Synthesis and *O*-phosphorylation of 3,3,4,4-tetrafluoroaryl-*C*-nucleoside analogues†

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Enantioenriched tetrafluorinated aryl-*C*-nucleosides were synthesised in four steps from 1-benzyloxy-4-bromo-3,3,4,4-tetrafluorobutan-2-ol. The presence of the tetrafluorinated ethylene group is compatible with *O*-phosphorylation of the primary alcohol, as demonstrated by the successful preparation of the tetrafluorinated naphthyl-*C*-nucleotide.

In contrast to most natural nucleosides, the sugar moiety and aglycon of *C*-nucleosides are united by a C–C bond, a structural characteristic accounting for their advantageous resistance to hydrolytic and enzymatic cleavage. Although some derivatives have been isolated from natural sources (*e.g.* pseudouridine, 1-methylpseudouridine and 2′-*O*-methylpseudouridine),[1] most *C*-nucleosides are synthetic compounds tailored to fulfil specific biological functions. In addition to their chemotherapeutic properties (*e.g.* antibiotic, antiviral or anticancer activity), *C*-nucleosides have proved useful for the development of universal bases and the synthesis of triplex DNA constructs for gene therapy.[2]

Since the properties of these compounds may be tuned upon structural modification, the synthesis of *C*-nucleosides is an active research area. Structural diversity emerges from the aglycon motif and/or the carbohydrate unit. Representative examples of sugar-modified *C*-nucleosides are the aza-analogues Immucillin-H and Immucillin-G, known to act as transition state analogue inhibitors of purine nucleoside phosphorylase, a therapeutic target for the control of T-cell proliferation.[3]

To date, a very limited number of *C*-nucleosides featuring fluorine substituents on the sugar moiety have been prepared.

Notable exceptions are the isostere of the well-documented antiviral agent 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)thymine **I** and the aza-derivative (1*S*)-1-(9-deazahypoxanthin-9-yl)-1,2,4-trideoxy-2,2-difluoro-1,4-imino-D-*erythro* pentitol) **II**, a fluorinated analogue of Immucillin-H.[4] Our research activity in fluorine chemistry[5] and a programme aimed at applying a chemical genetic approach for the identification of kinase substrates[6] led us to explore synthetic routes towards the novel sugar-modified tetrafluorinated aryl-*C*-nucleosides **III** for biological investigations (Fig. 1). We opted for aryl-*C*-nucleosides, as the aryl base analogues are particularly useful due to their advantageous base stacking ability.

DiMagno and co-workers launched the concept of "polar hydrophobicity", and suggested that the binding affinities of

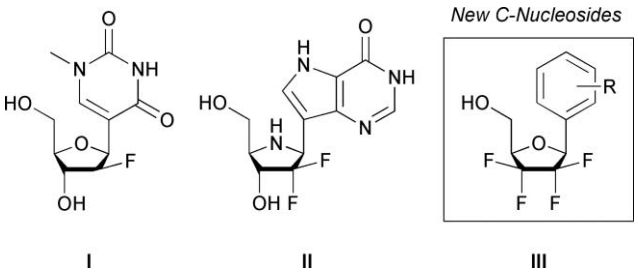

Fig. 1 Monofluoro-, difluoro- and tetrafluoro-*C*-nucleosides.

carbohydrates may be significantly modulated by extensive replacement of CHOH groups by CF_2 groups. For example, the hexafluoropyranose **1** was shown to cross the erythrocyte membrane at a rate significantly superior to glucose, an acceleration effect resulting from enhanced affinity for the transporter protein.[7] This observation fuelled an interest in the preparation of heavily fluorinated sugars. The *de novo* asymmetric synthesis of the tetrafluoropyranose **2**, and more recently of the structurally related derivatives **3** and **4**, was validated by Linclau *et al.* (Fig. 2).[8] This background information led us to believe that the synthesis of tetrafluorinated *C*-nucleosides **III** is of interest and within reach, offering the prospect of understanding their physicochemical and biological properties. Herein, we describe the first synthesis of tetrafluoro-*C*-nucleosides. We also demonstrate that these tetrafluorinated *C*-nucleosides are amenable to *O*-phosphorylation.

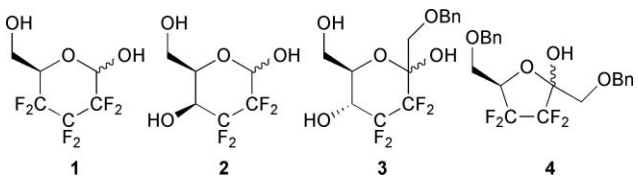

Fig. 2 Tetrafluorinated carbohydrate analogues.

Based on literature precedents reporting the preparation of non-fluorinated *C*-nucleosides,[9] we opted to prepare the non-natural motif **III** by direct attachment of the aglycon to the tetrafluorinated sugar precursor. This strategy was selected in preference to an approach based on the introduction of a functional group at the anomeric position of the sugar analogue, followed by the construction of the aglycon motif, since it is documented that for non-fluorinated precursors, this more lengthy synthetic route may

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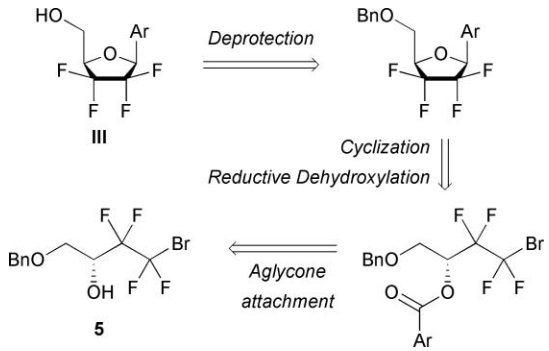
suffer from poor stereoselectivity. In our retrosynthetic analysis, we opted for an esterification of the known tetrafluorinated alcohol (2*R*)-**5** for the attachment of the aglycon motif, followed by a cyclization and dehydroxylation event.[10] Points of interest are the possible impact of the presence of tetrafluoroethylene group on the feasibility and stereochemical outcome of the reductive dehydroxylation, and on the reactivity of the primary alcohol within **III** if further functionalization is required (Scheme 1).



Scheme 1 Retrosynthetic scheme.

The racemic alcohol **(±)-5** was synthesized to validate, optimise, and delineate the scope and limitation of the proposed synthetic sequence. The synthesis of (2*R*)-**5** was performed according to literature procedures.[8a] This material will serve as the key precursor for the synthesis of enantioenriched tetrafluoro-*C*-nucleosides.

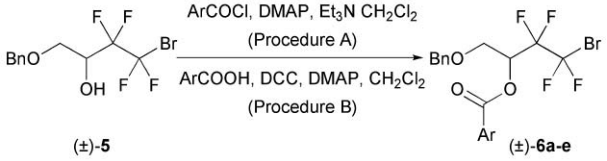
Our studies began with the attachment of the aglycon motif to **(±)-5**. The esterifications were performed in dichloromethane using Et_3N and DMAP for acyl chlorides, or using DCC and DMAP for carboxylic acids. All reactions were high yielding (entries 1–5, Table 1).

Esters **6a–e** were subjected to bromine–lithium exchange with MeLi at low temperature, a process triggering ring closure. The resulting cyclized lactols **7a–e** were used unpurified for the subsequent reduction (Table 2). Pleasingly, the Lewis acid-promoted reductive dehydroxylation with triethylsilane gave **8a–c** in moderate yields, with the β-anomers being formed predominantly (d.r. up to 5 : 1) (entries 1–3, Table 2).[11] Attempts to improve the β : α ratio using triisopropylsilane instead of triethylsilane were not successful. The relative stereochemistry of **8a** was assigned based on ^{1}H NMR NOE experiments, and by analogy with **8a** for **8b–c**. For esters **6d** and **6e**, the cyclization was found to be successful, but the reduction did not proceed. The tetrafluorinated tetrahydrofuran-2-ols **7d** and **7e** were isolated as a mixture of anomers (~1 : 1) in 97% and 60% yield, respectively (entries 4 and 5, Table 2). The failure of **7d** and **7e** to undergo reductive dehydroxylation indicates that the presence of the electron withdrawing groups on both the sugar and aglycon motifs prevents the formation of the putative oxonium intermediate.

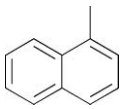
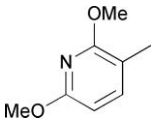
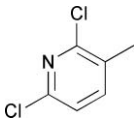
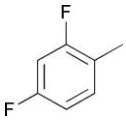
The *C*-nucleosides **8a–c** engaged as diastereomeric mixtures were deprotected in good yields with a large excess of NaI and trimethylsilyl chloride in acetonitrile, or using boron tribromide in dichloromethane. The debenzylation of **7d** and **7e** delivered the tetrafluorotetrahydro-2*H*-pyrano-2,5-diols **10d** and **10e** in 80% and 74% yield, respectively (Table 3).[12]

Having validated a synthetic route to **(±)-9a–c**, we next examined the synthesis of the corresponding enantioenriched tetrafluoro-*C*-nucleosides. Since the synthetic value of this chemistry will rely on the availability of anomerically pure *C*-nucleoside, a separation process was programmed after reductive dehydroxylation. Model compounds **9a** and **9b** were chosen for this study. Compound (2*R*)-**5**[8a] was subjected to esterification, cyclization and reduction. Enantiomeric excesses were measured by chiral stationary phase HPLC on (2*R*)-**5**, (2*R*,5*S*)-**8a** and (2*R*,5*S*)-**8b**, and were found to be 93%, 90% and 89%, respectively. In order to identify which step may be responsible for the slight erosion of enantiomeric excess,

Table 1 Aglycone attachment

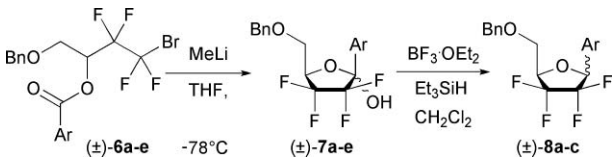


(±)-**5** (±)-**6a-e**

Entry	Ar-	Procedure	Product	Yield (%)[a]
1		A	**6a**	97
2		A	**6b**	94
3		B	**6c**	87
4		B	**6d**	96
5		A	**6e**	57

[a] Isolated yield.

Table 2 Cyclization and dehydroxylation of **(±)-6a–e**

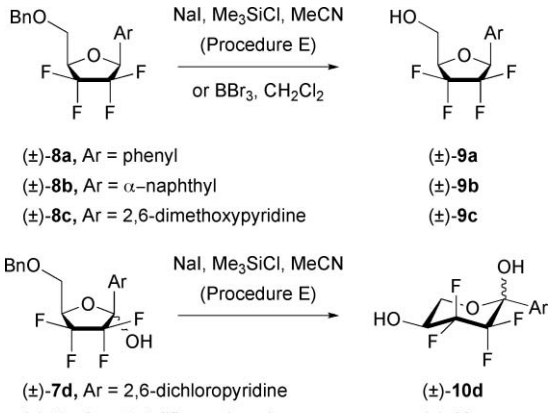


(±)-**6a-e** (±)-**7a-e** (±)-**8a-c**

Entry	Ester	Product	Yield (%)[a]	β : α ratio
1	**(±)-6a**	**(±)-8a**	60	5 : 1[b]
2	**(±)-6b**	**(±)-8b**	63	4 : 1[b]
3	**(±)-6c**	**(±)-8c**	77	2 : 1[b]/5 : 1[c]
4	**(±)-6d**	**(±)-7d**	97	1.2 : 1[b]
5	**(±)-6e**	**(±)-7e**	60	1.1 : 1[b]

[a] Isolated yield. [b] Determined by ^{1}H NMR on crude product. [c] Determined by ^{1}H NMR after purification.

