl-6-(phthalimido)purine-8(7H,9H)-thione (**21a**) *and 9-[(R)-4,4-C-(1,1-difluoroethane-1,2-diyl)-2,3-O-isopropylidene-β-D-erythrofuranosyl]-8-difluoromethyl-6-N-phthaloyladenine* (**21b**). Treatment [toluene (2.0 mL), overnight] of **20b** (75 mg, 0.18 mmol) with TFDA (0.10 mL, 127 mg, 0.5 mmol, added at the rate of 0.10 mL/h) as described for **2a**/**2b** (column chromatography: 30 → 70% EtOAc/hexane) gave crude **21a** (19 mg, 19%) and **21b** (8 mg, 8%) as yellow oils. Repurification of the crude **21a** (column chromatography: 20 → 50% EtOAc/hexane) gave **21a** [24] (11 mg, 11%): UV (MeOH) λ_{max} 319 nm, λ_{min} 272 nm; ^{1}H NMR δ 1.40 (s, 3H), 1.57 (s, 3H), 1.70 (ddd, J = 5.9, 10.1, 14.8 Hz, 1H), 1.80 (ddd, J = 7.1, 10.3, 15.0 Hz, 1H), 5.32 (d, J = 5.9 Hz, 1H), 5.43 (d, J = 6.1 Hz, 1H), 6.87 (s, 1H), 7.77–7.82 (m, 2H), 7.83 (t, J = 58.2 Hz, 1H), 7.90–7.96 (m, 2H), 8.84 (s, 1H); ^{13}C NMR δ 17.0 (t, J = 10.6 Hz), 25.6, 26.5, 73.6 (t, J = 9.3 Hz), 79.9, 85.0, 90.9, 109.65 (t, J = 281.7 Hz), 109.69 (t, J = 255.9 Hz), 114.2, 124.4, 124.5, 131.7, 131.8, 133.7, 134.7, 135.0, 135.1, 153.1, 154.1, 165.3,165.7, 172.1; ^{19}F NMR δ −99.52 (dd, J = 57.8, 224.1 Hz, 1F), −100.84 (dd, J = 59.0, 223.9 Hz, 1F), −135.01 (ddd, J = 6.2, 15.0, 163.5 Hz, 1F), −143.92 (ddd, J = 6.4, 14.1, 164.1 Hz, 1F); MS m/z 552 (100, MH^+); HRMS calcd for $C_{23}H_{18}F_4N_5O_5S$ $[M+H]^+$: 552.0959; found: 552.0957.

Repurification of the crude **21b** (column chromatography: 20 → 50% EtOAc/hexane) gave **21b** (6 mg, 6%): UV (MeOH) λ_{max} 278 nm, 302 nm (sh), 321 nm (sh), λ_{min} 259 nm; ^{1}H NMR δ 1.38 (s, 3H), 1.52 (s, 3H), 1.70 (ddd, J = 6.0, 10.2, 14.7 Hz, 1H), 1.79 (ddd, J = 6.8, 10.2, 14.8 Hz, 1H), 5.20 (d, J = 6.0 Hz, 1H), 5.37 (d, J = 6.0 Hz, 1H), 6.28 (s, 1H), 7.18 (t, J = 57.1 Hz, 1H), 7.77–7.94 (m, 4H), 8.79 (s, 1H); ^{19}F NMR δ −98.82 ("dm" J = 58.4 Hz, 2F), −135.48 (ddd, J = 6.1, 14.7 Hz, 163.7 Hz, 1F), −144.45 (ddd, J = 6.8, 14.4, 163.6 Hz, 1F); ^{13}C NMR δ 17.2 (t, J = 11.0 Hz), 25.6, 26.4, 72.8 (t, J = 10.7 Hz), 79.4, 84.6, 87.6, 107.2 (t, J = 247.2 Hz), 109.8 (t, J = 285.6 Hz), 114.1, 117.2, 123.6, 124.4, 131.8, 134.4, 134.9, 149.6, 151.3, 153.7, 165.3, 165.6; HRMS (ESI) calcd for $C_{23}H_{17}F_4LiN_5O_5$ $[M+Li]^+$: 526.1320; found: 526.1328.

