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Synthesis of fluorinated carbocyclic pyrimidine nucleoside analogues†

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Analogues of the canonical nucleosides have a longstanding presence and proven capability within medicinal chemistry and drug discovery research. The synthesis reported herein successfully replaces furanose oxygen with CF_2 and CHF in pyrimidine nucleosides, granting access to an alternative pharmacophore space. Key diastereoselective conjugate addition and fluorination methodologies are developed from chiral pool materials, establishing a robust gram-scale synthesis of 6′-(*R*)-monofluoro- and 6′-*gem*-difluorouridines. Vital intermediate stereochemistries are confirmed using X-ray crystallography and NMR analysis, providing an indicative conformational preference for these fluorinated carbanucleosides. Utilising these 6′-fluorocarbauridine scaffolds enables synthesis of related cytidine, ProTide and 2′-deoxy analogues alongside a preliminary exploration of their biological capabilities in cancer cell viability assays. This synthetic blueprint offers potential to explore fluorocarbanucleoside scaffolds, indicatively towards triphosphate analogues and as building blocks for oligonucleotide synthesis.

Introduction

Nucleoside analogues possess a privileged and accomplished history within therapeutic intervention strategies, most notably in the fight against viruses and cancer.[1,2] They are also present within synthetic sequences of DNA and RNA, providing a cornerstone to nucleic acid therapies.[3] Since its foundation in the 1950s, the field of nucleoside analogue chemistry has continually evolved, delivering generations of landscape defining therapeutics; notably this includes recent frontline treatments against COVID-19.[4,5] As a result of these successes, the requirement for synthetic capability, both chemical and enzymatic, to evolve new pharmacophore space and manufacture these materials efficiently is ever growing.[6–8]

A commonly encountered structural change is modification of the ribose ring (Fig. 1a); examples here include cytarabine, remdesivir and gemcitabine. Within this subtext of ribose ring modification, replacement of furanose oxygen with other heteroatoms or functional groups is often explored (Fig. 1b). Examples here include forodosine, a 4′-azanucleoside, and 4′-thionucleosides.[9,10] The templating of additional ribose ring modifications, ontop of furanose oxygen replacement, enables further divergence to explore new modalities.[11,12]

A third and perhaps more extensively interrogated class of ethereal replacement harnesses carbon;[13] carbanucleosides (a cyclopentane core with oxygen replaced by CH_2) exist naturally as highly cytotoxic agents aristeromycin and neplanocin A. Carbocyclic nucleosides are resistant to enzymatic degradation, as the hemi-aminal linkage targeted by nucleoside phosphorylases is absent, and adopt alternative ring conformations compared to classical (C3′ or C2′ *endo*) systems.[14,15] The carbocylic structural motif has successfully underpinned development of the therapeutics abacavir and entecavir and has recently been included within synthetic RNA oligonucleotides.[16]

In addition to using CH_2 to replace the furanose ring oxygen, there are a limited number of reports that concomitantly build fluorine into this carbocylic modification, effectively introducing CF_2 (Fig. 1c). For example, 6′6′-difluorinated purines have been developed to target RNA virus activity.[17] This suggested bioisosteric replacement (and the related CHF), originally proposed by Blackburn to replace ethereal oxygen in pyrophosphates,[18] remains underexplored as a pharmacophore.[19–21] Synthetic methods to expedite accessing it,[22] and further analogues therefrom, are therefore required to sustain the evolution of new generations of biorelevant nucleoside analogues.[17,23–25]

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† Electronic supplementary information (ESI) available: Relevant spectral NMR, X-ray crystallography and HPLC data for compounds **2–40** alongside cell viability assay data. CCDC 2193041–2193043 and 2218823. For ESI and crystallographic data in CIF or other electronic format see DOI: **https://doi.org/10.1039/d2ob01761j**

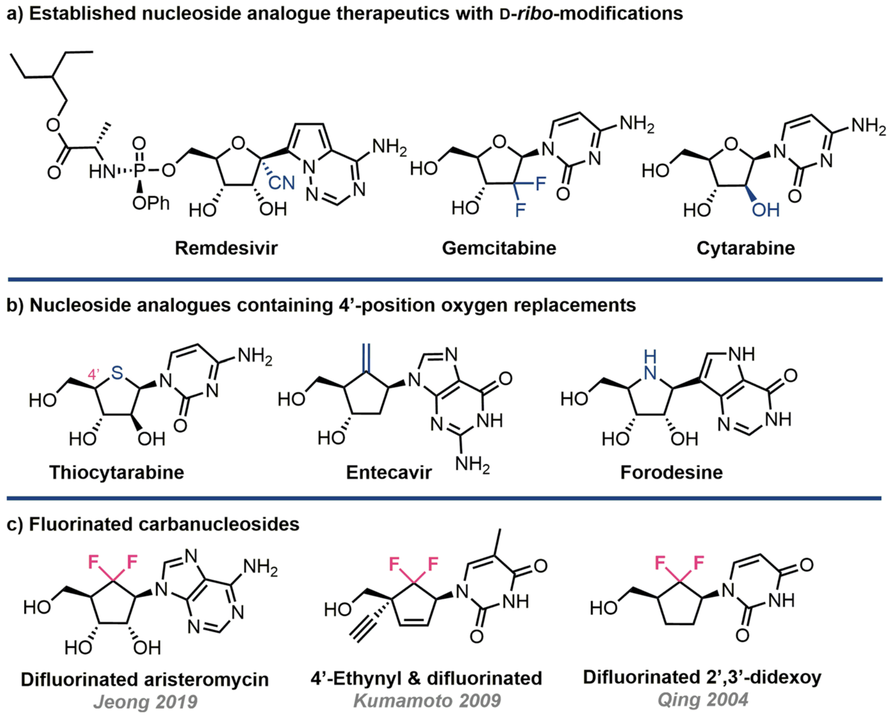


Fig. 1 (a) Examples of nucleoside analogue drugs with furanose ring modifications shown in blue (b) replacement of furanose oxygen with other heteroatoms and carbon, in blue (c) key recent examples of the bioisosteric O → CF_2 replacement for nucleoside analogues.

Established benefits from introducing fluorine to nucleoside analogues are evidenced by the drugs sofosbuvir (2′-deoxy-2′-C-methyl-2′-fluoro) and gemcitabine (2′,2′-difluoro-2′-deoxycytidine), alongside the biological capabilities of including 2′-fluorinated monomer components within oligonucleotides for medicinal chemistry.[23,26] Notwithstanding this, the structural effect of replacing furanose oxygen with CF_2, both in free nucleosides and nucleotides, and related DNA/RNA sequences is an area primed for exploration.[27–29]

In line with the achievements highlighted in Fig. 1c, we present herein our synthesis of a series of pyrimidine (uridine and cytidine) carbocyclic nucleosides, modified with β-mono- and di-fluorination at the 6′-position (Fig. 2). In addition, we access their ProTide prodrug forms and demonstrate the first examples of diversification to 2′-deoxygentated materials.

Results and discussion

To access our fluorinated carbocylic nucleoside analogue series, we first required building blocks suitable for nucleobase installation and further diversification. Previous syntheses of bioisosteric CF_2 replacement involved starting from commercially available fragments, where the *gem*-difluorina-

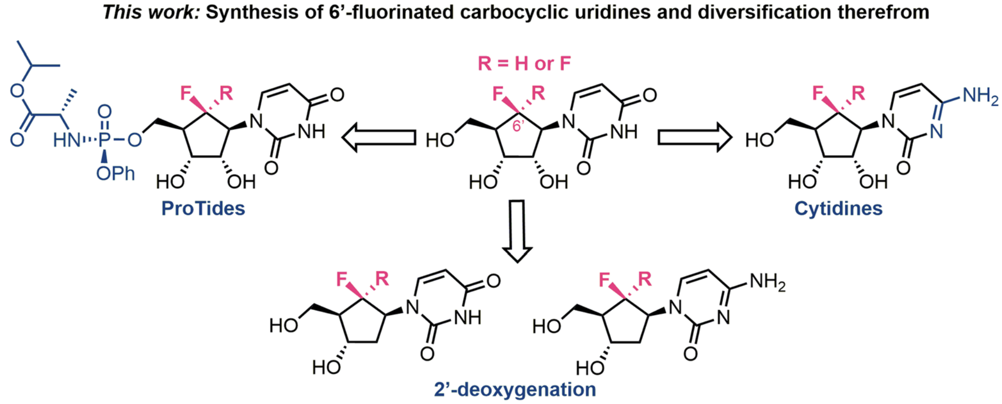


Fig. 2 Overview of synthetic targets: access to 6′-mono- and di-fluorinated carbocylic uridines as a point to diversify analogues series to ProTide, cytidine and 2′-deoxygenated forms.

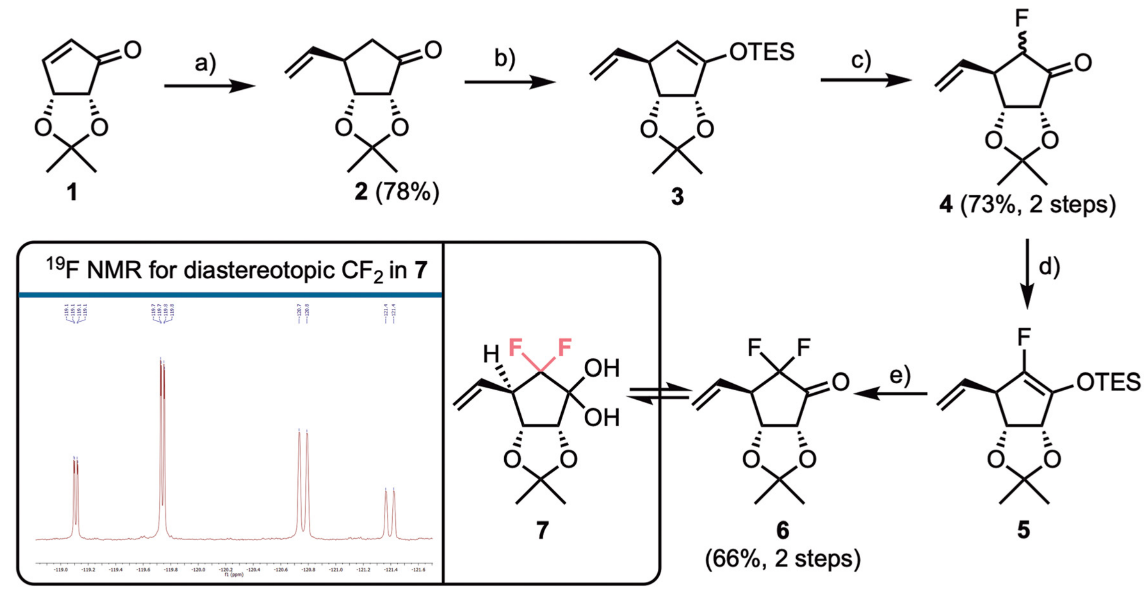
tion is already in place,[25] alongside methods that add fluorine to the scaffold using electrophilic fluorination.[24] Jeong and colleagues have reported syntheses of fluorinated nucleoside analogues, where the core nucleoside is accessed from enone **1**, most commonly effecting conjugate addition of a Gilman reagent, to diastereoselectively install a ^{t}Bu ether protected C5′-hydroxymethyl unit, followed by electrophilic fluorination of an appropriate silyl enol ether.[17,30,31]

Our synthesis began similarly, using commercial isopropylidine protected cyclopentenone **1**, where we envisaged conjugate addition of a vinyl group (Scheme 1), effectively masking the C5′-primary alcohol until a later oxidative cleavage step. To achieve this, we adopted a report by Schneller accessing aristeromycin analogues, that used a combination of vinyl magnesium bromide, TMSCl, HMPA, and CuBr·Me$_2$S. However, in our hands we were unable to consistently replicate the yield of 80% reported for this transformation.[32] Gratifyingly, when we modified the reagent combination to just vinyl magnesium bromide and CuI in THF, the successful isolation of **2** in 78% yield was enabled. This reaction proved reliable on scales up to 20 g and only one diastereoisomer of **2** was isolated, following chromatography. NMR data matched those reported by Schneller, indicating top face addition of the organocuprate, with the bottom face blocked by the 2,3-di-*O*-isopropylidine.

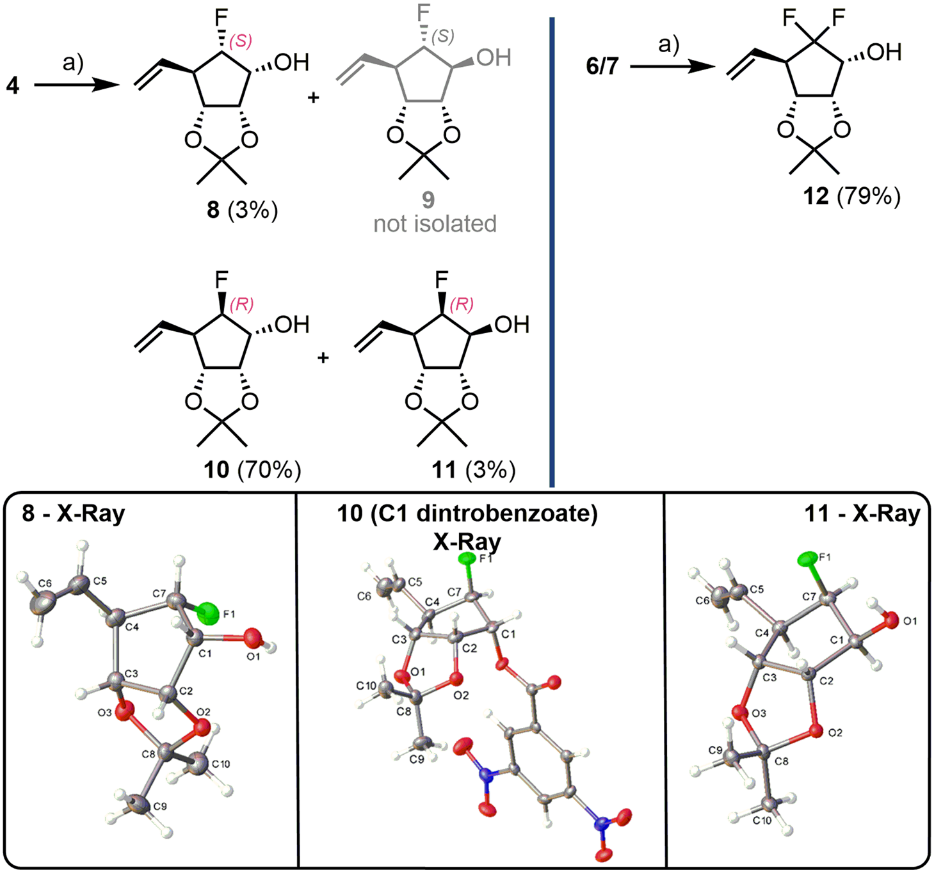
α-Ketofluorination of **2** was completed using a two-step procedure of silyl enol ether formation, followed by reaction with Selectfluor®. Formation of **3** proceeded in quantitative crude yield with a significant downfield chemical shift observed for the vinyl ether proton (δ_H = 4.65 ppm). Silyl enol ether **3** was used immediately for electrophilic fluorination, delivering **4** in an isolated yield of 73% and with an 8 : 1 preference for fluorination having occurred on the β-face of the system (*i.e.*, giving the (*R*)-F diastereoisomer). Installation of fluorine α to the ketone in **2** was confirmed using ^{1}H and ^{13}C NMR, with large ^1J and ^2J couplings observed for the remaining α-proton in **4** ($^2J_{H,F}$ = 50.5 Hz and $^1J_{C,F}$ = 201.2 Hz). Electrophilic fluorination of **2** with a C4-vinyl group in place has not been reported previously and compares favourably to results obtained by Jeong using a ^{t}Bu protected hydroxymethyl C4 substituent [5 : 1, (*R*)/(*S*)] and a C4-hydroxyethyl homologue [(*R*)-F selective].[17,31]

The diastereomeric mixture **4** was inseparable by silica gel chromatography and the mixture was used in a second fluorination *via* TES-enol either **5**, affording difluorinated **6** in 66% yield over the two steps and reliably delivering this material in >10 g quantities. Ketone **6** was observed by ^{1}H NMR to be in equilibrium with its hydrate form, **7**. The presence of the diastereotopic CF$_2$ group within **7** was confirmed using ^{19}F NMR; the expected doublet of doublets observed for each fluorine, with a ^{19}F–^{19}F geminal coupling constant of J = 237.5 Hz, alongside smaller $^3J_{F,H}$ couplings to H$_4$ of 9.0 and 21.6 Hz respectively. In addition, for one fluorine a small coupling (J = 1.8 Hz, presumably to OH) could be observed, altering the multiplicity to a doublet of doublets of doublets (Scheme 1, box).

After a diastereoselective NaBH$_4$ reduction of monofluoroketone mixture **4** (Scheme 2), the resultant secondary alcohols **8–11** could be separated using chromatography with isolation of **10** as the major product in 70% yield. For this major (*R*)-F analogue, stereochemical assignment at C1 was confirmed through an X-Ray crystal structure of a derived C1-dinitrobenzoate (Scheme 2, boxes). The minor (*S*)-F diastereoisomer **8** was also obtained, in 3% yield, alongside the (*R*)-F C1 epimer **11**, in 3% yield (compound **9** was not isolated). Both **8** and **11** were crystalline solids and X-ray crystallography also confirmed



Scheme 1 Synthesis of fluorinated cyclopentanone building blocks. (a) VinylMgBr, CuI, THF, −78 °C; (b) TESCl, Li/HMDS, THF, −78 °C; (c) Selectfluor®, DMF, 0 °C–rt, 8/1, **4-(*R*)**/**4-(*S*)**; (d) TESCl, Li/HMDS, THF, −78 °C; (e) Selectfluor®, DMF, 0 °C–rt, observed as hydrate; box illustrates ^{19}F NMR (377 MHz, CDCl$_3$) for **7**, with splitting patterns for diastereotopic fluorines shown.



Scheme 2 Diastereoselective reduction of fluorinated cyclopentanone building blocks. (a) $NaBH_4$, MeOH, rt.

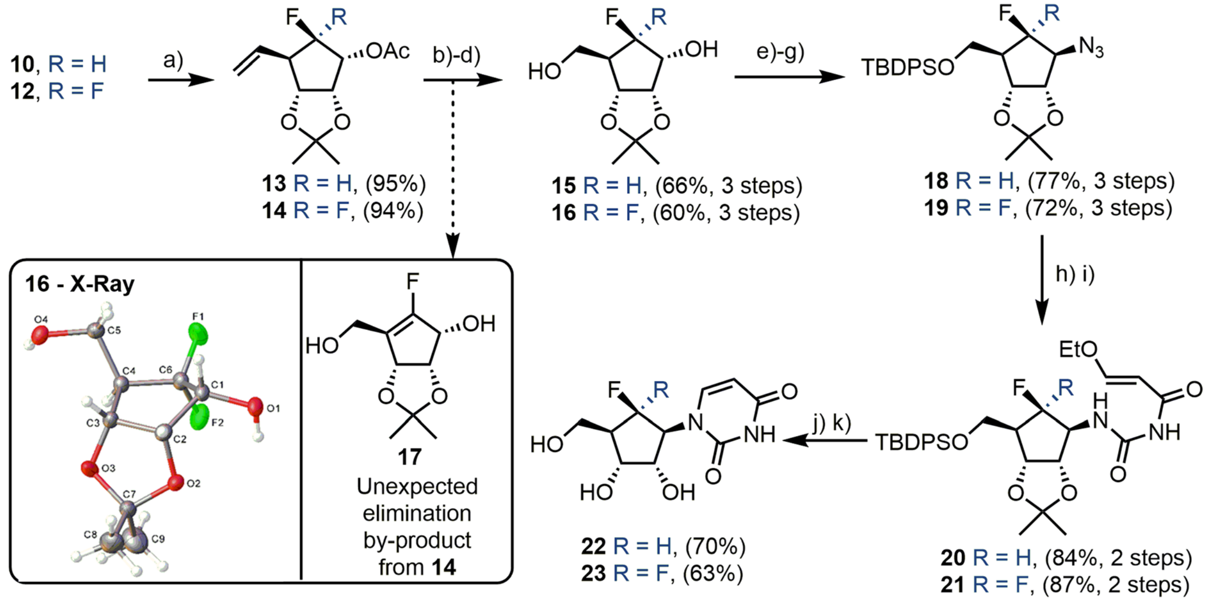
their stereochemical assignment at both C6 (fluorination site) and C1 (secondary alcohol, Scheme 2, boxes). Due to the small amount of **8** isolated, no further synthesis towards an (*S*)-F analogue was completed. Diastereoselective reduction of difluorinated **6**/**7** was completed in a similar manner giving alcohol **12** in 79% yield, with no evidence of a C1 epimer (Scheme 2).

Secondary alcohols **10** and **12** were next acetylated at C1 in excellent yield (95% and 94% for **13** and **14** respectively, Scheme 3). This delivered appropriate materials for oxidative alkene cleavage, first with AD-mix β, to give a vicinal diol mixture, followed by cleavage using $NaIO_4$. Subsequent reduction of the generated aldehyde with concomitant acetate removal furnished alcohols **15** and **16**. *gem*-Difluoroalcohol **16** was crystalline and X-ray crystallography was again used to confirm the previous diastereoselective reduction had occurred from the top face (Scheme 3, box), to provide appropriate material for later installation of the nucleobase *via* stereochemical inversion at C1.

This three-step cleavage proceeded efficiently in the case of the monofluorinated substrate, yielding **15** in 66% over three steps. A complication was however encountered with the difluorinated substrate **14**, resulting in the desired material from $NaIO_4$-mediated diol cleavage isolable only as a minor component and an elimination product (the enal) observed as the major product from this transformation. This led to the formation of **17** (Scheme 3, box) as the major product, following redcution. By lowering the reaction temperature to 0 °C and increasing the equivalents of $NaIO_4$ five-fold, the unwanted elimination was suppressed and the desired material (**16**) was obtained. Following this optimisation, concomitant reduction and deprotection delivered **15** and **16**, with **16** isolated in 60% yield over the three steps.

Alcohols **15** and **16** were next protected with TBDPS at the C5 position. Some additional TBDPS protection of the C1 secondary alcohol was observed in the case of **15**. However, **15** was easily recoverable following global silyl-deprotection using TBAF in THF. Azidation of the remaining secondary alcohol was achieved *via* formation of an α-triflate, followed by stereoinversion using NaN_3 to give **18** and **19** in yields of 77% and 72% respectively over three steps. Direct S_N2 displacement of an α-mesylate with pyrimidine nucleobases or using Mitsunobu inversion were unsuccessful, in line with results reported for the related synthesis of fluorinated aristeromycin derivatives.[30]

Acryloyl urea intermediates **20** and **21** were next obtained, first by reduction of **18** and **19** to the C1 amine, which was then treated with (3-ethoxy-acryloyl)isocyanate, freshly prepared by reaction of 3-ethoxy-acryloyl chloride with AgOCN in toluene,[33] to give **20** and **21** in yields of 84% and 87% over two



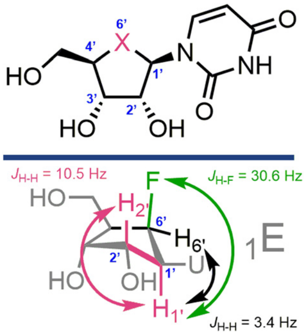
Scheme 3 Synthesis of mono- and *gem*-difluorinated uridines. (a) Ac_2O, pyridine, DCM, rt; (b) AD-mix β, ^iPrOH, H_2O, rt; (c) for **15**: $NaIO_4$ (1.7 equiv.), dioxane, H_2O, rt, 1 h; for **16**: $NaIO_4$ (10 equiv.), dioxane, H_2O, 0 °C, 6 h; (d) $NaBH_4$, MeOH, rt; (e) TBDPSCl, imidazole, DMF; (f) Tf_2O, pyridine; (g) NaN_3, DMF, 100 °C; (h) H_2, Pd/C, MeOH, rt; (i) (3-ethoxyacryloyl)isocyanate, DMF, rt; (j) H_2SO_4, 1,4-dioxane, reflux; (k) TBAF, THF, rt.

steps. Finally, cyclisation to the desired pyrimidine and acetonide removal was achieved by treatment with H_2SO_4 in dioxane. A final TBAF deprotection yielded fluorinated uridines **22** and **23** in total yields of 9% and 6% respectively, and over 15 and 17 steps from **1**.