Table 3 Deprotection of **(±)-8a–c** and **(±)-7d** and **(±)-7e**



Entry	Starting material	Procedure	Product	Yield (%)
1	**(±)-8a**	E	**(±)-9a**	90
2	**(±)-8b**	E	**(±)-9b**	98
3	**(±)-8c**	BBr_3, CH_2Cl_2	**(±)-9c**	69
4	**(±)-7d**	E	**(±)-10d**	80
5	**(±)-7e**	E	**(±)-10e**	74

ee measurement after the esterification was undertaken on (2*R*)-**6a**, and was found to be 89% (Fig. 3). These data indicate that detectable epimerization was observed upon esterification under our reaction conditions. Qing *et al.*[13] and Linclau *et al.*[8c] have discussed this issue of epimerization when benzylating or esterifying structurally related substrates featuring either an electron-withdrawing *gem*-difluoromethylene or tetrafluoroethylene group adjacent to a carbinol.

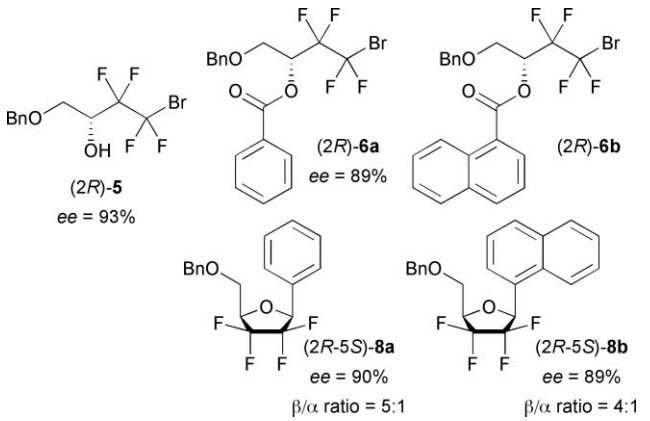
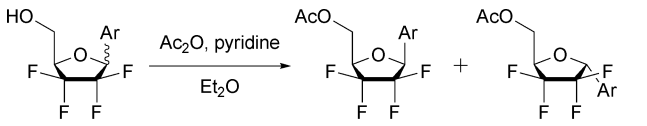


Fig. 3 Asymmetric synthesis of **8a** and **8b**.

At this stage we sought to separate the diastereomers to access anomerically pure compounds. The separation of the anomers of both the benzyl-protected *C*-nucleosides (2*R*,5*S*)-**8a** and (2*R*,5*S*)-**8b**, and the free alcohols (2*R*,5*S*)-**9a** and (2*R*,5*S*)-**9b** was unsuccessful by silica gel column chromatography (normal and reverse phase), preparative TLC or HPLC. Satisfyingly, upon acetylation, the anomers of both (2*R*,5*S*)-**11a** and (2*R*,5*S*)-**11b** could be separated by careful column chromatography (Table 4).

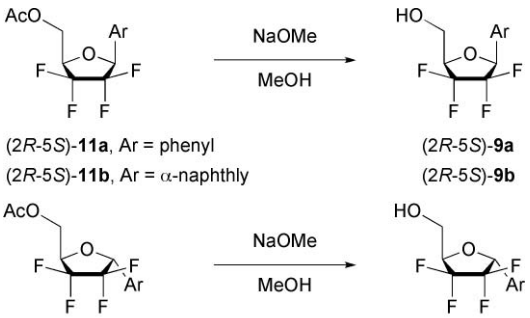
Deacetylation with sodium methoxide delivered the anomerically pure *C*-nucleosides (2*R*,5*S*)-**9a** and (2*R*,5*S*)–**9b**, and (2*R*,5*R*)-**9a** and (2*R*,5*R*)-**9b** in high yields (Table 5).

Table 4 Separation of anomers upon acetylation of **9a** and **9b**



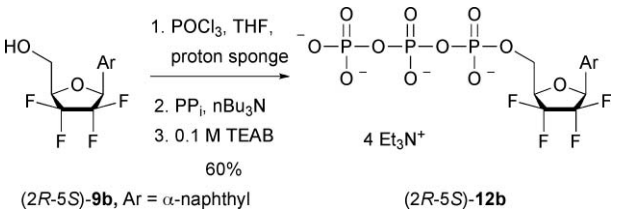
Entry	Alcohol	Products	Yield (%)
1	**9a**	(2*R*,5*S*)-**11a**	41
	β : α ratio 5 : 1	(2*R*,5*R*)-**11a**	5
2	**9b**	(2*R*,5*S*)-**11b**	88
	β : α ratio 4 : 1	(2*R*,5*R*)-**11b**	5

Table 5 Deacetylation of **11a** and **11b**



Entry	Acetate	Product	Yield (%)
1	(2*R*,5*S*)-**11a**	(2*R*,5*S*)-**9a**	77
2	(2*R*,5*R*)-**11a**	(2*R*,5*R*)-**9a**	96
3	(2*R*,5*S*)-**11b**	(2*R*,5*S*)-**9b**	97
4	(2*R*,5*R*)-**11b**	(2*R*,5*R*)-**9b**	83

With a new class of *C*-nucleosides in hand, we next studied the impact of the tetrafluoroethylene motif on the reactivity of the primary alcohol. We were particularly interested in *O*-phosphorylation, as bioactivation through phosphorylation is a key step in cellular nucleoside metabolism. In addition, the tetrafluorinated *C*-nucleoside triphosphates have the potential to become valuable chemical probes for elucidating and validating drug targets in the field of chemical genetics. Triphosphorylation of (2*R*,5*S*)-**9b** was performed in a one-pot three-step procedure using phosphoryl chloride and a catalytic amount of 1,8-bis(dimethylamino)naphthalene (proton sponge®) in THF. This first step was completed within 24 h at rt, a reaction time much longer than would be necessary for the *O*-phosphorylation of non-fluorinated analogues (usually complete within 2 h at 0 °C). Pleasingly, the crude dichlorophosphate could be converted into the triphosphate (2*R*,5*S*)-**12b** by successive treatment with pyrophosphate (PP_i, tributylammonium salt) in the presence of $n$$Bu_3N$ (24 h) followed by an excess of 0.1 M triethylammonium bicarbonate (TEAB) buffer (pH 7.5) (48 h). The triphosphate was purified by reverse phase HPLC and was isolated in 60% yield as the triethylammonium salt (Scheme 2).



Scheme 2 Triphosphorylation of (2*R*,5*S*)-**9b**.

Conclusions

In summary, we have validated the first asymmetric synthesis of a new class of aryl-*C*-nucleosides incorporating a tetrafluoroethylene motif. The first enantiomerically enriched 3,3,4,4-tetrafluoroaryl-*C*-nucleotide was also successfully prepared as a single anomer. Despite successful separation of anomers at a late stage, there is still opportunity for the development of more stereoselective synthetic routes to these tetrafluorinated-*C*-nucleosides.

Experimental

General experimental details

All ^{1}H NMR spectra were recorded in deuterated solvents using Bruker DPX200, DPX250, DPX400, AV400 and AV500 spectrometers. ^{13}C NMR spectra were recorded in deuterated solvents using Bruker DPX400, AV400 and AV500 spectrometers with a carbon-13 cryoprobe. ^{19}F spectra (both with and without proton decoupling) were recorded on a Bruker AVANCE AV400 spectrometer. ^{31}P spectra were recorded on a Bruker DPX250 spectrometer. NOE difference experiments were performed at 500 MHz on non-degassed solutions with saturation times totalling 5 s. These were performed with frequency cycling between the individual lines within each multiplet to ensure more even suppression of the wide multiplet structures. ^{1}H and ^{13}C NMR spectra are reported as chemical shifts (δ) in parts per million (ppm) relative to the solvent peak using the Bruker internal referencing procedure (edlock). ^{19}F NMR spectra are referenced relative to $CFCl_3$ in $CDCl_3$. ^{31}P NMR spectra are referenced relative to H_3PO_4 as an external standard. Coupling constants (J) are reported in units of hertz (Hz). The following abbreviations are used to describe multiplicities, s = singlet, d = doublet, t = triplet, q = quartet, br = broad m = multiplet. Low and high resolution mass spectra were recorded on Bruker MicroTof spectrometer using positive or negative electrospray ionization (ESI+/ESI–). Optical rotations were determined on a Perkin Elmer 241 polarimeter in a 1 dm cell. $[\alpha]_D$ Values are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded as thin films on NaCl plates, neat or in solution in $CHCl_3$ on a Bruker Tensor 27 FTIR spectrometer. Absorptions are measured in wavenumbers (cm^{-1}) and only peaks of interest are reported. UV spectra were recorded as solutions in methanol or water on a Perkin Elmer Lambda 25 UV/VIS spectrometer. Absorptions are measured in wavelength (nm) and only maxima are reported. All reactions requiring anhydrous conditions were conducted in dried apparatus under an inert atmosphere of argon or nitrogen. Solvents were dried and purified before use according to standard procedures. All reactions were monitored by TLC using Merck Kiesegel 60 F254 plates. Visualizations of the reaction components was achieved using UV fluorescence (254 nm) and $KMnO_4$ stain. Column chromatography was carried out over Merck silica gel C60 (40–60 μm). Reverse phase HPLC was performed using a Dionex P680 pump with UVD340U detector and a Phenomenex Jupiter 10μ; proteo 90 Å 250 × 21.2 mM column. Compounds were named according to IUPAC nomenclature.

General procedure A: esterification using an acid chloride

The relevant acid chloride (1.2 eq.) was added to a solution of alcohol **5** (1 eq.), triethylamine (2.2 eq.) and DMAP (0.1 eq.) in CH_2Cl_2 (0.2 M) at room temperature, and the reaction was stirred for 16 h before removal of the solvent. Purification by column chromatography (pet. ether 40–60°/Et_2O, 90 : 10) afforded the corresponding ester **6** as a colourless oil.

General procedure B: esterification using an acid

The relevant carboxylic acid (1.1 eq.) was added to a solution of alcohol **5** (1 eq.), DCC (1.1 eq.) and DMAP (0.1 eq.) in CH_2Cl_2 (0.2 M) at room temperature, and the reaction was stirred for 16 h before removal of the solvent. Purification by column chromatography (pet. ether 40–60°/Et_2O, 90 : 10) afforded the corresponding ester **6** as a colourless oil.

General procedure C: cyclisation

MeLi (1.6 M in Et_2O, 1 eq.) was added dropwise over 60 min to a solution of ester **6** (1 eq.) in THF (0.1 M) at −78 °C. The reaction was stirred for 1 h at −78 °C, then allowed to warm to room temperature slowly over 3 h. After dilution with Et_2O (100 mL) and addition of $NaHCO_3$ (100 mL sat. aq.), the suspension was stirred for 15 min. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Starting materials were removed by filtration through a silica pad (pet. ether 40–60°/Et_2O, 90 : 10); products were eluted in Et_2O to afford the crude material of the corresponding furanol **7**.

General procedure D: dehydroxylation

BF_3OEt_2 (2 eq.) and Et_3SiH (2 eq.) were added to a solution of crude furanol **7** in CH_2Cl_2 (0.2 M), dropwise at −78 °C. The reaction mixture was allowed to slowly warm to room temperature and stirred for 16 h. After dilution with Et_2O (100 mL) and addition of $NaHCO_3$ (100 mL sat. aq.), the suspension was stirred for 15 min. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (pet. ether 40–60°/Et_2O, 95 : 5) afforded the corresponding benzyl-protected *C*-nucleoside **8** as a mixture of diastereomers.

General procedure E: debenzylation

NaI (10 eq.) and chlorotrimethylsilane (5 eq.) were added to a solution of benzyl-protected *C*-nucleoside **8** (1 eq.) in acetonitrile (0.08 M) at room temperature and the reaction mixture was stirred in the dark for 3 d. Aqueous ammonia (5 mL mmol^{-1}) was added and the reaction mixture was stirred for 15 min, before removal of the solvent *in vacuo*. Purification by column chromatography (pet. ether 40–60°/Et_2O, 50 : 50) afforded the corresponding

C-nucleoside **9** as either a colourless oil or an amorphous white solid.

