Enantioselective synthesis of tetrafluorinated ribose and fructose†

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A perfluoroalkylidene lithium mediated cyclisation approach for the enantioselective synthesis of a tetrafluorinated aldose (ribose) and of a tetrafluorinated ketose (fructose), both in the furanose and in the pyranose form, is described.

Introduction

Carbohydrates are central to a multitude of critical biological functions.[1] Glycosylation of proteins impacts on both stability and folding, and can have a critical contribution to the activity of the conjugate.[2] In addition, glycosylation of natural products can significantly influence their biological activity.[3] Hence, the investigation of carbohydrate-based therapeutics is of great interest.[4] It is remarkable that typical experimental values for associated dissociation constants of monosaccharides for protein receptors are usually only in the millimolar to micromolar range. The energetics of protein–carbohydrate interactions are complex, not least because of the highly participatory nature of the aqueous solvent.[5] In general, polar interactions are thought to be largely responsible for the binding specificity and desolvation of non-polar surface areas (the "hydrophobic effect") for binding affinity.[6]

A strategy to enhance binding affinities consists of exploiting this hydrophobic effect. By increasing the hydrophobic surface of a (non-sugar derived) carbonic anhydrase inhibitor, Whitesides *et al.* observed increased binding constants.[7] It was noted that compared to a hydrocarbon chain, a perfluorocarbon chain of identical length exhibited a larger effect, which was attributed to the larger hydrophobic surface to be desolvated. In pioneering work, DiMagno *et al.* introduced the concept of "polar hydrophobicity".[8] By extensive replacement of carbohydrate CHOH groups by CF_2 groups, binding was expected to be enhanced due to the hydrophobic effect. Furthermore, favourable electrostatic interactions involving the polarised C–F bond with cationic or dipolar sites in the receptor would be possible,[9] with such interactions being negligible in an aqueous medium. It was shown that the hexafluorinated pyranose **1** (Fig. 1) crosses the erythrocyte membrane at a rate approximately 10 times higher than glucose itself, and it was demonstrated that this rate increase was due to enhanced affinity to the transporter protein (and not because of simple membrane diffusion originated from increased lipophilicity).

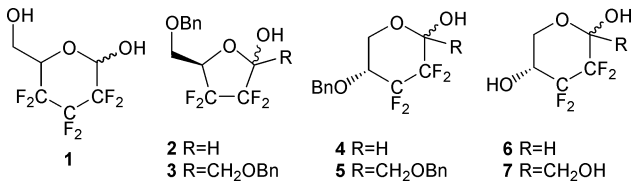

Fig. 1 Perfluoroalkylidene containing monosaccharides.

The modulation of carbohydrate ligand affinities by polyfluorination is very interesting and of great potential impact in glycobiology and drug-development. Hence, further studies in this area require reliable and short synthetic approaches to a wide range of polyfluorinated carbohydrates and carbohydrate precursors.

In this respect, we have developed an efficient perfluoroalkylidene lithium mediated cyclisation process to obtain tetrafluorinated carbohydrates. The synthesis of the ribose derivative **2** (Fig. 1), which upon deprotection leads to **6**, starting from the commercially available building block **8** (see below) has been communicated,[10a] as has the synthesis of tetrafluorinated glucose and galactose, which commenced from a different building block (not shown).[10b] We now report in full the synthesis of the other prototypical cyclisation precursors that can be obtained from building block **8**. In a significant expansion in scope for the cyclisation process, it was shown that the synthesis of ketosugars, in both the furanose and pyranose forms, is also possible in high yield. Overall, starting from a single building block **8**, a short, high-yielding access to a range of tetrafluorinated carbohydrates **2–7** is possible. In addition, a full account is provided of the enantioselective dihydroxylation of **8**, and of two complementary selective protection methods of the resulting diol.

Results and discussion

Synthetic plan

It was realised from the outset that versatile synthetic methodology to access tetrafluorinated monosaccharides would have to fulfil several conditions. First of all, selective and controlled access to the

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† Electronic supplementary information (ESI) available: Determination of the ee of the SAD of **8**, confirmation of the ee of **11** and **20**, crystal structures of **2** and **22**, HMBC spectra of **2**, **5**, **6**, **7**, ^{1}H, ^{13}C and ^{19}F NMR spectra of **2–7**, **9–11**, **20**, **22**, **24**, **25**, **27**, **30**, **32–34**. See DOI: 10.1039/b817260a

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appropriately protected furanose *and* pyranose forms is required, with the anomeric position available for further transformation. Ideally, in a polysaccharide synthesis setting, choice over the required protecting group(s) is necessary. The introduction of the fluorine atoms would need to be convenient, and a crucial requirement was that both enantiomeric forms would have to be obtainable.

Though the conversion of a ketone to a CF_2-group is well-known, the transformation of an aliphatic 1,2-diketone to a tetrafluoroethylene group was reported to be low-yielding.[11] This had led us to pursue a fluorinated building block approach,[12] with the introduction of chirality controlled by a catalytic enantioselective reaction.

Hence, it was envisioned (Scheme 1) that a Sharpless asymmetric dihydroxylation (SAD) reaction[13] of the commercially available **8**, followed by selective conversion to monoprotected derivatives **10** or **11**, would give rise to the required chiral precursors to synthesise aldopentoses and ketohexoses in both the furanose and pyranose forms, with the perfluoroalkyl bromide group as a handle for a one- or two-carbon chain extension. The required C–C bond formation was planned *via* a Br–Li exchange reaction, followed by *in situ* trapping with an appropriate ester electrophile (a formate and acetate ester moiety, as a 1C and a 2C fragment respectively). In order to minimise protecting group manipulations, it was decided to investigate an intramolecular version, where the ester moiety would be introduced prior to lithiation. Hence, this would lead to **12** or **13**, with subsequent cyclitive C–C bond formation to give the desired monosaccharides **2–5**. To the best of our knowledge, such an intramolecular CF_2–C bond formation process was unknown at the outset of this work.

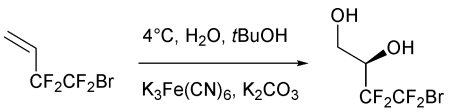
Perfluoroalkyllithium species, known to be stable only at very low temperatures, are prone to fluoride elimination to give the corresponding trifluorovinyl derivative (see below). Hence, a crucial issue in this plan was how the relative rate of this unwanted elimination process compared to the rate of the desired cyclisation reaction in the formation of both the 5- and the 6-membered ring using different acceptor groups.

The Sharpless asymmetric dihydroxylation

Literature precedents of SAD reactions on perfluoroalkyl-substituted terminal alkenes showed only moderate enantioselectivities.[14] For example, SAD of 3,3,3-trifluoropropene with $(DHQD)_2PHAL$ **14** (Fig. 2) as ligand, only returns the corresponding diol in 63% ee.[15a] With ligand **16**, an ee of 81% was obtained.[15b] SAD of $CF_3(CF_2)_5CH{=}CH_2$ with **14** and **16** gave the corresponding diols in 12% and 45% ee, but with **18**, an ee of 68% was obtained.[15c,d] Hence, the standard PHAL-based ligands appear not ideal for this type of substrate.

Our investigation of the SAD of **8** (Table 1) commenced by evaluating the commercially available AD-mix. Using a typical quantity (1.4 g $mmol^{-1}$, equal to 0.4 mol% OsO_4 and 1 mol% **15**), the yield of **9** was low even after stirring for 1 week, which reflects the unreactive nature of the electron poor double bond

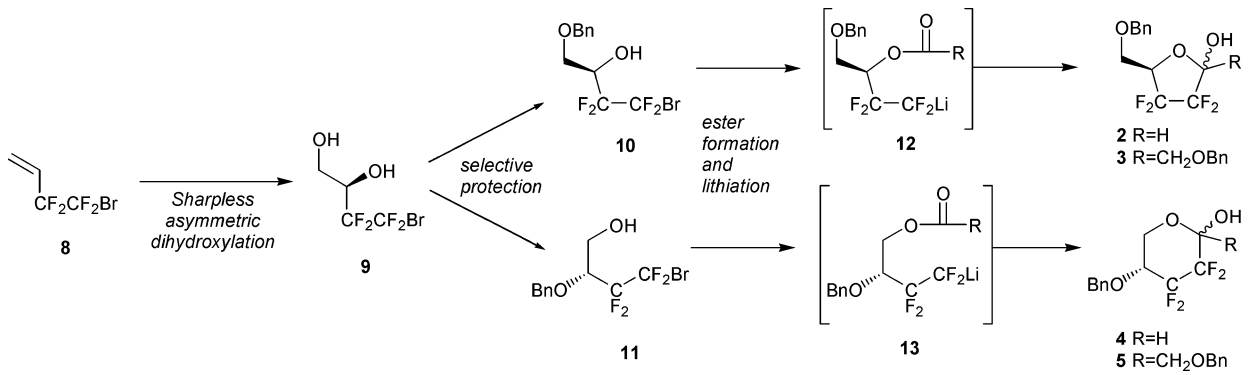
Table 1 The Sharpless asymmetric dihydroxylation of **8**



8 **9**

Entry	Ligand	Ligand (mol%)	OsO_4 (mol%)	Time (d)	Yield (%)[a]	ee **9** (%)[b]
1[c]	$(DHQ)_2PHAL$	2.0	0.8	18	74	50
2[d]	$(DHQ)_2PHAL$	2.0	2.0	7	98	54
3[d]	$(DHQ)_2AQN$	2.0	2.0	7	76	56
4[d]	$(DHQ)_2PYR$	2.0	2.0	9	93	78
5[d]	$(DHQ)_2PYR$	10[e]	2.0	9	96	81
6[d]	$(DHQD)_2PYR$	2.0	2.0	9	90[f]	83[g]

[a] Isolated yield. [b] Determined *via* chiral GC as the bis-acetate (see ESI†). [c] Commercial AD-mix, double amount. [d] In-house prepared AD-mix. [e] Heterogeneous reaction mixture. [f] *Ent*-**9**. [g] Determined *via* chiral HPLC as the bis-benzoate (see ESI†).



Scheme 1 Synthetic plan.

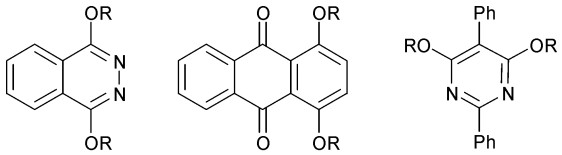


Fig. 2 Ligands used in the Sharpless asymmetric dihydroxylation reaction based on the phthalazine (PHAL), anthraquinone (AQN) and pyrimidine (PYR) spacer. DHQ = dihydroquinine, DHQD = dihydroquinidine.

towards dihydroxylation. For unreactive double bonds, an increase in OsO_4-loading is recommended. The reaction rate can also be enhanced by maintaining a high pH of the reaction mixture, either by external titration[16] or by using $NaClO_2$ as oxidant,[17] but these conditions have not been investigated by us. Hence, by doubling the amount of AD-mix, a 74% yield was obtained after 18 days, albeit the ee was low (50%, entry 1). A further improvement was made, in terms of yield, with an in-house AD-mix formulation consisting of 2 mol% of OsO_4 and ligand, where 98% yield was obtained after 7 days (entry 2). However, the ee remained low (54%), and other ligands were screened, in otherwise identical formulations and concentrations. With **17**, only a 56% ee was obtained (entry 3), but with **19**, a much improved ee of 78% was achieved (entry 4). In accord with empirical findings that the *pseudo*-enantiomeric DHQD-based ligands typically afford higher enantioselectivities, a slightly higher ee (83%, entry 6) was obtained with $(DHQD)_2PYR$ under otherwise identical conditions. So far, a 1 : 1 osmium : ligand molar ratio was applied, and next it was investigated whether a higher ee could be obtained by increasing the ligand concentration. While maintaining a 2 mol% of OsO_4, a 5 : 1 Os : ligand ratio was tried. This led to a heterogeneous reaction mixture, from which the diol **9** was isolated in 81% ee (entry 5). It was not attempted to dilute the reaction mixture as this would increase the already long reaction time. Unfortunately, attempts to improve the ee of the diol by recrystallisation of the crystalline 1-benzyl and 1-(2-naphthylmethyl) derivatives **10** and **20** (Fig. 3) proved to be fruitless.

