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# Applying asymmetric dihydroxylation to the synthesis of difluorinated carbohydrate analogues: a 1,1-difluoro-1-deoxy-D-xylulose

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**Abstract**—Readily available difluoroenol iodides and stannanes undergo palladium-catalysed coupling reactions with alkenylstannanes and iodides, respectively, to afford a trial set of difluorinated 1,3- and 1,4-dienes, which were then exposed to AD conditions. A number of issues were raised including generally low reactivity of simple 1,3-butadienes, and useful reactivity of certain 1,4- and substituted 1,3-pentadienes. Though the basic conditions used for the AD resulted in the decomposition of certain diol products, enol acetal chemistry allowed the asymmetric synthesis of a difluorinated analogue of a deoxyxylulose.


## 1. Introduction

Fluorosugars are of considerable current interest because they retain much of the shape, electron distribution and function of natural saccharides while lacking the ability to enter into critical hydrogen bonding interactions with nucleic acids or proteins.[1] In addition, the presence of one or two fluorine atoms close to the anomeric centre modulates the reactivity of the glycosidic bond strongly; the powerful inductive electron-withdrawing effect(s) exerted by one (or more) fluorine atom(s) raises the energy of oxacarbenium ion intermediates or transition states that resemble them, making hydrolytic reactions of fluorinated glycosides more difficult[2] and resulting in useful inhibition of glycosidases and glycosyltransferases (Fig. 1). This makes fluorinated sugars very useful molecular tools for identifying key interactions used by receptors in binding saccharide ligands, or even for the affinity labelling and ultimate sequencing of active site regions. For example, Withers has used 2-deoxy-2-fluorosaccharide **1** (inter alia) to obtain crystal structures of enzyme-modified substrate complexes (in this case a

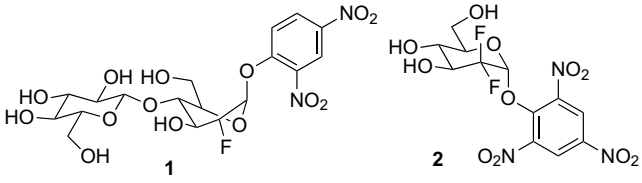


**Figure 1.** Fluorinated probes of sugar-processing enzymes.

β-glycoside hydrolase),[3] and 2-deoxy-2,2-difluorosugar derivatives (**2** for example) to label and identify the active site of an α-glycosidase enzyme.[4]

This field of glycobiology is in its infancy and the lack of availability of a wider range of saccharide analogues acts as a barrier to rapid progress.

Syntheses of difluorosugars using fluorination methods to transform a ketonic carbonyl group are common,[5] though not without difficulties, caused by side reactions associated with high electron demand (elimination, neighbouring group participation, 1,2-shifts).[6]

An attractive alternative, although as yet, greatly underused approach begins with inexpensive and readily

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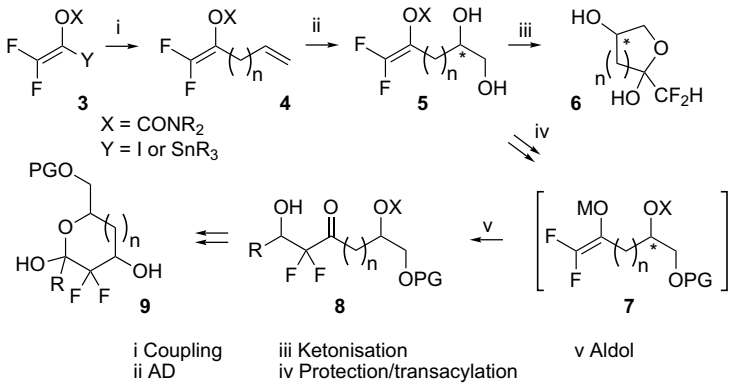



**Scheme 1.** Synthetic strategy connecting difluoroenol derivatives with difluorinated saccharide analogues.

available fluorinated feedstocks or building blocks.[7] One important method for the de novo synthesis of monosaccharides uses the Sharpless asymmetric dihydroxylation (AD) reaction of dienes. The groups of Corey[8] and Somfai[9] have used this method in total synthesis and while the method has considerable potential for the synthesis of monosaccharides, which are difficult to obtain by more conventional methods, extensive protecting group manipulation can be an unfortunate drawback of attempts to use this ostensibly simple approach in target synthesis as Armstrong[10] has shown. Ourselves[11] and Qing[12] have shown independently that the AD reaction can be used valuably to resolve racemic modifications of difluorinated precursors to aldonic acids and nucleosides, respectively, while Davis[13] used a similar tactic to synthesise an enantiomerically enriched monofluorinated nucleoside analogue.

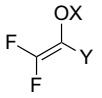
We wished to learn about the scope and limitations of the dihydroxylation approach to selectively fluorinated saccharides based upon a range of starting difluorinated dienes. These species were readily available via palladium-catalysed coupling reactions of difluoroenol derivatives; Scheme 1 shows how we proposed to approach the synthesis of analogues of pentoses, hexoses and higher sugars such as **9** from difluoroenol derivatives of general type **3**.

The key reactions are the synthesis and AD of dienes **4**, followed by either release of a difluoromethylketone, which would cyclise to **6** under mild acid conditions,[14] or alternatively, the use of basic conditions to trigger a transacylation reaction and formation of metal enolate **7**, setting the stage for a C–C bond-forming aldol reaction[15] with chain extension to **8**. Though the first goal was realised, the second proved very challenging and ultimately intractable within the scope of this study.

## 2. Results and discussion

### 2.1. Diene synthesis

We were able to use Stille coupling reactions for the construction of the desired diene precursors,[16] from **10**, **11**[17] or **13**,[18] and commercial, known **14**[19] or novel **15** and **16** co-reactants (Table 1).



**10**, X = $CONEt_2$ (DEC), Y = I
**11**, X = DEC, Y = $SnBu_3$
**12**, X = MEM, Y = I
**13**, X = MEM, Y = $SnBu_3$

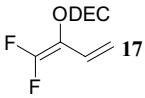
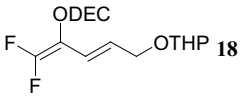
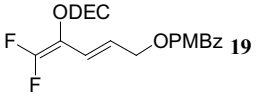
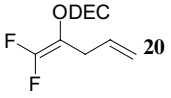
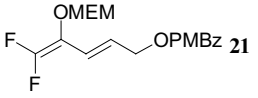
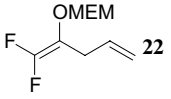
Difluoroenol ethers **10**, **11** and **13** were all synthesised easily from trifluoroethanol, and subsequent Stille homologation provided access to conjugated and non-conjugated (*N*,*N*-diethylcarbamoyloxy) and [methoxy(ethoxymethyl)] difluorodienes **17**–**22** (Table 1). Notable features of this cross-coupling chemistry included the use of modified Farina–Liebeskind conditions[20] in which copper(I) iodide is a crucial additive. The conditions represented in the table were arrived at after some optimisation for individual substrates. Generalities include the use of a palladium(II) acetate catalyst precursor and an arsine ligand (20 mol%, 2:1 stoichiometry with copper(I) iodide) for couplings of iodide **10** with stannanes, and the use of $Pd_2dba_3{\cdot}CHCl_3$ complex with triphenylphosphine ligand (19–21 mol%, ca. 2:1 stoichiometry with copper(I) iodide) for the coupling of stannane **11** with vinyl iodides or allyl bromide. One coupling using **10** (with tributylvinyltin) proceeded more rapidly under the palladium(II) acetate-catalysed conditions. The two methods used for the synthesis of 1,4-diene **20** delivered sharply contrasting results, which may relate to the known slow transfer of the allyl group from tin to palladium.[21]

Coupling reactions of iodide **12** were not explored because, while the iodide can be prepared, its stability during purification is low and material of adequate purity could not be secured.[22] Instead, stannane **13**, which can be prepared in 0.5 mole batches was used; the two couplings reported in this manuscript used palladium(II) acetate catalyst (at lower loading, ca. 2.5 mol%) and a triphenylphosphine:copper(I) iodide ratio of 1:2 (ca. 10% phosphine loading). These modified conditions emerged from optimisation studies of the coupling of **13** with aryl halides, which will be reported elsewhere.[23]

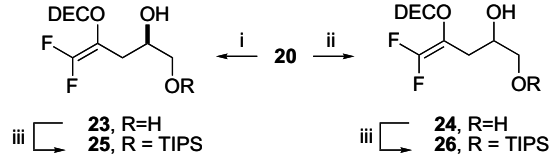
### 2.2. Asymmetric dihydroxylation reactions

With a supply of representative dienes in hand, our attention turned to the AD reaction.[24] First, we examined diene **17**; successful dihydroxylation would deliver a very useful four-carbon building block for the syn-

**Table 1.**

| Difluoroenol | Co-reactant | Catalyst | Ligand | CuI (%) | Temp (°C) | Time (h) | Product | % |
|---|---|---|---|---|---|---|---|---|
| **10** | $Bu_3Sn$ | 2.5% $Pd_2dba_3{\cdot}CHCl_3$ | 20% $AsPh_3$ | 10 | 100 | 16 |  **17** | 36 |
| | | 5% $Pd(OAc)_2$ | 20% $AsPh_3$ | 10 | 100 | 1.5 | | 77 |
| **10** | $Bu_3Sn$ **14** | 5% $Pd(OAc)_2$ | 20% $AsPh_3$ | 11 | 100 | 6.5 |  **18** | 31 |
| **11** | I **15** | 5% $Pd_2dba_3{\cdot}CHCl_3$ | 19% $PPh_3$ | 12.7 | 100 | 16 | | 25 |
| **11** | I **16** | 2% $Pd_2dba_3{\cdot}CHCl_3$ | 20% $PPh_3$ | 12.5 | 50 | 16 |  **19** | 83 |
| **10** | $Bu_3Sn$ | 5% $Pd(OAc)_2$ | 20% $AsPh_3$ | 10 | 100 | 16 |  **20** | 18 |
| **11** | Br | 4.5% $Pd_2dba_3{\cdot}CHCl_3$ | 21% $PPh_3$ | 13.5 | 100 | 18 | | 87 |
| **13** | I **16** | 2.2% $Pd(OAc)_2$ | 8.7% $PPh_3$ | 17.3 | 50 | 3 |  **21** | 41 |
| **13** | Br | 2.6% $Pd(OAc)_2$ | 10% $PPh_3$ | 20 | 100 | 18 |  **22** | 61 |

thesis of difluorinated saccharide analogues. However, even the racemic and reactive quinuclidine-catalysed conditions described by Warren[25] and co-workers failed to convert the starting material either reproducibly or at a useful rate. Signals consistent with the presence of a new difluoroalkene product were observed in the $^{19}F$ NMR spectrum of the crude product [$\delta_F$ −93.6 (1F, d, $^2J_{F-F}$ 50.1 and −105.4 (1F, dd, $^2J_{F-F}$ 50.1), $^4J_{F-H}$ 4.0)] but a conversion of ca. 5% after 24 h was typical. The addition of methanesulfonamide had no effect on the rate of consumption of starting material. Exposure of **17** to AD mix-β under typical conditions resulted in the quantitative recovery of starting material after 72 h. Park et al.[26] have described the stereoselective and high yielding (80%) oxidation of 1,3-butadiene to the corresponding tetrol ($OsO_4$/NMO oxidant) but unfortunately, as no details were reported, we cannot compare the reactivities of the two dienes. There are three inductively electron-withdrawing substituents on the second alkenyl group in **17**, which may be enough to disable the unsubstituted alkenyl group as a nucleophile. Though substituent effects on the AD reaction are complex, it is known that a perfluoroalkyl group can lower the rate of reaction.[27,28] Diene **18** was also unreactive, even after extended reaction times (144 h) and at osmium loading as high as 3 mol%. Non-conjugated 1,4-diene **20** was a more reactive substrate, being consumed completely within 16 h, affording diol **23** smoothly and in good yield (88%) on a 10 mmol scale when reacted with AD mix-β (Scheme 2). Quinuclidine-catalysed dihydroxylation was carried out to provide racemic modification **24** and both products were converted regioselectively to TIPS ethers