With **22** and **23** in hand we were interested to compare elements of their NMR data to canonical uridine. We noted an upfield chemical shift for the pseudo-anomeric position in **22** (δ_H = 4.89 ppm, δ_C = 62.3 ppm) relative to uridine (δ_H = 5.83 ppm, δ_C = 91.7 ppm); this effect was less pronounced in *gem*-difluorinated **23** (δ_H = 5.37 ppm, δ_C = 63.6 ppm). Furthermore, Table 1 illustrates selected observed ^3J and ^1J coupling constants for **22** and **23**.

First considering $^3J_{H-H}$ couplings, we noted changes between H_1 and H_2 for both the mono- and difluorinated systems. The $^3J_{H1'-H2'}$ coupling in uridine is 4.6 Hz, but this increased to >10 Hz for both **22** and **23**, indicating a change to this dihedral angle. Carbanucleosides tend to adopt a 1′-*exo* envelope conformation ($_1E$),[34] due to lack of the anomeric effect and *gauche* interactions between the furanose oxygen and the 2′- and 3′-OH groups. This $_1E$ conformation is suggested to be energetically and sterically favourable, placing the bulky nucleobase in a pseudoequatorial position.[14,15,34] The sizable $^3J_{H1'-H2'}$ coupling constants observed here for **22** and **23** are indicative of H_1–C_1–C_2–H_2 torsion angles tending to 150°, and tentatively support this $_1E$ conformational assign-

Table 1 Comparison of ^3J and ^1J couplings for carbanucleosides **22** and **23** and uridine in D_2O at 400 MHz. Indicative 1′-*exo* envelope ($_1E$) conformation for **22** and highlighting observed $^3J_{H1-H2}$, $^3J_{H1-H6}$ and $^3J_{H1-F}$ couplings. U = uridine



	^3J (Hz)		
X	1′-2′	1′-6′	1′-F
O	4.6	—	—
CHF	10.5	3.4	30.6
CF_2	10.2	—	18.8, 10.0

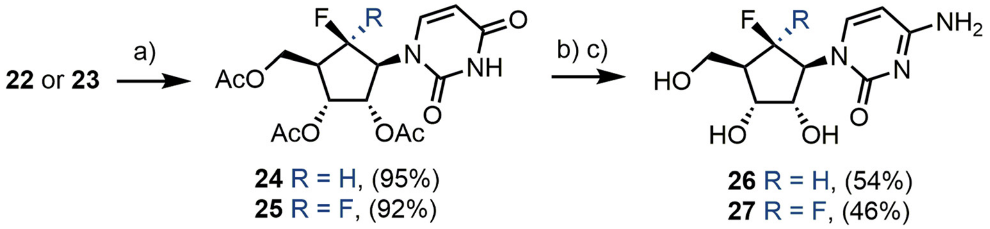
	^1J (Hz)			
X	1′	2′	3′	4′
O	171.8	152.4	149.7	150.1
CHF	140.9	145.9	151.4	128.1
CF_2	144.3	144.5	154.5	135.7

ment in solution-phase. However, these couplings are larger than related values observed for non-fluorinated carbanucleosides ($^{3}J_{\mathrm{H1'-H2'}}$ = 5.6 Hz for carbauridine in DMSO-d$_6$,[16] and $^{3}J_{\mathrm{H1'-H2'}}$ = 8.5 Hz for aristeromycin and carbaguanosine in D$_2$O).[35]

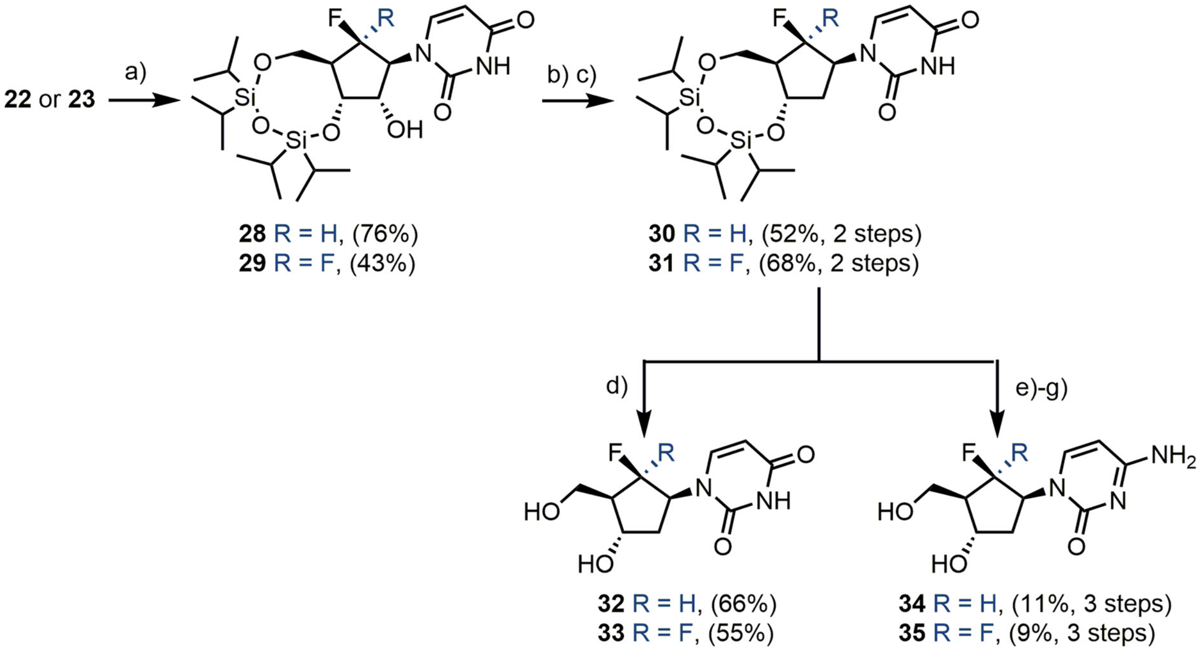
^{1}J coupling constants can serve as convenient identifiers for the anomeric carbon within nucleoside rings, alongside supporting patterns of stereochemical identity (α and β anomers).[36] Recording ^{1}J C–H values for **22** and **23** (Table 1), we noted a significant decrease in this coupling constant at C1′ and C4′ when replacing furanosyl oxygen with CHF or CF$_2$. CHF showed the largest change relative to uridine (for C1′: $^{1}J_{\mathrm{H,C}}$ = 171.8 Hz for uridine and 140.9 Hz for **22**). This effect was not pronounced for C2′ or C3′, where the coupling constants remained similar to uridine. Since ^{1}J C–H coupling constants of carbon generally increase with the electronegativity of attached functional groups, these data exhibit the effect of the removal of oxygen from the ring, and indicate that replacing with fluorinated motifs produces coupling constants that resemble those for ring carbons bearing OH groups (*i.e.*, $^{1}J_{\mathrm{H,C}}$ = 149.7 Hz for C3′ in uridine and 140.9 Hz for C1′ in **22**).

With established access to gram quantities of **22** and **23** we next sought to diversify these analogues, targeting modification of the pyrimidine base, ProTide forms and 2′-deoxygenation. Accordingly, cytidine analogues **26** and **27** were prepared in three steps from **22** and **23.** Global hydroxyl group protection was performed to give acetate protected uridines **24** and **25** in excellent yields (Scheme 4). This was followed by treatment with 1,2,4-triazole and POCl$_3$ to provide an intermediate 4-triazole which was subsequently aminated alongside simultaneous hydroxyl group deprotection, using 35% NH$_4$OH, to deliver **26** and **27** in yields of 53% and 42% respectively over three steps.

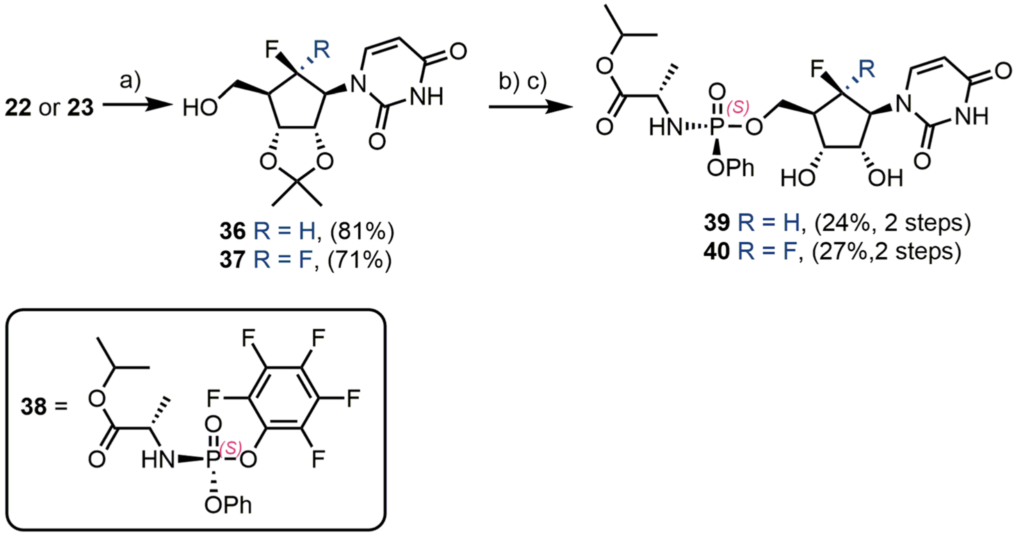
Uridine analogues **22** and **23** were next 3′,5′-*O*-protected with TIPDSiCl$_2$ in pyridine to give **28** and **29** in 76% and 43% yields respectively (Scheme 5). Some unwanted protection of



Scheme 4 Synthesis of mono- and *gem*-di-fluorinated cytidines. (a) Ac$_2$O, pyridine, DMAP, DCM, rt; (b) 1,2,4-triazole, POCl$_3$, Et$_3$N, MeCN, rt; (c) 35% NH$_4$OH, H$_2$O, rt.



Scheme 5 Synthesis of 2′-deoxy mono- and *gem*-di-fluorinated uridine and cytidine. (a) TIPDSiCl$_2$, pyridine, rt; (b) TCDI, DMAP, MeCN, 45 °C; (c) Bu$_3$SnH, AIBN, toluene, reflux; (d) TBAF, THF, rt; (e) 1,2,4-triazole, POCl$_3$, Et$_3$N, MeCN, 0 °C–rt; (f) 35% NH$_4$OH, 1,4-dioxane, rt; (g) TBAF, THF, rt.



Scheme 6 Synthesis of uridine phosphoramidates. (a) H_2SO_4, Me_2CO, reflux; (b) **38**, ^{t}BuMgCl, THF, −78 °C; (c) formic acid, H_2O, rt.

the 2′-*O*-hydroxyl group was also observed, however, **22** or **23** could easily be regenerated using a global TBAF deprotection. A Barton-McCombie 2′-deoxygenation was next performed *via* the 2′-*O*-thiocarbamate. This intermediate was obtained from treatment of either **28** or **29** with 1,1′-thiocarbonyldiimidazole in MeCN, followed by radical mediated deoxygenation using Bu_3SnH and AIBN, delivering 3′,5′-*O*-protected uridines **30** and **31** in 52% and 68% yields respectively, over two steps. The target 2′-deoxy uridines **32** and **33** were subsequently obtained in 66% and 55% yields, following TIPDS-deprotection with TBAF. The 3′,5′-*O*-protected uridines **30** and **31** were also converted through to their cytidine derivatives using the procedures described above for **24** and **25**, affording **34** and **35** in 11% and 9% yields respectively over three steps.

Finally, each of **22** and **23** were converted through to their ProTide phosphoramidate forms (Scheme 6).[37] Firstly, a 2′,3′-*O*-acetonide protecting group was installed, giving **36** and **37** in yields of 81% and 71% respectively. Deprotonation of the remaining 5′-OH with *tert*-butylmagnesium chloride, followed by reaction with commercial phosphoramidate reagent **38**,[38] delivered uridine phosphoramidate analogues **39** and **40** in 24% and 27% yields respectively, following acetonide removal.

Compounds **22**, **23**, **26**, **27**, **32–35**, **39** and **40** were evaluated in cellular viability assays against cancer cell lines U87-MG and PANC-1 (Table 2). 6-(*R*)-Monofluorocytidine **26** showed mild activity against U87-MG cells (Table 2, entry 5). Whilst the remaining compounds showed little activity below 100 µM, this may prove advantageous for exploring antiviral activity. In addition, whilst the ProTide strategy adopted here (compounds **39** and **40**, Table 2, entries 11 & 12) did not translate to biological activity, it is possible that enzymatic release of the masked monophosphate was prevented in this assay and that alternative pronucleotide design could be considered; for example, the cycloSal approach obviates enzymatic activation of a prodrug unit.[39,40] Within a wider program of work, we will explore antiviral activity for the compounds reported herein, alongside targeting nucleotide triphosphate derivatives and associated *in vitro* polymerase activity, to further inform potential monophosphate prodrug candidate development.

Table 2 Biological evaluation of compounds **22**, **23**, **26**, **27**, **32–35**, **39** and **40** against U87-MG and PANC-1 cell lines. Gemcitabine and cytarabine were included as positive controls

		Cell viability (%)			
		U87-MG		PANC-1	
Entry	Compound	100 µM	10 µM	100 µM	10 µM
1	Gemcitabine[a]	—	32	—	37
2	Cytarabine[b]	22	—	42	—
3	**22**	≥100	≥100	≥100	≥100
4	**23**	≥100	≥100	≥100	≥100
5	**26**	**42**	**63**	**70**	**≥100**
6	**27**	93	96	≥100	≥100
7	**32**	≥100	≥100	≥100	≥100
8	**33**	≥100	≥100	≥100	≥100
9	**34**	≥100	≥100	89	≥100
10	**35**	≥100	≥100	≥100	≥100
11	**39**	≥100	≥100	≥100	≥100
12	**40**	≥100	≥100	≥100	≥100

[a] Gemcitabine evaluated at top concentration of 10 µM. [b] Cytarabine evaluated at top concentration of 100 µM.

Conclusion

In summary, we have developed a reliable and scalable synthesis of 6′-(*R*)-monofluoro and 6′-*gem*-difluorouridines as common building blocks for wider diversification to alternative pyrimidines, ProTide prodrug forms and 2′-deoxygentated nucleoside analogues. A robust conjugate addition using a vinyl organocuprate, followed by diastereoselective Selectfluor α-keto fluorination *via* the silyl enol ether delivers key scaffold materials. These are elaborated through 5-position alkene oxidation/cleavage and nucleobase installation, building up from a C1 amine using (3-ethoxyacryloyl)isocyanate. Importantly this alkene manipulation methodology lays a foundation for exploration of 4′-position modifications within this fluorocarbanucleoside scaffold. The synthesis is supported by key X-ray structures confirming cyclopentane ring stereochemistries. Additionally, key differences to canonical pyrimidine nucleoside ^{1}H NMR data are observed and work to further understand the conformational preferences for this analogues class, alongside their wider biological evaluation is currently underway.

Experimental section

General experimental methods

All chemicals were purchased from Acros Organics, Alfa Aesar, Biosynth Carbosynth, Fisher Scientific, Fluorochem, Sigma Aldrich or TCI Chemicals and were used without further purification unless otherwise stated. CuI was purified prior to use.[41] The concentration of vinylmagnesium bromide was determined *via* iodometric titration[42] prior to use. Anhydrous DMF, MeOH, pyridine and Et_3N were obtained from Sure/Seal™ bottles *via* chemical suppliers. Anhydrous THF, DCM and toluene were obtained by passing solvent through activated alumina columns and dispensed from a PureSolv MD ASNA solvent purification system and stored over 4 Å molecular sieves. Unless otherwise stated, all reactions were conducted using anhydrous solvents, under an atmosphere of N_2 which was passed through a Drierite® drying column. Thin layer chromatography (TLC) was performed using pre-coated 0.25 mm 60 F_{254} silica gel plates (Merck). Visualisation was achieved using UV light (λ = 254 nm), and $KMnO_4$ staining followed by heating, or Ninhydrin staining followed by heating, or 5% H_2SO_4/EtOH staining followed by heating. Flash column chromatography was performed using silica gel, high purity grade, pore size 60 Å, 230–400 mesh particle size, 40–63 μm particle size (Sigma Aldrich). All final compounds were purified on an Agilent 1260 Infinity II preparative HPLC system equipped with a variable wavelength detector and a fraction collector, on a reverse phase column (Polaris 180 Å C18-A. 21.2 × 250 mm, 5 μm) to achieve a purity level >95%. Visualisation was achieved using UV detection at 254 nm. Optical rotations were recorded on a Bellingham + Stanley ADP430 (specific rotation, tube length: 50 mm, concentrations in g per 100 mL). All high-resolution mass spectra were measured at the EPSRC National Mass Spectrometry Facility at Swansea University, UK. All crystallographic data were collected on a Bruker D8 Quest ECO diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) and a Photon II-C14 CPAD detector. The ADPs are rendered at 50% probability level. NMR spectra were recorded on a Bruker Avance 400 spectrometer. The chemical shift data for each signal are given as δ in units of parts per million (ppm) relative to tetramethylsilane, where δ = 0.00 ppm. The number of protons (n) for a given resonance is indicated by nH. The multiplicity of each signal is indicated by: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), p (pentet), sep (septet), dd (doublet of doublets), ddd (doublet of doublet of doublets), dddd (doublet of doublet of doublet of doublets), dt (doublet of triplets), tt (triplet of triplets), dqd (doublet of quartets of doublets) or m (multiplet). Coupling constants (J) are quoted in Hz and calculated to the nearest 0.1 Hz. *Cell culture*: PANC-1 (ATCC, catalogue number: CRL-1469) cells were cultured at 37 °C with 5% CO_2 in DMEM (Corning, catalogue number: 10-013CV), supplemented with 10% heat-inactivated FBS (Corning, catalogue number: 35016CV) and 1X Non-essential amino acids [(0.1 mM per amino acid) (Corning, catalogue number: 25025CI)] and 1× Penicillin–Streptomycin Solution [Penicillin (100 IU) and Streptomycin (100 μg mL^{-1}) (Corning, catalogue number: 30002CI)]. U87-MG (ATCC, catalogue number: HTB-14) cells were cultured at 37 °C with 5% CO_2 in EMEM (Lonza, catalogue number: 12-611F), supplemented with 10% heat-inactivated FBS (Corning, catalogue number: 35016CV) and 1× non-essential amino acids (0.1 mM per amino acid) (Corning, catalogue number: 25025CI) and 1× Corning™ Penicillin–Streptomycin Solution [Penicillin (100 IU) and Streptomycin (100 μg mL^{-1}) (Corning, catalogue number 30002CI)].

(2*R*,3*R*,4*R*)-2,3-*O*-Isopropylidene-4-vinylcyclopentan-1-one 2. An oven dried multi-necked round bottom flask was charged with CuI (2.5 g, 13.0 mmol, 0.1 equiv.), evacuated and flushed with N_2 three times and heated to 100 °C under vacuum for 1 h with stirring. The reaction vessel was cooled to rt and THF (520 mL) was added. The mixture was stirred vigorously and cooled to −78 °C, at which point vinylmagnesium bromide (216 mL, 162 mmol, 1.3 equiv., 0.75 M in THF) was added dropwise. The reaction mixture was slowly warmed to −40 °C over 1 h, after which it was cooled to −78 °C again. (4*R*,5*R*)-4,5-*O*-Isopropylidene-2-cyclopentenone **1** (20.0 g, 130 mmol, 1.0 equiv.) in THF (130 mL) was added dropwise at 0.5 mL min^{-1} using a syringe pump, and the reaction mixture was stirred at −78 °C for 2 h. TLC analysis (petroleum ether/Et_2O, 4 : 1) showed complete consumption of the starting material to a higher R_f. The reaction mixture was warmed to 0 °C and quenched with 5 : 1 sat. NH_4Cl/sat. $Na_2S_2O_3$ (v/v, 600 mL). The aqueous phase was extracted with EtOAc (3 × 500 mL), and the combined organic phases were washed with H_2O (500 mL), brine (200 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude material was purified *via* flash column chromatography on silica gel (0–20% Et_2O/petroleum-ether) to give **2** as a colourless oil (18.4 g, 101 mmol, 78%). R_f = 0.39 (petroleum-ether/Et_2O, 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.83 (1H, ddd, $^3J_{H5-H6b}$ = 17.2 Hz, $^3J_{H5-H6a}$ = 10.6 Hz, $^3J_{H5-H4}$ = 6.5 Hz, H_5), 5.15 (1H, d, $^3J_{H6a-H5}$ = 10.6 Hz, H_{6a}), 5.10 (1H, dd, $^3J_{H6b-H5}$ = 17.4 Hz, $^2J_{H6b-H6a}$ = 1.6 Hz, H_{6b}), 4.64 (1H, d, $^3J_{H3-H2}$ = 5.2 Hz, H_3), 4.20 (1H, d, $^3J_{H2-H3}$ = 5.2 Hz, H_2), 3.11 (1H, dd, $^3J_{H4-H7a}$ = 7.9 Hz, $^3J_{H4-H5}$ = 7.0 Hz, H_4), 2.84 (1H, dd, $^2J_{H7a-H7b}$ = 18.3 Hz, $^3J_{H7a-H4}$ = 8.6 Hz, H_{7a}), 2.29 (1H, d, $^2J_{H7b-H7a}$ = 18.2 Hz, H_{7b}), 1.45 (3H, s, CH_3), 1.35 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 213.2 (C_1, C═O), 137.2 (C_5), 116.5 (C_6), 112.5 [C(CH_3)$_2$], 81.4 (C_3), 77.9 (C_2), 39.8 (C_4), 38.6 (C_7), 26.9 [C(CH_3)$_2$], 24.9 [C(CH_3)$_2$]; HRMS (ESI): calculated for $C_{10}H_{14}O_3Na$ $[M + Na]^+$ 205.0835, found 205.0827. These data were in good agreement with literature values.[32]

(2*R*,3*R*,4*R*)-2,3-*O*-Isopropylidene-4-vinyl-7-(*R*/*S*)-fluorocyclopentan-1-one 4. Ketone **2** (35.1 g, 193 mmol, 1.0 equiv.) was dissolved in THF (960 mL) and cooled to −78 °C. TESCl (64.0 mL, 386 mmol, 2.0 equiv.) was added followed by LiHMDS (64.5 g, 386 mmol, 2.0 equiv.) and the reaction was stirred at −78 °C for 2 h. TLC analysis (petroleum-ether/Et_2O, 4 : 1) showed complete conversion of the starting material to a higher R_f. The reaction was warmed to 0 °C and quenched with sat. NH_4Cl (400 mL). The aqueous phase was extracted with EtOAc (3 × 400 mL), and the combined organic phases were washed with H_2O (300 mL), brine (300 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The residue was dissolved in DMF (770 mL) and cooled to 0 °C, after which Selectfluor® (82.0 g, 231 mol, 1.2 equiv.) was added in three portions over 30 min. The reaction mixture was allowed to warm to rt and was stirred for 3 h, at which point TLC analysis (petroleum-ether/Et_2O, 4 : 1) showed complete conversion from a higher R_f to a lower R_f. The reaction mixture was cooled to 0 °C and quenched with sat. NH_4Cl (400 mL). The aqueous phase was extracted with EtOAc (4 × 300 mL), and the combined organic phases were washed with H_2O (3 × 200 mL), brine (200 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude material was purified *via* flash column chromatography on silica gel (0–50% Et_2O/petroleum-ether) to give **4**, as an 8 : 1 inseparable mixture of diastereomers and a colourless oil (28.2 g, 140 mmol, 73%). R_f = 0.09 (petroleum-ether/Et_2O, 4 : 1); ^1H NMR (400 MHz, $CDCl_3$) (major): δ 5.58 (1H, ddd, $^3J_{H5-H6b}$ = 17.3 Hz, $^3J_{H5-H6a}$ = 10.8 Hz, $^3J_{H5-H4}$ = 7.8 Hz, H_5), 5.50 (1H, ddd, $^2J_{H7-F}$ = 50.5 Hz, $^3J_{H7-H4}$ = 7.9 Hz, $^4J_{H7-H3}$ = 0.9 Hz, H_7), 5.31 (1H, dt, $^3J_{H6a-H5}$ = 10.8 Hz, $^2J_{H6a-H6b}$ = 0.9 Hz, H_{6a}), 5.26 (1H, dt, $^3J_{H6b-H5}$ = 17.3 Hz, $^2J_{H6b-H6a}$ = 1.1 Hz, H_{6b}), 4.74 (1H, ddd, $^3J_{H3-H2}$ = 5.7 Hz, $^3J_{H3-H4}$ = 4.7 Hz, $^4J_{H3-H7}$ = 0.9 Hz, H_3), 4.25 (1H, dd, $^3J_{H2-H3}$ = 6.0 Hz, $^4J_{H2-F}$ = 2.6 Hz, H_2), 3.42–3.38 (1H, m, H_4), 1.48 (3H, s, CH_3), 1.35 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) (major): δ 204.5 (d, $^2J_{C1-F}$ = 13.6 Hz, C_1, C═O), 130.1 (d, $^3J_{C5-F}$ = 5.4 Hz, C_5), 120.5 (d, $^4J_{C6-F}$ = 1.5 Hz, C_6), 113.1 [C(CH_3)$_2$], 91.0 (d, $^1J_{C7-F}$ = 201.2 Hz, C_7), 78.1 (d, $^3J_{C3-F}$ = 6.1 Hz, C_3), 74.0 (d, $^3J_{C2-F}$ = 2.3 Hz, C_2), 43.5 (d, $^2J_{C4-F}$ = 16.3 Hz, C_4), 26.3 [C(CH_3)$_2$], 24.0 [C(CH_3)$_2$]; ^{19}F NMR (376 MHz, $CDCl_3$) (major): δ −216.6 (d, $^2J_{F-H7}$ = 50.5 Hz); HRMS (ESI): calculated for $C_{10}H_{14}FO_3$ $[M + H]^+$ 201.0921, found 201.0919.