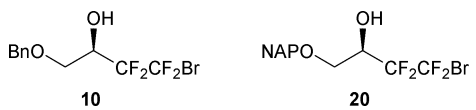
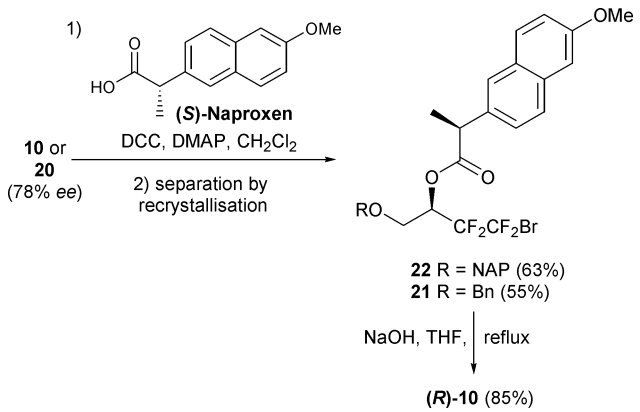


Fig. 3 Crystalline derivatives of the diol **9**.

For the up-scaling, a method to recycle the expensive $(DHQ)_2PYR$ was desirable, which was achieved by a modified Sharpless protocol[18] by extraction with aq. HCl (2 M), neutralisation of the acidic aqueous phase with aq. NaOH (2 M), extraction with EtOAc, followed by concentration and recrystallization (EtOAc) to yield pure $(DHQ)_2PYR$.

In order to confirm the absolute configuration of the diol, derivatization of **10** and **20** with the enantiopure (*S*)-Naproxen was carried out (Scheme 2). The reaction gave, as expected, a mixture of both diastereoisomers in 92 and 97% yield respectively, from which the major diastereomers **21** and **22** were obtained in 55% and 63% yield after slow recrystallisation from hexane–acetone (9 : 1). X-Ray crystallographic analysis (see ESI†) of **22** proved the



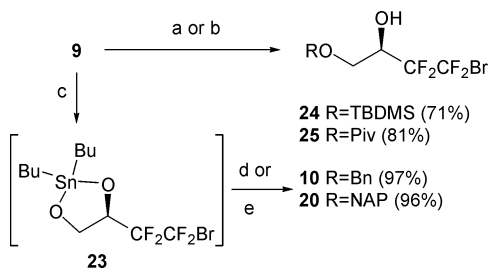
Scheme 2 Ester formation with (*S*)-Naproxen: confirmation of the absolute configuration and resolution.

relative stereochemistry and confirmed that the stereoselection in the Sharpless asymmetric dihydroxylation reaction occurred as expected.

The crystallisation of the major diastereomer of the Naproxen ester was possible on a large scale, and was exploited to obtain enantiopure material by subsequent saponification. This resulted in enantiopure **10** (Scheme 2).

The monofunctionalisation

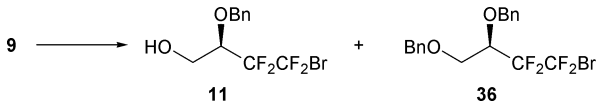
Selective protection of the primary alcohol group of perfluoroalkyl substituted terminal 1,2-diols as an ester[19a–c] or silyl ether[19c–d] is known. Interestingly, under thermodynamically controlled basic conditions, selective protection of the β-hydroxyl group is observed, even with internal 1,2-diol moieties.[19c,20] Hence, reaction with TBDMSCl (Scheme 3) in DCM[19c] led to **24** in good yield. However, the use of imidazole in DMF as solvent only gave **24** in 42% yield, with 7% of the corresponding secondary silyl ether isolated as well. Selective protection as pivaloate **25** also proceeded in good yield.



Scheme 3 Selective protection of the primary alcohol of **9**. *Reagents and conditions*: (a) TBDMSCl, DMAP, CH_2Cl_2, rt, 20 h. (b) PivCl, pyridine, 0 °C, 45 min. (c) Bu_2SnO, toluene, reflux, 6 h. (d) add BnBr, TBAI, reflux, 16 h. (e) add NAPBr, TBAI, reflux, 24 h.

In order to achieve selective benzylation of the primary alcohol, **9** was converted to the stannylene acetal[21] **23**, followed by direct alkylation with BnBr–TBAI. This led to complete regioselective formation of the primary benzyl ether **10** in excellent yield. Equally, reaction of **23** with 2-naphthylmethyl bromide yielded **20**. Confirmation of the regioselectivity was obtained by ^1H NMR *via* a D_2O exchange experiment, which showed a simplification of the C*H*OH multiplet. Efficient removal of the tin derivatives was

Table 2 Monobenzylation of **9** under basic conditions



11 **36**

Entry	Base (equiv.)	BnBr (equiv.)	Time (h)	Yield (%)[a] **11**	**36**	**9**[b]	**10**
1[d]	NaH (1)	1.0	16.5	8[g,h]	—	62	0.8
2[c]	NaOH (7)	1.1	48	3	44	—	—
3[d,e]	KO*t*-Bu (1)	1.0	16	51[i,h]	11	15	4
4[f]	BEMP (1)[l]	1.0	18	52	16	—	—
5[d,j]	Na_2CO_3 (27)	18	18	56[k,h]	<1%	—	2

[a] Isolated yield. [b] Recovered starting material. [c] *n*-$Bu_4N(HSO_4)$ (0.05 equiv. in H_2O–DCM). [d] *Ent*-**9** (85% ee) used as starting material. [e] Reaction at reflux temperature. [f] *n*-Bu_4NBr (0.1 equiv. in THF). [g] ee 62%. [h] Determined by chiral HPLC. [i] ee 79%. [j] 10 mol% of tetrabutyl ammonium bromide was present. [k] ee 85%. [l] BEMP = 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine.

achieved by an aqueous work-up with a KF (10% w/v) solution,[22] followed by column chromatography on silica gel. The analysis of the Mosher ester of **20** (^{19}F NMR) confirmed that the stannylene acetal procedure did not alter the ee of the product (see ESI†).

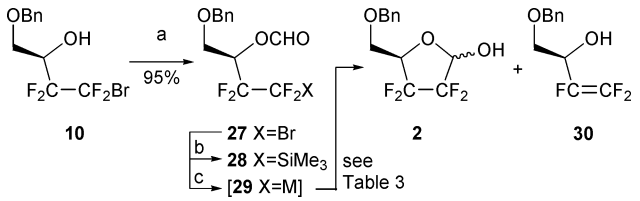
In addition to steric factors, the alcohol groups are also differentiated by the electronic influence of the fluoroalkyl group, resulting in the secondary alcohol group being less nucleophilic, but more basic compared to the primary alcohol group. Hence, selective benzylation of the secondary alcohol was expected under basic conditions (Table 2).[23]

However, low yields were obtained with NaH[23a,24] and NaOH[25] (entries 1,2). The use of KO*t*-Bu gave better results (entry 3), though a substantial amount of the dibenzylated product **36** was isolated as well. An equally good yield was achieved with BEMP (entry 4), with 16% of the dibenzylated **36** isolated as well. Finally, the use of excess Na_2CO_3 under phase-transfer conditions provided the best yield (56%, entry 5). Interestingly, virtually no dibenzylated **36** was obtained, while a small amount of primary benzyl ether **10** was isolated. It was confirmed that the benzylation did not affect the ee of the product when Na_2CO_3 or KO*t*-Bu was used. However, the ee of product formed when NaH was employed appeared to be only 60% (see ESI†), despite that only 1 equiv. of NaH was used. This erosion in ee was confirmed over duplicate experiments, and could be the result of product epimerisation.[24]

The anionic cyclisation

With both monobenzylated substrates **10** and **11** in hand, research was directed to investigate the cyclisation reaction. The cyclisation precursor **27** was synthesised by formylation of **10** (Scheme 4), which was found to proceed best under DCC mediated coupling conditions. It was initially envisaged to synthesise the corresponding silane **28** as a "Rupperts-equivalent", from which cyclisation could be achieved *via* treatment with a fluoride source,[26] but we were unable to introduce the silyl group starting from **27** following standard protocols.[27]

Explorations towards using perfluoroalkyl lithium intermediates[28] to achieve the cyclisation reaction proved to be very fruitful. Perfluoroalkyl lithium species, however, are unstable with



Scheme 4 The anionic cyclisation. *Reagents and conditions*: (a) HCOOH, DCC, DMAP, CH_2Cl_2, rt, 16 h. (b) Me_3SiCl, $(Et_2N)_3P$, PhCN.

β-fluoride elimination being a facile process.[28,29] While generation of perfluoroalkyl lithium *via* deprotonation is reported to lead to β-fluoride elimination,[30] *in situ* generation *via* a bromine–lithium exchange reaction using BuLi or MeLi has proven to be a suitable method for achieving subsequent intermolecular attack to electrophiles including esters.[29b,31] However, to the best of our knowledge, such addition reactions were not yet reported in an intramolecular fashion at the outset of this work, and we investigated whether the cyclisation process would be faster than the competing elimination process.