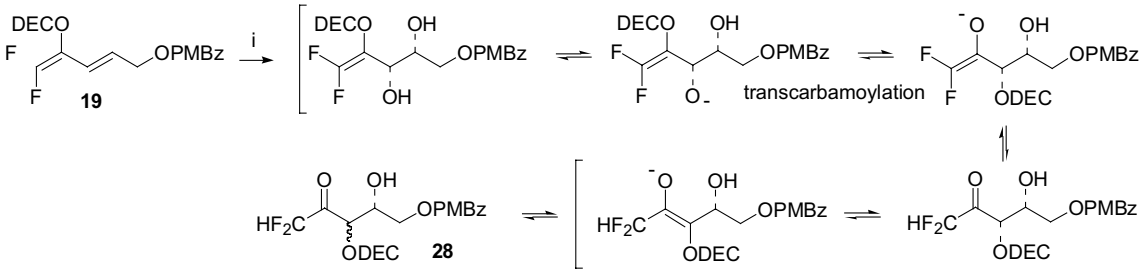



**Scheme 2.** Reagents and conditions: (i) AD-mix-β, $NaHCO_3$, *t*-BuOH/$H_2O$ (1:1), 0 °C, 18 h; (ii) $K_2OsO_4{\cdot}2H_2O$, $K_3Fe(CN)_6$, quinuclidine, $K_2CO_3$, *t*-BuOH/$H_2O$ (1:1); (iii) TIPSCl, imidazole, DMAP, DCM, rt, 48 h.

**25** and **26** in very high yield and purity (up to 99% by capillary GC).

The extent of asymmetric induction (*er*) as determined by chiral HPLC (Chiralcel OD column, 10% *i*-PrOH in hexane) was 95:5 {$[\alpha]_D = -2.1 \pm 0.4$, (*c* 18.4, 294 K, MeOH)}; the sense of asymmetric induction is predicted from the Sharpless mnemonic; all the examples of simple terminal alkenes in the literature appear to be dealt with entirely adequately using this tool.

A more complex situation prevailed in the case of **18** and **19**. The THP-protected allylic alcohol **18** was inert to the AD conditions used for **20**, but we were able to consume **19** under buffered AD-mix-β conditions (pH 10.3, adjusted with $NaHCO_3$). The PMBz group is known to be a good choice for the protection of allylic alcohols, and apparently assists the AD reaction through the development of a favourable interaction between the substrate and catalyst π-systems;[8] in our system, the PMBz group increased the rate of AD reaction, but it was still an extremely slow process.[29]




**Scheme 3.** Reagents and conditions: (i) $K_2OsO_4{\cdot}2H_2O$ (2 mol%), $(DHQD)_2PHAL$ (4 mol%), $K_3Fe(CN)_6$ (3 equiv), $NaHCO_3$, *t*-BuOH/$H_2O$ (1:1), pH 10.3, rt, 5 days.

The reaction was followed by $^{19}F$ NMR spectroscopy, until the starting material was consumed (5 days), and while small signals consistent with the presence of diol **27** ($\delta_F$ −90 to −110 ppm) were observed, an extremely complex set of AB-type signals developed at ca. −138 ppm, consistent with the formation of *more than one* difluoromethyl ketone, presumed to be **28**. Not only had transacylation occurred but also epimerisation, arising from the acidity of the methine proton next to the ketone (Scheme 3).

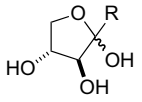
Transacylation, driven by the formation of the carbonyl group is a direct consequence of the high pH of the AD reaction; unfortunately, since the reaction medium must be basic to ensure osmate ester hydrolysis,[30] there seems no prospect of switching off the transacylation reaction when there is an allylic hydroxyl group. Effective molarities for nucleophilic catalysed intramolecular reactions involving five-membered intermediates are typically $10^2$ higher than for analogous species involving six-membered rings.[31] This difference in EM will be expressed in the lower rate of attack by the homoallylic alkoxide at the carbamate carbonyl group (which seems likely to be the rate-determining step), being consistent with our ability to isolate diol **23** from the AD reaction.

### 2.3. Attempted transacylation and enolate release

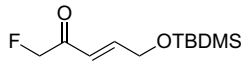
We treated **23** with bases, which would irreversibly deprotonate the exposed homoallylic alcohol; these included *n*-BuLi, NaH, NaHMDS, KH and KHMDS in THF. Typically the base was added at low temperature (−78 °C) and the solution allowed to warm[15] to −10 °C before the addition of a protic quench (higher temperatures were avoided because of the known instability of difluoroenolates). Starting material was recovered in all cases, except where the reactions were protracted in which case decomposition occurred. Our failure to control the AD/transacylation sequence means that this carbamate-based route cannot be considered viable.

### 2.4. Deploying enol acetal chemistry: a pentulose analogue synthesis

To solve the problem of transacylation, we sought to use enol acetal derivative **21** as a dihydroxylation substrate,[32] with the 1-deoxy-D-xylulose analogue **29**, which fulfils a pivotal role in the biosyntheses[33] of pyridoxol phosphate, thiamine pyrophosphate and the phytyl chain of ubiquinone in *E. coli*, as an illustrative target.




**29**, R = $CH_2OH$;
**30**, R = $CH_2F$;
**31**, R = $CHF_2$.



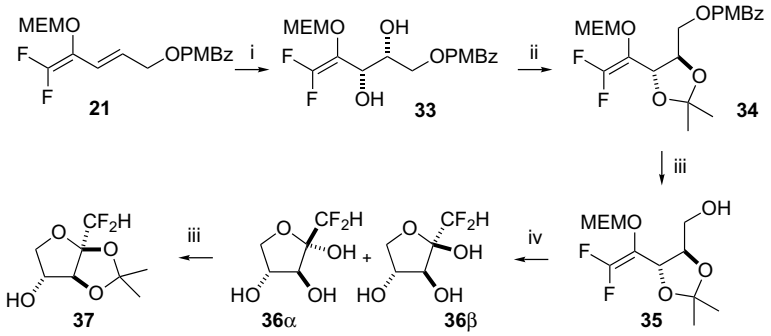

**32**

Bouvet and O'Hagan[34] proposed **30** and **31** as potential inhibitors of enzymes involved in the metabolism of 1-deoxy-D-xylulose and the 5-phosphate, and attempted a synthesis based on the asymmetric dihydroxylation of enone **32**; however, the diol product could not be isolated cleanly from the reaction due to the high electrophilicity of the fluoroketone. We hoped that a route based upon **21** in which the difluoromethyl ketone could be released after AD would offer a solution to this problem.

Dihydroxylation of diene **21** occurred very slowly under standard AD conditions (Scheme 4); typical reactions required one week to reach 70–85% conversion and a significant fall in the pH of the medium was observed over this period. However, when the pH was maintained[30] in the range 11.0–12.0, the reaction reached completion in only 1 h and we were able to isolate diol **33** in 55% yield. The effect of pH maintenance is spectacular and demonstrates the critical importance of rapid osmate ester turnover for efficient catalysis. The use of the PMBz protecting group is also critical. Ester hydrolysis probably prevents recovery of the diol in higher yield and it is possible that a PMB ether or PMP ether would offer similar reactivity and greater stability under the reaction conditions. However, we wished to be able to cleave the primary hydroxyl group under mild nucleophilic conditions so these possibilities were not investigated.

Diol **33** was protected in acetonide **34**, and the synthesis completed by hydrolysis of the ester to **35** followed by removal of both acetals, to afford deoxy difluorosugar **36** as a mixture of α- and β-anomers (1:3). The major anomer **36**β was assigned by NOE experiments, and both anomers converged on **37** when the mixture was treated with acetone and an acid catalyst.

The material exhibited the same magnitude and sign of rotation as that reported by Bouvet and O'Hagan, con-




**Scheme 4.** Reagents and conditions: (i) $K_2OsO_4{\cdot}2H_2O$ (2 mol%), $(DHQD)_2PHAL$ (4 mol%), $K_3Fe(CN)_6$ (3 equiv), *t*-BuOH/$H_2O$ (1:1), pH 11.0–12.0, rt, 54%; (ii) anhydrous $CuSO_4$ (2 equiv), PTSA (1 mol%), acetone, rt, 68%; (iii) 30%$H_2O_2$ (4.2 equiv), LiOH·$H_2O$ (2.2 equiv), THF/$H_2O$ (3:1), 0 °C, 61%; (iv) $Me_3SiCl$ (1.2 equiv), MeOH, rt, 88%.

firming that the sense of enantioselection conforms with the Sharpless model. Use of the $(DHQD)_2PHAL$ ligand predicts that **33** is the product; we determined an ee for the AD reaction by preparing the bis-(*S*)-Mosher ester[35] **38** of **33** and the bis-(*S*)-Mosher ester of racemic diol **39** and examining their $^{19}F$ NMR spectra (Fig. 2).