5′-O-Benzoyl-2′,3′-O-isopropylidene-6-N-phthaloyladenosine (**22b**). BzCl (36 μL, 44 mg, 0.31 mmol) was added to a stirred solution of 2′,3′-*O*-isopropylidene-6-*N*-phthaloyladenosine [29] (**22a**, 120 mg, 0.27 mmol; prepared by standard protection of 6-*N*-phthaloyladenosine [22] with acetone) in pyridine (3 mL) at 0 °C. After 16 h, the volatiles were evaporated and the residue was partitioned (1N HCl/H_2O//$CHCl_3$). The organic layer was separated and was washed ($NaHCO_3$/H_2O//brine), dried (Na_2SO_4), evaporated and chromatographed (30 → 70% AcOEt/hexane) to give **22b** (110 mg, 74%) as a white foam: UV (MeOH) λ_{max} 275 nm, λ_{min} 255 nm; ^{1}H NMR δ 1.37 (s, 3H), 1.63 (s, 3H), 4.52 (dd, J = 6.6, 13.1 Hz, 1H), 4.63–4.67 (m, 2H), 5.17 (dd, J = 3.2, 6.3 Hz, 1H), 5.53 (dd, J = 2.3, 6.3 Hz, 1H), 6.21 (d, J = 2.3 Hz, 1H), 7.37 (t, J = 7.9 Hz, 2H), 7.52 (t, J = 7.5 Hz, 1H), 7.79–7.83 (m, 2H), 7.89 (d, J = 7.5 Hz, 2H), 7.97–8.01 (m, 2H), 8.28 (s, 1H), 8.97 (s, 1H); ^{13}C NMR δ 25.4, 27.3, 64.2, 81.5, 84.3, 85.1, 91.6, 115.1, 124.5, 125.4, 128.6, 129.4, 129.7, 130.3, 132.0, 133.5, 135.0, 144.7, 144.9, 152.8, 153.1, 165.6, 166.1; MS m/z 542 (MH^+). Anal. calcd for $C_{28}H_{23}N_5O_7$ (541.51): C, 62.10; H, 4.28; N, 12.93. Found: C, 61.86; H, 4.56; N, 12.61.

9-(5-O-Benzoyl-2,3-O-isopropylidene-β-D-ribofuranosyl)-7-difluoromethyl-6-(phthalimido)purine-8(7H,9H)-thione (**23**). Treatment [toluene (1.5 mL), NaF (1.4 mg, 0.03 mmol), 120 °C (oil bath), 8 h] of **22b** (40 mg, 0.07 mmol) with TFDA (0.24 mL, 305 mg, 1.22 mmol, at the rate of 0.05 mL/h) as described for **2a**/**2b** [column chromatography, 20 → 60% EtOAc/hexane] gave recovered **22b** (16 mg, 40%), **23** (8 mg, 18%) and **17** (7 mg, 32%): compound **23** had: UV (MeOH) λ_{max} 320 nm, λ_{min} 276 nm; ^{1}H NMR δ 1.37 (s, 3H), 1.63 (s, 3H), 4.51–4.57 (m, 2H), 4.67–4.74 (m, 1H), 5.25 (dd, J = 4.6, 6.4 Hz, 1H), 5.55 (dd, J = 2.1, 6.5 Hz, 1, H), 6.88 (d, J = 2.2 Hz, 1H), 7.44 (t, J = 7.4 Hz, 2H), 7.56 (t, J = 7.5 Hz, 1H), 7.74–7.87 (m, 2H), 7.92 (t, J = 58.1 Hz, 1H), 7.98–8.02 (m, 2H), 8.05 (d, J = 8.3 Hz, 2H), 8.75 (s, 1H); ^{19}F NMR δ −99.7 (dd, J = 58.2, 224.1 Hz, 1F), −100.6 (dd, J = 58.1, 224.1 Hz, 1F); ^{13}C NMR δ 25.7, 27.6, 64.1, 81.5, 83.1, 85.2, 89.8, 109.8 (t, J = 252.0 Hz), 115.5, 123.7, 124.6, 124.7, 128.6, 129.1, 130.0, 132.03, 132.05, 133.4, 134.9 (d, J = 1.4 Hz), 135.0, 135.2, 153.4, 154.2, 165.7, 166.40, 166.45, 172.0; MS m/z 624 (MH^+); HRMS calcd for $C_{29}H_{25}F_2N_5O_7S$ $[M+H]^+$: 624.1359; found: 624.1358.