Hence, a number of organometal reagents were screened (Table 3). We were pleased to observe that treatment of **27** with *n*-BuLi and *t*-BuLi resulted in the formation of the desired

Table 3 Anionic cyclisation experiments to give **2** from **27**

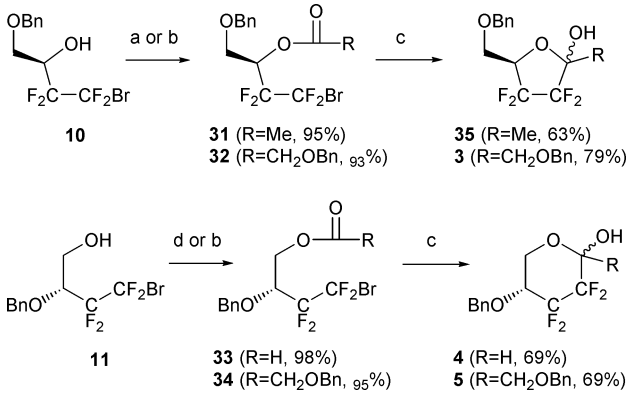
Entry	Reagent (equiv.)	Yield (%)[b] **2**	**30**	**10**	**27**[c]
1	*n*-BuLi (1)	43	11	17	—
2	*t*-BuLi (2)	11	29	49	—
3	*t*BuLi (1)	43	22	15	—
4[d]	PhMgBr (1)	—	—	63	11
5[d]	*i*-PrMgCl (1)	59	18	2	8
6	MeLi (1)	78	<5	—	—

[a] Reaction at −78 °C in THF for 1 h. [b] Isolated yield. [c] Recovered starting material. [d] Reaction time 3 h.

pentafuranose **2** (entries 1–3), but a considerable amount of the predicted elimination product was isolated as well. In addition, alkyl lithium attack on the formate ester was observed as well, leading to **10** in rather high yields. As perfluoroalkyl magnesium species have increased stability compared to their lithium counterparts,[28] a Br–Mg exchange reaction was investigated as well. However, phenyl magnesium bromide[32] mainly reacted directly at the ester group (entry 4), while the use of isopropylmagnesium chloride[33] still gave significant amounts of elimination by-product **30** (entry 5). In the event, with methyl lithium as reagent, the desired cyclisation product was obtained almost exclusively (entry 6). An X-ray structure of **2** was obtained (see ESI†). The alkene **30** was easily identified by a characteristic $CF{=}CF_2$ band of 1790 cm^{-1},[34a] and by ^{19}F NMR.[34b]

A solvent screen showed that tetrahydrofuran appeared to be the best solvent for the reaction. Yields of **2** were lower when Et_2O (58%) or toluene (55%) were used, and the addition of HMPA also resulted in a lower yield (34%). Employing MeLi·LiBr instead of LiBr-free MeLi did not increase the yield (60%). A low temperature is crucial for the reaction, but further lowering of the temperature from −78 °C to −100 °C did not significantly increase the yield, nor did the use of dried molecular sieves.

With a successful anionic cyclisation protocol developed, a range of substrates **31–34** were synthesised in order to investigate the scope of the reaction (Scheme 5). The acetate derivatives **31** and **32** were obtained from **10** by DMAP-catalysed ester formation using acetic anhydride and α-benzyloxyacetyl chloride. From the primary alcohol **11**, the corresponding formate and benzyloxyacetate esters **33** and **34** were prepared by aforementioned methods.

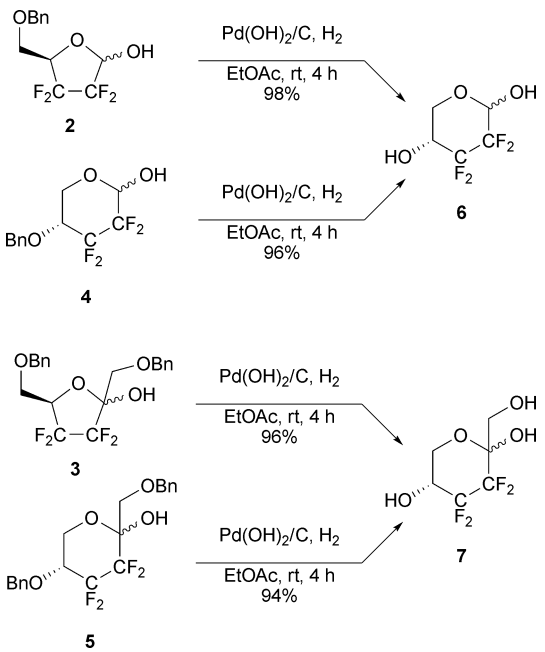


Scheme 5 Scope of the anionic cyclisation. *Reagents and conditions*: (a) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 2 h. (b) $BnOCH_2C(O)Cl$, Et_3N, DMAP, CH_2Cl_2, rt, 6 h. (c) MeLi (1 equiv.), THF, −78 °C, 3 h. (d) HCOOH, DCC, DMAP, CH_2Cl_2, rt, 16 h.

We were delighted to observe that all substrates **31–34** underwent smooth cyclisation after MeLi-induced Br–Li exchange, demonstrating the versatility of this methodology for both 5- and 6-membered rings, giving direct access to furanose and pyranose sugars. In addition, cyclisation towards enolisable acetate-type esters as electrophiles, gives access to ketose sugars. In all cases, the corresponding elimination by-product was only present in very small amounts and, pleasingly, no intramolecular deprotonation was observed.

Alcohol deprotection

Using Pd/C in EtOAc as solvent, hydrogenolysis proceeded very slowly, with **6** isolated in 85% yield after 14 days, together with 14% of starting material. However, by using Pearlman's catalyst (Scheme 6), the deprotection was completed in 4 h, giving **6** in almost quantitative yield. The deprotected tetrafluoropentose was isolated in the pyranose form as indicated by a HMBC experiment (in d_6-DMSO, see ESI†). Deprotection of **4** led to the same monosaccharide **6** in equally good yield. Similarly, deprotection of **3** and **5** led to the ketohexapyranose **7** in excellent yield. Again, a HMBC experiment proved that **7** existed in the pyranose form (see ESI†). Both the protected and deprotected sugars were obtained as a mixture of anomers.



Scheme 6 Deprotection leading to the pyranose form.

For the assignment of the pyranose-based anomers, the chemical shift of the anomeric proton, and the $^2J_{F2\text{–}C1}$ couplings appeared to be the most diagnostic data. An equatorial anomeric proton (α-anomer) is downfield compared to an axial anomeric proton (β-anomer). The magnitude of $^2J_{F2\text{–}C1}$ is dependent on the orientation of an electronegative substituent on the coupled carbon atom, with an increase in magnitude going from a *gauche* to a *trans* orientation with respect to the fluorine involved in the coupling.[35] In this respect, the anomeric OH group outweighs the ring oxygen in importance. For example, for the anomers of **4**, the anomer with the higher chemical shift for the anomeric proton is assigned as the α-anomer **4α**. This is confirmed by the $^2J_{F2\text{–}C1}$ values of 35.2 and 25.1 Hz with the large value being the coupling of F_{ax} with the anomeric carbon atom. For **4β**, the $^2J_{F2\text{–}C1}$ values are 28.9 and 21.6 Hz.[21c,36] Interestingly, the $^2J_{F3\text{–}C4}$ couplings (all between 19 and 20 Hz) confirmed that for both anomers the 4-OBn group is in the equatorial position, suggesting a $^4C_1$ chair conformation. Unfortunately, unambiguous assignment of the fructose anomers has not yet been achieved.

Conclusions

A short, enantioselective synthesis (81% ee) of tetrafluorinated monosaccharide derivatives has been achieved, with a novel perfluoroalkylidene lithium mediated cyclisation as the key step. This cyclisation works well for the formation of both 5- and 6-membered rings, and both formate and acetate groups are suitable electrophiles. This methodology is suitable for the synthesis of a range of tetrafluorinated aldo- and ketofuranoses and pyranoses, in both enantiomeric forms, with a reasonable choice of protecting groups. This process will also be useful for the synthesis of a wider range of cyclic substrates. Research towards the synthesis of other fluorinated saccharides, and towards efficient glycosylation reactions for this class of sugars, is underway.

Experimental section

^{1}H and ^{13}C NMR spectra were recorded at room temperature on a Bruker DPX400 or AV300 spectrometer as indicated. Chemical shifts are quoted in ppm relative to residual solvent peaks as appropriate. ^{19}F NMR spectra were recorded on a Bruker AV300 spectrometer or a Bruker DPX400 spectrometer and are referenced to C_6F_6 and $CFCl_3$ respectively. Assignments were assisted by COSY and HMQC experiments. EIMS were recorded on a Thermoquest Trace GCMS Quadrapole system. Infrared spectra were recorded as neat films on a Nicolet Impact 380 ATR spectrometer. Melting points were recorded on a Gallencamp Melting Point Apparatus and are uncorrected. Column chromatography was performed on 230–400 mesh Matrex silica gel. Preparative HPLC was carried out using a Biorad Biosil D 90-10, 250 × 22 mm column eluting at 20 mL min^{-1}, connected to a Kontron 475 refractive index detector. Reactions were monitored by TLC (Merck) with detection by alkaline $KMnO_4$ oxidation. Reaction solvents were dried before use as follows: THF and Et_2O were distilled from sodium/benzophenone ketyl; CH_2Cl_2, *m*-xylene and Et_3N were distilled from CaH_2; toluene and 1,2-dimethoxyethane were distilled from Na; pyridine was double distilled from CaH_2 and stored in a Schlenk flask; DMSO was distilled under reduced pressure from CaH_2 and was stored over molecular sieves; HMPA was distilled from CaH_2 and stored over 4 Å sieves. Reaction vessels were flame dried under vacuum and cooled under N_2 prior to use and all experiments were carried out under a N_2 atmosphere. All other reagents were purchased from commercial sources and used without further purification.

(2*R*)-4-Bromo-3,3,4,4-tetrafluorobutane-1,2-diol (9)

A single necked flask was charged with $K_3Fe(CN)_6$ (52.7 g, 0.16 mol), K_2CO_3 (22.1 g, 0.16 mol), $K_2OsO_4{\cdot}2H_2O$ (0.40 g, 1.08 mmol) and $(DHQ)_2PYR$ (0.85 g, 1.08 mmol). H_2O (270 mL) and *t*-BuOH (270 mL) were added, and the reaction stirred until complete dissolution occurred. The reaction was cooled to 4 °C whilst stirring and 4-bromo-3,3,4,4-tetrafluorobut-1-ene (11.2 g, 54.0 mmol) was added *via* syringe and the reaction stirred at 4 °C for 9 days. Solid Na_2SO_3 (81.0 g) was added and the reaction allowed to warm to rt with vigorous stirring over 2 h. The reaction was diluted with H_2O (50 mL) and Et_2O (200 mL), the layers were separated and the aqueous phase extracted with Et_2O (2 × 200 mL). The combined organic phases were washed with HCl (2 M, aq, 2 × 50 mL) and brine (50 mL) then dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a colourless oil. The acidic extracts were neutralised with NaOH (2 M, aq) and then extracted with EtOAc (2 × 100 mL). The EtOAc extracts were dried over $MgSO_4$, filtered then concentrated to give a white solid, which, after recrystallisation from EtOAc gives pure $(DHQ)_2PYR$. The colourless oil obtained was purified by vacuum distillation (55 °C, 0.1 mm Hg) to give a colourless oil which crystallised on standing to give a white deliquescent solid (12.0 g, 93%). ν_{max}(film)/cm^{-1} 3388 (br. s), 2956 (m), 2900 (w), 1414 (w), 1151 (s), 1087 (s), 919 (s); δ_H (400 MHz, CD_3CN) 4.20 (1H, m, C*H*OH, simplifies upon D_2O exchange), 4.00 (1H, d, *J* 7.3 Hz, CHO*H*, disappears upon D_2O exchange), 3.78 (1H, m, CH*H*OH simplifies upon D_2O exchange), 3.66 (1H, dt, *J* 11.8 and 6.0 Hz, C*H*HOH, upon D_2O exchange simplifies to 1H, dd, *J* 11.8 and 7.0 Hz), 3.08 (1H, t, *J* 6.2 Hz, CH_2OH, disappears upon D_2O exchange); δ_C(75 MHz, $CDCl_3$) 117.1 (tt, *J* 312.5 and 39.5 Hz, CF_2Br), 114.4 (ddt, *J* 262.0, 257.8 and 31.0 Hz, CF_2), 69.4 (dd, *J* 27.4 and 22.1 Hz, CHOH), 60.4 (CH_2); δ_F (282 MHz, $CDCl_3$) −64.12 (1F, dd, *J* 181.6 and 6.5 Hz, C*F*FBr), −64.93 (1F, dd, *J* 181.6 and 5.4 Hz, CF*F*Br), −116.93 (1F, dt, *J* 271.9 and 5.4 Hz, C*F*FCF$_2$Br), −123.29 (1F, ddd, *J* 271.9, 17.2 and 6.5 Hz, CF*F*CF$_2$Br); EIMS *m*/*z* 242 and 240 (M^+, 12%, 1 : 1 ratio), 223 and 221 (16, 1 : 1 ratio), 192 and 190 (16, 1 : 1 ratio), 111 (100).