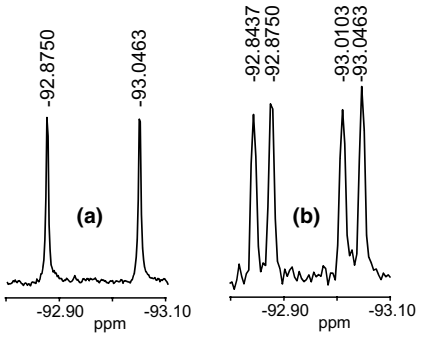
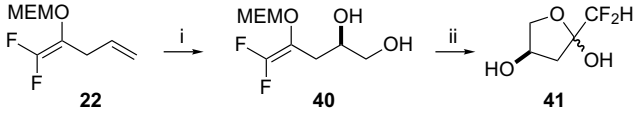



**Figure 2.** Partial $^{19}F$ NMR spectra [282 MHz, 300 K, $CDCl_3$] of (a) **38** with enhanced signal-to-noise (1579 data points between −90.0 and −95.0 ppm); (b) bis-(*S*)-Mosher ester of racemic diol **39**.

Whereas the $CF_3$ region of the spectrum contained a number of peaks from esters and unreacted derivatising agent, which could not be deconvoluted, the $CF_2$ region of the spectrum of **33** contained only a single doublet for each of the vinylic fluorine atoms, even when a large number of data points (1579 between −90.0 and −95.0 ppm) were recorded to optimise the signal-to-noise ratio (Fig. 2a). In contrast, two doublets were observed for each of the vinylic fluorine atoms in the bis-(*S*)-MTPA ester **39** of the racemic diol (Fig. 2b); the ee is calculated as $\geqslant$99.5% on this basis.

We were unable to use HPLC to estimate the extent of enantiomeric enrichment of diols **33**, finding that the compounds were rather unstable on the columns at our disposal, so the success of the NMR method and the correlation with a known compound derived from a chiral pool material are fortunate. Diene **22** could also be taken through a sequence of AD (in rather poor yield) and MEM cleavage (Scheme 5) to afford a pair of dideoxy-xylulose anomers **41** (which can be identified clearly by GOESY experiments) but we did not attempt to estimate the ee in this case, given the low recovery of diol **40**.




**Scheme 5.** Reagents and conditions: (i) AD-mix-β, $NaHCO_3$, *t*-BuOH/$H_2O$ (1:1), 0 °C, 18 h; (ii) $Me_3SiCl$, MeOH, rt, 18 h.

## 3. Conclusions

These findings show that dienes like **21** are useful substrates for Sharpless AD reactions, despite their relatively high lability. The dihydroxylation reaction is completely regioselective with the highly substituted alkenyl bond emerging untouched from the reaction. Sharpless and others have reported successful AD reactions of polyenes[27] but there are few examples where both alkenes bear a deactivating substitutent. Even with the use of a protecting group known to enhance AD reactivity, the dihydroxylation reaction was slow and pH control was essential for efficient conversion, suggesting that **21** lies close to the lower limit of substrate reactivity. A number of significant challenges must be met before the potential of terminally difluorinated 1,3- and 1,4-pentadienes for the synthesis of difluorosugar analogues can be realised, principally in unlocking the potential of the transacylation reaction and subsequent enolate release for the formation of further C–C bonds.

## 4. Experimental

### 4.1. General procedures

All NMR spectra were recorded on Bruker AC-300, AV-300, AMX-400 or DRX-500 spectrometers. $^1H$ NMR and $^{13}C$ NMR were recorded using deuterated solvent as the lock and residual protic solvent as the internal standard. $^{13}C$ NMR were recorded using the PENDANT pulse sequence unless otherwise stated. $^{19}F$ NMR spectra were recorded relative to chlorotrifluoromethane. All coupling constants are recorded in hertz

(Hz). *J* (italic) represents homonuclear coupling (i.e., H–H or F–F). Square brackets ([ ]) represent groups of resonances for a single nucleus resulting from rotamers. Chemical ionisation (CI) and electron impact (EI) mass spectra were recorded on a VG Prospec or Kratos MS-80 mass spectrometer with a DS-90 data system. Chemical ionisation methods used ammonia as the carrier gas. Fast atom bombardment (FAB) mass spectra were recorded using a VG Zabspec instrument. A Micromass LCT mass spectrometer was used for both low-resolution (ES-TOF) mass spectra (using methanol as the mobile phase) and HRMS measurements (using a lock mass incorporated into the mobile phase). HRMS measurements were also obtained from either the VG Prospec spectrometer or a VG Autospec instrument.

Thin layer chromatography was performed on either pre-coated aluminium-backed silica gel plates (E. Merck, A.G. Darmstadt, Germany. Silica gel 60 $F_{254}$, thickness 0.2 mm), pre-coated aluminium-backed alumina gel plates (E. Merck, A.G. Darmstadt, Germany. Alumina gel 60 $F_{254}$, thickness 0.2 mm) or plastic-backed RP-C18 plates. Column chromatography was performed on silica gel (E. Merck, A.G. Kieselgel 60, Art. 9385), alumina (pH 9–11, Brockmann 1, Fisher) or Florisil. GC analysis was carried out on a Carlo Erba GC 8000 Series with Flame Ionisation Detection (FID). An SPE BPX-5 Megabore column (15 m × 0.53 mm ID/Split Mode 20:1) was used with helium as the carrier gas. Analytical HPLC analysis was performed on a Dionex Summit HPLC system with Chromeleon software using a Summit P580 quaternary low-pressure gradient pump with built-in vacuum degasser. A Summit UVD 170s UV/VIS multi-channel detector with an analytical flow cell was used for detection. A Luna 10$\mu$ C18(2) column (250 mm × 4.6 mm) was used as the stationary phase unless otherwise stated. Semi-preparative HPLC of diols **33** was attempted on an identical system accept that a Prep flow cell was used in conjunction with a Luna 10$\mu$ C18(2) column (250 mm × 10 mm). Chiral HPLC of alcohols **25** and **26** was performed on a Chiralcel OD column (0.46 cm × 25 cm) using a 90% hexane: 10% *iso*propanol eluent.

Elemental analyses were performed on a Carlo Erba 1110 CHNS microelemental analysis machine. Optical rotations were performed on a PolAAr 2001 optical activity Ltd automatic polarimeter using 0.25 dm (1 mL) cells. IR spectra were recorded on a Perkin–Elmer Paragon 1000 FT-IR spectrometer using sodium chloride plates. Melting points were recorded on a Stuart scientific SMP1 melting point apparatus and are uncorrected.

Tetrahydrofuran was dried by heating under reflux with sodium metal and benzophenone, under dry nitrogen, until a deep purple colour persisted. The solvent was then collected by syringe as required. DMF was distilled from barium oxide under reduced pressure and stored under nitrogen. Dioxane was distilled from diphosphorus pentoxide. DCM was distilled from calcium hydride. Di*iso*propylamine was distilled from calcium hydride and stored over 4 Å molecular sieves. Dichloromethane was distilled from calcium hydride. 2,6-Lutidine was distilled from KOH and stored over KOH pellets. pH Measurements were taken using a pH tester ('Checker', Hanna instruments) available from Fisher chemicals. Degassing of solvents for couplings was performed by purging with dry nitrogen or dry argon for 20 min prior to use. *n*-Butyllithium was titrated against either 4-benzylidene benzylamine[36] or *N*-pivaloyl-*o*-toluidine[37] before use.

All crude coupling products were diluted with diethyl ether and aqueous KF (1 M, >3 molar equivalents) added and stirred rapidly for 30 min. The solution was then filtered and extracted with the appropriate solvent.

All materials were purchased from Aldrich, Lancaster, Acros (Fisher) or Avocado and used as received unless otherwise stated. (*R*)-(−)-α-Methoxy-α-(trifluoromethyl)-phenylacetyl chloride (Chiraselect, >99%) was purchased from the Aldrich chemical company PLC and stored in a Drikold freezer whilst not in use. Copper(I) iodide was recrystallised from potassium iodide according to the method of Taylor and Casy.[38] Allyl bromide was distilled prior to use. Tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct was prepared according to the method of Ishii and co-workers.[39]

### 4.2. Preparation of (*E*)-3-iodo-1-(tetrahydropyranyloxy)-prop-2-ene 15

**4.2.1. (*E*)-3-Iodoacrylic acid.** A mixture of propiolic acid (18 mL, 3 × 6 mL, 292 mmol) and aqueous HI (66 mL of a 57% w/w (7 M) aqueous solution, 3 × 22 mL, 462 mmol) was heated in three foil-wrapped Ace® tubes at 95 °C for 21 h. The resulting mixtures were allowed to cool to ambient temperature to afford a suspension of (*E*)-3-iodoacrylic acid (as large white crystals) in excess aqueous HI. The pressure was released (CARE), then the mixtures were diluted with water (5 mL) and filtered under vacuum, using water to wash out the product from the tube. A final washing of the suspended product with light petroleum (20 mL) followed by drying afforded the iodoacid as large white needles (54.32 g, 94%); mp 147–149 °C (lit. 147–148 °C, 144–147 °C);[40] [Found: C, 18.33; H, 1.36; Calcd for $C_3H_3O_2I$; C, 18.20; H, 1.53]; $\delta_H$ (300 MHz, $CDCl_3$) 10.54–8.66 (1H, bd s, OH), 8.08 (1H, d, $^3J$ 14.7, H-2), 6.89 (1H, d, $^3J$ 14.7, H-3). Spectral data were in agreement with those reported by Takeuchi et al.[40]

**4.2.2. (*E*)-Ethyl 3-iodoacrylate.** Sulfuric acid (9.0 mL of a 98% aqueous solution) was added to a solution of (*E*)-3-iodoacrylic acid (33.2 g, 168 mmol) in absolute ethanol (200 mL) to afford a colourless solution. This was then heated under reflux, with yellowing, for 23 h before being cooled to ambient temperature. A saturated aqueous solution of sodium bicarbonate (150 mL) was added, then the pH was adjusted to 7.4 by the addition (CARE) of solid sodium bicarbonate (until loss of effervescence). The ethanol was removed under reduced pressure and the residue diluted with ethyl acetate (40 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 × 150 mL). The combined

organic extracts were dried and concentrated under reduced pressure to afford the crude ethyl ester as a yellow oil. Filtration through a pad of silica using diethyl ether as eluent afforded an orange oil (28.3 g), after evaporation of solvents. Further purification by distillation under reduced pressure afforded the iodoester as a pale yellow oil (24.8 g, 65%); bp 65 °C/~10 mmHg (lit. 74–76 °C/9 Torr);[40] $R_f$ (15% diethyl ether in hexanes) 0.61; $\nu$ (film/cm$^{-1}$) 3070 w, 2982 m, 1722 s, 1593 s, 1465 w, 1446 w, 1391 w, 1368 m, 1298 s, 1259 s, 1216 s, 1146 s, 1034 s, 949 s; $\delta_H$ (300 MHz, $CDCl_3$) 7.85 (1H, d, $^3J$ 14.7, H-3), 6.84 (1H, d, $^3J$ 14.7, H-2), 4.17 (2H, q, $^3J$ 7.4, $CH_2CH_3$), 1.26 (3H, t, $^3J$ 7.4, $CH_2CH_3$); $\delta_C$ (75 MHz, $CDCl_3$) 164.2 (C-1), 136.6 (C-2), 99.4 (C-3), 61.0 ($CH_2$), 14.2 ($CH_3$). Spectral data were in agreement with those reported by Takeuchi et al.[40]

