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# Synthesis of 4,4-difluoroglycosides using ring-closing metathesis

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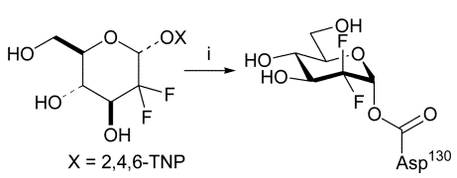
4-Deoxy-4,4-difluoro-glycosides have been synthesised for the first time *via* a direct sequence involving ring-closing metathesis and indium-mediated difluoroallylation with 1-bromo-1,1-difluoropropene in water. Two protecting group strategies were explored, one to allow protection of the primary C-6 hydroxyl group throughout the sequence, while the second was intended to allow deprotection after RCM and before dihydroxylation. The benzyl ether could be used in the first role, and pivaloyl is effective in the second. Dihydroxylations were highly stereoselective and controlled by the orientation of the glycosidic C–O bond.

## Introduction

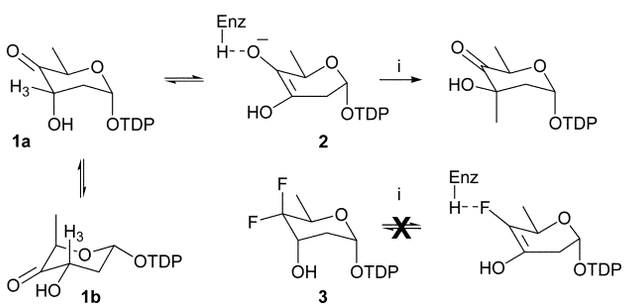
Fluorosugars are of considerable interest because they retain much of the reactivity of natural saccharides while lacking the ability to enter into critical hydrogen bonding interactions with nucleic acids or proteins. In addition, suitably placed fluorine atoms can modulate the chemistry of the glycosidic bond strongly,[1] an effect that has been exploited in the study of carbohydrate processing enzymes.[2] Most spectacularly, substitution at the 2-position has allowed crystallographic studies of glycosyl enzyme intermediates to be performed,[3] while 2,2-difluorosugars have been used to label active site nucleophiles in inverting glycosidases.[4] In the latter cases, the glycosidic bond is so stable that enzymatic digestion of the glycosyl enzyme intermediate can be achieved, yielding valuable sequence information (Scheme 1).




**Scheme 1** Reaction leading to the inhibition of α-galactosidase (i) from *Phanerochaete chrysosporium*.

Both electrophilic and nucleophilic fluorination methods have been applied to the synthesis of 2-deoxy-2-fluoro-[5] and 2-deoxy-2,2-difluoro-sugars.[4,6] Glycal fluorination typifies the former approach, while transformations of hydroxyl or ketonic carbonyl groups with DAST account for the latter. There have been well-documented complications arising from the well-defined stereoelectronic relationships around the sugar ring;[7] neighbouring group participation, group shifts and elimination reactions have all attended fluorinations and difluorinations with DAST.[8] While difluorination at the 2- and 3-positions has been described, we found no papers describing the synthesis of 4-deoxy-4,4-difluorosugars. Liu has however, published a DAST-based 10-step route to TDP 4,4-difluoro-2,4,6-trideoxy-sugar **3**, a proposed methyltransferase inhibitor, from a known sugar epoxide.[9]

The reaction catalysed by the C-3 methyltransferase is a key step in the biosynthesis of the antibiotic Tylosin by *Streptomyces fradiae*. The proposed mechanism (Scheme 2) involves deprotonation of the ketodeoxysugar **1** (drawn in conformer **1a**) to form enolate **2**; methylation occurs at C-3 with inversion of hydroxyl group configuration. Liu proposed that **3** would undergo dehydrofluorination: the fluoroenol product would not be able to undergo the C-3 methylation and the enzyme would be inhibited, but exposure of the enzyme to **3** failed to result in either inhibition or fluoride ion release. The proposal is a surprising one given the unsuitable stereoelectronic relationship between the C–$H_3$ bond and the carbonyl π* orbital; conformer **1b** appears a more likely precursor to the enolate.[10]




**Scheme 2** *Proposed C-3 methyltransferase mechanism*. i, TylC3, AdoMet (ref. 9).

Also, C–F bonds are very strong and dehydrofluorination normally requires quite forcing conditions, so it seems unlikely that an enzyme set up to enolise a ketone would be able to achieve this more demanding conversion. An alternative application for 4-deoxy-4,4-difluorosugars could involve activated derivatives like **3** in other roles. The effect of the two fluorine atoms would be to stabilize the bond to the TDP leaving group considerably (given that a single fluorine atom has a strong effect upon the ability to ascend to oxacarbenium ion-like transition states). Such compounds could be used to probe the binding sites of glycosyltransferase enzymes.[11]

Building block syntheses of 4,4-difluorohexose analogues had not yet been completed at the start of our study. Taguchi[12] synthesised dihydropyrone **5** from 1,1-difluoro-2,4-dialkoxy-1,3-butadiene **4** using a hetero Diels–Alder reaction (Scheme 3), and advanced the intermediate dihydropyrone to racemic 2,4-dideoxy-4,4-difluorosugar **6**, but did not describe the 4-deoxy-4,4-difluorosugars **7**. Since then, Uneyama[13] has shortened the synthesis of an analogue of **4**, and of pyrones **5**, though further elaboration has not been described. In this

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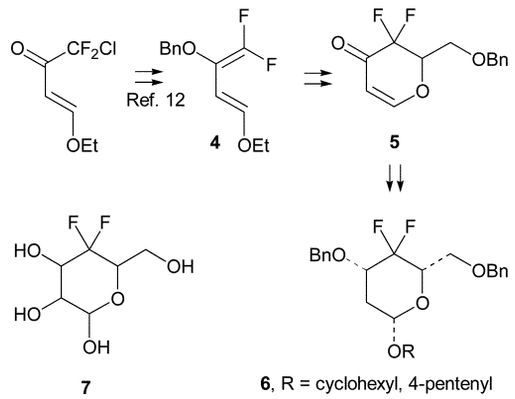
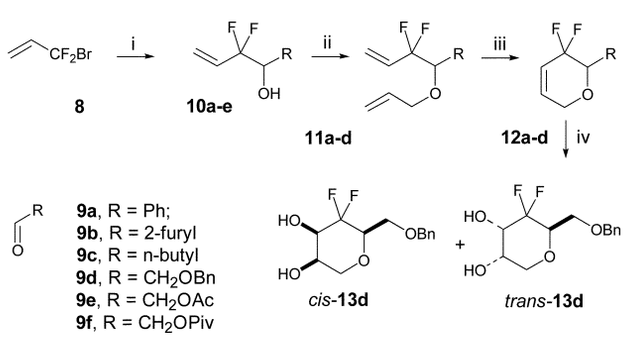



**Scheme 3** Taguchi route to racemic 2,4-dideoxy-4,4-difluorosugar **6**.

manuscript, we wish to describe completed syntheses of racemic **7**. The route delivers novel sugars, and tests the scope and limitations of RCM reactions which contain a difluorinated allyl fragment.

## Results and discussion

Recently, we described a useful combination of difluoroallylation and ring-closing metathesis reactions for the rapid synthesis of difluorinated pyrans.[14] Seyferth[15] and Burton[16] had described efficient additions of 1-bromo-1,1-difluoropropene to aldehydes, but the sub-millimole scale procedure reported by Kirihara and co-workers[17] seemed particularly convenient. We were surprised to note that stirring was used, given the propensity of indium powder to agglomerate; indeed, the method failed to work in our hands when stirring was employed. However, when suspensions of reactants were shaken vigorously or sonicated, we were able to reproduce their result with benzaldehyde (though not to match the reported yield of 99%) and achieve reaction with furfural, pentanal and benzyloxyacetaldehyde as an illustrative set of aldehydes in moderate to good yield (Scheme 4). The reaction required a modest excess of the propene (1.5 equivalents).

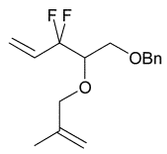



**Scheme 4** *Synthesis of pyrans from 1-bromo-1,1-difluoropropene*: i, In, DMF, RCHO **9**; ii, NaOH, $TBAHSO_4$, allyl bromide, water, rt; iii, 5% Grubbs' catalyst, DCM, rt; iv, $OsO_4$, NMO, *t*-BuOH, acetone, water, rt.

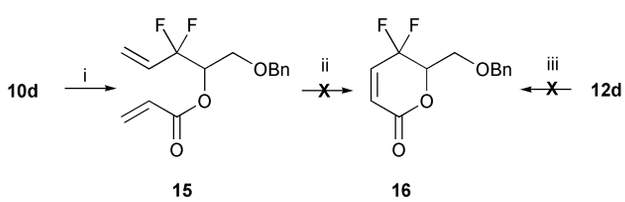
Allylations of **10a**–**10d** were facile under phase transfer-catalysed conditions,[18] delivering the ethers **11a**–**11d** in high purity (shown by GC). The ethers were sufficiently pure for use in the RCM reaction, directly following removal of the extraction solvent. All four ethers delivered pyran products upon exposure to Grubbs' catalyst[19] in DCM for 24 hours at room temperature, with a particularly good yield being obtained for **9d** (97%). A rather poor yield (23%) of **9d** was obtained when polymer-supported Grubbs' catalyst[20] was used for the reaction, even after an extended reaction time (5 days) with a relatively high loading of catalyst (10%).

Dihydroxylation occurred slowly and without discrimination between the alkene faces to afford **13d** as a 1 : 1 mixture of separable *cis* and *trans* isomers in moderate yield.

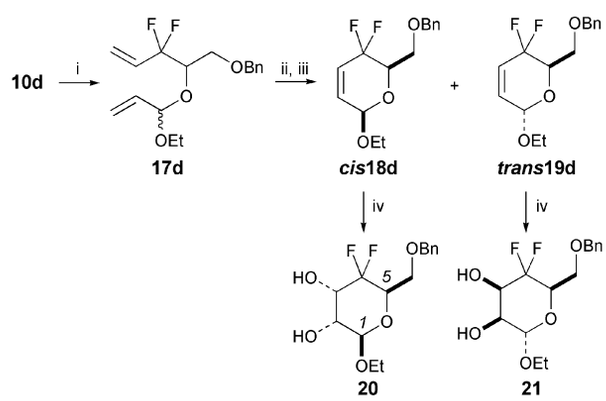
Methallyl ether **14d** was prepared in the same way but failed to undergo RCM, even after one week in DCM at reflux with Grubbs' catalyst; this result has implications for the sequence of events in these RCM reactions, which we will discuss later.




The most direct approach to the synthesis of unknown difluorosugars **7** would involve either direct oxidation of **12d** to the lactone **16** using $CrO_3$/3,5-dimethylpyrazole[21] or RCM of acryloyl ester **15** (Scheme 5). Exposure of **12d** to the oxidation conditions resulted in destruction of the starting material; no identifiable fluorinated products were obtained following solvent extraction of the black tar that formed the reaction products. Acryloyl ester **15** was prepared, but failed to undergo RCM to any appreciable extent in the presence of either of the Grubbs' or Nolan catalysts,[22] either in DCM or DCE over 7 days. We decided also to explore the transacetalisation with acrolein diethyl acetal described by Mulzer,[23] followed by RCM which would deliver a mixture of diastereoisomeric dihydropyrans. Ideally, these would be separated before dihydroxylation to avoid potential problems with the separation of highly polar sugars (Scheme 6).




**Scheme 5** *Reagents and conditions:* i, acryloyl chloride, $Et_3N$, DCM, 0 °C to rt, 16 h; ii, 5–10% Grubbs' or Nolan catalyst, DCM or DCE, reflux 7 days; iii, 3,5-dimethylpyrazole, $CrO_3$, DCM, −20 °C.




**Scheme 6** *Synthesis of fully-functionalised pyrans*. i, acrolein diethyl acetal, PhMe, heat, 60 mmHg; ii, 5% Grubbs' catalyst, DCM, reflux, see text; iii, separate; iv, $OsO_4$, NMO, *t*-BuOH, acetone, water, rt.

Alcohol **10d** was transacetalised with acrolein diethyl acetal to afford **17d** in acceptable (63%) yield after column chromatography. The inseparable mixture of diastereoisomers underwent RCM smoothly to afford a 1 : 1 mixture of *cis*-**18d** and *trans*-**19d** (Fig. 1) in dichloromethane at reflux with either Grubbs' (3 days, 76%) or Nolan[22] (4 hours, 75%) catalysts under relatively concentrated conditions (0.17 M). The reactions were followed by TLC, so the *ca*. 20-fold difference in reaction time represents a genuine difference in rate. Dihydroxylation of the mixture under conventional UpJohn conditions[24] was very slow, taking 10 days to reach completion with the addition of additional osmium tetroxide after 5 days, but affording the

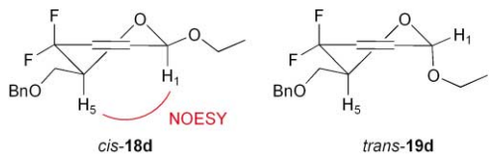


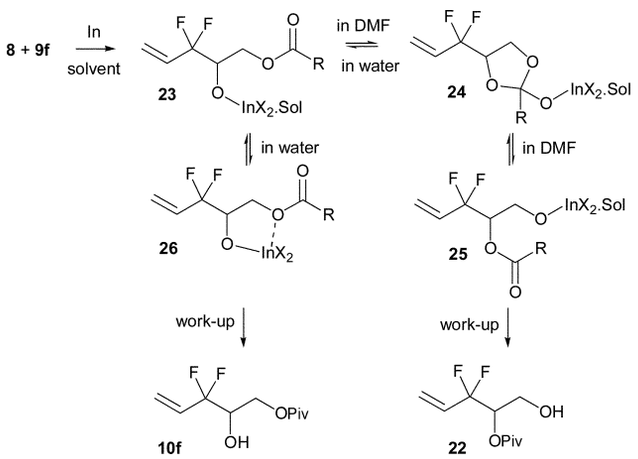

**Fig. 1** Three-dimensional representations of **18d** and **19d** showing the protons giving rise to the key NOESY cross peak.

sugars in 65% yield. The sluggishness with which the substrates react may be due to the fact that each alkene bears two -*I* substitutents at each allylic position. Fortunately, very careful flash column chromatography with a non-polar eluent (5% diethylether in 40–60 petroleum ether) allowed the almost complete separation of **18d** and **19d** though the $R_F$'s were rather close (0.25 and 0.28); this procedure was used to prepare 500 mg of each pure racemic diastereoisomer.

The *cis* and *trans* dihydropyrans **18d** and **19d** were identified by NOESY experiments. The H-5 proton can be identified easily from COSY experiments and by the clear coupling to fluorine within a rather complex splitting pattern. A clear cross peak between H-1 and H-5 in the NOESY could be observed for only one of the pyran diastereoisomers, which was assigned as **18d**. The H-5 signal occurs at significantly different chemical shifts in the two diastereoisomers (4.50 ppm in the *trans*, 4.10 ppm in the *cis*). In the *trans*-diastereoisomer, the location of the ethoxy group in a *pseudo*-axial environment allows an n–σ* interaction between the pyran oxygen and the glycosidic bond which may deshield the $H_5$ proton inductively relative to the corresponding environment in the *cis* diastereoisomer. The NMR spectra of both diastereoisomers show large $^3J_{H-F}$ couplings consistent with the presence of *pseudo*-diaxial H–F relationships (22.8 Hz *trans*, 17.8 Hz *cis*) and, where resolved, much smaller *pseudo*-axial–*pseudo*-equatorial $^3J_{H-F}$ couplings (*ca.* 3 Hz). Pleasingly, the H-5 protons in both diastereoisomers resolved into identifiable splitting patterns at 400 MHz (*trans* ddt, *cis* dddd), allowing all the coupling constants to be extracted. Dihydroxylation afforded a single sugar product in each case; the assignment of sugar stereochemistry shown in Scheme 6 will be justified later in the manuscript.