(2*R*)-1-Benzyloxy-4-bromo-3,3,4,4-tetrafluorobutan-2-ol (10)

A solution of **9** (5.0 g, 20.75 mmol) and Bu_2SnO (6.20 g, 24.89 mmol) in dry toluene (75 mL) was refluxed, using a Dean and Stark condenser, for 6 h. BnBr (2.96 mL, 24.89 mmol) and TBAI (1.92 g, 5.19 mmol) were added and the reaction was refluxed for further 16 h. The mixture was allowed to cool, diluted with Et_2O (100 mL), washed with KF (10% w/v, aq, 2 × 25 mL), dried over $MgSO_4$, filtered and then concentrated *in vacuo*. Purification by column chromatography (petroleum ether–Et_2O, 80 : 20) gave a pale yellow oil (6.64 g, 97%) which solidified on standing to a low melting solid. $[\alpha]_D$ +9.43 (*c* 1.3, $CHCl_3$, 26 °C, value after Naproxen resolution); ν_{max}(film)/cm^{-1} 3432 (br. m), 2931 (m), 2875 (m), 1497 (w), 1455 (m), 1367 (m), 1154 (s), 1094 (s); δ_H (400 MHz, $CDCl_3$) 7.41–7.32 (5H, m, ArH), 4.62 (2H, s, CH_2Ph), 4.37 (1H, m, C*H*OH, simplifies upon D_2O exchange), 3.82–3.74 (2H, m, C*H*HOBn and CH*H*OBn), 2.98 (1H, br. s, CHO*H*, disappears upon D_2O exchange); δ_C (100 MHz, $CDCl_3$) 137.0 (ArC), 128.6 (2 × ArCH), 128.1 (ArCH), 127.8 (2 × ArCH), 73.8 (CH_2Ph), 68.5 (dd, *J* 28.2 and 22.3 Hz, CHOH), 67.5 (*C*H_2CH). The CF_2CF_2 carbons were not observed; δ_F (282 MHz, $CDCl_3$) −64.02 (1F, dd, *J* 178.5 and 6.5 Hz, C*F*FBr), −64.97 (1F, dd, *J* 178.5 and 4.3 Hz, CF*F*Br), −116.37 (1F, d, *J* = 269.9 Hz, CF*F*CF$_2$Br), −124.99 (1F, ddd, *J* 269.9, 19.6 and 6.5 Hz, C*F*FCF$_2$Br); EIMS *m*/*z* 332 and 330 (M^+, 4%, 1 : 1 ratio), 249 (10), 91 (100); HRMS (EI) for $C_{11}H_{11}{}^{79}BrF_4O_2$ $(M)^+$ calcd 329.9879, found 329.9785.

(2*R*)-2-Benzyloxy-4-bromo-3,3,4,4-tetrafluorobutan-1-ol (11)

The diol **9** (0.3 g, 1.25 mmol, 1 equiv.) was added to a 1.9 M aqueous solution (17.8 mL) of Na_2CO_3 (3.56 g, 33.61 mmol, 27 equiv.) and was stirred at rt for 15 min. Then BnBr (2.7 mL, 22.41 mmol, 18 equiv.) and TBAB (0.041 g, 0.125 mmol) were added and the reaction was stirred at rt for 18 h. To the aqueous

phase was added CH_2Cl_2 (10 mL) and after separation of the phases, the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phase was washed with brine (2 × 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (petroleum ether–EtOAc: 70 : 30) gave product **11** as a transparent gel (0.23 g, 0.70 mmol, 56%), **10** as a transparent gel (0.0083 g, 0.025 mmol, 2%) and **36** as a transparent gel (<1%). ν_{max}(film)/cm^{-1} 3407 (br. w), 2947 (w), 2887 (w), 1456 (w), 1212 (m), 1126 (s), 1086 (s), 915 (m); δ_H (400 MHz, $CDCl_3$) 7.42–7.34 (5H, ArH), 4.89 (1H, d, *J* 11.0 Hz, C*H*HPh), 4.68 (1H, d, *J* 11.3 Hz, CH*H*Ph), 4.14 (1H, m, C*H*OBn), 3.89 (1H, dd, *J* 12.2 and 3.1 Hz, C*H*HOH), 3.83 (1H, dd, *J* 12.4 and 7.1 Hz, CH*H*OH); δ_C (100 MHz, $CDCl_3$) 136.6 (ArC), 128.7 (2 × ArCH), 128.5 (ArCH), 128.2 (2 × ArCH), 77.7 (dd, *J* 25.3 and 21.9 Hz, *C*HCF$_2$), 75.1 (*C*H$_2$Ph), 60.3 (CH$_2$OH). The CF_2CF_2 carbons were not observed; δ_F (282 MHz, $CDCl_3$) −63.47 (2F, s, CF$_2$Br), −114.20 (1F, m, C*F*FCF$_2$Br), −117.87 (1F, ddt, *J* 275.6, 14.0 and 4.3 Hz, CF*F*CF$_2$Br); EIMS *m*/*z* 332 and 330 (M$^+$, 63%, 1 : 1 ratio), 249 (19), 181 (28), 127 (27), 107 (58), 91 (100); HRMS (ES$^+$) for $C_{11}H_{11}{}^{79}BrF_4NaO_2$ (M + Na)$^+$ calcd 352.9771, found 352.9766.

Data for (2*R*)-1,2-bisbenzyloxy-4-bromo-3,3,4,4-tetrafluorobutane (36)

ν_{max}(film)/cm^{-1} 3090 (w), 3065 (w), 3032 (w), 2922 (w), 2873 (w), 1497 (w), 1454 (m), 1127 (s); δ_H ($CDCl_3$, 400 MHz) 7.30–7.39 (10 H, m, ArH), 4.82 (1H, d, *J* 11.0 Hz, C*H*HPh), 4.77 (1H, d, *J* 11.0 Hz, CH*H*Ph), 4.58 (2H, s, C*H*$_2$Ph), 4.27 (1H, dtd, *J* 15.8, 7.3 and 2.8 Hz, C*H*OBn), 3.89 (1H, app d, *J* 10.6 Hz, C*H*HOBn), 3.79 (1H, dd, *J* 10.6 and 7.4 Hz, CH*H*OBn); δ_C (d$_6$-acetone, 100 MHz): 139.38 (ArC), 138.69 (ArC), 129.36 (ArCH), 129.29 (ArCH), 129.07 (ArCH), 128.89 (ArCH), 128.68 (ArCH), 128.65 (ArCH), 76.77 (dd, *J* 27.5 and 22.5 Hz, *C*HCF$_2$), 75.21 (*C*H$_2$Ph), 74.18 (*C*H$_2$Ph), 69.46 (CH*C*H$_2$). The CF_2CF_2 carbons were not observed; δ_F ($CDCl_3$) −62.43 (1F, dd, *J* 178.1 and 6.5 Hz, C*F*FBr), −63.15 (1F, dd, *J* 178.1 and 4.3 Hz, CF*F*Br), 112.42 (1F, app d, *J* 273.1 Hz, C*F*FCH), −120.43 (1F, ddd, *J* 273.1, 16.1 and 6.4 Hz, CF*F*CH); ES$^+$MS *m*/*z* 443 and 445 (M + Na$^+$, 100%, 1 : 1 ratio); HRMS (ES$^+$): for $C_{18}H_{17}{}^{79}BrF_4NaO_2$ (M + Na)$^+$: calcd: 443.0240, found 443.0238.

(2*R*)-4-Bromo-1-(naphth-2-ylmethyloxy)-3,3,4,4-tetrafluorobutan-2-ol (20)

Diol **9** (9.5 g, 39.42 mmol) and Bu_2SnO (11.8 g, 47.31 mmol) were dissolved in dry toluene (145 mL). The reaction was brought to reflux and stirred under Dean and Stark conditions for 16 h. 2-(Bromomethyl)naphthalene (10.5 g, 47.31 mmol) and TBAI (3.64 g, 9.86 mmol) were added and the reaction refluxed for a further 24 h. The reaction was allowed to cool, diluted with Et_2O (200 mL), washed with KF (10% w/v, aq, 2 × 100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (petroleum ether–Et_2O, 85 : 15) gave a pale yellow solid (14.4 g, 96%). Mp 80–82 °C; ν_{max}(film)/cm^{-1} 3386 (br. m), 3061 (w), 2946 (w), 1146 (m), 1113 (s), 1091 (s), 1055 (s), 1031 (m); δ_H (400 MHz, $CDCl_3$) 7.88–7.84 (3H, m, 3 × ArH), 7.79 (1H, br s, ArH), 7.54–7.49 (2H, m, ArH), 7.47 (1H, dd, *J* 8.4 and 1.6 Hz, ArH), 4.78 (2H, s, C*H*$_2$Ar), 4.40 (1H, m, C*H*OH), 3.86–3.78 (2H, m, C*H*$_2$ONap), 3.03 (1H, br s, OH); δ_C (100 MHz, $CDCl_3$) 134.41 (Ar*C*CH$_2$), 133.19 (ArC), 133.14 (Ar*C*), 128.49 (ArCH), 127.89 (ArCH), 127.73 (ArCH), 126.78 (ArCH), 126.32 (ArCH), 126.18 (ArCH), 125.52 (ArCH), 73.9 (*C*H$_2$Ar), 68.49 (dd, *J* 28.7 and 22.4 Hz, *C*HCF$_2$), 67.52 (*C*H$_2$CH). The CF_2CF_2 carbons were not observed; δ_F(282 MHz, $CDCl_3$) −63.38 (1F, dd, *J* 179.5 and 7.5 Hz, CF*F*Br), −64.30 (1F, dd, *J* 179.5 and 4.3 Hz, C*F*FBr), −115.85 (1F, d, *J* 269.3 Hz, CHCF*F*), −124.32 (1F, ddd, *J* 282, 18.2 and 7.5 Hz, CHC*F*F); EIMS: *m*/*z* 382 and 380 (M$^+$, 8%, 1 : 1 ratio), 207 (8), 141 (100); HRMS (ES$^+$) for $C_{15}H_{13}{}^{79}BrF_4NaO_2$ (M + Na)$^+$ calcd 402.9927, found 402.9929.