General procedure F: acetylation

Pyridine (1.2 eq.) and Ac_2O (1.2 eq.) were added sequentially to a solution of *C*-nucleoside **9** (1 eq.) in Et_2O (3 M) at room temperature. The reaction mixture was stirred for 16 h before removal of the solvents *in vacuo*. Purification by column chromatography (pet. ether 40–60°/Et_2O/CH_2Cl_2, 90 : 5 5) afforded the corresponding acetyl protected *C*-nucleoside **11** as an amorphous white solid.

General procedure G: deacetylation

NaOMe (0.01 eq.) was added to a solution of acetyl-protected *C*-nucleoside **11** (1 eq.) in MeOH (3 M) at room temperature. The reaction mixture was stirred for 20 min before addition of H^+-Dowex 50WX8 100-200. Filtration and removal of the solvent under reduced pressure afforded the corresponding *C*-nucleoside **9** as an amorphous white solid.

(2*R*)-1-(Benzyloxy)-4-bromo-3,3,4,4-tetrafluorobutan-2-yl benzoate (2*R*)-6a

Following general procedure A, using benzoyl chloride (0.21 mL, 1.8 mmol) and alcohol **(2*R*)-5** (0.50 g, 1.5 mmol), ester **(2*R*)-6a** was isolated as a colourless oil (0.64 g, 1.5 mmol, 97%.). ee = 89% (determined on Chiracel OD 10 μm column 250 × 4.6 mm (ID), 1 mL min^{-1}, hexane–*i*PrOH 98 : 2; R_T = 5.21, 5.74 min). $[\alpha]_D^{19}$ = +12.1 (*c* 1, MeOH); IR (neat, cm^{-1}): *ν* 3050, 2957 (C–H), 1733 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.14 (2H, dm, *J* = 8.1 Hz, H-2′), 7.65 (1H, tm, *J* = 7.5 Hz, H-4′), 7.50 (2H, m, H-3′), 7.38-7.27 (5H, m, H_{Ph}), 6.13 (1H, dtd, *J* = 17, 7.0, 3.5 Hz, CHOR), 4.68 (1H, d, *J* = 12.1 Hz, CH_APh), 4.58 (1H, d, *J* = 12.1 Hz, CH_BPh), 4.02 (1H, dd, *J* = 11.1, 3.5, 1.7 Hz, CH_AOBn), 3.93 (1H, dd, *J* = 11.1, 7.2 Hz, CH_BOBn); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 164.6 (CO_2), 137.2 (C_{Ph}), 133.8 (C-4′), 130.2 (C-3′), 128.6 (C-1′), 128.6 (C_{HPh}), 128.5 (C-2′), 127.9 (C_{HPh}), 127.7 (C_{HPh}), 116.8 (tt, *J* = 313, 39 Hz, CF_2Br), 113.6 (ddt, *J* = 262, 256, 31 Hz, CF_2), 73.3 (CH_2Ph), 68.1 (dd, *J* = 30, 22 Hz, CHOR), 66.5 (CH_2OBn); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$): *δ* −63.9 (2F, t, *J* = 4 Hz, CF_2Br), −113.6 (1F, dt, *J* = 274, 4 Hz, CF_{2A}), −119.0 (1F, dt, *J* = 274, 4 Hz, CF_{2B}); HRMS (ESI+) Calcd for $C_{18}H_{15}BrF_4O_3$ [M + Na]$^+$: 457.0033, found 457.0035.

(2*R*)-1-(Benzyloxy)-4-bromo-3,3,4,4-tetrafluorobutan-2-yl 1-naphthoate (2*R*)-6b

Following general procedure A, using naphthoyl chloride (0.27 ml, 1.8 mmol) and alcohol **(2*R*)-5** (0.50 g, 1.5 mmol), ester **(2*R*)-6b** was isolated as a colourless oil (0.65 g, 1.4 mmol, 94%.). $[\alpha]_D^{19}$ = +15.3 (*c* 1, MeOH); IR (neat, cm^{-1}): *ν* 3020, 2956 (C–H), 1732 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.92 (1H, d, *J* = 8.8 Hz, H-8′), 8.24 (1H, dd, *J* = 7.3, 1.2 Hz, H-4′), 8.08 (1H, d, *J* = 8.2 Hz, H-2′), 7.91 (1H, d, *J* = 8.0 Hz, H-5′), 7.63 (1H, ddd, *J* = 8.5, 6.8, 1.4 Hz, H-6′/H-7′), 7.57 (1H, ddd, *J* = 8.5, 6.8, 1.2 Hz, H-6′/H-7′), 7.53 (1H, dd, *J* = 8.0, 7.5 Hz, H-3′), 7.32-7.25 (5H, m, H_{Ph}), 6.19 (1H, dtd, *J* = 17, 7.3, 3.4 Hz, CHOR), 4.68 (1H, d, *J* = 12.0 Hz, CH_APh), 4.57 (1H, d, *J* = 12.0 Hz, CH_BPh), 4.04 (1H, ddd, *J* = 11.2, 3.3, 2.0 Hz, CH_AOBn), 3.96 (1H, dd, *J* = 11.2, 7.5 Hz, CH_BOBn); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 165.1 (CO_2), 137.2 (C_{Ph}), 134.3 (C-2′), 133.8 (C-10′), 131.5 (C-9′), 130.8 (C-4′), 128.6 (C-4′), 128.4 (C_{Ph}), 128.2 (C-6′/C-7′), 127.9 (C_{Ph}), 127.6 (C_{Ph}), 126.4 (C-6′/C-7′), 125.6 (C-8′), 125.2 (C-1′), 124.5 (C-3′), 116.8 (tt, *J* = 313, 39 Hz, CF_2Br), 113.5 (ddt, *J* = 263, 256, 32 Hz, CF_2), 73.4 (CH_2Ph), 67.7 (dd, *J* = 30, 22 Hz, CHOR), 66.5 (CH_2OBn); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$): *δ* −63.9 (2F, t, *J* = 4 Hz, CF_2Br), −113.6 (1F, dt, *J* = 273 Hz, CF_{2A}), −119.0 (1F, dt, 273, 4 Hz, CF_{2B}); HRMS (ESI+) Calcd for $C_{22}H_{17}BrF_4O_3$ [M + Na]$^+$: 507.0189, found 507.0194.

(1-(Benzyloxy)-4-bromo-3,3,4,4-tetrafluorobutan-2-yl 2,6-dimethoxynicotinate (±)-6c

Following general procedure B, using 2,6-dimethoxypyridine-3-carboxylic acid (0.30 g, 1.7 mmol) and alcohol **(±)-5** (0.50 g, 1.5 mmol), ester **(±)-6c** was isolated as a colourless oil (0.65 g, 1.3 mmol, 87%.). IR (neat, cm^{-1}): *ν* 3059, 2951 (C–H), 1734 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.17 (1H, d, *J* = 8.5 Hz, H-6′), 7.40-7.25 (5H, m, H_{Ph}), 6.35 (1H, d, *J* = 8.5 Hz, H-5′), 6.03 (1H, dtd, *J* = 17, 6.8, 3.7 Hz, CHOR), 4.65 (1H, d, *J* = 12.0 Hz, CH_APh), 4.55 (1H, d, *J* = 12.0 Hz, CH_BPh), 4.07 (3H, s, CH_3), 3.99 (3H, s, CH_3), 3.95 (1H, ddd, *J* = 11.3, 3.8, 1.8 Hz, CH_AOBn), 3.87 (1H, dd, *J* = 11.3, 6.9 Hz, CH_BOBn); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 166.1 (CO_2), 163.7 (C-2′/C-4′), 161.9 (C-2′/C-4′), 144.1 (C-6′), 137.3 (C_{Ph}), 128.4, 127.8, 127.6 (C_{HPh}), 116.8 (tt, *J* = 314, 40 Hz, CF_2Br), 113.7 (ddt, *J* = 264, 256, 32 Hz, CF_2), 102.9 (C-1′), 102.1 (C-5′), 73.2 (CH_2Ph), 67.2 (dd, *J* = 30, 22 Hz, CHOR), 66.5 (CH_2OBn), 54.2, 54.0 (OCH_3); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$): *δ* −63.8 (2F, dd, *J* = 7, 4 Hz, CF_2Br), −113.4 (1F, dt, *J* = 274, 3 Hz, CF_{2A}), −119.3 (1F, dd, *J* = 274, 4 Hz, CF_{2B}); HRMS (ESI+) Calcd for $C_{19}H_{18}BrF_4NO_5$ [M + Na]$^+$: 518.0197, found 518.0199.

1-(Benzyloxy)-4-bromo-3,3,4,4-tetrafluorobutan-2-yl 2,6-dichloronicotinate (±)-6d

Following general procedure B, using 2,6-dichloropyridine-3-carboxylic acid (0.32 g, 1.7 mmol) and alcohol **(±)-5** (0.50 g, 1.5 mmol), ester **(±)-6d** was isolated as colourless oil (0.73 g, 1.4 mmol, 96%). IR (neat, cm^{-1}): *ν* 3047, 2955 (C–H), 1758 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.12 (1H, d, *J* = 8.0 Hz, H-6′), 7.36 (1H, d, *J* = 8.0 Hz, H-5′), 7.35-7.27 (5H, m, H_{Ph}), 6.05 (1H, dddd, *J* = 15, 7.5, 7.5, 3.2 Hz, CHOR), 4.63 (1H, d, *J* = 12.0 Hz, CH_APh), 4.53 (1H, d, *J* = 12.0 Hz, CH_BPh), 3.96 (1H, ddd, *J* = 11.1, 3.1, 2.2 Hz, CH_AOBn), 3.89 (1H, dd, *J* = 11.1, 8.0 Hz, CH_BOBn); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 161.4 (CO_2), 153.8, 150.5 (C-2′, C-4′), 142.6 (C-6′), 136.8 (C_{Ph}), 128.5, 128.0, 127.7 (C_{HPh}), 123.6 (C-1′), 122.9 (C-5′), 116.5 (tt, *J* = 313, 39 Hz, CF_2Br), 113.2 (ddt, *J* = 263, 257, 32 Hz, CF_2), 73.4 (CH_2Ph), 68.7 (dd, *J* = 30, 22 Hz, CHOR), 66.1 (CH_2OBn); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$): *δ* −64.2 (2F, dd, *J* = 7, 4 Hz, CF_2Br), −114.1 (1F, dt, *J* = 275, 3 Hz, CF_{2A}), −118.7 (1F, dtd, *J* = 275, 5, 3 Hz, CF_{2B}); HRMS (ESI+) Calcd for $C_{17}H_{12}BrCl_2F_4NO_3$ [M + Na]$^+$: 525.9206, found 525.9208.

1-(Benzyloxy)-4-bromo-3,3,4,4-tetrafluorobutan-2-yl 2,4-difluorobenzoate (±)-6e

Following general procedure A, using 2,4-difluorobenzoic acid (0.21 ml, 1.8 mmol) and alcohol **(±)-5** (0.50 g, 1.5 mmol), ester **(±)-6e** was isolated as a colourless oil (0.41 g, 0.9 mmol, 57%.).