**4.2.3. (*E*)-3-Iodoprop-2-en-1-ol.** Di*iso*butylaluminium hydride (8.84 mL of a 1 M solution in hexanes, 8.84 mmol) was added dropwise to a solution of the ethyl acrylate ester (1.00 g, 4.42 mmol) in dry DCM (10 mL) at −75 °C under an atmosphere of nitrogen. The addition was controlled so that the temperature did not exceed −70 °C. The pale yellow solution was stirred for 45 min at −75 °C and then allowed to warm to 0 °C. The mixture was quenched at this temperature with methanol (10 mL), methanol/water (20 mL, 3:1 v/v) and water (10 mL) with the formation of a white emulsion. DCM (30 mL) was added followed by Rochelle's salt (30 mL of a 10% aqueous solution) and the organic layer separated. The aqueous layer was extracted with DCM (3 × 20 mL) and the combined organic extracts dried and concentrated under reduced pressure to afford a mobile pale yellow oil (0.76 g). Purification by column chromatography over silica gel (60% diethyl ether in light petroleum) afforded the iodoalcohol as a colourless oil (410 mg, 50%); $R_f$ (60% diethyl ether in light petroleum) 0.40; $\delta_H$ (300 MHz, $CDCl_3$) 6.69 (1H, dt, $^3J$ 14.5, 5.3, H-2), 6.39 (1H, d, $^3J$ 14.5, H-3), 4.09 (2H, dd, $^3J$ 5.3, 1.8, H-1), 1.71 (1H, s, OH); $\delta_C$ (75 MHz, $CDCl_3$) 144.8 (C-2), 78.1 (C-3), 65.1 (C-1); *m/z* (EI) 184 (32%, $M^+$), 127 (20%, I), 57 (100%, M − I), 39 (17%).

**4.2.4. (*E*)-3-Iodo-1-(tetrahydropyranyloxy)-prop-2-ene 15.** A solution of (*E*)-3-iodoprop-2-en-1-ol (5.20 mmol, 0.96 g) and dihydropyran (4.70 mmol, 0.40 g) in hexane (70 mL) containing Amberlyst-15 (7 mg) was stirred at room temperature in the dark 18 h. The reaction had gone to completion by TLC, so the Amberlyst-15 was removed by filtration and the filtrate was washed with sodium hydrogen carbonate (10 mL of an aqueous solution), dried ($MgSO_4$) and concentrated under reduced pressure to afford THP ether **15** (0.94 g, 67%) as a colourless oil; $R_f$ (40% diethyl ether in light petroleum) 0.45; $\nu_{max}$ (film)/cm$^{-1}$ 3049 m, 2940 m; $\delta_H$ 6.63 (1H, dt, $^3J$ 14.3, $^3J$ 5.5), 6.37 (1H, d, $^3J$ 14.3), 4.70–4.60 (1H, m), 4.13 (1H, ddd, $^2J$ 13.6, $^3J$ 5.1, $^4J$ 1.8), 3.91 (1H, ddd, $^2J$ 13.6, $^3J$ 6.3, $^4J$ 1.3), 3.86–3.76 (1H, m), 3.55–3.45 (1H, m), 1.90–1.50 (6H, m); $\delta_C$ (75 MHz, $CDCl_3$) 142.3, 97.8, 78.6, 68.7, 62.1, 30.4, 25.4, 19.3. The material was taken on without further characterisation.

**4.3. (*E*)-3-Iodo-1-(4′-methoxybenzoyl)-prop-2-ene 16**

4-Anisoyl chloride (2.02 g, 11.84 mmol) was added to a solution of (*E*)-3-iodoprop-2-en-1-ol (2.00 g, 10.88 mmol), pyridine (0.9 mL, 11.0 mmol) and 4-(dimethylamino)pyridine (78 mg, 0.64 mmol) in DCM (20 mL) at 0 °C. The resulting solution was allowed to warm to ambient temperature and then stirred for 18 h. The reaction mixture was quenched with water (10 mL), followed by extraction of the aqueous phase with DCM (3 × 15 mL). The combined organic extracts were washed with 1.0 M HCl (20 mL), before being dried and concentrated under reduced pressure to afford a pale yellow oil. Purification by column chromatography over silica gel (10% diethyl ether in light petroleum) afforded iodoester **16** as a colourless oil (3.36 g, 97%); 93% by GC; 98% by HPLC at 225 nm; HPLC $t_r$ (10% water in MeCN, 1 mL/min) 4.44 min; $R_f$ (10% diethyl ether in light petroleum) 0.24; $\nu$ (film/cm$^{-1}$) 1714 s (C=O), 1607 s (C=C), 1512 m, 1371 w, 1317 m, 1257 s, 1169 s, 1102 m, 1030 m, 847 m, 770 m; $\delta_H$ (300 MHz, $CDCl_3$) 7.99 (2H, d, $^3J$ 8.8, ArH), 6.91 (2H, d, $^3J$ 8.8, ArH), 6.74 (1H, dt, $^3J$ 14.7, 5.9, H-2), 6.55 (1H, dt, $^3J$, 14.7, $^4J$ 1.4, H-3), 4.70 (2H, dd, $^3J$ 5.9, $^4J$ 1.4, H-1), 3.85 (3H, s, ArO*Me*); $\delta_C$ (75 MHz, $CDCl_3$) 165.7 (CO), 163.6 ($C_q$–OMe), 140.0 (C-2), 131.8 (Ar*C*H), 122.1 ($C_q$–CO), 113.7 (Ar*C*H), 80.8 (C-3), 65.9 (C-1), 55.5 ($OCH_3$); [HRMS (ES-TOF, M+Na) Found: 340.9646; Calcd for $C_{11}H_{11}O_3INa$: 340.9651]; *m/z* (ES-TOF) 341.0 (100%, M+Na).

**4.4. Coupling reactions**

**4.4.1. 2-(*N*,*N*-Diethylcarbamoyloxy)-1,1-difluoro-1,3-butadiene 17.** A mixture of copper(I) iodide (94 mg, 0.50 mmol), triphenylarsine (331 mg, 1.08 mmol), palladium(II) acetate (593 mg, 0.26 mmol), **10** (1.56 g, 5.11 mmol) and tributylvinyltin (1.77 g, 5.58 mmol) in dry, degassed DMF (10 mL) was heated at 100 °C. The solution had an initial yellow colour, which changed to black after 6 min leaving a Pd black suspension. TLC after 80 min indicated that iodoalkene **10** had been consumed. The mixture was diluted with diethyl ether (10 mL) and decanted from the Pd into a separating funnel. Water (30 mL) was added and the organic phase separated. The aqueous phase was extracted with diethyl ether (3 × 15 mL). The combined organic extracts were dried and concentrated under reduced pressure to afford a crude yellow oil. Purification by column chromatography over silica gel (10% diethyl ether in light petroleum) afforded 1,3-diene **17** as a pale yellow oil (925 mg, 88%, 88% by GC); $R_f$ (10% diethyl ether in light petroleum) 0.29; $\delta_H$ (300 MHz, $CDCl_3$) 6.34 (1H, dddd, $^3J_{trans}$ 17.3, $^3J_{cis}$ 11.2, $^4J_{HF}$ 3.3, 1.8), 5.21 (1H, d, $^3J_{trans}$ 17.3), 5.17–5.12 (1H, m), [3.42–3.30] (4H, m), [1.23–1.13] (6H, m, two overlapping t); $\delta_C$ (75 MHz, $CDCl_3$) 154.2 (dd, $^1J_{CF}$ 294.4, 292.2), 152.3, 124.1 (d, $^3J_{CF}$ 5.1), [113.3, 113.1] (2 × d, $^4J_{CF}$ 4.5), 112.3 (dd, $^2J_{CF}$ 40.7, 18.1), [42.5, 41.9], [14.0, 13.20]; $\delta_F$ (282 MHz, $CDCl_3$) −95.50 (1F, d, $^2J$ 40.7), −105.50 (1F, dd, $^2J$ 40.7, $^4J_{HF}$ 3.8); [HRMS (CI, M+H) Found: 206.0995; Calcd for $C_9H_{14}NO_2F_2$: 206.0993]; *m/z* (Cl) 223 (47%, M+$NH_4$), 206 (100%, M+H), 100 (11%, $CONEt_2$).

**4.4.2. (*E*)-2-[4-(*N*,*N*-Diethylcarbamoyloxy)-5,5-difluoropenta-2,4-dienyloxy]-tetrahydropyran 18.** Pyran **18** was prepared as for **17** using palladium(II) acetate (12.8 mg, 57.0 μmol), triphenylarsine (68 mg, 0.22 mmol), CuI (22.3 mg, 0.12 mmol), iodoalkene **10** (340 mg, 1.11 mmol) and (*E*)-2-[3-(tributylstannyl)-prop-2-enyloxy]-tetrahydropyran **14**[19] (460 mg, 1.07 mmol) in DMF (10 mL). After 6.5 h, the usual work-up afforded a yellow oil. Purification over silica gel (20% diethyl ether in light petroleum) afforded 1,3-diene **18** as a pale yellow oil (90 mg, 31%); $R_f$ (20% diethyl ether in light petroleum) 0.05; $\delta_H$ (300 MHz, $CDCl_3$) 6.31–6.22 (1H, m), 5.74 (1H, dt, $^3J$ 15.4, 5.9), 4.62 (1H, t, $^3J$ 3.3), 4.34–4.26 (1H, m), 4.08–4.00 (1H, m), 3.87–3.80 (1H, m), 3.52–3.45 (1H, m), 3.40–3.29 (4H, m), 1.87–1.45 (6H, envelope), 1.21–1.13 (6H, envelope); $\delta_C$ (75 MHz, $CDCl_3$) 154.2 (dd, $^1J_{CF}$ 293.9, 291.6), 152.3, 125.6 (dd, $^3J_{CF}$ 11.9, 4.3), 119.0 (d, $^4J_{CF}$ 5.1), 111.7 (dd, $^2J_{CF}$ 40.7, 18.6), 97.9, 66.7, 62.1, [42.5, 41.9], 30.5, 25.3, 19.3, [14.0, 13.2]; $\delta_F$ (282 MHz, $CDCl_3$) −95.66 (1F, d, $^2J$ 41.9), −105.72 (1F, dd, $^2J$ 41.9, $^4J_{HF}$ 3.2); [HRMS (ES-TOF, M+Na) Found: 342.1490; Calcd for $C_{15}H_{23}NO_4F_2Na$: 342.1493]; *m/z* (Cl) 337.7 (49%, M+$NH_4$), 319.0 (3%, M), 253.5 (100%, M+$NH_4$−THP), 218.4 (32%, M−OTHP), 102.3 (13%, OTHP+H).