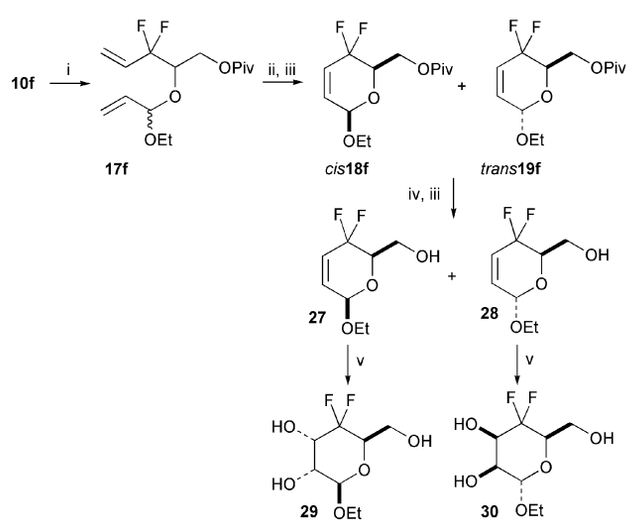
The C-6 hydroxyl group is protected in the products from these sequences, which may be advantageous in subsequent transformations, but we also wished to explore the effect of deprotection of the C-6 hydroxyl group just after RCM in the hope that the diastereoisomer separation would be more facile, and the dihydroxylation more rapid. It was difficult to see how to cleave the benzyl group while leaving the alkenyl group and the acetal function intact, so we explored other potential protecting groups. Attempted transacetalisation of acetoxyacetaldehyde adduct **10e** with acrolein diethyl acetal resulted in cleavage of the acetate and the formation of a complex reaction mixture. Next, we investigated the bulky pivaloyl group to attempt to suppress side reactions in the transacetalisation. The aldehyde was prepared from *Z*-1,4-butenediol on a 10g scale. Surprisingly, allylation in DMF afforded a mixture of products with the same mass and very similar retention times in the GC (10.78 and 10.86 minutes). These were identified as isomeric products **10f** (58%) and **22** (13%), which contained the pivaloxy group at the *more hindered* position. However, addition in water afforded **10f** alone in excellent (91%) yield on a multigram scale.

The formation of **22** is surprising; given the bulk of the protecting group, it would not be expected to migrate into a more crowded environment. The behaviour of indium(III) alkoxides in solution is quite complex, leading to issues of kinetic and thermodynamic control in crotylation reactions. Chelation is also documented quite extensively, and strong solvent effects have been observed. Solvents such as DMF and THF are believed to coordinate strongly to indium(III) salts,[25] while water seems to favour the formation of chelated species wherever possible.[26] Of course, a significant p$K_a$ difference between the two hydroxyl groups is likely; the adjacent $CF_2$ centre would lower the p$K_a$ of the secondary hydroxyl group by up to 3 p$K_a$ units. A migratory mechanism (Scheme 7) involving a tetrahedral intermediate could lead to what appears to be the expulsion of the poorer of the two leaving groups. In DMF and THF, weak chelation involving the ester alkyl oxygen is overwhelmed by interactions with the solvent, and the monodentate indium alkoxide **23** can exchange through tetrahedral intermediate **24**. The interaction between the C-1 hydroxyl group and indium is stronger than that with the less basic C-2 hydroxyl group, so when **24** breaks down, it releases **25** and not **23**. In water where chelation is extremely important, **26** is stabilized and the exchange reaction through monodentate **23** is not established.




**Scheme 7** Different solvents lead to different regiochemical outcomes in the indium-mediated reaction.

Transacetalisation proceeded smoothly on a 20 gram scale to afford **17f** as a 1 : 1 mixture of diastereoisomeric acetals, then RCM occurred in reasonable yield, though more slowly than for **17d**, under high dilution conditions (0.005 M) with commercial first generation Grubbs' catalyst (added in two portions over 5 days) to afford inseparable pyrans **18f** and **19f** (Scheme 8).




**Scheme 8** *Reagents and conditions*: i, acrolein diethyl acetal, PhMe, heat, 60 mmHg; ii, 5% Grubbs' catalyst, DCM, reflux, see text; iii, separate; iv, DIBAl–H, −78 °C to 0 °C; v, $OsO_4$, NMO, *t*-BuOH, acetone, water, 0 °C to rt, 5d, **29**, 62% and **30**, 62%.

The need for more rigorous conditions (30-fold higher dilution, catalyst replenished, longer reaction time) compared to those employed for **17d** suggests that the presence of an ester protecting group impedes the RCM reaction to a significant extent. After removal of the pivaloyl group by reduction (80% combined isolated yield, 1 : 1 mixture), flash column chromato-

graphic separation of **27** and **28** was straightforward. The $^{19}$F NMR spectra of **27** and **28** raised the same issues encountered for **18d** and **19d**. Dihydroxylation under UpJohn conditions[24] occurred in acceptable (60% isolated) yields in each case. The higher (twofold) rate of dihydroxylation is presumably due to a lower degree of steric hindrance as the smaller hydroxyl group replaces the benzyloxy. Dihydroxylations were spot-to-spot by TLC: the relatively low yields are a result of performing triol isolations from the highly aqueous reaction media.

Both reactions were highly stereospecific; indeed we were only able to detect a single product in each case in the $^{19}$F NMR spectra of crude reaction mixtures. In the $^{1}$H NMR spectra in $d_6$-DMSO, distinct signals were obtained for the three OH protons, whereas most of the CH protons were overlapped. The hydroxyl proton at C-6 appears as a triplet, allowing identification of the H-6 AB system (COSY) and allowing partial assignment of the rest of the spectrum (HMBC). The sense of stereoselection predicted by literature precedent involves attack *trans* to the exocyclic glycosidic C–O bond in each case,[27] so that *cis* **27** affords **29**, and *trans* **28** leads to **30**. The diastereoisomeric triols displayed quite different splitting patterns for the axial fluorine atom in each case; in the first instance, we assigned the relative configurations as shown in Scheme 6 on the basis of the number of large $^{3}J_{H-F}$ splittings (Fig. 2).

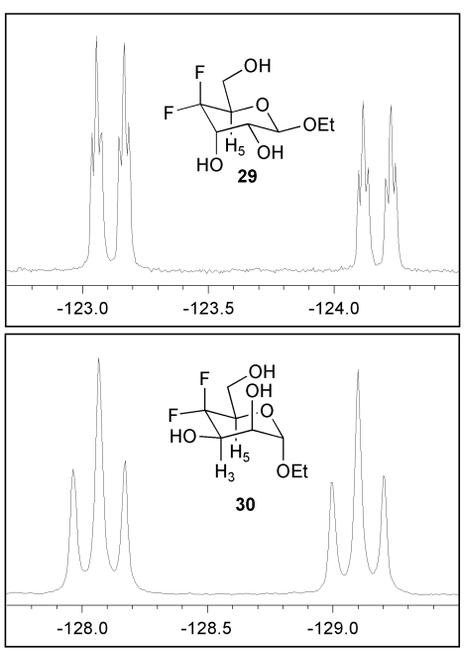



**Fig. 2** Partial $^{19}$F NMR spectra (axial fluorine only shown for each) for **29** and **30**. Both partial spectra show the large $^{2}J_{F-F}$ coupling (249.5 Hz and 242.8 Hz respectively).

Isomer **30** should show two relatively large H–F couplings given that there are two large H–F dihedral angles (to H-3 and H-5) and should therefore display the axial fluorine as a doublet of triplets, whereas **29** should show only one large coupling (to H-5). The axial fluorine in this latter case is a more finely split doublet of doublets. We were able to crystallise **29**‡ and obtain the crystal structure (Fig. 3) to verify the NMR assignment.

This result also confirms the sense of stereoselection in the dihydroxylation and the assignment of relative stereochemistry

‡ Crystallographic data for **29**: $C_8H_{14}F_2O_5$, crystal size 0.29 × 0.18 × 0.16 mm, $M$ = 228.19, triclinic, $a$ = 6.9777(8), $b$ = 8.3569(10), $c$ = 9.3808(11) Å, $\alpha$ = 82.847(2), $\beta$ = 71.230(2), $\gamma$ = 77.901(2) deg, $U$ = 505.45(10) Å$^3$, $T$ = 150(2) K, space group $P$-1, $Z$ = 2, $\mu$(Mo–K$\alpha$) = 0.145 mm$^{-1}$, 3650 reflections measured, 1756 unique ($R_{int}$ = 0.0127) which were used in all calculations. Final $R$ indices [$F^2>2\sigma(F^2)$] $R1$ = 0.0334, w$R2$ = 0.0892; $R$ indices (all data) $R1$ = 0.0359, w$R2$ = 0.0907. CCDC reference numbers 196719. See http://www.rsc.org/suppdata/ob/b3/b313731g/ for crystallographic data in.cif or other electronic format.

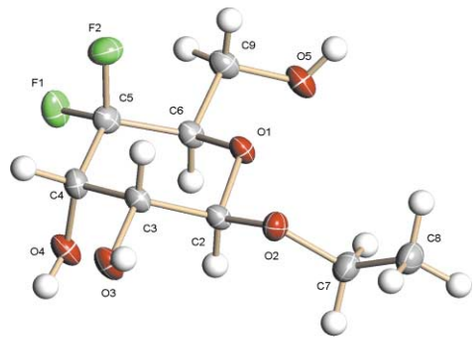
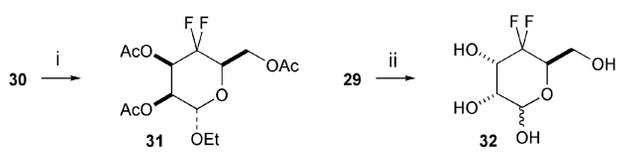



**Fig. 3** ORTEP diagram for **29** showing thermal ellipsoids at 50%.

at the dihydropyran stage. Pyrans **18d** and **19d** behaved identically, leading to the formation of **20** and **21** respectively; product stereochemistries for these sugars, and for pyrans *cis*-**13d** and *trans*-**13d** were assigned in the same way. Pyrans **18d** and **27**, and **19d** and **28** have almost identical $^{19}$F NMR spectra, so the NOESY experiment is validated by the crystal structure of **29**.

Elemental analysis was obtained for **29** and for the triacetate **31** of **30** (Scheme 9). The triacetate shows an extremely well dispersed $^{1}$H NMR spectrum which could be assigned straightforwardly using 2D methods (COSY/HMBC).



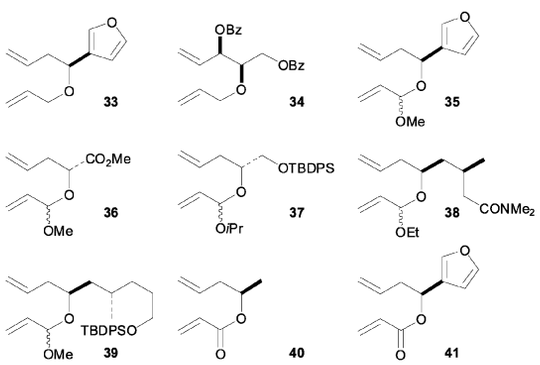

**Scheme 9** *Peracetylation and glycoside hydrolysis*. i, $Ac_2O$, pyridine, 17 h, rt; ii, HCl, 80 °C, 3 days.

Glycoside hydrolysis is a pre-requisite for any useful chemistry of our target molecules, so we explored hydrolysis reactions under simple aqueous conditions. Hydrolysis was complete after 3 days in hot (80 °C) dilute aqueous hydrochloric acid, but the product **32** proved surprisingly difficult to isolate and characterise. The sugar was extracted successfully with ethyl acetate; the aqueous phase was checked carefully for the presence of product, by TLC, concentrating spots of the reaction solution repeatedly and using the phosphomolybdic acid stain to visualise the plates. We were unable to detect any pyranose in the aqueous phase, but the removal of the ethyl acetate returned an extremely disappointing (<20%) yield of product. We were more successful when an ethyl acetate solution was allowed to evaporate slowly at room temperature and pressure but could not obtain a dry sample of material for NMR characterisation. We believe that **32** is surprisingly volatile. Dramatically increased volatility has been described as a consequence of fluorination of sugars. DiMagno synthesised a volatile 2,2,3,3,4,4-hexafluoro-2,3,4-trideoxy 'sugar' from hexafluoroglutaric anhydride and 2-lithiofuran,[28] but we were surprised that **32** proved so elusive, given that only a single hydroxyl group has been replaced. We therefore carried out the hydrolysis in DCl–$D_2O$ to allow direct NMR characterisation of the sugar products. Fortunately, minimal overlap occurred between the ethanol released and the sugar (we could resolve the overlap completely by homodecoupling of the methyl group of the ethanol).

Both anomers can be seen clearly in the $^{1}$H and $^{19}$F NMR spectra. The anomers were distinguished on the basis of the appearance of the H-1 or anomeric proton. In the major β-anomer (the β : α ratio is 6 : 1), the hemiacetal proton appears as a dd with one large (8.0 Hz) coupling consistent with a diaxial coupling to H-2, and a small (0.6 Hz) coupling which was not visible in the $^{1}$H{$^{19}$F} spectrum, indicating that one of the small splittings arises from a long range ($^{5}J_{H-F}$) coupling.[29]

In the minor anomer, H-1 appears as a triplet with a 3.2 Hz splitting; again simplification to a doublet occurred in the $^{1}H\{^{19}F\}$ spectrum so the $^{5}J_{H-F}$ coupling is considerably larger in this case. The size of the *J* value is consistent with an equatorial-axial splitting to H-2. Unfortunately, neither of the long range couplings could be identified readily in the $^{19}F$ NMR spectrum at the highest field strength available to us locally (376.5 MHz). Sugar **32** is related most closely to allose and gulose, for which the normal β : α anomer ratios are 5.5 : 1 and 5.1 : 1 respectively[30] so the introduction of a more electrophilic centre at C-4 has exerted only a modest effect on the composition of the anomeric mixture. We would retain protecting groups on one or more of the other hydroxyl groups during any subsequent processing, to attenuate this volatility.

We were pleased that simple ethers **11a–d** underwent RCM smoothly, and also that acetals **17d** and **17f** could be ring closed, albeit slowly. The failure of acrylate ester **15** to undergo RCM is interesting. There appear to be different fluorine substitutent effects at the three oxidation levels: we believe these effects are electronic rather than conformational. At the ether level, there is no difference in reactivity between the fluorinated and non-fluorinated systems, indicating that the fluorine atoms exert no conformational effect. The fluorinated and non-fluorinated *acetals* are different; **17d** and **17f** both ring-close more slowly than comparable examples **35–39** from the literature (Fig. 4).[23,31–37]




| Substrate | Cat. load (mol%) | T (°C) | Solvent | t (h) | Yield (%) | Ref |
|---|---|---|---|---|---|---|
| 33 | 2 | rt | PhH | (-) | 90 | 31 |
| 34 | 5-7 | 40 | (-) | 1 | 90 | 32 |
| 35 | 0.75 | rt | neat | (-) | 95 | 33 |
| 36 | 5 | rt | DCM | 4 | 74 | 34 |
| 37 | 4.6 | 40 | DCM | 2 | 88 | 35 |
| 38 | 4.9 | 40 | DCM | 6 | 92 | 23 |
| 39 | 10 | rt | DCM | 36 | 85 | 36 |
| 40 | 10 | 40 | DCM | (-) | 81 | 37 |
| 41 | 10c | 40 | DCM | (-) | 65 | 33 |

[a] Not reported. [b] reaction at 0.5 mbar. [c] With 30% $Ti(OiPr)_4$ co-catalyst.

**Fig. 4** Related RCM reactions from the literature.

Terminal allyl groups are highly reactive in both RCM and reversible cross metathetical homodimerisation reactions. Ethers **33** and **34**, and acetals **35–39** can all react *via* a common mechanism in which rapid formation and turnover of a reactive new alkylidene from a terminal allyl group precedes rapid six-membered ring closure. Acrylate esters **40** and **41** can react by the same mechanism.

It is very difficult to compare reaction rates accurately from the literature data, but it appears that the electronic properties of the alkene that takes part in the intramolecular metallocycloaddition reaction exert a modest effect on the overall rate. Furthermore, there are no consistent and major differences between the reactions of the ethers, acetals and esters, which have very different conformational properties. The key intramolecular metallocycloaddition reaction must involve a conformation in which the reacting termini can encounter each other; for the esters, this means s-*cis* arrangement **42**, whereas s-*trans* **43** would always be expected to be more stable and more highly populated because of the the n–π* interaction shown (Fig. 5).[38] This preference has a dramatic effect on free radical cyclisation reactions of esters to lactones under tin hydride conditions.