IR (neat, cm^{-1}): ν 3046, 2952 (C–H), 1749 (C=O); ^1H NMR (500 MHz, $CDCl_3$): δ 8.00 (1H, td, J = 8.4, 6.5 Hz, H-6′), 7.34-7.27 (5H, m, H_{Ph}), 6.97 (1H, dddd, J = 9.7, 8.5, 2.4, 0.8 Hz, H-5′), 6.92 (1H, ddd, J = 11.1, 8.5, 2.4 Hz, H-3′), 6.06 (1H, dddd, J = 16, 7.6, 7.3, 3.3 Hz, CHOR), 4.64 (1H, d, J = 12.1 Hz, CH_APh), 4.55 (1H, d, J = 12.1 Hz, CH_BPh), 3.97 (1H, ddd, J = 11.2, 3.1, 1.9 Hz, CH_AOBn), 3.89 (1H, dd, J = 11.2, 7.6 Hz, CH_BOBn); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.3 (dd, J = 258, 12 Hz, C-2′/C4′), 163.3 (dd, J = 266, 13 Hz, C-2′/C4′), 161.2 (d, J = 4 Hz, CO_2), 137.1 (C_{Ph}), 134.2 (dd, J = 11, 1 Hz, C-1′), 128.4, 127.9, 127.6 (C_{HPh}), 116.7 (tt, J = 313, 40 Hz, CF_2Br), 113.6 (dd, J = 10, 3 Hz, C-6′), 113.3 (ddt, J = 263, 257, 31 Hz, CF_2), 111.8 (dd, J = 22, 4 Hz, C-5′), 105.5 (t, J = 26 Hz, C-3′), 73.3 (CH_2Ph), 68.1 (dd, J = 30, 23 Hz, CHOR) 66.3 (CH_2OBn); ^{19}F {^1H} NMR (376 MHz, $CDCl_3$): δ –64.0 (2F, s, CF_2Br), –99.9 (1F, d, J = 13 Hz, F-2′/F-4′), –102.5 (1F, d, J = 14 Hz, F-2′/F-4′), –113.7 (1F, dd, J = 275, 2 Hz, CF_{2A}), –119.0 (1F, dt, J = 275, 4 Hz, CF_{2B}); HRMS (ESI+) Calcd for $C_{18}H_{13}BrF_6O_3$ [M + Na]$^+$: 492.9844, found 492.9849.

5-[(Benzyloxy)methyl]-2-(2,6-dichloropyridin-3-yl)-3,3,4,4-tetrafluorotetrahydrofuran-2-ol (±)-7d

Following general procedure C, using ester **(±)-6d** (1.0 g, 2.0 mmol), furanol **(±)-7d** was isolated as a colourless oil (0.81 g, 1.9 mmol, 97%) in a 1.2 : 1 mixture of anomers after purification by column chromatography (gradual elution, pet. ether 40–60°/Et_2O, 90 : 10–50 : 50). IR (neat, cm^{-1}): ν 3502 (O–H), 3049, 2981 (C–H); ^1H NMR (400 MHz, $CDCl_3$): δ 8.07 (1.2 H, d, J = 8.2 Hz, H-4′$_{major}$), 8.01 (1H, d, J = 8.2 Hz, H-4′$_{minor}$), 7.42-7.33 (11H, m, H_{Ph}), 7.32 (1H, d, J = 8.2 Hz, H-5′$_{minor}$), 7.32 (1.2H, d, J = 8.2 Hz, H-5′$_{major}$), 5.64 (1.2 H, s, OH_{major}), 4.74 (1H, dddd, J = 16, 9.6, 6.4, 4.8 Hz, H-5$_{minor}$), 4.71 (2.2 H, d, J = 12.3 Hz, CH_APh), 4.64 (2.2 H, d, J = 12.3 Hz, CH_BPh), 4.63 (1.2H, dddd, J = 16, 6.5, 6.3, 3.3 Hz, H-5$_{major}$), 4.09 (1H, s, OH_{minor}), 3.92 (1H, dd, J = 10.9, 4.7 Hz, CH_AOBn_{minor}), 3.87 (1.2H, dd, J = 11.1, 3.6 Hz, CH_AOBn_{major}), 3.85-3.80 (2.2H, m, CH_BOBn); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.6 (C-2′/C-6′$_{minor}$), 151.1 (C-2′/C-6′$_{major}$), 149.2 (C-2′/C-6′$_{major}$), 149.1 (C-2′/C-6′$_{minor}$), 140.7 (C-4′$_{minor}$), 140.5 (C-4′$_{major}$), 137.0 ($C_{Ph_{minor}}$), 135.6 ($C_{Ph_{major}}$), 129.1 (C-3′$_{major}$), 128.8, 128.6 (C_{HPh}), 128.6 (C-3′$_{minor}$), 128.6, 128.1, 127.8 (C_{HPh}), 122.9 (C-5′$_{minor}$), 122.5 (C-5′$_{major}$), 122-116 (m, C-3, C-4), 100.4 (t, J = 27 Hz, C-2$_{major}$), 99.2 (dd, J = 33, 23 Hz, C-2$_{minor}$), 78.9 (dd, J = 30, 24 Hz, C-5$_{major}$), 77.2 (m, overlapping with $CDCl_3$, C-5$_{minor}$), 74.4 (CH_2Ph_{major}), 73.8 (CH_2Ph_{minor}), 66.2 (dd, J = 5, 3 Hz, CH_2OBn_{major}), 65.6 (d, J = 8 Hz, CH_2OBn_{minor}); ^{19}F {^1H} NMR –113.7 (1F, dt, J = 243, 3 Hz, F-3/F-4$_{A_{minor}}$), –117 (1.2F, dt, J = 245, 4 Hz, F-3/F-4$_{A_{major}}$), –120.8 (2.4F, t, J = 4 Hz, F-3/F-4$_{major}$), –121.1 (1F, ddd, J = 240, 5, 3 Hz, F-3/F-4$_{X_{minor}}$), –121.5 (1.2F, dt, J = 245, 4 Hz, F-3/F-4$_{B_{major}}$), –122.2 (1F, d, J = 240 Hz, F-3/F-4$_{Y_{minor}}$), –134.5 (1F, dd, J = 243, 5 Hz, F-3/F-4$_{B_{minor}}$); HRMS (ESI+) Calcd for $C_{17}H_{13}Cl_2F_4NO_3$ [M + Na]$^+$: 448.0101, found 448.0106.

5-[(Benzyloxy)methyl]-2-(2,4-difluorophenyl)-3,3,4,4-tetrafluorotetrahydrofuran-2-ol (±)-7e

Following general procedure C, using ester **(±)-6e** (0.36 g, 0.78 mmol), furanol **(±)-7d** was isolated as a colourless oil (0.18 g, 0.46 mmol, 60%) as 1.1 : 1 mixture of anomers after purification by column chromatography (pet. ether 40–60°/Et_2O, 90 : 10). IR (neat, cm^{-1}): ν 3510 (O–H), 3055, 2978 (C–H); ^1H NMR (400 MHz, $CDCl_3$): δ 7.66 (1.1H, td, J = 8.7, 6.5 Hz, H-6′$_{major}$), 7.61 (1H, td, J = 8.8, 6.4 Hz, H-6′$_{minor}$), 7.41-7.30 (10.5H, m, H_{Ph}), 6.95-6.89 (2.1H, m, H-3′), 6.87 (2.1H, ddd, J = 13, 8.7, 2.4 Hz, H-5′), 5.15 (1.1H, br s, OH_{major}), 4.74 (1.1H, dddd, J = 15, 10.5, 6.7, 4.8 Hz, H-5$_{major}$), 4.68 (2.1H, s, CH_APh), 4.64 (2.1H, s, CH_BPh), 4.64-4.58 (1H, m, H-5$_{minor}$), 3.91-3.85 (2.1H, m, CH_AOBn), 3.83 (1H, dd, J = 11.1, 2.9 Hz, CH_BOBn_{minor}), 3.78 (1.1H, dd, J = 11.1, 7.0 Hz, CH_BOBn_{major}), 3.69 (1H, br s, OH_{minor}); ^{13}C NMR (125 MHz, $CDCl_3$): δ ^{13}C Signals could not be assigned as major or minor product 164.1 (dd, J = 253, 12 Hz, C-2′/C-4′), 164.1 (dd, J = 251, 11 Hz, C-2′/C-4′), 160.8 (dd, J = 256, 12 Hz, C-2′/C-4′), 160.7 (dd, J = 254, 12 Hz, C-2′/C-4′), 137.1 (C_{Ph}), 136.0 (C_{Ph}), 130.0 (d, J = 4 Hz, C-1′), 129.9 (d, J = 4 Hz, C-1′), 128.7, 128.5, 128.4, 128.0, 128.0, 127.8 (C_{HPh}), 120-115 (m, 2 × C-3/C-4), 118.6 (dd, J = 12, 4 Hz, C-6′), 118.3 (dd, J = 12, 4 Hz, C-6′), 118-112 (m, 2 × C-3/C-4), 111.3 (dd, J = 22, 4 Hz, C-5′), 110.9 (dd, J = 21, 4 Hz, C-5′), 104.8 (t, J = 26 Hz, C-3′), 104.7 (t, J = 26 Hz, C-3′), 100.0 (ddd, J = 31, 23, 2 Hz, C-2), 99.1 (ddd, J = 33, 23, 2 Hz, C-2), 78.6 (ddd, J = 30, 23, 3 Hz, C-5), 77.0 (dmd, J = 30, 2 Hz, overlapping with $CDCl_3$, C-5), 74.2 (CH_2Ph), 73.7 (CH_2Ph), 66.1 (t, J = 4 Hz, CH_2OBn), 60.0 (d, J = 8 Hz, CH_2OBn); ^{19}F {^1H} NMR (376 MHz, $CDCl_3$): δ –106.5 (1.1F, d, J = 9 Hz, F-2′/F-4′$_{major}$), –107.2 (1F, m, F-2′/F-4′$_{minor\ or\ major}$), –107.5 (1F, d, J = 9 Hz, F-2′/F-4′$_{minor}$), –108.5 (1F, ddd, J = 23, 10, 6 Hz, F-2′/F-4′$_{minor\ or\ major}$), –111.5 (1.1F, dm, J = 243 Hz, F-3/F-4$_{A_{major}}$), –118.7 (1.1F, ddd, J = 246, 11, 6 Hz, F-3/F-4$_{X_{major}}$), 121.5 (1.1F, dd, J = 246, 6 Hz, F-3/F-4$_{Y_{major}}$), –122.3 (1F, ddm, J = 241, 10 Hz, F-3/F-4$_{A_{minor}}$), –122.9 (1F, dd, J = 238, 4 Hz, F-3/F-4$_{X_{minor}}$), –127.4 (1F, ddt, J = 241, 15, 7 Hz, F-3/F-4$_{B_{minor}}$), –128.4 (1F, ddt, J = 238, 23, 5 Hz, F-3/F-4$_{Y_{minor}}$), –132.7 (1.1F, dd, J = 243, 5 Hz, F-3/F-4$_{B_{major}}$); HRMS (ESI+) Calcd for $C_{18}H_{14}F_6O_3$ [M + Na]$^+$: 415.0739, found 415.0738.