(2*R*,3*R*,4*R*)-2,3-*O*-Isopropylidene-4-vinyl-7-*gem*-difluorocyclopentan-1-one 6 (and hydrate 7). Monofluoroketone **4** (15.2 g, 76.0 mmol, 1.0 equiv.) was dissolved in THF (380 mL) and cooled to 78 °C. TESCl (25.5 mL, 152 mmol, 2.0 equiv.) was added dropwise, followed by LiHMDS (25.4 g, 152.0 mmol, 2.0 equiv.). The reaction was slowly warmed to rt, and stirred for a further 18 h, at which point TLC analysis (petroleum-ether/Et_2O, 4 : 1) showed complete conversion of the starting material to a higher R_f. The reaction was cooled to 0 °C and quenched with sat. NH_4Cl (200 mL). The aqueous phase was extracted with EtOAc (3 × 200 mL). The combined organic phases were washed with H_2O (150 mL), brine (150 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The residue was dissolved in DMF (380 mL) and cooled to 0 °C, after which Selectfluor® (32.3 g, 91.2 mmol, 1.2 equiv.) was added in two portions over 20 min. The reaction mixture was allowed to warm to rt, and stirred for 16 h, at which point TLC analysis (petroleum-ether/Et_2O, 4 : 1) showed complete conversion from a higher R_f to a lower R_f. The reaction mixture was cooled to 0 °C and quenched with sat. NH_4Cl (200 mL), and the aqueous phase was extracted with EtOAc (4 × 200 mL). The combined organic phases were washed with H_2O (3 × 100 mL), brine (150 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude material was purified *via* flash column chromatography on silica gel (0–50% Et_2O/petroleum-ether) to give **6**, as a colourless oil (11.8 g, 50.1 mmol, 66%). R_f = 0.10 (petroleum-ether/Et_2O, 4 : 1); ^1H NMR (400 MHz, $CDCl_3$) (hydrate **7**): δ 5.85 (1H, ddd, $^3J_{H5-H6a}$ = 17.3 Hz, $^3J_{H5-H6b}$ = 10.4 Hz, $^3J_{H5-H4}$ = 8.3 Hz, H_5), 5.38–5.34 (2H, m, H_{6a}, H_{6b}), 4.504.46 (1H, m, H_2), 4.44–4.42 (1H, m, H_3), 4.26 (1H, d, $^4J_{OH-F}$ = 1.7 Hz, OH), 3.15–3.05 (1H, m, H_4), 3.02 (1H, s, OH), 1.57 (3H, s, CH_3), 1.37 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) (hydrate **7**): δ 129.7 (d, $^3J_{C5-F}$ = 4.1 Hz, C_5), 124.1 (dd, $^1J_{C7-F}$ = 271.1 Hz, $^1J_{C7-F}$ = 253.5 Hz, C_7), 121.1 (C_6), 114.2 [C(CH_3)$_2$], 95.2 (dd, $^2J_{C1-F}$ = 25.7 Hz, $^2J_{C1F}$ = 22.0 Hz, C_1), 79.3 (d, $^3J_{C3-F}$ = 3.2 Hz, C_3), 78.6 (dd, $^3J_{C2-F}$ = 7.7 Hz, $^3J_{C2-F}$ = 1.2 Hz, C_2), 52.5 (dd, $^2J_{C4-F}$ = 20.6 Hz, $^3J_{C4-F}$ 20.1 Hz, C_4), 26.2 [C(CH_3)$_2$], 24.8 [C(CH_3)$_2$]; ^{19}F NMR (376 MHz, $CDCl_3$) (hydrate **7**): δ −119.4 (ddd, $^2J_{F-F}$ = 237.5, $^3J_{F-H4}$ = 9.0 Hz, $^4J_{F-OH}$ = 1.8 Hz), −121.1 (dd, $^2J_{F-F}$ = 237.5 Hz, $^3J_{F-H4}$ = 21.7 Hz); HRMS (ketone **6**) (ESI): calculated for $C_{10}H_{13}F_2O_3$ $[M + H]^+$ 219.0827, found 219.0826.

General procedure for the synthesis of 8–11. Ketone **4**/**6** (1.0 equiv.) was dissolved in MeOH (0.20 M) and cooled to 0 °C. $NaBH_4$ (2.0 equiv.) was added in three portions over 10 min, and the reaction mixture was allowed to warm to rt. The reaction mixture was stirred at rt for 16 h, at which point TLC analysis (petroleum-ether/Et_2O, 1 : 1) showed complete consumption of the starting material to a higher R_f. The reaction mixture was cooled to 0 °C and H_2O (200 mL) was added. The solvent was removed *in vacuo*, and the residue was partitioned between H_2O (200 mL) and EtOAc (200 mL). The aqueous phase was extracted with EtOAc (3 × 200 mL), and the combined organic phases were washed with brine (200 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude material was purified *via* flash column chromatography on silica gel (10–20% Et_2O/hexane).

(1*R*,2*S*,3*R*,4*R*,7*S*)-2,3-*O*-Isopropylidine-4-vinyl-7-fluorocyclopentan-1-ol 8. Alcohol **8** (403 mg, 2.0 mmol, 3%) a white crystalline solid, was obtained following the above procedure from a mixture of **4** (13.0 g, 65.0 mmol, 1.0 equiv.). R_f = 0.42 (petroleum-ether/Et_2O, 1 : 1); mp: 48–50 °C; $[\alpha]_D^{24.9}$ = −15.5 (*c* 2.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 5.62 (1H, ddd, $^3J_{H5-H6a}$ = 17.6 Hz, $^3J_{H5-H6b}$ = 10.7 Hz, $^3J_{H5-H4}$ = 7.0 Hz, H_5), 5.20–5.12 (2H, m, H_{6a}, H_{6b}), 4.79–4.65 (1H, m, H_7), 4.60–4.59 (2H, m, H_2, H_3), 4.11–4.00 (1H, m, H_1), 3.12 (1H, dd, $^3J_{H4-F}$ = 18.6 Hz,

$^{3}J_{\mathrm{H4-H3/H5}}$ = 6.4 Hz, H$_4$), 2.76 (1H, d, $^{3}J_{\mathrm{OH-H1}}$ = 10.5 Hz, OH), 1.51 (3H, s, CH$_3$), 1.34 (3H, s, CH$_3$); ^{13}C NMR (101 MHz, CDCl$_3$): δ 133.6 (d, $^{3}J_{\mathrm{C5-F}}$ = 6.1 Hz, C$_5$), 117.9 (C$_6$), 112.0 [*C*(CH$_3$)$_2$], 97.1 (d, $^{1}J_{\mathrm{C7-F}}$ = 189.6 Hz, C$_7$), 83.0 (C$_3$), 77.7 (C$_2$), 72.6 (d, $^{2}J_{\mathrm{C1-F}}$ = 17.0 Hz, C$_1$), 50.4 (d, $^{2}J_{\mathrm{C4-F}}$ = 19.1 Hz, C$_4$), 26.3 [C(*C*H$_3$)$_2$], 24.5 [C(*C*H$_3$)$_2$]; ^{19}F NMR (376 MHz, CDCl$_3$): δ −197.9 (ddd, $^{2}J_{\mathrm{F-H}}$ = 52.0 Hz, $^{3}J_{\mathrm{F-H1}}$ = 26.2 Hz, $^{3}J_{\mathrm{F-H4}}$ = 18.4 Hz); HRMS (NSI): calculated for $C_{10}H_{15}FO_3Na$ [M + Na]$^+$ 225.0897, found 225.0898.

(1*R*,2*S*,3*R*,4*R*,7*R*)-2,3-*O*-Isopropylidine-4-vinyl-7-fluorocyclopentan-1-ol 10. Alcohol **10** (9.1 g, 45.1 mmol, 70%) a colourless oil, was obtained following the above procedure from a mixture of **4** (13.0 g, 65.0 mmol, 1.0 equiv.). R_f = 0.5 (petroleum-ether/Et$_2$O, 1 : 1); $[\alpha]_{\mathrm{D}}^{24.9}$ = +8.6 (*c* 0.2, CH$_2$Cl$_2$); ^{1}H NMR (400 MHz, CDCl$_3$): δ 5.87 (1H, ddd, $^{3}J_{\mathrm{H5-H6a}}$ = 17.9 Hz, $^{3}J_{\mathrm{H5-H6b}}$ = 10.4 Hz, $^{3}J_{\mathrm{H5-H4}}$ = 7.7 Hz, H$_5$), 5.30–5.24 (2H, m, H$_{6a}$, H$_{6b}$), 4.90 (1H, dt, $^{2}J_{\mathrm{H7-F}}$ = 50.7 Hz, $^{3}J_{\mathrm{H7-H1/H4}}$ = 4.2 Hz, H$_7$), 4.73–4.69 (1H, m, H$_2$), 4.64–4.61 (1H, m, H$_3$), 4.17–4.11 (1H, m, H$_1$), 3.05–2.94 (1H, m, H$_4$), 2.76 (1H, dd, $^{3}J_{\mathrm{OH-H1}}$ = 4.5 Hz, $^{4}J_{\mathrm{OH-F}}$ = 2.4 Hz, OH), 1.54 (3H, s, CH$_3$), 1.38 (3H, s, CH$_3$); ^{13}C NMR (101 MHz, CDCl$_3$): δ 132.5 (d, $^{3}J_{\mathrm{C5-F}}$ = 6.1 Hz, C$_5$), 118.7 (C$_6$), 113.8 [*C*(CH$_3$)$_2$], 100.6 (d, $^{1}J_{\mathrm{C7-F}}$ = 181.0 Hz, C$_7$), 82.8 (d, $^{3}J_{\mathrm{C3-F}}$ = 2.0 Hz, C$_3$), 77.7 (d, $^{3}J_{\mathrm{C2-F}}$ = 2.7 Hz, C$_2$), 72.0 (d, $^{2}J_{\mathrm{C1-F}}$ = 26.3 Hz, C$_1$), 50.0 (d, $^{2}J_{\mathrm{C4-F}}$ = 17.6 Hz, C$_4$), 26.3 [C(*C*H$_3$)$_2$], 24.5 [C(*C*H$_3$)$_2$]; ^{19}F NMR (376 MHz, CDCl$_3$): δ −204.2 (ddd, $^{2}J_{\mathrm{F-H7}}$ = 50.7 Hz, $^{3}J_{\mathrm{F-H4}}$ = 26.2 Hz, $^{3}J_{\mathrm{F-H1}}$ = 10.5 Hz); HRMS (NSI): calculated for $C_{10}H_{15}FO_3Na$ [M + Na]$^+$ 225.0897, found 225.0898.

(1*S*,2*S*,3*R*,4*R*,7*R*)-2,3-*O*-Isopropylidine-4-vinyl-7-fluorocyclopentan-1-ol 11. Alcohol **11** (391 mg, 1.9 mmol, 3%), a white crystalline solid, was obtained following the above procedure from **4** (13.0 g, 65.0 mmol, 1.0 equiv.). R_f = 0.38 (petroleum-ether/EtOAc, 1 : 1); mp: 86–87 °C; $[\alpha]_{\mathrm{D}}^{21.4}$ = +33.4 (*c* 5, DCM); ^{1}H NMR (400 MHz, CDCl$_3$): δ 5.95 (1H, ddd, $^{3}J_{\mathrm{H5-H6a}}$ = 17.4 Hz, $^{3}J_{\mathrm{H5-H6b}}$ = 10.3 Hz, $^{3}J_{\mathrm{H5-H4}}$ = 8.1 Hz, H$_5$), 5.31–5.22 (2H, m, H$_{6a}$, H$_{6b}$), 5.00 (1H, dt, $^{2}J_{\mathrm{H7-F}}$ = 52.4 Hz, $^{3}J_{\mathrm{H7-H1}}$ = 3.8 Hz, H$_7$), 4.63 (1H, ddd, $^{3}J_{\mathrm{H3-H2}}$ = 7.0 Hz, $^{3}J_{\mathrm{H3-H4}}$ 5.2 Hz, $^{4}J_{\mathrm{H3-F}}$ = 1.7 Hz, H$_3$), 4.57–4.53 (1H, m, H$_2$), 4.20 (1H, ddt, $^{3}J_{\mathrm{H1-F}}$ = 19.6 Hz, $^{3}J_{\mathrm{H1-OH}}$ = 6.8 Hz, $^{3}J_{\mathrm{H1-H2/H7}}$ = 3.4 Hz, H$_1$), 2.81 (1H, ddt, $^{3}J_{\mathrm{H4-F}}$ = 28.4 Hz, $^{3}J_{\mathrm{H4-H5}}$ = 8.5 Hz, $^{3}J_{\mathrm{H4-H3}}$ = 4.5 Hz, H$_4$), 2.18 (1H, dd, $^{3}J_{\mathrm{OH-H1}}$ = 7.3, $^{4}J_{\mathrm{OH-F}}$ = 2.5 Hz, OH), 1.50 (3H, s, CH$_3$), 1.31 (3H, s, CH$_3$); ^{13}C NMR (101 MHz, CDCl$_3$): δ 133.0 (d, $^{3}J_{\mathrm{C5-F}}$ = 5.6 Hz, C$_5$), 118.6 (C$_6$), 113.0 [*C*(CH$_3$)$_2$], 98.4 (d, $^{1}J_{\mathrm{C7-F}}$ = 181.8 Hz, C$_7$), 84.7 (d, $^{3}J_{\mathrm{C2-F}}$ = 1.0 Hz, C$_2$), 82.6 (d, $^{3}J_{\mathrm{C3-F}}$ = 1.7 Hz, C$_3$), 78.0 (d, $^{2}J_{\mathrm{C1-F}}$ = 16.7 Hz, C$_1$), 51.9 (d, $^{2}J_{\mathrm{C4-F}}$ = 17.5 Hz, C$_4$), 27.0 [C(*C*H$_3$)$_2$], 24.4 [C(*C*H$_3$)$_2$]; ^{19}F NMR (377 MHz, CDCl$_3$): δ −210.9 (ddd, $^{2}J_{\mathrm{F-H7}}$ = 49.9 Hz, $^{3}J_{\mathrm{F-H4}}$ = 28.4 Hz, $^{3}J_{\mathrm{F-H1}}$ = 19.6 Hz); HRMS (NSI): calculated for $C_{10}H_{15}FO_3Na$ [M + Na]$^+$ 225.0897, found 225.0898.

(1*R*,2*S*,3*R*,4*R*)-2,3-*O*-Isopropylidine-4-vinyl-7-*gem*-difluorocyclopentan-1-ol 12. Alcohol **12** (6.9 g, 31.3 mmol, 79%) a white waxy solid, was obtained following the above procedure from **6**/**7** (9.4 g, 40.0 mmol, 1.0 equiv.). R_f = 0.56 (petroleum ether/Et$_2$O, 1 : 1); $[\alpha]_{\mathrm{D}}^{24.3}$ = −18.5 (*c* 4.0, CH$_2$Cl$_2$); ^{1}H NMR (400 MHz, CDCl$_3$): δ 5.80 (1H, ddd, $^{3}J_{\mathrm{H5-H6a}}$ = 17.8 Hz, $^{3}J_{\mathrm{H5-H6b}}$ = 10.2 Hz, 7.9 Hz, H$_5$), 5.17–5.32 (1H, m, H$_{6a}$, H$_{6b}$), 4.63–4.59 (1H, m, H$_2$), 4.55–4.52 (1H, m, H$_3$), 4.04 (1H, app. p, *J* = 6.0 Hz, H$_1$), 3.17–3.07 (1H, m, H$_4$), 2.90 (1H, dd, $^{3}J_{\mathrm{OH-H1}}$ = 5.4 Hz, $^{4}J_{\mathrm{OH-F}}$ = 1.4 Hz, OH), 1.55 (3H, s, CH$_3$), 1.37 (3H, s, CH$_3$); ^{13}C NMR (101 MHz, CDCl$_3$): δ 129.8 (dd, $^{3}J_{\mathrm{C5-F}}$ = 4.6 Hz, $^{3}J_{\mathrm{C5-F}}$ = 2.3 Hz, C$_5$), 126.9 (dd, $^{1}J_{\mathrm{C7-F}}$ = 266.6 Hz, $^{1}J_{\mathrm{C7-F}}$ = 249.7 Hz, C$_7$), 120.6 (C$_6$), 113.3 [*C*(CH$_3$)$_2$], 80.4 (dd, $^{3}J_{\mathrm{C3-F}}$ = 6.2 Hz, $^{3}J_{\mathrm{C3-F}}$ = 1.4 Hz, C$_3$), 75.1 (t, $^{3}J_{\mathrm{C2-F}}$ = 3.3 Hz, C$_2$), 70.8 (dd, $^{2}J_{\mathrm{C1-F}}$ = 31.8 Hz, $^{2}J_{\mathrm{C1-F}}$ = 20.0 Hz, C$_1$), 51.8 (dd, $^{2}J_{\mathrm{C4-F}}$ = 21.4 Hz, $^{2}J_{\mathrm{C4-F}}$ = 19.8 Hz, C$_4$), 26.0 [C(*C*H$_3$)$_2$], 24.5 [C(*C*H$_3$)$_2$]; ^{19}F NMR (376 MHz, CDCl$_3$): δ −112.8 (dt, $^{2}J_{\mathrm{F-F}}$ = 245.0 Hz, $^{3}J_{\mathrm{F-H1/H4}}$ = 6.6 Hz), −114.7 (ddd, $^{2}J_{\mathrm{F-F}}$ = 245.0 Hz, $^{3}J_{\mathrm{F-H1}}$ = 19.6 Hz, $^{3}J_{\mathrm{F-H4}}$ = 4.7 Hz); HRMS (ESI): calculated for $C_{10}H_{14}F_2O_3Na$ [M + Na]$^+$ 243.0803, found 243.0803.

General procedure for the synthesis of 13 & 14. Alcohol **10**/**12** (1.0 equiv.) was dissolved in DCM (0.5 M) and DMAP (0.1 equiv.), pyridine (2.0 equiv.) and Ac$_2$O (2.0 equiv.) were added. The reaction was stirred at rt for 2–4 h, at which point TLC analysis (hexane/EtOAc, 4 : 1) showed complete consumption of the starting material to a higher R_f. The reaction mixture was poured onto 1.0 M aqueous HCl (50 mL), and the aqueous phase was extracted with DCM (3 × 100 mL). The combined organic phases were washed with sat. NaHCO$_3$ (50 mL), H$_2$O (100 mL), brine (100 mL), dried over MgSO$_4$, filtered and the solvent removed *in vacuo*. This material was used without further purification.

(1*R*,2*R*,3*R*,4*R*,7*R*)-1-*O*-Acetyl-2,3-*O*-isopropylidine-4-vinyl-7-fluorocyclopentane 13. Acetate **13** (6.6 g, 26.9 mmol, 95%) a colourless oil, was obtained following the above procedure from **10** (5.4 g, 26.9 mmol, 1.0 equiv.). R_f = 0.54 (hexane/EtOAc, 4 : 1); $[\alpha]_{\mathrm{D}}^{24.9}$ = −62.5 (*c* 0.2, CH$_2$Cl$_2$); ^{1}H NMR (400 MHz, CDCl$_3$): δ 5.78 (1H, ddd, $^{3}J_{\mathrm{H5-H6a}}$ = 17.9 Hz, $^{3}J_{\mathrm{H5-H6b}}$ = 10.3 Hz, $^{3}J_{\mathrm{H5-H4}}$ = 7.8 Hz, H$_5$), 5.30–5.25 (2H, m, H$_{6a}$, H$_{6b}$), 5.14 (1H, dt, $^{2}J_{\mathrm{H7-F}}$ = 52.5 Hz, $^{3}J_{\mathrm{H7-H4/H1}}$ = 6.6 Hz, H$_7$), 4.96 (1H, dt, $^{3}J_{\mathrm{H1-F}}$ = 14.4 Hz, $^{3}J_{\mathrm{H1-H2/H7}}$ = 6.4 Hz, H$_1$), 4.79 (1H, td, $^{3}J_{\mathrm{H1-H7}}$ = 6.0 Hz, $^{3}J_{\mathrm{H2-H3}}$ = 2.4 Hz, H$_2$), 4.58 (1H, dt, $^{3}J_{\mathrm{H3-H4}}$ = 5.8 Hz, $^{3}J_{\mathrm{H3-H2}}$ = 2.2 Hz, H$_3$), 3.11–3.05 (1H, m, H$_4$), 2.14 (3H, s, Ac–CH$_3$), 1.46 (3H, s, CH$_3$), 1.30 (3H, s, CH$_3$); ^{13}C NMR (101 MHz, CDCl$_3$): δ 170.3 (C═O), 131.6 (d, $^{3}J_{\mathrm{C5-F}}$ = 6.1 Hz, C$_5$), 119.3 (C$_6$), 112.1 [*C*(CH$_3$)$_2$], 95.9 (d, $^{1}J_{\mathrm{C7-F}}$ = 188.2 Hz, C$_7$), 81.7 (d, $^{3}J_{\mathrm{C3-F}}$ = 4.2 Hz, C$_3$), 75.1 (d, $^{2}J_{\mathrm{C1-F}}$ = 22.7 Hz, C$_1$), 74.9 (d, $^{3}J_{\mathrm{C2-F}}$ = 6.8 Hz, C$_2$), 47.5 (d, $^{2}J_{\mathrm{C4-F}}$ = 17.5 Hz, C$_4$), 26.1 [C(*C*H$_3$)$_2$], 24.5 [C(*C*H$_3$)$_2$], 20.7 (Ac-*C*H$_3$); ^{19}F NMR (377 MHz, CDCl$_3$): δ −207.3 (dddt, $^{2}J_{\mathrm{F-H7}}$ = 51.6 Hz, $^{3}J_{\mathrm{F-H1}}$ = 14.5 Hz, $^{3}J_{\mathrm{F-H4}}$ = 9.5 Hz, $^{4}J_{\mathrm{F-H2/H3}}$ = 2.5 Hz); HRMS (ESI): calculated for $C_{12}H_{18}FO_4$ [M + H]$^+$ 245.1184, found 254.1180.

