JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • Publication Date (Web): 23 Jan 2015

Synthesis of 2,3-Dideoxy-2-fluoro-2,3-*endo*-methylene- and 2,3-Dideoxy-2-fluoro-3-*C*-hydroxymethyl-2,3-*endo*-methylene-pentofuranoses and Their Use in the Preparation of Conformationally Locked Bicyclic Nucleosides

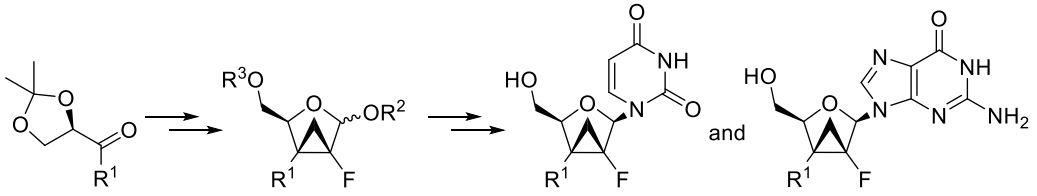
Rob Clarkson,[†] Zofia Komsta,*[,†] Benjamin A. Mayes,*[,‡] Adel Moussa,[‡] Montserrat Shelbourne,[†] Alistair Stewart,[‡] Andrew J. Tyrrell,[†] Laura L. Wallis,[†] Alexander C. Weymouth-Wilson[†]

[†]Dextra, Science and Technology Centre, Earley Gate, Whiteknights Road, Reading, RG6 6BZ, UK and [‡]Idenix Pharmaceuticals, 320 Bent Street, Cambridge, MA 02141, USA.

E-mail: zofia.komsta@dextrauk.com (Z. Komsta), mayes.ben@idenix.com (B. Mayes)

ABSTRACT

Construction of protected 2,3-dideoxy-2-fluoro-2,3-*endo*-methylene-pentofuranoses from D-glyceraldehyde and 2,3-dideoxy-2-fluoro-3-*C*-hydroxymethyl-2,3-*endo*-methylene-pentofuranoses from D-isoascorbic acid, via Simmons-Smith type stereoselective cyclopropanations on the respective fluoroallyl alcohols is described. Synthesis of the corresponding conformationally locked sugar modified uridine and guanosine nucleosides was achieved via Vorbrüggen or Mitsunobu methodologies. Stereochemical confirmation of the novel nucleosides was performed on the basis of 2D NOESY NMR experiments. Analysis of 2′,3′-dideoxy-2′-fluoro-3′-*C*-hydroxymethyl-2′,3′-*endo*-methylene-uridine by X-ray crystallography yielded the principal conformational parameters and indicated the furanoid ring adopted a $^{o}E/^{o}T_1$, East pucker. The uridine and guanosine nucleosides were found to be inactive in the hepatitis C virus (HCV) cell-based replicon assay, which was corroborated on examination of the corresponding nucleoside triphosphates against the HCV NS5B polymerase.



R^1 = H or CH_2OH

INTRODUCTION

Structurally diverse sugar modified nucleosides continue to be investigated for their pharmacological potential, upon which ostensibly minor compositional or configurational alterations may have a substantial impact.[1] The substitution of hydrogen or a hydroxyl group in the

furanose ring by fluorine is one such modification which, either alone or in combination with other features, has provided a range of biologically active nucleosides,[2] exemplified by the naturally occurring 4′-fluorinated antibiotic nucleocidin **1**,[3] the 2′-fluorinated antitumor agents gemcitabine **2**[4] and clofarabine **3**[5] and by the first direct acting antiviral approved for the treatment of chronic hepatitis C virus (HCV) infection, sofosbuvir **4**, a monophosphate prodrug of 2′-deoxy-2′-fluoro-2′-methyluridine (Figure 1A).[6]

Sugar modification by introduction of a fused ring system to provide conformational restriction is well established: the resultant 'locked' bicyclic nucleosides have been exploited in the context of antisense oligonucleotides, short interfering RNA and in the design of potential antiviral agents.[7]

With respect to herpes simplex virus (HSV) and human immunodeficiency virus (HIV), Marquez *et al.* have described the divergent preferences, South and North respectively (as described by the pseudorotational cycle), of various host and viral kinases versus cellular DNA- and viral RNA-dependent DNA polymerases (reverse transcriptase) with regard to sugar ring conformation.[8] Based on structural similarities between the catalytic domains of the HIV reverse transcriptase and HCV RNA-dependent RNA polymerase (RdRp),[9] these sugar conformational preferences are anticipated to be broadly similar. Interestingly, in the case of HCV, examples of both Southern-type bicyclic systems, bearing a 3′,4′-oxetane (C2′-*endo*) **5**,[10] and Northern-type 2′-*O*,4′-*C*-methylene bridged ribonucleoside analogs (C3′-*endo*) **6**,[11] have demonstrated activity at the nucleoside triphosphate (NTP) level against the HCV NS5B RdRp, however both suffered from inefficient phosphorylation cascades (Figure 1B).

2′,3′-Dideoxy-2′,3′-*exo*- and 2′,3′-*endo*-methylene nucleosides (2′,3′-cyclopropane nucleosides) are a relatively underexplored class of ring fused sugar modified system, wherein their respective O4′-*exo* (West) and O4′-*endo* (East) furanose ring conformations represent intermediates between the conventional C3′-*endo* (North) and C2′-*endo* (South) pseudorotational cycle antipodes (Figure 1B).[12] Of the three 2′,3′-dideoxy-2′,3′-*exo*-methylene (α-cyclopropane) nucleosides with natural pyrimidine bases, only the cytidine **7** was found to possess weak inhibitory activity against HIV,[13] whereas the analogs bearing a 2′,3′-cyclopropane in the β-orientation (2′,3′-*endo*-methylene) **8** were found to be devoid of anti-HIV activity.[14] No further furanose functionalization has been reported for the 2′,3′-*endo*-methylene nucleosides beyond these initial reports.

In contrast, sugar modified nucleosides incorporating a 3′-*C*-hydroxymethyl group have been investigated with respect to a broad range of potential therapeutic applications; as antiviral (HIV),[15] antimicrobial (*Mycobacterium tuberculosis*)[16] and anticancer (lymphoblastic leukemia)[17] agents (**9**-**11** Figure 1C). Furthermore, combination of a 3′-*C*-hydroxymethyl and 2′-*arabino*-fluoro substitution provided a pyrimidine nucleoside (**12**) with antiviral activity against both HIV and hepatitis B virus (HBV).[18]

Notwithstanding the recent regulatory approval of sofosbuvir for the treatment of chronic HCV, the search for novel sugar modified nucleoside inhibitors of HCV NS5B RdRp continues.[19] In this regard, and as part of a wider program to investigate novel, functionalized nucleosides with a high degree of structural diversity, the synthesis of a series of bicyclic systems was undertaken based on the 2′,3′-dideoxy-2′,3′-*endo*-methylene-2′-fluoro motif, either with or without a 3′-*C*-hydroxymethyl moiety **13**-**16**, which were anticipated to adopt a relatively atypical East sugar ring conformation (Figure 1D). The synthesis and structural confirmation of the respective uridine and guanosine analogs thereof are described herein, along with their antiviral activity against HCV.

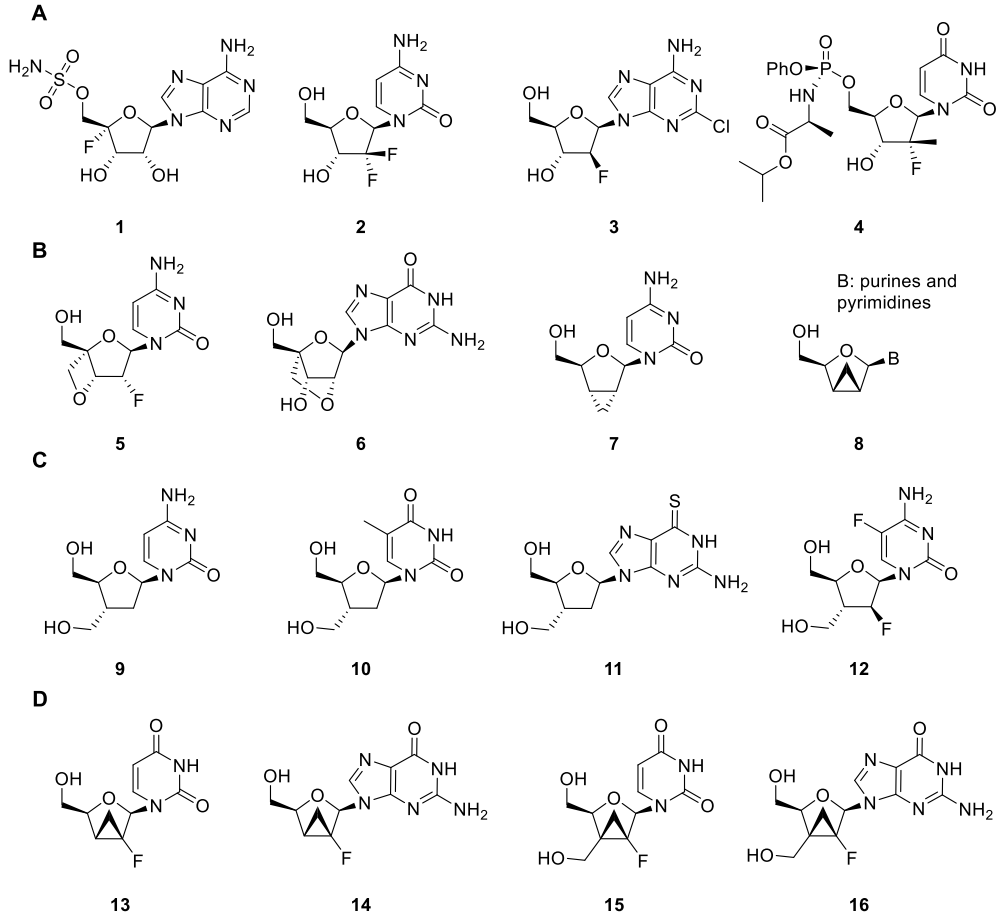


Figure 1. (A) Examples of therapeutic nucleosides bearing sugar ring fluorine substitutions; nucleocidin **1**, gemcitabine **2**, clofarabine **3**, sofosbuvir **4**. (B) Examples of conformationally restricted bicyclic nucleosides; 3′,4′-oxetane **5**, 2′-*O*,4′-*C*-methylene bridged **6**, 2′,3′-dideoxy-2′,3′-*exo*-methylene **7**, 2′,3′-dideoxy-2′,3′-*endo*-methylene **8**. (C) Examples of biologically active 3′-deoxy-3′-*C*-hydroxymethyl nucleosides; antiviral **9**, antimicrobial **10**, anticancer **11**, antiviral **12**. (D) Target uridine and guanosine 2′,3′-dideoxy-2′,3′-*endo*-methylene-2′-fluoro nucleosides **13**-**16**.

RESULTS AND DISCUSSION

Uridine and guanosine nucleosides **13**, **14** and **15**, **16** were approached using a similar synthetic strategy, via the respective bicyclic pentofuranoses bearing either 2-fluoro-2,3-*endo*-methylene or 2-fluoro-3-*C*-hydroxymethyl-2,3-*endo*-methylene substituents (Figure 2). Analogous construction of a [3.1.0]-bicyclic system was reported for the non-fluorinated 2,3-dideoxy derivative.[14]

The key transformations en route to the *endo*-methylene furanoses **c** were determined to be the stereoselective Simmons-Smith cyclopropanations of vinyl fluorides **a**. Subsequent glycosylations with persilylated nucleobases were then anticipated to provide the conformationally locked target nucleosides.

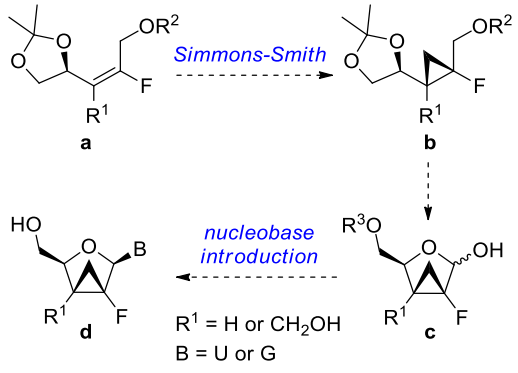
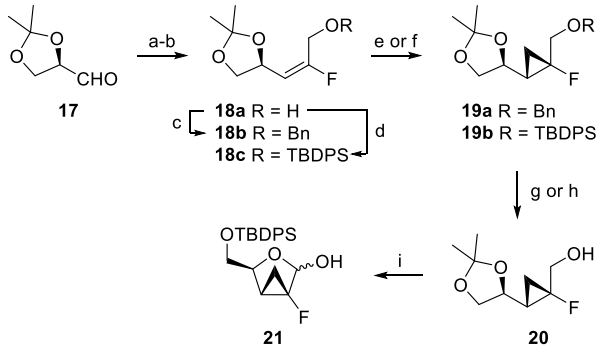


Figure 2. Synthetic strategy towards bicyclic nucleosides **d** via 2-fluoro-2,3-*endo*-methylene-pentofuranose scaffold **c**.

Synthesis of **13** and **14** began with the formation of fluoroallyl alcohol **18a**, in two steps from D-glyceraldehyde following literature procedures.[20,21] (Scheme 1). Initially, work focused on optimization of the precedented Simmons-Smith type cyclopropanation of the benzylated derivative **18b**.[20b,22] The reaction resulted in the formation of the desired cyclopropane **19a** in a highly diastereoselective manner, however, the requirement for a large excess of $ZnEt_2$ (>2.5 equivalents), irreproducible yields, modest conversions (30–40%) and a complex impurity profile rendered this method unsuitable for scale up. Therefore, the trifluoroacetic acid activated reagent developed by Shi was investigated,[23] which proved to be more reliable and efficient, requiring only 1.1 equivalents of $ZnEt_2$ for the complete consumption of the starting material. On 33 g scale **19a** was obtained in 59% yield as a single diastereoisomer. It was, however, observed that the benzylated fluoroallyl alcohol **18b** slowly degraded upon storage at room temperature and thermal analysis by differential scanning calorimetry (DSC) revealed a sharp exothermic onset at 71 ºC. In pursuit of a safer synthesis, cyclopropanation of the more thermally stable silyl protected derivative **18c** was investigated. Furukawa's conditions[24] with 1.5 eq of $ZnEt_2$ reproducibly furnished **19b** in 58% yield on 10 g scale. The Shi modification also proved to be reliable, but lower yielding (48%) due to the partial removal of the TBDPS protecting group.

In similar fashion to the non-fluorinated analog,[14] alcohol **20**, obtained by deprotection of **19a** or **19b**, was transformed into the 2-fluorolactol **21** (anomeric ratio β/α = 1/8, determined by ^{1}H NMR spectroscopy) in 50% yield over three steps (Scheme 1).

Scheme 1

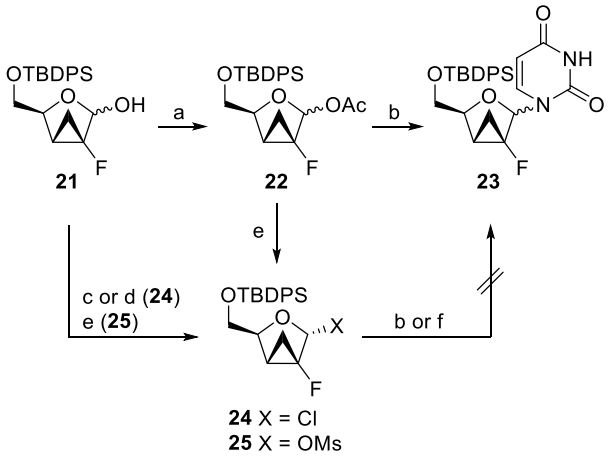


Conditions: (a) triethyl 2-fluoro-2-phosphonoacetate, NaHMDS, THF, −78 °C (47%); (b) DIBAL-H, Et_2O, −78 °C; (c) BnBr, NaH, DMF, 0 °C to rt (85%, 2 steps); (d) TBDPSCl, imidazole, THF, 45 °C (92%, 2 steps); (e) $ZnEt_2$, TFA, CH_2I_2, CH_2Cl_2, 0 °C (59% of **19a**); (f) $ZnEt_2$, CH_2I_2, CH_2Cl_2, 0 °C (58% of **19b**); (g) H_2, Pd/C, MeOH, rt (84%); (h) TBAF, THF, rt (99%); (i) i. $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then NEt_3, −78 °C to rt, ii. 0.1 M aq HCl, 1,4-dioxane, iii. TBDPSCl, py, CH_2Cl_2 (50%, 3 steps).

Post acetylation of the anomeric hydroxyl, the acetate **22** was coupled with silylated uracil under Vorbrüggen conditions[25] in anhydrous CH_3CN, using TMSOTf as an activator (Scheme 2). The reaction required elevated temperatures, possibly due to both the deactivating effect of the fluorine on the anomeric position and steric hindrance imparted by the bulky TBDPS group and the β-cyclopropane moiety. The desired nucleoside **23** was obtained in a favorable 8:1 mixture of β:α anomers, however, in a disappointingly low 12% yield. Attempts to improve the reaction of the glycosyl acetate **22** by varying the temperature, activator and solvent were unsuccessful, prompting investigation of alternate coupling approaches. Treatment of the lactol **21** with methanesulfonyl chloride and triethylamine resulted in the clean formation of the α-chloro sugar **24**, rather than the mesylate **25** (Scheme 2). The formation of an anomeric chloride byproduct upon anomeric mesylation has been similarly observed with 2-deoxy-2-fluoro-ribose and arabinose derivatives.[26] The chloride **24** was also formed directly from the acetate **22** via reaction with HCl/Et_2O and although **24** was stable to aqueous workup and prolonged storage at 2-8^o C without significant decomposition, it was observed to readily hydrolyze on silica gel to lactol **21**. Mesylation of the anomeric position was achieved by treatment of lactol **21** with Ms_2O and NEt_3, however, the product **25** was significantly less stable than the respective chloride and almost completely hydrolyzed upon subjecting to an aqueous workup (pH neutral). Interestingly, in contrast to the reported non-fluorinated analog,[14] neither the chloride nor the mesylate (in both cases the resulting

material was used in crude form) appeared to form the desired nucleoside when treated with silylated uracil in an S_N2-type or Vorbrüggen-type condensation.

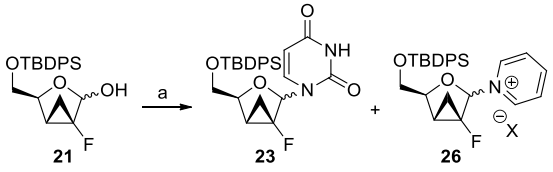
Scheme 2



Conditions: (a) Ac_2O, py (99%, β:α = 1:8); (b) persilylated uracil, TMSOTf, CH_3CN, 80 °C (12%, β:α = 8:1); (c) MsCl, NEt_3, CH_2Cl_2, 0 °C (crude **24**); (d) HCl, 1,4-dioxane (crude **24**); (e) Ms_2O, NEt_3, CH_2Cl_2, 0 °C (crude **25**) (f) persilylated uracil, $CHCl_3$, rt.

When lactol **21** was treated with MsCl in the presence of both NEt_3 and pyridine, gradually a multicomponent mixture was formed, consisting mainly of chloride **24** and pyridinium-type adduct **26** (Scheme 3). After aqueous $CuSO_4$ workup to remove excess pyridine, the crude mixture was coupled with silylated uracil under Vorbrüggen-type conditions[25] using TMSOTf as an activator in anhydrous 1,2-DCE, providing desired uridine **23** in 45% yield (over two steps) as a 4:1 β:α mixture of anomers.[27] Approximately 20% of the glycosylpyridinium adduct **26** bearing the triflate counter-anion was also isolated from the reaction.[28]

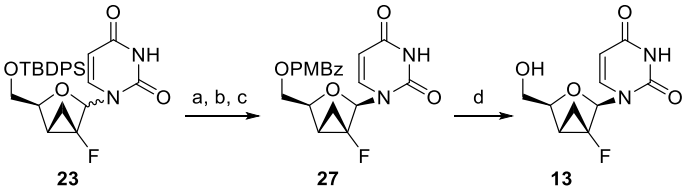
Scheme 3



Conditions: (a) i. MsCl, NEt_3, py, CH_2Cl_2, rt, ii. persilylated uracil, TMSOTf, 1,2-DCE, 90 °C (45% over 2 steps, β:α = 4:1).

Anomers of the 5′-silyl protected uridine analog **23** were inseparable at this stage using traditional purification techniques, however, the clean β-anomer was isolated via recrystallization after switching protecting groups to the more crystalline 5′-*p*-methoxybenzoyl ester **27** (Scheme 4). Target 2′,3′-dideoxy-2′,3′-*endo*-methylene-2′-fluorouridine **13** was obtained in 92% yield after deprotection using NaOMe in MeOH. Stereochemical investigation was performed by 2D NOESY NMR spectroscopy and NOE correlations from H-1′ to H-4′, H-3′ to H-4′ and correlation between one of the methylene protons of the cyclopropane ring and the uracil H-6 proton indicated their respective close spatial relationships and confirmed the desired 2′,3′-*endo*-methylene and β-anomeric configuration (Figure 3).