(2*S*)-[(2*R*)-4-Bromo-1-(2-benzyl)-3,3,4,4-tetrafluorobut-2-yl]-2-(6-methoxy-2-naphthyl) propanoate (21)

To a stirred solution of **10** (4.606 g, 12.8 mmol) and DCC (14.1 mmol, 2.91 g) in CH_2Cl_2 (65 mL) was added DMAP (1.28 mmol, 157 mg). The suspension was stirred until complete dissolution, upon which (*S*)-Naproxen (14.1 mmol, 3.25 g) was added and the reaction stirred overnight. The mixture was filtered to remove the precipitate formed and the residue washed with CH_2Cl_2 (20 mL). The filtrate was concentrated *in vacuo* to give a suspension which was loaded directly onto a silica gel column. Elution with petroleum ether–acetone (85 : 15) gave a yellow solid as a mixture of diastereomers. The desired major diastereomer was then obtained by recrystallisation from hexane as an off-white solid (3.843 g, 55%). The remaining supernatant was reduced *in vacuo* to give 2.588 g (37%) as a mixture of diastereomers. Data for **21**: mp 69–71 °C (hexane); $[\alpha]_D$ +33.2 (*c* 0.87, $CHCl_3$, 26 °C); ν_{max}(film)/cm^{-1} 2938 (br), 1754 (s), 1633 (w), 1606 (m), 1506 (w), 1485 (w), 1454 (w), 1140 (s); δ_H (400 MHz, $CDCl_3$) 7.68–7.64 (3 H, m, ArH), 7.40 (1H, dd, *J* 8.5 and 1.7 Hz, ArH), 7.24–7.10 (5H, m, ArH), 7.01 (2H, d, *J* 6.7 Hz, ArH), 5.86 (1H, dtd, *J* 16.4, 7.5 and 3.2 Hz, CHCF$_2$), 4.31 (1H, d, *J* 11.9 Hz, C*H*HPh), 4.22 (1H, d, *J* 11.9 Hz, CH*H*Ph), 4.00–3.92 (4H, m, C*H*CH$_3$ + OC*H*$_3$), 3.76 (1H, ddd, *J* 11.2, 3.2 and 2.0 Hz, C*H*HOBn), 3.60 (1H, dd, *J* 11.0 and 7.8 Hz, CH*H*OBn), 1.62 (1H, d, *J* 7.2 Hz, CHC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 172.7 (C=O), 157.7 (CAr), 137.1 (CAr), 134.6 (CAr), 133.8 (CAr), 129.3 (CAr), 128.9 (CAr), 128.2 (2 × CAr), 127.3 (2 × CAr), 127.2 (CAr), 126.2 (CAr), 126.1 (CAr), 119.0 (CAr), 105.6 (CAr), 73.2 (*C*H$_2$Ph), 67.8 (dd, *J* 29.7 and 21.9 Hz, *C*HCF$_2$), 66.5 (*C*HOBn), 55.3 (CH*C*H$_3$), 45.1 (*C*CH$_3$), 18.4 (OC*H*$_3$). CF_2CF_2 carbons were not visible; δ_F (282 MHz, $CDCl_3$) −119.5 (1 F, dd, *J* 275.1 and 17.2 Hz, CHC*F*F), −114.0 (1 F, d, *J* 275.1 Hz, CHCF*F*), −64.2 (2 F, s, C*F*$_2$Br); LRMS (ESI$^+$) *m*/*z* 565.3 and 567.2 ((M + Na)$^+$, 100%, 1 : 1 ratio); HRMS (ESI$^+$) for $C_{25}H_{23}{}^{81}BrF_4O_4$ (M + Na)$^+$ calcd 565.0614, found 565.0605.

(2*S*)-[(2*R*)-4-Bromo-1-(2-naphthylmethyl)-3,3,4,4-tetrafluorobut-2-yl]-2-(6-methoxy-2-naphthyl) propanoate (22)

To a stirred solution of **20** (0.5 g, 1.31 mmol) and DCC (0.3 g, 1.44 mmol) in CH_2Cl_2 (7 mL) was added DMAP (0.016 g, 0.131 mmol). The suspension was stirred until complete dissolution, upon which (*S*)-Naproxen (0.33 g, 1.44 mmol) was added and the reaction stirred overnight. The mixture was filtered to remove the white precipitate formed and the residue washed with CH_2Cl_2 (2 × 10 mL). The filtrate was concentrated *in vacuo* to give a white suspension which was loaded directly onto a silica gel column. Elution with petroleum ether–acetone (90 : 10) gave a

white solid (1.27 g, 97%). HPLC (hexane–acetone, 90 : 10) followed by slow evaporation of the desired fractions gave **22** as white needles of a single diastereomer (0.489 g, 63%). Mp 86–88 °C; ν_{max}(film)/cm^{-1} 2975 (w), 2936 (w), 1758 (m), 1135 (s), 1072 (s), 1027 (m), 861 (m); δ_H (400 MHz, $CDCl_3$) 7.78 (1H, m, ArH), 7.69–7.67 (2H, m, 2 × ArH), 7.60 (3H, m, 3 × ArH), 7.47–7.44 (2H, m, 2 × ArH), 7.39 (1H, dd, *J* 8.4 and 1.6 Hz, ArH), 7.09 (1H, dd, *J* 8.7 and 1.9 Hz, ArH), 7.04 (1H, d, *J* 2.3 Hz, ArH), 5.89 (1H, dtd, 15.7, 7.8 and 3.0 Hz, CHO), 4.45 (1H, d, *J* 12.1 Hz, CH*H*Nap), 4.36 (1H, d, *J* 12.1 Hz, C*H*HNap), 3.96 (1H, q, *J* 7.3 Hz, CH_3CH), 3.90 (3H, s, OCH_3), 3.81 (1H, m, CHC*H*HO), 3.65 (1H, dd, *J* 11.3 and 7.8 Hz, CHCH*H*O), 1.62 (3H, d, *J* 7.3 Hz, $CHCH_3$); δ_C (100 MHz, $CDCl_3$): 172.7 (CO), 157.7 ($COCH_3$), 134.7 (ArC), 134.6 (ArC), 133.8 (ArC), 133.1 (ArC), 132.9 (ArC), 129.3 (ArCH), 128.9 (ArC), 128.1 (ArCH), 127.9 (ArCH), 127.6 (ArCH), 127.2 (ArCH), 126.2 (ArCH), 126.1 (ArCH), 126.0 (ArCH), 125.9 (ArCH), 125.2 (ArCH), 119.0 (ArCH), 105.6 (ArCH), 73.4 (CH_2Nap), 67.9 (dd, *J* 28.7 and 21.9 Hz, $CHCF_2$), 66.6 ($CHCH_2$), 55.3 ($CHCH_3$), 45.1 (OCH_3), 18.4 ($CHCH_3$). The CF_2CF_2 carbons were not observed; δ_F (282 MHz, $CDCl_3$) –64.42 (2F, m, CF_2Br), –114.33 (1F, app. d, *J* 274.0 Hz, CHC*F*F), 119.69 (1F, ddt, *J* 274.0, 16.1 and 4.8 Hz, CHCF*F*); ESMS (ES$^-$) *m*/*z* 591 and 593 ((M – H)$^+$, 55%, 1 : 1 ratio), 212 (100).

(2*R*)-4-Bromo-1-(*t*-butyldimethylsilyloxy)-3,3,4,4-tetrafluorobutan-2-ol (24)

To a stirred solution of **9** (0.250 g, 1.04 mmol) and TBDMSCl (0.170 g, 1.15 mmol) in DCM (1.2 mL) was added DMAP (0.270 g, 2.25 mmol) and the mixture was stirred for 20 h. DCM (10 mL) was added, and the mixture was extracted with water (5 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by column chromatography (hexane–acetone 95 : 5) gave a colourless oil (0.264 g, 71%). A small amount of the secondary alcohol protected product was also isolated (0.033 g, 9%). ν_{max}(film)/cm^{-1} 3550 (w, br), 2932 (m), 1472 (m), 1255 (m), 1082 (s), 834 (s), 777 (s); δ_H (300 MHz, $CDCl_3$) 4.20 (m, 1H, C*H*OH), 3.94 (1H, ddd, *J* 10.5, 4.5 and 1.5 Hz, C*H*HOSi), 3.89 (1H, ddd, *J* 10.5, 4.0 and 2.3 Hz, CH*H*OSi), 3.07 (1H, d, *J* 7.3 Hz, C*H*OH), 0.93 (9H, s, *t*-Bu), 0.12 (6H, s, 2 × CH_3); δ_C (100 MHz, $CDCl_3$) 69.18 (dd, *J* 29.2 and 21.9 Hz, CHOH), 60.39 (CH_2OSi), 25.70 (3 × CH_3), 18.19 ($C(CH_3)_3$), –5.60 (2 × CH_3). The CF_2CF_2 carbons were not observed; δ_F (282 MHz, $CDCl_3$) –63.01 (1F, dd, *J* 179.2 and 8.6 Hz, C*F*FBr), –64.06 (1F, d, *J* 178.1 and 4.3 Hz, CF*F*Br), –115.44 (1F, d, *J* 270.4 Hz, C*F*FCF$_2$Br), –124.72 (1F, ddd, *J* 269.4, 19.3 and 8.6 Hz, CF*F*CF$_2$Br); EIMS *m*/*z* 297 and 299 ((M – *t*-Bu)$^+$, 4%, 1 : 1 ratio), 210 and 203 (5, 1 : 1 ratio), 107 (100); HRMS (ES$^+$) for $C_{10}H_{19}{}^{79}BrF_4NaO_2$ (M + Na)$^+$ calcd 377.0166, found 377.0168.

(2*R*)-[(4-Bromo-2-hydroxy-3,3,4,4-tetrafluorobut-1-yl)]-2,2-dimethyl propanoate (25)

To a stirred solution of **9** (0.444 g, 1.84 mmol) in dry pyridine (3.45 mL) at 0 °C was added pivaloyl chloride (0.45 mL, 3.68 mmol) and the reaction was stirred for 45 min at 0 °C. Ice (5 g) was added and the reaction was stirred for 5 min. The mixture was concentrated *in vacuo* to give a colourless oil. Purification by column chromatography (petroleum ether–Et_2O, 80 : 20) gave a white solid (0.478 g, 81%). Mp 49–52 °C; ν_{max}(film)/cm^{-1} 3045 (m), 2984 (m), 1735 (m), 1266 (s), 1156 (m), 740 (s); δ_H (300 MHz, $CDCl_3$) 4.50–4.38 (3H, m, CH_2O and C*H*OH), 3.04 (1H, d, *J* 7.2 Hz, CHO*H*), 1.24 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 179.2 (CO), 68.5 (dd, *J* 28.0 and 23.0 Hz, CHOH), 62.8 (CH_2O), 38.9 (C), 27.0 (3 × CH_3). The CF_2CF_2 carbons were not observed; δ_F (282 MHz, $CDCl_3$) –64.10 (1F, dd, *J* 178.5 and 6.5 Hz, CF*F*Br), –65.03 (1F, dd, *J* 180.7 and 4.3 Hz, C*F*FBr), –116.33 (1F, d, *J* 272.1 Hz, CF*F*CF$_2$Br), –124.90 (1F, ddd, *J* 269.9, 19.6 and 6.5 Hz, C*F*FCF$_2$Br); EIMS: *m*/*z* 327 and 325 (M + H$^+$, 10%, 1 : 1 ratio), 281 (5), 225 (8), 129 (10), 103 (52), 85 (90), 69 (50); HRMS (EI) for $C_9H_{14}{}^{79}BrF_4O_3$ (M + H)$^+$ calcd 325.0062, found 325.0067.