(2*R*,5*S*)-2-[(Benzyloxy)methyl]-3,3,4,4-tetrafluoro-5-phenyltetrahydrofuran (2*R*,5*S*)-8a

Following general procedure D, starting with crude furanol **(2*R*,5*S*)-7a** (1.3 mmol, obtained from ester **(2*R*)-6a** following general procedure C), benzyl protected *C*-nucleoside **(2*R*,5*S*)-8a** was isolated as a colourless oil (0.26 g, 0.76 mmol, 60%) as a 5 : 1 β : α anomeric mixture. **ee** = 90% (determined on Chiracel OD 10 μm column 250 × 4.6 mm (ID), 1 mL min^{-1}, hexane–*i*PrOH 99 : 1; R_T (major diastereomer) = 19.7, 22.7 min); $[\alpha]_D^{19}$ = +16.7 (*c* 1, MeOH); IR (neat, cm^{-1}): ν 3035, 2924 (C–H); ^1H NMR (400 MHz, $CDCl_3$): δ 7.50-7.30 (50H, m, H_{arom}), 5.23 (1H, dd, J = 20, 6.9 Hz, H-5$_{minor}$), 4.99 (4H, ddd, J = 17, 9.6, 1.3 Hz, H-5$_{major}$), 4.70 (4H, d, J = 11.9 Hz, CH_APh_{major}), 4.69 (1H, d, J = 12.0 Hz, CH_APh_{minor}), 4.66 (4H, d, J = 11.9 Hz, CH_BPh_{major}), 4.64 (1H, d, J = 12.0 Hz, CH_BPh_{minor}), 4.63-4.55 (1H, m, H-2$_{minor}$), 4.45-4.36 (4H, m, H-2$_{major}$), 3.93 (4H, dd, J = 10.8, 4.8 Hz, CH_AOBn_{major}), 3.91-3.79 (2H, m, CH_2OBn_{minor}), 3.84 (4H, dd, J = 10.8, 6.8 Hz, CH_BOBn_{major}); ^{13}C NMR (100 MHz, $CDCl_3$): δ ^{13}C signals of the minor diastereomer were not assigned. 137.3 (C_{Ph}), 130.9 (br s, C-1′), 129.5, 128.5, 128.4, 128.0, 127.8, 127.3 (C_{Harom}), 117.9 (dddd, J = 270, 263, 25, 23 Hz, C-3/C-4), 116.9 (ddt, J = 267, 265, 23 Hz, C-3/C-4), 81.1 (dd, J = 29, 24 Hz, C-2/C-5), 78.9 (ddd, J = 28, 23, 2 Hz, C-2/C-5), 73.8 (CH_2Ph), 66.4 (d, J = 7 Hz, CH_2OBn); ^{19}F

{^{1}H} NMR (376 MHz, $CDCl_3$): δ −115.6 (4F, dd, J = 243, 6 Hz, F-3$_{A_{major}}$), −122.0 (4F, ddd, J = 238, 6, 3 Hz, F-4$_{A_{major}}$), −127.5 (1F, dt, J = 238, 4 Hz, F-4$_{A_{minor}}$), −127.6 (2F, dd, J = 7, 4 Hz, F-3$_{minor}$), −128.0 (4F, d, J = 238 Hz, F-4$_{B_{major}}$), −131.0 (1F, dt, J = 238, 7 Hz, F-4$_{B_{minor}}$), −133.9 (4F, dt, J = 243, 3 Hz, F-3$_{B_{major}}$); HRMS (ESI+) Calcd for $C_{18}H_{16}F_4O_2$ [M + H]$^+$: 341.1165, found 341.1170.

(2*R*,5*S*)-2-[(Benzyloxy)methyl]-3,3,4,4-tetrafluoro-5-(1-naphthyl)tetrahydrofuran (2*R*,5*S*)-8b

Following general procedure D, starting with crude furanol **(2*R*,5*S*)-7b** (1.1 mmol, obtained from ester **(2*R*)-6b** following general procedure C), benzyl-protected *C*-nucleoside **(2*R*,5*S*)-8a** was isolated as a colourless oil (0.26 g, 0.66 mmol, 63%) in a 4 : 1 β : α anomeric mixture. **ee** = 89% (determined on Chiracel 10 μm AD column 250 × 4.6 mm (ID), 1 mL min^{-1}, hexane–*i*PrOH 99 : 1, R_T (major diastereomer) = 11.3 and 23.4 min); $[\alpha]_D^{19}$ = +18.6 (*c* 1, MeOH); IR (neat, cm^{-1}): ν 3065, 2910 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (4H, d, J = 8.2 Hz, H-8′$_{major}$), 7.94-7.88 (11H, m, H-4′, H-5′, H-8′$_{minor}$), 7.77-7.71 (5H, m, H-2′), 7.66-7.50 (15H, m, H-7′, H-6′, H-3′), 7.44-7.37 (20H, m, H$_{Ph_{major}}$), 7.37 (5H, m, H$_{Ph_{minor}}$), 6.12 (1H, ddd, J = 18, 6.6, 2.6 Hz, H-5$_{minor}$), 5.85, (4H, dd, J = 14, 10.8 Hz, H-5$_{major}$), 4.76-4.63 (1H, m, H-2$_{minor}$), 4.73 (4H, d, J = 12.1 Hz, CH_APh_{major}), 4.71 (1H, d, J = 12.1 Hz, CH_APh_{minor}), 4.69 (4H, d, J = 12.1 Hz, CH_BPh_{major}), 4.66 (1H, d, J = 12.1 Hz, CH_BPh_{minor}), 4.57-4.45 (4H, m, H-2$_{major}$), 4.01 (4H, dd, J = 10.8, 4.6 Hz, CH_AOBn_{major}), 3.96 (1H, dd, J = 10.8, 5.1 Hz, CH_AOBn_{minor}), 3.95 (4H, dd, J = 10.8, 6.4 Hz, CH_BOBn_{major}), 3.91 (1H, dd, J = 10.8, 6.2 Hz, CH_BOBn_{minor}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.3 (C$_{Ph_{major}}$), 137.3 (C$_{Ph_{minor}}$), 133.5 (C-9′/C-10′$_{minor}$), 133.5 (C-9′/C-10′$_{major}$), 130.8 (C-9′/C-10′$_{minor}$), 130.7 (C-9′/C-10′$_{major}$), 129.8 (C-4′/C-5′$_{major}$), 129.7 (C-4′/C-5′$_{minor}$), 129.0 (C-4′/C-5′$_{major}$), 128.9 (C-4′/C-5′$_{minor}$), 128.5 (C$_{HPh_{major}}$), 128.5 (C$_{HPh_{minor}}$), 128.0 (C-3′/C-6′/C-7′$_{major}$), 128.0 (C-3′/C-6′/C-7′$_{minor}$), 127.8 (C-3′/C-6′/C-7′$_{major}$), 127.8 (C-3′/C-6′/C-7′$_{minor}$), 127.4 (br s, C-1′$_{minor}$), 127.0 (br s, C-1′$_{major}$), 126.8 (C-2′$_{major}$), 126.7 (C-2′$_{minor}$), 125.9 (C$_{HPh_{major}}$), 125.9 (C$_{HPh_{minor}}$), 125.6 (C-3′/C-6′/C-7′$_{minor}$), 125.3 (C-3′/C-6′/C-7′$_{major}$), 122.5 (m, C-8′$_{minor}$), 122.5 (d, J = 3.6 Hz, C-8′$_{major}$), 117.8 (ddt, J = 267, 264, 24 Hz, C-3/C-4$_{major}$), 117.6 (ddt, J = 269, 264, 23 Hz, C-3/C-4$_{major}$), (C-3/C-4 of the minor diastereomer were not assigned), 78.6 (dd, J = 28, 24 Hz, C-2/C-5$_{major}$), 78.5 (dd, J = 27, 23 Hz, C-2/C-5$_{major}$), 77.8 (dd, J = 27, 22 Hz, C-2/C-5$_{minor}$), 77.8 (dd, J = 27, 23 Hz, C-2/C-5$_{minor}$), 73.9 (CH_2Ph_{minor}), 73.8 (CH_2Ph_{major}), 66.7 (d, J = 7 Hz, CH_2OBn_{minor}), 66.2 (d, J = 7 Hz, CH_2OBn_{major}); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$): δ −117.8 (4F, ddd, J = 238, 6, 2 Hz, F-3$_{A_{major}}$), −118.5 (4F, ddd, J = 241, 6, 2 Hz, F-4$_{A_{major}}$), −124.7 (1F, dd, J = 239, 9 Hz, F-3$_{A_{minor}}$) −125.8 (1F, ddd, J = 243, 9, 4 Hz, F-4$_{A_{minor}}$), −127.1 (4F, dm, J = 238 Hz, F-3$_{B_{major}}$), −127.3 (1F, ddd, J = 239, 8, 4 Hz, F-3$_{B_{minor}}$), −127.6 (1F, dd, J = 243, 8 Hz, F-4$_{B_{minor}}$), −133.2 (4F, dm, J = 241 Hz, F-4$_{B_{major}}$); HRMS (ESI+) Calcd for $C_{22}H_{18}F_4O_2$ [M + H]$^+$: 391.1321, found 391.1324.

3-{5-[(Benzyloxy)methyl]-3,3,4,4-tetrafluorotetrahydrofuran-2-yl}-2,6-dimethoxypyridine (±)-8c

Following general procedure D, starting with crude furanol **(±)-7c** (0.41 mmol, obtained from ester **(±)-6c** following general procedure C), benzyl-protected *C*-nucleoside **(±)-8c** was isolated as an amorphous white solid (0.13 g, 0.31 mmol, 77%) as a 2 : 1 β : α anomeric mixture. Careful purification by column chromatography afforded benzyl-protected *C*-nucleoside **(±)-8c** (80 mg, 0.20 mmol, 50%) as a 5 : 1 β : α anomeric mixture. IR (neat, cm^{-1}): ν 3062, 2962 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (1H, d, J = 8.1 Hz, H-4′$_{minor}$), 7.60 (5H, d, J = 8.1 Hz, H-4′$_{major}$), 7.42-7.28 (29H, m, H$_{Ph}$), 6.38 (1H, d, J = 8.1 Hz, H-5′$_{minor}$), 6.38 (5H, d, J = 8.1 Hz, H-5′$_{major}$), 5.53 (1H, ddd, J = 18, 7.1, 3.5 Hz, H-2$_{minor}$), 5.33 (5H, dd, J = 15, 10.4 Hz, H-2$_{major}$), 4.67 (6H, d, J = 12.0 Hz, CH_APh), 4.62 (5H, d, J = 12.0 Hz, CH_BPh_{major}), 4.61 (1H, d, J = 12.0 Hz, CH_BPh_{minor}), 4.60-4.50 (1H, m, H-5$_{minor}$), 4.40-4.27 (5H, m, H-5$_{major}$), 3.97 (15H, s, $OCH_{3_{major}}$), 3.96 (3H, s, $OCH_{3_{minor}}$), 3.94 (18H, s, OCH_3), 3.90 (5H, dd, J = 10.8, 4.6 Hz, CH_AOBn_{major}), 3.85 (1H, dd, J = 10.8, 5.1 Hz, CH_AOBn_{minor}), 3.83-3.75 (3H, m, CH_BOBn); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.7 (C-2′/C-6′$_{minor}$), 163.7 (C-2′/C-6′$_{major}$), 160.3 (C-2′/C-6′$_{minor}$), 160.2 (C-2′/C-6′$_{major}$), 140.3 (C-4′$_{major}$), 140.2 (C-4′$_{minor}$), 137.9 (C$_{Ph_{major}}$), 137.3 (C$_{Ph_{minor}}$), 128.5 (C$_{HPh_{major}}$), 128.5 (C$_{HPh_{minor}}$), 127.9 (C$_{HPh_{major}}$), 127.9 (C$_{HPh_{minor}}$), 127.8 (C$_{HPh_{major}}$), 127.7 (C$_{HPh_{minor}}$), 118.5 (dddd, J = 261, 257, 28, 22 Hz, C-3/C-4$_{minor}$), 117.8 (ddt, J = 268, 265, 23 Hz, C-3/C-4$_{major}$), 117.2 (ddt, J = 267, 264, 22 Hz, C-3/C-4$_{major}$), 117.2 (dddd, J = 264, 260, 26, 21 Hz, C-3/C-4$_{minor}$), 104.9 (C-3′$_{minor}$), 104.7 (C-3′$_{major}$), 101.3 (C-5′$_{major}$), 101.3 (C-5′$_{minor}$), 78.2 (dd, J = 27, 23 Hz, C-5$_{major}$), 77.5 (ddd, J = 27, 22, 2 Hz, C-5$_{minor}$), 75.7 (dd, J = 30, 24 Hz, C-2$_{major}$), 77.5 (ddd, J = 29, 22, 3 Hz, C-2$_{minor}$), 73.8 (CH_2Ph_{minor}), 73.7 (CH_2PH_{major}), 66.5 (d, J = 7 Hz, CH_2OBn_{minor}), 66.2 (d, J = 7 Hz, CH_2OBn_{major}), 53.6, 53.6, 53.5, 53.5 (OCH_3); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$): δ −118.6 (2F, ddd, J = 241, 6, 2 Hz, F-3/F-4$_{A_{major}}$), −119.9 (2F, ddd, J = 237, 6, 2 Hz, F-3/F-4$_{X_{major}}$), −126.2 (1F, ddd, J = 243, 9, 4 Hz, F-3/F-4$_{A_{minor}}$), 126.9 (1F, dd, J = 237, 9 Hz, F-3/F-4$_{X_{minor}}$), −127.9 (1F, dd, J = 243, 9 Hz, F-3/F-4$_{B_{minor}}$), −128.4 (2F, dt, J = 237, 2 Hz, F-3/F-4$_{Y_{major}}$), −129.7 (1F, ddd, J = 237, 9, 4 Hz, F-3/F-4$_{Y_{minor}}$), −133.8 (2F, dt, J = 241, 2 Hz, F-3/F-4$_{B_{major}}$); HRMS (ESI+) Calcd for $C_{12}H_{13}F_4NO_4$ [M + Na]$^+$: 334.0673, found 334.0673.