Scheme 4



Conditions: (a) TBAF, THF, rt; (b) *p*-MeOBzCl, py (80% over 2 steps, β:α = 4:1); (c) crystallization from EtOAc to obtain pure β (73% recovery of β anomer); (d) NaOMe, MeOH, rt (92%).

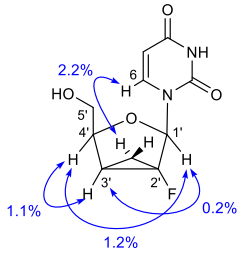
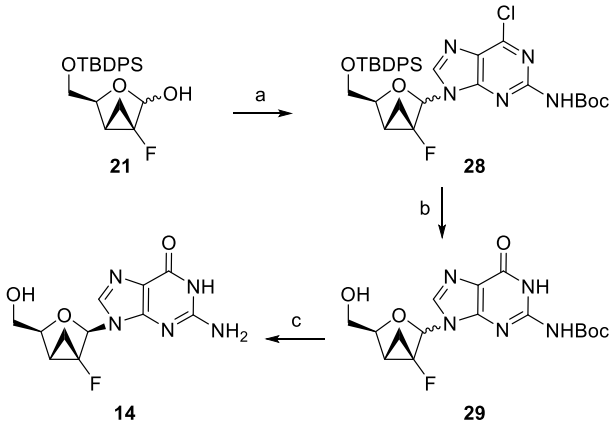


Figure 3. Confirmation of **13** stereochemistry by 2D NOESY NMR spectroscopy (400 MHz). NOE correlations reported from extracted 1D data sets.

Synthesis of the corresponding 2′,3′-dideoxy-2′,3′-*endo*-methylene-2′-fluoroguanosine **14** was initially attempted under conditions previously successful for the uridine analog. Thus, lactol **21** was treated with MsCl, NEt_3 and pyridine, and after aqueous workup the crude mixture was reacted with silylated 2-*N*-acetyl-6-*O*-diphenylcarbamoylguanine (Robins' reagent[29]) in the presence of TMSOTf. The desired guanosine product was obtained in only 12% yield as a 1.3:1 mixture of β:α anomers. Alternatively, utilizing the acetate donor **22** under analogous conditions did not furnish any nucleoside. Installation of the purine moiety was, however, more efficiently achieved via condensation of lactol **21** (1:8 mixture of β:α anomers) with *N*-Boc-2-amino-6-chloropurine under Mitsunobu conditions. Purine nucleoside **28** was obtained in 58% yield as an 8:1 mixture of β:α anomers. Treatment of **28** with the sodium salt of 3-hydroxypropionitrile[30] to effect S_NAr displacement of the chloride moiety followed by β-elimination of the acrylonitrile resulted in

formation of the protected guanosine **29** in moderate yield (55%). Conveniently, the TBDPS protecting group was also cleanly removed under the reaction conditions and, after isolation, **29** was obtained in a 10:1 β:α anomeric mixture. Removal of the Boc protection in **29** was accomplished with AcOH, however, it was necessary to stop the reaction prior to completion to minimize acid-induced product degradation. Alternative deprotection conditions were also investigated using HCl/MeOH and TFA/H_2O mixtures, however, in all cases low product yields and/or poor recovery of starting material were obtained. After removal of the Boc moiety, sequential desalting using basic resin and trituration with MeOH provided guanosine **14** as the clean β anomer (16% yield of pure β-anomer over 2 steps). As with uridine analog **13**, the stereochemical assignment of the final compound was made on the basis of 2D NOESY NMR spectroscopy (Figure 4). Correlation between H-1′ to H-4′, H-3′ to H-4′ and between one of the methylene protons of the cyclopropane ring and the guanine H-8 proton confirmed the required 2′,3′-*endo*-methylene and β-anomeric configuration.

Scheme 5



Conditions: (a) PPh_3, 2-NHBoc-6-Cl-purine, DIAD, THF, rt (β:α = 8:1, 58%); (b) NaH, 3-hydroxypropionitrile, THF 0 °C to rt (β:α = 10:1, 55%); (c) i. AcOH, 90 °C (β:α = 10:1, 34% of **14** and 28% recovery of **29**), ii. trituration from MeOH to obtain pure β (47% recovery).

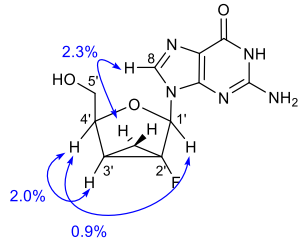
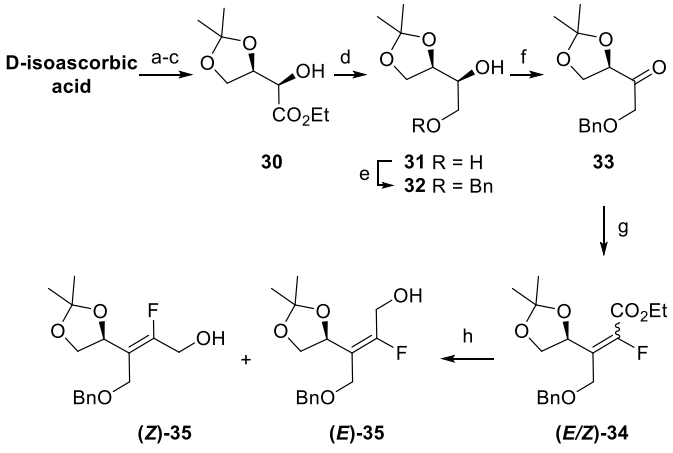


Figure 4. Confirmation of **14** stereochemistry by 2D NOESY NMR spectroscopy (400 MHz). NOE correlations reported from extracted 1D data sets.

Synthesis of the 3′-*C*-hydroxymethyl analogs **15** and **16** started with readily available D-isoascorbic acid, which was transformed into the ethyl ester **30** in three steps according to published procedures (Scheme 6).[31] Reduction to diol **31** was achieved cleanly with $NaBH_4$ in EtOH at room temperature, conditions to which most esters remain unreactive, presumably facilitated by close proximity of the hydroxyl group to the alkoxycarbonyl in **30**.[32] The crude diol **31** was treated with Bu_2SnO in refluxing MeOH and the resulting stannylene acetal was opened with BnBr in the presence of TBAI to effect benzyl protection with 4:1 selectivity for the desired primary over secondary hydroxyl.[33] The appropriately protected D-erythritol **32** was isolated in 30% yield over six steps from D-isoascorbic acid, with only a single purification step required.

Oxidation to the corresponding D-erythrulose **33** was initially performed using Dess-Martin periodinane then switched to the more cost effective Swern conditions on larger scale (Scheme 6). Subsequent formation of the fluorinated alkene isomers **34** was achieved via Horner–Wadsworth–Emmons (HWE) olefination with triethyl 2-fluoro-2-phosphonoacetate.[20,34] The exact identity and ratio of geometric isomers obtained was established at the subsequent allyl alcohol **35**, *vide infra*. Accordingly, it was determined that selectivity of the HWE reaction favored **(*Z*)-34** over **(*E*)-34**. The best selectivity of ~1.8:1 (*Z*):(*E*) was achieved when the least chelating potassium base (KHMDS) was used, in comparison with 2.8:1 for NaHMDS and 4:1 for *n*-BuLi. After workup, the crude **34** mixture was telescoped. The next step, ester reduction, was performed using $NaBH_4$, LiCl and EtOH in THF. The *cis*/*trans* isomers were separated at this stage using column chromatography and the desired **(*E*)-35** was isolated in 24% yield over three steps (47% for the **(*Z*)-35** isomer).

Scheme 6



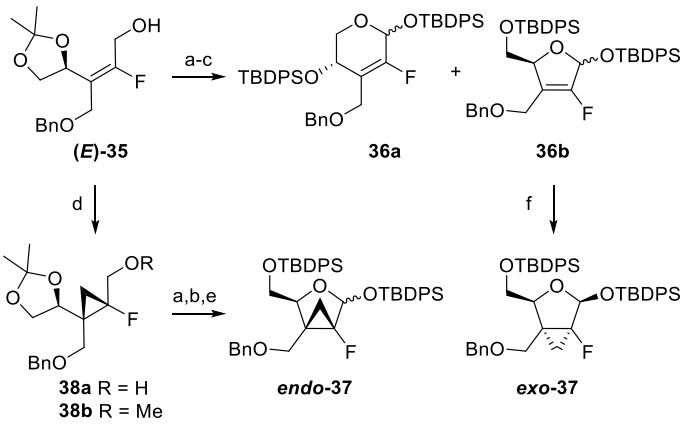
Conditions: (a) Amberlyst 120 H^+, acetone, reflux then NEt_3; (b) H_2O_2, K_2CO_3, H_2O, 0°C to rt; (c) EtI, MeCN, reflux; (d) $NaBH_4$, EtOH, rt; e) i. Bu_2SnO, MeOH, reflux; ii. BnBr, TBAI, PhMe, reflux (30% yield from D-isoascorbic acid); (f) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then NEt_3, −78

°C to rt; (g) triethyl 2-fluoro-2-phosphonoacetate, KHMDS, THF, −78 °C (1.8:1 *Z*:*E* ratio); (h) $NaBH_4$, LiCl, EtOH, THF, rt (47% **(*Z*)-35** and 24% **(*E*)-35** over 3 steps).

To confirm the desired *trans* stereochemistry of the minor isomer **(*E*)-35**, and by extension precursor **34**, the compound was cyclized in a three step process, which would have been sterically unfeasible with the isomeric alkene **(*Z*)-35** (Scheme 7). The alcohol was first oxidized using Dess-Martin periodinane and then treated with acid to remove the acetonide. Protection as the *t*-butyldiphenylsilyl (TBDPS) ethers was then accomplished using imidazole in THF.[36] Two cyclic systems were isolated, the di-silylated furanose **36b** (17% yield over 3 steps, 4:1 mixture of β:α anomers) and the di-silylated pyranose **36a** (60% yield over 3 steps, 6:1 mixture of anomers[37]), thus establishing the identities of the respective geometric isomers at the prior olefination.

Furanose **36b** is a potential substrate for cyclopropanation. In recent work we have demonstrated the possibility of high yielding and stereoselective Simmons-Smith-type cyclopropanation performed at the non-fluorinated 2,3-positions of a carbohydrate furanose ring system.[38] The *endo*-stereoselectivity of the reaction was attributed to chelation of the zinc carbenoid species to the oxygen atoms at C5OBn and/or C1OBn, directing the methylene group onto the same (β) face of the ring. Fluorine-substituted olefins are generally regarded as deactivated substrates for Simmons-Smith reactions due to their reduced electron density.[20a] Therefore, the presence of the 2-fluoro substituent as well as the sterically hindered environment caused by the large silyl groups in **36b** was anticipated to be problematic for the successful installation of a methylene moiety. The standard Furukawa ($ZnEt_2/CH_2I_2$)[24] and Shi ($ZnEt_2/CH_2I_2/CF_3CO_2H$)[23] conditions did not promote cyclopropanation and only a reaction performed using the procedure established by Denmark,[39] with $ZnEt_2$ and chloroiodomethane in 1,2-DCE, gave the bicyclic product **37** as a single undesired *exo*-diastereoisomer in a good yield (55%). Stereochemical investigation was performed by 2D NOESY NMR spectroscopy and NOE correlation between H-4 and the one of the CH_2 protons of the cyclopropane ring (NOE of 1.2% at 400 MHz) indicated their close spatial relationship. It is feasible that the high stereoselectivity of the reaction was driven by the steric hindrance and lack of oxygen chelation on the β-face of the ring. In contrast, the pyranose derivative **36a** appeared unreactive to any of the aforementioned cyclopropanation conditions.

Scheme 7

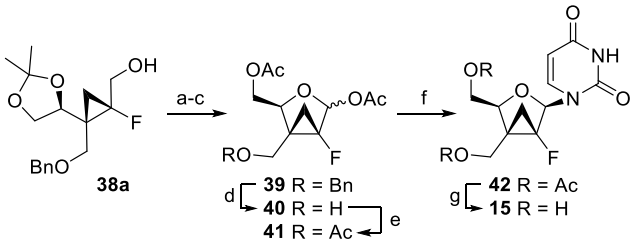


Conditions: (a) Dess-Martin periodinane, CH_2Cl_2, rt; (b) 0.1 M aq HCl, 1,4-dioxane; (c) TBDPSCl, imidazole, THF, rt (over 3 steps: 1:6 mixture of β:α; **36b** 17%, 4:1 mixture of β:α and **36a** 60%, 6:1 mixture of anomers); (d) 1 M $ZnEt_2$ in hexanes, CH_2I_2, CH_2Cl_2, 0 °C to rt (47% for **38a** dr = 50:10 and 10% for **38b**); (e) TBDPSCl, imidazole, THF, rt (over 3 steps: ***endo*-37** 50%) (f) 1 M $ZnEt_2$ in hexanes, $ClCH_2I$, 1,2-DCE, −10 °C to rt (55%, only β anomer isolated).

Based on the formation of the undesired *exo*-methylene on cyclopropanation of dihydrofuran **36b**, the methodology utilized previously in the synthesis of lactol **21** was pursued. Thus, the alkene **(*E*)-35** was protected with TBDPSCl in pyridine and then submitted to various cyclopropanation conditions; Furukawa ($ZnEt_2/CH_2I_2$),[24] Denmark ($ZnEt_2/ICH_2Cl$)[39] and Shi ($ZnEt_2/CH_2I_2/CF_3CO_2H$).[23] None of the tested reactions were successful and only unchanged starting material was recovered in each case. It was, however, observed that reaction of the *unprotected* allyl alcohol **(*E*)-35** under Furukawa's conditions did lead to formation of the cyclopropane **38a** with 5:1 diastereoselectivity, favoring the desired (2*R*,3*R*) product (Scheme 7).[40] Unexpectedly, aqueous quenching of the reaction was accompanied by significant methylation of the hydroxyl group in both the product as well as the unreacted alkene. To minimize formation of the methyl ethers, a reverse quenching procedure was implemented. The reaction mixture was transferred via cannula into a vigorously stirred biphasic mixture of EtOAc and aqueous NH_4Cl. The yield of the desired cyclopropane **38a** ranged between 35–47%, with formation of the methyl ether **38b** at 10–20% and recovery of the starting material **(*E*)-35** at 10–20%.[41] After oxidation of **38a** to the corresponding aldehyde using Dess-Martin periodinane and acid catalyzed removal of the acetonide, the ring was closed exclusively to the di-silylated furanose ***endo*-37** using TBDPSCl and imidazole in THF (1:6 β:α anomer ratio) in good yield (50% over three steps).[42] To the best of our knowledge these are the first reported examples of such 2-fluoro-3-*C*-hydroxymethyl functionalized bicyclic furanoses (Scheme 7): the presented methodologies allow access to both 2′,3′-*endo*- and *exo*-methylene diastereoisomers of **37**.

Unsurprisingly, the sterically hindered di-TBDPS furanoses ***endo*-37** and ***exo*-37** did not readily undergo nucleosidation using a variety of solvents and Lewis acids, providing only low yield of the corresponding uridine derivatives (<10%, as judged by NMR spectroscopy, not isolated). It was anticipated that peracetylated derivative **41** would be a preferable substrate (Scheme 8). Accordingly, oxidation of the alcohol **38a** and acetonide removal were followed by acetylation with Ac_2O in pyridine. The diacetylated sugar **39** was obtained exclusively in its furanose form[43] as an inseparable 1:7 β:α mixture of anomers in 88% yield over three steps. Removal of the 3-*C*-hydroxymethyl benzyl protection via hydrogenolysis and subsequent acetylation furnished the desired triacetate **41** (91% over 2 steps). The triacetate successfully underwent nucleosidation with silylated uracil under Vorbrüggen conditions,[25] giving the acetylated uridine derivative **42** in excellent yield (84%) as a 10:1 mixture of β:α anomers. The pure β-anomer was isolated via recrystallization from EtOAc/*n*-heptane and after deprotection with methanolic ammonia the desired nucleoside **15** was isolated in 78% yield. 2D NOESY NMR spectroscopy indicated correlation between H-1′ to H-4′ and from one of the methylene protons of the cyclopropane ring to the uracil H-6 proton, demonstrating the desired 2′,3′-*endo*-methylene and β-anomeric configuration, which was confirmed by X-ray crystallography (Figures 5 and 7).

Scheme 8



Conditions: (a) Dess-Martin periodinane, CH_2Cl_2, rt; (b) 0.1 M aq HCl, 1,4-dioxane; (c) Ac_2O, py, 0 °C to rt (88% over 3 steps, 1:7 β:α mixture of anomers); (d) H_2, 10% Pd/C, MeOH, rt; (e) Ac_2O, py, 0 °C to rt (91% over 2 steps, 1:7 β:α mixture of anomers); (f) i. persilylated uracil, TMSOTf, CH_3CN, 50 °C (84%), ii. recrystallization from EtOAc/*n*-heptane to obtain clean β-anomer (72%); (g) NH_3, MeOH, rt (78%).

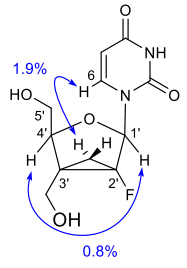
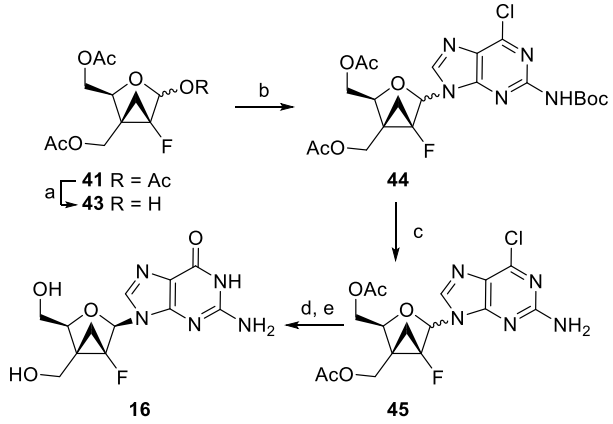


Figure 5. Confirmation of **15** stereochemistry by 2D NOESY NMR spectroscopy (400 MHz). NOE correlations reported from extracted 1D data sets.

Synthesis of the guanosine analog **16** was initially attempted under Vorbrüggen conditions,[25] whereby acetate **41** was treated with silylated 2-*N*-acetyl-6-*O*-diphenylcarbamoylguanine[29] and TMSOTf in anhydrous acetonitrile. As in the case of the corresponding acetate **22** (Scheme 2) without the 3-*C*-hydroxymethyl substitution, the reaction resulted mainly in decomposition of the starting material and the desired protected nucleoside was isolated in low yield (20%), as an inseparable 1:1 mixture of anomers. Thus, a Mitsunobu approach was employed, which had been successfully implemented in the prior synthesis of guanosine **14** (Scheme 5). The anomeric acetate **41** was therefore hydrolyzed and the resulting lactol **43** (1:6 mixture of β:α) was coupled with *N*-Boc-2-amino-6-chloropurine in the presence of PPh_3 and DIAD in THF (Scheme 9). The desired protected nucleoside **44** was isolated as an inseparable 5:1 mixture of β:α anomers in 46% yield. Removal of the *N*-Boc protection was attempted under various acidic conditions (MeOH/HCl, AcOH/H_2O, HCO_2H/H_2O and TFA/H_2O/CH_2Cl_2) but in each case significant decomposition of the material was observed. The deprotection was however, cleanly achieved in good yield (76% yield, 5:1 β:α anomer ratio) using excess TMSOTf (8 equivalents) in CH_2Cl_2, followed by aqueous $NaHCO_3$ workup. Interestingly, when the reaction was performed in the presence of 2,6-lutidine or triethylamine according to literature precedent,[44] the conversion rate slowed significantly. Transformation of the chloropurine base in **45** to guanine and concomitant deacetylation was achieved by treatment with 2-mercaptoethanol and NaOMe in refluxing methanol giving the desired nucleoside **16** in 79% yield. This method gave superior yield (79% vs 50%) in comparison with the reaction performed with the sodium salt of 3-hydroxypropionitrile,[30] which was previously utilized with the analogous guanosine derivative **28** (Scheme 5). Due to the very low solubility of the final product in multiple solvents and solvent mixtures, separation of the anomers was troublesome. An analytically pure sample of **16** was isolated by preparative HPLC. Stereochemical assignment of the final guanosine nucleoside **16** was made on the basis of 2D NOESY NMR spectroscopy. Correlations from H-1′ to H-4′ and from one of the methylene protons of the cyclopropane ring to the guanine H-8 proton were observed, confirming the desired 2′,3′-*endo*-methylene and β-anomeric configuration (Figure 6).

Scheme 9



Conditions: a) H_2O, TMSOTf, CH_3CN (84%, 1:6 β:α); (b) 2-NHBoc-6-Cl-purine, DIAD, PPh_3, THF, rt (46%, 5:1 β:α); (c) TMSOTf, CH_2Cl_2, 0 °C (76%, 5:1 β:α); (d) 2-mercaptoethanol, NaOMe, MeOH, reflux (79%, 5:1 β:α); (e) anomer separation by HPLC.