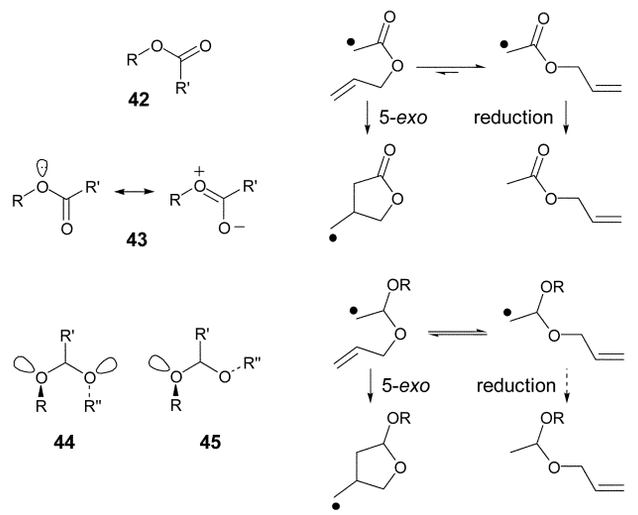
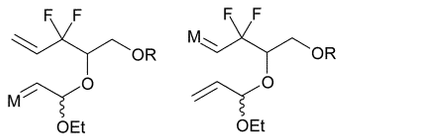



**Fig. 5** Conformations and conformationally-dependent reactions of acetals and esters.

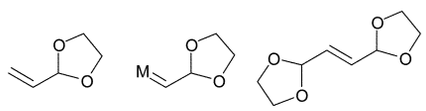
In the favoured s-*trans* conformer, the precursor radical is removed rapidly by reduction, which competes very effectively with the conformational equilibrium. Atom transfer methods,[39] in which the free radical precursor is constantly regenerated, provide an effective solution, *as does a change of oxidation state to the acetal level*. The n–σ* interactions in the acetals are much weaker, so these more flexible precursor radicals interconvert rapidly between conformers such as **44** and **45**. Stork used this property effectively in his eponymous lactonisation sequence (the oxidation level is raised *after* radical cyclisation)[40] and Itoh[41] used a similar indirect approach for the synthesis of difluorolactones from bromodifluoroacetic acid esters, proving that the conformational barriers in the acetal systems are significantly lower.

For acetals **17d** and **17f**, which are significantly less reactive than their non-fluorinated counterparts, we believe that **46** is the key intermediate rather than **47**. Two inductively electron-withdrawing substituents at the allylic position will make the intermediate metal alkylidene less reactive; Hoye and Zhao[42] estimated that a single allylic alkoxy group slowed the formation of a 5-membered ring by RCM by almost an order of magnitude relative to an unsubstituted system. However, alkene **50** can be prepared by the homodimerisation of vinyl dioxolane **48** (though the reaction is slow), consistent with the utility of both vinyl dioxolane and acrolein diethyl acetal in kinetic cross-metathesis reactions with terminal alkenes,[43] and indicating that alkylidene **49** is sufficiently reactive to undergo intermolecular metallocyclobutanation. Alkylidene **46** would therefore be expected to be a competent (if sluggish) intermediate in an intramolecular metallocyclobutanation reaction.[44]

Presumably, methallyl ether **14** fails to react for steric reasons, while acrylate ester **15** cannot react with the catalyst to



46 47



48 49 50

form a competent metal alkylidene complex; the alkoxycarbonyl group is known to have an extremely deleterious effect on the competence of the derived alkylidene. At the start of the study, there were no examples of RCM reactions in which fluorine atoms were located next to one of the alkenyl groups. Now, Blechert[45] and Grubbs[44] have shown examples of *cross* metathesis reactions that involve perfluoroalkyl-substituted alkene components, though they are not reactive substrates for the reaction. Indeed, perfluoroalkyl alkenes are considerably less reactive than acrolein dialkyl acetals in cross metathesis reactions. The key step in both reactions will involve metallocyclobutanation of the first-formed metal alkylidene across the perfluoroalkyl alkene *and not* the formation of a perfluoroalkyl alkylidene complex which would be strongly deactivated by the powerful inductive effect of the perfluoroalkyl group. Metathesis reactions of perfluoroalkyl alkenes remain an area where significant improvements in catalyst activity are required.[46]

Our outcomes show that RCM can be used to cyclise systems like **17** smoothly to build highly-functionalised oxacycles containing a $CF_2$ centre, particularly when the second generation catalysts are used, and that conventional dihydroxylation conditions oxidise electron-deficient alkenes such as **13** effectively and stereoselectively.

The target sugars have great potential for the construction of probes and inhibitors of sugar processing enzymes, work which continues in our laboratories.

## Experimental

NMR spectra were recorded on Bruker ARX-250, Bruker DPX-300, Bruker AC-300 or Bruker DRX-400 spectrometers. $^1$H and $^{13}$C NMR spectra were recorded using the deuterated solvent as the lock and the residual solvent as the internal reference. $^{19}$F NMR spectra were recorded relative to chlorotrifluoromethane as the external standard. The multiplicities of the spectroscopic data are presented in the following manner: app. = apparent, s = singlet, d = doublet, t = triplet, pent. = pentet, q = quartet, m = multiplet and br = broad. The appearance of complex signals is indicated by app. Homocouplings (H–H, F–F) are given in Hertz and specified by *J*; the nuclei involved in heteronuclear couplings are defined with the observed nucleus given first. Unless stated otherwise, all refer to $^3J$ couplings. Carbohydrate numbering is used for the products of dihydroxylation reactions to simplify the reading of the NMR data. Chemical ionisation (CI) mass spectra were recorded on a Micromass Prospec or a Kratos Concept 1H spectrometer using ammonia as the reagent gas. Electron impact (EI) spectra were recorded on a Kratos MS-80, a Micromass Prospec or a Kratos Concept 1H spectrometer. Fast atom bombardment (FAB) spectra were recorded on a Kratos Concept 1H spectrometer at about 7 kV using xenon and *m*-nitrobenzyl alcohol as the matrix. GC-MS was carried out on a Perkin Elmer TurboMass spectrometer fitted with a Zebron ZB-5 column (30 m × 0.25 μm) running a 20–350 °C ramp over 27 minutes. Electrospray (ES) mass spectra were recorded on a Micromass LCT or a Micromass Quattro LC spectrometers. High resolution mass spectrometry measurements were carried out either on the Micromass LCT or the Kratos Concept 1H spectrometers using peak matching to suitable reference peaks, depending on the technique used. Thin Layer Chromatography (TLC) was performed on precoated aluminium silica gel plates supplied by E. Merck, A.G. Darmstadt, Germany (Silica gel 60 $F_{254}$, thickness 0.2 mm, Art. 1.05554) or on precoated plastic silica gel plates supplied by Macherey-Nagel (Polygram® SIL G/UV$_{254}$, thickness 0.25 mm, Art. 805 023) or on precoated glass plates supplied by Merck (Silica gel 60 $F_{254}$, art. 1.05715). Visualisation was achieved by UV light and/or potassium permanganate stain. Flash column chromatography was performed using silica gel (Fluorochem, Silica gel 60, 40–63μ, Art. 02050017) or using a Biotage flash chromatography system. A Transsonic T460/H sonicator was used for sonicated reactions. Ozone was generated by a 500M Fischer Technology ozone generator.THF was dried by refluxing with benzophenone over sodium wire until a deep purple color developed and persisted, then distilled and collected by dry syringe as required. Dichloromethane was dried by refluxing with calcium hydride; it was distilled and collected by dry syringe as required. All other chemicals were used as received without any further purification. Where required, solvents were degassed by bubbling argon or nitrogen through them for at least 30 minutes.

### (Pivaloyloxy)acetaldehyde 9f

Trimethylacetyl chloride (200 mmol, 24.9 mL) was added dropwise to a cold (0 °C) solution of *Z*-2-butene-1,4-diol (100 mmol, 8.2 mL) and pyridine (200 mmol, 16.2 mL). The mixture was allowed to warm to room temperature and stirred for 18 hours. The reaction mixture was quenched with water (100 mL) and extracted with DCM (3 × 100 mL). The combined organic extracts were washed successively with HCl (50 mL of a 1 M solution) and sodium hydrogencarbonate (50 mL of a saturated aqueous solution), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale yellow oil (26.03 g) which was taken up in DCM (250 mL). The solution was cooled to −78 °C and ozone was bubbled through it until complete consumption of the starting alkene (TLC), by which time a persistent blue color had developed in the solution. Nitrogen was bubbled through the solution to remove the excess ozone and the reaction mixture was quenched with triphenylphosphine (110 mmol, 28.85 g), allowed to warm to room temperature and concentrated under reduced pressure to afford a yellow oil (55.02 g), from which part of the triphenylphosphine oxide crystallised. The remaining oil was decanted from the solid and purified by short column chromatography (50% diethyl ether in light petroleum) to afford the desired aldehyde **9f** as a colourless oil (10.24 g, 71% over two steps). $R_f$ (50% diethyl ether in light petroleum) 0.35; $\nu_{max}$ (film)/cm$^{-1}$ 2975s (H–CO), 2874m (C–H), 2719w (H–CO), 1734s (C=O); $\delta_H$ (250 MHz, $CDCl_3$) 9.51 (1H, s, C*H*O), 4.57 (2H, s, H-1′), 1.20 (9H, s, −C(C$H_3$)$_3$); $\delta_C$ (63 MHz, $CDCl_3$) 196.3, 178.3, 68.9, 39.1, 27.5. Spectral data were in agreement with those reported by Grubbs *et al.*[47]

### General procedure for the preparation of difluoro homoallylic alcohols 10a–10d

3-Bromo-3,3-difluoroprop-1-ene **8** (7.5 mmol, 0.76 mL) and the aldehyde **9** (5 mmol) were added successively to a sonicated suspension of indium powder (7.5 mmol, 0.86 g) in DMF (15 mL). The mixture was sonicated for 3 to 5 hours at room temperature. The reaction mixture was then quenched with HCl (20 mL of a 1 M aqueous solution) and extracted with dichloromethane (3 × 25 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford pale yellow oils which were purified by column chromatography.

**2,2-Difluoro-1-phenylbut-3-en-1-ol 10a**

As above from benzaldehyde (5.0 mmol, 0.51 mL) with sonication for 4 hours and purification by column chromatography (15% diethyl ether in light petroleum) to afford **10a** as a colourless oil (0.52 g, 57%, 100% by GC). $R_f$ (15% diethyl ether in light petroleum) 0.28; $\nu_{max}$ (film)/cm$^{-1}$ 3410s br (O–H), 2980w (=C–H), 1647w (C=C); $\delta_H$ (300 MHz, $CDCl_3$) 7.44–7.35 (5H, m, –$C_6H_5$), 5.94–5.77 (1H, m, H-3), 5.59 (1H, d, $J_{trans}$ 17.3, H-4a), 5.47 (1H, d, $J_{cis}$ 11.0, H-4b), 4.89 (1H, td, $J_{H-F}$ 10.6, $J$ 4.1, H-1), 2.60–2.56 (1H, m, –O*H*); $\delta_C$ (63 MHz, $CDCl_3$) 136.4, 129.8 (t, $^2J_{C-F}$ 25.9), 129.1, 128.6, 128.0, 122.0 (t, $^3J_{C-F}$ 9.2), 120.0 (t, $^1J_{C-F}$ 244.4), 76.3 (t, $^2J_{C-F}$ 29.8); $\delta_F$ (282 MHz, $CDCl_3$) −107.9 (1F, dt, $^2J$ 246.8, $J_{F-H}$ 10.6, 10.6), −109.3 (1F, dt, $^2J$ 246.8, $J_{F-H}$ 10.6, 10.6); *m/z* (ES) 207 (100%, $[M + Na]^+$). Spectral data were in agreement with those reported by Burton *et al.*[16]

**2,2-Difluoro-1-phenylbut-3-en-1-ol 10a**

As above from furfuraldehyde (5.0 mmol, 0.41 mL) to afford **10b** as a pale yellow oil (1.24 g, 95%, 100% by GC); $R_f$ (20% diethyl ether in light petroleum) 0.27; $\nu_{max}$ (film)/cm$^{-1}$ 3415s br (O–H), 2923m (C–H), 1652w (C=C); $\delta_H$ (300 MHz, $CDCl_3$) 7.41 (1H, dd, $J$ 1.8, $^4J$ 0.8, H-3′), 6.42 (1H, d, $J$ 3.3, H-5′), 6.37 (1H, dd, $J$ 3.3, 1.8, H-4′), 6.04–5.87 (1H, m, H-2), 5.70 (1H, dtd, $J_{trans}$ 17.3, $^4J_{H-F}$ 2.2, $^2J$ 0.7, H-4a), 5.51 (1H, dd, $J_{cis}$ 11.0, $^2J$ 0.7, H-4b), 4.88 (1H, td, $^3J_{H-F}$ 9.9, $J$ 6.6, H-1), 2.98 (1H, d, $J$ 6.6, –O*H*); $\delta_C$ (75 MHz, $CDCl_3$) 149.5 (t, $^3J_{C-F}$ 3.1), 142.9, 129.5 (t, $^2J_{C-F}$ 25.7), 121.8 (t, $^3J_{C-F}$ 9.3), 118.7 (t, $^1J_{C-F}$ 244.7), 110.6, 109.5 (t, $^4J_{C-F}$ 1.7), 70.2 (t, $^2J_{C-F}$ 31.7); $\delta_F$ (282 MHz, $CDCl_3$) −108.8 (t, $J_{F-H}$ 11.4, 11.4); [HRMS (CI, $[M + NH_4]^+$) Found: 192.084434. Calc. for $C_8H_{12}NO_2F_2$: 192.083614]; *m/z* (CI) 192 (52%, $[M + NH_4]^+$), 174 (62), 157 (28), 139 (100).

**2,2-Difluoro-1-furan-2′-ylbut-3-en-1-ol 10b**

As above from furfuraldehyde (5.0 mmol, 0.41 mL) to afford **10b** as a pale yellow oil (1.24 g, 95%, 100% by GC); $R_f$ (20% diethyl ether in light petroleum) 0.27; $\nu_{max}$ (film)/cm$^{-1}$ 3415s br (O–H), 2923m (C–H), 1652w (C=C); $\delta_H$ (300 MHz, $CDCl_3$) 7.41 (1H, dd, $J$ 1.8, $^4J$ 0.8, H-3′), 6.42 (1H, d, $J$ 3.3, H-5′), 6.37 (1H, dd, $J$ 3.3, 1.8, H-4′), 6.04–5.87 (1H, m, H-2), 5.70 (1H, dtd, $J_{trans}$ 17.3, $^4J_{H-F}$ 2.2, $^2J$ 0.7, H-4a), 5.51 (1H, dd, $J_{cis}$ 11.0, $^2J$ 0.7, H-4b), 4.88 (1H, td, $^3J_{H-F}$ 9.9, $J$ 6.6, H-1), 2.98 (1H, d, $J$ 6.6, –O*H*); $\delta_C$ (75 MHz, $CDCl_3$) 149.5 (t, $^3J_{C-F}$ 3.1), 142.9, 129.5 (t, $^2J_{C-F}$ 25.7), 121.8 (t, $^3J_{C-F}$ 9.3), 118.7 (t, $^1J_{C-F}$ 244.7), 110.6, 109.5 (t, $^4J_{C-F}$ 1.7), 70.2 (t, $^2J_{C-F}$ 31.7); $\delta_F$ (282 MHz, $CDCl_3$) −108.8 (t, $J_{F-H}$ 11.4, 11.4); [HRMS (CI, $[M + NH_4]^+$) Found: 192.084434. Calc. for $C_8H_{12}NO_2F_2$: 192.083614]; *m/z* (CI) 192 (52%, $[M + NH_4]^+$), 174 (62), 157 (28), 139 (100).