[(2*R*,5*S*)-3,3,4,4-Tetrafluoro-5-phenyltetrahydrofuran-2-yl]methanol (2*R*,5*S*)-9a

Following general procedure E, using benzyl-protected *C*-nucleoside **(2*R*,5*S*)-8a** (0.24 g, 0.71 mmol), *C*-nucleoside **(2*R*,5*S*)-9a** was isolated as an amorphous white solid (0.16 g, 0.64 mmol, 90%) as a 5 : 1 β : α anomeric mixture. Or:

Following general procedure G, using diastereomerically pure acetyl-protected *C*-nucleoside **(2*R*,5*S*)-11a** (38 mg, 0.13 mmol), *C*-nucleoside **(2*R*,5*S*)-9a** was isolated as an amorphous white solid (25 mg, 0.10 mmol, 77%). $[\alpha]_D^{21}$ = +16.7 (*c* 1, $CHCl_3$); mp = 48 °C; IR (neat, cm^{-1}): ν 3545 (O–H), 3054, 2932 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.39 (5 H, m, H$_{Ph}$), 5.00 (1H, ddd, J = 17, 8.3, 1.5 Hz, H-5), 4.31 (1H, ddd, J = 20, 12.5, 5.6 Hz, H-2), 4.06 (1H, dd, J = 12.5, 5.6 Hz, CH_AOH), 4.02 (1H, dd, J = 12.5, 6.3 Hz, CH_BOH), 1.94 (1H, br s, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 130.6 (br s, C$_{Ph}$), 129.6, 128.5, 127.3 (C$_{HPh}$), 118.1 (dddd, J = 270, 262, 26, 23 Hz, C-3/C-4), 116.8 (tt, J = 266, 23 Hz, C-3/C-4), 80.7 (dd, J = 28, 24 Hz, C-5), 79.9 (ddd, J = 28, 23, 3 Hz, C-2), 59.7 (dd, J = 7, 2 Hz, CH_2OH); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$): δ −113.6 (1F, dd, J = 244, 7 Hz, F-3$_A$), −124.1 (1F, ddd, J = 238, 6, 4 Hz, F-4$_A$), −128.7 (1F, dd, J = 238, 4 Hz, F-4$_B$),

–134.6 (1F, dt, J = 244, 3 Hz, F-3$_B$); HRMS (ESI+) Calcd for $C_{11}H_{10}F_4O_2$ [M + Na]$^+$: 273.0533, found 273.0535.

[(2*R*,5*R*)-3,3,4,4-Tetrafluoro-5-phenyltetrahydrofuran-2-yl]methanol (2*R*,5*R*)-9a

Following general procedure G, using diastereomerically pure acetyl-protected *C*-nucleoside **(2*R*,5*R*)-11a** (6 mg, 0.02 mmol), *C*-nucleoside **(2*R*,5*R*)-9a** was isolated as a colourless oil (5 mg, 0.02 mmol, 96%). $[\alpha]_D^{21}$ = –17.0 (*c* 0.1, $CHCl_3$); mp = 53 °C; IR (neat, cm^{-1}): ν 3550 (O–H), 3055, 2988 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.39 (5 H, m, H$_{Ph}$), 5.22 (1H, ddd, J = 20, 6.9, 3.0 Hz, H-5), 4.53 (1H, dddd, J = 22, 11.3, 5.5, 3.2 Hz, H-2), 4.02 (2H, d, J = 5.5 Hz, CH_2OH), 1.88 (1H, br s, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.1 (d, J = 2 Hz, C$_{Ph}$), 129.5, 128.5, 127.1 (C$_{HPh}$), 122-116 (m, C-3, C-4), 79.4 (ddd, J = 27, 23, 3 Hz, C-5), 78.4 (ddd, J = 27, 22, 3 Hz, C-2), 59.5 (dd, J = 8, 2 Hz, CH_2OH); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$): δ –126.7 (1F, dd, J = 244, 9, 5 Hz, F-3/F-4$_A$), –127.8 (1F, dd, J = 244, 9 Hz, F-3/F-4$_B$), –127.9 (1F, dd, J = 239, 9 Hz, F-3/F-4$_X$), –130.7 (1F, ddd, J = 239, 9, 5 Hz, F-3/F-4$_Y$); HRMS (ESI+) Calcd for $C_{11}H_{10}F_4O_2$ [M + Na]$^+$: 273.0509, found 273.0524.

[(2*R*,5*S*)-3,3,4,4-Tetrafluoro-5-(1-naphthyl)tetrahydrofuran-2-yl]methanol (2*R*,5*S*)-9b

Following general procedure E, using benzyl-protected *C*-nucleoside **(2*R*,5*S*)-8b** (0.24 g, 0.61 mmol), *C*-nucleoside **(2*R*,5*S*)-9b** was isolated as an amorphous white solid (0.18 mg, 0.60 mmol, 98%) as a 4 : 1 β : α anomeric mixture. Or:

Following general procedure G, using diastereomerically pure acetyl-protected *C*-nucleoside **(2*R*,5*S*)-11b** (0.10 g, 0.29 mmol), *C*-nucleoside **(2*R*,5*S*)-9b** was isolated as an amorphous white solid (85 mg, 0.28 mmol, 97%). $[\alpha]_D^{19}$ = +26.1 (*c* 1, $CHCl_3$); mp = 115 °C; IR (neat, cm^{-1}): ν 3540 (O–H), 3054, 2933 (C–H); UV (MeOH, nm): λ_{max} 221, 270, 280, 290; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99-7.91 (3H, m, H-4′, H-5′, H-8′), 7.76 (1H, d, J = 7.2 Hz, H-2′), 7.62-7.52 (3H, m, H-3′, H-6′, H-7′), 5.86 (1H, dd, J = 15, 9.0 Hz, H-5), 4.50-4.37 (1H, m, H-2), 4.20-4.10 (2H, m, CH_2OH), 1.97 (1H, t, J = 6.5 Hz, OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 133.5, 130.7 (C-9′, C-10′), 129.9, 129.0 (C-4′, C-5′), 126.9 (C-3′/C-6′/C-7′), 126.7 (br s, C-1′), 126.0 (C-2′), 125.6 (C-3′/C-6′/C-7′), 125.1 (C-3′/C-6′/C-7′), 122.4 (d, J = 3 Hz, C-8′), 118.0 (ddt, J = 268, 264, 24 Hz, C-3/C-4), 117.6 (ddt, J = 269, 265, 23 Hz, C-3/C-4), 79.6 (dd, J = 27, 23 Hz, C-5), 78.1 (dd, J = 28, 25 Hz, C-2), 59.6 (d, J = 7 Hz, CH_2OH); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$): δ –116.4 (ddd, J = 242, 5, 2 Hz, F-3/F-4$_A$), –119.9 (ddd, J = 239, 6, 3 Hz, F-3/F-4$_X$), –127.4 (ddd, J = 239, 3, 2 Hz, F-3/F-4$_Y$), –133.7 (dt, J = 242, 3 Hz, F-3/F-4$_B$); HRMS (ESI+) Calcd for $C_{15}H_{12}F_4O_2$ [M – Na]$^+$: 323.0671, found 323.0685

[(2*R*,5*R*)-3,3,4,4-Tetrafluoro-5-(1-naphthyl)tetrahydrofuran-2-yl]methanol (2*R*,5*R*)-9b

Following general procedure G, using diastereomerically pure acetyl-protected *C*-nucleoside **(2*R*,5*R*)-11b** (22 mg, 0.06 mmol), *C*-nucleoside **(2*R*,5*R*)-9b** was isolated as an amorphous white solid (16 mg, 0.05 mmol, 83%). $[\alpha]_D^{19}$ = –23.4 (*c* 0.5, $CHCl_3$); mp = 119 °C; IR (neat, cm^{-1}): ν 3543 (O–H), 3054, 2987 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96-7.90 (3H, m, H-4′, H-5′, H-8′), 7.76 (1H, d, J = 7.1 Hz, H-2′), 7.61-7.52 (3H, m, H-3′, H-6′, H-7′), 6.12 (1H, ddd, J = 17, 6.8, 2.7 Hz, H-5), 4.76-4.56 (1H, m, H-2), 4.16-4.05 (2H, m, CH_2OH), 1.97 (1H, br s, OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 133.6, 130.8 (C-9′/C-10′), 129.9, 129.0 (C-4′/C-5′), 127.1 (br s, C-1′), 126.8 (C-3′/C-6′/C-7′), 126.0 (C-2′), 125.3 (C-3′/C-6′/C-7′), 125.2 (C-3′/C-6′/C-7′), 122.4 (d, J = 4 Hz, C-8′), 118.7 (dddd, J = 269, 261, 27, 27 Hz, C-3/C-4), 117.6 (dddd, J = 270, 266, 27, 24 Hz, C-3/C-4), 78.8 (ddd, J = 26, 22, 2 Hz, C-5), 76.9 (ddd, J = 27, 21, 2 Hz, C-2), 59.6 (d, J = 8 Hz, CH_2OH); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$): δ –125.1 (dd, J = 239, 10 Hz, F-4$_A$), –125.5 (ddd, J = 244, 10, 4 Hz, F-3$_A$), –127.3 (ddd, J = 239, 7, 4 Hz, F-4$_B$), –128.1 (dd, J = 244, 8 Hz, F-3$_B$); HRMS (ESI+) Calcd for $C_{15}H_{12}F_4O_2$ [M – Na]$^+$: 323.0671, found 323.0693

[5-(2,6-Dimethoxypyridin-3-yl)-3,3,4,4-tetrafluorotetrahydrofuran-2-yl]methanol (±)-9c