(1*R*,2*R*,3*R*,4*R*)-1-*O*-Acetyl-2,3-*O*-isopropylidine-4-vinyl-7-*gem*-difluorocyclopentane 14. Acetate **14** (7.9 g, 30.4 mmol, 94%) a colourless oil, was obtained following the above procedure from **12** (6.1 g, 30.1 mmol, 1.0 equiv.). R_f = 0.39 (hexane/EtOAc, 4 : 1); $[\alpha]_{\mathrm{D}}^{24.5}$ = −87.0 (*c* 2.0, CH$_2$Cl$_2$); ^{1}H NMR (400 MHz, CDCl$_3$): δ 5.82 (1H, ddd, $^{3}J_{\mathrm{H5-6a}}$ = 17.4 Hz, $^{3}J_{\mathrm{H5-H6b}}$ = 10.5 Hz, $^{3}J_{\mathrm{H5-H4}}$ = 7.9 Hz, H$_5$), 5.45–5.33 (2H, m, H$_{6a}$, H$_{6b}$), 5.10 (1H, dt, $^{3}J_{\mathrm{H1-F}}$ = 8.1 Hz, $^{3}J_{\mathrm{H1-H2}}$ = 5.4 Hz, H$_1$), 4.72 (1H, ddd, $^{3}J_{\mathrm{H2-H3}}$ = 6.8 Hz, $^{3}J_{\mathrm{H2-H1}}$ = 5.6 Hz, $^{4}J_{\mathrm{H2-F}}$ = 3.8 Hz, H$_2$), 4.53 (1H, ddd, $^{3}J_{\mathrm{H3-H2}}$ = 6.3 Hz, $^{4}J_{\mathrm{H3-H4}}$ = 3.8 Hz, $^{3}J_{\mathrm{H3-F}}$ = 1.7 Hz, H$_3$), 3.18–3.05 (1H, m, H$_4$), 2.19 (3H, s, Ac–CH$_3$), 1.50 (3H, s, CH$_3$), 1.33 (3H, s, CH$_3$); ^{13}C NMR (101 MHz, CDCl$_3$): δ 169.3 (C═O), 129.4 (dd, $^3J_{C5-F}$ = 4.9 Hz, $^3J_{C5-F}$ = 1.5 Hz, C_5), 126.1 (dd, $^1J_{C7-F}$ = 269.7 Hz, $^1J_{C7-F}$ = 248.4 Hz, C_7), 121.0 (C_6), 113.6 [$C(CH_3)_2$], 80.6 (dd, $^3J_{C3-F}$ = 6.8 Hz, $^3J_{C3-F}$ = 0.8 Hz, C_3), 74.9 (dd, $^3J_{C2-F}$ = 3.3 Hz, $^3J_{C2-F}$ = 1.8 Hz, C_2), 71.8 (dd, $^2J_{C1-F}$ = 33.5 Hz, $^2J_{C1-F}$ = 18.7 Hz, C_1), 52.8 (dd, $^2J_{C4-F}$ = 21.0 Hz, $^2J_{C4-F}$ = 19.9 Hz, C_4), 26.1 [$C(CH_3)_2$], 24.7 [$C(CH_3)_2$], 20.6 (Ac–CH_3); ^{19}F NMR (377 MHz, $CDCl_3$): δ −110.7 (dddd, $^2J_{F-F}$ = 245.4 Hz, $^3J_{F-H1}$ = 9.2 Hz, $^4J_{F-H4}$ = 5.4 Hz, $^4J_{F-H3}$ = 1.5 Hz), −112.9 (ddddd, $^2J_{F-F}$ = 245.5 Hz, $^3J_{F-H4}$ = 21.4 Hz, $^3J_{F-H1}$ = 8.1 Hz, $^4J_{F-H2}$ = 3.6 Hz, $^4J_{F-H3}$ = 1.8 Hz); HRMS (ESI): calculated for $C_{12}H_{16}FO_4Na$ $[M + Na]^+$ 285.0909, found 285.0914.

General procedures for the synthesis of 15 & 16

Sharpless asymmetric dihydroxylation. AD-mix β (1.4 g per 1 mmol of substrate) was suspended in 1 : 1 $^iPrOH : H_2O$ (v/v, 0.1 M), cooled to 0 °C and stirred vigorously for 30 min, before it was added to **13** or **14** (1.0 equiv.). The reaction mixture was allowed to warm to rt over 1 h and stirred for a further 6–16 h. TLC analysis (hexane/EtOAc, 1 : 1) showed complete consumption of the starting material to two spots of lower R_f. The reaction was quenched by the addition of Na_2SO_3 (1.5 g per 1 mmol of substrate), and the mixture was stirred for 30 min, at which point H_2O (200 mL) was added. The aqueous phase was extracted with EtOAc (3 × 300 mL), and the combined organic phases were washed with H_2O (400 mL), brine (200 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. This material was used without further purification.

Oxidative cleavage conditions A. Vicinal diol intermediate was dissolved in 1 : 5 H_2O/1,4-dioxane (v/v, 0.1 M) and $NaIO_4$ (1.7 equiv.) was added. The reaction mixture was stirred at rt for 1 h, at which point TLC analysis (hexane/EtOAc, 1 : 1) showed complete conversion from two spots to one with a higher R_f. The reaction mixture was diluted with H_2O (200 mL) and extracted with EtOAc (3 × 300 mL). The combined organic phases were washed with H_2O (500 mL), brine (200 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. This material was used without further purification.

Oxidative cleavage conditions B. Vicinal diol intermediate was dissolved in 1 : 5 H_2O/1,4-dioxane (v/v, 0.1 M) and cooled to 0 °C. $NaIO_4$ (10 equiv.) was added, and the reaction mixture was stirred at this temperature for 6 h, at which point TLC analysis (hexane/EtOAc, 1 : 1) showed complete conversion of two spots to two spots with a higher R_f. The reaction mixture was diluted with H_2O (200 mL) and extracted with EtOAc (3 × 300 mL). The combined organic phases were washed with H_2O (500 mL), brine (200 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. This material was used without further purification.

Reduction and acyl deprotection. Aldehyde intermediate was dissolved in MeOH (0.27 M), cooled to 0 °C and $NaBH_4$ (1.5 equiv.) was added in two portions over 10 min. The reaction mixture was allowed to warm to rt and stirred for a further 16 h, at which point TLC analysis (hexane/EtOAc, 1 : 1) showed complete conversion to a lower R_f. The reaction mixture was cooled to 0 °C and H_2O (100 mL) was added. The mixture was allowed to warm to rt and stirred for a further 2 h. The solvent was removed *in vacuo* and the residue was partitioned between H_2O (200 mL) and EtOAc (300 mL). The aqueous phase was extracted with EtOAc (3 × 300 mL) and the combined organic phases were washed with H_2O (200 mL), brine (100 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude material was purified *via* flash column chromatography on silica gel (10–50% EtOAc/hexane).

(1*R*,2*S*,3*R*,4*R*,6*R*)-2,3-*O*-Isopropylidine-4-hydroxymethyl-6-fluorocyclopentan-1-ol 15. Diol **15** (3.7 g, 18.0 mmol, 66%) a colourless oil, was obtained following the above procedures, using oxidative cleavage conditions A, from **13** (6.6 g, 26.9 mmol, 1.0 equiv.). R_f = 0.39 (petroleum-ether/EtOAc, 1 : 4); $[\alpha]_D^{24.1}$ = −13.8 (*c* 2.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.05 (1H, ddd, $^2J_{H6-F}$ = 51.4 Hz, $^3J_{H6-H4}$ = 5.4 Hz, $^3J_{H6-H1}$ = 4.6 Hz, H_6), 4.67–4.65 (2H, m, H_2, H_3), 4.23 (1H, dd, $^3J_{H1-F}$ = 13.3 Hz, $^3J_{H1-H2/H6/OH}$ = 4.5 Hz, H_1), 3.90–3.82 (2H, m, H_{5a}, H_{5b}), 2.76 (1H, d, $^3J_{OH-H1}$ = 3.8 Hz, OH), 2.53 (1H, dddd, $^3J_{H4-F}$ = 20.2 Hz, $^3J_{H4-H5a/H5b}$ = 11.4 Hz, $^3J_{H4-H6}$ = 5.6 Hz, $^3J_{H4-H3}$ = 2.8 Hz, H_4), 1.51 (3H, s, CH_3), 137 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 113.0 [$C(CH_3)_2$], 100.1 (d, $^1J_{C6-F}$ = 180.7 Hz, C_7), 81.2 (d, $^3J_{C3-F}$ = 2.2 Hz, C_3), 77.6 (d, $^3J_{C2-F}$ = 4.8 Hz, C_2), 73.1 (d, $^2J_{C1-F}$ = 25.7 Hz, C_1), 59.5 (d, $^3J_{C5-F}$ = 8.4 Hz, C_5), 47.8 (d, $^2J_{C4-F}$ = 17.7 Hz, C_4), 26.2 [$C(CH_3)_2$], 24.3 [$C(CH_3)_2$]; ^{19}F NMR (376 MHz, $CDCl_3$): δ −206.5 (ddd, $^2J_{F-H6}$ = 51.5 Hz, $^3J_{F-H4}$ = 20.3 Hz, $^3J_{F-H1}$ = 13.7 Hz); HRMS (ESI): calculated for $C_9H_{15}FO_4Na$ $[M + Na]^+$ 229.0847, found 229.0848.

(1*R*,2*S*,3*R*,4*R*)-2,3-*O*-Isopropylidine-4-hydroxymethyl-6-*gem*-difluorocyclopentan-1-ol 16. Diol **16** (3.7 g, 16.7 mmol, 60%), a colourless crystalline solid, was obtained following the above procedures, oxidative cleavage conditions B, from **14** (7.2 g, 27.8 mmol, 1.0 equiv.). R_f = 0.21 (hexane/EtOAc, 1 : 1); mp: 92–95 °C; $[\alpha]_D^{24.9}$ = −36.3 (*c* 4.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.66 (1H, ddd, $^3J_{H2-H1}$ = 6.4 Hz, $^3J_{H2-H3}$ = 3.1 Hz, $^4J_{H2-OH}$ = 1.3 Hz, H_2), 4.57 (1H, td, $^3J_{H3-H4}$ = 6.4 Hz, $^3J_{H3-H2}$ = 3.0 Hz, H_3), 4.19 (1H, dddd, $^3J_{H1-F}$ = 14.0 Hz, $^3J_{H1-OH}$ = 9.4 Hz, $^3J_{H1-F}$ = 8.1 Hz, $^3J_{H1-H2}$ = 6.2 Hz, H_1), 3.96–3.81 (2H, m, H_{5a}, H_{5b}), 2.82 (1H, dd, $^3J_{OH-H1}$ = 9.4 Hz, $^4J_{OH-H2}$ = 1.1 Hz, OH), 2.56–2.48 (1H, m, H_4), 1.52 (3H, s, CH_3), 1.36 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 127.2 (dd, $^1J_{C7-F}$ = 258.8 Hz, $^1J_{C7-F}$ = 256.6 Hz, C_7), 111.9 [$C(CH_3)_2$], 79.0 (dd, $^3J_{C2-F}$ = 4.6 Hz, $^3J_{C2-F}$ = 2.5 Hz, C_2), 75.4 (app. d, $^3J_{C3-F}$ = 8.8 Hz, C_3), 73.1 (dd, $^2J_{C1-F}$ = 28.0 Hz, $^2J_{C1-F}$ = 18.9 Hz, C_1), 58.9 (dd, $^3J_{C5-F}$ = 6.2 Hz, $^3J_{C5-F}$ = 5.8 Hz, C_5), 50.0 (dd, $^2J_{C4-F}$ = 21.0 Hz, $^2J_{C4-F}$ = 20.0 Hz, C_4), 26.0 [$C(CH_3)_2$], 24.3 [$C(CH_3)_2$]; ^{19}F NMR (377 MHz, $CDCl_3$): δ −107.8 – −108.7 (m), −114.6 – −115.3 (m); HRMS (ESI): calculated for $C_{25}H_{32}FO_4Si$ $[M - H]^-$ 223.0787, found 223.0792.

(1*R*,2*S*,3*R*)-2,3-*O*-Isopropylidine-4-hydroxymethyl-6-fluoro-4,6-cyclopenten-1-ol 17. Diol **17** (200 mg, 0.98 mmol, 49%), a colourless syrup, was obtained following the above procedures, oxidative conditions A, from **14** (593 mg, 2.0 mmol, 1.0 equiv.). R_f = 0.11 (hexane/EtOAc, 1 : 1), $[\alpha]_D^{21.6}$ = +41.7 (*c* 2.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.07 (1H, app t, $^3J_{H3-H2}$ = 6.6 Hz, H_3), 4.72 (1H, td, $^3J_{H2-H3}$ = 6.1 Hz, $^3J_{H2-H1}$ = 3.5 Hz, H_2), 4.48 (1H, app. br s, H_1), 4.41–4.28 (2H, m, H_{5a}, H_{5b}), 2.84 (1H, d, $^3J_{OH-H1}$ = 9.0 Hz, OH), 1.48 (3H, s, CH_3), 1.42 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.7 (d, $^1J_{C6-F}$ = 289.8 Hz, C_6), 116.6 (d, $^2J_{C4-F}$ = 5.5 Hz, C_4), 112.7 [$C(CH_3)_2$], 78.8 (d, $^3J_{C3-F}$ =

9.5 Hz, C_3), 73.8 (d, $^3J_{C2–F}$ = 7.8 Hz, C_2), 69.0 (d, $^2J_{C1–F}$ = 21.0 Hz, C_1), 55.0 (C_5), 27.5 [C(CH_3)$_2$], 26.2 [C(CH_3)$_2$]; ^{19}F NMR (377 MHz, $CDCl_3$): δ −129.73 – −129.79 (m).

General procedure for the synthesis of 18 & 19. Diol (1.0 equiv.) was dissolved in DMF (0.5 M). Imidazole (2.0 equiv.) and TBDPSCl (1.0 equiv.) were added, and the reaction mixture was stirred at rt for 1–4 h, at which point TLC analysis (hexane/EtOAc, 4 : 1) showed complete consumption of the starting material to a higher R_f. H_2O (50 mL) was added and aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic phases were washed with H_2O (2 × 100 mL), brine (100 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude material was purified *via* flash column chromatography (0–10% EtOAc/hexane).

(1*R*,2*S*,3*R*,4*S*,6*R*)-2,3-*O*-Isopropylidine-4-*O*-(*tert*-butyldiphenylsilyl)methyl-6-fluorocyclopentan-1-ol. TBDPS alcohol (6.8 g, 15.3 mmol, 85%) a colourless oil, was obtained following the above procedure from **15** (3.7 g, 18.0 mmol, 1.0 equiv.). R_f = 0.16 (hexane/EtOAc, 9 : 1); $[\alpha]_D^{25.0}$ = −13.5 (*c* 0.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70–7.67 (4H, m, ArH), 7.48–7.36 (6H, m, ArH), 5.06 (1H, dt, $^2J_{H6–F}$ = 52.0 Hz, $^3J_{H6–H1/H4}$ = 6.0 Hz, H_6), 4.62 (1H, dt, $^3J_{H2–H1}$ = 6.3 Hz, $^3J_{H2–H3}$ = 2.1 Hz, H_2), 4.55 (1H, dt, $^3J_{H3–H4}$ = 6.3 Hz, $^3J_{H3–H2}$ = 2.2 Hz, H_3), 4.42 (1H, app. dq, $^3J_{H1–F}$ = 14.6 Hz, $^3J_{H1–H2/H6}$ = 6.3 Hz, H_1), 3.89 (1H, dd, $^2J_{H5a–H5b}$ = 10.3 Hz, $^3J_{H5a–H4}$ = 4.2 Hz, H_{5a}), 3.74 (1H, ddd, $^2J_{H5b–H5a}$ = 10.4 Hz, $^3J_{H5b–H4}$ = 5.7 Hz, $^4J_{H5b–F}$ = 1.9 Hz, H_{5b}), 2.81 (1H, dd, $^3J_{OH–H1}$ = 6.9 Hz, $^4J_{OH–F}$ = 1.2 Hz, OH), 2.56–2.48 (1H, m, H_4), 1.51 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.08 (9H, s, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 135.68 (ArC), 135.66 (ArC), 133.0 (ArC), 132.8 (ArC), 129.89 (ArC), 129.85 (ArC), 127.83 (ArC), 127.81 (ArC), 112.0 [*C*(CH_3)$_2$], 99.3 (d, $^1J_{C6–F}$ = 185.0 Hz, C_6), 80.8 (d, $^3J_{C3–F}$ = 3.5 Hz, C_3), 77.0 (d, $^3J_{C2–F}$ = 7.1 Hz, C_2), 73.8 (d, $^2J_{C1–F}$ = 24.4 Hz, C_1), 59.9 (d, $^3J_{C5–F}$ = 8.3 Hz, C_5), 46.9 (d, $^2J_{C4–F}$ = 18.0 Hz, C_4), 26.9 [C(CH_3)$_3$], 26.2 [*C*(CH_3)$_2$], 24.2 [*C*(CH_3)$_2$], 19.2 [*C*(CH_3)$_3$]; ^{19}F NMR (376 MHz, $CDCl_3$): δ −208.5 (app. dt, $^2J_{F–H6}$ = 52.2 Hz, $^3J_{F–H1/H4}$ = 13.7 Hz); HRMS (NSI) calculated for $C_{25}H_{33}FO_4SiNa$ $[M + Na]^+$ 476.2024, found 467.2021.

(1*R*,2*S*,3*R*,4*S*)-2,3-*O*-Isopropylidine-4-*O*-(*tert*-butyldiphenylsilyl)methyl-6-*gem*-difluorocyclopentan-1-ol. TBDPS alcohol (7.5 g, 16.2 mmol, 97%) a colourless oil, was obtained following the above procedure from **16** (3.7 g, 16.7 mmol, 1.0 equiv.). R_f = 0.27 (hexane/EtOAc, 9 : 1); $[\alpha]_D^{24.3}$ = −4.6 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.61 (4H, m, ArH), 7.49–7.37 (6H, m, ArH), 4.64–4.57 (2H, m, H_2, H_3), 4.46–4.34 (1H, m, H_1), 3.90 (1H, dd, $^2J_{H5a–H5b}$ = 10.7 Hz, $^3J_{H5a–H4}$ = 2.5 Hz, H_{5a}), 3.68 (1H, dddd, $^2J_{H5b–H5a}$ = 10.6 Hz, $^3J_{H5b–H4}$ = 3.3 Hz, $^4J_{H5b–F}$ = 2.0 Hz, $^4J_{H5b–F}$ = 1.3 Hz, H_{5b}), 2.84 (1H, dd, $^3J_{OH–H1}$ = 11.0 Hz, $^3J_{OH–F}$ = 1.5 Hz, OH), 2.41 (1H, dt, $^3J_{H4–F}$ = 17.0 Hz, $^3J_{H4–H5}$ = 3.0 Hz, H_4), 1.49 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.05 (9H, s, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 135.6 (ArC), 135.6 (ArC), 132.3 (ArC), 132.1 (ArC), 130.1 (ArC), 130.0 (ArC), 128.0 (ArC), 127.9 (ArC), 124.2 (dd, $^1J_{C6–F}$ = 275.3 Hz, $^1J_{C6–F}$ = 252.5 Hz, C_6), 111.4 [*C*(CH_3)$_2$], 79.2 (d, $^3J_{C2–F}$ = 5.5 Hz, C_2), 75.5 (d, $^3J_{C3–F}$ = 10.2 Hz, C_3), 74.0 (dd, $^2J_{C1–F}$ = 26.3 Hz, $^2J_{C1–F}$ = 19.0 Hz, C_1), 60.3 (dd, $^3J_{C5–F}$ = 8.3 Hz, $^3J_{C5–F}$ = 4.9 Hz, C_5), 50.2 (dd, $^2J_{C4–F}$ = 21.0 Hz, $^2J_{C4–F}$ = 20.2 Hz, C_4), 26.9 [C(CH_3)$_3$], 25.9 [C(CH_3)$_2$], 24.2 [C(CH_3)$_2$], 19.1 [*C*(CH_3)$_3$]; ^{19}F NMR (377 MHz, $CDCl_3$): δ −107.4 (dt, $^2J_{F–F}$ = 240.7 Hz, $^3J_{F–H1/H4}$ = 16.5 Hz), −114.0 – −114.9 (m); HRMS (NSI): calculated for $C_{25}H_{32}F_2O_4SiNa$ $[M + Na]^+$ 485.1930, found 485.1936.

Triflation. TBDPS alcohol (1.0 equiv.) was dissolved in pyridine (0.32 M) and cooled to −10 °C. Tf_2O (2.0 equiv.) was added dropwise. The reaction mixture was stirred at this temperature for 10 min, at which point TLC analysis (hexane/EtOAc, 9 : 1) showed complete consumption to a higher R_f. H_2O (50 mL) was added and the aqueous phase was extracted with Et_2O (3 × 200 mL). The combined organic phases were washed with sat. $CuSO_4$ (200 mL), followed by H_2O (200 mL), brine (200 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. This material was used without further purification.

Azidation. Triflate intermediate was dissolved in DMF (0.2 M), and NaN_3 (3.0 equiv.) was added. The reaction was stirred at 80–100 °C for 3–6 h, at which point TLC analysis (hexane/EtOAc 9 : 1) showed complete conversion from a lower R_f to higher R_f. The reaction was cooled to rt, and H_2O (100 mL) was added. The aqueous phase was extracted with Et_2O (3 × 200 mL), and the combined organic phases were washed with H_2O (2 × 100 mL), brine (100 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude material was purified *via* flash column chromatography (0–10% EtOAc/hexane).

(1*S*,2*S*,3*R*,4*S*,6*R*)-1-Azido-2,3-*O*-isopropylidine-4-*O*-(*tert*-butyldiphenylsilyl)methyl-6-fluorocyclopentan-1-ol 18. Azide **18** (6.5 g, 13.9 mmol, 91%) a colourless oil, was obtained following the above procedure from TBDPS alcohol (6.8 g, 15.3 mmol, 1.0 equiv.). R_f = 0.74 (hexane/EtOAc, 9 : 1); $[\alpha]_D^{24.9}$ = −8.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68–7.64 (4H, m, ArH), 7.46–7.35 (6H, m, ArH), 5.28 (1H, app. dt, $^2J_{H6–F}$ = 52.5 Hz, $^3J_{H6–H1/H4}$ = 3.2 Hz, H_6), 4.66 (1H, ddd, $^3J_{H2–H3}$ = 7.3 Hz, $^3J_{H2–H1}$ = 6.0 Hz, $^4J_{H2–F}$ = 1.3 Hz, H_2), 4.38–4.34 (1H, m, H_3), 3.87 (2H, d, $^3J_{H5a/H5b–H4}$ = 8.3 Hz, H_{5a}, H_{5b}), 3.71 (1H, ddd, $^3J_{H1–F}$ = 28.0 Hz, $^3J_{H1–H2}$ = 5.8 Hz, $^3J_{H1–H6}$ = 3.0 Hz, H_1), 2.46 (1H, m, H_4), 1.50 (3H, s, CH_3), 1.28 (3H, s, CH_3), 1.06 (9H, s, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 135.6 (ArC), 135.6 (ArC), 133.3 (ArC), 133.1 (ArC), 129.8 (ArC), 127.8 (ArC), 127.7 (ArC), 114.26 [*C*(CH_3)$_2$], 97.0 (d, $^1J_{C6–F}$ = 184.0 Hz, C_6), 82.1 (C_2), 79.7 (C_3), 68.1 (d, $^3J_{C5–F}$ = 16.0 Hz, C_5), 60.3 (d, $^2J_{C1–F}$ = 7.4 Hz, C_1), 50.9 (d, $^2J_{C4–F}$ = 17.7 Hz, C_4), 27.1 [*C*(CH_3)$_3$], 26.8 [C(CH_3)$_3$], 24.6 [C(CH_3)$_2$], 19.2 [C(CH_3)$_2$]; ^{19}F NMR (377 MHz, $CDCl_3$): δ −206.64 (ddd, $^2J_{F–H6}$ = 52.5 Hz, $^3J_{F–H1}$ = 32.6 Hz, $^3J_{F–H4}$ = 28.1 Hz); HRMS (ASAP): calculated for $C_{25}H_{33}FNO_3Si$ $[M + H–N2]^+$ 442.2208, found 442.2203.

(1*S*,2*S*,3*R*,4*S*)-1-Azido-2,3-*O*-isopropylidine-4-*O*-(*tert*-butyldiphenylsilyl)methyl-6-*gem*-difluorocyclopentane 19. Azide **19** (5.8 g, 12.0 mmol, 74%) a colourless oil, was obtained following the above procedure from TBDPS alcohol (7.5 g, 16.2 mmol, 1.0 equiv.). R_f = 0.58 (hexane/EtOAc, 9 : 1); $[\alpha]_D^{24.4}$ = −28.0 (*c* 2.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70–7.65 (4H, m, ArH), 7.47–7.37 (6H, m, ArH), 4.41–4.36 (1H, m, H_3), 4.36–4.30 (1H, m, H_2), 3.99–3.80 (3H, m, H_1, H_{5a}, H_{5b}), 2.75–2.62 (1H, m, H_4), 1.52 (3H, s, CH_3), 1.28 (3H, s, CH_3), 1.06 (9H, s, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 135.8 (ArC), 135.8 (ArC), 127.9 (ArC), 127.9 (ArC), 127.0 (dd, $^1J_{C6-F}$ = 264.0 Hz, $^1J_{C6-F}$ = 256.1 Hz, C_6), 113.5 [$C(\mathrm{CH}_3)_2$], 79.7 (d, $^3J_{C2-F}$ = 6.7 Hz, C_2), 77.5 (d, $^3J_{C3-F}$ = 8.1 Hz, C_3) 69.2 (dd, $^2J_{C1-F}$ = 23.9 Hz, $^2J_{C1-F}$ = 18.7 Hz, C_1), 59.5 (d, $^3J_{C5-F}$ = 6.8 Hz, C_5), 52.0 (t, $^2J_{C4-F}$ = 19.7 Hz, C_4), 27.1 [$C(\mathrm{CH}_3)_3$], 26.9 [$\mathrm{C}(CH_3)_2$], 24.8 [$\mathrm{C}(CH_3)_2$], 19.3 [$\mathrm{C}(CH_3)_3$]; ^{19}F NMR (377 MHz, $CDCl_3$): δ −99.7 (dt, $^2J_{F-F}$ = 238.7 Hz, $^3J_{F-H1/H4}$ = 7.9 Hz), −118.8 – −119.6 (m); HRMS (ASAP): calculated for $C_{25}H_{32}F_2N_3O_3Si$ [M + H]$^+$ 488.2176, found 488.2182.