**3,3-Difluorooct-1-en-4-ol 10c**

As above from valeraldehyde (5.0 mmol, 0.53 mL) to afford **10c** as a colourless oil (0.47 g, 57%); $R_f$ (10% diethyl ether in light petroleum) 0.22; $\nu_{max}$ (film)/cm$^{-1}$ 3425s br (O–H), 1990w (=C–H), 2915m (C–H), 1650w (C=C); $\delta_H$ (300 MHz, $CDCl_3$) 6.02–5.88 (1H, m, H-2), 5.71 (1H, dtd, $J_{trans}$ 17.3, $^4J_{H-F}$ 4.8, $^2J$ 1.1, H-1a), 5.53 (1H, d, $J_{cis}$ 10.7, H-1b), 3.82–3.69 (1H, m, H-4), 1.95 (1H, d, $J$ 5.5, –O*H*), 1.65–1.25 (6H, m, H-5, H-6 and H-7), 0.91 (3H, t, $J$ 7.0, H-8); $\delta_C$ (75 MHz, $CDCl_3$) 129.7 (t, $^2J_{C-F}$ 26.0), 121.9 (dd, $^1J_{C-F}$ 246.1, 244.3), 121.5 (t, $^3J_{C-F}$ 9.6), 74.5 (dd, $^2J_{C-F}$ 30.2, 25.6), 28.3 (dd, $^3J_{C-F}$ 4.3, 1.0), 27.7, 22.6, 14.0; $\delta_F$ (282 MHz, $CDCl_3$) −108.7 (1F, dt, $^2J$ 248.7, $J_{F-H}$ 10.5, 10.5), −112.1 (1F, dt, $^2J$ 248.7, $J_{F-H}$ 10.6, 10.6); *m/z* (ES) 187 (100%, $[M + Na]^+$). Spectral data were in agreement with those reported by Seyferth *et al.*[15]

**1-Benzyloxy-3,3-difluoropent-4-en-2-ol 10d**

As above from benzyloxyacetaldehyde (5.0 mmol, 0.70 mL) with sonication for 6 hours to afford **10d** as a colourless oil (0.99 g, 96%, 100% by GC); $R_f$ (30% diethyl ether in light petroleum) 0.28; $\nu_{max}$ (film)/cm$^{-1}$ 3431s br (O–H), 3064w (Ar–H), 3031w (=C–H), 2872m (C–H), 1652w (C=C); $\delta_H$ (300 MHz, $CDCl_3$) 7.40–7.28 (5H, m, –$C_6H_5$), 6.09–5.91 (1H, m, H-4), 5.72 (1H, dt, $J_{trans}$ 17.6, $^2J$ 2.6, $^4J_{H-F}$ 2.6, H-5a), 5.52 (1H, d, $J_{cis}$ 11.0, H-5b), 4.57 (2H, s, –O$CH_2$Ph), 4.10–3.98 (1H, m, H-2), 3.70 (1H, dd, $^2J$ 9.9, $J$ 3.3, H-1a), 3.59 (1H, dd, $^2J$ 9.9, $J$ 7.0, H-1b), 2.76 (1H, d, $J$ 5.2, –O*H*); $\delta_C$ (75 MHz, $CDCl_3$) 137.3, 129.9 (t, $^2J_{C-F}$ 25.5), 128.4, 127.9, 127.7, 120.9 (t, $^3J_{C-F}$ 9.5), 119.1 (t, $^1J_{C-F}$ 243.2), 73.6, 72.2 (t, $^2J_{C-F}$ 29.8), 68.6; $\delta_F$ (282 MHz, $CDCl_3$) −107.3 (1F, dt, $^2J$ 252.8, $J_{F-H}$ 10.3, 10.3), −111.3 (1F, dt, $^2J$ 252.8, $J_{F-H}$ 11.3, 11.3); [HRMS (ES, $[M + Na]^+$) Found: 251.0872. Calc. for $C_{12}H_{14}F_2O_2Na$: 251.0860]; *m/z* (EI) 228 (30%, $M^+$), 121 (100, $M^+$–OBn).

**1-Acetoxy-3,3-difluoropent-4-en-2-ol 10e**

3-Bromo-3,3-difluoroprop-1-ene **8** (2.2 mmol, 0.22 mL) and (acetoxy)acetaldehyde (2.0 mmol, 204 mg) were added to a sonicated suspension of indium (2.2 mmol, 230 mg) in DMF (4 mL). The mixture was sonicated at room temperature for 4.5 h, quenched with water (10 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a yellow oil (373 mg). Purification by column chromatography (40% diethyl ether in light petroleum) afforded **10e** as a colourless oil (233 mg, 65%, 98% by GC). $R_f$ (40% diethyl ether in light petroleum) 0.29; $\nu_{max}$ (film)/cm$^{-1}$ 3458s (O–H), 2974s (=C–H), 2875m (C–H), 1718s (C=O), 1654 (C=C); $\delta_H$ (300 MHz, $CDCl_3$) 6.01–5.89 (1H, m, H-4), 5.73 (1H, dt, $^3J_{trans}$ 17.3, $^4J_{H-F}$ 2.5, H-5a), 5.55 (1H, d, $^3J_{cis}$ 11.0, H-5b), 4.27 (1H, dd, $^2J_{H-H}$ 12.0, $^3J_{H-H}$ 3.3, H-1a), 4.17 (1H, dd, $^2J_{H-H}$ 12.0, $^3J_{H-H}$ 7.4, H-1b), 4.09–3.97 (1H, m, H-2), 3.08 (1H, br s, –O*H*), 2.08 (3H, s, –C$H_3$); $\delta_C$ (75 MHz, $CDCl_3$) 171.4, 129.4 (t, $^2J_{C-F}$ 25.4), 121.6 (t, $^3J_{C-F}$ 9.6), 118.9 (dd, $^1J_{C-F}$ 244.2, 243.0), 71.9 (t, $^2J_{C-F}$ 29.7), 63.5 (tdd, $^3J_{C-F}$ 4.5, 2.8), 20.7; $\delta_F$ (282 MHz, $CDCl_3$) −107.6 (1F, dt, $^2J$ 254.3, $^3J_{F-H}$ 8.9, 8.9), −111.8 (1F, dt, $^2J$ 254.3, $^3J_{F-H}$ 11.4, 11.4); [HRMS (ES, $[M + Na]^+$) Found: 203.0488, calc. for $C_7H_{10}O_3F_2Na$: 203.0496]; *m/z* (ES) 203 (100, $[M + Na]^+$).

**Attempted preparation of 10f in DMF; preparation of 10f and 22**

3-Bromo-3,3-difluoro-prop-1-ene **8** (5.5 mmol, 0.56 mL) and aldehyde **9f** (5.0 mmol, 0.721 g) were added successively to a sonicated suspension of indium (5.5 mmol, 0.632 g) in DMF (10 mL) at room temperature. The mixture was sonicated for 2 hours, then usual work-up and flash column chromatography afforded alcohols **10f** (0.643 g, 58%)* and **22** (0.149 g, 13%, GC retention time 10.86 min), $R_f$ (20% diethyl ether in light petroleum) 0.14, $\delta_H$ (300 MHz, $CDCl_3$) 5.98–5.85 (1H, m, C*H*=$CH_2$), 5.65 (1H, app. dt, $J_{trans}$ 17.4, $^4J_{H-F}$2.3, CH=C$H_a$H$_b$), 5.45 (1H, d, $J_{cis}$ 11.1, CH=CH$_a$$H_b$), 4.20 (1H, dd, $^2J$ 11.8, $J$ 3.8, C$H_a$H$_b$OH), 4.10 (1H, dd, $^2J$ 11.8, $J$ 7.0, CH$_a$$H_b$OH), 4.03–3.92 (1H, m, C*H*OPiv), 1.11 (9H, s, *t*-Bu) (the O*H* signal was not observed); $\delta_C$ (75 MHz, $CDCl_3$) 170.9, 129.6 (t, $^2J_{C-F}$25.1), 121.3 (t, $^3J_{C-F}$9.5), 119.0 (t, $^1J_{C-F}$243.9), 71.7 (t, $^2J_{C-F}$29.9), 63.3 (t, $^3J_{C-F}$ 4.25), 38.6, 26.9, 26.8; $\delta_H$ (282 MHz, $CDCl_3$) −107.5 (1F, dt, $^2J$ 253.3, $J_{H-F}$ 9.9), −111.5 (1F, dt, $^2J$253.3, $J_{H-F}$11.4); *m/z* (EI) 223 (3%, $[M + H]^+$), 179 (10), 167 (10), 145 (70), 103 (100). Further characterisation was not obtained for this unwanted side product. *Characterisation of **10f** follows.

**3,3-Difluoro-1-pivaloxyloxy-pent-4-en-2-ol 10f**

A mixture of **9f** (7.21 g, 50.0 mmol), 3-bromo-3,3-difluoroprop-1-ene **8** (5.10 mL, 50.0 mmol) and indium powder (5.74 g, 50.0 mmol) in water (100 mL) was sonicated at room temperature for 2 hours and then stirred vigorously overnight. The reaction mixture was quenched with HCl (50 mL of a 1 M solution) and extracted with diethyl ether (3 × 100 mL). The combined organic extracts were washed with brine (50 mL),

dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a yellow oil (10.31 g). Purification by column chromatography (20% diethyl ether in light petroleum) afforded **10f** as a pale yellow oil (9.09 g, 82%, 100% by GC, retention time 10.78 min); $R_f$ (20% diethyl ether in light petroleum) 0.27; $\nu_{max}$ (film)/cm$^{-1}$ 3458s br (O–H), 2974s (=C–H), 2875m (C–H), 1718s (C=O), 1651w (C=C); $\delta_H$ (300 MHz, $CDCl_3$) 6.07–5.90 (1H, m, C*H*=$CH_2$), 5.70 (1H, dtd, $J_{trans}$, 17.3, $^4J_{H-F}$ 2.2, $^2J$ 0.8, CH=C$H_aH_b$), 5.55 (1H, d, $J_{cis}$ 11.0, CH=C$H_aH_b$), 4.30–4.18 (2H, m, $CH_2$OPiv), 4.07–3.97 (1H, m, C*H*OH), 2.85 (1H, br s, –O*H*), 1.19 (9H, s, –C(C*H*$_3$)$_3$); $\delta_C$ (75 MHz, $CDCl_3$) 179.3, 129.8 (t, $^2J_{C-F}$ 25.4), 121.8 (t, $^3J_{C-F}$ 9.6), 119.2 (t, $^1J_{C-F}$ 243.9), 72.4 (t, $^2J_{C-F}$ 29.7), 63.6 (dd, $^3J_{C-F}$ 4.2, 3.1), 39.1, 27.3; $\delta_F$ (282 MHz, $CDCl_3$) −107.8 (1F, dt, $^2J$ 253.0, $^3J_{F-H}$ 10.2, 10.2), −111.6, (1F, dt, $^2J$ 253.0, $^3J_{F-H}$ 12.7, 12.7); [HRMS (FAB, $[M + H]^+$) Found: 223.11454, calc. for $C_{10}H_{17}O_3F_2$: 223.11458]; *m*/*z* (ES) 245 (100, $[M + Na]^+$).

### General procedure for the preparation of difluorohomoallylallyl ethers 11a–11d

Mixtures of difluorohomoallylic alcohols **11a**–**11d**, allyl bromide (1.2 eq.), sodium hydroxide (7 eq. of a 50 wt% aqueous solution) and tetra-*n*-butylammonium hydrogensulfate (5 mol% based on the alcohol) were stirred at 0 °C for 30 minutes, allowed to warm to room temperature and stirred overnight at this temperature. The reaction mixtures were quenched with a saturated aqueous solution of ammonium chloride and extracted with diethyl ether. The combined organic extracts were washed with water, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford pale yellow oils, which were used for RCM without further purification.

### 1-Allyloxy-2,2-difluoro-1-phenylbut-3-ene 11a

Alcohol **10a** (1.5 mmol, 276 mg), allyl bromide (1.8 mmol, 0.16 mL), sodium hydroxide (10.5 mmol, 0.55 mL of a 50 wt% aqueous solution) and tetra-*n*-butylammonium hydrogensulfate (75 μmol, 26 mg) were treated as described above. The mixture was quenched with ammonium chloride (10 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 15 mL). The combined organic extracts were washed with water (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude ether **11a** as a pale yellow oil (330 mg, 100%, 99% by GC); $R_f$ (5% diethyl ether in light petroleum) 0.49; $\nu_{max}$ (film)/cm$^{-1}$ 2985m (=C–H), 2867m (C–H), 1651w (C=C); $\delta_H$ (300 MHz, $CDCl_3$) 7.38–7.35 (5H, m, –$C_6H_5$), 6.07–5.93 (2H, m, H-3 and $OCH_2CH$), 5.57 (1H, d, $J_{trans}$ 17.3, H-4a), 5.45 (1H, d, $J_{cis}$ 11.0, H-4b), 5.31–5.18 (2H, m, $OCH_2$-CH=C$H_2$), 4.59 (1H, t, $J_{H-F}$ 10.3, H-1), 4.10 (1H, ddd, $^2J$ 13.0, $J$ 6.3, $^4J$ 1.1, H-1′a), 3.92 (1H, ddd, $^2J$ 13.0, $J$ 4.8, $^4J$ 1.1, H-1′b); $\delta_C$ (75 MHz, $CDCl_3$) 134.8, 134.0, 130.2 (t, $^2J_{C-F}$ 25.4), 128.8, 128.6 (t, $^4J_{C-F}$ 1.1), 128.2, 120.9 (t, $^3J_{C-F}$ 9.3), 119.0 (t, $^1J_{C-F}$ 244.2), 117.7, 82.1 (t, $^2J_{C-F}$ 30.0), 70.5; $\delta_F$ (282 MHz, $CDCl_3$) −104.3 (1F, dt, $^2J$ 248.6, $J_{F-H}$ 10.2, 10.2), −109.0 (1F, dt, $^2J$ 248.6, $J_{F-H}$ 11.4, 11.4); [HRMS (CI, $[M + NH_4]^+$) Found: 242.135869. Calc. for $C_{13}H_{18}N_1O_1F_2$: 242.135646]; *m*/*z* (CI) 242 (16%, $[M + NH_4]^+$), 147 (100).

### 1-Allyloxy-2,2-difluoro-1-(2′-furyl)but-3-ene 11b

Alcohol **10b** (1.5 mmol, 261 mg), allyl bromide (1.8 mmol, 0.16 mL), sodium hydroxide (10.5 mmol, 0.55 mL of a 50 wt% aqueous solution) and tetra-*n*-butylammonium hydrogensulfate (75 μmol, 26 mg) were treated as described above. The mixture was quenched with ammonium chloride (10 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 15 mL). The combined organic extracts were washed with water (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude ether as a pale yellow oil **11b** (319 mg, 99%, 97% by GC); $R_f$ (5% diethyl ether in light petroleum) 0.43; $\nu_{max}$ (film)/cm$^{-1}$ 3085w (=C–H), 2985w (=C–H), 2924m (C–H), 2871m (C–H), 1649w (C=C); $\delta_H$ (300 MHz, $CDCl_3$) 7.44 (1H, dd, $J$ 1.5, $^4J$ 0.8, H-3), 6.44 (1H, d, $J$ 2.9, H-5), 6.39 (1H, dd, $J$ 2.9, 1.5, H-4), 6.13–5.95 (1H, m, H-3′), 5.92–5.79 (1H, m, $OCH_2CH$), 5.67 (1H, dtd, $J_{trans}$ 17.3, $^2J$ 2.6, $^4J_{H-F}$ 0.8, H-4′a), 5.50 (1H, d, $J_{cis}$ 11.0, H-4′b), 5.30–5.19 (2H, m, $OCH_2CH$=C$H_2$), 4.64 (1H, t, $J_{H-F}$ 9.2, H-1′), 4.10 (1H, dd, $^2J$ 12.9, $J$ 5.1, OC$H_aH_b$CH), 3.93 (1H, dd, $^2J$ 12.9, $J$ 6.3, $OCH_aH_b$CH); $\delta_C$ (75 MHz, $CDCl_3$) 148.6 (dd, $^3J_{C-F}$ 4.8, 1.4), 143.2, 133.6, 130.0 (t, $^2J_{C-F}$ 25.2), 121.0 (t, $^3J_{C-F}$ 9.3), 118.3 (t $^1J_{C-F}$ 244.4), 118.2, 110.7 (t, $^4J_{C-F}$ 1.1), 110.5, 75.9 (t, $^2J_{C-F}$ 31.7), 70.6; $\delta_F$ (282 MHz, $CDCl_3$) −107.7 (1F, dt, $^2J$ 250.5, $J_{F-H}$ 10.5), −105.0 (1F, dt, $^2J$ 250.5, $J_{F-H}$ 9.9); [HRMS (ES, $[M + Na]^+$) Found 237.0709, calc. for $C_{11}H_{12}O_2F_2Na$: 237.0703]; *m*/*z* (ES) 237 (100%, $[M + Na]^+$).