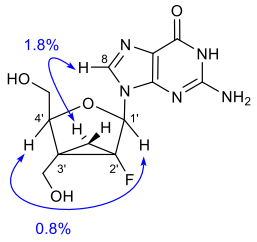
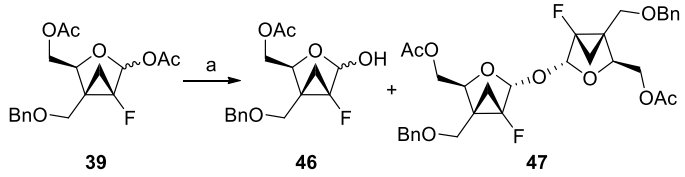


Figure 6. Confirmation of **16** stereochemistry by 2D NOESY NMR spectroscopy (400 MHz). NOE correlations reported from extracted 1D data sets.

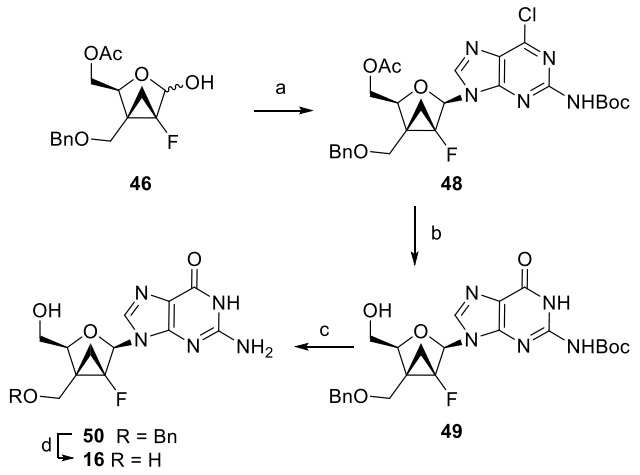
In anticipation of improved solubility and therefore potentially easier anomer separation at earlier stages of the synthesis, the route to **16** was modified by starting with the benzyl protected furanose **39**. Hydrolysis of the anomeric acetate **39** furnished the desired lactol **46** in good yield (69%, 1:6 β:α anomer ratio) but was accompanied by formation of significant amount of 1,1′-α,α′-linked disaccharide **47** (18% yield) (Scheme 10). The nucleoside **48** was obtained via coupling of the lactol with 2-NHBoc-6-Cl-purine under Mitsunobu conditions (Scheme 11). Notably, the anomeric ratio was higher than in case of the fully acetylated derivative **44** (7:1 vs 5:1 of β:α) (Scheme 9). Synthesis of the partially protected guanosine **49** was achieved on treatment of the chloropurine **48** with 2-mercaptoethanol and NaOMe in good yield (66%, >30:1 β:α). On removal of the Boc group with TMSOTf in CH_2Cl_2, partial deprotection of the benzyl moiety and formation of the target product **16** was observed. With a large excess of TMSOTf (20 equivalents) followed by treatment of the crude mixture with solid $NaHCO_3$ and MeOH, the amount of the debenzylated material significantly increased. Isolation of the clean β-anomer **16** (30% yield) could be accomplished by sequential chromatographic purification on normal and reverse phase silica gel. Benzyl protected nucleoside **50** was isolated in 40% yield and was further subjected to dilute hydrogenolysis using 10% Pd/C in EtOAc:*i*PrOH:H_2O 5:3:1, allowing isolation of further guanosine **16** in 30% yield.[45]

Scheme 10



Conditions: a) H_2O, TMSOTf, CH_3CN (**46** 69%, 1:6 β:α; and **47** 18%, single α-α′-linked).

Scheme 11



Conditions: a) 2-NHBoc-6-Cl-purine, DIAD, PPh_3, THF, rt (50%, 7:1 β:α); (b) 2-mercaptoethanol, NaOMe, MeOH, reflux (66%, >30:1 β:α); (c) TMSOTf (18 eq), CH_2Cl_2, 0 °C then $NaHCO_3$ and MeOH (**50** 40% β; and **16** 30% β); (d) Pd/C, H_2, EtOAc, *i*-PrOH, H_2O, rt (30%).

Stereochemical assignment of the final compounds **13**, **14**, **15** and **16** were made on the basis of 1D and 2D NMR spectroscopy and NOESY experiments (see Figures 4, 3, 5 and 6).

The X-ray crystallographic structure of nucleoside **15** is illustrated in Figure 7: the principal conformational parameters obtained therefrom are presented in Table 1. Analysis of the solid state structure revealed that the cyclopropane ring is not a perfect equilateral triangle, with the C3′–CH_2 bond being 2.6% and 2.0% longer than the C2′F–CH_2 and C3′–C2′F bonds respectively. The cyclopropane ring is inclined at an angle of 116.7° to the mean plane of the furanose ring. The conformation around the glycosyl bond is *anti* with a torsion angle χ of −153.4° (C2–N1–C1′–O4′). In contrast to the analogous 2′,3′-deoxy-2′,3′-*endo*-methylene systems,[14] the conformation around the C4′–C5′ bond is *synclinal (–sc*) with a torsion angle γ of −71.41° (C3′–C4′–C5′–O5′): an intramolecular hydrogen bond is evident between O5′H and the C3′-hydroxymethyl group. As anticipated, the furanoid ring adopts an almost East pucker with a pseudorotational angle *P* of 99.6° and a maximum puckering amplitude v_m of 35.3° placing it midway between ^oE and $^oT_1$ conformations.[8b,46,47,48]

Table 1. Major conformational and geometric parameters from X-ray structure of uridine **15**.

	Uridine 15
Bond lengths:	
C1′–C2′	1.504 (Å)
C2′–C3′	1.493 (Å)
C3′–C4′	1.513 (Å)

C2′–CH_2	1.484 (Å)
C3′– CH_2	1.523 (Å)
C1′–N1	1.467 (Å)
Bond angles:	
C1′–C2′–C3′	106.93°
C2′–C3′–C4′	104.53°
C1′–C2′–CH_2	119.72°
C2′–C3′–CH_2	58.94°
C3′–C2′–CH_2	61.54°
C2′–CH_2–C3′	59.52°
CH_2–C3′–C4′	113.73°
Torsion angles:	
C1′–C2′–C3′–C4′ (v_2)	−5.89°
C2′–C3′–C4′–O4′ (v_3)	−14.87°
C3′–C4′–O4′–C1′ (v_4)	31.95°
C4′–O4′–C1′–C2′ (v_0)	−35.23°
O4′–C1′–C2′–C3′ (v_1)	24.89°
C3′–C4′–C5′–O5′ (γ)	−71.41°
C2–N1–C1′–O4′ (χ)	−153.37°
Phase angle of pseudorotation (P)[a]	99.6°
Maximum puckering amplitude (v_m)[b]	35.3°

[a] Calculated from: $\tan P = [(v_4 + v_1) – (v_3 + v_0)]/3.077v_2$, as $v_2 < 0$, 180° is added to the calculated value of P. [b] Calculated from: $v_m = v_2/\cos P$.[42]

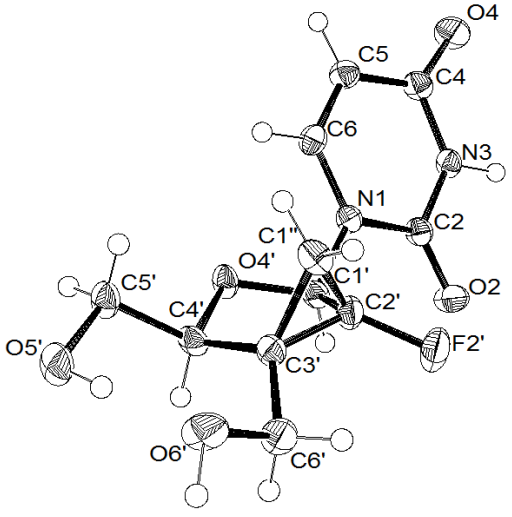


Figure 7 ORTEP drawing of the X-ray crystallographic structure of the uridine derivative **15**.

2′-Fluoro-2′,3′-*endo*-methylene nucleosides **13**, **14**, **15** and **16** were evaluated in a whole cell-based HCV replicon assay: neither anti-HCV activity (EC_{50} >100 μM) nor cytotoxicity (CC_{50} >100 μM) was observed in vitro.[49] In order to determine whether the lack of activity in the replicon was due to a failure of cellular kinases to recognize these nucleosides as substrates for conversion to the respective NTPs, or due to the lack of activity of the NTPs themselves against the RdRp, **13-TP**, **14-TP** and **15-TP** were evaluated against the purified HCV NS5B 1b wild type polymerase.[50] All three NTPs were found to be inactive (IC_{50} >100 μM) indicating that these highly functionalized, fused sugar ring systems were not incorporated by the HCV RdRp, presumably either due to the resultant unnatural East conformational or additional stereoelectronic deficiencies.

CONCLUSION

Two conformationally locked sugar modified bicyclic nucleoside systems were investigated based on a 2′,3′-dideoxy-2′,3′-*endo*-methylene-2′-fluoro motif. Synthesis of the first example of a 2,3-dideoxy-2,3-*endo*-methylene-pentofuranose featuring a 2-fluoro group is described. Access to two novel 2-fluoro-3-*C*-hydroxymethyl-pentofuranoses bearing either 2,3-*endo*- or *exo*-methylene moieties is provided. Uridine and guanosine nucleosides of the respective *endo*-methylene systems were structurally confirmed and the 3′-*C*-hydroxymethyl-uridine analog was determined by X-ray crystallography to adopt an East sugar ring conformation ($^{o}E/^{o}T_1$). Anti-HCV activity was evaluated and the nucleosides were found to be inactive in a whole cell replicon assay and as their respective NTPs against the HCV NS5B polymerase.

EXPERIMENTAL

General Experimental Reactions requiring anhydrous conditions were conducted in oven dried apparatus under dry argon atmosphere, utilizing commercially available dry solvents and reagents. All common reagents (including Dess-Martin periodinane) were purchased from commercial sources and used without further purification. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a 400 MHz Fourier transformation spectrometer using an internal deuterium lock. ^{19}F NMR spectra were recorded with ^{1}H decoupling. Spectra were obtained from samples prepared in 5 mm diameter tubes in $CDCl_3$, CD_3OD or DMSO-d_6. Multiplicities are as quoted: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet, app = apparent. Coupling constants (*J*) are reported in Hz. Signal assignments are based on COSY, DEPT, HSQC and HMBC spectra. Melting points were not corrected. HRMS spectra were obtained using electrospray ionisation (ESI). Optical rotations were recorded using a light source at λ= 589 nm.Crystallographic data for the nucleoside **15** have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1018857.

β-D-2′,3′-Dideoxy-2′-fluoro-2′,3′-*endo*-methyleneuridine (13)

To a solution of **27** (140 mg, 0.37 mmol, β anomer) in MeOH (15 mL) at rt was added NaOMe in MeOH (25% w/w) to obtain pH ~12. The mixture was stirred for 2 h and solid CO_2 was added to achieve pH 7. The crude mixture was concentrated onto silica and purified by column chromatography (SiO_2, EtOAc/MeOH/H_2O gradient) to give clean **13** as a white amorphous solid (83 mg, 0.34 mmol, 92% yield).

^{1}H NMR (400 MHz, MeOD): δ = 7.67 (1H, d, *J* = 8.2, C6**H**), 6.41 (1H, d, *J* = 2.9, C1′**H**), 5.63 (1H, app d, *J* = 8.2, C5**H**), 4.34 (1H, dt, *J* = 3.4, 5.4 Hz, C4′**H**), 3.48 (2H, d, *J* = 5.4, C5′**H**$_2$), 2.12–2.05 (1H, m, C3′**H**), 1.50–1.36 (2H, m, CFC**H**$_2$);^{13}C NMR (100 MHz, MeOD): δ = 165.8 (**C**4=O), 152.5 (**C**2=O), 141.9 (**C**6H), 103.1 (**C**5H), 84.9 (d, *J* = 248, **C**2′F), 84.7 (d, *J* = 28 Hz, **C**1′H), 79.4 (**C**4′H), 62.5 (**C**5′H$_2$), 22.9 (d, *J* = 7, **C**3′H), 10.2 (d, *J* = 11, CF**C**H$_2$); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$ δ = −210.9; (IR) ν_{max}(cm^{-1}): 3300, 1698, 1462, 1381, 1265, 1214, 1115, 1054; HRMS (ESI-TOF) *m/z*: (M+H)$^+$ calcd for $C_{10}H_{12}FN_2O_4$ 243.0781; found 243.0770; $[\alpha]_D^{21}$ +19.4 (*c* 0.6, MeOH).

β-D-2′,3′-Dideoxy-2′-fluoro-2′,3′-*endo*-methyleneguanosine (14)

Nucleoside **29** (1.0 g, 2.62 mmol) was dissolved in AcOH (20 mL) and stirred at 90 °C for 8 h. The mixture was concentrated *in vacuo*, concentrated onto silica gel and purified by column chromatography (SiO_2, EtOAc:MeOH:H_2O) to give product **14** as an acetic acid salt (10:1 mixture of β:α anomers, 306 mg, 0.90 mmol, 34%). Starting material **29** was also isolated (280 mg, 0.73 mmol, 28%). The product was re-purified using reverse phase column chromatography (30 g C18 column, H_2O:CH_3CN 0→5% gradient) and then de-salted using Dowex-Marathon free base resin to give 150 mg of free amine **14** (10:1 mixture of β:α anomers) as a white amorphous solid. The product was triturated 3 times from MeOH to give 70 mg (0.24 mmol) of clean β **14** as off-white amorphous solid.

^{1}H NMR (400 MHz, *d*$_6$-DMSO): δ = 10.69 (1H, bs, N**H**), 7.98 (1H, s, C8**H**), 6.56 (2H, bs, N**H**$_2$), 6.30 (1H, d, *J* = 3.2, C1′**H**), 4.83 (1H, t, *J* = 5.7, C5′O**H**), 4.39 (1H, dt, *J* = 3.2, 5.7, C4′**H**), 3.4–3.36 (2H, m, C5′**H**$_2$), 2.34–2.28 (1H, m, C3′**H**), 1.76 (1H, app q, *J* = 5.4, CFC**H**$_A$H$_B$), 1.60–1.51 (1H, m, CFCH$_A$**H**$_B$); ^{13}C NMR (100 MHz, *d*$_6$-DMSO): δ = 156.7 (**C**), 154.0 (**C**), 151.6 (**C**), 134.5 (**C**8H), 116.4 (**C**), 84.4 (d, *J* = 247, **C**2′F), 81.5 (d, *J* = 27, **C**1′H), 79.1 (**C**4′H), 60.6 (**C**5′H$_2$), 22.3 (d, *J* = 7, **C**3′H), 9.7 (d, *J* = 11, CF**C**H$_2$); ^{19}F{^{1}H} NMR (376 MHz, *d*$_6$-DMSO) δ = −208.8; (IR) ν_{max}(cm^{-1}): 3307, 3134, 1691, 1639, 1596, 1533, 1482, 1365, 1174, 1046, 1022; HRMS (ESI-TOF) *m/z*: (M+Na)$^+$ calcd for $C_{11}H_{12}FN_5NaO_3$ 304.0816; found: 304.0810; $[\alpha]_D^{21}$ −20.0 (*c* 0.1, DMSO).

β-D-2′,3′-Dideoxy-3′-*C*-hydroxymethyl-2′-fluoro-2′,3′-*endo*-methyleneuridine (15)

To a solution of the acetylated uridine **42** (150 mg, 0.45 mmol) in MeOH (8 mL) was added 7N methanolic NH_3 (2.4 mL, 16.80 mmol) and the mixture was stirred for 16 h at rt. The crude mixture was concentrated *in vacuo*. The desired nucleoside **15** was isolated by column chromatography (SiO_2, EtOAc:MeOH:H_2O gradient) in 78% yield (95 mg, 0.35 mmol) as white amorphous solid. The product was recrystallized from $CHCl_3$:MeOH to give needles, mp: 85–87 ˚C.

^{1}H NMR (400 MHz, MeOD): δ = 7.77 (1H, d, *J* = 8.2, C6**H**), 6.50 (1H, d, *J* = 2.7, C1′**H**), 5.72 (1H, d, *J* = 8.2, C5**H**), 4.47 (1H, t, *J* = 5.4, C4′**H**), 3.84 (1H, d, *J* = 12.3, C**H**$_{A}$H$_{B}$), 3.77 (1H, d, *J* = 12.3, CH$_{A}$**H**$_{B}$), 3.72–3.63 (2H, m, C5′**H**$_2$), 1.71 (1H, app. t, *J* = 7.7, CFC**H**$_{A}$H$_{B}$), 1.44 (1H, ddd, *J* = 0.8, 7.8, CFCH$_{A}$**H**$_{B}$); ^{13}C NMR (100 MHz, MeOD): δ = 165.8 (**C**4=O), 152.5 (**C**2=O), 141.8 (**C**6), 103.2 (**C**5), 86.0 (d, *J* = 250.0, **C**2′F), 84.3 (d, *J* = 27.0, **C**1′H), 81.0 (**C**4′H), 62.0 (d, *J* = 20, **C**5′H$_2$), 60.5 (d, *J* = 5.0, **C**H$_2$), 34.2 (d, *J* = 8.0, **C**3′), 13.8 (d, *J* = 11, CF**C**H$_2$); ^{19}F NMR (376 MHz, MeOD): δ −215.58 (1F, C**F**); (IR) ν_{max}(cm^{-1}): 3370, 2942, 2883, 1680, 1461, 1380, 1264, 1029; HRMS (ESI-TOF) *m/z*: (M+Na^{+}) calcd for $C_{11}H_{13}FN_2NaO_5$ 295.0701; found 295.0711; $[\alpha]_D^{21}$ +31.7 (0.69, MeOH);

β-D-2′,3′-Dideoxy-3′-*C*-hydroxymethyl-2′-fluoro-2′,3′-*endo*-methyleneguanosine (16)

To a solution of compound **45** (81 mg, 0.20 mmol) in anhydrous MeOH (1.5 mL) was added 2-mercaptoethanol (0.55 µL, 0.78 mmol) followed by sodium methoxide (42.2 mg, 0.78 mmol) at rt. The mixture was stirred for 5 h at 66 °C, then cooled to rt and neutralised by the addition of solid CO_2. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (SiO_2, EtOAc:water:methanol) to give **16** as a white solid (48 mg, 0.15 mmol, 79%, mixture of 5:1 β:α anomers).[35] The pure β anomer (white amorphous solid) was isolated using reverse phase HPLC.

^{1}H NMR (400 MHz, *d*$_6$-DMSO) δ = 10.79 (1H, br s, N**H**), 7.97 (1H, s, C**H**8), 6.61 (2H, br s, N**H**$_2$), 6.26 (1H, d, *J* = 3.6 C1′**H**), 4.98 (1H, br s, O**H**), 4.85 (1H, br s, O**H**), 4.41 (1H, app t, *J* = 5.4, C4′**H**), 3.77 (1H, d, *J* = 12.2, (C3′)C**H**$_{A}$H$_{B}$), 3.62 (1H, d, *J* = 12.2, (C3′)CH$_{A}$**H**$_{B}$), 3.56 (1H, dd, *J* = 4.7, 11.8, C5′H$_{A}$**H**$_{B}$), 3.45 (1H, dd, *J* = 6.5, 11.8, C5′**H**$_{A}$H$_{B}$), 1.88 (1H, app t, *J* = 7.5, CFC**H**$_{A}$H$_{B}$), 1.46 (1H, dd, *J* = 7.8, 18.2, CFCH$_{A}$**H**$_{B}$); ^{13}C NMR (100 MHz, *d*$_6$-DMSO) δ = 156.8 (**C**), 154.1 (**C**), 151.6 (**C**), 134.5 (**C**8H), 116.3 (**C**), 85.6 (d, *J* = 248, **C**2′F), 81.3 (d, *J* = 26, **C**1′H), 79.4 (**C**′4H), 60.4 (**C**5′H$_2$), 58.5 ((C3′)**C**H$_2$), 33.3 (d, *J* = 8, **C**3′), 13.2 (d, *J* = 11, CF**C**H$_2$); ^{19}F{^{1}H} NMR (376 MHz, d$_6$-DMSO) −213.8; (IR) ν_{max}(cm^{-1}): 3309, 3115, 2929, 1687, 1603, 1531, 1362, 1029; HRMS (ESI-TOF) *m/z*: (M+Na^{+}) calcd for $C_{12}H_{14}FN_5NaO_4$ 334.0922; found 334.0912.

(*S*,*E*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-fluoroprop-2-en-1-ol (18a)

Alcohol **18a** was prepared in two steps from D-glyceraldehyde according to the literature procedures.[20,21] The spectroscopic data for this compound was unavailable in the literature.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.27 (1H, dd, *J* = 8.9, 19.2, C**H**CF), 4.77–4.71 (1H, m, OC**H**), 4.32 (1H, dd, *J* = 1.5, 6.5, C**H**$_2$OH), 4.27 (1H, dd, *J* = 2.6, 6.5, C**H**$_2$OH), 4.13 (1H, dd, *J* = 6.0, 8.3, OC**H**$_2$), 3.62 (1H, app. t, *J* = 7.6 , OC**H**$_2$), 2.22 (1H, br s, O**H**), 1.43 (3H, s, C(C**H**$_3$)$_2$), 1.39 (3H, s, C(C**H**$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ =161.7 (d, *J* = 256, **C**F), 109.7 (**C**(CH$_3$)$_2$), 107.5 (d, *J* = 22, **C**HCF), 70.9 (d, *J* = 13, **C**HO), 69.7 (d, *J* = 3, O**C**H$_2$), 57.8 (d, *J* = 31, **C**H$_2$OH), 26.7 (C(**C**H$_3$)$_2$), 25.8 (C(**C**H$_3$)$_2$); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −105.4 (1F, m, C**F**); (IR) ν_{max}(cm^{-1}):

3420, 2990, 2940, 2880, 1700, 1450, 1370,1290, 1150, 1050, 1020; HRMS (ESI-TOF) *m/z*: ($M+Na^+$) calcd for $C_8H_{13}FNaO_3$ 199.0741; found 199.0745; $[\alpha]_D^{21}$ −18.0° (*c* 1.1, $CHCl_3$).