(2*R*)-(1-Benzyloxy-4-bromo-3,3,4,4-tetrafluoro)but-2-yl formate (27)

To a stirred solution of **10** (8.85 g, 26.73 mmol) and DCC (6.07 g, 29.4 mmol) in CH_2Cl_2 (140 mL) was added DMAP (0.33 g, 2.67 mmol). The reaction was stirred until complete dissolution upon which formic acid (98%, 1.1 mL, 29.4 mmol) was added and the reaction stirred overnight. The reaction was diluted with hexane (100 mL), filtered to remove the white precipitate formed and the residue was washed with hexane (2 × 20 mL). The filtrate was concentrated *in vacuo* to give a colourless oil. Purification by column chromatography (petroleum ether–Et_2O, 90 : 10) gave a colourless oil (8.89 g, 93%); ν_{max}(film)/cm^{-1} 3033 (m), 2949 (m), 2874 (m), 1744 (s), 1369 (m), 1152 (s); δ_H (400 MHz, $CDCl_3$) 8.13 (1H, s, CHO), 7.39–7.31 (5H, m, ArH), 5.91 (1H, dtd, *J* 15.4, 7.8 and 3.3 Hz, C*H*CF$_2$), 4.62 (1H, d, *J* 12.1 Hz, CH*H*Ph), 4.55 (1H, d, *J* 11.8 Hz, C*H*HPh), 3.89 (1H, dt, *J* 11.3 and 2.4 Hz, C*H*HCH), 3.80 (1H, dd, *J* 11.2 and 7.9 Hz, CH*H*CH); δ_C (100 MHz, $CDCl_3$) 158.5 (CHO), 137.0 (ArC), 128.5 (2 × ArCH), 128.0 (ArCH), 127.7 (2 × ArCH), 73.4 (PhCH_2O), 66.9 (dd, *J* 29.2 and 22.4, $CHCF_2$), 66.2 (CH_2CH). The CF_2CF_2 carbons were not observed; δ_F (282 MHz, $CDCl_3$) –67.18 (2F, s, CF_2Br), –117.24 (1F, d, *J* 272.5 Hz, CF*F*CF$_2$Br), –122.52 (1H, dd, *J* 274.7 and 15.5 Hz, CF*F*CF$_2$Br); EIMS *m*/*z* 360 and 358 (M$^+$, 10%, 1 : 1 ratio), 253 and 251 (26, 1 : 1 ratio), 181 (12), 91 (100); HRMS (EI) for $C_{12}H_{11}{}^{79}BrF_4O_3$ (M)$^+$ calcd 357.9828, found 357.9831.

(2*R*)-[(1-Benzyloxy-4-bromo-3,3,4,4-tetrafluoro)but-2-yl] benzyloxyethanoate (32)

To a stirred solution of **10** (0.5 g, 1.5 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (0.23 mL, 1.65 mmol) and DMAP (0.018 g, 0.15 mmol). The solution was stirred at rt for 5 min and then benzyloxyacetyl chloride (0.36 mL, 2.25 mmol) was added dropwise. The reaction was stirred at rt for 4 h. The reaction was diluted with CH_2Cl_2 (10 mL) then washed with HCl (1 M, aq., 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resultant oil was purified by column chromatography (petroleum ether–acetone, 90 : 10) to give a colourless oil (0.703 g, 98%). ν_{max}(film)/cm^{-1} 2881 (w), 1777 (m), 1122 (s), 1079.8 (m), 908 (m); δ_H (400 MHz, $CDCl_3$) 7.37–7.29 (10H, m, ArH), 5.92 (1H, dtd, *J* 15.6, 7.8 and 3.2 Hz, CHO), 4.66–4.60 (3H, m, CH_2Ph + CH*H*CO_2), 4.52 (1H, d, *J* 11.9 Hz, C*H*HCO_2), 4.21 (1H, d, *J* 16.9 Hz, C*H*HPh), 4.16 (1H, d, *J* 16.9 Hz, CH*H*Ph), 3.88 (1H, dt, *J* 11.1 and 2.5 Hz, CHCH*H*), 3.78 (1H, dd, *J* 11.0 and 8.0 Hz, CHC*H*H); δ_C (100 MHz, $CDCl_3$) 168.6 (CO), 137.1 (ArC), 136.8

(ArC), 128.5 (4 × ArCH), 128.1 (2 × ArCH), 128.0 (2 × ArCH), 127.7 (2 × ArCH), 73.3 (2 × PhCH_2), 67.6 (dd, *J* 29.2 and 22.4 Hz, $CHCF_2$), 66.5 (CH_2CO_2), 66.2 (CH_2CH). The CF_2CF_2 carbons were not observed; δ_F (282 MHz, $CDCl_3$) −67.3 (2F, s, CF_2Br), −117.2 (1F, app. d, *J* 269.2 Hz, C*F*FCF_2Br), −122.4 (1F, ddt, *J* 273.6, 16.6 and 4.8 Hz, CF*F*CF_2Br); EIMS: *m*/*z* 389 and 387 ((M − CH_2Ph)$^+$, 8%, 1 : 1 ratio), 283 and 281 (1 : 1 ratio, 21), 107 (32), 91 (100); HRMS (ES+) for $C_{20}H_{19}{}^{79}BrF_4O_4$ (M + Na)$^+$ calcd 501.0295, found 501.0305.

(2*R*)-(2-Benzyloxy-4-bromo-3,3,4,4-tetrafluoro)but-1-yl formate (33)

To a stirred solution of **11** (0.60 g, 1.8 mmol) and DCC (0.41 g, 1.99 mmol) in CH_2Cl_2 (9.6 mL) was added DMAP (0.022 g, 0.18 mmol). The reaction was stirred until complete dissolution upon which formic acid (98%, 0.075 mL, 1.99 mmol) was added and the reaction stirred overnight. The reaction was diluted with hexane (10 mL), then filtered to remove the white precipitate formed and the residue washed with hexane (2 × 5 mL). The filtrate was concentrated *in vacuo* to give a colourless oil. Purification by column chromatography (petroleum ether–Et_2O, 90 : 10) gave a colourless oil (0.633 g, 98%). ν_{max}(film)/cm^{-1} 3035 (w), 2944 (w), 1728 (s), 1134 (s), 1079 (s), 1027 (m), 907 (m); δ_H (300 MHz, $CDCl_3$) 8.01 (1H, s, OCHO), 7.42–7.31 (5H, m, ArH), 4.80 (1H, d, *J* 11.2 Hz, PhC*H*H), 4.72 (1H, d, *J* 11.2 Hz, PhCH*H*), 4.57 (1H, dd, *J* 12.0 and 3.4 Hz, OC*H*HCH), 4.39 (1H, dd, *J* 12.2 and 6.7 Hz, OCH*H*CH), 4.29 (1H, dtd, *J* 14.2, 7.1 and 3.4 Hz, $CHCF_2$); δ_C (75 MHz, $CDCl_3$) 160.1 (CO), 136.1 (ArC), 128.5 (2 × ArCH), 128.4 (ArCH), 128.3 (2 × ArCH), 74.7 (dd, *J* 27.1 and 22.3 Hz, *C*HCF$_2$), 74.6 (CH_2Ph), 60.9 (CH_2CH). The CF_2CF_2 carbons were not observed; δ_F (282 MHz, $CDCl_3$) −63.22 (2F, m, CF_2Br), −112.91 (1F, d, *J* 272.9 Hz, CHC*F*F), −119.64 (1F, app ddd, *J* 277.2 can be observed, CHCF*F*); EIMS: *m*/*z* 360 and 358 (M$^+$, 26%, 1 : 1 ratio), 253 and 251 (6, 1 : 1 ratio), 91 (100); HRMS (ES$^+$) for $C_{12}H_{11}{}^{79}BrF_4NaO_3$ (M + Na)$^+$ calcd 380.9720, found 380.9719.

(2*R*)-[(2-Benzyloxy-4-bromo-3,3,4,4-tetrafluoro)but-1-yl] benzyloxyethanoate (34)

To a stirred solution of **11** (0.5 g, 1.5 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (0.25 mL, 1.81 mmol) and DMAP (0.018 g, 0.15 mmol). The solution was stirred at rt for 5 min and then benzyloxyacetyl chloride (0.29 mL, 1.81 mmol) was added dropwise. The reaction was stirred at rt for 4 h. The reaction was diluted with CH_2Cl_2 (10 mL) then washed with HCl (1 M, aq., 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resultant oil was purified by column chromatography (petroleum ether–acetone, 90 : 10) to give a colourless oil (0.683 g, 95%). ν_{max}(film)/cm^{-1} 2877 (w), 1760 (m), 1455 (m), 1120 (s), 736 (m); δ_H (400 MHz, $CDCl_3$) 7.37–7.33 (10H, m, ArH), 4.78 (1H, d, *J* 11.3 Hz, OCH*H*Ph), 4.69 (1H, d, *J* 11.3 Hz, OC*H*HPh), 4.62 (2H, s, CH_2Ph), 4.58 (1H, dd, *J* 12.1 and 3.5 Hz, CHCH*H*), 4.38 (1H, dd, *J* 12.1 and 6.8 Hz, CHC*H*H), 4.27 (1H, dtd, *J* 14.2, 7.3 and 3.6 Hz, C*H*OBn), 4.07 (2H, s, CH_2CO_2); δ_C (100 MHz, $CDCl_3$) 169.8 (CO), 136.9 (ArC), 136.2 (ArC), 128.5 (4 × ArCH), 128.4 (ArCH), 128.3 (ArCH), 128.1 (2 × ArCH), 128.0 (2 × ArCH), 74.8 (dd, *J* 27.0 and 22.7 Hz, *C*HOBn), 74.5 (CH_2Ph), 73.4 (CH_2Ph), 66.8 (CH_2CO_2), 61.6 ($CHCH_2$). The CF_2CF_2 carbons were not observed; δ_F (282 MHz, $CDCl_3$) −63.51 (2F, m, CF_2Br), −113.21 (1F, app. d, *J* 274.7 Hz, CHCF*F*), −120.05 (1F, ddd, *J* 274.7, 12.9 and 6.4 Hz, CHC*F*F); EIMS *m*/*z* 389 and 387 ((M − $PhCH_2$)$^+$, 29%, 1 : 1 ratio), 331 and 329 (18, 1 : 1 ratio), 283 and 281 (13, 1 : 1 ratio), 181 (24), 132 (28), 107 (72), 91 (100); HRMS (EI) for $C_{20}H_{19}{}^{79}BrF_4NaO_4$ (M + Na)$^+$ calcd 501.0295, found 501.0298.