### 4-Allyloxy-3,3-difluorooct-1-ene 11c

Alcohol **10c** (1.5 mmol, 246 mg), allyl bromide (1.8 mmol, 0.16 mL), sodium hydroxide (10.5 mmol, 0.55 mL of a 50 wt% aqueous solution) and tetra-*n*-butylammonium hydrogensulfate (75 μmol, 26 mg) were treated as described above. The mixture was quenched with ammonium chloride (10 mL a saturated aqueous solution) and extracted with diethyl ether (3 × 15 mL). The combined organic extracts were washed with water (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude ether **11c** as a pale yellow oil (301 mg, 98%, 96% by GC); $R_f$ (5% diethyl ether in light petroleum) 0.62; $\nu_{max}$ (film)/cm$^{-1}$ 2990w (=C–H), 2871s (C–H), 1649w (C=C); $\delta_H$ (300 MHz, $CDCl_3$) 6.04–5.81 (2H, m, C*H*=$CH_2$), 5.65 (1H, dddd, $J_{trans}$ 17.6, $^4J_{H-F}$ 2.9, 1.8, $^2J$ 1.1, H-1a), 5.47 (1H, dt, $J_{cis}$ 11.0, $^4J_{F-H}$ 2.2, H-1b), 5.28–5.13 (2H, m, $OCH_2CH$=C$H_2$), 4.24 (1H, dd, $^2J$ 12.4, $J$ 5.0, OC$H_aH_b$CH), 4.03 (1H, dd, $^2J$ 12.4, $J$ 6.2, $OCH_aH_b$CH), 3.50–3.41 (1H, m, H-4), 1.54–1.22 (6H, m, H-5, H-6 and H-7), 0.87 (3H, t, $J$ 7.7, H-8); $\delta_C$ (75 MHz, $CDCl_3$) 134.6, 130.1 (t, $^2J_{C-F}$ 25.7), 121.0 (dd, $^1J_{C-F}$ 245.9, 244.2), 120.5 (t, $^3J_{C-F}$ 9.6), 117.4, 80.6 (dd, $^2J_{C-F}$ 30.5, 26.0), 73.5, 29.6 (dd, $^3J_{C-F}$4.5, 1.1), 27.8, 22.6, 14.0; $\delta_F$ (282 MHz, $CDCl_3$) −102.6 (1F, dt, $^2J$ 250.5, $J_{F-H}$ 10.2, 10.2), −108.8 (1F, ddd, $^2J$ 250.5, $J_{F-H}$ 14.0, 6.4); [HRMS (ES, $[M + Na]^+$) Found: 227.1219. Calc. for $C_{11}H_{18}OF_2Na$: 227.1223]; *m*/*z* (ES) 227 (100%, $[M + Na]^+$).

### 2-Allyloxy-1-benzyloxy-3,3-difluoropent-4-ene 11d

Alcohol **10d** (4.4 mmol, 993 mg), allyl bromide (6.5 mmol, 0.56 mL), sodium hydroxide (30.5 mmol, 1.60 mL of a 50 wt% aqueous solution) and tetra-*n*-butylammonium hydrogensulfate (220 μmol, 74 mg) were treated as described above. The mixture was quenched with ammonium chloride (25 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 25 mL). The combined organic extracts were washed with water (25 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude ether **11d** as a pale yellow oil (1.16 g, 100%, 100% by GC); $R_f$ (5% diethyl ether in light petroleum) 0.24; $\nu_{max}$ (film)/cm$^{-1}$ 3066w (Ar–H), 3029 m (=C–H), 2920m (C–H); 2870m (C–H), 1649w (C=C); $\delta_H$ (300 MHz, $CDCl_3$) 7.40–7.29 (5H, m, –$C_6H_5$), 6.10–5.88 (2H, m, H-4 and H-2′), 5.70 (1H, d, $J_{trans}$ 17.3, H-5$_a$), 5.50 (1H, d, $J_{cis}$ 11.0, H-5$_b$), 5.32 (1H, dt, $J_{trans}$ 17.1, $^2J$ 1.5, $J$ 1.5, $OCH_2CH$=C$H_aH_b$), 5.22 (1H, d, $J_{cis}$ 10.3, $OCH_2CH$=C$H_aH_b$), 4.57 (2H, s, –O$CH_2$-Ph), 4.27 (2H, d, $J$ 5.5, O$CH_2$CH), 3.88–3.79 (1H, m, H-2), 3.73 (1H, dt, $^2J$ 9.9, $J$ 1.5, $^4J_{H-F}$ 1.5, H-1$_a$), 3.59 (1H, dd, $^2J$ 9.9, $J$ 7.5, H-1$_b$); $\delta_C$ (75 MHz, $CDCl_3$) 138.0, 134.5, 130.3 (t, $^2J_{C-F}$ 25.4), 128.5, 127.7, 127.6, 120.6 (t, $^3J_{C-F}$ 9.6), 119.5 (t, $^1J_{C-F}$ 244.7), 117.6, 79.8 (dd, $^2J_{C-F}$ 29.1, 28.0), 73.6, 73.4, 69.6 (dd, $^3J_{C-F}$ 5.4, 2.5); $\delta_F$ (282 MHz, $CDCl_3$) −103.8 (1F, dt, $^2J$ 254.3, $J_{F-H}$ 10.2, 10.2), −109.1 (1F, dt, $^2J$ 254.3, $J_{F-H}$ 11.1, 11.1); [HRMS (EI, $M^+$) Found: 268.12754. Calc. for $C_{15}H_{18}F_2O_2$: 268.12749]; *m*/*z* (ES) 268 (25%, $M^+$), 227 (58, $M^+$–$C_3H_5$), 177 (49, $M^+$–$CH_2Ph$), 91 (100, $CH_2Ph^+$).

**General procedure for the preparation of dihydropyrans 12a–12d**

Solutions of ethers **11a**–**11d** and Grubbs' catalyst benzylidene bis-(tricyclohexylphosphino)dichloro ruthenium (5 mol%) in degassed DCM were stirred for 24 hours at room temperature, then oxygen was bubbled through the reaction mixture for 15 minutes. Concentration under reduced pressure left black oils, which were purified by column chromatography to afford the desired difluorinated dihydropyrans **12a**–**12d**.

**3,3-Difluoro-2-phenyl-3,6-dihydro-2*H*-pyran 12a**

Ether **11a** (0.75 mmol, 167 mg) and Grubbs' catalyst (75 μmol, 62 mg) were treated as described above in DCM (15 mL). Purification by column chromatography (5% diethyl ether in light petroleum) afforded **12a** as a colourless oil (118 mg, 81%). $R_f$ (5% diethyl ether in light petroleum) 0.30; $\nu_{max}$ (film)/cm$^{-1}$ 2990w (=C–H), 2865m (C–H), 1648w (C=C); $\delta_H$ (300 MHz, $CDCl_3$) 7.53–7.38 (5H, m, –C$_6H_5$), 6.30 (1H, ddd, $J$ 10.3, $^4J_{H-F}$ 3.3, 1.9, H-4), 6.05 (1H, br app. t, $J$, $J_{H-F}$10.3, H-5), 4.70 (1H, dd, $^3J_{H-F}$ 18.7, 2.6, H-2′), 4.52–4.29 (2H, m, H-6); $\delta_C$ (75 MHz, $CDCl_3$) 135.2 (dd, $^3J_{C-F}$ 9.6, 8.5), 133.8 (t, $^3J_{C-F}$ 1.1), 128.7, 128.2, 127.8, 122.3 (dd, $^2J_{C-F}$ 30.5, 26.6), 113.7 (dd, $^1J_{C-F}$ 245.6, 234.3), 78.9 (dd, $^2J_{C-F}$ 31.1, 25.4), 65.9 (t, $^4J_{C-F}$ 1.1); $\delta_F$ (282 MHz, $CDCl_3$) −102.2 (1F, dddd, $^2J$ 274.3, $J_{F-H}$ 18.7, 8.8, $^4J_{F-H}$ 7.6), −106.5 (1F, br d, $^2J$ 274.3); [HRMS (ES, [M + Na]$^+$) Found: 219.0596. Calc. for $C_{11}H_{10}N_1OF_2Na$: 219.0598]; *m/z* (EI) 196 (30%, M$^+$), 105 (74), 90 (100), 77 (40).

**3,3-Difluoro-2-(2′-furyl)-3,6-dihydro-2*H*-pyran 12b**

Ether **11b** (0.75 mmol, 161 mg) and Grubbs' catalyst (37 μmol, 31 mg) were treated as described above in DCM (15 mL). Purification by column chromatography (10% diethyl ether in light petroleum) afforded **12b** as a colourless oil (97 mg, 69%). $R_f$ (10% diethyl ether in light petroleum) 0.35; $\nu_{max}$ (film)/cm$^{-1}$ 3079w (=C–H), 2986w (=C–H), 2925m (C–H), 1647w (C=C); $\delta_H$ (300 MHz, $CDCl_3$) 7.47 (1H, dd, $J$ 1.8, $^4J$ 0.7, H-3′), 6.55 (1H, d, $J$ 3.3, H-5′), 6.41 (1H, dd, $J$ 3.3, 1.8, H-4′), 6.29 (1H, dt, $J$ 10.3, $J_{H-F}$ 2.6, H-4), 6.07–5.98 (1H, m, H-5), 4.84 (1H, dd, $J_{H-F}$ 14.0, 5.9, H-2), 4.37–4.32 (2H, m, H-6); $\delta_C$ (75 MHz, $CDCl_3$) 147.1, 143.2, 135.2 (t, $^3J_{C-F}$ 9.3), 121.8 (dd, $^2J_{C-F}$ 29.1, 27.4), 113.2 (dd, $^1J_{C-F}$ 243.3, 237.7), 110.5, 110.4 (t, $^4J_{C-F}$ 1.7), 73.2 (dd, $^2J_{C-F}$ 36.6, 31.1), 65.2 (t. $^4J_{C-F}$2.0); $\delta_F$ (282 MHz, $CDCl_3$) −102.9 (1F, dddd, app. d pent., $^2J$ 274.5, $J_{F-H}$ 14.0, 10.2, $^4J_{F-H}$ 5.1), (−103.4)-(−103.5) and (−104.4)-(−104.5) (1F, m including $^2J$ 274.5); [HRMS (ES, [M + Na]$^+$) Found: 209.0387. Calc. for $C_9H_8O_2F_2Na$: 209.0390]; *m/z* (ES) 209 (100%, [M + Na]$^+$).

**2-Butyl-3,3-difluoro-3,6-dihydro-2*H*-pyran 12c**

Ether **11c** (0.75 mmol, 153 mg) and Grubbs' catalyst (37 μmol, 31 mg) were treated as described above in DCM (15 mL). Purification by column chromatography (5% diethyl ether in light petroleum) afforded **12c** as a colourless oil (73 mg, 56%). $R_f$ (5% diethyl ether in light petroleum) 0.43; $\nu_{max}$ (film)/cm$^{-1}$ 2980w (=C–H), 2890m (C–H), 1640w (C=C); $\delta_H$ (300 MHz, $CDCl_3$) 6.22 (1H, ddd, $J$ 10.3, $J_{H-F}$ 3.3, 1.9, H-4), 5.94–5.85 (1H, m, H-5), 4.30–4.07 (2H, m, H-6), 3.52 (1H, ddt, $^3J_{H-F}$ 17.8, 9.2, $J$ 3.6, H-2), 1.82–1.31 (6H, m, H-1′, H-2′ and H-3′), 0.91 (3H, t, $J$ 7.2, H-4′); $\delta_C$ (75 MHz, $CDCl_3$) 135.4 (t, $^3J_{C-F}$ 9.3), 122.0 (dd, $^2J_{C-F}$ 29.7, 27.4), 114.6 (dd, $^1J_{C-F}$ 243.6, 234.6), 77.4 (dd, $^2J_{C-F}$ 31.1, 26.0), 65.2 (t, $^4J_{C-F}$ 2.0), 27.6, 26.6, 22.6, 14.0; $\delta_F$ (282 MHz, $CDCl_3$) −106.4 (1F, dddd, $^2J$ 271.5, $J_{F-H}$9.0, 8.2, $^4J_{F-H}$ 7.6), −108.0 (1F, br d, $^2J$ 271.5,); [HRMS (ES, [M + Na]$^+$) Found: 199.0906. Calc. for $C_9H_{14}OF_2Na$: 199.0910]; *m/z* (ES) 199 (100%, [M + Na]$^+$).

**2-(Benzyloxy)methyl-3,3-difluoro-3,6-dihydro-2*H*-pyran 12d**

Ether **11d** (1.5 mmol, 403 mg,) and Grubbs' catalyst (75 μmol, 62 mg,) were treated as described above in DCM (30 mL). Purification by column chromatography (20% diethyl ether in light petroleum) afforded **12d** as a colourless oil (350 mg, 97%). $R_f$ (20% diethyl ether in light petroleum) 0.30; $\nu_{max}$ (film)/cm$^{-1}$ 3058w (Ar–H), 2977m (=C–H), 2865m (C–H), 1641w (C=C); $\delta_H$ (300 MHz, $CDCl_3$) 7.33–7.27 (5H, m, –C$_6H_5$), 6.27 (1H, ddd, $J$ 10.7, $J_{H-F}$ 3.7, 1.8, H-4), 5.95–5.86 (1H, m, H-5), 4.67 (1H, d, $^2J$ 12.1, –OC$H_a$H$_b$Ph), 4.59 (1H, d, $^2J$ 12.1, –OCH$_a$H$_b$Ph), 4.37–4.18 (2H, m, H-6), 3.98–3.94 (1H, m, H-2), 3.90 (1H, dd, $^2J$ 10.9, $J$ 2.4, –C$H_a$H$_b$OBn), 3.71 (1H, dd, $^2J$ 10.9, $J$ 7.9, –CH$_a$H$_b$OBn); $\delta_C$ (75 MHz, $CDCl_3$) 137.8, 135.7 (t, $^3J_{C-F}$ 9.0), 128.5, 127.9, 121.4 (t, $^2J_{C-F}$ 28.0), 113.9 (dd, $^1J_{C-F}$ 243.0, 235.7), 76.8 (t, $^2J_{C-F}$ 30.5), 73.8, 67.2, 65.2; $\delta_F$ (282 MHz, $CDCl_3$) −105.6 (1F, dddd, $^2J$ 273.4, $J_{F-H}$ 17.8, 8.9, $^4J_{F-H}$ 8.9), −107.7 (1F, ddd, $^2J$ 273.4, $^3J_{F-H}$ 6.4, 3.8); [HRMS (ES, [M + Na]$^+$) Found: 263.0853. Calc. for $C_{13}H_{14}N_1O_2F_2Na$: 263.0860]; *m/z* (ES) 263 (100%, [M + Na]$^+$).