Methyl-3,5-di-O-(4-chlorobenzyl)-2-deoxy-(R)-2,2-C-(1,1-difluoroethane-1,2-diyl)-α-D-erythro-pentofuranoside (**25a**) *and 3,5-di-O-(4-chlorobenzyl)-2-deoxy-(S)-2,2-C-(1,1-difluoroethane-1,2-diyl)-α-D-erythro-pentofuranose* (**25b**). Treatment [benzene (2.0 mL), 80 °C, 5 h] of methyl-3,5-di-*O*-(4-chlorobenzyl)-2-deoxy-2-methylene-β-D-ribofuranoside [25] **24** (150 mg, 0.37 mmol) with TFDA [(0.3 mL, 380 mg, 1.5 mmol; added at the rate of 0.15 mL/h], as described for **2a**/**2b**, gave **25a**(2*R*) (51 mg, 30%) and **25b**(2*S*) (8 mg, 5%): compound **25a**: ^{1}H NMR δ 1.58–1.65 (m, 2H), 3.40 (s, 3H), 3.50 (dd, J = 3.3, 10.9 Hz, 1H), 3.53 (dd, J = 3.3, 10.9 Hz, 1H), 3.92 (d, J = 5.4 Hz, 1H), 4.32 ("q", J = 4.2 Hz, 1H), 4.42 (s, 2H), 4.47 (s, 2H), 4.76 (s, 1H), 7.14–7.27 (m, 8H); ^{19}F NMR δ −135.17 (ddd, J = 7.1, 10.3, 154.0 Hz, 1F), −135.90 (ddd, J = 6.6, 11.7, 154.3 Hz, 1F); ^{13}C NMR δ 14.4 (t, J = 10.9 Hz), 39.7 (t, J = 9.9 Hz), 55.3, 69.6, 71.8, 74.6, 77.1, 82.2, 102.6 (d, J = 4.8 Hz), 111.7 (t, J = 285.0 Hz), 128.5, 128.6, 129.1, 129.2, 133.6, 133.6, 136.1, 136.2; HRMS calcd for $C_{22}H_{23}{}^{35}Cl_2F_2O_4$ $[M+H]^+$: 459.0942; found: 459.0948. Compound **25b**: ^{1}H NMR δ 1.54 ("ddd",

J = 6.5, 10.7, 11.4 Hz, 1H), 1.61 ("ddd", J = 5.7, 10.7, 11.0 Hz, 1H), 3.43 (dd, J = 4.5, 10.6 Hz, 1H), 3.49 (dd, J = 4.1, 10.6 Hz, 1H), 3.89 (d, J = 5.7 Hz, 1H), 4.34 ("q", J = 4.6 Hz, 1H), 4.32–4.43 (m, 3H), 4.67 (d, J = 12.0 Hz, 1H), 4.96 (s, 1H), 7.12–7.23 (m, 8H); ^{19}F NMR δ −135.09 (ddd, J = 6.3, 10.5, 154.3 Hz, 1F), −135.76 (ddd, J = 6.8, 12.0, 154.3 Hz, 1F); ^{13}C NMR δ 14.5 (t, J = 10.9 Hz), 39.6 (t, J = 9.9 Hz), 68.2, 69.3, 71.7, 72.3, 82.1, 100.7 (d, J = 4.1 Hz), 111.7 (t, J = 285.0 Hz), 128.62, 128.64, 129.0, 129.2, 129.3, 133.5, 133.6, 136.1, 136.3; HRMS calcd for $C_{21}H_{21}{}^{35}Cl_2F_2O_4$ $[M+H]^+$: 445.0785; found: 445.0788.

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