(*S*,*E*)-4-(3-(Benzyloxy)-2-fluoroprop-1-en-1-yl)-2,2-dimethyl-1,3-dioxolane (18b)

Benzylated alcohol **18b** was prepared from **18a** according to the literature procedure and the ^1H and ^{13}C NMR data agreed with those published in the literature.[20a]

(*S*,*E*)-4-(3-(*tert*-Butyldiphenylsilyloxy)-2-fluoroprop-1-en-1-yl)-2,2-dimethyl-1,3-dioxolane (18c)

To a solution of alcohol **18a** (5.2 g, 29.5 mmol) in anhydrous THF (80 mL) was added imidazole (5.0 g, 74 mmol), followed by *tert*-butyl(chloro)diphenylsilane (11.5 mL, 44 mmol). After stirring for 10 min at rt the slurry was stirred at 45 °C for 1 h. The reaction was quenched by the addition of MeOH (50 mL), concentrated and the residue purified by column chromatography (SiO_2, EtOAc/*n*-heptane) to afford the alkene **18c** as a yellow oil (11.2 g, 27.0 mmol, 92% over 2 steps).

^1H NMR (400 MHz, $CDCl_3$) δ = 7.69–7.65 (4H, m, Ar**H**), 7.47–7.37 (6H, m, Ar**H**), 5.17 (1H, dd, *J* = 9.5, 19.2, C**H**CF), 4.48-4.45 (1H, m, OC**H**), 4.31 (1H, dd, *J* = 13.5, 26.3 ($^3J_{H,F}$), $CFCH_A\mathbf{H_B}OSi$), 4.26 (1H, dd, *J* = 13.5, 20.6 ($^3J_{H,F}$), $CFC\mathbf{H}_AH_BOSi$), 3.89 (1H, dd, *J* = 6.0, 8.2, OC$\mathbf{H}_2$), 3.47 (1H, dd, *J* = 7.5, 8.2, OC$\mathbf{H}_2$), 1.37 (3H, s, C(C$\mathbf{H}_3$)$_2$), 1.29 (3H, d, *J* = 0.4, C(C$\mathbf{H}_3$)$_2$), 1.06 (9H, s, C(C$\mathbf{H}_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.2 (d, *J* = 260, **C**F), 135.63, (2 × Ar-**C**H), 135.61, (2 × Ar-**C**H), 132.9 (Ar-**C**), 132.7 (Ar-**C**), 130.0 (2 × Ar-**C**H), 129.9 (2 × Ar-**C**H), 127.9 (2 × Ar-**C**H), 127.8 (2 × Ar-**C**H), 109.3 (**C**(CH$_3$)$_2$), 107.4 (d, *J* = 21.8 **C**HCF), 70.8 (d, *J* = 13.2, O**C**H), 69.7 (d, *J* = 2.7, O**C**H$_2$), 58.9 (d, *J* = 31.0, CF**C**H$_2$), 26.7 (C(**C**H$_3$)$_2$), 26.7 (C(**C**H$_3$)$_3$), 25.8 (C(**C**H$_3$)$_2$), 19.2 Si**C**(CH$_3$)$_3$; ^{19}F NMR (376 MHz, $CDCl_3$) δ = −104.3 (1F, m, C**F**); (IR) ν_{max}(cm^{-1}): 3070, 3050, 2985, 2930, 2860, 1700, 1470, 1430, 1380, 1370, 1110, 1060; HRMS (ESI-TOF) *m/z*: ($M+Na^+$) calcd for $C_{24}H_{31}FO_3SiNa$ 437.1919; found 437.1914; $[\alpha]_D^{21}$ −8.0° (*c* 1.0, $CHCl_3$).

(*S*)-4-((1*S*,2*R*)-2-((Benzyloxy)methyl)-2-fluorocyclopropyl)-2,2-dimethyl-1,3-dioxolane (19a)

To 138.0 mL of $ZnEt_2$ (1M in hexane, 138.0 mmol) in anhydrous CH_2Cl_2 (138 mL) at 0 °C was added TFA (9.6 mL, 125.0 mmol) in anhydrous CH_2Cl_2 (30 mL) drop-wise over 40 min. The reaction was stirred for 30 min and then a solution of CH_2I_2 (10.9 mL, 135.0 mmol) in anhydrous CH_2Cl_2 (100 mL) was added over 15 min. After a further 30 min stirring alkene **18b** (33.0 g, 125.0 mmol) in anhydrous CH_2Cl_2 (100.0 mL) was added over 20 min. The reaction was stirred at 0 °C for 30 min and then warmed to 15 °C over 1 h, before re-cooling to 3 °C and stirring for a further 16 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (300 mL) over 30 min at 3°C. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 500 mL), the combined organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness. Purification by column chromatography (SiO_2, EtOAC:*n*-heptane) gave 20.7 g (73.8 mmol, 59%) of **19a** as a yellow oil. The ^1H and ^{13}C NMR data agreed with those published in the literature.[20b]

(*S*)-4-((1*S*,2*R*)-2-((*tert*-Butyldiphenylsilyloxy)methyl)-2-fluorocyclopropyl)-2,2-dimethyl-1,3-dioxolane (19b)

To the alkene **18c** (10.0 g, 24 mmol) in anhydrous CH_2Cl_2 (185 mL) at 2 °C was added $ZnEt_2$ (15% wt. in toluene, 30.0 mL, 36 mmol) drop-wise over 15 min. The reaction was stirred for a further 15 min at 2 °C and then a solution of CH_2I_2 (2.9 mL, 36 mmol) in anhydrous CH_2Cl_2 (15 mL) was added drop-wise over 15 min. The reaction was allowed to warm to rt and stirred for 3 days. The reaction mixture was re-cooled to 0 °C and sat. aq. NH_4Cl (300 mL) was added slowly to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (2 × 500 mL) and the combined organic layers dried over $MgSO_4$, filtered and concentrated. The residue purified by column chromatography (SiO_2, EtOAc:*n*-heptane) to give 6.0 g of **19b** (14 mmol, 58%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73–7.67 (4H, m, Ar-**H**), 7.43–7.36 (6H, m, Ar-**H**), 4.27 (1H, ddd, *J* = 0.9, 12.7, 16.4, CFC**H$_A$**H$_B$O), 4.21 (1H, dd, *J* = 5.7, 7.8, C**H$_A$**H$_B$O), 3.86 (1H, t, *J* = 7.8, CH$_A$**H$_B$**O), 3.80 (1H, app q, *J* = 7.2, C**H**O), 3.67 (1H, dd, *J* = 12.7, 32.8 ($^3J_{H,F}$), CFCH$_A$**H$_B$**O), 1.63–1.55 (1H, m, C**H**=CF), 1.43 (3H, s, C(C**H**$_3$)$_2$), 1.33 (3H, s, C(C**H**$_3$)$_2$), 1.29–1.20 (1H, m, CFC**H$_A$**H$_B$CH), 1.08 (9H, s, C(C**H**$_3$)$_3$), 0.75 (1H, dd, *J* = 8.8, 7.2, CFCH$_A$**H$_B$**CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 135.6 (2 × Ar-**C**H), 133.4 (Ar-**C**), 132.9 (Ar-**C**), 127.9 (4 × Ar-**C**H), 127.8 (4 × Ar-**C**H), 109.3 (**C**(CH$_3$)$_2$), 80.1 (d, *J* = 210, **C**F), 75.4 (d, *J* = 2, O**C**H), 70.0 (O**C**H$_2$), 65.1 (d, *J* = 21, **C**H$_2$OH), 26.9 ((**C**H$_3$)$_3$CSi), 26.8 (**C**H$_3$), 25.8 (**C**H$_3$), 25.0 (d, *J* = 12, **C**HCF), 19.3 (Si**C**(CH$_3$)$_2$ 13.7 (d, *J* = 11, CF**C**H$_2$); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) = −177.5; (IR) ν_{max}(cm^{-1}): 2985, 2957, 2957, 2858, 1428, 1107, 1067, 848, 701; $[\alpha]_D^{21}$ −3.8 (*c* 1.0, $CHCl_3$).

((1*R*,2*S*)-2-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-1-fluorocyclopropyl)methanol (20)

Method A: To 10% Pd/C (5.00 g, 50% wet) was added cyclopropane **19a** (7.20 g, 25.7 mmol) in MeOH (200 mL) under argon. The flask was de-gassed, charged with hydrogen, and then heated to reflux for 3.5 h. The reaction was cooled to rt and the Pd/C filtered and rinsed with EtOAc (400 mL), followed by CH_2Cl_2 (200 mL). The filtrate was concentrated and the residue purified by column chromatography (SiO_2, EtOAc:*n*-heptane) to give the alcohol **20** as a yellow oil (4.10 g, 21.6 mmol, 84%).

Method B: To cyclopropane **19b** (4.86 g, 11.3 mmol) in anhydrous THF (120 mL) was added TBAF (1M in THF, 13.6 mL, 13.6 mmol) at 5 °C. The reaction was stirred for 16 h and then concentrated. The residue was purified by column chromatography (SiO_2, EtOAc/*n*-heptane) to give the alcohol **20** as a yellow oil (2.15 g, 11.3 mmol, quant. yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.29–4.19 (2H, m, C**H**$_2$OH and OC**H**$_2$), 3.93 (1H, app q, *J* = 6.8, OC**H**), 3.79–3.63 (2H, m, C**H**$_2$OH and OC**H**$_2$), 2.09 (1H, dd, *J* = 5.3, 7.4, O**H**), 1.60–1.50 (1H, m, C**H**CF), 1.44 (3H, s, C(C**H**$_3$)$_2$), 1.38–1.29 (1H, m, CFC**H$_A$**H$_B$CH), 1.36 (3H, s, C(C**H**$_3$)$_2$), 0.92–0.86 (1H, m, CFCH$_A$**H$_B$**CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 109.3 (**C**(CH$_3$)$_2$), 81.6 (d, *J* = 219, **C**F), 74.5 (d, *J* = 2.1, O**C**H), 69.72 (d, *J* = 0.8, O**C**H$_2$), 63.8 (d, *J* = 22.5, **C**H$_2$OH), 26.6 (C(**C**H$_3$)$_2$), 25.7 (C(**C**H$_3$)$_2$), 24.4 (d, *J* = 11.9, **C**HCF), 13.4 (d, *J* = 11.1, CF**C**H$_2$); ^{19}F{^{1}H} NMR (376 MHz,

$CDCl_3$) δ = −178.8; (IR) $\nu_{max}(cm^{-1})$: 3425, 2987, 2935, 2877, 1455, 1247, 1156, 1050, 843; HRMS (ESI-TOF) *m/z*: ($M+Na^+$) calcd for $C_9H_{15}FO_3Na$ 213.0897; found 213.0890.$[\alpha]_D^{21}$ −58.7 (*c* 1.0, $CHCl_3$).

α/β-5-*O*-*tert*-Butyldiphenylsilyl-2,3-dideoxy-2-fluoro-2,3-*endo*-methylene-D-pentofuranose (21)

To oxalyl chloride (3.65 mL, 43 mmol) in anhydrous CH_2Cl_2 (100 mL) at −78 °C was added DMSO (6.89 mL, 97 mmol) in anhydrous CH_2Cl_2 (50 mL) drop-wise over 15 min. After 10 min alcohol **20** (4.10 g, 22 mmol) in anhydrous CH_2Cl_2 (50 mL) was added drop-wise over 15 min. The reaction was stirred for 45 min and then quenched by the addition of triethylamine (30.0 mL, 215 mmol) over 15 min. The resultant slurry was stirred for 5 min and then slowly warmed to rt. CH_2Cl_2 (50 mL) and H_2O (150 mL) were added. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 100 mL) and the combined organic extracts dried over Na_2SO_4, filtered and concentrated to give a yellow oil, which was used in the next step without further purification. To a solution of the crude aldehyde in 1,4-dioxane (50 mL) was added 0.1 N HCl (50 mL), ensuring the pH is 1-2, and the resultant solution was stirred for 16 h at rt. The reaction was adjusted to pH 9–10 with K_2CO_3 and concentrated in vacuo. The residue was triturated with CH_2Cl_2 (3 × 200 mL) and $CHCl_3$ (100 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The residue was dissolved in anhydrous CH_2Cl_2 (200 mL) and pyridine (13.6 mL, 168 mmol) was added, followed by TBDPSCl (13.6 mL, 54 mmol). The reaction was stirred at rt for 16 h, then quenched by the addition of MeOH (20 mL) and then concentrated. The residue was purified by column chromatography (SiO_2, EtOAc:*n*-heptane) to give lactol **21** as a yellow oil (4.15 g, 11 mmol inseparable mixture of anomers, 1:8 β:α, 50 % over 3 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66–7.64 (4Hα + 4Hβ, m, Ar-**H**), 7.44–7.25 (6Hα + 6Hβ, m, Ar-**H**), 5.66 (1Hβ, ddd, *J* = 1.0, 4.3, 8.4, C1**H**), 5.38 (1Hα, dd, *J* = 2.3, 4.8, C1**H**), 4.63–4.59 (1Hα, m, C4**H**), 4.36–4.33 (1Hβ, m, C4**H**), 3.67 (1Hα + 1Hβ, ddd for α: *J* = 1.3, 5.0, 10.3, C5$\mathbf{H_A}H_B$), 3.48–3.43 (1Hα + 1Hβ, m, C5$H_A\mathbf{H_B}$), 3.07 (1Hα, d, *J* = 4.8, O**H**), 2.89 (1Hβ, d, *J* = 8.4, O**H**), 2.17–2.08 (1Hα + 1Hβ, m, C3**H**), 1.29–1.21 (1Hα + 1Hβ, m, CFC$\mathbf{H_A}H_B$), 1.06 (3Hα + 3Hβ, s, C(C$\mathbf{H}_3)_3$), 0.89–0.82 (1Hα + 1Hβ, m, CFC$H_A\mathbf{H_B}$); ^{13}C NMR (100 MHz, $CDCl_3$, α anomer) δ = 135.61 (Ar-**C**H), 135.59 (Ar-**C**H), 133.4 (Ar-**C**), 133.3 (Ar-**C**), 129.7 (4 × Ar-**C**H), 127.72 (2 × Ar-**C**H), 127.71 (2 × Ar-**C**H), 95.1 (d, *J* = 19, **C**1H), 84.4 (d, *J* = 254, **C**F), 76.7 (**C**4H), 63.2 (**C**5H_2), 26.8 (C(**C**$H_3)_3$), 21.6 (d, *J* = 7.9, **C**3H), 19.2 (Si**C**$(CH_3)_3$), 10.9 (d, *J* = 11, CF**C**H_2); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ = −211.5; (IR) $\nu_{max}(cm^{-1})$: 3406, 3071, 3049, 2956, 2930, 2857, 1589, 1390, 1234, 1105, 1055, 946, 700; HRMS (ESI-TOF) *m/z*: ($M+Na^+$) calcd for $C_{22}H_{27}FNaO_3Si$ 409.1606; found 409.1625.

α/β-1-*O*-Acetyl-5-*O*-*tert*-butyldiphenylsilyl-2,3-dideoxy-2-fluoro-2,3-*endo*-methylene-D-pentofuranose (22)

To the solution of lactol **21** (125 mg, 0.32 mmol) in pyridine (2.5 mL) was added Ac_2O (0.5 mL, 5.30 mmol) drop-wise at 0 °C and the mixture was gradually warmed out to rt and stirred for 16 h. MeOH (0.5 mL) was added drop-wise and the mixture concentrated *in vacuo*. The residue was

purified by column chromatography (SiO_2, acetone:*n*-heptane) to give **22** as a colorless oil in quantitative yield (138 g, 0.32 mmol, mixture of anomers, 1:8 β:α).

^{1}H NMR (400 MHz, $CDCl_3$): δ (major, α anomer) = 7.67–7.64 (4H, m, Ar-**H**), 7.43–7.35 (6H, m, Ar-**H**), 6.32 (1H, d, *J* = 2.3, C1**H**), 4.62–4.58 (1H, m, C4**H**), 3.69 (1H, ddd, *J* = 1.5, 4.8, 10.4, C5**H**$_A$H$_B$), 3.44 (1H, dd, *J* = 7.3, 10.4, C5H$_A$**H$_B$**), 2.20–2.13 (1H, m, C3**H**), 2.14 (3H, s, COC**H**$_3$), 1.34–1.26 (1H, m, CFC**H**$_A$H$_B$), 1.06 (9H, s, C(C**H**$_3$)$_3$), 0.90–0.85 (1H, m, CFCH$_A$**H$_B$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major α anomer) = 170.0 (**C**O), 135.59 (2 × Ar-**C**H), 135.58 (2 × Ar-**C**H), 133.3 (Ar-**C**), 133.2 (Ar-**C**), 129.8 (2 × Ar-**C**H), 127.75 (2 × Ar-**C**H), 127.74 (2 × Ar-**C**H), 94.0 (d, *J* = 18, **C**1H), 82.9 (d, *J* = 254, **C**F), 78.5 (**C**4H), 62.8 (d, *J* = 2.9, **C**5H$_2$), 26.8 (C(**C**H$_3$)$_3$), 21.7 (d, *J* = 7.7, **C**3H), 21.2 (CO**C**H$_3$), 19.2 (Si**C**(CH$_3$)$_3$), 10.7 (d, *J* = 10.8, CF**C**H$_2$); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ = −212.4; (IR) ν_{max}(cm^{-1}): 3071, 3016, 2969, 2931, 2858, 1752, 1427, 1363, 1217, 1104, 1007, 970, 700; HRMS (ESI-TOF) *m/z*: (M+Na$^+$) calcd for $C_{24}H_{29}FO_4SiNa$ 451.1717; found 451.1722.

β/α-D-5′-*O*-*tert*-Butyldiphenylsilyl-2′,3′-dideoxy-2′-fluoro-2′,3′-*endo*-methyleneuridine (23)

To a solution of lactol **21** (1.04 g, 2.69 mmol)) in anhydrous CH_2Cl_2 (100 mL) at 0 °C was added NEt_3 (4.3 mL) followed by MsCl (0.96 mL, 12.40 mmol). The mixture was stirred at 0 °C for 1 h, then 15 min at rt. Pyridine (5.02 mL) was added followed by an additional portion of MsCl (2.4 mL, 31.01 mmol) and the mixture was stirred for 30 min at rt. The mixture was diluted with CH_2Cl_2 (100 mL) and washed with 10% aqueous $CuSO_4$ solution (300 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic layers dried over Na_2SO_4, filtered and concentrated *in vacuo* to give yellow oil. (The product was unstable on silica gel). The residue was dissolved in anhydrous 1,2-DCE (70 mL) and added to the silylated uracil (11.24 mmol , see the general method for silylation of uracil below), followed by the drop-wise addition of TMSOTf (1.12 mL, ~2 min addition) at rt. The mixture was stirred for 10 min then transferred to a pre-heated oil bath at 90 °C and stirred for 1 h 10 min. The mixture was then cooled to rt and quenched with sat. aq. $NaHCO_3$ (100 mL). The aqueous layer was extracted with $CHCl_3$ (3 × 100 mL), the combined organic layers dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography (SiO_2, *n*-heptane:acetone, 0→50%) to give 0.58 g (1.22 mmol, 45% yield over 2 steps) of a 4:1 mixture of β:α anomers of the nucleoside **23** (glass solid).[51] The pyridinium adduct **26** was isolated in 11% yield (177 mg, 0.30 mmol, α anomer, amorphous off-white solid).

General procedure for silylation of uracil: Uracil (1.26 g, 11.24 mmol) was treated with HMDS (50 mL) in the presence of $(NH_4)_2SO_4$ (140 mg, 1.06 mmol) under argon and stirred at 130 °C for 2.5 h. Excess HMDS was evaporated under reduced pressure at 50 °C to give a cloudy oil, which was directly used in the nucleosidation reaction.