**4.4.3. (*E*)-4-(*N*,*N*-Diethylcarbamoyloxy)-5,5-difluoro-1-(4′-methoxybenzoyl)-penta-2,4-diene 19.** Ester **19** was prepared from tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (23 mg, 22 μmol), triphenylphosphine (58 mg, 0.22 mmol), CuI (26 mg, 0.14 mmol), iodoalkene **16** (359 mg, 1.1 mmol) and stannane **11** (520 mg, 1.11 mmol). Following the usual work-up, a crude brown oil was isolated. Purification by column chromatography over silica gel (15% diethyl ether in light petroleum ⇒ 20% ethyl acetate in light petroleum) afforded pentadienyl ester **19** as a pale orange oil (355 mg, 83%); $R_f$ (20% ethyl acetate in light petroleum) 0.35; $\nu$ (film/$cm^{-1}$) 1734 bd s, 1606 m, 1511 m, 1421 m, 1381 w, 1251 s, 1168 m, 1097 m, 1031 m, 955 w, 847 w, 770 w; $\delta_H$ (300 MHz, $CDCl_3$) 8.03–7.98 (2H, m), 6.94–6.89 (2H, m), 6.38 (1H, ddt, $^3J$ 15.5, $^4J$ 1.5, $^4J_{HF}$ 2.4), 5.84 (1H, dt, $^3J$ 15.5, 6.1), 4.86 (2H, dd, $^3J$ 6.1, $^4J$ 1.5), 3.86 (3H, s), 3.42–3.32 (4H, two overlapping q, $^3J$ 7.0), 1.23–1.15 (6H, two overlapping t, $^3J$ 7.0); $\delta_C$ (75 MHz, $CDCl_3$) 165.7, 163.3, 154.2 (dd, $^1J_{CF}$ 294.4, 292.2), 152.1 (t, $^4J_{CF}$ 2.2), 131.5, 123.0 (dd, $^3J_{CF}$ 11.9, 4.5), 122.1, 120.1 (d, $^4J_{CF}$ 4.5), 113.5, 111.6 (dd, $^2J_{CF}$ 40.1, 18.7), 63.9, 55.2, [42.4, 41.8], [13.9, 13.0]; $\delta_F$ (282 MHz, $CDCl_3$) −94.32 (1F, d, $^2J$ 39.4), −104.59 (1F, dd, $^2J$ 39.4, $^3J_{HF}$ 2.5); [HRMS (ES-TOF, M+Na) Found: 392.1289; Calcd for $C_{18}H_{21}NO_5F_2Na$: 392.1285]; *m/z* (EI) 369 (27%, M), 269 (11%, M−ODEC), 218 (8%, M−$OCOC_6H_4OMe$), 152 (5%), 135 (58%, $MeOC_6H_4$-CO), 100 (100%, $CONEt_2$), 72 (68%, $H_2NEt_2$).

**4.4.4. 2-(*N*,*N*-Diethylcarbamoyloxy)-1,1-difluoro-1,4-pentadiene 20.** 1,4-Diene **20** was prepared from tris(dibenzylideneacetone)-dipalladium(0)-chloroform adduct (26 mg, 50 μmol Pd), CuI (29 mg, 0.15 mmol), triphenylphosphine (60 mg, 0.23 mmol), freshly distilled allyl bromide (100 μL, 1.16 mmol) and stannane **11** (519 mg, 1.11 mmol). After 18 h, the usual work-up afforded an orange oil. Purification by column chromatography over silica gel (10% diethyl ether in light petroleum) afforded 1,4-diene **20** as a pale yellow oil (213 mg, 87%); $R_f$ (10% diethyl ether in light petroleum) 0.32; $\nu$ (film/$cm^{-1}$) 3085 w, 1782 s (C=$CF_2$), 1730 s (C=O), 1643 m (C=C), 1476 m, 1460 m, 1426 s, 1383 m, 1288 s, 1246 s, 1211 s, 1157 s, 1074 s, 1036 m, 992 m, 958 m, 924 m, 785 m, 757 m; $\delta_H$ (300 MHz, $CDCl_3$) 5.79–5.66 (1H, m), 5.14–5.04 (2H, m), 3.30–3.20 (4H, m), 3.00–2.95 (2H, m), 1.10 (6H, t, $^3J$ 7.0); $\delta_C$ (75 MHz, $CDCl_3$) 154.2 (t, $^1J_{CF}$ 288.0), 152.7, 132.0 (t, $^4J_{CF}$ 3.0), 117.6, 110.6–109.8 (m), [42.2, 41.7], 31.2 (d, $^3J_{CF}$ 2.3), [13.7, 13.0]; $\delta_F$ (282 MHz, $CDCl_3$) −99.32 (1F, dt, $^2J$ 63.6, $^4J_{HF}$ 2.5), −111.49 (1F, dt, $^2J$ 63.6, $^4J_{HF}$ 3.8); [HRMS (EI, M+H) Found: 220.1159; Calcd for $C_{10}H_{16}NO_2F_2$: 220.1149]; *m/z* (EI) 237 (35%, M+$NH_4$), 220 (100%, M+H), 170 (24%), 100 (66%, ODEC), 74 (69%, $NH_2Et_2$), 58 (23%), 44 (12%).

**4.4.5. (*E*)-5,5-difluoro-1-(4′-methoxybenzoyl)-4-([methoxyethoxy]methoxy)-penta-2,4-diene 21.** A flask containing palladium(II) acetate (28 mg, 0.13 mmol), copper(I) iodide (199 mg, 1.04 mmol) and triphenylphosphine (136 mg, 0.52 mmol) was evacuated and the vacuum released to a nitrogen inlet. The procedure was repeated twice. Dry, degassed DMF (5 mL) was added and the resulting dark solution warmed to 30 °C. Iodoalkene **16** (1.59 g, 5.0 mmol) was added as a solution in DMF (1 mL). The reaction mixture was warmed to 50 °C. Stannane **13** (2.76 g, 6.0 mmol) was added at 40 °C as a solution in DMF (1 mL). The resulting solution was heated for 3 h at 50 °C and monitored by TLC. Upon consumption of the starting material, the solution was diluted with diethyl ether (20 mL), then transferred to a conical flask. An aqueous solution of KF (20 mL of a 0.97 M solution) was added and the resulting mixture stirred rapidly for 1 h. The precipitated solid ($Bu_3SnF$) was filtered under vacuum and washed with ethyl acetate (20 mL). The organic layer was separated and the aqueous phase extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried and concentrated under reduced pressure to afford an orange oil, containing a red sediment ([$(PPh_3)_2PdI_2$]). Purification by column chromatography over alumina (Brockmann 1, pH 9–11, 10% ethyl acetate in hexanes) afforded pentadienyl ester **21** as a pale yellow oil (730 mg, 41%); $R_f$ (20% ethyl acetate in hexanes) 0.32; $\nu$ (film/$cm^{-1}$) 1716 s, 1697 s, 1606 s, 1511 s, 1257 bd s, 1168, 910, 848; $\delta_H$ (300 MHz, $CDCl_3$) 7.97 (2H, d, $^3J$ 8.8), 6.91 (2H, d, $^3J$ 8.8), 6.24 (1H, br d, $^3J$ 15.6), 6.03 (1H, dt, $^3J$ 15.6, 6.0), 4.91 (2H, s), 4.84 (2H, br d, $^3J$ 6.3), 3.82 (3H, s), 3.84–3.81 (2H, m), 3.55–3.51 (2H, m), 3.35 (3H, s); $\delta_C$ (75 MHz, $CDCl_3$) 165.9, 163.5, 155.3 (dd, $^1J_{CF}$ 295.0, 293.9), 131.7, 123.8 (dd, $^3J_{CF}$ 11.9, 4.5), 122.4, 121.3 (d, $^4J_{CF}$ 5.1), 115.2 (dd, $^2J_{CF}$ 35.6, 17.5), 113.6, 96.4 (t, $^4J_{HF}$ 2.8), 71.6, 68.7, 64.2, 59.0, 55.4; $\delta_F$ (282 MHz, $CDCl_3$) −97.03 (1F, d, $^2J$ 45.8), −105.68 (1F, dd, $^2J$ 45.8, $^3J_{HF}$ 4.0); [HRMS (ES-TOF, M+Na) Found: 381.1134; Calcd for $C_{17}H_{20}O_6F_2Na$: 381.1126]; *m/z* (ES-TOF) 381.0 (100%, M+Na). This material is unstable (neat), has a lifetime of ca. 24 h even in a refrigerated (−5 °C) environment

and should ideally be used immediately after preparation or stored as a solution in $CH_2Cl_2$ under a positive nitrogen atmosphere.

**4.4.6. 1,1-Difluoro-2-([2-methoxyethoxy]methoxy)-penta-1,4-diene 22.** 1,4-Diene **22** was prepared as for **21** from palladium(II) acetate (70 mg, 0.31 mmol), CuI (460 mg, 2.43 mmol), triphenylphosphine (320 mg, 1.22 mmol), allyl bromide (1.5 mL, 17.3 mmol) and stannane **13** (6.86 g, 12.15 mmol) in DMF (10 mL). After 18 h, the usual work-up afforded a yellow oil (3.25 g). Purification by column chromatography over silica gel (20% diethyl ether in hexanes) afforded 1,3-diene **22** as a pale yellow oil (1.48 g, 62%); $R_f$ (20% diethyl ether in hexanes) 0.32; $\nu$ (film/cm$^{-1}$) 2929 s, 2896 s, 2822 m, 1765 s, 1717 w, 1643 w, 1456 m, 1431 m, 1416 w, 1368 w, 1274 s, 1250 s, 1212 s, 1160 s, 1111 s, 1053 s, 994 s, 974 s, 923 s, 887 w, 851 m, 773 m; $\delta_H$ (300 MHz, $CDCl_3$) 5.88–5.71 (1H, m), 5.21–5.08 (2H, m), 4.88 (2H, s), 3.80–3.77 (2H, m), 3.57–3.54 (2H, m), 3.38 (3H, s), 2.97–2.89 (2H, m); $\delta_C$ (75 MHz, $CDCl_3$) 155.3 (dd, $^1J_{CF}$ 295.0, 293.9), 132.8, 117.4, 115.2 (dd, $^2J_{CF}$ 36.3, 15.0), 94.7–94.6 (m), 71.5, 68.1, 59.0, 30.4. $\delta_F$ (282 MHz, $CDCl_3$) −102.50 (1F, dt, $^2J$ 70.9, $^4J_{HF}$ 2.5) −113.14 (1F, dt, $^2J$ 70.9, $^4J_{HF}$ 3.8); *m/z* (ES-TOF) 231.0 (100%, M+Na). A satisfactory accurate mass measurement could not be obtained. This material was taken on without further characterisation.