**5-(Benzyloxy)methyl-4,4-difluoro-2,3-dihydroxytetrahydropyrans 13d**

A solution of NMO (0.66 mmol, 0.078 g) in water (0.1 mL) was added to a cold (0 °C) solution of **12d** (0.33 mmol, 0.068 g) in acetone (0.35 mL) and *tert*-butanol (0.35 mL) in a screw-capped vial. The mixture was stirred for 10 minutes and osmium tetroxide (0.007 mmol, 0.1 mL of a 2.5 wt% solution in *tert*-butanol, 2 mol%) was added. The reaction mixture was stirred at 0 °C for 2 hours, allowed to warm to room temperature and stirred at this temperature for 7 days. It was then quenched with sodium sulfite (3.5 mmol, 0.44 g), diluted with water (3 mL), stirred for an additional 30 minutes and extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford **13d**, a separable mixture of *cis*- and *trans*-diastereoisomers, as a yellow oil. Column chromatography (40% ethyl acetate in light petroleum) afforded in order of elution: *trans* ((±)-2*S*,3*S*,5*R*) **13d** as a powder (0.02 g, 31%) $R_f$ (40% ethyl acetate in light petroleum) 0.25; GC retention time 20.49 min; mp 101–102 °C; Found: C, 57.22; H, 6.12. Calc. for $C_{13}H_{16}F_2O_4$: C, 56.93; H, 5.88%. $\delta_H$ (400 MHz, $CDCl_3$) 4.66 (1H, d, one half of an AB q, $^2J$ 12.0, OC$H_a$CH$_b$Ph), 4.57 (1H, d, one half of an AB q, $^2J$ 12.0, OCH$_a$C$H_b$Ph), 4.11 (1H, ddd, $J$ 3.3, $^3J_{H-F_{eq}}$ 6.9, $^3J_{H-F_{ax}}$ 4.6, H-3), 4.02 (1H, ddd, $^3J_{H-F_{ax}}$ 24.3, $J$ 7.8, 2.5, H-5), 3.99–3.92 (1H, m, H-2), 3.89 (1H, ddd, $^2J$ 11.0, $J$ 5.0, $^5J_{H-F}$2.2, H-1$_{eq}$), 3.84 (1H, ddd, $^2J$ 11.0, $J$ 2.5, $^4J_{H-F}$1.5, H-6$_{eq}$), 3.67 (1H, dd, $^2J$ 11.0, $J$ 7.8, H-6$_{ax}$), 3.55 (1H, t, $^2J$, $J$ 11.0, H-1$_{ax}$), 3.15 (1H, br, OH), 2.58 (1H, br s, OH); $\delta_C$ (75 MHz, $CDCl_3$) 137.5, 128.5, 127.9 (2 signals), 117.9 (dd, $^1J_{C-F}$254.9, 250.1), 73.8, 73.2 (dd, $^2J_{C-F}$27.5, 21.6), 69.5 (dd, $^2J_{C-F}$34.7, 20.3), 66.8 (d, $^3J_{C-F}$4.7), 66.1 (d, $^3J_{C-F}$4.7), 65.4; $\delta_F$ (376 MHz, $CDCl_3$) −116.2 (1F, dd, $^2J$ 260.5, $J_{F-H}$6.9), −124.5 (1F, dd, $^2J$ 260.5, $J_{F-H}$24.3); *m/z* (EI) 274 (10%, M$^+$), 107 (60, [OCH$_2$Ph]$^+$), 91 (100, PhCH$_2^+$) and *cis* ((±)-2*R*,3*R*,5*R*) **13d** as a powder (0.02 g, 31%), mp 96–97 °C; $R_f$ (40% ethyl acetate in light petroleum) 0.11; GC retention time 20.26min; $\delta_H$ (400 MHz, $CDCl_3$) 4.65 (1H, d, one half of an AB q, $^2J$ 12.0, OC$H_a$CH$_b$Ph), 4.58 (1H, d, one half of an AB q, $^2J$ 12.0, OCH$_a$C$H_b$Ph), 4.15 (1H, ddd, $^2J$ 12.9, $J$ 2.0, $^5J_{H-F}$2.2, H-1$_{eq}$), 4.02–3.97 (1H, m, H-2), 3.89 (1H, br dd, $^2J$ 10.8, $J$ 2.0, H-6$_{ax}$), 3.90–3.70 (1H, br d, contains $^3J_{H-F_{ax}}$ 21.5, H-3*), 3.75 (1H, br dd, $^2J$ 10.8, $J$ 7.7, H-6$_{eq}$), 3.80–3.65 (1H. br m, contains $^3J_{H-F_{ax}}$ 21.5, H-5*), 3.65 (1H, br dd, $^2J$ 12.9, $J$ 1.5, H-1$_{ax}$), 3.15 (1H, br, OH), 2.35 (1H, br OH); $\delta_C$ (75 MHz, $CDCl_3$) 137.4, 128.5, 128.0, 127.9, 117.6 (t, $^1J_{C-F}$252.1, 250.1), 78.6 (dd, $^2J_{C-F}$27.4, 22.8), 73.9, 70.3, 70.1 (dd, $^2J_{C-F}$39.4, 19.2), 69.1(d, $^3J_{C-F}$7.1), 66.6 (d, $^3J_{C-F}$7.8), 65.4; $\delta_F$ (376 MHz, $CDCl_3$) −114.6 (1F, dt, $^2J$ 253.3, $J_{F-H}$5.8), −129.1 (1F, dt, $^2J$ 253.5, $J_{F-H}$ 21.5); [HRMS (EI, M$^+$) 274.10163. Calc. for $C_{13}H_{16}F_2O_4$: 274.10167]; *m/z* (EI) 274 (3%, M$^+$), 107 (60, [OCH$_2$Ph]$^+$), 91 (100, PhCH$_2^+$). *Signals for H-3 and H-5 in the $^1$H NMR spectrum are very broad because both contain a large diaxial H–F coupling. Though we were not able to

assign these signals accurately using 2D NMR methods, integration of the 1D NMR spectrum yields the correct number of protons, an appropriate HSQC pattern was obtained and the presence of a 7.7 Hz coupling (to H-6) could be detected in the $^{1}H\{^{19}F\}$ NMR spectrum for the signal assigned as H-5.

**1-(Benzyloxy)methyl-3,3-difluoro-2-(methallyloxy)pent-4-ene 14**

A mixture of **10d** (2.0 mmol, 456 g), methallyl chloride (2.2 mmol, 0.22 mL), sodium hydroxide (14.0 mmol, 0.75 mL of a 50 wt% aqueous solution), tetra-*n*-butylammonium hydrogensulfate (100 μmol, 34 mg) and tetra-*n*-butylammonium iodide (100 μmol, 37 mg) was stirred at 0 °C for 30 minutes, allowed to warm to room temperature and stirred overnight at this temperature. The reaction mixture was quenched with ammonium chloride (10 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with water (15 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford **14** as a pale yellow oil (0.56 g, 99%), which was used without further purification. $R_f$ (5% diethyl ether in light petroleum) 0.57; $\nu_{max}$ (film)/cm$^{-1}$ 3065w (Ar–H), 3030m (=C–H), 2916m (C–H), 2808m (C–H), 1654w (C=C); $\delta_H$ (300 MHz, $CDCl_3$) 7.41–7.28 (5H, m, –$C_6H_5$), 6.05 (1H, ddt, $J_{trans}$ 17.3, $^{3}J_{H-F}$ 12.9, $J_{cis}$ 11.0, H-4), 5.72 (1H, d, $J_{trans}$ 17.3, H-5a), 5.51 (1H, d, $J_{cis}$ 11.0, H-5b), 5.04 (1H, s, C(Me)=C$H_a$H$_b$), 4.95 (1H, s, C(Me)=CH$_a$$H_b$), 4.58 (2H, s, –OC$H_2$Ph), 4.18 (2H, s, H-1′), 3.90–3.80 (1H, m, H-2), 3.75 (1H, ddd, $^{2}J$ 10.5, $J$ 2.9, $^{4}J_{H-F}$ 1.8, H-1a), 3.61 (1H, ddd, $2J$ 10.5, $J$ 7.0, $^{4}J_{H-F}$ 1.1, H-1b), 1.79 (3H, s, –C$H_3$); $\delta_C$(63 MHz, $CDCl_3$) 142.3, 138.4, 130.8 (t, $^{2}J_{C-F}$ 25.2), 128.8, 128.1, 128.0, 120.8 (t, $^{3}J_{C-F}$ 9.7), 119.9 (t, $^{1}J_{C-F}$ 244.9), 113.4, 80.3 (t, $^{2}J_{C-F}$ 28.7), 76.7, 74.0, 70.0 (dd, $^{3}J_{C-F}$ 5.6, 2.5), 19.9; $\delta_F$ (282 MHz, $CDCl_3$) −103.3 (1F, dt, $^{2}J$ 254.3, $^{3}J_{F-H}$ 10.2, 10.2), −108.9 (1F, ddd, $^{2}J$ 254.3, $^{3}J_{F-H}$ 12.1, 9.5); [HRMS (ES, [M + Na]$^+$) Found: 305.1326, calc. for $C_{16}H_{20}O_2F_2Na$: 305.1329]; *m/z* (ES) 305 (100%, [M + Na]$^+$).

**2-(Acryloyloxy)-1-(benzyloxymethyl)-2,2-difluorobut-3-ene 15**

Freshly-distilled acryloyl chloride (4.7 mmol, 0.38 mL) was added dropwise to a cold (0 °C) solution of **10d** (4.7 mmol, 1.06 g) and triethylamine (4.7 mmol, 0.65 mL) in DCM (20 mL) under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 2 hours and at room temperature for 16 hours. The reaction mixture was quenched with water (20 mL) and extracted with DCM (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a pale yellow oil (1.33 g). Purification by column chromatography (10% diethyl ether in light petroleum) afforded **15** as a colourless oil (0.66 g, 50%, 100% by GC). $R_f$ (10% diethyl ether in light petroleum) 0.43; $\nu_{max}$(film)/cm$^{-1}$ 3065w (Ar–H), 3032w (Ar–H), 2960m (=C–H), 2932m (C–H), 2872m (C–H), 1738s (C=O); $\delta_H$ (300 MHz, $CDCl_3$); 7.37–7.28 (5H, m, –$C_6H_5$), 6.49 (1H, dd, $J_{trans}$ 17.3, $^{2}J$ 1.1, C(=O)CH=C$H_a$H$_b$), 6.18 (1H, dd, $J_{trans}$ 17.3, $J_{cis}$ 10.3, C(=O)C$H$=CH$_2$), 6.01–5.84 (2H, m, C(=O)CH=C$H_a$H$_b$ and H-3), 5.71 (1H, dt, $J_{trans}$ 17.3, $^{4}J_{H-F}$ 2.2, H-4a), 5.56–5.45 (2H, m, H-1 and H-4b), 4.58 (1H, d, $^{2}J$ 12.1, –OC$H_a$H$_b$Ph), 4.50 (1H, d, $^{2}J$12.1, –OCH$_a$$H_b$Ph), 3.81 (1H, dd, $^{2}J$ 11.4, $J$ 3.1, –C$H_a$H$_b$OBn), 3.71 (1H, dd, $^{2}J$ 11.4, $J$ 7.5, –CH$_a$$H_b$OBn); $\delta_C$(75 MHz, $CDCl_3$) 164.8, 137.5, 132.3, 129.8 (t, $^{2}J_{C-F}$ 25.4), 128.5, 127.8. 127.6, 127.5, 121.6 (t, $^{3}J_{C-F}$ 9.6), 118.0 (dd, $^{1}J_{C-F}$ 245.3, 243.6), 73.2, 71.9 (dd, $^{2}J_{C-F}$ 31.7, 29.4), 66.9 (t, $^{3}J_{C-F}$ 3.4); $\delta_F$ (282 MHz, $CDCl_3$) −105.8 (1F, dt, $^{2}J$ 254.3, $^{3}J_{F-H}$ 2.7, 2.7), −110.1 (1F, dt, second half of an AB quartet, $^{2}J$ 254.3, $^{3}J_{F-H}$ 3.2, 3.2); [HRMS (FAB, [M + H]$^+$) Found: 283.11459, calc. for $C_{15}H_{17}O_3F_2$: 283.11458; *m/z* (EI) 282 (30%, M$^+$), 227 (15, M–H$_2$C=CHCHO), 175 (50, M–OCH$_2$Ph), 107 (49, OCH$_2$Ph$^+$), 91 (100, CH$_2$Ph$^+$).

**6,6-Difluoro-3-ethoxy-5-(benzyloxy)methyl-4-oxa-1,7-octadiene 17d**

A solution of alcohol **10d** (4.4 mmol, 1.00 g), acrolein diethyl acetal (22 mmol, 3.4 mL) and PPTS (0.44 mmol, 0.125 g) in dry toluene (12.5 mL) was stirred at 30–40 °C under reduced pressure (60 mmHg) for 14 hours to remove ethanol by azeotropic distillation. The reaction mixture was quenched with sodium carbonate (13 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a pale yellow oil. Purification by column chromatography (5% diethyl ether in light petroleum) afforded **17d** (an inseparable 1 : 1 mixture of diastereoisomers) as a clear oil (0.85 g, 63%), $R_f$ 0.4; GC retention times 16.18, 16.21min; $\nu_{max}$ (film)/cm$^{-1}$ 2977m (=C–H), 2934w (C–H), 1652w (C=C); $\delta_H$ (300 MHz, $CDCl_3$) mixture: 6.08–5.80 (2H, m, –C$H$=CH$_2$), 5.72–5.10 (4H, m, –CH=C$H_2$), 4.61–4.47 (2H, m, –OC$H_2$Ph), 4.13–3.98 (1H, m, CF$_2$C$H$), 3.74–3.46 (4H, m, –C$H$CH$_2$O, OC$H_2$CH$_3$), 1.20–1.18 (3H, m, CH$_2$C$H_3$); $\delta_C$ (376 MHz, $CDCl_3$) mixture: 138.9, 138.3, 130.6 (app. q, $^{2}J_{C-F}$ 19.8, 2 signals), 128.9, 128.3, 128.2 (2 signals), 128.0 (2 signals), 121.0 (t, $^{3}J_{C-F}$ 9.5), 120.7 (t, $^{3}J_{C-F}$ 9.5), 119.8 (t, $^{1}J_{C-F}$ 243.5), 119.5 (t, $^{1}J_{C-F}$ 252.5), 119.2, 119.0, 103.4, 102.8, 77.0 (t, $^{2}J_{C-F}$ 29.3), 76.0 (t, $^{2}J_{C-F}$ 29.3), 73.9 (2 signals), 72.8 (t, $^{2}J_{C-F}$ 28.8, 2 signals), 70.0 (br), 69.1 (br), 61.7, 61.4, 15.6, 15.5; $\delta_F$ (376 MHz, $CDCl_3$) diastereoisomer 1: −104.2 (1F, dt, $^{2}J$ 252.1, $^{3}J_{F-H}$ 9.0, 9.0), −109.3 (1H, ddd, $^{2}J$ 252.1, $^{3}J_{F-H}$ 11.3, 8.1), diastereoisomer 2: −104.3 (1F, dt, $^{2}J$ 253.7, $^{3}J_{F-H}$ 9.6), −109.4 (1F, dt, $^{2}J$ 253.7, $^{3}J_{F-H}$ 11.3); [HRMS (EI, M$^+$) Found: 312.15383. Calc. for $C_{17}H_{22}F_2O_3$: 312.15370]; *m/z* (EI, 20eV) 312 (20%, M$^+$), 311 (20, [M–H]$^+$), 285 (100, [M–CH=CH$_2$]$^+$).

**6,6-Difluoro-3-ethoxy-5-(pivaloyloxy)methyl-4-oxa-1,7-octadiene 17f**

A solution of alcohol **10f** (85.0 mmol, 18.90 g), acrolein diethyl acetal (425 mmol, 65 mL) and PPTS (8.5 mmol, 2.14 g) in dry toluene (250 mL) was stirred at 30–40 °C under reduced pressure (60 mmHg) for 9 hours to remove ethanol by azeotropic distillation. The reaction mixture was quenched with sodium carbonate (250 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 200 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a pale yellow oil (29.71 g). Purification by column chromatography (5% diethyl ether in light petroleum) afforded an inseparable diastereoisomeric mixture (1 : 1) of the desired acetal as a colourless oil **17f** (14.67 g, 56%) along with starting alcohol **10f** (36.9 mmol, 8.20g), which was reacted with acrolein diethyl acetal (184.4 mmol, 28.0 mL) and PPTS (3.7 mmol, 0.93 g) in toluene (100 mL) as described above. After work-up and purification, products of the two different batches were combined to afford an inseparable diastereoisomeric mixture (1 : 1) of the desired acetal **17f** as a pale yellow oil (18.92 g, 73% total yield, 100% by GC). $R_f$ (5% diethyl ether in light petroleum) 0.25; $\nu_{max}$ (film)/cm$^{-1}$ 2977m (=C–H), 2934w (C–H), 1735s (C=O), 1652w (C=C); $\delta_H$ (300 MHz, $CDCl_3$) mixture: 6.15–5.28 (6H, m, C$H$=CH$_2$, CH=C$H_2$), 5.13–5.08 (1H, m, CH(OEt)O), 4.37–4.23 (1H, m, C$H$CH$_2$), 4.18–4.03 (2H, m, CHC$H_2$), 3.77–3.47 (2H, m, –OC$H_2$CH$_3$), 1.21 (9H, s, –C(C$H_3$)$_3$), 1.24–1.18 (3H, m, –OCH$_2$C$H_3$); $\delta_C$ (63 MHz, $CDCl_3$) mixture: 178.3, 135.0, 130.3 (t, $^{2}J_{C-F}$ 25.4), 130.2 (t, $^{2}J_{C-F}$ 25.7), 121.3, 119.5, 119.1, 103.1, 102.5, 75.0 (t, $^{2}J_{C-F}$ 28.7), 74.4 (t, $^{2}J_{C-F}$ 30.3), 63.0, 61.6, 39.0, 27.4, 15.4, 15.3; $\delta_F$ (282 MHz, $CDCl_3$) diastereoisomer 1: −103.1 (1F, dt, $^{2}J$ 254.6, $^{3}J_{F-H}$ 8.9, 8.9), −108.9 (1H, ddd, $^{2}J$ 254.6, $^{3}J_{F-H}$ 14.0, 6.4), diastereoisomer 2: −103.2 (1F, dt, $^{2}J$ 252.8, $^{3}J_{F-H}$ 10.2, 10.2), −109.2 (1F, ddd, $^{2}J$ 252.8, $^{3}J_{F-H}$ 14.0, 7.6). These acetals were taken on without further purification.