^{1}H NMR (400 MHz, $CDCl_3$): δ (minor, α anomer) = 9.12 (1H, bs, N**H**), 7.66–7.63 (4H, m, 4 × Ar-**H**), 7.47-7.37 (6H, m, 6 × Ar-**H**), 7.29 (1H, dd, *J* = 2.0, 8.1, C6**H**), 6.30 (1H, app s, C1′**H**), 5.79

(1H, dd, *J* = 1.7, 8.1, C5**H**), 4.62–4.58 (1H, m, C4′**H**), 3.68 (1H, ddd, *J* = 1.3, 5.0, 10.5, C5′**H$_A$**H$_B$), 3.43 (1H, dd, *J* = 7.2, 10.4, C5′H$_A$**H$_B$**), 2.42–2.37 (1H, m, C3′**H**), 1.48 (1H, ddd, *J* = 7.2, 10.0, 17.4, CFC**H$_A$**H$_B$), 1.06 (9H, s, C(C**H**$_3$)$_3$, 0.97 (1H, app q, *J* = 5.4, CFCH$_A$**H$_B$**); ^{13}C NMR (100 MHz, $CDCl_3$): δ (minor, α anomer) = 162.8 (**C**4=O), 150.7 (**C**2=O), 140.6 (**C**6H), 135.6 (4 × Ar-**C**H), 133.02 (Ar-**C**), 132.96 (Ar-**C**), 129.97 (Ar-**C**H), 129.94 (Ar-**C**H), 127.9 (2 × Ar-**C**H), 127.8 (2 × Ar-**C**H), 103.0 (**C**5H), 83.4 (d, *J* = 28, **C**1′H), 81.8 (d, *J* = 255, **C**2′F), 79.1 (**C**4′H), 62.9 (**C**5′H$_2$), 26.8 ((**C**H$_3$)$_3$C), 24.0 (d, *J* = 7, **C**3′H), 19.2 (**C**(CH$_3$)$_3$), 11.5 (d, *J* = 11, CF**C**H$_2$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (major, β anomer) = 8.82 (1H, bs, N**H**), 7.66–7.63 (4H, m, Ar-**H**), 7.47–7.35 (7H, m, 6 × Ar-**H** and C6**H**), 6.52 (1H, d, *J* = 2.8, C1′**H**), 5.66 (1H, d, *J* = 8.2, C5**H**), 4.49 (1H, m, C4′**H**), 3.72 (1H, ddd, *J* = 0.8, 4.5, 10.8, C5′**H$_A$**H$_B$), 3.62 (1H, dd, *J* = 5.8, 10.9, C5′H$_A$**H$_B$**), 2.19–2.12 (1H, m, C3′**H**), 1.47–1.40 (1H, m, CFC**H$_A$**H$_B$), 1.06 (9H, s, C(C**H**$_3$)$_3$, 1.31–1.26 (1H, m CFCH$_A$**H$_B$**); ^{13}C NMR (100 MHz, $CDCl_3$): δ (major, β anomer) = 162.4 (**C**4=O), 150.3 (**C**2=O), 139.3 (**C**6H), 135.6 (4 × Ar-**C**H), 132.9 (Ar-**C**), 132.8 (Ar-**C**), 129.99 (Ar-**C**H), 129.98 (Ar-**C**H) 127.85 (2 × Ar-**C**H), 127.81 (2 × Ar-**C**H), 102.6 (**C**5H), 83.5 (d, *J* = 27, **C**1′H), 83.5 (d, *J* = 250, **C**2′F), 77.6 (**C**4′H), 63.1 (**C**5′H$_2$), 26.8 ((**C**H$_3$)$_3$C), 22.3 (d, *J* = 7, **C**3′H), 19.2 (**C**(CH$_3$)$_3$), 10.0 (d, *J* = 11, CF**C**H$_2$); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ = −206.4 (β), −208.8 (α); (IR) ν_{max}(cm^{-1}): 3070, 2931, 2858, 1681, 1457, 1141, 701; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ calcd for $C_{26}H_{30}FN_2O_4Si$ 481.1959; found: 481.1960.

α/β-5-*O*-*tert*-Butyldiphenylsilyl-2,3-dideoxy-2-fluoro-2,3-*endo*-methylene-D-pentofuranosyl pyridin-1-ium triflate (26)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.14 (2H, app d, *J* = 6.6, 2 × Ar-**H**), 8.77 (1H, ddd, *J* = 1.3, 2.6, 7.8, Ar-**H**), 8.27 (2H, app t, *J* = 7.2, 2 × Ar-**H**), 7.73–7.70 (4H, m, 4 × Ar-**H**), 7.51-7.43 (6H, m, 6 × Ar-**H**), 6.69 (1H, d, *J* = 1.7, C1′**H**), 5.23–5.19 (1H, m, C4′**H**), 5.84 (1H, dd, *J* = 1.0, 10.8, C5′**H$_A$**H$_B$), 3.73 (1H, dd, *J* = 6.0, 10.8, C5′H$_A$**H$_B$**), 2.76–2.71 (1H, m, C3′**H**), 1.80 (1H, ddd, *J* = 7.5, 10.2, 18.0, CFC**H$_A$**H$_B$), 1.34 (1H, app q, *J* = 6.0, CFCH$_A$**H$_B$**), 1.09 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.2 (Ar-**C**H), 143.4 (2 × Ar-**C**H), 136.8 (2 × Ar-**C**H), 136.7 (2 × Ar-**C**H), 134.12 (2 × Ar-**C**), 131.18 (Ar-**C**H), 131.15 (Ar-**C**H), 129.6 (2 × Ar-**C**H), 128.97 (2 × Ar-**C**H), 128.96 (2 × Ar-**C**H), 97.2 (d, *J* = 17, **C**1′H), 86.3 (d, *J* = 257, **C**2′F), 83.7 (**C**4′H), 64.2 (**C**5′H$_2$), 27.3 ((**C**H$_3$)$_3$C), 24.5 (d, *J* = 8, **C**3′H), 20.0 (**C**(CH$_3$)$_3$), 13.1 (d, *J* = 11, CF**C**H$_2$), (signal for CF_3 was not observed); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ = −80.1 (TfO), −206.6; (IR) ν_{max}(cm^{-1}):3133, 2932, 2859, 1739, 1259, 1155, 1112, 1030; HRMS (ESI-TOF) *m/z*: $(M)^+$ calcd for $C_{27}H_{31}FNO_2Si$ 448.2108; found: 448.2108; (ESI-TOF) *m/z*: $(TfO)^-$ calcd for CO_3F_3S 148.9520; found: 148.9516; $[\alpha]_D^{21}$ −69.6 (*c* 1.1, $CHCl_3$).

β-D-5′-*O*-*p*-Methoxybenzoyl-2′,3′-dideoxy-2′-fluoro-2′,3′-*endo*-methyleneuridine (27)

To a solution of nucleoside **23** (4:1 β:α mixture, 390 mg, 0.81 mmol) in THF (10 mL) was added a solution of TBAF (1 mL, 1M in THF, 1 mmol) drop-wise at 0 °C and the mixture was allowed to gradually warm up to rt over 3 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in pyridine (8 mL) and solid *para*-methoxybenzoyl chloride (273 mg, 1.60 mmol) was

added in one portion at rt. After 4 h an additional portion of *para*-methoxybenzoyl chloride (273 mg, 1.60 mmol) was added and the reaction stirred for 16 h. The reaction mixture was quenched with MeOH (2 mL) and concentrated *in vacuo*. The residue was concentrated onto silica and purified by column chromatography (SiO_2, *n*-heptane:acetone) to give 245 mg (0.65 mmol, 80% yield over two steps) of ester **27** as a yellow solid (4:1 β:α mixture). The product was recrystallized from EtOAc to give 135 mg of clean β anomer as colorless needle clusters, mp. 230–232 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (β anomer) = 8.23 (1H, bs, N**H**), 8.00-7.96 (2H, m, 2 × Ar-**H**), 7.47 (1H, d, *J* = 8.2, C6**H**), 7.00–6.91 (2H, m, 2 × Ar-**H**), 6.55 (1H, d, *J* = 2.8, C1′**H**), 5.75 (1H, dd, *J* = 2.4, 8.2, C5**H**), 4.74 (1H, app q, *J* = 5.1, C4′**H**), 4.38 (1H, dd, *J* = 5.7, 12, C5′**H**$_A$H$_B$), 4.34 (1H, dd, *J* = 5.0, 12, C5′H$_A$**H**$_B$), 3.87 (3H, s, OC**H**$_3$), 2.24–2.17 (1H, m, C3′**H**), 1.65–1.55 (1H, m, CFC**H**$_A$H$_B$), 1.41 (1H, app q, *J* = 6.9, CFCH$_A$**H**$_B$); ^{13}C NMR (100 MHz, $CDCl_3$): δ (β anomer) = 165.9 (**C**), 163.8 (**C**), 162.1 (**C**), 150.2 (**C**2=O), 139.1 (**C**6H), 131.8 (2 × Ar-**C**H), 121.7 (Ar-**C**), 113.8 (2 × Ar-**C**H), 102.9 (**C**5H), 83.5 (d, *J* = 27, **C**1′H), 82.9 (d, *J* = 251, **C**2′F), 75.4 (**C**4′H), 63.1 (**C**5′H$_2$), 55.5 (**C**H$_3$O), 21.8 (d, *J* = 7, **C**3′H), 10.1 (d, *J* = 11, CF**C**H$_2$); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ = −209.35; (IR) ν_{max}(cm^{-1}): 3116, 2361, 2341, 1685, 1607, 1458, 1257, 1170; HRMS (ESI-TOF) *m/z*: (M+H)$^+$ calcd for $C_{18}H_{18}FN_2O_6$ 377.1140; found: 377.1162; $[\alpha]_D^{21}$ +10.3 (*c* 0.2, $CHCl_3$).

2-*tert*-Butyloxycarbonylamino-9-(5′-*O*-*tert*-butyldiphenylsilyl-2′,3′-dideoxy-2′-fluoro-2′,3′-*endo*-methylene-β/*α*-D-pentofuranosyl)-6-chloro-9*H*-purine (28)

To a solution of lactol **21** (100 mg, 0.26 mmol) in anhydrous THF (5 mL) was added PPh_3 (122 mg, 0.47 mmol) followed by *N*-Boc-2-amino-6-chloropurine (125 mg, 0.47 mmol) at rt. The mixture was stirred for 10 min and DIAD was added drop-wise (92 μL, 0.47 mmol). The mixture was stirred for 4 h and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, *n*-heptane:acetone) to give **28** as a mixture of 8:1 β:α anomers (98 mg, 0.15 mmol, 58%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (major, β anomer) = 8.07 (1H, s, C8**H**), 7.67–7.63 (4H, m, Ar**H**), 7.50 (1H, bs, N**H**), 7.45–7.36 (6H, m, Ar**H**), 6.62 (1H, dd, *J* = 1.1, 4.0 Hz, C1′**H**), 4.60–4.56 (1H, m, C4′**H**), 3.75 (1H, ddd, *J* = 0.9, 4.9, 10.7, C5′C**H**$_A$H$_B$), 3.64 (1H, dd, *J* = 6.2, 10.7, C5′H$_A$**H**$_B$), 2.30–2.23 (1H, m, C3′**H**), 1.58–1.51 (1H, m, CFC**H**$_A$H$_B$), 1.52 (9H, s, (C**H**$_3$)$_3$CSi), 1.27–1.24 (1H, m, CFCH$_A$**H**$_B$), 1.06 (9H, s, (C**H**$_3$)$_3$C); ^{13}C NMR (100 MHz, $CDCl_3$): δ (major, β anomer) = 153.1 (**C**=O Boc), 152.7 (**C**), 151.5 (**C**), 149.9 (**C**), 141.4 (**C**8H), 135.5 (4 × Ar-**C**H), 133.0 (Ar-**C**), 132.9 (Ar-**C**), 129.9 (2 × Ar-**C**H), 127.8 (4 × Ar-**C**H), 84.1 (d, *J* = 251, **C**2′F), 83.4 (d, *J* = 27, **C**1′H), 81.7 ((CH$_3$)$_3$**C**O), 78.1 (**C**4′H), 63.0 (**C**5′H$_2$), 28.2 ((**C**H$_3$)$_3$CSi) 26.8 ((**C**H$_3$)$_3$CO), 23.1 (d, *J* = 7, **C**3′H), 19.2 ((CH$_3$)$_3$**C**Si), 10.6 (d, *J* = 11, CF**C**H$_2$); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ = −206.6 (α anomer), −209.5 (β anomer); (IR) ν_{max}(cm^{-1}): 2932, 1751, 1572, 1449, 1135, 1111, 1076; HRMS (ESI-TOF) *m/z*: (M+H)$^+$ calcd for $C_{32}H_{38}ClFN_5O_4Si$ 638.2366; found: 638.2363.

***N*-*tert*-Butyloxycarbonyl-β/α-D-2′,3′-dideoxy-2′-fluoro-2′,3′-*endo*-methyleneguanosine (29)**

To a suspension of NaH (60% in mineral oil, 94 mg, 2.35 mmol) in anhydrous THF (2 mL) at −78 °C was added 3-hydroxypropionitrile (162 μL, 2.35 mmol) drop-wise. The mixture was stirred at −78 °C for 20 min then 1 h at 0 °C. A solution of **28** (300 mg, 0.47 mmol) in anhydrous THF (2 mL) was added drop-wise and the mixture stirred at 0 °C for 2 h and then further 3h at rt. The reaction was quenched at 0 °C with MeOH and concentrated *in vacuo*. The residue was concentrated onto silica gel and purified by column chromatography (SiO_2, $CHCl_3$:MeOH, 0→10%) to give **29** as a white amorphous solid (11:1 mixture of β:α anomers, 100 mg, 0.26 mmol, 55% yield).

^{1}H NMR (400 MHz, d_6-DMSO) δ (major, β anomer) = 11.16 (2H, bs, N**H** and N**H**Boc), 8.24 (1H, s, C8**H**), 6.38 (1H, d, *J* = 3.4, C1′**H**), 4.85 (1H, t, *J* = 5.2, C5′O**H**), 4.43 (1H, app dt, *J* = 3.3, 5.7, C4′**H**), 3.44–3.42 (2H, m, C5′**H**$_2$), 2.36–2.33 (1H, m, C3′**H**), 1.76 (1H, app q, *J* = 6.8, CFC**H**$_A$H$_B$), 1.60–1.51 (1H, m, CFCH$_A$**H**$_B$), 1.50 (9H, s, (C**H**$_3$)$_3$C); ^{13}C NMR (100 MHz, d_6-DMSO): δ (major, β anomer) = 155.0 (**C**6=O), 153.8 (**C**=O Boc), 149.3 (**C**), 148.1 (**C**), 137.0 (**C**8H), 119.6 (**C**), 84.6 (d, *J* = 247, **C**2′F), 82.6 (**C**(CH$_3$)$_3$), 82.3 (d, *J* = 28, **C**1′H), 78.2 (**C**4′H), 60.6 (**C**5′H$_2$), 27.7 ((**C**H$_3$)$_3$C), 22.5 (d, *J* = 7 Hz, **C**3′H), 9.9 (d, *J* = 11, CF**C**H$_2$); ^{19}F{^{1}H} NMR (376 MHz, d_6-DMSO) δ = −206.1 (α anomer), −208.5 (β anomer); (IR) ν_{max}(cm^{-1}): 3230, 2979, 2933, 1680, 1606, 1562, 1478, 1455, 1402, 1367, 1244, 1150, 1097, 1052, 784; HRMS (ESI-TOF) *m/z*: (M+H)$^+$ calcd for $C_{16}H_{21}FN_5O_5$ 382.1527; found: 382.1519.

(*S*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol (31)

To a solution of crude ester **30**[32] (157.0 g, 0.77 mol) in EtOH (1.5 L) at 0 °C was added $NaBH_4$ (58.2 g, 1.54 mol) portion-wise over 30 min. The reaction was stirred at rt for 2 h, then quenched by the addition of AcOH (90 mL) and MeOH (150 mL). The mixture was stirred for 16 h at room temperature and concentrated *in vacuo.* The resulting moist solid was triturated with EtOAc and the filtrate was concentrated *in vacuo* to give **31** as a pale brown oil (133.9 g, 0.83 mol). This material was used in the next step without further purification. The ^{1}H and ^{13}C NMR spectroscopic data agreed with those published in the literature.[31]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.10–4.04 (2H, m, HOC**H** and OC**H**$_2$), 3.99–3.92 (1H, m, OC**H**$_2$), 3.79 (1H, dd, *J* = 3.3, 11.1, HOC**H**$_2$), 3.75–3.70 (1H, m, HOC**H**), 3.64 (1H, dd, *J* = 5.5, 11.1, HOC**H**$_2$), 2.81 (2H, br. s, 2 × O**H**), 1.42 (3H, s, OC(C**H**$_3$)$_2$), 1.36 (3H, s, OC(C**H**$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 109.2 (**C**(CH$_3$)$_2$), 76.3 (HO**C**H), 72.2 (HO**C**H), 65.9 (O**C**H$_2$), 63.6 (HO**C**H$_2$), 26.5 (C(**C**H$_3$)$_2$), 25.3 (C(**C**H$_3$)$_2$).

(*S*)-2-(Benzyloxy)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (32)

To a solution of crude **31** (133.9 g, 0.83 mol) in anhydrous toluene (2.6 L) was added dibutyltin oxide (200 g, 0.83 mol) and the mixture was heated at reflux for 4 h with Dean-Stark apparatus. After cooling to 40 °C, benzyl bromide (147 mL, 1.24 mol) and TBAI (61.0 g, 0.17 mol) were added and the reaction heated at reflux overnight. After cooling to rt, the mixture was diluted with CH_2Cl_2 (2.6 L) and washed with sat. aq. $NaHCO_3$ (2.6 L). The aq. layer was then extracted with

CH_2Cl_2 (2 × 1 L). The combined organic layers were washed with 10% NaCl (2.6 L). The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting 4:1 mixture of diastereoisomers was separated by column chromatography (EtOAc:*n*-heptane gradient) to give the desired **32** as a major isomer (84.6 g, 0.34 mol, 30% yield over 6 steps) and its diastereoisomer (minor isomer, 21.0 g, 7% yield over 6 steps). The ^{1}H and ^{13}C NMR spectroscopic data of **32** and its regioisomer agreed with those published in the literature.[33]

(*R*)-2-(Benzyloxy)-1-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanone (33)

To a solution of oxalyl chloride (12.6 mL, 147.0 mmol) in anhydrous CH_2Cl_2 (100 mL) at −78 °C was added a solution of DMSO (23.5 mL, 330.7mmol) in anhydrous CH_2Cl_2 (20 mL) drop-wise over 50 min. After 15 min a solution of alcohol **32** (18.5 g, 73.5 mmol) in anhydrous CH_2Cl_2 (35 mL) was added drop-wise over 15 min. The reaction was stirred for 90 min at −78 °C and quenched by the drop-wise addition of Et_3N (102 mL, 734.8 mmol) over 15 min. The resultant slurry was stirred for 5 min and gradually warmed to rt. Then CH_2Cl_2 (150 mL) and H_2O (150 mL) were added and the mixture stirred for further 5 min. The aqueous layer was separated and extracted with CH_2Cl_2 (150 mL), the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* at rt to give ketone **33** as a yellow oil, which was used in the next step without further purification. A small sample of the ketone was purified by column chromatography (SiO_2, *n*-heptane:acetone) for analysis.[35]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.27 (5H, m, Ar-**H**), 4.60–4.56 (3H, m, OC**H**$_2$Ph and OC**H**), 4.39 (2H, s, C=OC**H**$_2$OCH_2Ph), 4.23 (1H, dd, *J* = 7.9, 8.8, OC**H**$_2$), 4.02 (1H, dd, *J* = 5.5, 8.8, OC**H**$_2$), 1.43 (3H, s, OC(C**H**$_3$)$_2$), 1.36 (3H, s, OC(C**H**$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.75 (**C**=O), 137.03 (Ar-**C**), 128.6 (2 × Ar-**C**H), 128.1 (Ar-**C**H), 128.0 (2 × Ar-**C**H), 111.0 (**C**(CH$_3$)$_2$), 79.1 (O**C**H), 73.5 (O**C**H$_2$Ph), 72.8 (**C**H$_2$OCH$_2$Ph), 66.5 (O**C**H$_2$), 25.9 (C(**C**H$_3$)$_2$), 24.9 (C(**C**H$_3$)$_2$); (IR) ν_{max}(cm^{-1}): 3031, 2988, 2937, 2886, 1734, 1373, 1258, 1214, 1070; HRMS (ESI-TOF) *m/z*: (M+Na$^+$) calcd for $C_{14}H_{18}NaO_4$ 273.1097; found: 273.1121; $[\alpha]_D^{21}$ +37.1 (*c* 1.0, $CHCl_3$).

(*S*,*E*)-4-(Benzyloxy)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-fluorobut-2-en-1-ol ((*E*)-35) and **(*S*,*Z*)-4-(Benzyloxy)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-fluorobut-2-en-1-ol ((*Z*)-35)**

To a solution of triethyl 2-fluoro-2-phosphonoacetate (21.4 g, 88.2 mmol) in anhydrous THF (148 mL) at −78 °C was added KHMDS (1M in THF, 88 mL, 88.2 mmol) drop-wise over 45 min. The reaction was stirred at −78 °C for 30 min and a solution of the crude ketone **33** (73.5 mmol) in THF (150 mL) was added drop-wise over 40 min maintaining the temperature below −70 °C. The reaction was stirred at −78 °C for 1 h, then at rt for 90 min. The mixture was then poured onto vigorously stirred sat. aq. NH_4Cl (200 mL) and the aqueous layer was extracted with TBME (2 × 250 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give crude alkene **34** as a yellow oil (27.2 g, mixture of (*Z*):(*E)* isomers, dr = 18:10). The mixture was used in the next step without further purification.