### 4.5. Asymmetric dihydroxylation reactions and ee determination

**4.5.1. (2*R*)-4-(*N*,*N*-Diethylcarbamoyloxy)-5,5-difluoro-pent-4-en-1,2-diol 23.** A solution of AD-mix-β (11.7 g, 1.41 g/mmol) and sodium hydrogen carbonate (1.8 g, 21.4 mmol) in $^t$BuOH/$H_2O$ (82 mL, 1:1 v/v) was stirred vigorously at ambient temperature until the phases became clear. Diene **20** (1.82 g, 8.32 mmol) was added in one portion and the slurry stirred vigorously at 0 °C until TLC indicated the consumption of starting material. The yellow mixture was quenched with sodium sulfite (12 g) then stirred for 30 min to afford a grey solution. The reaction mixture was diluted with DCM (5 mL) and the layers were separated. The aqueous phase was extracted with DCM (3 × 20 mL). The combined organic extracts were dried and concentrated under reduced pressure to afford a yellow oil. Purification by column chromatography over silica gel (60% ethyl acetate in light petroleum) afforded diol **23** as a colourless oil (1.85 g, 88%); $R_f$ (60% ethyl acetate in light petroleum) 0.25; [Found: C, 47.14; H, 6.77; N, 5.53; Calcd for $C_{10}H_{17}NO_4F_2$: C, 47.43; H, 6.77; N, 5.53]; $\nu$ (film/cm$^{-1}$) 3600–3100 bd, 1780 m (C=$CF_2$), 1706 s (C=O), 1476 m, 1429 s, 1382 m, 1291 s, 1239 s, 1217 s, 1158 m, 1115 s, 1047 m, 956 w, 935 w, 785 w, 757 w; $\delta_H$ (300 MHz, $CDCl_3$) 3.80–3.72 (1H, m), 3.65 (1H, dd, $^2J$ 11.4, $^3J$ 3.3), 3.50 (1H, dd, $^2J$ 11.4, $^3J$ 6.6), 3.30 (2H, q, $^3J$ 7.0), 3.29 (2H, q, $^3J$ 7.0), 2.40 (1H, ddd, $^2J$ 15.1, $^3J$ 9.9, $^4J_{HF}$ 3.7), 2.27–2.18 (1H, m), 1.14 (3H, t, $^3J$ 7.0), 1.13 (3H, t, $^3J$ 7.0); $\delta_C$ (75 MHz, $CDCl_3$) 155.6 (dd, $^1J_{CF}$ 289.0, 288.0), 154.4 (d, $^4J_{CF}$ 2.3), 109.0 (dd, $^2J_{CF}$ 44.7, 16.0), 67.8 (t, $^4J_{CF}$ 2.8), 65.8, [42.7, 42.1], 31.9 (d, $^3J_{CF}$ 2.8), [13.9, 13.2]; $\delta_F$ (282 MHz, $CDCl_3$) −96.40 (1F, dd, $^2J$ 59.8, $^4J_{HF}$ 5.1), −109.98 (1F, dt, $^2J$ 59.8, $^4J_{HF}$ 3.7); [HRMS (ES-TOF, M+Na) Found: 276.1034; Calcd for $C_{10}H_{17}NO_4F_2Na$: 276.1023]; *m/z* (Cl) 254 (100%, M+H), 100 (20%, CON-$Et_2$); *m/z* (ES) 276 (100%, M+Na). Stereochemical assignment is based upon the Sharpless model.

**4.5.2. (2*RS*)- 4-(*N*,*N*-Diethylcarbamoyloxy)-5,5-difluoro-pent-4-en-1,2-diol 24.** A solution of potassium osmate dihydrate (9 mg, 24.5 μmol), potassium ferricyanide (3.03 g, 9.20 mmol), potassium carbonate (1.32 g, 9.54 mmol), quinuclidine (13 mg, 119 μmol) and sodium hydrogen carbonate (260 mg, 3.09 mmol) in *t*-BuOH/$H_2O$ (15 mL, 1:1 v/v) was stirred vigourously at ambient temperature until the phases became clear. Diene **20** (669 mg, 3.05 mmol) was added in one portion and the slurry stirred vigorously at ambient temperature for 16 h. The yellow mixture was quenched with sodium sulfite (3 g) and then stirred for 30 min to afford a grey solution. The reaction mixture was diluted with DCM (10 mL) and the layers were separated. The aqueous phase was extracted with DCM (3 × 20 mL). The combined organic extracts were dried and concentrated under reduced pressure to afford a pale yellow oil. Purification by column chromatography over silica gel (80% ethyl acetate in light petroleum) afforded diol **24** as a colourless oil (368 mg, 48%); $R_f$ (80% ethyl acetate in light petroleum) 0.38; $\delta_F$ (282 MHz, $CDCl_3$) −96.91 (1F, dd, $^2J$ 61.0, $^4J_{HF}$ 3.8), −110.51 (1F, dd, $^2J$ 61.0, $^4J_{HF}$ 3.8). This material was taken on without further characterisation.

**4.5.3. (2*R*)-4-(*N*,*N*-Diethylcarbamoyloxy)-5,5-difluoro-1-(tri*iso*propylsilyloxy)-pent-4-en-2-ol 25.** Chlorotri-*iso*propylsilane (0.22 mL, 1.05 mmol) was added to a solution of diol **23** (266 mg, 1.05 mmol) in DCM (2 mL) containing imidazole (170 mg, 2.50 mmol) and DMAP (cat.). The mixture was stirred at ambient temperature for 48 h, then diluted with DCM (2 mL). The organic layer was washed consecutively with water (10 mL), a saturated solution of ammonium chloride (10 mL) and brine (10 mL). The organic extracts were dried and concentrated under reduced pressure to afford alcohol **25** as a colourless oil (430 mg, 100%); 99% by GC; $R_f$ (25% diethyl ether in light petroleum) 0.27; $[\alpha]_D = -2.1$ (*c* 18.4, 21 °C, MeOH, est. error = ± 0.4); $\delta_H$ (300 MHz, $CDCl_3$) 3.78–3.61 (2H, m), 3.44 (1H, dd, $^3J$ 7.0, $^3J$ 7.0), 3.35–3.26 (4H, m), 2.53–2.44 (1H, m), 2.37–2.28 (1H, m), 1.19–1.01 (27H, m); $\delta_C$ (75 MHz, $CDCl_3$) 155.4 (t, $^1J_{CF}$ 288), 153.9, 109.4 (dd, $^2J_{CF}$ 45.8, 15.8), 68.3 (t, $^4J_{CF}$ 2.5), 66.6, [42.6, 42.0], 32.1 (d, $^3J_{CF}$ 2.8), 17.9, [13.9, 13.2], 11.9; $\delta_F$ (282 MHz, $CDCl_3$) −96.91 (1F, dd, $^2J$ 61.0, $^4J_{HF}$ 3.8), −110.51 (1F, dd, $^2J$ 61.0, $^4J_{HF}$ 3.8); [HRMS (ES-TOF, M+Na) Found: 432.2344; Calcd for $C_{19}H_{37}NO_4F_2NaSi$: 432.2358]; *m/z* (ES-TOF) 432.4 (100%, M+Na); Chiral HPLC $t_r$ (Chiralcel OD, 10% *iso*propanol in hexane, 1 mL/min) 6.53 min; 95:5 *er*.

**4.5.4. (2*RS*)-4-(*N*,*N*-Diethylcarbamoyloxy)-5,5-difluoro-1-(tri*iso*propylsilyloxy)-pent-4-en-2-ol 26.** Chlorotri-*iso*propylsilane (0.31 mL, 1.45 mmol) was added to a solution of diol **24** (368 mg, 1.45 mmol) in DCM (3 mL) containing imidazole (220 mg, 3.24 mmol) and DMAP (cat.). The mixture was stirred at ambient

temperature for 96 h, then diluted with DCM (3 mL). The organic layer was washed consecutively with water (10 mL), a saturated solution of ammonium chloride (10 mL) and brine (10 mL). The organic extracts were dried and concentrated under reduced pressure to afford crude alcohol **26** as a colourless oil (570 mg, 96%); Chiral HPLC $t_r$ (Chiralcel OD, 20% IPA in hexane, 0.5 mL/min) 6.16 and 6.72 min; 50:50 *er*.

### 4.6. Attempted transacylation reactions with 26

In a typical procedure, strong base (*n*-BuLi, LDA, LHMDS or KHMDS, ca. 1 mmol, 1 equiv) was added to a cold (−78 °C) solution of **26** (ca. 1 mmol) in THF (ca. 1 mL, 1 M in **26**). The mixture was stirred for 1 h then allowed to warm to −30, −20, −10 or 0 °C and maintained there for 1–18 h before quenching with ammonium chloride (1 mL of a saturated methanolic solution). The mixture was evaporated to a small volume, diluted with water (5 mL) and extracted with diethyl ether (3 × 5 mL). The combined ether extracts were dried ($MgSO_4$), concentrated and investigated by $^{19}F$ NMR revealing one of two outcomes. Either **26** was recovered unchanged, or a very complex mixture of products, indicating decomposition was observed.