General procedure for the synthesis of 20 and 21

Reduction. Azide **18** or **19** (1.0 equiv.) was dissolved in MeOH (0.2 M) and Pd/C (0.1 equiv.) was added. The reaction vessel was evacuated and refilled with H_2 seven times, and the reaction was stirred at rt for 4–18 h. TLC analysis (hexane/EtOAc, 9 : 1) showed complete consumption of the starting material to a lower R_f. The reaction mixture was filtered through a Celite® pad and eluted with MeOH. This material was used without further purification.

(1*S*,2*S*,3*R*,4*S*,6*R*)-1-Amino-2,3-*O*-isopropylidine-4-*O*-(*tert*-butyldiphenylsilyl)methyl-6-fluorocyclopentane. C1-Amine (6.1 g, 13.6 mmol, 98%) a colourless syrup, was obtained following the above procedure from **20** (6.5 g, 13.9 mmol, 1.0 equiv.). R_f = 0.12 (hexane/EtOAc, 1 : 1); $[\alpha]_{\mathrm{D}}^{24.7}$ = +3.2 (*c* 0.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_{3:}$) δ 7.70–7.65 (4H, m, ArH), 7.45–7.34 (6H, m, ArH), 5.10 (1H, dt, $^3J_{H6-F}$ = 53.0 Hz, $^3J_{H6-H1/H4}$ = 3.1 Hz, H_6), 4.35–4.27 (2H, m, H_2, H_3), 3.88–3.85 (2H, m, H_{5a}, H_{5b}), 3.36–3.25 (1H, m, H_1), 2.50–2.34 (1H, m, H_4), 1.49 (3H, s, CH_3), 1.26 (3H, s, CH_3), 1.05 (9H, s, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 135.6 (ArC), 135.6 (ArC), 133.5 (ArC), 133.6 (ArC), 129.7 (ArC), 129.7 (ArC), 127.7 (ArC), 127.7 (ArC), 113.5 [$C(\mathrm{CH}_3)_2$], 99.2 (d, $^1J_{C6-F}$ = 176.3 Hz, C_6), 86.8 (C_2), 80.2 (C_3), 61.8 (d, $^2J_{C1-F}$ = 17.3 Hz, C_1), 60.7 (d, $^3J_{C5-F}$ = 7.4 Hz, C_5), 51.4 (d, $^2J_{C4-F}$ = 18.0 Hz, C_4), 27.3 [$C(\mathrm{CH}_3)_3$], 26.8 [$\mathrm{C}(CH_3)_3$], 24.7 [$\mathrm{C}(CH_3)_2$], 19.3 [$\mathrm{C}(CH_3)_2$]; ^{19}F NMR (377 MHz, $CDCl_3$): δ −210.5 (ddd, $^2J_{F-H6}$ = 53.0 Hz, $^3J_{F-H4}$ = 34.9 Hz, $^3J_{F-H1}$ = 30.5 Hz). HRMS (ESI): calculated for $C_{25}H_{35}FNO_3Si$ [M + H]$^+$ 444.2365, found 444.2365.

(1*S*,2*S*,3*R*,4*S*)-1-Amino-2,3-*O*-isopropylidine-4-*O*-(*tert*-butyldiphenylsilyl)methyl-6-*gem*-difluorocyclopentane. C1-Amine (5.1 g, 11.0 mmol, 99%) a colourless syrup, was obtained following the above procedure from **21** (5.4 g, 11.1 mmol, 1.0 equiv.). R_f = 0.51 (hexane/EtOAc, 1 : 4); $[\alpha]_{\mathrm{D}}^{22.3}$ = −9.8 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70–7.66 (4H, m, ArH), 7.46–7.36 (6H, m, ArH), 4.35–4.31 (1H, m, H_3), 4.17–4.11 (1H, m, H_2), 3.96–3.86 (2H, m, H_{5a}, H_{5b}), 3.38 (1H, app. dt, $^3J_{H1-F}$ = 17.7 Hz, $^3J_{H1-H2}$ = 5.9 Hz, H_1), 2.69–2.56 (1H, m, H_4), 1.51 (3H, s, CH_3), 1.28 (3H, s, CH_3), 1.06 (9H, s, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7 (ArC), 135.6 (ArC), 133.2 (ArC), 133.1 (ArC), 129.8 (ArC), 129.8 (ArC), 112.7 (ArC), 82.8 (d, $^3J_{C2-F}$ = 8.3 Hz, C_2), 77.2 (app. d, $^3J_{C3-F}$ = 7.7 Hz, C_3), 62.7 (dd, $^2J_{C1-F}$ = 23.2 Hz, $^2J_{C1-F}$ = 21.0 Hz, C_1), 59.9 (d, $^3J_{C5-F}$ = 6.8 Hz, C_5), 51.9 (t, $^2J_{C4-F}$ = 20.5 Hz, C_4), 27.1 [$\mathrm{C}(CH_3)_2$], 26.7 [$\mathrm{C}(CH_3)_3$], 24.7 [$\mathrm{C}(CH_3)_2$], 19.2 [$C(\mathrm{CH}_3)_3$]; ^{19}F NMR (377 MHz, $CDCl_3$): δ −104.4 (app. dt, $^2J_{F-F}$ = 234.9 Hz, $^3J_{F-H1/H4}$ = 8.0 Hz), −123.2 (app. dt, $^2J_{F-F}$ = 234.9 Hz, $^3J_{F-H1/H4}$ = 19.4 Hz); HRMS (ESI): calculated for $C_{25}H_{34}F_2NO_3Si$ [M + H]$^+$ 462.2271, found 462.2269.

(3-Ethoxy-acryloyl)isocyanate. An oven dried multi-necked round bottom flask was charged with AgOCN (13.9 g, 92.9 mmol, 2.5 equiv.), heated to 100 °C for 1 h with stirring, and evacuated and flushed with N_2 three times. The reaction vessel was cooled to rt and toluene (106 mL) was added and the mixture stirred vigorously at reflux for 30 min. 3-Ethoxyacryloylchloride (5.0 g, 37.2 mmol, 1.0 equiv.) was added dropwise and the reaction mixture was stirred at reflux for a further 1 h. The reaction mixture was allowed to cool to rt, and the supernatant, a 0.35 M solution of (3-ethoxy-acryloyl)isocyanate, was transferred to an oven-dried round bottom flask *via* cannula and stored under an atmosphere of N_2. The product was stored at −25 °C prior to use.

Nucleobase synthesis. C1-Amine was dissolved in DMF (0.2 M) and cooled to 0 °C. (3-Ethoxy-acryloyl)isocyanate (2.0 equiv., 0.35 M in toluene,) was added dropwise, and the reaction was allowed to warm to rt and stirred for a further 16 h. TLC analysis (hexane/EtOAc, 1 : 1) showed complete consumption of the starting material to a higher R_f. The reaction mixture was cooled to 0 °C and quenched with sat. $NaHCO_3$ (100 mL) and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic phases were washed with H_2O (2 × 100 mL), brine (100 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude material was purified *via* flash column chromatography (10–50% EtOAc/hexane).

(1′*S*,2′*S*,3′*R*,4′*S*,6′*R*)-1′-(6-Ethoxyacryloylurea)-2′,3′-*O*-isopropylidine-4′-*O*-(*tert*-butyldiphenylsilyl)methyl-6′-fluorocyclopentane 20. Acryloyl urea 20 (5.3 g, 9.2 mmol, 68%) a white foam, was obtained following the above procedure from C1-amine (6.1 g, 13.6 mmol, 1.0 equiv.). R_f = 0.44 (hexane/EtOAc, 1 : 1); $[\alpha]_{\mathrm{D}}^{24.9}$ = −9.0 (*c* 2.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.68 (1H, s, H_3), 9.24 (1H, d, $^3J_{H1-H1'}$ = 8.5 Hz, H_1), 7.69–7.65 (4H, m, ArH, H_6), 7.45–7.36 (6H, m, ArH), 5.40 (1H, d, $^3J_{H5-H6}$ = 12.2 Hz, H_5), 5.26 (1H, dt, $^2J_{H6'-F}$ = 53.0 Hz, $^3J_{H6'-H1'/H4'}$ = 3.0 Hz, $H_{6'}$), 4.58 (1H, dd, $^3J_{H2'-H1'}$ = 6.2 Hz, $^3J_{H2'-H3'}$ = 7.0 Hz, $H_{2'}$), 4.45 (1H, dddd, $^3J_{H1'-F}$ = 31.2 Hz, $^3J_{H1'-H1}$ = 8.8 Hz, $^3J_{H1'-H2'}$ = 6.1 Hz, $^3J_{H1'-H6'}$ = 3.0 Hz, $H_{1'}$), 4.32 (1H, t, $^3J_{H3'-H2'/H4'}$ = 6.8 Hz, $H_{3'}$), 3.98 (2H, q, *J* = 7.1 Hz, $-\mathrm{OC}H_2\mathrm{CH}_3$), 3.89 (2H, app. d, *J* = 8.1 Hz, $H_{5'a}$, $H_{5'b}$), 2.49 (1H, dddd, $^2J_{H4'-F}$ = 35.8 Hz, $^2J_{H4'-H5'a}$ = 10.3 Hz, $^2J_{H4'-H5'b}$ = 8.0 Hz, $^2J_{H4'-H6'}$ = 2.9 Hz, $H_{4'}$), 1.51 (3H, s, CH_3), 1.35 (3H, t, *J* = 7.1 Hz, $-\mathrm{OCH_2C}H_3$), 1.26 (3H, s, CH_3), 1.05 (9H, s, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.3 (C_4, C=O), 163.1 (C_6), 155.2 (C_2, C=O), 135.6 (ArC), 133.4 (ArC), 133.2 (ArC), 129.7 (ArC), 127.8 (ArC), 127.7 (ArC), 114.0 [$C(\mathrm{CH})_3$], 98.1 (C_5), 84.5 ($C_{2'}$), 79.7 ($C_{3'}$), 67.6 ($\mathrm{-O}C\mathrm{H_2CH_3}$), 60.5 (d, $^3J_{C5'-F}$ = 7.1 Hz, $C_{5'}$), 58.9 (d, $^2J_{C1'-F}$ = 16.0 Hz, $C_{1'}$), 51.5 (d, $^2J_{C4'-F}$ = 17.7 Hz, $C_{4'}$), 27.3 (CH_3), 26.8 (CH_3), 24.7 (CH_3), 14.6 ($\mathrm{-OCH_2}C\mathrm{H_3}$); ^{19}F NMR (376 MHz, $CDCl_3$): δ −206.4 (ddd, $^1J_{F-H6'}$ = 53.2 Hz, $^2J_{F-H4'}$ = 35.7 Hz, $^2J_{F-H1'}$ = 31.5 Hz); HRMS (ESI): calculated for $C_{31}H_{41}FN_2O_6SiNa$ [M + Na]$^+$ 607.2610, found 607.2604.

(1′*S*,2′*S*,3′*R*,4′*S*)-1′-(6-Ethoxyacryloylurea)-2′,3′-*O*-isopropylidine-4′-*O*-(*tert*-butyldiphenylsilyl)methyl-6′-*gem*-difluorocyclo-

pentane 21. Acryloyl urea 21 (4.9 g, 8.1 mmol, 74%) a white foam, was obtained following the above procedure from C1-amine (5.1 g, 11 mmol, 1.0 equiv.). R_f = 0.76 (EtOAc/hexane, 4 : 1); $[\alpha]_D^{24.5}$ = −21.2 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.96 (1H, br s, H_3), 9.29 (1H, d, $^3J_{H1-H1'}$ = 9.0 Hz, H_1, 7.74–7.63 (5H, m, ArH, H_6), 7.46–7.36 (6H, m, ArH), 5.39 (1H, d, $^3J_{H5-H6}$ = 12.3 Hz, H_5), 4.76–4.64 (1H, m, $H_{1'}$), 4.38–4.31 (2H, m, $H_{2'}$, $H_{3'}$), 4.04–3.93 (3H, m, $H_{5'a}$, $-OCH_2CH_3$), 3.89 (1H, dd, $^2J_{H5'b-H5'a}$ = 10.6 Hz, $^3J_{H5'b-H4'}$ = 6.3 Hz, $H_{5'b}$), 2.79–2.65 (1H, m, $H_{4'}$), 1.55 (1H, s, CH_3), 1.34 (3H, t, *J* = 7.1 Hz, $-OCH_2CH_3$), 1.29 (3H, s, CH_3), 1.07 (9H, s, 3 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.5 (C_4, C=O), 163.1 (C_6), 155.6 (C_2, C=O), 135.67 (ArC), 135.65 (ArC), 133.2 (ArC), 133.1 (ArC), 129.8 (ArC), 127.8 (ArC), 126.4 (dd, $^1J_{C6'-F}$ = 266.9 Hz, $^1J_{C6'-F}$ = 250.2 Hz, $C_{6'}$), 113.3 [$C(CH_3)_2$], 98.0 (C_5), 81.0 (d, $^3J_{C2'-F}$ = 8.5 Hz, $C_{2'}$), 76.8 (d, $^3J_{C3'-F}$ = 8.2 Hz, $C_{3'}$), 67.4 ($-OCH_2CH_3$), 59.6 (dd, $^2J_{C1'-F}$ = 22.2 Hz, $^2J_{C1'-F}$ = 18.3 Hz, $C_{1'}$), 59.4 (d, $^3J_{C5'-F}$ = 6.7 Hz, $C_{5'}$), 51.6 (t, $^3J_{C4'-F}$ = 19.6 Hz, $C_{4'}$), 27.2 [$C(CH_3)_2$], 26.7 [$C(CH_3)_3$], 24.9 [$C(CH_3)_2$], 19.2 [$C(CH_3)_3$], 14.5 ($-OCH_2CH_3$); ^{19}F NMR (377 MHz, $CDCl_3$): δ −104.5 (dt, $^2J_{F-F}$ = 237.8 Hz, $^3J_{F-H1'/H4'}$ = 5.8 Hz), −120.1 (dt, $^2J_{F-F}$ = 236.9 Hz, $^3J_{F-H1'/H4'}$ = 23.0 Hz); HRMS (ESI): calculated for $C_{31}H_{40}F_2N_2O_6SiNa$ $[M + Na]^+$ 625.2516, found 625.2507.

General procedure for the synthesis of 22 & 23

Cyclisation. Acryloyl urea **20** or **21** was dissolved in 1,4-dioxane (0.5 M), and H_2SO_4 (0.5 equiv., 2.0 M) was added. The reaction mixture was stirred at reflux for 3 h, at which point TLC analysis (EtOAc/hexane, 4 : 1) showed complete conversion of the starting material to a lower R_f. The reaction mixture was cooled to rt and solid Na_2CO_3 was added to adjust the pH to 7. The mixture was filtered, and the solvent of the filtrate removed *in vacuo*. This material was used without further purification.

Silyl deprotection. Uridine intermediate was dissolved in THF (0.2 M) and TBAF (1.0 equiv., 1.0 M in THF) was added. The reaction mixture was stirred at rt for 3 h, at which point TLC analysis (10% MeOH/DCM) showed complete conversion from a higher R_f to a lower R_f. The solvent was removed *in vacuo*, and the residue was purified *via* flash column chromatography on silica gel (0–10% MeOH/EtOAc).

HPLC purification. A sample of **22** or **23** was dissolved in H_2O (100 mg mL^{-1}), and injected onto a reverse phase column (see general experimental) and purified at a flow rate of 20.00 ml min^{-1} using the following gradient system:

Time (min)	%*A* (H_2O)	%*B* (MeOH)
0.0	95	5
5.0	95	5
12.0	0	100
15.0	0	100
15.1	95	5
20.0	95	5

(6′*R*)-6′-Fluorocarbauridine 22. Uridine derivative **22** (1.3 g, 4.7 mmol, 70%) a white solid after freeze drying, was obtained following the above procedure from **20** (3.9 g, 6.7 mmol, 1.0 equiv.). R_f = 0.12 (10% MeOH/DCM); ^{1}H NMR (400 MHz, D_2O): δ 7.69 (1H, dd, $^3J_{H6-H5}$ = 8.1 Hz, $^5J_{H6-F}$ = 1.5 Hz, H_6), 5.79 (1H, d, $^3J_{H5-H6}$ = 7.6 Hz, H_5), 5.11 (1H, ddd, $^2J_{H6'-F}$ = 54.9 Hz, $^3J_{H6'-H4'}$ = 4.5 Hz, $^3J_{H6'-H1'}$ = 3.7 Hz, $H_{6'}$), 4.86 (1H, ddd, $^3J_{H1'-F}$ = 30.6 Hz, $^3J_{H1'-H2'}$ = 10.5 Hz, $^3J_{H1'-H6'}$ = 3.4 Hz, $H_{1'}$), 4.53 (1H, dd, $^3J_{H2'-H1'}$ = 10.4 Hz, $^3J_{H2'-H3'}$ = 6.6 Hz, $H_{2'}$), 3.99 (1H, dd, $^3J_{H3'-H2'}$ = 6.4 Hz, $^3J_{H3'-H4'}$ = 4.8 Hz, $H_{3'}$), 3.75 (2H, m, $H_{5'a}$, $H_{5'b}$) 2.37 (dddd, $^3J_{H4'-F}$ = 31.3 Hz, $^3J_{H4'-H5'a}$ = 12.2 Hz, $^3J_{H4'-H5'b}$ = 7.7 Hz, $^3J_{H4'-H3'/H6'}$ = 4.7 Hz, $H_{4'}$); ^{13}C NMR (101 MHz, D_2O): δ 167.0 (C_4, C=O), 153.4 (C_2, C=O), 144.0 (d, $^4J_{C6-F}$ = 4.8 Hz, C_6), 101.6 (C_5), 90.9 (d, $^1J_{C6'-F}$ = 180.8 Hz, $C_{6'}$), 70.2 ($C_{2'}$), 69.2 ($C_{3'}$), 61.6 (d, $^2J_{C1'-F}$ = 16.4 Hz, $C_{1'}$), 58.3 (d, $^3J_{C5'-F}$ = 11.3 Hz, $C_{5'}$), 50.6 (d, $^2J_{C4'-F}$ = 18.1 Hz, $C_{4'}$); ^{19}F NMR (377 MHz, D_2O): δ −207.8 (dt, $^2J_{F-H6'}$ = 55.0 Hz, $^3J_{F-H1'/H4'}$ = 30.9 Hz); HRMS (ESI): calculated for $C_{10}H_{12}FN_2O_5$ $[M - H]^-$ 259.0736, found 259.0738. These data were in good agreement with the literature.[17]

6′-*gem*-Difluorocarbauridine. Uridine derivative **23** (1.4 g, 5.1 mmol, 63%) a white solid after freeze drying, was obtained following the above procedure from **21** (4.9 g, 8.1 mmol, 1.0 equiv.). R_f = 0.13 (10% MeOH/DCM); ^{1}H NMR (400 MHz, MeOD): δ 7.68 (1H, dd, $^3J_{H6-H5}$ = 8.0 Hz, $^5J_{H6-F}$ = 2.3 Hz, H_6), 5.73 (1H, d, $^3J_{H5-H6}$ = 8.1 Hz, H_6), 5.37 (1H, dt, $^3J_{H1'-F}$ = 18.3 Hz, $^3J_{H1'-H2'}$ = 10.2 Hz, $H_{1'}$), 4.43 (1H, dd, $^3J_{H2'-H1'}$ = 10.7 Hz, $^3J_{H2'-H3'}$ = 5.1 Hz, $H_{2'}$), 4.10–4.08 (1H, m, $H_{3'}$), 3.86–3.71 (2H, m, $H_{5'a}$, $H_{5'b}$), 2.63–2.46 (1H, m, $H_{4'}$); ^{13}C NMR (101 MHz, MeOD): δ 165.9 (C_4, C=O), 153.3 (C_2, C=O), 144.5 (d, $^4J_{C6-F}$ = 4.2 Hz, C6), 126.0 (dd, $^1J_{C6'-F}$ = 260.0 Hz, $^1J_{C6'-F}$ = 253.7 Hz, $C_{6'}$), 102.6 (C_5), 71.7 (d, $^3J_{C2'-F}$ = 8.0 Hz, $C_{2'}$), 71.0 (dd, $^3J_{C3'-F}$ = 5.3 Hz, $^3J_{C3'-F}$ = 2.5 Hz, $C_{3'}$), 63.6 (dd, $^2J_{C1'-F}$ = 24.3 Hz, $^2J_{C1'-F}$ = 18.3 Hz, $C_{1'}$), 58.7 (d, $^4J_{C5'-F}$ = 10.9 Hz, $C_{5'}$), 55.4 (t, $^3J_{C4'-F}$ = 20.2 Hz, $C_{4'}$); ^{19}F NMR (377 MHz, MeOD): δ −96.7 (ddd, $^2J_{F-F}$ = 238.6 Hz, $^3J_{F-H4'}$ = 15.4 Hz, $^3J_{F-H1'}$ = 9.9 Hz), −117.0 (app. dt, $^2J_{F-F}$ = 238.6 Hz, $^3J_{F-H1'/H4'}$ = 15.6 Hz). HRMS (ESI): calculated for $C_{10}H_{11}F_2N_2O_5$ $[M - H]^-$ 277.0642, found 277.0643. These data are in good agreement with literature values.[17]

General procedure for the synthesis of 24 & 25. Uridine **22** or **23** was suspended in DCM (0.2 M) and DMAP (0.1 equiv.), pyridine (6.0 equiv.) and Ac_2O (6.0 equiv.) were added. The reaction mixture was stirred at rt for 16 h, at which point TLC analysis (10% MeOH/DCM) showed complete consumption of the starting material to a higher R_f. The reaction mixture was poured onto 1.0 M aqueous HCl (2 mL), and the aqueous phase was extracted with DCM (3 × 10 mL). The combined organic phases were washed with sat. $NaHCO_3$ (5 mL), H_2O (5 mL), brine (5 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude material was purified *via* flash column chromatography on silica gel (50–100%, EtOAc/Hexane).

(6′*R*)-2′,3′,5′-Tri-*O*-acetyl-6′-fluorocarbauridine 24. Triacetate **24** (68 mg, 0.18 mmol, 88%.) as a colourless syrup, was obtained following the above procedure from **22** (50.0 mg, 0.18 mmol, 1.0 equiv.). R_f = 0.53 (hexane/EtOAc, 1 : 4); $[\alpha]_D^{22.1}$ = −10.7 (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.87 (1H, br s, NH), 7.32 (1H, dd, $^3J_{H6-H5}$ = 8.2 Hz, $^5J_{H6-F}$ = 1.8 Hz, H_6), 5.77

(1H, dd, $^{3}J_{\text{H5–H6}}$ = 8.2 Hz, $^{6}J_{\text{H5–F}}$ = 2.1 Hz, H_5), 5.64 (1H, dd, $^{3}J_{\text{H2′–H1′}}$ = 9.9 Hz, $^{3}J_{\text{H2′–H3′}}$ = 7.0 Hz, $\text{H}_{2′}$), 5.32–5.22 (2H, m, $\text{H}_{1′}$, $\text{H}_{3′}$), 5.13 (1H, dt, $^{2}J_{\text{H6′–F}}$ = 50.7 Hz, $\text{H}_{6′}$), 4.34 (1H, ddd, $^{2}J_{\text{H5′a–H5′b}}$ = 11.2 Hz, $^{3}J_{\text{H5′a–H4′}}$ = 6.3 Hz, $^{4}J_{\text{H5′a–F}}$ = 1.4 Hz, $\text{H}_{5′\text{a}}$), 4.26 (1H, dd, $^{2}J_{\text{H5′b–H5′a}}$ = 11.3 Hz, $^{3}J_{\text{H5′b–H4′}}$ = 8.8 Hz, $\text{H}_{5′\text{b}}$), 2.83–2.68 (1H, m, $\text{H}_{4′}$), 2.11 (3H, s, Ac–CH_3), 2.07 (3H, s, Ac–CH_3), 2.05 (3H, s, Ac–CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 170.5 (C═O), 169.8 (C═O), 169.7 (C═O), 162.4 (C_2, C═O), 151.2 (C_4, C═O), 141.2 (d, $^{4}J_{\text{C6–F}}$ = 5.2 Hz, C_6), 102.8 (C_5), 90.3 (d, $^{1}J_{\text{C6′–F}}$ = 184.5 Hz, $C_{6′}$), 69.6 (C_2), 69.4 (C_3), 59.8 (d, $^{3}J_{\text{C5′–F}}$ = 10.1 Hz, $C_{5′}$), 59.7 (d, $^{2}J_{\text{C1′–F}}$ = 16.4 Hz, $C_{1′}$), 46.0 (d, $^{2}J_{\text{C4′–F}}$ = 18.2 Hz, $C_{4′}$), 20.7 (Ac–*C*H_3), 20.5 (Ac–*C*H_3), 20.4 (Ac–*C*H_3); ^{19}F NMR (377 MHz, $CDCl_3$) *δ* −206.2 (dt, $^{2}J_{\text{F–H6′}}$ = 54.5 Hz, $^{3}J_{\text{F–H1′/H4′}}$ = 30.2 Hz); HRMS (NSI): calculated for $C_{16}H_{20}FN_2O_8$ $[M + H]^+$ 387.1198, found 387.1200.