To a solution of crude **(*E*/*Z*)-34** (73.5 mmol) in anhydrous THF (460 mL) was added anhydrous LiCl (7.8 g, 187.7 mol) and $NaBH_4$ (6.9 g, 183.7 mmol). The mixture was cooled to 0 °C and EtOH was added drop-wise (166.5 mL). The reaction was allowed to warm to rt and vigorously stirred for 3 d. The mixture was then diluted with EtOAc (1 L) and quenched by the addition of 10% aq. citric acid solution (0.7 L). The mixture was then washed successively with 10% aq. citric acid solution (1 L), water (0.5 L) and sat. aq. $NaHCO_3$ solution (0.5 L). The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (SiO_2, EtOAc:*n*-heptane) to give the desired minor isomer **(*E*)-35** (yellow oil, 5.3 g, 18.0 mmol, 24% yield over 3 steps) and the major isomer **(*Z*)-35** (yellow oil, 10.2 g, 34.5 mmol, 47% yield over 3 steps).[35]

(*E*)-35: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.25 (5H, m, Ar-**H**), 4.77 (1H, d, *J* = 6.4, 8.2, OC**H**), 4.48 (2H, 2 × d, *J* = 11.8, OC**H**$_2$Ph), 4.38–4.23 (2H, m, HOC**H**$_2$), 4.19 (1H, dd, *J* = 2.7, 10.8, C=CC**H**$_2$OCH$_2$Ph), 4.12–4.05 (2H, m, C**H**$_2$OC(CH$_3$)$_2$ and C=CC**H**$_2$OCH$_2$Ph), 3.88 (1H, t, *J* = 8.3, C**H**$_2$OC(CH$_3$)$_2$), 2.72 (1H, t, *J* = 6.5, OH), 1.41 (3H, s, OC(C**H**$_3$)$_2$), 1.38 (3H, s, OC(C**H**$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3 (d, *J* = 259.7, CHC=**C**F), 137.9 (Ar-**C**), 128.4 (2 × Ar-**C**H), 127.9 (Ar-**C**H), 127.8 (2 × Ar-**C**H), 114.4 (d, *J* = 14.0, CH**C**=CF), 109.3 (**C**(CH$_3$)$_2$), 73.2 (d, *J* = 7.9, O**C**H), 72.6 (O**C**H$_2$Ph), 68.5 (d, *J* = 3.0, **C**H$_2$OC(CH$_3$)$_2$), 62.5 (d, *J* = 8.6, C=C**C**H$_2$OCH$_2$Ph), 58.0 (d, *J* = 31.3, **C**H$_2$OH), 26.2 (C(**C**H$_3$)$_2$), 25.6 (C(**C**H$_3$)$_2$); ^{19}F NMR (376 MHz, $CDCl_3$): δ −104.5 (1F, C**F**); (IR) ν_{max}(cm^{-1}): 3433, 3031, 2934, 2875, 1697, 1454,1371, 1212, 1155, 1026, 895; HRMS (ESI-TOF) *m/z*: (M+Na$^+$) calcd for $C_{16}H_{21}FNaO_4$ 319.1316; found 319.1329; $[\alpha]_D^{21}$ +13.1 (*c* 1.0, $CHCl_3$).

(*Z*)-35: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.25 (5H, m, Ar-**H**), 5.12 (1H, m, OC**H**), 4.52 (2H, 2 × d, *J* = 11.7, OC**H**$_2$Ph), 4.28–4.14 (2H, m, HOC**H**$_2$), 4.14–4.01 (3H, m, C**H**$_2$OC(CH$_3$)$_2$ and C=CC**H**$_2$OCH$_2$Ph), 3.69 (1H, t, *J* = 8.1, C**H**$_2$OC(CH$_3$)$_2$), 2.76 (1H, t, *J* = 6.5, OH), 1.38 (3H, OC(C**H**$_3$)$_2$), 1.37 (3H, OC(C**H**$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.3 (d, *J* = 261.8, CHC=**C**F), 137.4 (Ar-**C**), 128.6 (2 × Ar-**C**H), 128.1 (Ar-**C**H), 128.0 (2 × Ar-**C**H), 114.7 (d, *J* =9.8, CH**C**=CF), 109.3 (**C**(CH$_3$)$_2$), 72.9 (O**C**H$_2$Ph), 70.7 (d, *J* = 9.4, O**C**H), 67.7 (d, *J* = 2.9, **C**H$_2$OC(CH$_3$)$_2$), 63.4 (d, *J* = 8.5, C=C**C**H$_2$OCH$_2$Ph), 58.5 (d, *J* = 31.0, **C**H$_2$OH), 26.2 (C(**C**H$_3$)$_2$), 25.4 (C(**C**H$_3$)$_2$); ^{19}F NMR (376 MHz, $CDCl_3$): δ −109.6 (1F, CF). (IR) ν_{max}(cm^{-1}): 3422, 3031, 2934, 2881, 1696, 1454,1371, 1213, 1154, 1053, 1026, 856; HRMS (ESI-TOF) *m/z*: (M+Na$^+$) calcd for $C_{16}H_{21}FNaO_4$ 319.1316; found 319.1326; $[\alpha]_D^{21}$ +22.4 (c 1.0, $CHCl_3$).

(((5*S*)-4-((Benzyloxy)methyl)-3-fluoro-5,6-dihydro-2*H*-pyran-2,5-diyl)bis(oxy))bis(*tert*-butyldiphenylsilane) (36a) and **(((5S)-4-((Benzyloxy)methyl)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-fluoro-2,5-dihydrofuran-2-yl)oxy)(*tert*-butyl)diphenylsilane (36b)**

To a solution of **(*E*)-35** (3.0 g, 10.1 mmol) in CH_2Cl_2 (45 mL) at 0 °C was added Dess-Martin periodinane (10.7 g, 25.3 mmol) in one portion. The cooling bath was removed and the reaction allowed to stir at rt for 3 h. An aqueous 10% solution of $Na_2S_2O_3$ (100 mL) was then added and the

mixture vigorously stirred for 1 h. Phases were separated and the aqueous extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude aldehyde was dissolved in 1,4-dioxane (47 mL) and 0.5 M HCl (23 mL) was added, the resultant cloudy solution was stirred on the rotary evaporator at 40 °C for 2 h occasionally turning on the vacuum to remove produced acetone. The reaction was then cooled to 0 °C and solid $NaHCO_3$ was added to adjust the pH 9–10. The mixture was concentrated and the residue was triturated with CH_2Cl_2 (3 × 50 mL). The combined organic washes were filtered and concentrated *in vacuo.* The residue was dissolved in anhydrous CH_2Cl_2 (70 mL) and imidazole (2.60 g, 38.20 mmol) and TBDPSCl (7.5 mL, 28.65 mmol) were added. The reaction was stirred at rt for 48 h and then quenched by the addition of water (5 mL). The mixture was diluted with CH_2Cl_2 (100 mL) then washed successively with 1 M aq. HCl (70 mL) and sat. aq. $NaHCO_3$ (70 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo.* The crude material was purified by column chromatography (SiO_2, Acetone/*n*-heptane) to give a 3.5:1 mixture of di-TBDPS protected pyranose **36a** and furanose **36b** (5.7 g, 7.8 mmol, 77% combined yield over 3 steps) as colorless oil. Additional column chromatography, eluting with a toluene:*n*-heptane gradient (0→100%), allowed these products to be separated. The furanose **36b** was isolated as a 4:1 mixture of β:α anomers (colorless oil), while the pyranose **36a** (colorless oil) as a 6:1 mixture of anomers (the stereochemistry of the major and minor anomers of **36a** could not be assigned from analysis of the NOESY NMR spectroscopy).

36a, major anomer, isolated: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.64 (8H, m, Ar**H**), 7.44–7.21 (17H, m, Ar**H**), 5.24 (1H, app s, C1**H**), 4.40–4.32 (4H, m, PhC**H**$_2$, C4**H** and (C3)C**H**$_A$H$_B$), 4.07 (1H, ddd, *J* = 1.4, 3.9, 11.5, (C3)CH$_A$**H$_B$**), 3.93 (1H, dd, *J* = 2.2, 12.6, C5**H**$_A$H$_B$), 3.63 (1H, d, *J* = 12.6, C5H$_A$**H$_B$**), 1.04 (9H, s, C(C**H**$_3$)$_3$), 1.01 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.3 (d, *J* = 267, **C**F), 138.1 (Ar-**C**), 136.0 (Ar-**C**H), 135.9 (Ar-**C**H), 135.8 (Ar-**C**H), 133.9 (Ar-**C**), 133.0 (Ar-**C**), 133.0 (Ar-**C**), 132.9 (Ar-**C**), 129.80 and 129.79 (Ar-**C**H), 129.6 (Ar-**C**H), 128.3 (Ar-**C**H), 127.8 (Ar-**C**H), 127.7 (Ar-**C**H), 127.58 and 127.57 (Ar-**C**H), 112.8 (d, *J* = 5, **C**3), 87.4 (d, *J* = 37, **C**1H), 72.3 (**C**H$_2$Ph), 65.0 (d, *J* = 7, **C**H4), 64.6 (**C**5H$_2$), 61.8 (d, *J* = 5, (C3)**C**H$_2$), 26.9 (C(**C**H$_3$)$_3$), 26.7 (C(**C**H$_3$)$_3$), 19.4, (Si**C**(CH$_3$)$_3$), 19.3 (Si**C**(CH$_3$)$_3$); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ = −122.6; (IR) ν_{max}(cm^{-1}): 3071, 3049, 2999, 2957, 2930, 2858, 1427, 1361, 1111, 1077, 1026, 700; HRMS (ESI-TOF) *m/z*: (M+Na$^+$) calcd for $C_{45}H_{51}FNaO_4Si_2$ 753.3202; found 753.3185; $[\alpha]_D^{21}$ +11.4 (*c* 1.0 $CHCl_3$).

36a, minor anomer, isolated: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.71–7.63 (8H, m, Ar**H**), 7.45–7.20 (17H, m, Ar**H**), 5.07 (1H, app s, C1**H**), 4.60–4.55 (1H, m, C4**H**), 4.38 (2H, app br s, PhC**H**$_2$), 4.36 (1H, d, *J* = 11.6, (C3)C**H**$_A$H$_B$), 4.32 (1H, d, *J* = 11.6, (C3)CH$_A$**H$_B$**), 3.83 (1H, dd, *J* = 9.3, 10.8, C5**H**$_A$H$_B$), 3.28 (1H, ddd, *J* = 1.1, 5.4, 10.8, C5H$_A$**H$_B$**), 1.09 (9H, s, C(C**H**$_3$)$_3$), 1.07 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.0 (d, *J* = 237, **C**F), 138.2 (Ar-**C**), 136.0 (Ar-**C**H), 135.9 (Ar-**C**H), 135.79 (Ar-**C**H), 135.77 (Ar-**C**H), 133.9 (Ar-**C**), 132.9 (Ar-**C**), 132.8 (Ar-**C**), 132.6 (Ar-**C**), 129.89 (Ar-**C**H), 129.87 (Ar-**C**H), 129.8 (Ar-**C**H), 128.2 (Ar-**C**H), 127.70 (Ar-**C**H), 127.69 (Ar-**C**H), 127.64 (Ar-**C**H), 127.61 (Ar-**C**H), 127.59 (Ar-**C**H), 127.5 (Ar-**C**H), 115.8 (d, *J* =

5, **C**3), 88.0 (d, *J* = 37, **C**1H), 72.0 (**C**H_2Ph), 65.5 (d, *J* = 5, **C**H4), 63.3 (**C**5H_2), 60.6 (d, *J* = 5, (C3)**C**H_2), 26.9 (C(**C**H_3)$_3$), 26.7 (C(**C**H_3)$_3$), 19.4, (Si**C**$(CH_3)_3$), 19.3 (Si**C**$(CH_3)_3$); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ = −122.4. (IR) ν_{max}(cm^{-1}): 3071, 3049, 2999, 2957, 2930, 2858, 1427, 1368, 1112, 1076, 1037, 701; HRMS (ESI-TOF) *m/z*: (M+Na^+) calcd for $C_{45}H_{51}FNaO_4Si_2$ 753.3202; found: 753.3219; $[\alpha]_D^{21}$ +10.4 (*c* 1.0 $CHCl_3$).

36b: ^1H NMR (400 MHz, $CDCl_3$) δ (major, β anomer) = 7.78–7.64 (5H, m, Ar**H**), 7.58–7.56 (3H, m, Ar**H**), 7.43–7.22 (17H, m, Ar**H**), 5.95 (1H, app t, *J* = 4.1, C1**H**), 4.83–4.73 (1H, m, C4**H**), 4.44 (1H, d, *J* = 11.8, PhC**H**$_A$H$_B$), 4.42 (1H, d, *J* = 11.8, PhCH$_A$**H**$_B$), 4.18 (1H, d, *J* = 12.5 (C3)C**H**$_A$H$_B$), 4.02 (1H, d, *J* = 12.5, (C3)CH$_A$**H**$_B$), 3.85 (1H, ddd, *J* = 1.4, 2.8, 11.2, C5**H**$_A$H$_B$), 3.65 (1H, dd, *J* = 3.9, 11.2, C5H$_A$**H**$_B$), 1.10 (9H, s, C(C**H**$_3$)$_3$), 0.92 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major, β anomer) = 154.4 (d, *J* = 281, **C**F), 137.7 (Ar-**C**), 135.74 (Ar-**C**H), 135.69 (Ar-**C**H), 135.6 (Ar-**C**H), 133.52 (Ar-**C**), 133.51 (Ar-**C**), 133.42 (Ar-**C**), 132.40 (Ar-**C**), 129.8 (Ar-**C**H), 129.6 (Ar-**C**H), 129.6 (Ar-**C**H), 129.5 (Ar-**C**H), 128.4 (Ar-**C**H), 127.9 (Ar-**C**H), 127.8 (Ar-**C**H), 127.7 (Ar-**C**H), 127.61 (Ar-**C**H), 127.60 (Ar-**C**H), 127.56 (Ar-**C**H), 112.3 (d, *J* = 6, **C**3), 96.7 (d, *J* = 29, **C**1H), 82.3 (d, *J* = 8, **C**H4), 72.3 (**C**H_2Ph), 64.6 (**C**5H_2), 60.74 ((C3)**C**H_2), 26.8 (C(**C**H_3)$_3$), 26.7 (C(**C**H_3)$_3$), 19.3, (Si**C**$(CH_3)_3$), 19.1 (Si**C**$(CH_3)_3$); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ = −140.8 (major, β anomer), −172.8 (minor, α anomer). (IR) ν_{max}(cm^{-1}): 3071, 3050, 2956, 2929, 2857, 1428, 1368, 1112, 1026, 1037, 701; HRMS (ESI-TOF) *m/z*: (M+Na^+) calcd for $C_{45}H_{51}FNaO_4Si_2$ 753.3202; found: 753.3214.

β-1,5-Di-*O*-*tert*-butyldiphenylsilyl-2,3-dideoxy-2-fluoro-2,3-*exo*-methylene-D-pentofuranose (*exo*-37)

To a solution of **36b** (101 mg, 0.21 mmol) in anhydrous 1,2-DCE (3 mL) at −10 °C was added $ZnEt_2$ (1 M in hexanes, 610 μL, 0.62 mmol) drop-wise. The reaction was stirred for 15 min at −10 °C and then a solution of $ClCH_2I$ (90 μL, 1.23 mmol) in anhydrous 1,2-DCE (0.5 mL) was added drop-wise. The reaction was allowed to gradually warm to rt and stirred for 4h. The mixture was then cooled to 0 °C and quenched by addition of sat. aq. NH_4Cl (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic layers dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude mixture was purified by column chromatography (SiO_2, EtOAc:*n*-heptane) to give ***exo*-37** as a colorless oil (56 mg, 0.08 mmol, 55% %, β anomer only). Additionally starting material **36b** was recovered (26 mg, 0.04 mmol, 26%).

^1H NMR (400 MHz, $CDCl_3$) δ = 7.77 (2H, app dd, *J* = 1.3, 8.0, Ar**H**), 7.69 (2H, app dd, *J* = 1.4, 8.1, Ar**H**), 7.57 (2H, app dd, *J* = 1.4, 8.1, Ar**H**), 7.45 (2H, app dd, *J* = 1.3, 8.0, Ar**H**), 7.40–7.17 (17H, m, Ar**H**), 6.12 (1H, d, *J* = 3.4, C1**H**), 4.24 (2H, s, PhC**H**$_2$), 4.02–3.99 (1H, m, C4**H**), 3.88 (1H, app d, *J* = 10.7, (C3)C**H**$_A$H$_B$), 3.83 (1H, dd, *J* = 2.2, 11.4, C5**H**$_A$H$_B$), 3.64 (1H, dd, *J* = 1.5, 11.4, C5H$_A$**H**$_B$), 3.31 (1H, dd, *J* = 1.4, 10.7, (C3)CH$_A$**H**$_B$), 1.54 (1H, dt, *J* = 1.4, 6.4, CFC**H**$_A$H$_B$), 1.21 (1H, ddd, *J* = 1.2, 6.6, 17.9, CFCH$_A$**H**$_B$), 1.10 (9H, s, C(C**H**$_3$)$_3$), 1.82 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 137.9 (Ar-**C**), 135.8 (Ar-**C**H), 135.8 (Ar-**C**H), 135.7 (Ar-**C**H), 133.5 (Ar-**C**), 133.3 (Ar-**C**), 132.9 (Ar-**C**), 132.8 (Ar-**C**), 129.8 (Ar-**C**H), 129.7 (Ar-**C**H), 129.6 (Ar-**C**H),

129.5 (Ar-**C**H), 128.4 (Ar-**C**H), 127.8 (Ar-**C**H), 127.8 (Ar-**C**H), 127.71 (Ar-**C**H), 127.70 (Ar-**C**H), 127.61 (Ar-**C**H), 127.59 (Ar-**C**H), 127.57 (Ar-**C**H), 98.6 (d, *J* = 27, **C**1H), 89.8 (d, *J* = 250, **C**F), 81.8 (**C**H4), 73.0 (**C**H_2Ph), 68.5 ((C3)**C**H_2), 64.3 (**C**5H_2), 30.7 (d, *J* = 8, **C**3), 26.8 (C(**C**H_3)$_3$), 22.7 (C(**C**H_3)$_3$), 19.3, (Si**C**(CH_3)$_3$), 18.8 (Si**C**(CH_3)$_3$), 16.6 (d, *J* = 10, CF**C**H_2); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ = −215.6; (IR) ν_{max}/cm^{-1}: 2960, 2930, 2858, 1672, 1462, 1428, 1228, 1112, 1048, 997, 698; HRMS (ESI-TOF) *m/z*: ($M+Na^+$) calcd for $C_{46}H_{53}FNaO_4Si_2$ 767.3359; found: 767.3352. $[\alpha]_D^{21}$ −10.7 (*c* 1.0 $CHCl_3$).

α/β-1,5-Di-*O*-*tert*-butyldiphenylsilyl-2,3-dideoxy-2-fluoro-2,3-*endo*-methylene-D-pentofuranose (*endo*-37)

The di-TBDPS protected furan ***endo*-37** was synthesized from alcohol **38a** according to the procedure described for synthesis of compounds **36a** and **36b**. It was isolated by column chromatography (SiO_2, heptane:acetone) as colorless oil in 50% yield (over 3 steps) as an inseparable 1:6 mixture of β:α anomers.

^1H NMR (400 MHz, $CDCl_3$) δ (major, α anomer) = 7.77–7.67 (8H, m, Ar**H**), = 7.73–7.23 (17H, m, Ar**H**), 5.39 (1H, d, *J* = 2.4, C1**H**), 4.79 (1H, app t, *J* = 5.4, C4**H**), 4.73 (1H, d, *J* = 12.1, PhCH_A**H$_B$**), 4.48 (1H, d, *J* = 12.1, PhC**H$_A$**H$_B$), 4.02 (1H, d, *J* = 11.4, (C3)C**H$_A$**H$_B$), 3.82 (1H, dd, *J* = 4.6, 10.9, C5**H$_A$**H$_B$), 3.63 (1H, dd, *J* = 6.5, 10.9, C5H$_A$**H$_B$**), 3.58 (1H, d, *J* = 11.4, (C3)CH_A**H$_B$**), 1.09 (9H, s, C(C**H**$_3$)$_3$), 1.05 (9H, s, C(C**H**$_3$)$_3$), 1.08–0.98 (2H, m, CF**C**H_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major, α anomer) = 138.5 (Ar-**C**), 135.9 (Ar-**C**), 135.7 (Ar-**C**), 135.6 (Ar-**C**H), 133.6 (Ar-**C**), 133.43 (Ar-**C**), 133.40 (Ar-**C**), 133.2 (Ar-**C**), 129.71 (Ar-**C**H), 129.67 (Ar-**C**H), 129.60 (Ar-**C**H), 129.59 (Ar-**C**H), 128.3 (Ar-**C**H), 127.63-127.60 (Ar-**C**H), 127.4-127.3 (Ar-**C**H), 95.7 (d, *J* = 18, **C**1H), 85.6 (d, *J* = 255, **C**F), 78.0 (**C**H4), 72.0 (**C**H_2Ph), 67.3 (d, *J* = 2, (C3)**C**H_2), 63.7 (d, *J* = 3, **C**5H_2), 30.0 (d, *J* = 9, **C**3), 26.8 (C(**C**H_3)$_3$), 22.7 (C(**C**H_3)$_3$), 19.4, (Si**C**(CH_3)$_3$), 19.2 (Si**C**(CH_3)$_3$), 14.4 (d, *J* = 11, CF**C**H_2); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ = −212.4 (major, α anomer), −214.7 (minor, β anomer); (IR) ν_{max}/cm^{-1}: 3071, 2956, 2930, 2892, 2857, 1427, 1361, 1905, 1035, 736, 699; HRMS (ESI-TOF) *m/z*: ($M+Na^+$) calcd for $C_{46}H_{53}FNaO_4Si_2$ 767.3359; found: 767.3368.