BBr_3 (0.18 ml of a 1 M solution in CH_2Cl_2, 0.18 mmol) was added dropwise over 45 min to a solution of benzyl-protected *C*-nucleoside **(±)-8c** (60 mg, 0.15 mmol, 2 : 1 β : α anomeric ratio), in CH_2Cl_2 (12 mL) at –78 °C. The solution was left to warm up to room temperature over 16 h, then MeOH was added and the solvents were removed *in vacuo*. Purification by column chromatography afforded *C*-nucleoside **(±)-9c** (32 mg, 0.10 mmol, 69%) as an amorphous white solid as a 1.4 : 1 β : α anomeric mixture. IR (neat, cm^{-1}): ν 3570 (OH), 3062, 2962 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (2.4H, m, H-4′), 6.38 (1H, d, J = 8.2 Hz, H-5′$_{minor}$), 6.37 (1.4H, d, J = 8.2 Hz, H-5′$_{major}$), 5.52 (1H, ddd, J = 18, 6.8, 3.1 Hz, H-5$_{minor}$), 5.33 (1.4H, dd, J = 16, 8.9 Hz, H-5$_{major}$), 4.53-4.40 (1H, m, H-2$_{minor}$), 4.30-4.19 (1.4H, m, H-2$_{major}$), 4.05-3.98 (3.8H, m, CH_2OH), 3.97 (4.2H, s, OCH$_{3_{major}}$), 3.96 (3H, s, OCH$_{3_{minor}}$), 3.94 (7.2 H, s, OCH$_3$), 2.18 (1.4H, br s, OH$_{major}$), 1.81 (1H, br s, OH$_{minor}$); ^{13}C NMR (100 MHz, $CDCl_3$) ^{13}C Signals could not be assigned as major or minor product, δ 163.8, 163.8, 160.4, 160.3 (C-2′, C-6′), 140.4, 140.1 (C-4′), 122-116 (m, C-3, C-4), 104.6, 104.3 (C-3′), 101.4, 101.4 (C-5′), 79.3 (ddd, J = 27, 23, 1 Hz, C-2), 78.6 (ddd, J = 27, 22, 3 Hz, C-2), 75.3 (dd, J = 30, 23 Hz, C-5), 74.1 (ddd, J = 29, 22, 3 Hz, C-5), 59.6 (d, J = 7 Hz, CH_2OH), 59.4 (d, J = 9 Hz, CH_2OH), 53.6, 53.6, 53.6, 53.5 (CH_3); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$): δ –116.2 (1.4F, dd, J = 243, 6 Hz, F-3$_{A_{major}}$), –122.3 (1.4F, ddd, J = 238, 5, 3 Hz, F-4$_{A_{major}}$), –125.4 (1F, ddd, J = 244, 10, 4 Hz, F-3$_{A_{minor}}$), –127.3 (1F, dd, J = 238, 10 Hz, F-4$_{A_{minor}}$), –128.0 (1F, dd, J = 244, 8 Hz, F-3$_{B_{minor}}$), –128.7 (1.4F, dd, J = 238, 3 Hz, F-4$_{B_{major}}$), –129.1 (1F, ddd, J = 238, 8. 4 Hz, F-4$_{B_{minor}}$), –134.3 (1.4F, dt, J = 243, 3 Hz, F-3$_{B_{major}}$); HRMS (ESI+) Calcd for $C_{12}H_{13}F_4NO_4$ [M + Na]$^+$: 334.0673, found 334.0673;

2-(2,6-Dichloropyridin-3-yl)-3,3,4,4-tetrafluorotetrahydro-2*H*-pyran-2,5-diol (±)-10d

Following general procedure E, using furanol **(±)-8d** (25 mg, 0.06 mmol), pyrandiol **(±)-10d** was isolated as an amorphous white solid (16 mg, 0.05 mmol, 80%) as a 4 : 1 β : α anomeric mixture. IR (neat, cm^{-1}): ν 3423 (O–H), 2969 (C–H), 1644 (C=C); ^{1}H NMR (400 MHz, MeOD): δ 8.33 (1H, d, J = 8.4 Hz, H-4′$_{minor}$), 8.21 (4H, d, J = 8.3 Hz, H-4′$_{major}$), 7.50 (4H, d, J = 8.3 Hz, H-5′$_{major}$), 7.49 (1H, d, J = 8.4 Hz, H-5′$_{minor}$), 4.56 (1H, ddd, J = 13, 3.5, 1.7 Hz, H-6$_{A_{minor}}$), 4.22-4.08 (9H, m, H-4, H-6$_{A_{major}}$), 3.99-3.90 (5H, m, H-6$_B$); ^{13}C NMR (100 MHz, CD_3OD): δ 151.8 (C2′/C-6′$_{major}$), 151.6 (C2′/C-6′$_{minor}$), 150.6 (C2′/C-6′$_{major}$), 150.5 (C2′/C-6′$_{minor}$),

145.2 (C-4′$_{minor}$), 144.8 (C-4′$_{minor}$), 131.9 (C-3′$_{minor}$), 131.7 (C-3′$_{major}$), 123.7 (C-5′$_{major}$), 123.6 (C-5′$_{minor}$), 120-113 (m, C-3$_{major}$, C-4$_{major}$), (C-2, C-3 and C-4 of the minor diastereomer were not assigned), 97.4 (dd, J = 30, 22 Hz, C-2$_{major}$), 70.1 (dd, J = 32, 20 Hz, C-5$_{minor}$), 67.7 (t, J = 19 Hz, C-5$_{major}$), 63.1 (d, J = 6 Hz, C-6$_{minor}$), 61.2 (d, J = 7 Hz, C-6$_{major}$); ^{19}F {^{1}H} NMR (376 MHz, CD_3OD): δ −117.4 (1F, ddd, J = 267, 15, 10 Hz, F-3/F-4$_{A_{minor}}$), −117.5 (1F, ddd, J = 264, 15, 10 Hz, F-3/F-4$_{X_{minor}}$), −119.8 (4F, ddd, J = 264, 17, 11 Hz, F-3/F-4$_{A_{major}}$), −129.6 (4F, ddd, J = 251, 17, 10 Hz, F-3/F-4$_{X_{major}}$), −129.7 (1F, ddd, J = 267, 18, 12 Hz, F-3/F-4$_{B_{minor}}$), −132.3 (4F, ddd, J = 251, 15, 11 Hz, F-3/F-4$_{Y_{major}}$), −132.7 (1F, ddd, J = 264, 15, 12 Hz, F-3/F-4$_{Y_{minor}}$), −134.1 (4F, ddd, J = 264, 15, 10 Hz, F-3/F-4$_{B_{major}}$); HRMS (ESI−) Calcd for $C_{10}H_7Cl_2F_4NO_3$ [M − H]$^-$: 333.9666, found 333.9666.

2-(2,4-Difluorophenyl)-3,3,4,4-tetrafluorotetrahydro-2*H*-pyran-2,5-diol (±)-10e

Following general procedure E, using furanol **(±)-8e** (33 mg, 0.08 mmol), pyrandiol **(±)-10e** was isolated as an amorphous white solid (19 mg, 0.06 mmol 74%) as a 5 : 1 β : α anomeric mixture. IR (cm^{-1}): 3424 (O–H), 2960 (C–H); ^{1}H NMR (400 MHz, CD_3OD): δ 7.83 (1H, dt, J = 8.9, 6.9 Hz, H-6′$_{minor}$), 7.76 (5H, dt, J = 8.8, 6.7 Hz, H-6′$_{major}$), 7.03-6.94 (12H, m, H-3′, H-5′), 4.56 (1H, ddd, J = 13, 3.6, 2.0 Hz, H-6$_{A_{minor}}$), 4.22-4.06 (11H, m, H-5, H-6$_{A_{major}}$), 3.94 (1H, dd, J = 13, 6.1 Hz, H-6$_{B_{minor}}$), 3.89, (5H, dd, J = 10.2, 5.2 Hz, H-6$_{B_{major}}$); ^{13}C NMR (100 MHz, CD_3OD): δ 165.3 (dd, J = 249, 12 Hz, C-2′/C-4′$_{major}$), 165.2 (dd, J = 250, 11 Hz, C-2′/C-4′$_{minor}$), 162.7 (dd, J = 257, 12 Hz, C-2′/C-4′$_{major}$), 162.7 (dd, J = 257, 12 Hz, C-2′/C-4′$_{minor}$), 133.6 (dd, J = 10, 4 Hz, C-1′$_{minor}$), 133.3 (dd, J = 10, 4 Hz, C-1′$_{major}$), 121.7 (dm, J = 13 Hz, C-6′$_{minor}$), 121.5 (dm, J = 11 Hz, C-6′$_{major}$), 116.3 (dddd, J = 260, 254, 31, 20 Hz, C-3/C-4), 113.2 (dddd, J = 254, 245, 28, 21 Hz, C-3/C-4), (C-3 and C-4 of the minor diastereomer were not assigned), 111.5 (dd, J = 21, 4 Hz, C-5′$_{major}$), 111.4 (dd, J = 21, 4 Hz, C-5′$_{minor}$), 105.6 (dd, J = 28, 26 Hz, C-3′$_{major}$), 105.4 (dd, J = 27, 26 Hz, C-3′$_{minor}$), 97.8-97.2 (m, C-2$_{major}$), (C-2 of the minor diastereomer were not assigned), 70.3 (dd, J = 32, 20 Hz, C-5$_{minor}$), 67.8 (t, J = 20 Hz, C-5$_{major}$), 62.8 (d, J = 6 Hz, C-6$_{minor}$), 61.0 (d, J = 7 Hz, C-6$_{minor}$); ^{19}F {^{1}H} NMR (376 MHz, CD_3OD): δ −106.1 (5F, ddd, J = 22, 11, 10 Hz, F-2′/F-4′$_{major}$), −106.6 (1F, ddd, J = 28, 9, 7 Hz, F-2′/F-4′$_{minor}$), −110.8 (5F, d, J = 10 Hz, F-2′/F-4′$_{major}$), −111.0 (1F, d, J = 9 Hz, F-2′/F-4′$_{minor}$), −117.4 (1F, ddd, J = 266, 14, 10 Hz, F-3/F-4$_{A_{minor}}$), −118.2 (1F, dddd, J = 264, 18, 9, 7 Hz, F-3/F-4$_{X_{minor}}$), −120.7 (5F, ddt, J = 264, 17, 11 Hz, F-3/F-4$_{A_{major}}$), −129.6 (5F, J = 251, 18, 11 Hz, F-3/F-4$_{X_{major}}$), −129.6 (1F, ddd, J = 266, 18, 11 Hz, F-3/F-4$_{B_{minor}}$), −132.4 (5F, ddd, J = 251, 15, 10 Hz, F-3/F-4$_{Y_{major}}$), −135.3 (1F, dddd, J = 264, 27, 14, 11 Hz, F-3/F-4$_{Y_{minor}}$), −136.2 (5F, dddd, J = 264, 23, 15, 10 Hz, F-3/F-4$_{B_{major}}$); HRMS (ESI−) Calcd for $C_{11}H_8F_6O_3$ [M − H]$^-$: 301.0305, found 301.0304.

[(2*R*,5*S*)-3,3,4,4-Tetrafluoro-5-phenyltetrahydrofuran-2-yl]methyl acetate (2*R*,5*S*)-11a and [(2*R*,5*R*)-3,3,4,4-tetrafluoro-5-phenyltetrahydrofuran-2-yl]methyl acetate (2*R*,5*R*)-11a

Following general procedure F, using *C*-nucleoside **(2*R*,5*S*)-9a** (0.10 g, 0.40 mmol), acetyl-protected *C*-nucleoside was isolated as an amorphous white solid (0.10 g, 0.36 mmol, 89%) as a 5 : 1 β : α anomeric mixture. Careful column chromatography afforded **(2*R*,5*S*)-11a** (48 mg, 0.16 mmol, 41%) and **(2*R*,5*R*)-11a** (6 mg, 0.02 mmol, 5%) as amorphous white solids. **(2*R*,5*S*)-11a**: $[\alpha]_D^{19}$ = −2.5 (*c* 1.0, $CHCl_3$); mp = 91 °C (decomp.); IR (neat, cm^{-1}): ν 3042, 2928 (C–H), 1752 (C=O);^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.37 (5H, m, H-2′-H-6′), 5.01 (1H, ddd, J = 17, 9.0, 1.8 Hz, H-5), 4.57-4.49 (1H, m, H-2), 4.47-4.36 (2H, m, CH_2OAc), 2.14 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3 (CO_2), 130.5 (C-1′), 129.7, 128.5, 127.3 (C-2′-C-6′), 117.8 (dddd, J = 271, 263, 26, 23 Hz, C-3/C-4), 116.6 (tt, J = 265, 23 Hz, C-3/C-4), 80.9 (dd, J = 29, 24 Hz, C-5), 77.4 (ddd, J = 29, 23, 2 Hz, C-2), 60.2 (dd, J = 7, 2 Hz, CH_2OAc), 20.6 (CH_3); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$): δ −114.7 (dd, J = 244, 7 Hz, F-3$_A$), −123.4 (ddd, J = 239, 7, 4 Hz, F-4$_A$), −128.4 (dd, J = 239, 4 Hz, F-4$_B$), −133.0 (dt, J = 244, 4 Hz, F-3$_B$); HRMS (ESI+) Calcd for $C_{13}H_{12}F_4O_3$ [M + Na]$^+$: 315.0615, found 315.0629.