General procedure for the cyclisation reaction

A solution of the substrate (1 equiv.) in dry CH_2Cl_2 (0.17 M) was filtered through a plug of $MgSO_4$ into a round-bottomed flask. The CH_2Cl_2 was removed under a stream of dry nitrogen, followed by drying under high vacuum for 16 h. The resulting oil was dissolved in THF (10 mL mmol^{-1} substrate) and cooled to −100 to −78 °C. MeLi (1.6 M in Et_2O, 1 equiv) was slowly added dropwise. The reaction was stirred for 3–4 h at −100 to −78 °C. A saturated aqueous solution of NH_4Cl (around 3 mL mmol^{-1} substrate) was added at that temperature, after which the resulting suspension was allowed to warm to room temperature. The mixture was then diluted with H_2O and Et_2O or EtOAc. The layers were separated and the aqueous phase extracted with Et_2O or EtOAc. The organic phases where combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a colourless oil. The mixture was purified by column chromatography and preparative HPLC (hexane or petroleum ether–acetone 80–85 : 20–15).

(5*R*)-5-Benzyloxymethyl-3,3,4,4-tetrafluoro-tetrahydro-furan-2-ol (2)

A colourless oil (0.734 g, 85%) as an inseparable mixture of anomers (approximately 1.4 : 1 ratio). ν_{max}(film)/cm^{-1} 3388 (br. m), 3034 (w), 2928 (w), 1621 (br. w), 1497 (w), 1455 (m), 1239 (m), 1146 (s), 1023 (s); δ_H (400 MHz, $CDCl_3$) 7.42–7.31 (10H, m, ArH), 5.37 (1H, br s, C*H*OH, minor isomer, simplifies upon D_2O exchange), 5.28 (1H, t, *J* 8.9 Hz, C*H*OH, major isomer, simplifies upon D_2O exchange), 4.74 (1H, d, *J* 11.04 Hz, CHO*H*, major isomer, disappears upon D_2O exchange), 4.67–4.52 (5H, m, CH_2Ph, major and minor isomer, C*H*CH$_2$, minor isomer), 4.39 (1H, m, C*H*CH$_2$, major isomer), 3.88 (1H, m, CHO*H*, minor isomer, disappears upon D_2O exchange), 3.88–3.67, (4H, m, CH_2OBn, major and minor isomer); δ_C (100 MHz, $CDCl_3$) 136.87 (ArC), 135.87 (ArC), 128.72 (ArCH), 128.55 (ArCH), 128.51 (ArCH), 128.13 (ArCH), 128.08 (ArCH), 127.94 (ArCH), 96.12 (dddd, *J* 40.1, 22.2, 2.4 and 1.4 Hz, CHOH), 94.72 (dddd, *J* 38.6, 21.3, 2.4 and 1.4 Hz, CHOH, major isomer), 79.34 (dddd, *J* 29.5, 22.7, 2.4 and 1.4 Hz, *C*HCH$_2$, minor or major isomer), 77.20 (m, *C*HCH$_2$, minor or major isomer), 74.22 (Ph*C*H$_2$), 73.87 (Ph*C*H$_2$), 66.36–66.24 (m, 2 × *C*H$_2$OBn); δ_F (376 MHz, $CDCl_3$) −116.84 (1F, dd, *J* 245.0 and 6.5 Hz, HOCHCF*F*), −119.24 (1F, dd, *J* 248.0 and 13.0 Hz, HOCHCF*F*), −124.83 (1F, d, *J* 247.0 Hz, CH_2CHCFF), −125.65 (1F, dd, *J* 250.0 and 8.0 Hz, HOCHC*F*F), −127.67 (1F, dd, *J* 247.0 and 7.0 Hz, HOCHC*F*F), −128.11 (1F, m, CH_2CHCFF), −130.82 (1F, d, *J* 249.0 Hz, CH_2CHCFF), −134.06 (1F, dd, *J* 246.0, 15.0 Hz, CH_2CHCFF); EIMS: *m*/*z* 280 (M$^+$, 5%), 91 (100). HRMS (EI) for $C_{12}H_{12}F_4O_3$ (M)$^+$: calcd 280.07226, found 280.07206.

(2*R*)-1-Benzyloxy-3,4,4-trifluorobut-3-en-2-ol (30)

Colourless oil. ν_{max}(film)/cm^{-1} 3396 (m, br), 2870 (m), 1790 (s), 1455 (m), 1309 (s), 1257 (s), 1104 (s); δ_H (300 MHz, $CDCl_3$) 7.42–7.31 (5H, m, ArH), 4.67–4.54 (3H, m, C*H*$_2$Ph and C*H*OH), 3.70 (1H, dd, *J* 9.6 and 7.5 Hz, CHC*H*H), 3.65 (1H, dd, *J* 9.6 and 5.2 Hz, CHCH*H*), 2.82 (1H, br s, OH); δ_C (100 MHz, $CDCl_3$) 137.2 (ArC), 128.5 (2 × ArCH), 128.0 (ArCH), 127.8 (2 × ArCH), 73.5 (*C*H$_2$Ph), 69.7 (*C*H$_2$CH), 64.7 (CH, d, *J* 20.9 Hz, CHOH). The CF_2CF_2 carbons were not observed; δ_F (282 MHz, $CDCl_3$ referenced to $CFCl_3$) –100.94 (1F, dd, *J* 76.2 and 33.2 Hz, C*F*F), –119.18 (1F, ddd, *J* 114.8, 76.2 and 2.1 Hz, CF*F*), –188.88 (1F, ddd, *J* 114.8, 32.2 and 24.7 Hz, CF); ES$^+$MS *m*/*z* 255.2 ((M + Na)$^+$, 100%); HRMS (ES+) for $C_{11}H_{11}F_3NaO_2$ (M + Na)$^+$ calcd 255.0603, found 255.0603.

(5*R*)-2,5-Bisbenzyloxymethyl-3,3,4,4-tetrafluoro tetrahydrofuran-2-ol (3)

A colourless oil (0.084 g, 75%), as an inseparable mixture of anomers. ν_{max}(film)/cm^{-1} 3398 (w), 3032 (w), 2876 (w), 1497 (w), 1454 (m), 1366 (w), 1148 (s), 1101 (s); δ_H (400 MHz, $CDCl_3$) 7.21–7.10 (20H, m, ArH), 4.51–4.21 (10H, m), 4.07 (1H, br s), 3.66–3.45 (8H, m); δ_C (100 MHz, $CDCl_3$) 137.3 (C), 136.9 (C), 136.8 (C), 136.6 (C), 128.59 (2 × CH), 128.52 (2 × CH), 128.51 (2 × CH), 128.4 (2 × CH), 128.25 (CH), 128.11 (CH), 128.04 (CH), 127.94 (2 × CH), 127.88 (3 × CH), 127.85 (2 × CH), 127.72 (2 × CH), 99.3 (m, C), 98.7 (dd, *J* 31.1 and 21.4 Hz, C), 78.2 (dd, *J* 29.1 and 24.3 Hz, CH), 77.2 (dd, *J* 28.0 and 23.2 Hz, CH), 74.10 (CH_2), 74.03 (CH_2), 73.79 (CH_2), 73.64 (CH_2), 68.6 (m, CH_2), 68.1 (d, *J* 4.9 Hz, CH_2), 67.3 (dd, *J* 6.3 and 3.4 Hz, CH_2), 66.12 (d, *J* 7.8 Hz, CH_2); δ_F (282 MHz, $CDCl_3$) –111.1 (1F, dddd, *J* 243.0, 11.7, 4.2 and 2.7 Hz, CF*F*C), –122.35 (1F, ddt, *J* 245.5, 13.8 and 5.4 Hz, C*F*FC), –123.49 (1F, m, CF*F*C), –129.4 (1F, dt, *J* 239.4 and 5.0 Hz, CHCF*F*), –130.81 (1F, d, *J* 185.7 Hz, CHCF*F*), –131.45 (1F, d, *J* 184.5, CHCF*F*), –131.90 (1F, dt, *J* 241.0 and 6.3 Hz, CHC*F*F), –134.10 (1F, dd, *J* 243.5, 13.9 and 5.4 Hz, C*F*FC); CIMS: *m*/*z* 418 ((M + NH_4)$^+$, 8%), 309 (2), 106 (100), 91 (65); HRMS (ES+) for $C_{20}H_{20}F_4O_4$ (M)$^+$ calcd 423.1190, found 423.1186.

(2*S*,5*R*)-5-Benzyloxy-3,3,4,4-tetrafluoro tetrahydropyran-2-ol (4α) and (2*R*,5*R*)-5-benzyloxy-3,3,4,4-tetrafluoro tetrahydropyran-2-ol (4β)

White solids: **4α** (0.028 g, 18%) and **4β** (0.08 g, 51%).

Data for **4α**: mp 85–88 °C; ν_{max}(film)/cm^{-1} 3380 (m), 1216 (m), 1134 (s), 1115 (m), 1067 (s), 1053 (s), 1028 (m), 988 (m); δ_H (400 MHz, $CDCl_3$) 7.41–7.33 (5H, m, ArH), 5.09 (1H, br s, C*H*OH), 4.89 (1H, d, *J* 11.8 Hz, CH*H*Ph), 4.68 (1H, d, *J* 12.1 Hz, C*H*HPh), 4.05 (1H, m, CHCH*H*), 3.89 (1H, m, C*H*OBn), 3.72 (1H, dt, *J* 11.9 and 4.1 Hz, CHC*H*H), 3.56 (1H, m, OH); δ_C (100 MHz, $CDCl_3$) 136.5 (ArC), 128.7 (2 × ArCH), 128.4 (ArCH), 128.1 (2 × ArCH), 92.0 (dd, *J* 35.2 and 25.1 Hz, CHOH), 74.1 (*C*H$_2$Ph), 73.1 (dd, *J* 20.4 and 19.0 Hz, *C*HOBn), 60.5 (*C*HCH$_2$); δ_F (282 MHz, $CDCl_3$ referenced to $CFCl_3$) –124.51 (1F, br d, *J* 268.6 Hz, CF*F*), –124.98 (1F, br d, *J* 262.2 Hz, C*F*F), –130.76 (1F, dt, *J* 264.3 and 15.0 Hz, C*F*F), –136.24 (1F, dd, *J* 269.7 and 15.0 Hz, CF*F*); EIMS *m*/*z* 280 (M$^+$, 50%), 262 (8), 107 (49), 91 (100); HRMS (ES$^+$) for $C_{12}H_{12}F_4NaO_3$ (M + Na)$^+$ calcd 303.0615, found 303.0614.