((1*R*,2*R*)-2-((Benzyloxy)methyl)-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-fluorocyclopropyl)methanol (38a) and **((1*S*,2S)-2-((Benzyloxy)methyl)-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-fluorocyclopropyl)methanol**

To a solution of alkene (***E*)-35** (2.00 g, 6.75 mmol) in anhydrous CH_2Cl_2 (46 mL) at 0 °C was added $ZnEt_2$ (15% wt. in toluene, 13.7 mL, 16.87 mmol) drop-wise over 14 min. The reaction was stirred for a further 5 min and neat CH_2I_2 (2.5 mL, 30.37 mmol) was added drop-wise over 2 min. The reaction was allowed to gradually warm to rt and stirred for 4.5 h. The mixture was then diluted with EtOAc (100 mL) and transferred over to a vigorously stirred ice-cold solution of sat. aq. NH_4Cl (60 mL) via cannula. The phases were separated and the aqueous layer was extracted with EtOAc (2 × 100 mL), the combined organic extracts were dried (Na_2SO_4), filtered and

concentrated *in vacuo*. The crude material (containing cyclopropane **38a** (*R*,*R* stereochemistry) and its (*S*,*S* isomer) in a 5:1 ratio) was purified by column chromatography (SiO_2, EtOAc:*n*-heptane) to give the desired **38a** as a pale yellow oil (0.99 g, 3.18 mmol, 47%) and its cyclopropane stereoisomer (*S*,*S*) as a yellow oil (0.16 g, 0.52 mmol, 8% yield). Additionally, 0.19 g (0.67 mmol, 10% yield) of the starting material **(*E*)-35** was recovered (colorless oil).

38a major, (*R*,*R*) cyclopropane: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.26 (5H, m, Ar**H**), 4.57 (1H, d, *J* = 12.0, OC**H**$_A$H$_B$Ph), 4.46 (1H, d, *J* = 12.0, OCH$_A$**H**$_B$Ph), 4.35 (1H, dd, *J* = 6.1, 8.2, OC**H**), 4.26 (1H, app. dd, *J* = 13.4, 20.8 ($^3J_{H,F}$), HOC**H**$_A$H$_B$CF), 4.15 (1H, dd, *J* = 6.0, 8.3, C**H**$_A$H$_B$OC(CH$_3$)$_2$), 3.93 (1H, app. dd, *J* = 13.4, 32.0 ($^3J_{H,F}$), HOCH$_A$**H**$_B$CF), 3.83 (1H, t, *J* = 8.3, CH$_A$**H**$_B$OC(CH$_3$)$_2$), 3.74 (1H, dd, *J* = 2.7, 10.8, C**H**$_A$H$_B$OBn), 3.50 (1H, dd, *J* = 2.1, 10.8, CH$_A$**H**$_B$OBn), 2.25 (1H, s, O**H**), 1.35 (3H, s, OC(C**H**$_3$)$_2$), 1.34 (3H, s, OC(C**H**$_3$)$_2$), 1.06 (1H, dd, *J* = 7.1, 10.5 ($^3J_{H,F}$), CFC**H**$_A$H$_B$C), 1.03 (1H, ddd, *J* = 0.5, 7.1, 20.4 ($^3J_{H,F}$), CFCH$_A$**H**$_B$C); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.0 (Ar-**C**), 128.5 (2 × Ar-**C**H), 127.9 (Ar-**C**H), 127.7 (d, *J* = 2, 2 × Ar-**C**H), 108.9 (**C**(CH$_3$)$_2$), 84.7 (d, *J* = 222, CF), 74.7 (O**C**H), 72.8 (O**C**H$_2$Ph), 69.3 (d, *J* = 11, **C**H$_2$OBn), 68.4 (d, *J* = 2, **C**H$_2$OC(CH$_3$)$_2$), 64.1 (d, *J* = 24, **C**H$_2$OH), 30.2 (d, *J* = 10, **C**CH$_2$OBn), 26.2 (CH$_3$), 25.7 (CH$_3$), 16.3 (d, *J* = 11, CF**C**H$_2$); ^{19}F NMR (376 MHz, $CDCl_3$): δ −184.3; (IR) ν_{max}(cm^{-1}): 3440, 3064, 2986, 2875, 1497, 1370, 1249, 1058, 908. HRMS (ESI-TOF) *m/z*: (M+Na$^+$) calcd for $C_{17}H_{23}FNaO_4$ 333.1473; found 333.1480; $[\alpha]_D^{21}$ +3.8 (*c* 1.0, $CHCl_3$).

Minor, (*S*,*S*) cyclopropane: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.26 (5H, m, ArH), 4.50 (2H, s, C**H**$_2$Ph), 4.26 (1H, ddd, *J* = 10.0, 13.2, 15.6, HOC**H**$_A$H$_B$CF), 4.18 (1H, dd, *J* = 7.6, 8.7, C**H**$_A$H$_B$OC(CH$_3$)$_2$), 4.06 (1H, dd, *J* = 6.3, 8.7, CH0$_A$**H**$_B$OC(CH$_3$)$_2$), 3.84-3.69 (3H, m, OC**H** and C**H**$_A$H$_B$OBn and HOCH$_A$**H**$_B$CF), 3.54 (1H, dd, *J* = 1.2, 10.8, CH$_A$**H**$_B$OBn), 2.98 (1H, dd, *J* = 3.4, 10.6, OH), 1.38 (3H, s, OC(C**H**$_3$)$_2$), 1.34 (3H, s, OC(C**H**$_3$)$_2$), 1.28 (1H, dd, *J* = 7.4, 20.4 ($^3J_{H,F}$), CFC**H**$_A$H$_B$C), 0.96 (1H, dd, *J* = 0.8, 7.4, 10.9, CFCH$_A$**H**$_B$C); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.0 (Ar-**C**), 128.4 (2 × Ar-**C**H), 127.9 (2 × Ar-**C**H), 127.7 (Ar-**C**H), 108.7 (**C**(CH$_3$)$_2$), 84.6 (d, *J* = 225, CH$_2$**C**F), 78.3 (d, *J* = 1, O**C**H), 73.0 (O**C**H$_2$Ph), 67.0 (**C**H$_2$OC(CH$_3$)$_2$), 66.6 (d, *J* = 11, **C**H$_2$OBn), 64.0 (d, *J* = 23, **C**H$_2$OH), 29.6 (d, *J* = 10, **C**CH$_2$OBn), 26.1 (CH$_3$), 25.1 (CH$_3$), 18.0 (d, *J* = 11, CF**C**H$_2$); ^{19}F NMR (376 MHz, $CDCl_3$): δ −187.4. (IR) ν_{max}(cm^{-1}): 3468, 3030, 2986, 2879, 1371, 1214, 1158, 1062; HRMS (ESI-TOF) *m/z*: (M+Na$^+$) calcd for $C_{17}H_{23}FNaO_4$ 333.1473; found 333.1482; $[\alpha]_D^{21}$ +20.1 (*c* 0.6, $CHCl_3$).

α/β-5-*O*-Acetoxy-1-*O*-acetyl-3-benzyloxymethyl-2,3-dideoxy-2-fluoro-2,3-*endo*-methylene-D-pentofuranose (39)

To a solution of **38a** (0.90 g, 2.91 mmol) in anhydrous CH_2Cl_2 (13.5 mL) was added Dess-Martin periodinane (3.08 g, 7.28 mmol) at rt. The reaction was stirred for 6 h, then an aqueous solution of 10% Na_2SO_3 and 2% $NaHCO_3$ (28 mL) was added and the mixture vigorously stirred for 30 min. Phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was dissolved in 1,4-dioxane (13 mL) and 1 M HCl (6.5 mL) was added, the resultant mixture was

stirred on the rotary evaporator at 40 °C for 2 h occasionally turning on the vacuum. The reaction was cooled to 0 °C and solid $NaHCO_3$ was added to adjust the pH to 9–10. The mixture was concentrated and the residue triturated with CH_2Cl_2 (3 × 25 mL), the combined organic extracts were filtered and concentrated *in vacuo*. The residue (crude lactol) was dissolved in pyridine (7.8 mL) and acetic anhydride (2 mL) was added drop-wise at 0 °C. The reaction was then stirred at rt for 3.5 h, then cooled to 0 °C and quenched by the addition of MeOH (6 mL). The mixture was concentrated *in vacuo* and the residue purified by column chromatography (SiO_2, EtOAc/*n*-heptane) to give **39** as a pale yellow oil (0.79 g, 2.26 mmol, mixture of anomers, 1:7 β:α, 88% over 3 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ (major, α anomer) = 7.35–7.18 (5H, m, Ar**H**), 6.45 (1H, d, *J* = 2.3, C1**H**), 4.72 (1H, dd, *J* = 3.6, 7.0, C4**H**), 4.64 (1H, d, *J* = 12.0, PhC**H**$_A$H$_B$), 4.49 (1H, d, *J* = 12.0, PhCH$_A$**H**$_B$), 4.30 (1H, dd, *J* = 3.7, 12.0, C5**H**$_A$H$_B$), 4.00 (1H, dd, *J* = 7.2, 12.0, C5H$_A$**H**$_B$), 3.83 (1H, d, *J* = 11.4, (C3)C**H**$_A$H$_B$), 3.66 (1H, d, *J* = 11.4, (C3)CH$_A$**H**$_B$), 2.13 (3H, s, C**H**$_3$), 2.05 (3H, s, C**H**$_3$), 1.33 (1H, dd, *J* = 7.3, 17.8, CFC**H**$_A$H$_B$), 1.31 (1H, app t, *J* = 6.6, CFCH$_A$**H**$_B$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major, α anomer) = 170.6 (**C**=O), 169.8 (**C**=O), 137.8 (Ar-**C**), 128.5 (2 × Ar-**C**H), 127.8 (Ar-**C**H), 127.6 (2 × Ar-**C**H), 93.8 (d, *J* = 18, **C**1H), 83.5 (d, *J* = 258, **C**F), 77.9 (**C**H4), 72.7 **C**H$_2$Ph), 66.7 (d, *J* = 3, **C**H$_2$(C3)), 63.3 (d, *J* = 3, **C**5H$_2$), 30.0 (d, *J* = 9, **C**3), 21.1 (**C**H$_3$), 20.8 (**C**H$_3$), 14.7 (d, *J* = 11, CF**C**H$_2$); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ = −215.2 (minor, β anomer), −217.7 (major, α anomer); (IR) ν_{max}(cm^{-1}): 2929, 2862, 1741, 1454, 1369, 1220, 1078, 1008, 966, 904; HRMS (ESI-TOF) *m/z*: (M+Na$^+$) calcd for $C_{18}H_{21}FNaO_6$ 375.1214; found 375.1213.

α/β-5-*O*-Acetoxy-1-*O*-acetyl-2,3-dideoxy-2-fluoro-3-*C*-hydroxymethyl-2,3-*endo*-methylene-D-pentofuranose (40)

To a suspension of 10% Pd/C (50% wet, 0.53 g, 0.25 mmol) in MeOH (4 mL) was added a solution of furanose **39** (1.72 g, 4.88 mmol) in MeOH (20 mL). The flask was de-gassed and charged with hydrogen, then stirred at rt for 3.5 h. The mixture was filtered and the catalyst rinsed with MeOH. The filtrate was concentrated *in vacuo* and the crude alcohol **40** was used in the next step without further purification. A small sample of **40** (1:7 β:α mixture of anomers) was purified by column chromatography (SiO_2, EtOAc/*n*-heptane) for analysis.

^{1}H NMR (400 MHz, $CDCl_3$): δ (major, α anomer) = 6.42 (1H, d, *J* = 2.3, C1**H**), 4.71 (1H, app t, *J* = 5.3, C4**H**), 4.21 (1H, dd, *J* = 4.4, 12.0, C5**H**$_A$H$_B$), 4.13 (1H, dd, *J* = 6.2, 12.0, C5H$_A$**H**$_B$), 4.94 (1H, d, *J* = 12.5, (C3)C**H**$_A$H$_B$), 3.90 (1H, d, *J* = 12.6, (C3)CH$_A$**H**$_B$), 3.48 (1H, s, O**H**), 2.15 (3H, s, C**H**$_3$), 2.09 (3H, s, C**H**$_3$), 1.43 (1H, dd, *J* = 7.3, 18.2, CFC**H**$_A$H$_B$), 1.22 (1H, app t, *J* = 6.8, CFCH$_A$**H**$_B$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major, α anomer) = 170.8 (**C**=O), 169.8 (**C**=O), 93.7 (d, *J* = 18, **C**1H), 83.9 (d, *J* = 256, **C**F), 77.8 (d, *J* = 1, **C**4), 63.2 (d, *J* = 3, **C**5H$_2$), 60.2 (d, *J* = 4, (C3)**C**H$_2$), 32.2 (d, *J* = 8, **C**3), 21.1 (**C**H$_3$), 20.8 (**C**H$_3$), 14.8 (d, *J* = 11, CF**C**H$_2$); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ = −216.3 (minor, β anomer), −217.6 (major, α anomer); (IR) ν_{max}(cm^{-1}): 3468, 2941, 1738, 1368, 1221, 1007, 965; HRMS (ESI-TOF) *m/z*: (M+Na$^+$) calcd for $C_{11}H_{15}FNaO_6$ 285.0745; found 285.0768.

α/β-5-*O*-Acetoxy-3-*C*-acetoxymethyl-1-*O*-acetyl-2,3-dideoxy-2-fluoro2,3-*endo*-methylene-D-pentofuranose (41)

To a solution of the crude **40** (4.88 mmol) in anhydrous pyridine (17 mL) at 0 °C was added acetic anhydride (4.3 mL, 45.5 mmol) drop-wise. The reaction was stirred at rt for 2.5 h, then cooled to 0 °C and quenched by the addition of MeOH (6 mL). The mixture was concentrated *in vacuo*, diluted with CH_2Cl_2 (100 mL) and subsequently washed with 2 M HCl (70 mL) and sat. aq. $NaHCO_3$ (70 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, EtOAc:*n*-heptane) to give triacetate **41** as a yellow oil (1.34 g, 4.43 mmol, 91% over 2 steps, 1:6 mixture of β:α anomers).[52]

^{1}H NMR (400 MHz, $CDCl_3$) δ (major, α anomer) = 6.44 (1H, d, *J* = 2.2, C1**H**), 4.60 (1H, dd, *J* = 4.0, 6.7, C4**H**), 4.44 (1H, d, *J* = 12.6, (C3)C**H$_A$**H$_B$), 4.30 (1H, d, *J* = 12.6, (C3)CH$_A$**H$_B$**), 4.21 (1H, dd, *J* = 4.0, 12.0, C5**H$_A$**H$_B$), 4.05 (1H, dd, *J* = 6.8, 12.0, C5H$_A$**H$_B$**), 2.15 (3H, s, C**H**$_3$), 2.11 (3H, s, C**H**$_3$), 2.08 (3H, s, C**H**$_3$), 1.50 (1H, dd, J = 7.5, 18.0, CFC**H$_A$**H$_B$), 1.31 (1H, dd, J =6.8, 7.4, CFCH$_A$**H$_B$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major, α anomer) = 170.6 (**C**=O), 170.5 (**C**=O), 170.7 (**C**=O), 93.4 (d, *J* = 19, **C**1H), 83.6 (d, *J* = 256, **C**F), 78.1 (d, *J* = 1, **C**4), 63.0 (**C**5H$_2$), 61.5 ((C3)**C**H$_2$), 29.1 (d, *J* = 8, **C**3), 21.0 (**C**H$_3$), 20.7 (2 × **C**H$_3$), 15.4 (d, *J* = 11, CF**C**H$_2$); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ = −215.6 (minor, β anomer), −216.3 (major, α anomer); (IR) ν_{max}(cm^{-1}): 1733, 1373, 1232, 1214, 1008, 901; HRMS (ESI-TOF) *m/z*: (M+Na$^+$) calcd for $C_{13}H_{17}FNaO_7$ 327.0856; found 327.0853.

β-D-5′-*O*-Acetyl-3′-*C*-acetoxymethyl-2′,3′-dideoxy-2′-fluoro-2′,3′-*endo*-methyleneuridine (42)

A solution of **41** (140 mg, 0.46 mmol) in anhydrous acetonitrile (5.6 mL) was added to the silylated uracil (3.69 mmol, see general procedure for silylation of the uracil). The mixture was cooled to 0 °C and TMSOTf (0.17 mL, 0.92 mmol) was added drop-wise. The cooling bath was removed and the reaction placed for 4 h at 50 °C. The mixture was then diluted with CH_2Cl_2 (50 mL) and poured onto a vigorously stirred solution of sat. aq. $NaHCO_3$ (25 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, EtOAc:*n*-heptane gradient) to give uridine **42** as a white powder (145 mg, ~10:1 mixture of β:α anomers). The solid was then recrystallized from EtOAc and *n*-heptane to give pure β nucleoside (117 mg, 0.33 mmol, 72%) as colorless needles, mp: 138–139 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.92 (1H, s, N**H**), 7.41 (1H, d, *J* = 8.2, C6**H**), 6.54 (1H, d, *J* = 2.9, C1′**H**), 5.80 (1H, d, *J* = 8.2, C5**H**), 4.54 (1H, dd, *J* = 4.4, 6.0, C4′**H**), 4.51 (1H, d, *J* = 13, (C3)C**H$_A$**H$_B$), 4.25–4.14 (3H, m, (C3)CH$_A$**H$_B$** and C5′**H**$_2$), 2.12 (3H, s, OC(C**H**$_3$)$_2$), 2.09 (3H, s, OC(C**H**$_3$)$_2$), 1.60–1.54 (2H, m, CFC**H**$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6 (**C**=O), 170.5 (**C**=O), 162.4 (**C**4=O), 150.4 (**C**2=O), 138.8 (**C**6H), 103.30 (**C**5H), 83.7 (d, *J* = 253.57, **C**2′F), 82.7 (d, *J* = 26.4, **C**1′H), 76.6 (**C**4′H), 62.5 (d, *J* = 1.9, **C**H$_2$), 61.1 (d, *J* = 4.0, **C**H$_2$), 29.4 (d, *J* = 7.4, **C**3′), 20.7 (2 × **C**H$_3$), 14.1 (d, *J* = 10.9, CF**C**H$_2$); ^{19}F NMR (376 MHz, $CDCl_3$): δ −213.38 (1F, C**F**);

(IR) ν_{max}(cm^{-1}): 3052, 1739, 1689, 1458, 1374, 1246, 1033; HRMS (ESI-TOF) *m/z*: ($M+Na^+$) calcd for $C_{15}H_{17}FN_2NaO_7$ 379.0912; found 379.0921; $[\alpha]_D^{21}$ +2.0 (*c* 1.0, $CHCl_3$).

α/β-5-*O*-Acetyl-3-*C*-acetoxymethyl-2,3-dideoxy-2-fluoro2,3-*endo*-methylene-D-pentofuranose (43)

To a solution of triacetate **41** (328 mg, 1.08 mmol) in anhydrous acetonitrile (20 mL) at 0 °C was added drop-wise TMSOTf (0.4 mL, 2.16 mmol) followed by H_2O (0.1 mL, 5.39 mmol) and the reaction was stirred for 2 h at rt. The mixture was diluted with EtOAc (10 mL) and poured into a vigorously stirred solution of sat. aq. $NaHCO_3$ (12 mL). The layers were separated and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, *n*-heptane/EtOAc) to give lactol **43** as a pale yellow oil (239 mg, 0.91 mmol, 84%, 1:6 mixture of β:α anomers).

^{1}H NMR (400 MHz, $CDCl_3$) δ (major, α anomer) = 6.44 (1H, dd, *J* = 2.3, 4.8 C1**H**), 4.61 (1H, dd, *J* = 4.0, 7.0, C4**H**), 4.47 (1H, d, *J* = 12.5, (C3)C**H**$_A$H$_B$), 4.25 (1H, d, *J* = 12.5, (C3)CH$_A$**H**$_B$), 4.21 (1H, dd, *J* = 4.0, 11.8, C5**H**$_A$H$_B$), 4.02 (1H, dd, *J* = 7.1, 11.8, C5H$_A$**H**$_B$), 3.32 (1H, d, *J* = 5.0, C1O**H**), 2.10 (3H, s, C**H**$_3$), 2.09 (3H, s, C**H**$_3$), 1.43 (1H, dd, *J* = 7.3, 18.2, CFC**H**$_A$H$_B$), 1.26 (1H, app t, *J* = 7.1, CFCH$_A$**H**$_B$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major, α anomer) = 170.9 (**C**=O), 170.7 (**C**=O), 94.9 (d, *J* = 18, **C**1H), 85.0 (d, *J* = 255, **C**F), 76.0 (**C**4), 63.3 (**C**5H$_2$), 61.8 ((C3)**C**H$_2$), 28.9 (d, *J* = 8, **C**3), 20.8 (**C**H$_3$), 20.7 (**C**H$_3$), 15.5 (d, *J* = 11, CF**C**H$_2$); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ = −213.6 (minor, β anomer), −216.1 (major, α anomer); (IR) ν_{max}(cm^{-1}): 3426, 1736, 1240, 1028; HRMS (ESI-TOF) *m/z*: ($M+Na^+$) calcd for $C_{11}H_{15}FNaO_6$ 285.0745; found 285.0755.