**Ethyl 4,4-difluoro-2,3,4-trideoxy-6-*O*-benzyloxy-DL-*glycero*-hex-2-enopyranoside 18d and 19d; procedure with Grubbs' catalyst**

A mixture of diastereoisomeric acetals **17d** (5.2 mmol, 1.63 g) and Grubbs' catalyst (0.26 mmol, 0.22 g) in dry degassed DCM (30 mL) was refluxed for 3 days under a nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to leave a dark brown oil (1.88 g). Purification by column chromatography (5% diethyl ether in light petroleum) afforded a mixture (1 : 1) of *cis*-**18d** and *trans*-**19d** (as a 1 : 1 mixture of diastereoisomers) as a clear oil (1.05 g, 68%, 100% by GC-MS); careful column chromatography (5% ether in light petroleum) afforded (in order of elution) *cis*-**18d** (0.51 g, 35%), $R_f$ 0.28, GC retention time 15.8 mins., $\nu_{max}$ (film)/cm$^{-1}$ 2977m (=C–H), 2934w (C–H), 1652w (C=C); $\delta_H$ (400 MHz, $CDCl_3$) 7.25–7.08 (5H, m, Ph), 6.19 (1H, dd, *J* 10.4, 1.3, =C*H*CH), 6.00 (1H, dddd, *J* 10.4, 7.7, $^3J_{H-F}$ 6.9, 3.0, $^4J$ 1.8, =C*H*$CF_2$), 5.23–5.10 (1H, m, C*H*OEt), 4.70 (1H, d, $^2J$ 12.1, OC$H_a$$H_b$Ph), 4.64 (1H, d, $^2J$ 12.1, OC$H_a$$H_b$Ph), 4.10 (1H, dddd, $^3J_{H-F}$ 17.8, 5.0, *J* 7.8, 3.0, $CF_2$C*H*), 4.01 (1H, dq, $^2J$ 9.5, *J* 7.0, OC$H_a$$H_b$$CH_3$), 4.00 (1H, dd, $^2J$ 12.3, *J* 3.0, C$H_a$$H_b$OBn), 3.84 (1H, dd, $^2J$ 12.3, *J* 7.8, $CH_a$$H_b$OBn), 4.01 (dq, $^2J$ 9.5, *J* 7.0, OC$H_a$$H_b$$CH_3$), 1.12 (3H, t, *J* 7.0, $CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 138.0, 136.4 (t, $^3J_{C-F}$9.5), 128.5, 127.8, 127.7, 127.4 (t, $^2J_{C-F}$28.6), 113.7 (dd, $^1J_{C-F}$242.7, 236.7), 96.8, 75.4 (dd, $^2J_{C-F}$30.0, 25.3), 73.7, 67.3 (d, $^3J_{C-F}$5.1), 64.4, 15.1; $\delta_F$ (376 MHz, $CDCl_3$) −105.2 (1F. br d, one half of an AB q, $^2J$ 278.3), −106.7 (1F. dddd, one half of an AB q, $^2J$ 278.3, $^3J_{H-F}$17.8, 6.9, 3.0); [HRMS (EI) Found: 284.12243. Calc. for $C_{15}H_{18}F_2O_3$: 284.12240]; *m*/*z* (EI, 40eV) 284 (18%, $[M + H]^+$), 145 (40), 91 (100, $[CH_2Ph]^+$): and *trans*-**19d** (0.50 g, 33%), $R_f$ 0.25, GC retention time 16.1 mins., $\nu_{max}$ (film)/cm$^{-1}$ 2977m (=C–H), 2934w (C–H), 1652w (C=C); $\delta_H$ (400 MHz, $CDCl_3$) $\delta_H$ (400 MHz, $CDCl_3$) 7.30–7.10 (5H, m, Ph), 6.18 (1H, dd, *J* 10.3, 3.0, =C*H*CH), 6.00 (1H, br t, *J* 10.3, $^3J_{H-F}$ 10.3, =C*H*$CF_2$), 5.16 (1H, t, *J* 3.0, $^4J$ 3.0, C*H*OEt), 4.70 (1H, d, $^2J$ 12.1, OC$H_a$$H_b$Ph), 4.66 (1H, d, $^2J$ 12.1, OC$H_a$$H_b$Ph), 4.51 (1H, ddt, $^3J_{H-F}$ 22.8, 3.0, *J* 7.9, 3.0, $CF_2$C*H*), 4.01 (1H, dd, $^2J$ 11.1, *J* 3.0, C$H_a$$H_b$OBn), 3.96 (1H, dq, $^2J$ 9.6, *J* 7.0, OC$H_a$-$H_b$$CH_3$), 3.81 (1H, dd, $^2J$ 11.1, *J* 7.9, $CH_a$$H_b$OBn), 3.66 (1H, dq, $^2J$ 9.6, *J* 7.0, OC$H_a$$H_b$$CH_3$), 1.15 (3H, t, *J* 7.0, $CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 138.1, 133.7 (t, $^3J_{C-F}$8.7), 128.4, 127.7, 127.5, 124.3 (dd, $^2J_{C-F}$30.0, 26.1), 113.4 (dd, $^1J_{C-F}$244.1, 233.9), 93.4, 73.4, 69.7 (dd, $^2J_{C-F}$29.9, 23.9), 66.9 (d, $^3J_{C-F}$6.2), 64.7, 15.1; $\delta_F$ (376 MHz, $CDCl_3$) −109.3 (1F, dd, one half of an AB q, $^2J$ 279.0, $^3J_{H-F}$22.5), −113.2 (1F. ddd, one half of an AB q, $^2J$ 279.0, $^3J_{H-F}$10.3, $^3J_{H-F}$ 3.0); [HRMS (EI) Found: 284.12248. Calc. for $C_{15}H_{18}F_2O_3$: 284.12240]; *m*/*z* (EI, 40eV) 284 (18%, $[M + H]^+$), 145 (40), 91 (100, $[CH_2Ph]^+$).

**Ethyl 4,4-difluoro-2,3,4-trideoxy-6-*O*-benzyloxy-DL-*glycero*-hex-2-enopyranoside 18d and 19d; procedure with Nolan catalyst**

A mixture of diastereoisomeric acetals **17d** (0.43 mmol, 0.135 g) and Nolan catalyst 1,3-(bis(mesityl)-2-imidazolidinylidene) dichloro(phenylmethylene) (tricyclohexylphosphino) ruthenium (0.022 mmol, 0.20 g) in dry degassed DCM (2.5 mL) was refluxed for 3 hours under a nitrogen atmosphere. The reaction mixture was treated as described previously to afford a mixture (1 : 1) of *cis*-**18d** and *trans*-**19d** (as a 1 : 1 mixture of diastereoisomers) as a clear oil (0.091 g, 75%, 100% by GC-MS). Data for **17d** as described previously.

**Ethyl 4,4-difluoro-2,3,4-trideoxy-6-*O*-pivaloyloxy-DL-*glycero*-hex-2-enopyranoside 18f and 19f**

A mixture of acetal **17f** (62 mmol, 19.00 g) and Grubbs' catalyst (1.55 mmol, 1.28 g) in dry degassed DCM (1.2 L) was refluxed for 3 days under a nitrogen atmosphere after which time some more Grubbs' catalyst (1.55 mmol, 1.28 g) was added as a solution in dry degassed DCM (10 mL). The reaction mixture was refluxed for an additional 2 days and concentrated under reduced pressure to leave a dark brown oil (20.03 g). Purification by column chromatography (10% diethyl ether in light petroleum) afforded an inseparable mixture (1 : 1) of the *cis*- and *trans*- dihydropyran diastereoisomers **18f** and **19f** as a pale yellow oil (11.47 g, 66%, 100% by GC-MS); $R_f$ (10% diethyl ether in light petroleum) 0.29; $\nu_{max}$ (film)/cm$^{-1}$ 2977m (C–H), 2935w (=C–H), 1735s (C=O), 1657w (C=C); $\delta_H$ (250 MHz, $CDCl_3$) *cis*–*trans*-mixture 6.11–6.05 (1H, m, H-3), 5.95–5.85 (1H, m, H-2), 5.10–5.01 (1H, m, H-1), 4.43–3.34 (5H, m, –OC$H_2$$CH_3$, H-6 and H-5), 1.20–1.15 (12H, m, –OC$H_2$C$H_3$ and –C(C$H_3$)$_3$); $\delta_c$ (63 MHz, $CDCl_3$) *cis*–*trans*-mixture: 178.0, 136.6 (t, $^3J_{C-F}$ 9.4), 134.0 (t, $^3J_{C-F}$ 9.2), 124.7 (t, $^2J_{C-F}$ 25.9), 124.2 (t, $^2J_{C-F}$ 21.9), 113.7 (dd, $^1J_{C-F}$ 243.6, 236.5), 113.4 (dd, $^1J_{C-F}$ 245.2, 235.5), 96.8, 93.5, 73.4 (t, $^2J_{C-F}$ 27.7), 68.6 (t, $^2J_{C-F}$ 27.0), 64.6, 61.1, 38.9, 27.2, 15.2; $\delta_F$ (235 MHz, $CDCl_3$) diastereoisomer 1: −104.3 (1F, ddd, $^2J$ 279.0, $^3J_{F-H}$ 11.9, 5.3), −107.6 (1F, ddt, $^2J$ 279.0, $^3J_{F-H}$ 14.6, 5.4, $^4J_{F-H}$ 5.4) diastereoisomer 2: −110.1 (1F, dd, $^2J$ 279.3, $^3J_{F-H}$ 21.2), −113.9 (1F, ddd, $^2J$ 279.3, $^3J_{F-H}$ 9.3, 2.6); [HRMS (EI, $[M + Na]^+$) Found: 277.12509, calc. for $C_{13}H_{19}F_2O_4$:277.12514]; *m*/*z* (EI) 277 (16%, $M^+ - H$), 249 (5, $M^+ - C_2H_5$), 233 (13, $M^+ - OEt$), 205 (50), 176 (80), 134 (100).

**Ethyl 6-*O*-benzyl-4,4-difluoro-4-deoxy-*β*-DL-*ribo*-pyranoside 20**

A solution of NMO (3.5 mmol, 0.41 g) in water (1 mL) was added to a cold (0 °C) solution of *cis*-**18d** (1.76 mmol, 0.50 g) in acetone (2 mL) and *tert*-butanol (2 mL). The mixture was stirred for 10 minutes and osmium tetroxide (0.035 mmol, 0.36 mL of a 2.5 wt% solution in *tert*-butanol, 2 mol%) was added. The reaction mixture was stirred at 0 °C for 2 hours, allowed to warm to room temperature and stirred at this temperature for 10 days. It was then quenched with sodium sulfite (7 mmol, 0.88 g), diluted with water (7 mL), stirred for an additional 30 minutes and extracted with ethyl acetate (3 × 7 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a yellow oil. Purification by column chromatography (50% ethyl acetate in light petroleum) afforded the desired pyranoside **20** as a pale yellow oil (0.428 g, 65%, 100% by GC) as a low melting solid, $R_f$ 0.38; GC retention time 21.27min; Found: C, 56.90; H, 6.01%. Calc. for $C_{15}H_{20}F_2O_5$: C, 56.60; 6.29%. $\delta_H$(400 MHz, $CDCl_3$); 4.71 (1H, d, *J* 8.0, H-1), 4.63 (1H, d, one half of an AB q, $^2J$ 12.1, C$H_a$$CH_b$Ph), 4.57 (1H, d, one half of an AB q, $^2J$ 12.1, $CH_a$C$H_b$Ph), 4.24 (1H, ddd, $^3J_{H-F}$ 25.1, *J* 7.5, 2.5, H-5), 4.20–4.13 (1H, br m, H-3), 4.10–3.88 (3H, m [including 4.03 (1H, dq, $^2J$ 9.6, *J* 7.1, OC$H_a$$CH_b$$CH_3$) and 3.92 (1H, br dd, $^2J$ 11.1, *J* 2.5, H-6a)], OC$H_a$$CH_b$$CH_3$, H-6a, OH), 3.79–3.46 (4H, m [including 3.76 (1H, dd, $^2J$ 11.1, *J* 7.5, H-6b)]), OC$H_a$C$H_b$$CH_3$, H-2, H-6b and OH), 1.30 (3H, t, *J* 7.1, $CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 137.8, 128.5, 127.8, 127.7, 117.7 (dd, $^1J_{C-F}$256.1, 248.9), 99.7, 71.7 (dd, $^2J_{C-F}$29.2, 22.1), 70.0 (dd, $^2J_{C-F}$34.2, 21.0), 69.8 (d, $^3J_{C-F}$4.5), 65.8, 15.1; $\delta_F$ (282 MHz, $CDCl_3$) −118.7 (1F, dd, $^2J$ 259.3, $J_{F-H}$5.9), −124.3 (1F, dd, $^2J$ 259.3, $J_{F-H}$25.1); *m*/*z* (EI) 318 (40%, $M^+$), 300 (10, $M - H_2O$), 272 (21, $M - 2H_2O$), 91 (100, $PhCH_2^+$).

**Ethyl 6-*O*-benzyl-4,4-difluoro-4-deoxy-*β*-DL-*lyxo*-pyranoside 21**

Was prepared as for **20** from 19d (0.7 mmol, 0.20 g), NMO (1.4 mmol, 0.165 g), osmium tetroxide (0.014 mmol, 0.15 mL of a 2.5% w/v solution in *tert*-butanol), *tert*-butanol (0.7 mL) and water (0.35 mL). The reaction required 8 days to reach completion. The usual work-up and purification afforded **21** (0.151 g, 68%, 100% by GC) as a powder, mp 77–78 °C; $R_f$ (50% ethyl acetate in light petroleum) 0.36; GC retention time 21.13min; Found: C, 56.77; H, 6.47. Calc. for $C_{15}H_{20}F_2O_5$: C, 56.60; H, 6.29%. $\delta_H$(400 MHz, $CDCl_3$) 4.63 (1H, s), H-1), 4.66 (1H, d, one half of an AB q, $^2J$ 12.1, C$H_a$$CH_b$Ph), 4.59 (1H, d, one half of an AB q, $^2J$ 12.1, $CH_a$C$H_b$Ph), 4.15–3.99 (2H, m, [including 4.10 (1H, ddd, $^3J_{H-F}$ 24.7, *J* 7.6, 2.5, H-5)], H-5 and H-3), 3.99–

3.91 (2H, m, [including 3.94 (1H, dd, $^2J$ 10.9, $J$ 2.5, H-6a)], H-2 and H-6a), 3.82 (1H, dq, $^2J$ 9.8, $J$ 7.0, OC$H_a$CH$_b$CH$_3$), 3.78 (1H, dd, $^2J$ 10.9, $J$ 7.6, H-6b), 3.58 (1H, dq, $^2J$ 9.8, $J$ 7.0, OCH$_a$-C$H_b$CH$_3$), 3.34–3.23 (1H, m, C(3)O$H$), 2.70–2.58 (1H, m, C(2)O$H$), 1.28 (3H, t, $J$ 7.0, C$H_3$); $\delta_C$ (75 MHz, CDCl$_3$) 137.8, 128.4, 127.8, 127.7, 118.0 (dd, $^1J_{C-F}$252.1, 250.8), 99.3, 73.6, 70.7, 69.4 (dd, $^2J_{C-F}$28.6, 22.6), 67.2 (dd, $^2J_{C-F}$20.6, 18.6), 66.4 (d, $^3J_{C-F}$5.0), 63.9, 14.8; $\delta_F$ (282 MHz, CDCl$_3$) −114.8 (1F, d, $^1J$ 251.2, $J_{F-H}$5.9), −124.3 (1F, dt, $^1J$ 251.2, $J_{F-H}$24.7); [HRMS (EI, M$^+$) Found: 318.12761. Calc. for $C_{15}H_{20}F_2O_5$: 318.12788]; $m/z$ (EI) 318 (40%, M$^+$), 300 (10, M − H$_2$O), 272 (21, M − 2H$_2$O), 91 (100, PhCH$_2^+$).