Data for **4β**: mp 86–88 °C; ν_{max}(film)/cm^{-1} 3356 (br m), 2893 (w), 1346 (w), 1231 (m), 1136 (m), 1117 (m), 1066 (s), 975 (s), 949 (m); δ_H (400 MHz, $CDCl_3$) 7.41–7.35 (5H, m, ArH), 4.94 (1H, br s, C*H*OH), 4.89 (1H, d, *J* 12.0 Hz, C*H*HPh), 4.67 (1H, d, *J* 12.0 Hz, CH*H*Ph), 3.99 (1H, dt, *J* 12.1 and 4.7 Hz, CHC*H*H), 3.90 (1H, m, C*H*OBn), 3.57 (1H, m, CHCH*H*), 3.36 (1H, br s, OH); δ_C (100 MHz, $CDCl_3$) 136.5 (ArC), 128.7 (2 × ArCH), 128.5 (ArCH), 128.1 (2 × ArCH), 92.1 (ddd, *J* 28.9, 21.6 and 2.2 Hz, CHOH), 74.2 (*C*H$_2$Ph), 73.0 (t, *J* 19.2 Hz, *C*HOBn), 61.7 (dd, *J* 6.1 and 1.7 Hz, CH*C*H$_2$); δ_F (282 MHz, $CDCl_3$ referenced to $CFCl_3$) –127.99 (1F, d, *J* 263.3 Hz, C*F*FCHOH), –133.1 (1F, dt, *J* 261.1 and 16.1 Hz, C*F*FCHOBn), –134.18 (1F, d, *J* 263.3 Hz, CF*F*CHOH), –139.27 (1F, m, *J* 262.2 Hz can be observed, CF*F*CHOBn); EIMS *m*/*z* 280 (M$^+$, 19%), 262 (3), 107 (22), 91 (100); HRMS (ES$^+$) for $C_{12}H_{12}F_4NaO_3$ (M + Na)$^+$ calcd 303.0615, found 303.0615.

(5*R*)-2,5-Bisbenzyloxymethyl-3,3,4,4-tetrafluoro tetrahydropyran-2-ol (5)

Preparative HPLC (hexane–acetone, 85 : 15) gave **5** as a single anomer (0.11 g, 65%) and mixed fractions containing both **5a** and **5b** (0.017 g, 10%). The data given are for the major isomer **5a**. ν_{max}(film)/cm^{-1} 3489 (br w), 3033 (w), 2879 (w), 1455 (m), 1303 (m), 1214 (m), 1104 (s), 1062 (s), 926 (m); δ_H (400 MHz, $CDCl_3$) 7.41–7.31 (10H, m, ArH), 4.90 (1H, d, *J* 12.1 Hz, CHOC*H*HPh), 4.70 (1H, d, *J* 12.0 Hz, CH$_2$OC*H*HPh), 4.68–4.62 (2H, m, CH$_2$OCH*H*Ph + CHOCH*H*Ph), 4.20 (1H, t, *J* 2.8 Hz, OH), 4.04 (1H, t, *J* 11.2 Hz, CHC*H*H), 3.90 (1H, m, C*H*OBn), 3.75 (1H, d, *J* 10.7 Hz, C*H*HOBn), 3.72 (1H, m, CHCH*H*), 3.62 (1H, app d, *J* 10.6 Hz, CH*H*OBn); δ_C (100 MHz, $CDCl_3$) 136.8 (ArC), 136.6 (ArC), 128.63 (2 × ArCH), 128.61 (2 × ArCH), 128.33 (ArCH), 128.30 (ArCH), 127.98 (2 × ArCH), 127.92 (2 × ArCH), 95.5 (dd, *J* 28.2 and 25.3 Hz, *C*CF$_2$), 74.4 (*C*H$_2$Ph), 74.2 (*C*H$_2$Ph), 72.7 (t, *J* 18.5 Hz, *C*HCF$_2$), 68.4 (d, *J* 3.9 Hz, *C*H$_2$OBn), 59.3 (d, *J* 7.8 Hz, CH*C*H$_2$); δ_F (282 MHz, $CDCl_3$ referenced to $CFCl_3$) –127.41 (1F, dddd, *J* 254.7, 19.9, 9.7 and 5.4 Hz, CF*F*COH), –127.92 (1F, m, *J* 264.0 Hz can be observed, C*F*FCOH), –130.39 (1F, dtd, *J* 255.8, 17.2 and 7.5 Hz, CHCF*F*), –135.71 (1F, ddd, *J* 266.5, 17.3 and 9.9 Hz, CHC*F*F); EIMS *m*/*z* 309 ((M – Bn)$^+$, 10%), 91 (100); HRMS (ES+) for $C_{20}H_{20}F_4NaO_4$ (M + Na)$^+$ calcd 423.1190, found 423.1192.

(5*R*)-3,3,4,4-Tetrafluoro tetrahydropyran-2,5-diol (2,3-dideoxy-2,2,3,3-tetrafluororibopyranose) (6)

To a stirred solution of **2** (0.1 g, 0.36 mmol) in EtOAc (2.9 mL) was added Pd(OH)$_2$/C (10% Pd/C, 0.12 g). The flask was evacuated and purged with H_2. This sequence was repeated twice more and then the reaction allowed to stir for 4 h. The reaction was diluted with EtOAc (10 mL) and then filtered through celite. The residue was washed with EtOAc (2 × 10 mL) and the combined filtrates concentrated *in vacuo*. The resulting oil was purified by column chromatography (petroleum ether–acetone, 70 : 30) to give a colourless oil (0.067 g, 98%) which solidified on standing, which was found to be **6** as an inseparable 2.8 : 1 mixture of anomers. Mp 87–89 °C; ν_{max}(film)/cm^{-1} 3313 (br m), 2968 (w), 1635 (br w), 1264 (m), 1206 (m), 1111 (s), 1065 (s), 1040 (s),

997 (s); δ_H (400 MHz, d_6-DMSO) 7.87 (1H, d, *J* 6.52 Hz, OCHO*H*, major isomer, disappears upon D_2O exchange), 7.69 (1H, d, *J* 4.02 Hz, OCHO*H*, minor isomer, disappears upon D_2O exchange), 6.18 (1H, d, *J* 5.77 Hz, CH_2CHOH, major isomer, disappears upon D_2O exchange), 6.13 (1H, d, *J* 6.53 Hz CH_2CHOH, minor isomer, disappears upon D_2O exchange), 5.14 (1H, m, OC*H*OH, minor isomer, simplifies to ddd, *J* 7.0, 5.2 and 1.7 Hz upon D_2O exchange), 4.90 (1H, m, OC*H*OH, major isomer, simplifies to app. dd, *J* 14.7 and 3.9 Hz), 3.40–3.89 (3H, m, 2 × CF_2CH + C*H*H), 3.81 (1H, t, *J* 10.4 Hz, C*H*H, minor isomer), 3.66 (1H, m, CH*H*, minor isomer), 3.42 (1H, t, *J* 10.3 Hz, C*H*H, major isomer); δ_C (100 MHz, d_6-DMSO) 91.4 (m, OCHOH, major isomer), 90.9 (dd, *J* 35.1 and 24.3 Hz, OCHOH, minor isomer), 66.6–66.1 (m, 2 × CH_2CH), 62.7 (d, *J* 6.8 Hz, CH_2, major isomer), 60.0 (CH_2, minor isomer); δ_F (376 MHz, d_6-DMSO, recorded at 50 °C) −121.25 (1F, br d, *J* 261.0 Hz, CF_2CFFCH), −127.15 (1F, br d, *J* 250.7 Hz, CF_2CFFCH), −128.87 (1F, bdd, *J* 253.3 and 13.4 Hz, CF_2CFFCH), −130.95 (1F, ddd, *J* 252.6, 16.7 and 5.8 Hz, $CHCFFCF_2$), −132.66 (1F, br d, *J* 254.5 Hz, CF_2CFFCH), −132.86 (1F, ddd, *J* 214.3, 16.1 and 4.9 Hz Hz, $CHCFFCF_2$), −133.54 (1F, ddd, *J* 223.2, 16.1 and 6.5 Hz, $CHCFFCF_2$), −136.80 (1F, ddd, *J* 257.9, 16.8 and 5.4 Hz, $CHCFFCF_2$); ESMS (ES^-) *m*/*z* 189 ($M - H^+$, 100%), 161 (12), 149 (8), 129 (22); HRMS (ES^+) for $C_5H_6F_4NaO_3$ $(M + Na)^+$ calcd 213.0145, found 213.0148.

(5*R*)-2-Hydroxymethyl-3,3,4,4-tetrafluoro tetrahydropy-ran-2,5-diol (3,4-dideoxy-3,3,4,4-tetrafluorofructopyranose) (7)

To a stirred solution of **3** (0.50 g, 1.25 mmol) in EtOAc (10 mL) was added $Pd(OH)_2/C$ (10% Pd/C, 0.40 g). The flask was evacuated and purged with H_2. This sequence was repeated twice more and then the reaction allowed to stir for 16 h. The reaction was diluted with EtOAc (30 mL) and then filtered through celite. The residue was washed with EtOAc (2 × 30 mL) and the combined filtrates concentrated *in vacuo.* The resulting oil was purified by column chromatography (petroleum ether–acetone, 60 : 40) to give a colourless oil (0.26 g, 96%), which was found to be **7** as an inseparable mixture of anomers (ratio approximately 14 : 1). ν_{max}(film)/cm^{-1} 3354 (br m), 1698 (m), 1150 (s), 1094 (s), 1046 (s), 870 (s); δ_H (400 MHz, d_6-DMSO) 6.83 (1H, br s, OH, major isomer), 6.70 (1H, br s, OH, minor isomer), 6.10 (1H, br s, OH, major isomer), 5.96 (1H, br s, OH, minor isomer), 5.13 (2H, m, 2 × CH_2OH, major and minor isomer), 4.09 (1H, d, *J* 12.8 Hz, CH*H*OH, minor isomer), 3.90 (2H, m, 2 × C*H*OH), 3.77 (1H, t, *J* 10.39 Hz, CHCH*H*, major isomer), 3.65 (1H, m, CHC*H*H, major + minor isomer), 3.58 (1H, d, *J* 12.1 Hz, C*H*HOH, major isomer), 3.53 (1H, app. s, CH*H*OH, minor isomer), 3.48 (1H, d, *J* 11.8, CH*H*OH, major isomer); δ_C (100 MHz, d_6-DMSO) 95.6 (dd, *J* 29.2 and 21.9 Hz, CCF_2, major isomer, signal minor isomer is obscured), 67.9 (dd, *J* 30.8 and 18.7 Hz, $CHCF_2$, minor isomer), 66.0 (t, *J* 18.95 Hz, $CHCF_2$, major isomer), 61.7 (CH_2OH, major isomer), 61.6 (CH_2OH, minor isomer), 59.4 (d, *J* 7.3 Hz, 2 × CH_2OC, major isomer, signal minor isomer is obscured); δ_F (282 MHz, d_6-DMSO referenced to $CFCl_3$) −115.83 (1F, ddt, *J* 260.0, 15.0 and 7.5 Hz, CF*F*COH, minor isomer), −123.80 (1F, ddd, *J* 261.8, 17.2 and 7.5 Hz, C*F*FCOH, minor isomer), −124.51 (1F, m, *J* 262.2 can be observed, C*F*FCOH, major isomer), −128.06 (1F, m, *J* 248.2 Hz can be seen, C*F*FCHOH, major isomer), −128.27 (1F, m, *J* 260.5 Hz can be seen, CF*F*COH, minor isomer), −129.39 (1F, dddd, *J* 247.8, 18.2, 16.1 and 6.4 Hz, CF*F*CHOH, major isomer), −132.32 (1F, dddd, *J* 261.8, 15.0, 9.7 and 5.4 Hz, CF*F*CHOH, minor isomer), −133.88 (1F, m, C*F*FCHOH, major isomer); ESMS (ES+) *m*/*z* 243 ($(M + Na)^+$, 55), 139 (100); HRMS (ES^+) for $C_6H_8F_4NaO_4$ $(M + Na)^+$ calcd 243.0257, found 243.0251.

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