2-*tert*-Butyloxycarbonylamino-9-(β/α-5′-*O*-acetyl-3′-*C*-acetoxymethyl-2′,3′-dideoxy-2′-fluoro-2′,3′-*endo*-methylene-D-pentofuranosyl)-6-chloro-9*H*-purine (44)

To a solution of lactol **43** (224 mg, 0.85 mmol) in anhydrous THF (7 mL) was added PPh_3 (269 mg, 1.02 mmol) followed by *N*-Boc-2-amino-6-chloropurine (276 mg, 1.02 mmol) at rt. The mixture was stirred for 5 min and DIAD was added drop-wise (200 µL, 1.02 mmol). The mixture was stirred for 1 h, quenched with MeOH (2 mL) and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc:*n*-heptane gradient) to give **44** as an amorphous off-white solid (200 mg, 0.39 mmol, 46%, mixture of 5:1 β:α anomers).

^{1}H NMR (400 MHz, $CDCl_3$) δ (major, β anomer) = 8.14 (1H, s, C**H**8), 7.59 (1H, br s, N**H**), 6.62 (1H, d, *J* = 2.8 C1′**H**), 4.63 (1H, app t, *J* = 5.8, C4′**H**), 4.60 (1H, d, *J* = 12.6, (C3′)C**H**$_A$H$_B$), 4.31–4.25 (2H, m, (C3′)CH$_A$**H**$_B$ and C5′**H**$_A$H$_B$), 4.20 (1H, d, *J* = 12.6, C5′H$_A$**H**$_B$), 2.20 (1H, app t, *J* = 8.2, CFC**H**$_A$H$_B$), 2.15 (3H, s, C**H**$_3$), 2.08 (3H, s, C**H**$_3$), 1.65 (1H, dd, *J* = 9.3, 17.6, CFCH$_A$**H**$_B$), 1.55 (9H, s, ((C**H**$_3$)$_3$C); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major, β anomer) = 170.5 (**C**=O), 170.4 (**C**=O), 153.0 (**C**=O Boc), 152.8 (**C**), 151.7 (**C**), 149.9 (**C**), 141.5 (**C**8H), 128.0 (**C**), 83.5 (d, *J* = 27, **C**1′H), 84.7 (d, *J* = 253, **C**2′F), 81.8 (**C**(CH$_3$)$_3$), 77.2 (**C**′4H), 62.7 (**C**5′H$_2$), 61.3 (d, *J* = 4, (C3′)**C**H$_2$), 30.7 (d, *J* = 8, **C**3′), 28.1 (**C**H$_3$)$_3$C), 20.74 (**C**H$_3$), 20.70 (**C**H$_3$), 15.2 (d, *J* = 11, CF**C**H$_2$); ^{19}F{^{1}H} NMR

(376 MHz, $CDCl_3$) δ = −211.2 (minor, α anomer), −213.4 (major, β anomer); (IR) $\nu_{max}(cm^{-1})$: 3243, 2978, 2932, 2873, 1741, 1608, 1510, 1448, 1219, 1150, 1131, 1037; HRMS (ESI-TOF) *m/z*: ($M+H^+$) calcd for $C_{21}H_{26}ClFN_5O_7$ 514.1505; found 514.1485.

2-Amino-9-(β/α-5′-*O*-acetyl-3′-*C*-acetoxymethyl-2′,3′-dideoxy-2′-fluoro-2′,3′-*endo*-methylene-D-pentofuranosyl)-6-chloro-9*H*-purine (45)

To a solution of **44** (144 mg, 0.28 mmol) in anhydrous CH_2Cl_2 (15 mL) at 0 °C was added TMSOTf (0.4 mL, 2.23 mmol) drop-wise over 10 min. The reaction was stirred for 1 h. The mixture was diluted with $CHCl_3$ (50 mL) then poured into a vigorously stirred solution of sat. aq. $NaHCO_3$ (40 mL). The layers were separated and the aqueous layer was extracted with $CHCl_3$ (2 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (toluene:acetone gradient) to give **45** as a pale yellow amorohous solid (87 mg, 0.21 mmol, 76%, 5:1 mixture of β:α).

^{1}H NMR (400 MHz, $CDCl_3$) δ (major, β anomer) = 7.98 (1H, s, C**H**8), 6.48 (1H, d, *J* = 2.6 C1′**H**), 5.42 (2H, br s, N**H**$_2$), 4.63 (1H, dd, *J* = 4.2, 5.6, C4′**H**), 4.56 (1H, d, *J* = 12.6, (C3′)C**H**$_A$H$_B$), 4.28–4.20 (3H, m, (C3′)CH$_A$**H$_B$** and C5′**H**$_2$), 2.14 (3H, s, C**H**$_3$), 2.09 (3H, s, C**H**$_3$), 1.88 (1H, app t, *J* = 7.7, CFC**H**$_A$H$_B$), 1.68 (1H, dd, *J* = 7.8, 17.0, CFCH$_A$**H$_B$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major, β anomer) = 170.5 (**C**=O), 170.4 (**C**=O), 159.5 (**C**), 154.0 (**C**), 151.8 (**C**), 138.9 (**C**8H), 125.5 (**C**), 84.7 (d, *J* = 253, **C**2′F), 82.6 (d, *J* = 26, **C**1′H), 77.2 (**C**′4H), 62.7 (d, *J* = 2, **C**5′H$_2$), 61.1 (d, *J* = 4, (C3′)**C**H$_2$), 30.6 (d, *J* = 8, **C**3′), 20.7 (2 × **C**H$_3$), 14.8 (d, *J* = 11, CF**C**H$_2$); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$,) δ = −211.1 (minor, α anomer), −213.9 (major, β anomer); (IR) $\nu_{max}(cm^{-1})$: 3478, 3318, 2924, 2854, 1773, 1613, 1563, 1470, 1223, 1034; HRMS (ESI-TOF) *m/z*: ($M+Na^+$) calcd for $C_{16}H_{17}ClFN_5O_5$ 436.0800; found 436.0812 and *m/z*: ($M+H^+$) calcd for $C_{16}H_{18}ClFN_5O_5$ 414.0980; found 414.0990.

α/β-5-*O*-Acetyl-3-*C*-benzyloxymethyl-2,3-dideoxy-2-fluoro2,3-*endo*-methylene-D-pentofuranose (46) and **1,1′-α,α′ linked-disaccharide (47)**

Synthesis of **46** was performed on 1.31 g scale of **39** (4.25 mmol) according to the procedure described for the synthesis of **43**. The product was isolated by column chromatography (SiO_2, heptane:EtOAc) as a 1:6 mixture of β:α anomers (pale yellow oil, 0.91 g, 2.93 mmol, 69% yield). The disaccharide **47** was also isolated from the mixture in 18% yield (colorless oil, 0.24 g, 0.39 mmol).

46: ^{1}H NMR (400 MHz, $CDCl_3$) δ (major, α anomer) = 7.33–7.27 (5H, m, Ar**H**), 5.48 (1H, d, *J* = 2.0, C1**H**), 4.72 (1H, dd, *J* = 3.7, 7.2, C4**H**), 4.63 (1H, d, *J* = 12.0, PhCH$_A$**H$_B$**), 4.51 (1H, d, *J* = 12.0, PhC**H**$_A$H$_B$), 4.28 (1H, dd, *J* = 3.7, 11.8, C5**H**$_A$H$_B$), 3.98 (1H, dd, *J* = 7.4, 11.8, C5H$_A$**H$_B$**), 3.81 (1H, d, *J* = 11.1, (C3)C**H**$_A$H$_B$), 3.62 (1H, d, *J* = 11.1, (C3)CH$_A$**H$_B$**), 3.24 (1H, br s, OH), 2.05 (3H, s, C**H**$_3$), 1.28 (1H, dd, *J* = 7.2, 18.0, CFC**H**$_A$H$_B$), 1.21 (1H, app t, *J* = 6.8, CFCH$_A$**H$_B$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major, α anomer) = 170.7 (C=O), 137.8 (Ar-**C**), 128.5 (2 × Ar-**C**H), 127.8 (Ar-**C**H), 127.7 (2 × Ar-**C**H), 95.1 (d, *J* = 18, **C**1H), 84.9 (d, *J* = 257, **C**2F), 75.6 (**C**4), 72.9

(**C**H_2Ph), 66.9 (d, *J* = 3, (C3)**C**H_2), 63.5 (d, *J* = 3, **C**5H_2), 30.0 (d, *J* = 9, **C**3), 20.7 (**C**H_3), 15.1 (d, *J* = 11, CF**C**H_2); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ = −214.2 (minor, β anomer), −215.9 (major, α anomer); (IR) $\nu_{max}(cm^{-1})$: 3421, 3064, 3031, 2867, 1740, 1497, 1371, 1234, 1027; HRMS (ESI-TOF) *m/z*: ($M+Na^+$) calcd for $C_{16}H_{19}FNaO_5$ 333.1109; found 333.1119.

47: ^1H NMR (400 MHz, $CDCl_3$) δ = 7.35–7.24 (10H, m, 2 × Ar**H**), 5.57 (2H, d, *J* = 2.0, 2 × C1**H**), 4.69 (2H, ddd, *J* = 1.0, 3.7, 7.0, 2 × C4**H**), 4.61 (2H, d, *J* = 11.8, 2 × PhCH_A**H$_B$**), 4.32 (2H, d, *J* = 11.5, 2 × PhC**H$_A$**H_B), 4.30 (2H, dd, *J* =, 3.7, 12.0, 2 × C5**H$_A$**H_B), 4.04 (2H, dd, *J* = 7.0, 12.0, 2 × C5H_A**H$_B$**), 3.83 (2H, d, *J* = 11.8, 2 × (C3)C**H$_A$**H_B), 3.58 (2H, d, *J* = 11.8, 2 ×(C3)CH_A**H$_B$**), 2.06 (6H, s, 2 × C**H**$_3$), 1.26-1.20 (4H, 2 × CFC**H**$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.7 (2 × **C**=O), 138.0 (2 × Ar-**C**), 128.4 (4 × Ar-**C**H), 127.8 (4 × Ar-**C**H), 127.6 (2 × Ar-**C**H), 97.0 (d, *J* = 17, 2 × **C**1H), 83.8 (d, *J* = 255, 2 × **C**2F), 76.1 (2 × **C**4), 72.3 2 × **C**H_2Ph), 66.7 (d, *J* = 3, 2 × (C3)**C**H_2), 63.4 (d, *J* = 3, 2 × **C**5H_2), 29.7 (d, *J* = 9, 2 × **C**3), 20.8 (2 × **C**H_3), 14.5 (d, *J* = 11, 2 × CF**C**H_2); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ = −214.7; (IR) $\nu_{max}(cm^{-1})$: 2942, 2861, 1739, 1497, 1368, 1228, 1087, 1012, 972; HRMS (ESI-TOF) *m/z*: ($M+Na^+$) calcd for $C_{32}H_{36}F_2NaO_9$ 625.2220; found 625.2247.

2-*tert*-Butyloxycarbonylamino-9-(β-5′-*O*-acetyl-3′-*C*-benzyloxymethyl-2′,3′-dideoxy-2′-fluoro-2′,3′-*endo*-methylene-D-pentofuranosyl)-6-chloro-9*H*-purine (48)

To a solution of lactol **46** (0.91 g, 2.93 mmol) in anhydrous THF (27 mL) was added PPh_3 (0.92 g, 3.51 mmol) followed by *N*-Boc-2-amino-6-chloropurine (0.95 g, 3.51 mmol) at rt. The mixture was stirred for 5 min and DIAD was added drop-wise (0.7 mL, 3.51 mmol). The mixture was stirred for 90 min at rt, quenched with MeOH (9 mL) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, EtOAc:*n*-heptane) to give **48** as a pale yellow oil (0.82 g, 1.46 mmol, 50%, mixture 7:1 β:α anomers).

^1H NMR (400 MHz, $CDCl_3$) δ (major, β anomer) = 8.12 (1H, s, C**H**8), 7.49 (1H, br s, N**H**), 7.40-7.26 (5H, m Ar**H**), 6.58 (1H, dd, *J* = 1.1, 3.8 C1′**H**), 4.74 (1H, dd, *J* = 3.6, 6.8, C4′**H**), 4.60 (1H, d, *J* = 12.1, (C3′)C**H$_A$**H_B), 4.55 (1H, d, *J* = 12.1, (C3′)CH_A**H$_B$**), 4.34 (1H, dd, *J* = 3.7, 12.1, C5′**H$_A$**H_B), 4.20 (1H, dd, *J* = 6.9, 12.1, C5′H_A**H$_B$**), 3.84 (1H, d, *J* = 11.0, PhC**H$_A$**H_B), 3.63 (1H, d, *J* = 11.0, PhCH_A**H$_B$**), 2.08 (1H, app t, *J* = 7.5, CFC**H$_A$**H_B), 2.05 (3H, s, C**H**$_3$), 1.52 (1H, ddd, *J* = 0.9, 7.6, 18.6, CFCH_A**H$_B$**), 1.54 (9H, s, ((C**H**$_3$)$_3$C); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major, β anomer) = 170.5 (**C**=O), 153.0 (**C**=O Boc), 152.7 (**C**), 151.7 (**C**), 149.9 (**C**), 141.6 (**C**8H), 137.5 (Ar-**C**), 128.6 (2 × Ar-**C**H), 128.0 (Ar-**C**H), 127.8 (**C**), 127.7 (2 × Ar-**C**H), 84.8 (d, *J* = 256, **C**2′F), 83.8 (d, *J* = 27, **C**1′H), 81.7 (**C**(CH$_3$)$_3$), 77.3 (**C**′4H), 73.2 (**C**H_2Ph), 66.8 (**C**5′H_2), 63.0 (d, *J* = 4, (C3′)**C**H_2), 31.8 (d, *J* = 8, **C**3′), 28.2 (**C**H_3)$_3$C), 20.7 (**C**H_3), 14.7 (d, *J* = 10, CF**C**H_2); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ = −211.2 (minor, α anomer), −213.4 (major, β anomer); (IR) $\nu_{max}(cm^{-1})$: 3276, 2979, 2931, 2864, 1745, 1608, 1572, 1512, 1368, 1230, 1152, 1074. HRMS (ESI-TOF) *m/z*: ($M+Na^+$) calcd for $C_{26}H_{29}ClFN_5NaO_6$ 584.1683; found 584.1685.

***N*-*tert*-Butyloxycarbonyl-β-D-3′-*C*-benzyloxymethyl-2′,3′-dideoxy-2′-fluoro-2′,3′-*endo*-methyleneguanosine (49)**

To a solution of **48** (821 mg, 1.46 mmol) in anhydrous MeOH (13 mL) was added 2-mercaptoethanol (0.61 mL, 8.76 mmol) followed by sodium methoxide (473 mg, 8.76 mmol) at rt. The mixture was stirred for 22 h at 66 °C, then cooled to rt, neutralised with solid CO_2 and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc:heptane followed by EtOAc: H_2O: MeOH gradient) to give **49** as a white amorphous solid (480 mg, 0.97 mmol, 66%, mixture of >30:1 β:α anomers).

^{1}H NMR (400 MHz, $CDCl_3$) δ (major, β anomer) = 11.39 (1H, br s, N**H**), 7.83 (1H, s, C**H**8), 7.43 (1H, br s, N**H**), 7.41–7.32 (5H, m Ar**H**), 6.29 (1H, dd, *J* = 1.1, 3.8 C1′**H**), 4.63 (1H, d, *J* = 11.8, PhC**H$_A$**H$_B$), 4.58 (1H, d, *J* = 11.8, PhCH$_A$**H$_B$**), 4.48 (1H, dd, *J* = 4.5, 6.6, C4′H), 3.85 (1H, d, *J* = 10.7, (C3′)C**H$_A$**H$_B$), 3.74–3.67 (1H, m, C5′H$_A$**H$_B$**), 3.64 (1H, d, *J* = 10.7, (C3′)CH$_A$**H$_B$**), 3.65–3.59 (1H, m, C5′**H$_A$**H$_B$), 3.17 (1H, dd, *J* = 3.7, 9.2, O**H**), 1.82 (1H, app t, *J* = 7.4, CFC**H$_A$**H$_B$), 1.56 (1H, dd, *J* = 7.4, 17.6, CFCH$_A$**H$_B$**), 1.52 (9H, s, ((C**H**$_3$)$_3$C); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major, β anomer) = 155.4 (**C**=O Boc), 152.3 (**C**), 148.9 (**C**), 147.4 (**C**), 136.8 (Ar-**C**), 135.7 (**C**8H), 128.7 (2×Ar-**C**H), 128.3 (Ar-**C**H), 127.9 (2 × Ar-**C**H), 121.1 (**C**), 85.5 (d, *J* = 253, **C**2′F), 82.3 (d, *J* = 26, **C**1′H), 84.8 (**C**(CH$_3$)$_3$), 81.0 (**C**′4H), 73.6 (**C**H$_2$Ph), 67.8 (**C**5′H$_2$), 63.3 ((C3′)**C**H$_2$), 32.7 (d, *J* = 8, **C**3′), 28.0 (**C**H$_3$)$_3$C), 15.1 (d, *J* = 11, CF**C**H$_2$); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ = −210.3 (minor, α anomer), −211.8 (major, β anomer); (IR) ν_{max}(cm^{-1}): 3417, 3231, 2926, 2857, 1667, 1608, 1562, 1401, 1368, 1247, 1151, 1001; HRMS (ESI-TOF) *m/z*: (M+H$^+$) calcd for $C_{24}H_{29}FN_5O_6$ 502.2096; found 502.2115.

β-D-3′-*C*-Benzyloxymethyl-2′,3′-dideoxy-2′-fluoro-2′,3′-*endo*-methyleneguanosine (50)

To a solution of **49** (20.0 mg, 0.040 mmol) in anhydrous CH_2Cl_2 (4 mL) was added TMSOTf (18 μL, 0.104 mmol) at 0 °C. The mixture was stirred for 2 h at 0 °C, then solid $NaHCO_3$ (50.0 mg, 0.595 mmol) was added, followed by MeOH (1 mL) and the mixture was concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, EtOAc:H_2O:MeOH gradient) to give **50** (6.4 mg, 0.016 mmol, 40%, >30:1 β:α mixture of anomers) and **16** (3.4 mg, 0.012 mmol, 30%, pure β anomer) as colorless amorphous solids.

^{1}H NMR (400 MHz, $CDCl_3$) δ (β anomer) = ^{1}H NMR (400 MHz, $CDCl_3$) δ) = 10.71 (1H, br s, N**H**), 7.99 (1H, s, C**H**8), 7.40–7.29 (5H, m, Ar-**H**), 6.57 (2H, s, N**H**$_2$), 6.28 (1H, d, *J* = 3.4, C1′**H**), 4.81 (1H, t, *J* = 5.7, O**H**), 4.55 (1H, d, *J* = 12.0, PhC**H$_A$**H$_B$), 4.52 (1H, d, *J* = 12.0, PhCH$_A$**H$_B$**), 4.43 (1H, dd, *J* = 4.4, 6.28, C4′**H**), 3.90 (1H, d, *J* = 11.1, (C3′)**C**H$_A$H$_B$), 3.65 (1H, d, *J* = 11.1, (C3′)CH$_A$**H$_B$**), 3.63–3.58 (1H, m, C5′**H$_A$**H$_B$), 3.51-3.45 (1H, m, C5′H$_A$**H$_B$**), 2.00 (1H, app. t, *J* = 7.6, CFC**H$_A$**H$_B$), 1.54 (1H, dd, *J* = 7.6, 17.9, CFCH$_A$**H$_B$**); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.6 (**C**), 154.0 (**C**), 151.5 (**C**), 138.2 (Ar-**C**), 134.6 (**C**8H), 128.3 (2 × Ar-**C**H), 127.5 (Ar-**C**H), 127.4 (2 × Ar-**C**H), 116.3 (**C**) , 85.3 (d, *J* = 248, **C**2′H), 81.3 (d, *J* = 27, **C**1′H), 79.3 (**C**4′H), 71.9 (**C**H$_2$Ph), 67.1 ((C3′)**C**H$_2$), 60.6 (**C**5′H$_2$), 31.2 (d, *J* = 8.0, **C**3′H), 13.4 (d, *J* = 10, CF**C**H$_2$); ^{19}F{^{1}H} NMR

(376 MHz, $CDCl_3$) δ = −211.8 (β anomer); (IR) $\nu_{max}(cm^{-1})$: 3430, 3307, 3141, 2923, 2853, 1713, 1692, 1594, 1534, 1335, 1252, 1027; HRMS (ESI-TOF) ($M+H^+$) calcd for $C_{19}H_{21}FN_5O_4$ 402.1572; found: 402.1559 and *m/z*: ($M+Na^+$) calcd for $C_{19}H_{20}FN_5NaO_4$ 424.1392; found: 424.1377.

Acknowledgments.
In vitro biology assays were performed at Idenix by C. Chapron, M. La Colla, J. F. McCarville, M. Seifer, and I. Serra. X-ray structure determination of nucleoside **15** was performed at the Chemical Analysis Facility, University of Reading, UK by Dr A. M. Chippindale and N. J. Spencer.

Supporting Information. Copies of ^1H and ^{13}C NMR of the products and the X-ray crystallographic data (CIF file) for compound **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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52. NMR spectra of the pure α anomer were obtained from the material recovered from the nucleosidation reaction to make **42**.