### Ethyl *cis*-4,4-difluoro-2,3,4-trideoxy-*α*-DL-*glycero*-hex-2-enopyranoside 27 and ethyl *trans*-4,4-difluoro-2,3,4-trideoxy-*β*-DL-*glycero*-hex-2-enopyranoside 28

DIBAL-H (117.8 mmol, 97.4 mL of a 20 wt%. solution in hexanes) was added dropwise to a cold (−78 °C) solution of *cis*-**18f** and *trans*-**19f** (47.1 mmol, 13.12 g) in dry DCM (500 mL). After completion of the addition the mixture was stirred at −78 °C for 1 hour and at 0 °C for an additional hour. The mixture was quenched carefully with water (200 mL) and HCl (150 mL of a 1 M solution). The phases were separated and the aqueous layer was extracted with DCM (3 × 230 mL). The combined organic extracts were dried (MgSO$_4$), filtered and concentrated under reduced pressure to afford a mixture (1 : 1) of alcohols **27** and **28** as a yellow oil (9.25 g). Purification by column chromatography (30% diethyl ether in light petroleum) allowed the separation of the two diastereoisomers. In order of elution, *trans*-**28** was obtained as a pale yellow oil (3.75 g, 41%, 100% by GC); $R_f$ (30% diethyl ether in light petroleum) 0.27; $\nu_{max}$ (film)/cm$^{-1}$ 3430s br (O–H), 2978m (=C–H), 1664w (C=C); $\delta_H$ (250 MHz, CDCl$_3$) 5.96 (1H, dd, $J$ 10.3, $^3J_{H-F}$ 3.0, H-3), 5.82–5.74 (1H, m, H-2), 4.93 (1H, t, $J$ 3.0, $^4J$ 3.0, H-1), 4.14–4.00 (1H, m, H-6a), 3.83–3.62 (3H, m H-6b, –OC$H_a$H$_b$CH$_3$ and H-5), 3.47–3.34 (1H, m, –OCH$_a$$H_b$CH$_3$), 1.81 (1H, br s, –O$H$), 1.06 (3H, t, $J$ 7.0, –OCH$_2$C$H_3$); $\delta_C$ (63 MHz, CDCl$_3$) 133.9 (t, $^3J_{C-F}$ 9.4), 124.6 (dd, $^2J_{C-F}$ 30.5, 25.9), 114.0 (dd, $^1J_{C-F}$ 244.1, 235.0), 93.7, 70.8 (dd, $^2J_{C-F}$ 31.0, 23.9), 65.1, 59.6 (d, $^3J_{C-F}$ 6.6), 15.4; $\delta_F$ (235 MHz, CDCl$_3$) −109.4 (1F, dd, $^2J$ 279.0, $^3J_{F-H}$ 21.9), −114.0 (1F, ddd, $^2J$ 279.0, $^3J_{F-H}$ 9.3, 2.7); [HRMS (EI, [M–H]$^+$) Found: 193.06756, calc. for $C_8H_{11}F_2O_3$:193.06763]; $m/z$ (EI) 193 (2%, M$^+$–H), 163 (42, M$^+$–CH$_2$OH), 149 (100, M$^+$–OEt): followed by *cis*-**27**, pale yellow oil (3.56 g, 39%); $R_f$ (30% diethyl ether in light petroleum) 0.19; $\nu_{max}$ (film)/cm$^{-1}$ 3426s br (O–H), 2979 m (=C–H), 1165w (C=C); $\delta_H$ (250 MHz, CDCl$_3$) 5.98 (1H, dd, $J$ 10.3, $^3J_{H-F}$ 1.4, H-3), 5.88–5.79 (1H, m, H-2), 5.05–5.00 (1H, m, H-1), 3.86–3.72 (4H, m, H-6, –OC$H_a$H$_b$CH$_3$ and H-5), 3.56–3.44 (1H, m, –OCH$_a$$H_b$CH$_3$), 2.28 (1H, br s, –O$H$), 1.10 (3H, t, $J$ 7.1, –OCH$_2$C$H_3$); $\delta_C$ (63 MHz, CDCl$_3$) 135.9 (t, $^3J_{C-F}$ 9.7, 9.7), 125.2 (t, $^2J_{C-F}$ 28.5, 28.5), 114.1 (dd, $^1J_{C-F}$ 263.0, 242.6), 96.4, 76.3 (dd, $^2J_{C-F}$ 30.8, 25.7), 64.8, 60.2 (d, $^3J_{C-F}$5.1), 15.4; $\delta_F$ (235 MHz, CDCl$_3$) −102.0 (1F, ddd, $^2J$ 279.3, $^3J_{F-H}$ 11.3, 6.0), −108.7 (1F, ddd, $^2J$ 279.3, $^3J_{F-H}$ 10.6, 4.0); [HRMS (EI, [M–H]$^+$) Found: 193.06762, calc. for $C_8H_{11}F_2O_3$:193.06763]; $m/z$ (EI) 193 (21%, M$^+$ − H), 163 (42, M$^+$ − CH$_2$OH), 149 (100, M$^+$ − OEt).

### Ethyl 4,4-difluoro-4-deoxy-*β*-DL-*ribo*-pyranoside 29

A solution of NMO (24.0 mmol, 2.81 g) in water (3 mL) was added to a cold (0 °C) solution of *cis*-**18f** (12.0 mmol, 2.33 g) in acetone (12 mL) and *tert*-butanol (12 mL). The mixture was stirred for 10 minutes and osmium tetroxide (0.24 mmol, 2.9 mL of a 2.5 wt% solution in *tert*-butanol) was added. The reaction mixture was stirred at 0 °C for 2 hours, allowed to warm to room temperature and stirred at this temperature for 5 days. It was then quenched with sodium sulfite (48.0 mmol, 6.05 g), diluted with water (50 mL), stirred for an additional 30 minutes and extracted with ethyl acetate (3 × 50 mL). The aqueous layer was separated and extracted further with diethyl ether in a continuous extractor for 4 days. The combined organic extracts were dried (MgSO$_4$), filtered and concentrated under reduced pressure to leave a yellow oil (2.85 g). Purification by column chromatography (80% ethyl acetate in light petroleum) afforded **29** as colourless oil, which solidified on standing (1.71 g, 62%). $R_f$ (80% ethyl acetate in light petroleum) 0.27; Mp 92–93 °C; (Found C, 42.28; H, 6.22; $C_8H_{14}F_2O_3$ requires: C, 42.11; H, 6.18%); $\nu_{max}$(KBr)/cm$^{-1}$ 3392s br (O–H), 2978m (C–H), 2934m (C–H); $\delta_H$ (250 MHz, DMSO-$d_6$) 6.16 (1H, d, $J$ 4.8, –O$H$), 5.41 (1H, d, $J$ 6.9, –O$H$), 5.01 (1H, t, $J$ 6.0, –O$H$), 4.71 (1H, d, $J$ 7.8, H-1), 4.11–3.96 (3H, m, H-3, H-5 and –OC$H_a$H$_b$CH$_3$), 3.91–3.83 (1H, m, H-6a), 3.77–3.63 (2H, m, –OCH$_a$$H_b$CH$_3$ and H-6b), 3.52–3.43 (1H, m, H-2), 1.33 (3H, t, $J$ 7.1 –OCH$_2$C$H$3; $\delta_C$ (63 MHz, DMSO-$d_6$) 119.2 (dd, $^1J_{C-F}$ 256.6, 247.4), 100.2, 72.7 (dd, $^2J_{C-F}$ 29.0, 21.9), 70.4 (dd, $^2J_{C-F}$ 32.3, 19.6), 69.6 (d, $^3J_{C-F}$ 6.1), 64.6, 58.2 (d, $^3J_{C-F}$ 4.6), 15.4; $\delta_F$ (235 MHz, DMSO-$d_6$) −117.8 (1F, dd, $^2J$ 249.5, $^3J_{F-H}$ 6.6), −123.6 (1F, ddt, $^2J$ 249.5, $^3J_{F-H}$ 26.5, 4.6, $^4J_{F-H}$ 4.6); [HRMS (FAB, [M + H]$^+$) Found: 229.08879, calc. for $C_{15}H_8O_5F_2$: 229.08876]; $m/z$ (FAB) 229 (41%, [M + H]$^+$), 211 (11), 183 (37). An analytical sample was recrystallised by vapour diffusion (diethyl ether–light petroleum) to afford colourless needles, which were used to obtain an X-ray crystal structure of **29**.

### Ethyl 4,4-difluoro-4-deoxy-α-DL-*lyxo*-pyranoside 30

Was prepared exactly as for **29**, on the same scale and with the same reaction times and work-up (including continuous extraction). The combined organic extracts were dried (MgSO$_4$), filtered and concentrated under reduced pressure to leave a yellow oil (2.85 g). Purification by column chromatography (80% ethyl acetate in light petroleum) afforded **30** as a pale yellow oil (1.70 g, 62%). $R_f$ (80% ethyl acetate in light petroleum) 0.24; $\nu_{max}$(film)/cm$^{-1}$ 3396s br (O–H), 2978m (C–H), 2934m (C–H); $\delta_H$ (250 MHz, DMSO-$d_6$) 5.50 (1H, d, $J$ 8.0, –O$H$), 5.17 (1H, d, $J$ 4.4, –O$H$), 5.03 (1H, t, $J$ 6.0, –O$H$), 4.89 (1H, s, H-1), 4.02–3.79 (5H, m, H-2, H-4, H-5, H-6a, –OC$H_a$H$_b$CH$_3$), 3.76–3.56 (2H, m, H-6b, –OCH$_a$$H_b$CH$_3$), 1.32 (3H, t, $J$ 7.1, –OCH$_2$C$H_3$); $\delta_C$ (63 MHz, DMSO-$d_6$) 118.8 (dd, $^1J_{C-F}$ 258.1, 244.4), 99.6, 71.5 (dd, $^2J_{C-F}$ 29.0, 22.9), 70.4 (d, $^3J_{C-F}$ 7.6), 67.0 (t, $^2J_{C-F}$ 19.1, 19.1), 62.8, 58.0 (d, $^3J_{C-F}$ 5.6), 15.0; $\delta_F$ (235 MHz, DMSO-$d_6$) −112.7 (1F, d, $^2J$ 242.8), −128.6 (1F, dt, $^2J$ 242.8, $^3J_{F-H}$ 24.5, 24.5); [HRMS (FAB, [M − H]$^-$) Found: 227.07300, calc. for $C_8H_{13}O_5F_2$: 227.07311]; $m/z$ (ES) 227 (100%, [M − H]$^-$).

### Ethyl 4,4-difluoro-4-deoxy-*α*-DL-*lyxo*-pyranoside triacetate 31

Acetic anhydride (0.5 mL, 5 mmol) was added to a solution of pyranoside **30** (228 mg, 1 mmol) in pyridine (5 mL). The reaction mixture was stirred at room temperature for 17 hours, poured onto ice–water (10 mL) and extracted with DCM (3 × 10 mL). The combined organic extracts were washed successively with sodium hydrogen carbonate (10 mL of a saturated aqueous solution) and water (10 mL), dried (MgSO$_4$), filtered and concentrated under reduced pressure to leave a pale yellow oil (262 mg). Purification by column chromatography (10% diethyl ether in light petroleum) afforded triacetate **31** as a pale yellow solid (251 mg, 72%). $R_f$ 0.26 (10% diethyl ether in light petroleum); mp 52–53 °C; (Found C, 47.59; H, 5.78; $C_{14}$-$H_{20}F_2O_8$ requires: C, 47.46; H, 5.69%); $\nu_{max}$(KBr)/cm$^{-1}$ 2988m (C–H), 1755s (C=O); $\delta_H$ (400 MHz, CDCl$_3$) 5.49 (1H, ddd, $^3J_{H-F}$ 22.4, 6.0, $J$ 4.0, H-3), 5.31–5.26 (1H, m, H-2), 4.88 (1H, s, H-1), 4.50 (1H, dd, $^2J$ 11.9, $J$ 3.3, H-6a), 4.38 (1H, dd, $^2J$ 11.9, $J$ 7.6, H-6b), 4.16 (1H, ddd, $^3J_{H-F}$ 22.4, $J$ 7.6, 3.3, H-5), 3.78 (1H, dq, $^2J$ 9.8, $J$ 7.1, –OC$H_a$H$_b$CH$_3$), 3.60 (1H, dq, $^2J$ 9.8, $J$ 7.1, –OCH$_a$$H_b$CH$_3$), 2.07 (3H, s, – C$H_3$CO), 2.05 (3H, s, C$H_3$CO), 2.02 (3H, s, C$H_3$CO), 1.20 (3H, t, $J$ 7.1, –OCH$_2$C$H_3$); $\delta_C$ (63 MHz, CDCl$_3$) 170.9, 170.5, 169.7, 116.3 (dd, $^1J_{C-F}$ 260.4, 248.7), 97.9, 69.4 (t, $^3J_{C-F}$ 8.9), 68.9 (dd, $^2J_{C-F}$ 28.5, 22.9), 66.5 (dd, $^2J_{C-F}$ 22.1, 17.0), 60.7, 60.6, 21.1, 21.0, 20.8, 15.2; $\delta_F$ (235 MHz,

$CDCl_3$) −115.9 (1F, d, $^2J$ 248.1), −129.0 (1F, dt, $^2J$ 248.1, $^3J_{F-H}$ 22.4); [HRMS (FAB, $[M + H]^+$) Found: 355.12041, calc. for $C_{14}H_{21}O_8F_2$: 355.12045]; *m/z*(FAB) 355 (50%, $[M + H]^+$), 309 (65), 249 (100).

### 4-Deoxy-4,4-difluoro-*β*-DL-*ribo*-pyranoside 32

Deuterium chloride (0.03 mL of a 35% w/v solution in $D_2O$) was added to a solution of ethyl glycoside **29** (0.080 g, 0.35 mmol) in $D_2O$ (0.4 mL). The reaction was heated to 80 °C and stirred for 3 days. The reaction was judged to be complete by TLC and electrospray MS, and analysed without any attempt at purification. Major (β) anomer $\delta_H$ ($D_2O$, 400 MHz) 4.52 (1H, dd, *J* 8.0, $^5J_{H-F}$0.6, H-1), 3.75 (1H, ddd, $^3J_{H-F}$7.1, 3.9, *J* 5.2, H-3), 3.67 (1H, ddd, $^3J_{H-F}$25.1, *J* 7.2, 3.2, H-5), 3.49 (1H, ddd, $^2J$ 12.2, *J* 3.2, 1.2, H-$6_a$), 3.34 (1H, dd, $^2J$ 12.2, *J* 7.2, H-$6_b$), 3.18–3.13 (1H, m, H-2); $\delta_C$ ($D_2O$, 100 MHz) 117.6 (dd, $^1J_{C-F}$255.3, 248.8), 93.1, 71.5 (dd, $^2J_{C-F}$30.5, 22.3), 69.6 (d, $^3J_{C-F}$6.2), 69.4 (dd, $^2J_{C-F}$33.1, 20.7), 57.6 (d, $^3J_{C-F}$4.4); $\delta_F$ ($D_2O$, 376 MHz) −120.1 (1F, dd, $^2J_{F-F}$257.8, $^3J_{H-F}$7.1), −125.0 (1F, ddt, $^2J_{F-F}$257.8, $^3J_{H-F}$25.1, 3.9, $^4J_{H-F}$ 3.9); *m/z* ($ES^-$ MeOH) 199 (8%, [M − H]), 171 (100, [M − HCHO]). The following significant peaks were observed for the minor (α) anomer: $\delta_H$ ($D_2O$, 376 MHz) 4.80 (1H, t, *J*, $^5J_{H-F}$3.2, H-1), 3.89 (1H, ddd, $^3J_{H-F}$25.4, 7.5, *J* 3.2, H-3), 3.55–3.44 (1H, m, H-5), 3.38 (1H, dd, $^2J$ 12.4, *J* 7.2, H-$6_b$); other signals were overlapped with those for the major anomer; $\delta_F$ ($D_2O$, 376 MHz) −116.6 (1F, dd, $^2J_{F-F}$257.0, $^3J_{H-F}$7.5), −125.3 (1F, br dd, $^2J_{F-F}$257.0, $^3J_{H-F}$25.4). The $^{13}C$ NMR was too weak to assign reliably.

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