2′,3′,5′-Tri-*O*-acetyl-6′-*gem*-difluorocarbauridine 25. Triacetate **25** (48.3 mg, 0.12 mmol, 92%) a colourless syrup was obtained following the above procedure from **23** (36.1 mg, 0.13 mmol, 1.0 equiv.). R_f = 0.55 (hexane/EtOAc, 1 : 4); $[\alpha]_D^{24.6}$ = −33.2 (*c* 0.4, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 9.58 (1H, br s, NH), 7.24 (1H, dd, $^{3}J_{\text{H6–H5}}$ = 8.2 Hz, $^{5}J_{\text{H6–F}}$ = 2.5 Hz, H_6), 5.80 (1H, d, $^{3}J_{\text{H5–H6}}$ = 8.2 Hz, H_5), 5.59–5.51 (2H, m, $\text{H}_{1′}$, $\text{H}_{2′}$), 5.32–5.29 (1H, m, $\text{H}_{3′}$), 4.37–4.33 (2H, m, $\text{H}_{5′\text{a}}$, $\text{H}_{5′\text{b}}$), 3.03–2.90 (1H, m, $\text{H}_{4′}$), 2.14 (3H, s, Ac–CH_3), 2.09 (3H, s, Ac–CH_3), 2.05 (3H, s, Ac–CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 170.3 (C═O), 169.7 (C═O), 169.7 (C═O), 162.7 (C_2, C═O), 151.1 (C_4, C═O), 141.0 (d, $^{4}J_{\text{C6–F}}$ = 4.8 Hz, C_6), 122.5 (dd, $^{1}J_{\text{C6′–F}}$ = 262.9 Hz, $^{1}J_{\text{C6′–F}}$ = 253.7 Hz, $C_{6′}$), 103.3 (C_5), 68.8 (d, $^{3}J_{\text{C3′–F}}$ = 5.5 Hz, $C_{3′}$), 68.6 (d, $^{3}J_{\text{C2′–F}}$ = 8.1 Hz, $^{3}J_{\text{C2′–F}}$), 60.4 (dd, $^{2}J_{\text{C1′–F}}$ = 25.9 Hz, $^{2}J_{\text{C1′–F}}$ = 18.6 Hz, $C_{1′}$), 58.6 (d, $^{3}J_{\text{C5′–F}}$ = 9.0 Hz, $C_{5′}$), 48.3 (dd, $^{2}J_{\text{C4′–F}}$ = 23.0 Hz, $^{2}J_{\text{C4′–F}}$ 20.7 Hz, $C_{4′}$), 20.7 (Ac–*C*H_3), 20.6 (Ac–*C*H_3), 20.4 (Ac–*C*H_3); ^{19}F NMR (377 MHz, $CDCl_3$): *δ* −100.8 (d, $^{2}J_{\text{F–F}}$ = 240.8 Hz), −115.5 (app. dt, $^{2}J_{\text{F–F}}$ = 240.5 Hz, $^{3}J_{\text{F–H1′/H4′}}$ = 17.5 Hz); HRMS (NSI) calculated for $C_{16}H_{19}F_2N_2O_8$ $[M + H]^+$ 405.1104, found 405.1104.

General procedure for the synthesis of 26 & 27

Installation of 1,2,4-triazole. Triacetate **24** or **25** (1.0 equiv.) was dissolved in MeCN (0.1 M) and cooled to 0 °C. 1,2,4-Triazole (23 equiv.), $POCl_3$ (2.4 equiv.) and Et_3N (23 equiv.) were added and the reaction mixture was allowed to slowly warm to rt and stirred for 18 h. TLC analysis (EtOAc/hexane, 4 : 1) showed majority conversion of the starting material to a lower R_f. The reaction mixture was cooled to 0 °C and quenched with sat. $NaHCO_3$ (5 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL), and the combined organic phases were washed with H_2O (10 mL), brine (10 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*.

Amination and deprotection. 1,2,4-Triazole derivative was dissolved in 35% NH_4OH/1,4-dioxane (1 : 1, v/v, 0.1 M) and the reaction vessel was sealed. The reaction mixture was stirred at rt for 18 h, at which point TLC analysis (5% MeOH/DCM) showed complete conversion from a higher R_f to a lower R_f. The solvent was removed *in vacuo*, and the residue was purified *via* flash column chromatography on silica gel (10% MeOH/EtOAc).

HPLC purification. A sample of **26** or **27** was dissolved in H_2O (100 mg mL^{-1}), and injected onto a reverse phase column (see general experimental) and purified at a flow rate of 20.00 ml min^{-1} using the following gradient system:

Time (min)	%*A* (H_2O)	%*B* (MeOH)
0.0	96	4
10.0	96	4
12.0	0	100
16.0	0	100
16.5	96	4
20.0	96	4

(6′*R*)-6′-Fluorocarbacytidine 26. Cytidine derivative **26** (23.7 mg, 90 μmol, 50%) a white solid after freeze drying, was obtained following the above procedure from **24** (68 mg, 0.18 mmol, 1.0 equiv.). R_f = 0.06 (10% MeOH/DCM); ^{1}H NMR (400 MHz, D_2O): *δ* 7.65 (1H, dd, $^{3}J_{\text{H6–H5}}$ = 7.6 Hz, $^{5}J_{\text{H6–F}}$ = 1.6 Hz, H_6), 5.97 (1H, d, $^{3}J_{\text{H5–H6}}$ = 7.5 Hz, H_5), 5.10 (1H, ddd, $^{2}J_{\text{H6′–F}}$ = 54.9 Hz, $^{3}J_{\text{H6′–H4′}}$ = 4.6 Hz, $^{3}J_{\text{H6′–H1′}}$ = 3.6 Hz, $\text{H}_{6′}$), 4.89 (1H, ddd, $^{3}J_{\text{H1′–F}}$ = 30.7 Hz, $^{3}J_{\text{H1′–H2′}}$ = 10.6 Hz, $^{3}J_{\text{H1′–H6′}}$ = 3.3 Hz, $\text{H}_{\text{H1′}}$), 4.52 (1H, dd, $^{3}J_{\text{H2′–H1′}}$ = 10.6 Hz, $^{3}J_{\text{H2′–H3′}}$ = 6.6 Hz, $\text{H}_{2′}$), 3.99 (1H, dd, $^{3}J_{\text{H3′–H2′}}$ = 6.5 Hz, $^{3}J_{\text{H3′–H4′}}$ = 4.5 Hz, $\text{H}_{3′}$), 3.77–3.73 (1H, m, $\text{H}_{5′\text{a}}$, $\text{H}_{5′\text{b}}$), 2.38 (1H, dddd, $^{3}J_{\text{H4′–F}}$ = 31.2 Hz, $^{3}J_{\text{H4′–H5′a}}$ = 12.0 Hz, $^{3}J_{\text{H4′–H5′b}}$ = 7.5 Hz, $^{3}J_{\text{H4′–H3′/H6′}}$ = 4.6 Hz, $\text{H}_{4′}$); ^{13}C NMR (101 MHz, D_2O): *δ* 166.0 (C_2, C═O), 158.7 (C_4), 143.8 (d, $^{4}J_{\text{C6–F}}$ = 4.2 Hz, C_6), 95.7 (C_5), 91.0 (d, $^{1}J_{\text{C6′–F}}$ = 180.6 Hz, $C_{6′}$), 70.3 (C_2), 69.3 (C_3), 62.3 (d, $^{2}J_{\text{C1′–F}}$ = 16.5 Hz, $C_{1′}$), 58.3 (d, $^{3}J_{\text{C5′–F}}$ = 11.3 Hz, $C_{5′}$), 50.6 (d, $^{2}J_{\text{C4′–F}}$ = 18.1 Hz, $C_{4′}$); ^{19}F NMR (377 MHz, D_2O): *δ* −208.2 (dt, $^{2}J_{\text{F–H6′}}$ = 55.0 Hz, $^{3}J_{\text{F–H1′/H4′}}$ = 31.0 Hz); HRMS (NSI): calculated for $C_{10}H_{13}FN_3O_4$ $[M - H]^-$ 258.0896, found 258.0895. These data are in good agreement with literature.[17]

6′-*gem*-Difluorocarbacytidine 27. Cytidine derivative **27** (19.3 mg, 70 μmol, 58%) a white solid after freeze drying, was obtained following the above procedure from **25** (48.3 mg, 0.12 mmol, 1.0 equiv.). R_f = 0.07 (10% MeOH/DCM); ^{1}H NMR (400 MHz, D_2O): *δ* 7.59 (1H, dd, $^{3}J_{\text{H6–H5}}$ = 7.6 Hz, $^{5}J_{\text{H6–F}}$ = 2.5 Hz, H_6), 6.00 (1H, d, $^{3}J_{\text{H5–H6}}$ = 7.5 Hz, H_5), 5.44–5.24 (1H, m, $\text{H}_{1′}$), 4.43 (1H, dd, $^{3}J_{\text{H2′–H1′}}$ = 10.7 Hz, $^{3}J_{\text{H2′–H3′}}$ = 5.6 Hz, $\text{H}_{2′}$), 4.11–4.00 (1H, m, $\text{H}_{3′}$), 3.90–3.70 (2H, m, $\text{H}_{5′\text{a}}$, $\text{H}_{5′\text{b}}$), 2.61 (1H, m, $\text{H}_{4′}$); ^{13}C NMR (101 MHz, D_2O): *δ* 166.0 (C_2, C═O), 158.7 (C_4), 143.5 (d, $^{4}J_{\text{C6–F}}$ = 4.0 Hz, C_6), 124.2 (dd, $^{1}J_{\text{C6′–F}}$ = 259.8 Hz, $^{1}J_{\text{C6′–F}}$ 253.5 Hz, $C_{6′}$), 96.4 (C_5), 69.9 (d, $^{3}J_{\text{C2′–F}}$ = 8.0 Hz, $C_{2′}$), 68.9 (dd, $^{3}J_{\text{C3′–F}}$ = 6.2 Hz, $^{3}J_{\text{C3′–F}}$ = 2.1 Hz, $C_{3′}$), 62.7 (dd, $^{2}J_{\text{C1′–F}}$ = 23.8 Hz, $^{2}J_{\text{C1′–F}}$ = 18.7 Hz, $C_{1′}$), 57.3 (d, $^{4}J_{\text{C5′–F}}$ = 10.2 Hz, $C_{5′}$), 52.9 (t, $^{3}J_{\text{C4′–F}}$ = 20.3 Hz, $C_{4′}$); ^{19}F NMR (377 MHz, D_2O): *δ* −97.9 (ddd, $^{2}J_{\text{F–F}}$ = 236.5 Hz, $^{3}J_{\text{F–H4′}}$ = 14.0 Hz, $^{3}J_{\text{F–H1′}}$ = 8.7 Hz), −117.2 (app. dt, $^{2}J_{\text{F–F}}$ = 236.7 Hz, $^{3}J_{\text{F–H1′/H4′}}$ = 16.9 Hz); HRMS (NSI): calculated for $C_{10}H_{12}F_2N_3O_4$ $[M - H]^-$ 276.0801, found 276.0797. These data were in good agreement with literature.[17]

General procedure for the synthesis of 28 & 29. Uridine derivative **22** or **23** (1.0 equiv.) was dissolved in pyridine (0.2 M), cooled to 0 °C and $TIPDSiCl_2$ (1.1 equiv.) was added. The reaction was allowed to warm to rt, and stirred for a further 2 h, at which point TLC analysis (10% MeOH/DCM) showed complete conversion of the starting material to a higher R_f. The reaction was quenched with MeOH (5 mL) and the solvent was removed *in vacuo*. The crude material was purified *via* flash column chromatography on silica gel (20–100% EtOAc/Hexane).

(6′*R*)-3′,5′-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-6′-fluorocarbauridine. Uridine derivative **28** (1.0 g, 2.1 mmol, 76%) a white foam, was obtained following the above procedure from **22** (720 mg, 2.8 mmol, 1.0 equiv.). R_f = 0.38 (hexane/EtOAc, 1 : 1); $[\alpha]_D^{23.4}$ = −73.4 (*c* 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 9.32 (1H, br s, NH), 7.41 (1H, d, $^3J_{H6-H5}$ = 7.6 Hz, H_6), 5.75 (1H, d, $^3J_{H5-H6}$ = 8.1 Hz, H_5), 5.09 (1H, ddd, $^2J_{H6'-F}$ = 55.2 Hz, $^3J_{H6'-H4'}$ = 4.1 Hz, $^3J_{H6'-H1'}$ = 3.1 Hz, $H_{6'}$), 4.74 (1H, ddd, $^3J_{H1'-F}$ = 30.4 Hz, $^3J_{H1'-H2'}$ = 9.2 Hz, $^3J_{H1'-H6'}$ = 2.7 Hz, $H_{1'}$), 4.55–4.45 (2H, m, $H_{2'}$, $H_{3'}$), 4.14 (1H, dd, $^2J_{H5'a-H5'b}$ = 12.2 Hz, $^3J_{H5'a-H4'}$ = 4.0 Hz, $H_{5'a}$), 3.93 (1H, dd, $^2J_{H5'b-H5'a}$ = 12.0 Hz, $^3J_{H5'b-H4'}$ = 10.4 Hz, $H_{5'b}$), 3.03 (1H, d, $^3J_{OH-H1'}$ = 8.6 Hz, OH), 2.46 (1H, m, $H_{4'}$), 1.11–1.01 (28H, m, $[-\mathrm{OSi}(\mathrm{C}\mathit{H})_2(\mathrm{C}\mathit{H}_3)_4]_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.1 (C_2, C═O), 151.8 (C_4, C═O), 141.7 (d, $^4J_{C6-F}$ = 4.1 Hz, C_6), 102.4 (C_5), 92.2 (d, $^1J_{C6'-F}$ = 180.6 Hz, $C_{6'}$), 71.3 (d, $^3J_{C3'-F}$ = 0.6 Hz, $C_{3'}$), 70.4 (d, $^3J_{C2'-F}$ = 1.7 Hz, $C_{2'}$), 63.0 (d, $^2J_{C1'-F}$ = 16.4 Hz, $C_{1'}$), 61.9 (d, $^3J_{C5'-F}$ = 11.8 Hz, $C_{5'}$), 53.3 (d, $^2J_{C4'-F}$ = 17.6 Hz, $C_{4'}$), 17.7 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 17.5 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 17.4 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 17.24 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 17.22 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 17.19 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 17.15 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 17.11 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 17.05 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 13.50 $\{[-\mathrm{OSi}(\mathit{C}\mathrm{H})_2(\mathrm{CH}_3)_4]_2\}$, 13.47 $\{[-\mathrm{OSi}(\mathit{C}\mathrm{H})_2(\mathrm{CH}_3)_4]_2\}$, 13.19 $\{[-\mathrm{OSi}(\mathit{C}\mathrm{H})_2(\mathrm{CH}_3)_4]_2\}$, 13.18 $\{[-\mathrm{OSi}(\mathit{C}\mathrm{H})_2(\mathrm{CH}_3)_4]_2\}$, 12.6 $\{[-\mathrm{OSi}(\mathit{C}\mathrm{H})_2(\mathrm{CH}_3)_4]_2\}$; ^{19}F NMR (377 MHz, $CDCl_3$) δ −207.0 (ddd, $^2J_{F-H6'}$ = 55.3 Hz, $^3J_{F-H4'}$ = 35.2 Hz, $^3J_{F-H1'}$ = 30.6 Hz); HRMS (NSI): calculated for $C_{22}H_{40}FN_2O_6Si_2$ $[M + H]^+$ 503.2403, found 503.2402.

3′,5′-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-6′-*gem*-difluorocarbauridine 29. Uridine derivative **29** (310 mg, 0.60 mmol, 43%) a cream foam, was obtained following the above procedure from **23** (400 mg, 1.4 mmol, 1.0 equiv.). R_f = 0.46 (hexane/EtOAc, 1 : 1); $[\alpha]_D^{20.3}$ = −65.9 (*c* 0.5, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 9.22 (1H, s, NH), 7.17 (1H, dd, $^3J_{H6-H5}$ = 8.2 Hz, $^5J_{H6-F}$ = 1.5 Hz, H_6), 5.76 (1H, d, $^3J_{H5-H6}$ = 8.1 Hz, H_5), 5.08 (1H, dt, $^3J_{H1'-F}$ = 19.4 Hz, $^3J_{H1'-H2'}$ = 7.2 Hz, $H_{1'}$), 4.57 (1H, app. t, $^3J_{H3'-H2'/H4'}$ = 6.5 Hz, $H_{3'}$), 4.37 (1H, app. q, $^3J_{H2'-H1'/H3'/OH}$ = 6.0 Hz, $H_{2'}$), 4.15 (1H, dd, $^2J_{H5'a-H5'b}$ = 12.3 Hz, $^3J_{H5'a-H4'}$ = 4.2 Hz, $H_{5'a}$), 4.02 (1H, dd, $^2J_{H5'b-H5'a}$ = 12.3 Hz, $^3J_{H5'b-H4'}$ = 7.5 Hz, $H_{5'b}$), 3.20 (1H, d, $^3J_{OH-H2'}$ = 6.0 Hz, OH), 2.72–2.58 (1H, m, $H_{4'}$), 1.10–1.04 (28H, m, $[-\mathrm{OSi}(\mathrm{C}\mathit{H})_2(\mathrm{C}\mathit{H}_3)_4]_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.8 (C_2, C═O), 151.0 (C_4, C═O), 141.9 (d, $^4J_{C6-F}$ = 4.3 Hz, C_6), 123.5 (dd, $^1J_{C6'-F}$ = 262.3 Hz, $^1J_{C6'-F}$ = 251.3 Hz, $C_{6'}$), 103.0 (C_5), 70.1 (d, $^3J_{C3'-F}$ = 6.8 Hz, $C_{3'}$), 69.6 (d, $^3J_{C2'-F}$ = 8.7 Hz, C_2), 64.4 (dd, $^2J_{C1'-F}$ = 22.3 Hz, $^2J_{C1'-F}$ = 17.7 Hz, $C_{1'}$), 58.1 (d, $^3J_{C5'-F}$ = 8.1 Hz, $C_{5'}$), 52.9 (t, $^2J_{C4'-F}$ = 19.5 Hz, $C_{4'}$), 17.4 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 17.3 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 17.2 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 17.1 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 17.00 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 16.99 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 16.9 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 13.3 $\{[-\mathrm{OSi}(\mathit{C}\mathrm{H})_2(\mathrm{CH}_3)_4]_2\}$, 13.2 $\{[-\mathrm{OSi}(\mathit{C}\mathrm{H})_2(\mathrm{CH}_3)_4]_2\}$, 12.9 $\{[-\mathrm{OSi}(\mathit{C}\mathrm{H})_2(\mathrm{CH}_3)_4]_2\}$, 12.5 $\{[-\mathrm{OSi}(\mathit{C}\mathrm{H})_2(\mathrm{CH}_3)_4]_2\}$; ^{19}F NMR (377 MHz, $CDCl_3$): δ −106.5 (d, $^2J_{F-F}$ = 237.5 Hz), −118.7 (dt, $^2J_{F-F}$ = 237.2 Hz, $^3J_{F-H1'/H4'}$ = 21.5 Hz); HRMS (NSI): calculated for $C_{22}H_{38}F_2N_2O_6Si_2Na$ $[M + Na]^+$ 543.2129, found 543.2121.

General procedure for the synthesis of 30 & 31

Synthesis of thiocarbamate. Uridine derivative **28** or **29** (1.0 equiv.) was dissolved in MeCN (0.2 M). TCDI (1.1 equiv.) was added followed by DMAP (0.1 equiv.) and the reaction mixture was heated to 45 °C and stirred for 4 h. TLC analysis (hexane/EtOAc, 1 : 1) showed complete consumption of the starting material to a lower R_f. The reaction mixture was cooled to rt, and the solvent was removed *in vacuo*. The residue was partitioned between H_2O (10 mL) and EtOAc (10 mL), and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. This material was used without further purification.

Barton McCombie deoxygenation. Thiocarbamate intermediate was charged to an oven dried multinecked RB flask equipped with a magnetic stirrer, and the reaction vessel was evacuated and refilled with N_2 × 3. The crude material was dissolved in degassed toluene (0.2 M), and Bu_3SnH (1.5 equiv.) and AIBN (0.16 equiv.) were added. The reaction mixture was stirred at reflux for 30 min, at which point TLC analysis (1 : 1, hexane/EtOAc) showed complete conversion from a lower R_f to a higher R_f. The reaction mixture was cooled to rt, and the solvent removed *in vacuo*. The residue was purified *via* flash column chromatography on silica gel (20–50% EtOAc/hexane).

(6′*R*)-2′-Deoxy-3′,5′-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-6′-fluorocarbauridine 30. 2′-Deoxyuridine derivative **30** (80 mg, 0.16 mmol, 75%) a colourless syrup, was obtained following the above procedure from **28** (100 mg, 0.21 mmol, 1.0 equiv.). R_f = 0.57 (hexane/EtOAc, 1 : 1); $[\alpha]_D^{24.3}$ = −52.3 (*c* 0.5, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 9.70 (1H, br s, NH), 7.23 (1H, dd, $^3J_{H6-H5}$ = 8.1 Hz, $^5J_{H6-F}$ = 0.9 Hz, H_6), 5.66 (1H, d, $^3J_{H5-F}$ = 8.1 Hz, H_5), 5.22 (1H, dddd, $^3J_{H1'-F}$ = 30.6 Hz, $^3J_{H1'-H2'a}$ = 11.3 Hz, $^3J_{H1'-H2'b}$ = 9.2 Hz, $^3J_{H1'-H6'}$ = 2.4 Hz, $H_{1'}$), 5.01 (1H, dt, $^2J_{H6'-F}$ = 56.0 Hz, $^3J_{H6'-H1'/H4'}$ = 3.0 Hz, $H_{6'}$), 4.60 (1H, ddd, $^3J_{H3'-H2'a}$ = 7.7 Hz, $^3J_{H3'-H4'}$ = 5.2 Hz, $^3J_{H3'-H2'b}$ = 2.3 Hz, $H_{3'}$), 4.08 (1H, dd, $^2J_{H5'a-H5'b}$ = 12.0 Hz, $^3J_{H5'a-H4'}$ = 3.7 Hz, $H_{5'a}$), 3.88 (1H, dd, $^2J_{H5'b-5'a}$ = 11.9 Hz, $^3J_{H5'b-H4'}$ = 9.4 Hz, $H_{5'b}$), 2.38 (1H, dt, $^2J_{H2'a-H2'b}$ = 12.8 Hz, $^3J_{H2'a-H1'}$ = 12.8 Hz, $^3J_{H2'a-H3'}$ = 8.3 Hz, $H_{2'a}$), 2.36–2.20 (1H, m, $H_{4'}$), 2.11 (1H, ddd, $^3J_{H2'b}$ = 11.8 Hz, $^3J_{H2'b-H1'}$ = 8.7 Hz, $^3J_{H2'b-H3'}$ = 2.0 Hz, $H_{2'b}$), 1.05–0.93 (28H, m, $[-\mathrm{OSi}(\mathrm{C}\mathit{H})_2(\mathrm{C}\mathit{H}_3)_4]_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.3 (C_2, C═O), 150.4 (C_4, C═O), 140.7 (d, $^4J_{C6-F}$ = 5.5 Hz, C_6), 101.0 (C_5), 95.3 (d, $^1J_{C6'-F}$ = 181.5 Hz, $C_{6'}$), 71.4 ($C_{3'}$), 60.8 (d, $^3J_{C5'-F}$ = 10.8 Hz, $C_{5'}$), 54.3 (d, $^2J_{C1'/C4'-F}$ = 17.1 Hz, $C_{1'}$, $C_{4'}$), 35.0 ($C_{2'}$), 16.6 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 16.4 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 16.4 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 16.4 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 16.4 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 16.2 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 15.98 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 15.95 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 12.33 $\{[-\mathrm{OSi}(\mathit{C}\mathrm{H})_2(\mathrm{CH}_3)_4]_2\}$, 12.30 $\{[-\mathrm{OSi}(\mathit{C}\mathrm{H})_2(\mathrm{CH}_3)_4]_2\}$, 11.9 $\{[-\mathrm{OSi}(\mathit{C}\mathrm{H})_2(\mathrm{CH}_3)_4]_2\}$, 11.5 $\{[-\mathrm{OSi}(\mathit{C}\mathrm{H})_2(\mathrm{CH}_3)_4]_2\}$; ^{19}F NMR (377 MHz, $CDCl_3$) δ −209.2 (ddd, $^2J_{F-H6'}$ = 55.9 Hz, $^3J_{F-H4'}$ = 36.6 Hz, $^3J_{F-H1'}$ = 30.7 Hz).