### 4.7. Pentulose syntheses

**4.7.1. (2*R*,3*S*)-(5,5-Difluoro-2,3-dihydroxy-4-[2-methoxyethoxy]methoxy)-1-(4′-methoxybenzoyl)-pent-4-ene 33.** A three-necked flask was charged with potassium osmate dihydrate (0.11 g, 0.30 mmol), potassium carbonate (6.25 g, 45.2 mmol), potassium ferricyanide (14.88 g, 45.2 mmol) and $(DHQD)_2PHAL$ (0.47 g, 0.60 mmol). The mixture was homogenised by the addition of *t*-BuOH/$H_2O$ (200 mL, 1:1 v/v) with rapid stirring at ambient temperature. Diene **21** (5.39 g, 15.03 mmol) was added dropwise as a solution in *t*-BuOH/$H_2O$ (10 mL, 1:1 v/v). The resulting orange solution was stirred at ambient temperature and the progress of the reaction monitored by TLC and pH measurements made using a pH probe. Aqueous sodium hydroxide (1 M) was added via syringe in order to maintain the pH in the 11.0–12.0 range at all times. pH monitoring was continued until a constant pH measurement was recorded over a period of 30 min indicating completion of reaction, with confirmation by TLC (ca. 1–3 h). Sodium sulfite (21 g) was then added and the solution stirred rapidly for 1 h. The *t*-BuOH was removed under reduced pressure and the mixture diluted with ethyl acetate (20 mL). The phases were separated and the aqueous phase extracted with ethyl acetate (6 × 200 mL). The combined organic extracts were dried and concentrated under reduced pressure to afford a pale yellow oil. Purification by column chromatography over silica gel (60% ethyl acetate in hexanes) afforded diol **33** as a colourless oil (3.16 g, 54%); 98% by HPLC at 225 nm; HPLC $t_r$ (40% water in MeCN; 1 mL/min) 3.52 min; $R_f$ (60% ethyl acetate in hexanes) 0.18; (film/$cm^{-1}$) 3430 bd s, 1754 m, 1694 m, 1608 m, 1514 w; $\delta_H$ (400 MHz, $CDCl_3$) 7.96 (2H, d, $^3J$ 8.9), 6.88 (2H, d, $^3J$ 8.9), 5.00 (1H, d, *one half of an AB*, $^3J$ 6.5), 4.87 (1H, d, *one half of an AB*, $^3J$ 6.5), 4.42 (1H, dd, *one half of an ABX*, $^2J$ 12.0, $^3J$ 3.9), 4.35–4.30 (1H, m), 4.27 (1H, dd, *one half of an ABX*, $^2J$ 12.0, $^3J$ 5.2), 4.13–4.07 (1H, m), 3.95–3.89 (2H, envelope, m + *one half of an ABXY*), 3.83 (3H, s), 3.77 (1H, ddd, *one half of an ABXY*, $^2J$ 10.9, $^3J$ 4.8, 2.9), 3.58–3.54 (2H, m), 3.38 (3H, s), 3.28–3.24 (1H, bd s); $\delta_C$ (100 MHz, $CDCl_3$) 166.3, 163.5, 155.1 (dd, $^1J_{CF}$ 292.8, 287.7), 131.7, 122.1, 116.0 (dd, $^2J_{CF}$ 36.6, 12.2), 113.6, 98.2, 71.3, 70.8, 68.7, 67.6, 64.9, 59.0, 55.4; $\delta_F$ (282 MHz, $CDCl_3$) −97.32 (1F, d, $^2J$ 59.5), −107.93 (1F, dd, $^2J$ 59.5, $^4J_{HF}$ 2.5); [HRMS (ES-TOF, M+Na) Found: 415.1178; Calcd for $C_{17}H_{22}O_8F_2Na$: 415.1180]; *m/z* (ES-TOF) 415.1 (100%, M+Na).

**4.7.2. (4*R*,5*S*)-(5-(2,2-Difluoro-1-([methoxyethoxy]methoxy)-vinyl)-2,2-dimethyl-[1,3]dioxalan-4-yl)-methyl 4-methoxybenzenecarboxylate 34.** Anhydrous copper(II) sulfate (2.57 g, 16.1 mmol) was added to a solution of diol **33** (3.16 g, 8.05 mmol) in acetone (100 mL) followed by a sub-stoichiometric amount of *p*TSA (few crystals). The mixture was stirred at ambient temperature for 42 h, then quenched with brine (50 mL). The residual copper(II) sulfate was removed by filtration and washed with acetone (30 mL). The acetone was removed under reduced pressure, then the mixture diluted with ethyl acetate (20 mL). The organic layer was separated and the aqueous phase extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried and concentrated under reduced pressure to afford the crude acetonide **34** as a pale green oil. Purification by chromatography over alumina (20% ethyl acetate in hexanes) afforded acetonide **34** as a colourless oil (2.38 g, 68%); 99% by HPLC at 225/254/275 nm; HPLC $t_r$ (20% water in MeCN; 1 mL/min) 5.19 min; $R_f$ (20% ethyl acetate in hexanes) 0.44; $\nu$ (film/$cm^{-1}$) 2988 m, 2936 m, 1756 s, 1716 s, 1608 s, 1582 m, 1513 m, 1456 m, 1383 m, 1373 m, 1258 bd s, 1169 s, 1030 s, 951 s, 849 m, 770 m; $\delta_H$ (300 MHz, $CDCl_3$) 7.98 (2H, d, $^3J$ 8.8), 6.91 (2H, d, $^3J$ 8.8), 5.08 (1H, d, *one half of an AB*, $^2J$ 5.9), 5.00 (1H, d, *one half of an AB*, $^2J$ 5.9), 4.62–4.34 (4H, envelope), 3.95–3.88 (1H, m, *one half of an ABXY*), 3.86 (3H, s), 3.80–3.73 (1H, m, *one half of an ABXY*), 3.58–3.55 (2H, m), 3.38 (3H, s), 1.45 (3H, s), 1.42 (3H, s); $\delta_C$ (75 MHz, $CDCl_3$) 165.6, 163.5, 156.3 (dd, $^1J_{CF}$ 293.4, 289.3), 131.6, 121.9, 113.6, 110.6 (dd, $^2J_{CF}$ 33.8, 14.9), 110.0, 98.4 (t, $^4J_{CF}$ 3.4), 74.5 (t, $^4J_{CF}$ 2.6), 74.0 (dd, $^3J_{CF}$ 4.3, 2.0), 71.4, 68.5 (d, $^6J_{CF}$ 1.7), 62.9, 58.9, 55.3, 26.8, 26.5; $\delta_F$ (282 MHz, $CDCl_3$) −93.61 (1F, d, $^2J$ 55.3), −107.09 (1F, dd, $^2J$ 55.3, $^4J_{HF}$ 3.0); [HRMS (ES-TOF, M+Na) Found: 455.1481; Calcd for $C_{20}H_{26}O_8F_2Na$: 455.1493]; *m/z* (ES-TOF) 455.1 (100%, M+Na).

**4.7.3. (4*R*,5*S*)-(5-(2,2-Difluoro-1-([methoxyethoxy]-methoxy)-vinyl)-2,2-dimethyl-[1,3]dioxalan-4-yl)-methanol 35.** A solution of ester **34** (2.38 g, 5.5 mmol) in THF/$H_2O$ (100 mL, 3:1 v/v) was cooled to 0 °C. Hydrogen peroxide (2.6 mL of a 30% w/w aqueous solution (8.8 M), 23 mmol) was added followed by lithium hydroxide monohydrate (0.51 g, 12 mmol). The resulting cloudy solution was stirred for 140 h at ambient temperature and the progress monitored by TLC. Upon completion, the reaction was quenched with sodium sulfite (2.5 g) and the resulting solution stirred rapidly for 1 h. The THF was removed under reduced pressure, then

the mixture diluted with ethyl acetate (20 mL). The organic layer was separated and the aqueous phase extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried and concentrated under reduced pressure to afford a colourless oil. Purification by column chromatography over alumina (Brockmann 1, pH 9–11, gradient: 40–100% ethyl acetate in hexanes) afforded alcohol **35** as a clear oil (1.00 g, 61%); 96% by HPLC at 245 nm; HPLC $t_r$ (Luna 5$\mu$ silica (2) 250 mm × 4.6 mm; 100% DCM; 1 mL/min) 13.59 min; $R_f$ (40% ethyl acetate in hexanes) 0.33; UV (254 nm) inactive; $\nu$ (film/cm$^{-1}$) 3468 bd s (OH), 1755 s (C=CF$_2$), 1456 w, 1373 m, 1291 m, 1247 s; $[\alpha]_D$ = +80.8 (*c* 11.63, acetone, 20 °C, est. error = ±0.01); [Found: C, 48.26; H, 6.93; Calcd for $C_{12}H_{20}O_6F_2$: C, 48.32; H, 6.76]; $\delta_H$ (300 MHz, $CDCl_3$) 5.03 (1H, d, *one half of an AB*, $^3J$ 5.9), 4.96 (1H, d, *one half of an AB*, $^3J$ 5.9), 4.56 (1H, ddd, $^3J$ 8.9, $^4J_{HF}$ 3.7, 2.4), 4.17 (1H, dt, $^3J$ 8.9, 3.5), 3.92–3.85 (1H, m, *one half of an ABXY*), 3.80 (1H, dd, $^3J$ 12.9, 3.5), 3.77–3.53 (2H, envelope, m + *one half of an ABXY*), 3.55 (2H, dd, $^3J$ 5.7, 3.9), 3.36 (3H, *s*), 2.32–2.23 (1H, bd s), 2.14 (6H, *s*); $\delta_C$ (75 MHz, $CDCl_3$) 156.5 (dd, $^1J_{CF}$ 293.3, 289.9), 110.9 (dd, $^2J_{CF}$ 33.6, 14.1), 109.7, 98.5 (dd, $^4J_{CF}$ 4.0, 2.8), 77.0, 72.8 (dd, $^3J_{CF}$ 4.2, 2.3), 71.6, 68.6 (d, $^6J_{CF}$ 1.7), 60.6, 59.1, 27.0, 26.7; $\delta_F$ (282 MHz, $CDCl_3$) −93.65 (1F, d, $^2J$ 56.6), −107.43 (1F, dd, $^2J$ 56.6, $^3J_{HF}$ 3.8); [HRMS (ES-TOF, M+Na) Found: 321.1134; Calcd for $C_{12}H_{20}O_6F_2Na$: 321.1126]; *m/z* (ES-TOF) 321.1 (100%, M+Na).