(2*R*,5*R*)-11a. $[\alpha]_D^{19}$ = −6.6 (*c* 0.5, $CHCl_3$); mp = 94 °C (decomp.); IR (neat, cm^{-1}): ν 3053, 2927 (C–H), 1751 (C=O);^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.38 (5H, m, H-2′-H-6′), 5.22 (1H, dd, J = 20, 7.5 Hz, H-5), 4.71-4.59 (1H, m, H-2), 4.48 (1H, dd, J = 12.1, 6.9 Hz, CH_AOAc), 4.40 (1H, dd, J = 12.1, 5.5 Hz, CH_BOAc), 2.14 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3 (CO_2), 130.5 (d, J = 2 Hz, C-1′), 129.6, 128.6, 127.1 (C-2′-C-6′), 118.3 (tdd, J = 266, 27, 22 Hz, C-3/C-4), 116.6 (ddt, J = 268, 261, 24 Hz, C-3/C-4), 79.5 (dd, J = 27, 23 Hz, C-5), 76.2 (td, J = 25, 3 Hz, C-2), 60.0 (t, J = 5 Hz, CH_2OAc), 20.6 (CH_3); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$): δ −127.4 (2F, br s, F-3), −127.7 (ddd, J = 239, 8, 4 Hz, F-4$_A$), −130.7 (dm, J = 239 Hz, F-4$_B$); HRMS (ESI+) Calcd for $C_{13}H_{12}F_4O_3$ [M + Na]$^+$: 315.0615, found 315.0634

[(2*R*,5*S*)-3,3,4,4-Tetrafluoro-5-(1-naphthyl)tetrahydrofuran-2-yl]methyl acetate (2*R*,5*S*)-11b and [(2*R*,5*R*)-3,3,4,4-tetrafluoro-5-(1-naphthyl)tetrahydrofuran-2-yl]methyl acetate (2*R*,5*R*)-11b

Following general procedure F using *C*-nucleoside **(2*R*,5*S*)-9b** (0.18 g, 0.60 mmol), afforded acetyl-protected *C*-nucleoside **(2*R*,5*S*)-11b** as an amorphous white solid (0.20 g, 0.36 mmol, 97%) as a 4 : 1 β : α anomeric mixture. Careful column chromatography afforded **(2*R*,5*S*)-11b** (0.18 g, 0.53 mmol, 88%) and **(2*R*,5*R*)-11b** (6 mg, 0.02 mmol, 5%) as amorphous white solids. **(2*R*,5*S*)-11b**: $[\alpha]_D^{19}$ = +21.5 (*c* 1, $CHCl_3$); mp = 78 °C; IR (neat, cm^{-1}): ν 3054, 2933 (C–H), 1751 (C=O);^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98-7.91 (3H, m, H-4′, H-5′, H-8′), 7.75 (1H, d, J = 7.3 Hz, H-2′), 7.62-7.52 (3H, m, H-3′, H-6′, H-7′), 5.88 (1H, dd, J = 15, 9.7 Hz, H-5), 4.65-4.48 (3H, m, H-2, CH_2OAc), 2.17 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4 (CO_2), 133.5, 130.7 (C-9′, C-10′), 129.9, 129.0 (C-4′, C-5′), 126.9 (C-3′/C-6′/C-7′), 126.6 (br s, C-1′), 125.9 (C-2′), 125.6, 125.2 (C-3′/C-6′/C-7′), 122.4 (d, J = 3 Hz, C-8′), 117.7 (ddt, J = 269, 265, 24 Hz, C-3/C-4), 117.4 (ddt, J = 269, 264, 23 Hz, C-3/C-4), 78.4 (dd, J = 29, 26 Hz, C-5), 77.0 (m, C-2, overlap with $CHCl_3$ signal), 60.1 (d, J = 7 Hz, CH_2OAc), 20.6 (CH_3); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$): δ −117.6 (ddd, J = 242, 6, 2 Hz, F-3/F-4$_A$), −118.9 (ddd, J = 239, 6, 2 Hz, F-3/F-4$_X$), −127.3 (ddd, J = 239, 4, 2 Hz, F-3/F-4$_Y$), −133.0 (ddd, J = 242, 5, 2 Hz, F-3/F-4$_B$); HRMS (ESI+) Calcd for $C_{17}H_{14}F_4O_3$ [M + Na]$^+$: 365.0771, found 365.0767

(2*R*,5*R*)-11b. $[\alpha]_D^{19}$ = −15.8 (*c* 1, $CHCl_3$); mp = 84 °C; IR (neat, cm^{-1}): ν 3054, 2933 (C–H), 1751 (C=O);^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95-7.90 (3H, m, H-4′, H-5′, H-8′), 7.74

(1H, d, J = 7.3 Hz, H-2′), 7.62-7.52 (3H, m, H-3′, H-6′, H-7′), 6.11 (1H, ddd, J = 17, 3.2, 2.8 Hz, H-5), 4.77 (1H, ddddd, J = 15, 9.7, 6.8, 5.4, 3.1 Hz, H-2) 4.59 (1H, dd, J = 12.2, 6.8 Hz, CH_AOAc), 4.48 (1H, dd, J = 12.2, 5.4 Hz, CH_BOAc), 2.17 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4 (CO_2), 133.5, 130.8 (C-9′, C-10′), 129.9, 129.0 (C-4′, C-5′), 127.0 (br s, C-1′), 126.9 (C-3′/C-6′/C-7′), 126.0 (C-2′), 125.2, 125.2 (C-3′/C-6′/C-7′), 122.4 (d, J = 3 Hz, C-8′), 118.3 (dddd, J = 269, 261, 26, 22 Hz, C-3/C-4), 117.4 (dddd, J = 268, 263, 25, 21 Hz, C-3/C-4), 77.0 (ddd, J = 31, 24, 2 Hz, C-2, overlap with $CHCl_3$ signal), 76.2 (ddd, J = 28, 22, 3 Hz, C-5), 60.0 (d, J = 8 Hz, CH_2OAc), 20.7 (CH_3); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$): δ −125.0 (dd, J = 239, 10 Hz, F-4_A), −125.9 (ddd, J = 243, 10, 4 Hz, F-3_A), −126.9 (ddd, J = 239, 8, 4 Hz, F-4_B), −128.0 (dd, J = 243, 8 Hz, F-3_B); HRMS (ESI+) Calcd for $C_{17}H_{14}F_4O_3$ [M + Na]$^+$: 365.0771, found 365.0775

(2*R*,5*S*)-[3,3,4,4-Tetrafluoro-5-(1-naphthyl)tetrahydrofuran-2-yl]methyl triphosphate triethylamine salt (2*R*,5*S*)-12b

Prior to the reaction, all solids used were dried over P_2O_5 overnight, and all solvents and amines were dried over molecular sieves overnight. Proton sponge® (1 mg, 5 µmol, 0.08 eq.) and phosphorous oxychloride (freshly distilled, 6.7 µl, 0.07 mmol, 1.1 eq.) were added to a solution of *C*-nucleoside **(2*R*,5*S*)-9b** (20 mg, 0.07 mmol, 1 eq.) in THF (2 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C and then for 20 h at room temperature. A solution of tributylammonium pyrophosphate (150 mg, 0.27 mmol, 4 eq.) and tributylamine (150 mg, 0.53 mmol, 8 eq.) was added and the reaction was stirred for further 16 h. TEAB (10 mL of a 0.1 M aqueous solution) was added and the reaction was stirred for another 24 h. The reaction mixture was then washed with EtOAc (10 mL) and the aqueous layer was concentrated *in vacuo* at room temperature. The crude oil was redissolved in TEAB (3 mL of a 0.1 M aqueous solution) and purified by reverse phase HPLC (TEAB (0.1 M, aq.)/MeCN (100%): t = 0 min, 1% MeCN, t = 5 min, 1% MeCN, t = 15 min, 5% MeCN, t = 45 min, 100% MeCN; R_T = 30 min) to afford *C*-nucleotide **(2*R*, 5*S*)-13b** (33 mg, 35 µmol, 60%) as a white foam after freeze drying. UV (H_2O, nm): λ_{max} 221, 270, 281, 291; ^{1}H NMR (400 MHz, D_2O): δ 8.22 (1H, dd, J = 8.0, 2.5 Hz, H-8′), 7.93 (2H, br d, J = 8.4 Hz, H-4′, H-5′), 7.77 (1H, dd, J = 6.9, 2.0 Hz, H-2′), 7.60-7.49 (3H, m, H-3′, H-6′, H-7′), 6.11 (1H, dd, J = 15, 9.8 Hz, H-5), 4.79-4.70 (1H, m, H-2 overlap with D_2O signal), 4.50-4.40 (1H, m, CH_AOP), 4.39-4.30 (1H, m, CH_BOP), 3.05 (24H, d, J = 7.2 Hz, NCH_2CH_3), 1.14 (39H, t, J = 7.2 Hz, NCH_2CH_3); ^{13}C NMR (125 MHz, D_2O): δ 133.3 (C-9′/C-10′), 130.3 (d, J = 2 Hz, C-9′/C-10′), 128.9, 127.2 (C-4′, C-5′), 126.8 (C-3′/C-6′/C-7′), 126.4 (d, J = 6 Hz, C-1′), 126.1 (C-3′/C-6′/C-7′), 126.1 (d, J = 7 Hz, C-2′), 125.6 (d, J = 4 Hz, C-3′/C-6′/C-7′), 122.7 (br s, C-8′), 120-115 (m, C-3, C-4), 78.8-77.4 (m, C-2, C-5), 62.1 (br s, CH_2OP), 46.3 (NCH_2), 8.4 (NCH_2CH_3); ^{19}F {^{1}H} NMR (376 MHz, D_2O): δ −118.0 (dd, J = 242, 30 Hz, F-3/F-4_A), −119.0 (dd, J = 237, 32 Hz, F-3/F-4_X), −126.8 (dd, J = 237, 20 Hz, F-3/F-4_Y), −132.8 (dd, J = 242, 24 Hz, F-3/F-4_B); ^{31}P {^{1}H} NMR (200 MHz, D_2O): δ −9.4 (d, J = 20 Hz, γ-P), −10.2–−10.7 (m, α-P), −22.0 (br s, β-P); MS (ESI) 538.93 [M − H]$^-$ (100%), 549.00 [M − H_2PO_3]$^-$ (75%), 379.04 [M − $H_3P_2O_6$]$^-$ (65%); HRMS (ESI−) Calcd for $C_{15}H_{14}F_4O_{11}P_3$ [M − H]$^-$: 538.9691, found 538.9693.

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12 Table 3 (entries 1–3) shows the structure of the major diastereomer only; entry 1: **8a** d.r.: 5 : 1, **9a** d.r.: 5 : 1; entry 2: **8b** d.r.: 4 : 1, **9b** d.r.: 4 : 1; entry 3: **8c** d.r.: 2 : 1, **9c** d.r.: 1.4 : 1. For entries 4 and 5, **10d** and **10e** were formed as a mixture of diastereomers (d.r. = 4 : 1 for **10d** and d.r. = 5 : 1 for **10e**).
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