2′-Deoxy-3′,5′-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-6′-*gem*-difluorocarbauridine 31. 2′-Deoxyuridine derivative **31** (170 mg, 0.34 mmol, 68%) a colourless syrup, was obtained following the above procedure from **29** (250 mg, 0.50 mmol, 1.0 equiv.). R_f = 0.54 (hexane/EtOAc, 1 : 1); $[\alpha]_\mathrm{D}^{25.9}$ = −46.5 (*c* 2.0, CH_2Cl_2); ^{1}H NMR (400 MHz, CDCl3): *δ* 8.29 (1H, br s, NH), 7.17 (1H, dd, $^{3}J_{\mathrm{H6-H5}}$ = 8.2 Hz, $^{5}J_{\mathrm{H6-F}}$ = 2.5 Hz, H_6), 5.76 (1H, dd, $^{3}J_{\mathrm{H5-H6}}$ = 8.2 Hz, $^{6}J_{\mathrm{H5-F}}$ = 1.9 Hz, H_5), 5.58 (1H, dtd, $^{3}J_{\mathrm{H1'-F}}$ = 16.7 Hz, $^{3}J_{\mathrm{H1'-H2'a}}$ = 9.9 Hz, $^{3}J_{\mathrm{H1'-H2'b}}$ = 6.5 Hz, $\mathrm{H}_{1'}$), 4.58 (1H, dd, $^{3}J_{\mathrm{H3'-H4}}$ = 13.4 Hz, $^{3}J_{\mathrm{H3'-H2'a/H2'b}}$ = 6.3 Hz, $\mathrm{H}_{3'}$), 4.17–3.98 (2H, m, $\mathrm{H}_{5'a}$, $\mathrm{H}_{5'b}$), 2.51–2.39 (1H, m, $\mathrm{H}_{4'}$), 2.38–2.24 (2H, m, $\mathrm{H}_{2'a}$, $\mathrm{H}_{2'b}$), 1.11–1.02 (28 H, m, $[-\mathrm{OSi}(\mathrm{C}H)_2(\mathrm{C}H_3)_4]_2$); ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 162.0 (C_2, C═O), 150.7 (C_4, C═O), 141.1 (d, $^{4}J_{\mathrm{C6-F}}$ = 5.9 Hz, C_6), 102.8 (C_5), 68.8 ($\mathrm{C}_{3'}$), 58.1 (d, $^{3}J_{\mathrm{C5'-F}}$ = 6.8 Hz, $\mathrm{C}_{5'}$), 55.0 ($\mathrm{C}_{1'}$), 54.7 ($\mathrm{C}_{4'}$), 34.7 (d, $^{3}J_{\mathrm{C2'-F}}$ = 5.2 Hz, $\mathrm{C}_{2'}$), 17.44 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 17.36 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 17.32 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 17.29 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 17.1 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 17.0 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 16.9 $\{[-\mathrm{OSi}(\mathrm{CH})_2(\mathit{C}\mathrm{H}_3)_4]_2\}$, 13.3 $\{[-\mathrm{OSi}(\mathit{C}\mathrm{H})_2(\mathrm{CH}_3)_4]_2\}$, 13.1 $\{[-\mathrm{OSi}(\mathit{C}\mathrm{H})_2(\mathrm{CH}_3)_4]_2\}$, 12.8 $\{[-\mathrm{OSi}(\mathit{C}\mathrm{H})_2(\mathrm{CH}_3)_4]_2\}$, 12.5 $\{[-\mathrm{OSi}(\mathit{C}\mathrm{H})_2(\mathrm{CH}_3)_4]_2\}$; ^{19}F NMR (377 MHz, CDCl3): *δ* −108.8 (dt, $^{2}J_{\mathrm{F-F}}$ = 232.4 Hz, $^{3}J_{\mathrm{F-H4'}}$ = 7.3 Hz), −121.6 (ddd, $^{2}J_{\mathrm{F-F}}$ = 232.2 Hz, $^{3}J_{\mathrm{F-H4'}}$ = 26.0 Hz, $^{3}J_{\mathrm{F-H1'}}$ = 20.3 Hz); HRMS (NSI): calculated for $C_{22}H_{39}F_2N_2O_5Si_2$ $[\mathrm{M + H}]^+$ 505.2360, found 505.2360.

General procedure for the synthesis of 32 & 33. 2′-Deoxyuridine derivative **30** or **31** (1.0 equiv.) was dissolved in THF (0.2 M) and TBAF (2.0 equiv., 1.0 M in THF) was added. The reaction was stirred at rt for 16 h, at which point TLC analysis (10% MeOH/DCM) showed complete consumption of the starting material to a lower R_f. DOWEX 50WX8 (H^+) resin (500 mg), $CaCO_3$ (180 mg) and MeOH (1.0 mL) were added, and the reaction mixture was stirred for a further 1 h. The reaction mixture was filtered through a Celite® plug and eluted with MeOH. The material was purified *via* flash column chromatography on silica gel (0–10% MeOH/EtOAc).

HPLC purification. A sample of **32** or **33** was dissolved in 9 : 1 H_2O/MeOH (v/v, 100 mg mL^{-1}), and injected onto a reverse phase column (see general experimental) and purified at a flow rate of 20.00 ml min^{-1} using the following gradient system:

Time (min)	%*A* (H_2O)	%*B* (MeOH)
0.0	90	10
5.0	90	10
12.0	0	100
15.0	0	100
15.1	90	10
20.0	90	10

(6′*R*)-2′-Deoxy-6′-fluorocarbauridine 32. 2′-Deoxyuridine analogue **32** (17 mg, 73 μmol, 66%) a white solid after freeze drying, was obtained following the above procedure from **30** (54 mg, 0.11 mmol, 1.0 equiv.). R_f = 0.27 (10% MeOH/DCM); $[\alpha]_\mathrm{D}^{23.6}$ = −68.9 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, D_2O): *δ* 7.64 (1H, dd, $^{3}J_{\mathrm{H6-H5}}$ = 8.1 Hz, $^{5}J_{\mathrm{H6-F}}$ = 1.4 Hz, H_6), 5.74 (1H, d, $^{3}J_{\mathrm{H5-H6}}$ = 8.0 Hz, H_5), 5.27–4.98 (2H, m, $\mathrm{H}_{1'}$, $\mathrm{H}_{6'}$), 4.28–4.16 (1H, m, $\mathrm{H}_{3'}$), 3.78–3.70 (2H, m, $\mathrm{H}_{5a'}$, $\mathrm{H}_{5'b}$), 2.47 (1H, ddd, $^{2}J_{\mathrm{H2'a-H2'b}}$ = 14.2 Hz, $^{3}J_{\mathrm{H2'a-H1'}}$ = 10.8 Hz, $^{3}J_{\mathrm{H2'a-H3'}}$ = 8.3 Hz, $\mathrm{H}_{2'a}$), 2.41–2.11 (1H, m, $\mathrm{H}_{4'}$), 2.11–1.96 (1H, m, $\mathrm{H}_{2'b}$); ^{13}C NMR (101 MHz, D_2O): *δ* 166.3 (C_2, C═O), 152.5 (C_4, C═O), 144.6 (d, $^{4}J_{\mathrm{C6-F}}$ = 5.3 Hz, C_6), 101.1 (C_5), 94.4 (d, $^{1}J_{\mathrm{C6'-F}}$ = 181.3 Hz, $\mathrm{C}_{6'}$), 70.2 ($\mathrm{C}_{3'}$), 58.1 (d, $^{3}J_{\mathrm{C5'-F}}$ = 9.7 Hz, $\mathrm{C}_{5'}$), 55.7 (d, $^{2}J_{\mathrm{C1'-F}}$ = 16.4 Hz, $\mathrm{C}_{1'}$), 53.2 (d, $^{2}J_{\mathrm{C4'-F}}$ = 17.7 Hz, $\mathrm{C}_{4'}$), 34.4 ($\mathrm{C}_{2'}$); ^{19}F NMR (377 MHz, D_2O) *δ* −209.7 (app. dt, $^{2}J_{\mathrm{F-H6'}}$ = 54.5 Hz, $^{3}J_{\mathrm{F-H1'/H4'}}$ = 32.2 Hz); HRMS (NSI): calculated for $C_{10}H_{12}FN_2O_4$ $[\mathrm{M - H}]^-$ 243.0787, found 243.0783.

2′-Deoxy-6′-*gem*-difluorocarbauridine 33. 2′-Deoxyuridine analogue **33** (0.12 mmol, 55%) as a white solid, was obtained following the above procedure from **31** (112 mg, 0.22 mmol, 1.0 equiv.). R_f = 0.30 (10% MeOH/DCM); $[\alpha]_\mathrm{D}^{25.4}$ = −82.1 (*c* 0.4, MeOH); ^{1}H NMR (400 MHz, D_2O) *δ* 7.57 (1H, dd, $^{3}J_{\mathrm{H6-H5}}$ = 8.1 Hz, $^{5}J_{\mathrm{H6-F}}$ = 2.5 Hz, H_6), 5.78 (1H, d, $^{3}J_{\mathrm{H5-H6}}$ = 8.0 Hz, H_5), 5.48 (1H, td, $^{3}J_{\mathrm{H1'-F}}$ = 18.5 Hz, $^{3}J_{\mathrm{H1'-H2'a/2'b}}$ = 10.0 Hz, $\mathrm{H}_{1'}$), 4.21–4.14 (1H, m, $\mathrm{H}_{3'}$), 3.88–3.74 (2H, m, $\mathrm{H}_{5'a/5'b}$), 2.51 (1H, tdd, $^{3}J_{\mathrm{H4'-F}}$ = 10.3 Hz, 9.8, $^{3}J_{\mathrm{H4'-H3'}}$ = 5.7 Hz, $\mathrm{H}_{4'}$), 2.41 (1H, ddd, $^{2}J_{\mathrm{H2'a-H2'b}}$ = 14.4 Hz, $^{3}J_{\mathrm{H2'a-H1'}}$ = 10.5 Hz, $^{3}J_{\mathrm{H2'a-H3'}}$ = 7.5 Hz, $\mathrm{H}_{2'a}$), 2.15 (1H, ddd, $^{2}J_{\mathrm{H2'b-H2'a}}$ = 14.0 Hz, $^{3}J_{\mathrm{H2'b-H1'}}$ = 9.8 Hz, $^{3}J_{\mathrm{H2'b-H3'}}$ = 3.9 Hz, $\mathrm{H}_{2'b}$); ^{13}C NMR (101 MHz, D_2O): *δ* 167.0 (C2, C═O), 153.2 (C_4, C═O), 143.9 (d, $^{4}J_{\mathrm{C6-F}}$ = 4.5 Hz, C_6), 127.1 (dd, $^{1}J_{\mathrm{C6'-F}}$ = 260.7 Hz, $^{1}J_{\mathrm{C6'-F}}$ = 254.0 Hz, $\mathrm{C}_{6'}$), 102.0 (C_5), 67.7 (d, $^{3}J_{\mathrm{C3'-F}}$ = 8.4 Hz, $\mathrm{C}_{3'}$), 57.1 (d, $^{3}J_{\mathrm{C5'-F}}$ = 8.8 Hz, $\mathrm{C}_{5'}$), 56.3 (dd, $^{2}J_{\mathrm{C1'-F}}$ = 25.2 Hz, $^{2}J_{\mathrm{C1'-F}}$ = 18.4 Hz, $\mathrm{C}_{1'}$), 53.6 (t, $^{2}J_{\mathrm{C4'-F}}$ = 19.5 Hz, $\mathrm{C}_{4'}$), 33.5 (d, $^{3}J_{\mathrm{C2'-F}}$ = 6.3 Hz, $\mathrm{C}_{2'}$); ^{19}F NMR (377 MHz, D_2O): *δ* −102.8 (app. dt, $^{2}J_{\mathrm{F-F}}$ = 232.4 Hz, $^{3}J_{\mathrm{F-H4'/H1'}}$ = 9.2 Hz), −120.5 (app. dt, $^{2}J_{\mathrm{F-F}}$ = 232.4 Hz, $^{3}J_{\mathrm{F-H1'/H4'}}$ = 19.6 Hz); HRMS (NSI): calculated for $C_{10}H_{11}F_2N_2O_4$ $[\mathrm{M\text{-}H}]^-$ 261.0692, found 261.0692

General procedure for the synthesis of 34 & 35

Installation of 1,2,4-triazole. Uridine **30** or **31** (1.0 equiv.) was dissolved in MeCN (0.1 M) and cooled to 0 °C. 1,2,4-Triazole (23 equiv.), $POCl_3$ (2.4 equiv.) and Et_3N (23 equiv.) were added and the reaction mixture was allowed to slowly warm to rt and stirred for 18 h. TLC analysis (4 : 1 EtOAc/hexane) showed majority conversion of the starting material to a lower R_f. The reaction mixture was cooled to 0 °C and quenched with sat. $NaHCO_3$ (5 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL), and the combined organic phases were washed with H_2O (10 mL), brine (10 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*.

Amination. 1,2,4-Triazole derivative was dissolved in 35% NH_4OH/1,4-dioxane (1 : 1, v/v, 0.1 M) and the reaction vessel was sealed. The reaction mixture was stirred at rt for 18 h, at which point TLC analysis (5% MeOH/DCM) showed complete conversion from a higher R_f to a lower R_f. The solvent was removed *in vacuo*, and the residue was passed through a silica plug (eluting first with 1 : 1 hexane/EtOAc, then 5% MeOH/EtOAc).

(6′*R*)-2′-Deoxy-3′,5′-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-6′-fluorocarbacytidine. 2′-Deoxycytidine derivative (24 mg, 50 μmol, 51%) a colourless syrup, was obtained following the above procedure from **30** (47 mg, 98 μmol, 1.0 equiv.). R_f = 0.49 (EtOAc/hexane, 4 : 1); $[\alpha]_\mathrm{D}^{24.5}$ = −55.8 (*c* 1.0, MeOH); ^{1}H NMR

(400 MHz, MeOD): δ 8.30 (2H, br s, NH_2), 7.62 (1H, dd, $^3J_{H6-H5}$ = 7.5 Hz, $^5J_{H6-F}$ = 1.3 Hz, H_6), 5.87 (1H, d, $^3J_{H5-H6}$ = 7.5 Hz, H_5), 5.27 (1H, dddd, $^3J_{H1'-F}$ = 30.5 Hz, $^3J_{H1'-H2'a}$ = 11.6 Hz, $^3J_{H1'-H2'b}$ = 8.2 Hz, $^3J_{H1'-H6'}$ = 2.5 Hz, $H_{1'}$), 5.21 (1H, dt, $^2J_{H6'-F}$ = 56.1 Hz, $^3J_{H6'-H1'/H4'}$ = 3.1 Hz, $H_{6'}$), 4.71 (1H, ddd, $^3J_{H3'-H2'a}$ = 7.3 Hz, $^3J_{H3'-H4'}$ = 4.9 Hz, $^3J_{H3'-H2'b}$ = 2.1 Hz, $H_{3'}$), 4.17 (1H, dd, $^2J_{H5'a-H5'b}$ = 11.9 Hz, $^3J_{H5'a-H4'}$ = 3.8 Hz, $H_{H5'a}$), 3.97 (1H, dd, $^2J_{H5'b-H5'a}$ = 11.8 Hz, $^3J_{H5'b-H4'}$ = 9.8 Hz, $H_{5'b}$), 2.64 (1H, td, $^2J_{H2'a-2'b}$ = 12.8 Hz, $^3J_{H2'a-H1'}$ = 12.8 Hz, $^3J_{H2'a-H3'}$ = 7.9 Hz, $H_{2'a}$), 2.40 (1H, dtd, $^3J_{H4'-F}$ = 35.8 Hz, $^3J_{H4'-H5'b}$ = 8.6 Hz, $^3J_{H4'-H3'/H5'a/H6'}$ = 4.0 Hz, $H_{4'}$), 2.10 (ddd, $^2J_{H2'b-H2'a}$ = 13.1 Hz, $^3J_{H2'b-H1'}$ = 8.3 Hz, $^3J_{H2'b-H3'}$ = 1.9 Hz, $H_{2'b}$), 1.14–1.02 (28H, m, $[-OSi(C\mathit{H})_2(C\mathit{H}_3)_4]_2$); ^{13}C NMR (101 MHz, MeOD): δ 167.3 (C_2, C=O), 159.0 (C_4), 144.6 (d, $^4J_{C6-F}$ = 4.3 Hz, C_6), 97.1 (d, $^1J_{C6'-F}$ = 180.7 Hz, $C_{6'}$), 95.5 (C_5), 74.1 ($C_{3'}$), 63.3 (d, $^3J_{C5'-F}$ = 11.5 Hz, $C_{5'}$), 58.0 (d, $^2J_{C1'-F}$ = 16.7 Hz, $C_{1'}$), 57.0 (d, $^2J_{C4'-F}$ = 17.1 Hz, $C_{4'}$), 36.8 ($C_{2'}$), 18.1 $\{[-OSi(CH)_2(\mathit{C}H_3)_4]_2\}$, 18.0 $\{[-OSi(CH)_2(\mathit{C}H_3)_4]_2\}$, 17.94 $\{[-OSi(CH)_2(\mathit{C}H_3)_4]_2\}$, 17.92 $\{[-OSi(CH)_2(\mathit{C}H_3)_4]_2\}$, 17.85 $\{[-OSi(CH)_2(\mathit{C}H_3)_4]_2\}$, 17.7 $\{[-OSi(CH)_2(\mathit{C}H_3)_4]_2\}$, 17.54 $\{[-OSi(CH)_2(\mathit{C}H_3)_4]_2\}$, 17.51 $\{[-OSi(CH)_2(\mathit{C}H_3)_4]_2\}$, 14.6 $\{[-OSi(\mathit{C}H)_2(CH_3)_4]_2\}$, 14.5 $\{[-OSi(\mathit{C}H)_2(CH_3)_4]_2\}$, 14.2 $\{[-OSi(\mathit{C}H)_2(CH_3)_4]_2\}$, 13.8 $\{[-OSi(\mathit{C}H)_2(CH_3)_4]_2\}$; ^{19}F NMR (377 MHz, $CDCl_3$): δ −207.68 (ddd, $^2J_{F-H6'}$ = 56.0 Hz, $^3J_{F-H4'}$ = 35.6 Hz, $^3J_{F-H1'}$ = 30.6 Hz); HRMS (NSI): calculated for $C_{22}H_{40}FN_3O_4Si_2$ $[M + H]^+$ 486.2614, found 486.2614.

2′-Deoxy-3′,5′-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-6′-*gem*-difluorocarbacytidine. 2′-Deoxycytidine derivative (38 mg, 76 μmol, 59%) a colourless syrup, was obtained following the above procedure from **31** (65 mg, 0.13 mol, 1.0 equiv.). R_f = 0.68 (5% MeOH/DCM); $[\alpha]_D^{24.6}$ = −36.7 (*c* 2.0, MeOH); ^1H NMR (400 MHz, MeOD): δ 8.31 (2H, br s, NH_2), 7.55 (1H, dd, $^3J_{H6-H5}$ = 7.5 Hz, $^5J_{H6-F}$ = 2.5 Hz, H_6), 5.93 (1H, d, $^3J_{H5-H6}$ = 7.5 Hz, H_5), 5.71 (1H, ddd, $^3J_{H1'-F}$ = 19.9 Hz, $^3J_{H1'-F}$ = 17.0 Hz, $^3J_{H1'-H2'a/H2'b}$ = 9.8 Hz, $H_{1'}$), 4.66 (1H, dd, $^3J_{H3'-H4'}$ = 12.9 Hz, $^3J_{H3'-H2'}$ 6.8 Hz, 1H), 4.17–4.02 (2H, m, $H_{5'a}$, $H_{5'b}$), 2.58–2.44 (2H, m, $H_{2'a}$, $H_{4'}$), 2.27 (1H, ddd, $^2J_{H2'b-H2'a}$ = 14.8 Hz, $^3J_{H2'b-H1'}$ = 10.5 Hz, $^3J_{H2'b-H3'}$ = 4.9 Hz, $H_{2'b}$), 1.14–1.06 (28H, m, $[-OSi(C\mathit{H})_2(C\mathit{H}_3)_4]_2$); ^{13}C NMR (101 MHz, MeOD) δ 167.1 (C_2, C=O), 158.6 (C_4), 144.6 (d, $^4J_{C6-F}$ = 5.0 Hz, C_6), 127.9 (dd, $^1J_{C6'-F}$ = 261.5 Hz, $^1J_{C6'-F}$ = 252.9 Hz, $C_{6'}$), 96.3 (C_5), 70.8 (d, $^3J_{C3'-F}$ = 9.2 Hz, $C_{3'}$), 59.6 (d, $^3J_{C5'-F}$ = 7.8 Hz, $C_{5'}$), 57.2 (dd, $^2J_{C1'-F}$ = 24.2 Hz, $^2J_{C1'-F}$ = 17.3 Hz, $C_{1'}$), 56.6 (t, $^2J_{C4'-F}$ = 19.0 Hz, $C_{4'}$), 35.7 (d, $^3J_{C2'-F}$ = 5.7 Hz, $C_{2'}$), 18.0 $\{[-OSi(CH)_2(\mathit{C}H_3)_4]_2\}$, 17.9 $\{[-OSi(CH)_2(\mathit{C}H_3)_4]_2\}$, 17.83 $\{[-OSi(CH)_2(\mathit{C}H_3)_4]_2\}$, 17.80 $\{[-OSi(CH)_2(\mathit{C}H_3)_4]_2\}$, 17.7 $\{[-OSi(CH)_2(\mathit{C}H_3)_4]_2\}$, 17.52 $\{[-OSi(CH)_2(\mathit{C}H_3)_4]_2\}$, 17.49 $\{[-OSi(CH)_2(\mathit{C}H_3)_4]_2\}$, 14.54 $\{[-OSi(\mathit{C}H)_2(CH_3)_4]_2\}$, 14.47 $\{[-OSi(\mathit{C}H)_2(CH_3)_4]_2\}$, 14.4 $\{[-OSi(\mathit{C}H)_2(CH_3)_4]_2\}$, 13.8 $\{[-OSi(\mathit{C}H)_2(CH_3)_4]_2\}$; ^{19}F NMR (377 MHz, MeOD) δ −109.35 (dt, $^2J_{F-F}$ = 231.6 Hz, $^3J_{F-H4'}$ = 6.8 Hz), −122.6 (dt, $^2J_{F-F}$ = 231.0 Hz, $^3J_{F-H1'/H4'}$ = 23.1 Hz); HRMS (NSI): calculated for $C_{22}H_{39}F_2N_3O_4Si_2$ $[M + H]^+$ 504.2520, found 504.2519.

Desilylation. 2′-Deoxycytidine derivative (1.0 equiv.) was dissolved in THF (0.2 M), and TBAF (2.0 equiv., 1.0 M in THF) was added. The reaction was stirred at rt for 16 h, at which point TLC analysis (10% MeOH/DCM) showed complete consumption of the starting material to a lower R_f. DOWEX 50WX8 (H^+) resin (400 mg), $CaCO_3$ (160 mg) and MeOH (1.0 mL) were added, and the reaction mixture was stirred for a further 1 h. The reaction mixture was filtered through a Celite® plug and eluted with MeOH. The solvent as removed *in vacuo*, and the residue was purified *via* flash column chromatography (0–10% MeOH/EtOAc).

HPLC purification. A sample of **34** or **35** was dissolved in H_2O (100 mg mL^{-1}), and injected onto a reverse phase column (see general experimental) and purified at a flow rate of 20.00 ml min^{-1} using the following gradient system:

Time (min)	%*A* (H_2O)	%*B* (MeOH)
0.0	96	4
12.0	96	4
15.0	0	100
18.0	0	100
18.5	96	4
22.0	96	4

(6′*R*)-2′-Deoxy-6′-fluorocarbacytidine 34. 2′-Deoxycyridine analogue **34** (4.3 mg, 18 μmmol, 22%) a white solid after freeze drying, was obtained following the above procedure (40 mg, 82 μmol, 1.0 equiv.). R_f = 0.05 (10% MeOH/DCM); ^1H NMR (400 MHz, MeOD): δ 7.64 (1H, dd, $^3J_{H6-H5}$ = 7.5 Hz, $^5J_{H6-F}$ = 1.6 Hz, H_6), 5.87 (1H, d, $^3J_{H5-H6}$ = 7.5 Hz, H_5), 5.30 (1H, dddd, $^3J_{H1'-F}$ = 30.7 Hz, $^3J_{H1'-H2'a}$ = 11.4 Hz, $^3J_{H1'-H2'b}$ = 8.6 Hz, $^3J_{H1'-H6'}$ = 2.8 Hz, $H_{1'}$), 5.15 (1H, app. dt, $^2J_{H6'-F}$ = 55.7 Hz, $^3J_{H6'-H1'/H4'}$ = 3.2 Hz, $H_{6'}$), 4.16 (1H, ddd, $^3J_{H3'-H2'a}$ = 8.5 Hz, $^3J_{H3'-H4'}$ = 6.2 Hz, $^3J_{H3'-H2'b}$ = 2.7 Hz, $H_{3'}$), 3.76 (2H, app. d, $^2J_{H5'a-H5'b}$ = 7.9 Hz, $^3J_{H5'a/H5'b-H4'}$ = 7.9 Hz, $H_{5'a}$, $H_{5'b}$), 2.49 (1H, ddd, $^2J_{H2'a-H2'b}$ = 13.3 Hz, $^3J_{H2'a-H1'}$ = 11.8 Hz, $^3J_{H2'a-H3'}$ = 8.1 Hz, $H_{2'a}$), 2.34–2.17 (1H, m, $H_{4'}$), 2.00 (1H, ddd, $^2J_{H2'b-H2'a}$ = 12.4 Hz, $^3J_{H2'b-H1'}$ = 8.8 Hz, $^3J_{H2'b-H3'}$ = 2.8 Hz, $H_{2'b}$); ^{19}F NMR (377 MHz, MeOD): δ −212.0 (app. dt, $^2J_{F-H6'}$ = 54.7 Hz, $^3J_{F-H1'/H4'}$ = 31.7 Hz); HRMS (NSI): calculated for $C_{10}H_{13}FN_3O_3$ $[M - H]^-$ 242.0946, found 242.0942.

2′-Deoxy-6′-*gem*-difluorocarbacytidine 35. 2′-Deoxycytidine analogue **35** (4.0 mg, 15 μmmol, 15%) a white solid after freeze drying, was obtained following the above procedure (50 mg, 0.1 mmol, 1.0 equiv.). R_f = 0.4 (10% MeOH/DCM); ^1H NMR (400 MHz, D_2O): δ 7.54 (1H, dd, $^3J_{H6-H5}$ = 7.6 Hz, $^5J_{H6-F}$ = 2.6 Hz, H_6), 5.96 (1H, d, $^3J_{H5-H6}$ = 7.6 Hz, H_5), 5.56 (1H, td, $^3J_{H1'-F}$ = 18.5 Hz, $^3J_{H1'-H2'a/H2'b/F}$ = 9.9 Hz, $H_{1'}$), 4.34–4.04 (1H, m, $H_{3'}$), 3.92–3.72 (2H, m, $H_{5'a}$, $H_{5'b}$), 2.58–2.44 (1H, m, $H_{4'}$), 2.39 (1H, ddd, $^2J_{H2'a-H2'b}$ = 14.3 Hz, $^3J_{H2'a-H1'}$ = 10.6 Hz, $^3J_{H2'a-H3'}$ = 7.5 Hz, $H_{2'a}$), 2.14 (1H, ddd, $^2J_{H2'b-H2'a}$ = 14.1 Hz, $^3J_{H2'b-H1'}$ = 9.9 Hz, $^3J_{H2'b-H3'}$ = 3.9 Hz, $H_{3'}$); ^{13}C NMR (101 MHz, D_2O): δ 165.9 (C_2, C=O), 158.5 (C_4), 143.8 (d, $^4J_{C6-F}$ = 4.6 Hz, C_6), 126.2 (m, $C_{6'}$), 96.0 (C_5), 67.8 (d, $^4J_{C3'-F}$ = 8.5 Hz, $C_{3'}$), 57.1 (d, $^4J_{C5'-F}$ = 8.5 Hz, $C_{5'}$), 56.8 (dd, $^3J_{C1'-F}$ = 25.3 Hz, $^3J_{C1'-F}$ = 18.3 Hz, $C_{1'}$), 53.8 (t, $^3J_{C4'-F}$ = 19.6 Hz, $C_{4'}$), 33.9 (d, $^4J_{C2'-F}$ = 6.5 Hz, $C_{2'}$); ^{19}F NMR (377 MHz, D_2O): δ −102.8 (app. dt, $^2J_{F-F}$ = 231.5 Hz, $^3J_{F-H1'/H4'}$ = 9.2 Hz), −120.7 (app. dt, $^2J_{F-F}$ = 231.5 Hz, $^3J_{F-H1'/H4'}$ = 19.6 Hz); HRMS (NSI): calculated for $C_{10}H_{12}F_2N_3O_3$ $[M - H]^-$ 260.0852, found 260.0848.

General procedure for the synthesis of 36 & 37. Uridine analogue **22** or **23** (1.0 equiv.) was suspended in acetone (0.2 M) and conc. H_2SO_4 (1 drop) was added. The reaction mixture was stirred at reflux for 2 h, at which point TLC analysis (10% MeOH/DCM) showed majority conversion of the starting material to a higher R_f. The reaction mixture was cooled to rt and the pH adjusted to 7 with solid Na_2CO_3. The mixture was filtered, and the solvent removed *in vacuo*. The crude material was purified *via* flash column chromatography on silica gel (0–10%, MeOH/EtOAc).

(6′*R*)-2′,3′-*O*-Isopropylidine-6′-fluorocarbauridine 36. Uridine derivative **36** (41 mg, 0.14 mmol, 81%) a colourless syrup, was obtained following the above procedure from **22** (43.3 mg, 0.17 mmol, 1.0 equiv.). R_f = 0.37 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.42 (1H, br s, NH), 7.40 (1H, d, $^{3}J_{\mathrm{H6-H5}}$ = 7.6 Hz, H_6), 5.76 (1H, d, $^{3}J_{\mathrm{H5-H6}}$ = 8.1 Hz, H_5), 5.27 (1H, dt, $^{2}J_{\mathrm{H6'-F}}$ = 54.3 Hz, $^{3}J_{\mathrm{H6'-H1'/H4'}}$ = 3.0 Hz, $H_{6'}$), 5.12 (1H, ddd, $^{3}J_{\mathrm{H1'-F}}$ = 33.9 Hz, $^{3}J_{\mathrm{H1'-H2'}}$ = 7.2 Hz, $^{3}J_{\mathrm{H1'-H6'}}$ = 2.5 Hz, $H_{1'}$), 4.92 (1H, app. t, $^{3}J_{\mathrm{H2'-H1'/H3'}}$ = 7.3 Hz, $H_{2'}$), 4.69–4.62 (1H, app. t, $^{3}J_{\mathrm{H3'-H2'/H4'}}$ = 6.2 Hz, $H_{3'}$), 3.97–3.86 (2H, m, $H_{5'a}$, $H_{5'b}$), 2.66–2.49 (1H, m, $H_{4'}$), 1.55 (3H, s, CH_3), 1.34 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.8 (C_2, C═O), 151.1 (C_4, C═O), 141.6 (C_6), 115.2 [$C(CH_3)_2$], 102.6 (C_5), 97.8 (d, $^{1}J_{\mathrm{C6'-F}}$ = 181.0 Hz, $C_{6'}$), 80.2 ($C_{2'}$), 79.7 ($C_{3'}$), 62.7 (d, $^{2}J_{\mathrm{C1'-F}}$ = 15.7 Hz, $C_{1'}$), 59.6 (d, $^{3}J_{\mathrm{C5'-F}}$ = 8.4 Hz, C_5), 50.6 (d, $^{2}J_{\mathrm{C4'-F}}$ = 17.5 Hz, $C_{4'}$), 27.3 [$C(CH_3)_2$], 24.9 [$C(CH_3)_2$]; ^{19}F NMR (377 MHz, $CDCl_3$): δ −205.2 (app. dt, $^{2}J_{\mathrm{F-H6'}}$ = 54.3 Hz, $^{3}J_{\mathrm{F-H1'/H4'}}$ = 34.8 Hz); HRMS (NSI) calculated for $C_{13}H_{17}FN_2O_5Na$ $[M + Na]^+$ 323.1014, found 232.1014. These data were in good agreement with literature.[17]

2′,3′-*O*-Isopropylidine-6′-*gem*-difluorocarbauridine 37. Uridine derivative **37** (34 mg, 0.11 mmol, 71%) a colourless syrup, was obtained following the above procedure from **23** (41.6 mg, 0.15 mmol, 1.0 equiv.). R_f = 0.38 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.45 (1H, br s, –NH), 7.29 (1H, dd, $^{3}J_{\mathrm{H6-H5}}$ = 8.1 Hz, $^{5}J_{\mathrm{H6-F}}$ = 1.7 Hz, H_6), 5.79 (1H, d, $^{3}J_{\mathrm{H5-H6}}$ = 8.1 Hz, H_5), 5.29 (1H, dt, $^{3}J_{\mathrm{H1'-F}}$ = 20.7 Hz, $^{3}J_{\mathrm{H1'-H2'}}$ = 6.7 Hz, $H_{1'}$), 4.79 (1H, app. t, $^{3}J_{\mathrm{H2'-H1'/H3'}}$ = 6.7 Hz, $H_{2'}$), 4.70 (1H, dd, $^{3}J_{\mathrm{H3'-H2'}}$ = 6.6 Hz, $^{3}J_{\mathrm{H3'-H4'}}$ = 5.3 Hz, $H_{3'}$), 4.05–3.93 (1H, m, $H_{5'a}$, $H_{5'b}$), 2.85–2.71 (1H, m, $H_{4'}$), 2.32 (1H, br s, OH), 1.57 (3H, s, CH_3), 1.34 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.9 (C_2, C═O), 151.1 (C_4, C═O), 141.8 (app. d, $^{4}J_{\mathrm{C6-F}}$ = 5.2 Hz, C_6), 127.1 (dd, $^{1}J_{\mathrm{C6'-F}}$ = 266.1 Hz, $^{1}J_{\mathrm{C6'-F}}$ = 253.3 Hz, $C_{6'}$), 114.2 [$C(CH_3)_2$], 103.2 (C_5), 77.9 (d, $^{3}J_{\mathrm{C2'-F}}$ = 7.8 Hz, $C_{2'}$), 77.2 (app. d, $^{3}J_{\mathrm{C3'-F}}$ = 8.1 Hz, $C_{3'}$), 64.2 (dd, $^{2}J_{\mathrm{H1'-F}}$ = 24.2 Hz, $^{2}J_{\mathrm{H1'-F}}$ = 17.8 Hz, $C_{1'}$), 58.1 (app. d, $^{3}J_{\mathrm{C5'-F}}$ = 7.9 Hz, $C_{5'}$), 52.1 (app. t, $^{2}J_{\mathrm{C4'-F}}$ = 19.7 Hz, $C_{4'}$), 27.2 [$C(CH_3)_2$], 25.0 [$C(CH_3)_2$]; ^{19}F NMR (377 MHz, $CDCl_3$): δ −100.0 (app. d, $^{2}J_{\mathrm{F-F}}$ = 237.2 Hz), −116.4 (app. dt, $^{2}J_{\mathrm{F-F}}$ = 237.4, $^{3}J_{\mathrm{F-H1'/H4'}}$ = 21.8 Hz); HRMS (NSI) calculated for $C_{13}H_{16}F_2N_2O_5Na$ $[M + Na]^+$ 341.0919, found 341.0921. These data were in good agreement with literature.[17]

General procedure for the synthesis of 39 & 40

Synthesis of phosphoramidate intermediate. Uridine derivative **36** or **37** (1.0 equiv.) was suspended in THF (0.2 M) and cooled to 0 °C. ^{t}BuMgCl (2.0 equiv., 1.0 M in THF) was added dropwise and the reaction mixture was stirred for 1 h. Isopropyl [(*S*)-(perfluorophenoxy)(phenoxy)phosphoryl]-L-alaninate **38** (1.1 equiv.) was added in one portion and the reaction mixture was allowed to warm to rt and stirred for 4 h. TLC analysis showed complete consumption of the starting material to a higher R_f. The reaction was quenched with MeOH (1 mL), and the solvent removed *in vacuo*. The residue was partitioned between H_2O (5 mL) and EtOAc (5 mL), and the aqueous phase was extracted with EtOAc (2 × 5 mL), washed with brine (5 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. This material was used without further purification.

Deprotection. Phosphoramidate intermediate was dissolved in 1 : 1 formic acid/H_2O (v/v, 0.1 M) and stirred at rt for 16 h. The solvent was removed *in vacuo* and the crude material was purified *via* flash column chromatography on silica gel (0–5% MeOH/EtOAc).

HPLC purification. A sample of **39** or **40** was dissolved in 1 : 1 H_2O/MeOH (v/v, 100 mg mL^{-1}), and injected onto a reverse phase column (see general experimental) and purified at a flow rate of 20.00 ml min^{-1} using the following gradient system:

Time (min)	%*A* (H_2O)	%*B* (MeOH)
0.0	50	50
5.0	50	50
12.0	0	100
15.0	0	100
15.1	50	50
20.0	50	50

[P(*S*),6′*R*]-5′-[Phenoxy(isopropyl-L-alaninate)]phosphate-6′-fluorocarbauridine 39. Phosphoramidate **39** (8.9 mg, 20 μmol, 24%) a white solid after freeze drying, was obtained following the above procedure from **36** (20.9 mg, 0.07 mmol, 1.0 equiv.). R_f = 0.09 (5% MeOH/DCM); ^{1}H NMR (400 MHz, MeOD): δ 7.65 (1H, dd, $^{3}J_{\mathrm{H6-H5}}$ = 8.2 Hz, $^{5}J_{\mathrm{H6'-F}}$ = 1.5 Hz, H_6), 7.39–7.34 (2H, m, ArH), 7.27–7.16 (3H, m, ArH), 5.69 (1H, d, $^{3}J_{\mathrm{H5-H6}}$ = 8.1 Hz, H_5), 5.06 (1H, dt, $^{2}J_{\mathrm{H6'-F}}$ = 55.2 Hz, $^{3}J_{\mathrm{H6'-H1'/H4'}}$ = 4.1 Hz, $H_{6'}$), 4.97 (1H, sep, $^{3}J_{[\mathrm{C}\mathit{H}\mathrm{(CH3)2}]-[\mathrm{CH(C}\mathit{H}\mathrm{3)2}]}$ = 6.3 Hz, [$C\mathit{H}(CH_3)_2$]), 4.89 (1H, ddd, $^{3}J_{\mathrm{H1'-F}}$ = 30.3 Hz, $^{3}J_{\mathrm{H1'-H2'}}$ = 10.0 Hz, $^{3}J_{\mathrm{H1'-H6'}}$ = 3.5 Hz, $H_{1'}$), 4.46 (1H, dd, $^{3}J_{\mathrm{H2'-H1'}}$ = 9.9 Hz, $^{3}J_{\mathrm{H2'-H3'}}$ = 6.6 Hz, $H_{2'}$), 4.27 (2H, m, $H_{5'a}$, $H_{5'b}$), 4.00 (1H, dd, $^{3}J_{\mathrm{H3'-H2'}}$ = 6.1 Hz, $^{3}J_{\mathrm{H3'-H4'}}$ = 5.1 Hz, $H_{3'}$), 3.90 (1H, dq, $^{3}J_{\mathrm{AlaC}\mathit{H}\mathrm{-P}}$ = 9.7 Hz, $^{3}J_{\mathrm{AlaC}\mathit{H}\mathrm{-AlaCH_3}}$ = 7.1 Hz, AlaC*H*), 2.63–2.48 (1H, m, $H_{4'}$), 1.34 (3H, dd, $^{3}J_{\mathrm{AlaC}\mathit{H}_3\mathrm{-AlaCH}}$ = 7.1 Hz, $^{4}J_{\mathrm{AlaC}\mathit{H}_3\mathrm{-P}}$ = 0.9 Hz, Ala–$C\mathit{H}_3$), 1.22 (6H, d, $^{3}J_{[\mathrm{CH(C}\mathit{H}_3\mathrm{)2}]-[\mathrm{C}\mathit{H}\mathrm{(CH_3)_2}]}$ = 6.3 Hz, [$CH(C\mathit{H}_3)_2$]); ^{13}C NMR (101 MHz, MeOD): δ 174.5 (d, $^{3}J_{\mathrm{Ala\ C{=}O-P}}$ = 5.4 Hz, Ala C═O), 166.3 (C_4, C═O), 153.4 (C_2, C═O), 152.3 (d, $^{2}J_{\mathrm{ArC-P}}$ = 7.0 Hz, ArC), 144.6 (d, $^{4}J_{\mathrm{C6-F}}$ = 3.9 Hz, C_6), 130.8 (d, $^{4}J_{\mathrm{ArC-P}}$ = 0.6 Hz, ArC), 126.1 (d, $^{5}J_{\mathrm{ArC-P}}$ = 1.2 Hz, ArC), 121.5 (d, $^{3}J_{\mathrm{ArC-P}}$ = 4.7 Hz, ArC), 102.0 (C_5), 91.8 (d, $^{1}J_{\mathrm{C6'-F}}$ = 182.3 Hz, $C_{6'}$), 71.6 ($C_{2'}$), 70.4 ($C_{3'}$), 70.1 [$\mathit{C}H(CH_3)_2$], 64.6 (dd, $^{2}J_{\mathrm{C5'-P}}$ = 11.3 Hz, $^{3}J_{\mathrm{C5'-F}}$ = 5.6 Hz, $C_{5'}$), 63.5 (d, $^{2}J_{\mathrm{C1'-F}}$ = 16.3 Hz, $C_{1'}$), 51.7 (Ala–*C*H), 51.0 (dd, $^{2}J_{\mathrm{C4'-F}}$ = 17.5 Hz, $^{3}J_{\mathrm{C4'-P}}$ = 7.5 Hz, $C_{4'}$), 22.0 [$CH(\mathit{C}H_3)_2$], 21.9 [$CH(\mathit{C}H_3)_2$], 20.5 (d, $^{3}J_{\mathrm{Ala}\mathit{C}\mathrm{H_3-P}}$ = 6.5 Hz, Ala–CH_3); ^{19}F NMR (377 MHz, MeOD): δ −208.4 (dt, $^{2}J_{\mathrm{F-H6'}}$ = 55.4 Hz, $^{3}J_{\mathrm{F-H1'/H4'}}$ = 30.3 Hz); ^{31}P {^{1}H} NMR (162 MHz, MeOD): δ 3.46 (s); HRMS (NSI): calculated for $C_{22}H_{28}FN_3O_9P$ $[M - H]^-$ 528.1553, found 528.1547. These data are in good agreement with literature.[17]

[P(*S*)]-5′-[Phenoxy(isopropyl-L-alaninate)]phosphate-6′-*gem*-difluorocarbauridine 40. Phosphoramidate **40** (14.9 mg, 30 μmol, 27%) a white solid after freeze drying, was obtained following the above procedure from **37** (33.6 mg, 0.11 mmol, 1.0 equiv.). $R_f = 0.11$ (5% MeOH/DCM); ^{1}H NMR (400 MHz, MeOD): δ 7.54 (dd, $^3J_{H6-C5} = 8.1$ Hz, $^5J_{H6-F} = 2.4$ Hz, H_6), 7.42–7.34 (2H, m, ArH), 7.28–7.18 (3H, m, ArH), 5.71 (d, $^3J_{H5-H6} = 8.1$ Hz, H_5), 5.35 (app. dt, $^3J_{H1'-F} = 18.9$ Hz, $^3J_{H1'-H2'} = 9.6$ Hz, $H_{1'}$), 4.98 (1H, sep, $^3J_{[CH(CH_3)2]-[CH(CH_3)_2]} = 6.7$ Hz, [C*H*(CH$_3$)$_2$]), 4.39–4.24 (3H, m, $H_{2'}$, $H_{5'a}$, $H_{5'b}$), 4.12–4.08 (1H, m, $H_{3'}$), 3.90 (1H, dq, $^3J_{AlaCH-P} = 9.8$ Hz, $^3J_{AlaCH-AlaCH_3} = 7.1$ Hz, AlaC*H*), 2.83–2.70 (1H, m, $H_{4'}$), 1.35 (3H, dd, $^3J_{AlaCH_3-AlaCH} = 7.1$ Hz, $^4J_{AlaCH_3-P} = 0.8$ Hz, AlaC*H*$_3$), 1.23 (6H, d, $^3J_{[CH(CH_3)_2]-[CH(CH_3)_2]} = 6.3$ Hz, [CH(C*H*$_3$)$_2$]); ^{13}C NMR (101 MHz, MeOD): δ 173.0 (d, $^3J_{C=O-P} = 5.3$ Hz, C=O Ala), 164.4 (C=O, C_2), 151.8 (C=O, C_4), 150.8 (d, $^2J_{ArC-P} = 7.0$ Hz, ArC), 142.9 (d, $^4J_{C6-F} = 4.1$ Hz, C_6), 129.4 (d, $^4J_{ArC-P} = 0.6$ Hz, ArC), 124.8 (d, $^5J_{ArC-P} = 1.0$ Hz, ArC), 123.8 (dd, $^1J_{C6'-F} = 261.1$, $^1J_{C6'-F} = 253.7$ Hz, C = 6′), 120.0 (d, $^3J_{ArC-P} = 4.8$ Hz, ArC), 101.3 (C_5), 69.8 (d, $^3J_{C2'-F} = 7.8$ Hz, $C_{2'}$), 68.9 (dd, $^3J_{C3'-F} = 5.6$ Hz, $^3J_{C3'-F} = 1.7$ Hz, C_3), 68.8 [*C*H(CH$_3$)$_2$], 62.2 (dd, $^2J_{C1'-F} = 24.2$ Hz, $^2J_{C1'-F} = 18.2$ Hz, $C_{1'}$), 61.9 (dd, $^3J_{C5'-P} = 11.0$ Hz, $^3J_{C5'-F} = 5.4$ Hz, $C_{5'}$), 51.9 (ddd, $^3J_{C4'-F} = 21.6$ Hz, $^3J_{C4'-F} = 19.0$ Hz, $^3J_{C4'-P} = 8.3$ Hz, $C_{4'}$) 50.2 (Ala–*C*H), 20.6 [CH(*C*H$_3$)$_2$], 20.5 [CH(*C*H$_3$)$_2$], 19.1 (d, $^3J_{CH_3-P} = 6.5$ Hz, Ala–CH$_3$); ^{19}F NMR (377 MHz, MeOD): δ −98.6 (ddd, $^2J_{F-F} = 238.7$ Hz, $^3J_{F-H4'} = 13.0$ Hz, $^3J_{F-H1'} = 9.7$ Hz), −117.0 (app. dt, $^2J_{F-F} = 238.6$ Hz, $^3J_{F-H1'/H4'} = 16.7$ Hz); ^{31}P {^{1}H} NMR (162 MHz, MeOD): δ 3.29 (s); HRMS (NSI): calculated for $C_{22}H_{27}F_2N_4O_9P$ $[M - H]^-$ 546.1458, found 541.1460. These data were in good agreement with literature.[17]

Conflicts of interest

There are no conflicts to declare.

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