**4.7.4. 1-Deoxy-1,1-difluoro-α-D-xylulofuranose and 1-deoxy-1,1-difluoro-β-D-xylulo-furanose 36.** A flask containing alcohol **35** (323 mg, 1.09 mmol) was evacuated and the vacuum released to a nitrogen atmosphere. Methanol (10 mL) was added and the resulting colourless solution cooled to 0 °C. Chlorotrimethylsilane (160 μL, 1.26 mmol) was added in one portion and the resulting colourless solution stirred at ambient temperature for 23 h. After consumption of starting material, the reaction was concentrated to afford a pale yellow oil. Purification by flash column chromatography over silica gel (80% ethyl acetate in hexanes) afforded pentuloses **36** as a clear oil (163 mg, 88%, ~3:1 α:β); $R_f$ (80% ethyl acetate in hexanes) 0.32; $[\alpha]_D$ = −27.7 (*c* 14.2, acetone, 20 °C, est. error = ±0.6, α:β = ~3:1), lit (−18.9, *c* 0.95, acetone, 25 °C);[34] [Found: C, 31.65; H, 5.39; Calcd for $C_5H_8O_4F_2{\cdot}H_2O$: C, 31.92; H, 5.36]; $\nu$ (film/cm$^{-1}$) 3402 bd s (OH), 2514 bd s (OD), 1470 m, 1401 m, 1347 m, 1204 m, 1078 s; $\delta_H$ (300 MHz, $CD_3OD$) 5.85 (0.23H, dd, $^2J_{HF}$ 55.9, 54.2), 5.72 (0.77H, t, $^2J_{HF}$ 55.5), 4.30–4.23 (1H, envelope), 4.19–4.12 (1H, envelope), 4.08–4.06 (0.23H, m), 4.06 (0.77H, bd d, $^3J$ 4.8), 3.94 (0.23H, ddd, $^2J$ 9.2, $^3J$ 3.7, $^4J$ 1.5), 3.62 (0.77H, dd, $^2J$ 9.0, $^3J$ 5.0); $\delta_C$ (100 MHz, $CD_3OD$) 115.2 (t, $^1J_{CF}$ 247.0), 114.6 (dd, $^1J_{CF}$ 246.0, 243.0), 103.9 (dd, $^2J_{CF}$ 26.2, 20.3), 101.3 (t, $^2J_{CF}$ 24.6), 82.6 (d, $^3J_{CF}$ 1.8), 78.0 (d, $^4J_{CF}$ 1.8), 77.6, 77.0, 75.1, 71.9; $\delta_F$ (282 MHz, $CD_3OD$) −132.09 (0.23F, dd, *one half of an ABX*, $^2J$ 291.5, $^3J_{HF}$ 54.05, β anomer), −133.41 (0.77F, dd, *one half of a highly distorted ABX*, $^2J$ 286.1, $^3J_{HF}$ 54.7, α anomer), −134.94 (0.77F, dd, *one half of a highly distorted ABX*, $^2J$ 286.1, $^3J_{HF}$ 55.95, α anomer), −140.42 (0.23F, dd, *one half of an ABX*, $^2J$ 291.5, $^3J_{HF}$ 55.95, β anomer) (3.3:1 α:β, $CD_3OD$); $\delta_F$ (282 MHz, $D_2O$) −132.07 (0.25F, dd, $^2J$ 293.3, $^3J_{HF}$ 53.4, β anomer), −133.76 (0.75F, dd, $^2J$ 288.6, $^3J_{HF}$ 54.8, α anomer), −135.15 (0.75F, dd, $^2J$ 288.6, $^3J_{HF}$ 54.8, α anomer), −139.77 (0.25F, dd, $^2J$ 293.4, $^3J_{HF}$ 55.4, β isomer)(3:1 α:β, $D_2O$); *m/z* (CI) 171 (100%, M+1), 153 (8%, M+1−$H_2O$). NMR data is in agreement with that reported by Bouvet and O'Hagan.[34]

**4.7.5. (3a*R*,6*R*,6a*S*)-3*a*-Difluoromethyl-2,2-dimethyl-tetrahydrofuro[2,3-*d*][1,3]-dioxol-6-ol 37.** Hydrochloric acid (five drops of a 12 M solution) was added to a solution of alcohol **35** (30.5 mg, 102 μmol) in THF (5 mL). The resulting solution was stirred at ambient temperature for 23 h. Sodium bicarbonate (1 microspatula) was added followed by direct concentration of the reaction mixture. The concentrate was taken up in acetone (5 mL) and anhydrous copper(II) sulfate (2 microspatulas) and *p*TSA (1 microspatula) were added consecutively. The resulting heterogeneous mixture was stirred for 66 h and monitored by TLC. Brine (5 mL) was added and the acetone removed under reduced pressure. Ethyl acetate (10 mL) was added and the organic layer separated. The aqueous layer was extracted with ethyl acetate (3 × 5 mL) and the combined organic extracts dried and concentrated under reduced pressure. Purification by column chromatography over silica gel (40% ethyl acetate in hexanes) afforded acetonide **37** as a white solid (14 mg, 66%); mp 77–80 °C; [Found: C, 45.87; H, 5.73; Calcd for $C_8H_{12}F_2O_4$: C, 45.72; H, 5.75]; $R_f$ (40% ethyl acetate in hexanes) 0.33; UV (254 nm) inactive; $\delta_H$ (300 MHz, $CDCl_3$) 5.87 (1H, t, $^2J_{HF}$ 55.5), 4.62 (1H, s), 4.32–4.27 (1H, m), 4.25 (1H, dd, $^2J$ 9.9, $^3J$ 2.9), 4.03 (1H, d, $^2J$ 9.9), 1.97 (1H, dd, *J* 8.5, 2.9), 1.52 (3H, s), 1.38 (3H, s); $\delta_F$ (282 MHz, $CDCl_3$) −128.99 (1F, dd, *one half of a highly distorted ABX*, $^2J$ 287.5, $^2J_{HF}$ 55.9), −130.23 (1F, ddd, *one half of a highly distorted ABXY*, $^2J$ 287.4, $^2J_{HF}$ 54.7, $^4J_{HF}$ 2.5); *m/z* (CI) 211 (100%, M+1), 194 (6), 178 (29), 151 (8), 133 (6), 116 (6), 107 (10), 59 (7), 47 (9), 45 (9). There was an insufficient material to obtain $^{13}C$ NMR or IR spectra.

**4.7.6. (2*R*,3*S*)-5,5-Difluoro-4-([methoxyethoxy]methoxy)-2,3-bis-(2*S*)-[(3,3,3-trifluoro-2-methoxy-2-phenylpropionyloxy)]-pent-4-enyl 4-methoxybenzenecarboxylate 38.** (*R*)-(−)-α-Methoxy-α-(trifluoromethyl)-phenylacetyl chloride (14 μL, 100 mg/100 μL DCM, 55 μmol) was added to a solution of analytically pure chiral diol **33** (6.0 mg, 15.3 μmol), 2,6-lutidine (20 μL) and 4-(dimethylamino)pyridine (one crystal) in DCM (1 mL) at 0 °C. The solution was warmed to ambient temperature and stirred for 4 h and monitored by TLC. Diol **33** was consumed within 1 h, with a concomitant build up of monoester. Bis-esterification was complete within a further 3 h. The reaction was diluted with diethyl ether (3 mL), then poured into a saturated aqueous solution of sodium bicarbonate (5 mL). The phases were separated and the aqueous phase extracted with diethyl ether (2 × 3 mL) and ethyl acetate (2 × 3 mL). The combined organic extracts were dried and concentrated under reduced pressure to afford crude bis-Mosher ester **38** as a colourless oil containing a brown sediment; $\delta_F$ (282 MHz, $CDCl_3$, 4096 scans, 512K data points)

−71.23 (3F, s), −71.71 (3F, s), −92.38 (1F, d, $^2J$ 47.7), −101.96 (1F, d, $^2J$ 47.7); [HRMS (ES-TOF, M+Na) Found: 847.1977; Calcd for $C_{37}H_{36}O_{12}F_8Na$: 847.1977]; $R_f$ (20% ethyl acetate in hexanes) 0.17; Estimated de >99.5%.

**4.7.7. (2*RS*,3*SR*)-(5,5-Difluoro-2,3-dihydroxy-4-([methoxyethoxy]methoxy)-1-(4′-methoxybenzoyl)-pent-4-ene 39.** Racemic diol **39** was prepared as for racemic diol **24** using potassium osmate dihydrate (10 mg, 28 μmol), potassium ferricyanide (1.36 g, 4.14 mmol), potassium carbonate (0.57 g, 4.14 mmol), quinuclidine (6 mg, 55 μmol), diene **21** (494 mg, 1.38 mmol) in *t*-BuOH/$H_2O$ (18 mL, 1:1 v/v). Sodium hydroxide (1 mL aliquots of a 1.0 M aqueous solution) was added intermittently to keep the pH of the reaction mixture above 11.0 for as long a period as possible. After 22 h, sodium sulfite (2.0 g) was added and the reaction stirred for 1 h. *t*-BuOH was removed under reduced pressure then ethyl acetate (20 mL) was added. The organic phase was separated and the aqueous phase extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried and concentrated under reduced pressure to afford a brown oil. Purification by column chromatography over silica gel (60% ethyl acetate in hexanes) afforded racemic diol **39** as a colourless oil (34 mg, 6%); 95% by HPLC at 254 nm; HPLC $t_r$ (40% water in MeCN, 1 mL/min) 3.52 min; $R_f$ (60% ethyl acetate in hexanes) 0.18; $\delta_F$ (282 MHz, $CDCl_3$) −97.15 (1F, d, $^2J$ 58.5), −107.68 (1F, dd, $^2J$ 58.5, $^4J_{HF}$ 3.2). Other spectral data were identical to those described for **33**. This material was further purified by semi-preparative HPLC (40% water in MeCN, 1 mL/min). Chiral HPLC (Chiralcel OD, 10% IPA in hexane, 1 mL/min, 225 nm) gave a single peak ($t_r$ 25.43 min).

**4.7.8. Conversion of 39 to bis-MTPA ester.** (*R*)-(−)-α-Methoxy-α-(trifluoromethyl)-phenylacetyl chloride (14 μL of a 100 mg/100 μL DCM, 55 μmol) was added to a solution of analytically pure racemic diol **39** (7.9 mg, 20.2 μmol), triethylamine (23 μL) and 4-(dimethylamino)pyridine (one crystal) in DCM (1 mL) at 0 °C. The solution was warmed to ambient temperature and stirred for 4 h. TLC indicated the presence of products resulting from *mono*- and *bis*-esterification. More triethylamine (10 μL) and acid chloride (10 μL) was added and the reaction stirred for a further 2 h. TLC indicated the formation of a single product. The reaction was diluted with diethyl ether (3 mL), then poured into a saturated aqueous solution of sodium bicarbonate (5 mL). The phases were separated and the aqueous phase extracted with ethyl actetate (2 × 3 mL). The combined organic extracts were dried and concentrated under reduced pressure to afford crude bis-Mosher ester as a 1:1 mixture of two diastereoisomers; $\delta_F$ (282 MHz, $CDCl_3$, 32 scans) −71.22 (3F, s, 2*R*,3*S* diastereoisomer), −71.71 (3F, s, 2*R*,3*S* diastereoisomer), −71.79 (3F, s, 2*S*,3*R* diastereoisomer), −71.86 (3F, s, 2*S*,3*R* diastereoisomer), −92.32 (1F, d, $^2J$ 47.0, 2*S*,3*R* diastereoisomer), −92.35 (1F, d, $^2J$ 48.3, 2*R*,3*S* diastereoisomer), −101.81 (1F, d, $^2J$ 47.0, 2*S*,3*R* diastereoisomer), −101.95 (1F, d, $^2J$ 48.3); $R_f$ (40% ethyl acetate in hexanes) 0.75; de 0%.

**4.7.9. (2*R*)-5,5-Difluoro-4-([methoxyethoxy]methoxy)-pent-4-en-1,2-diol 40.** A solution of AD-mix-β (10.00 g, 1.4g/mmol) in *t*-BuOH/$H_2O$ (76 mL, 1:1 v/v) was stirred vigorously until the phases became clear. Diene **22** (1.48 g, 6.23 mmol) was added to this solution and the resulting heterogeneous mixture stirred vigorously for 21 h. TLC indicated the slow formation of diol **40**, confirmed by $^{19}F$ NMR. The reaction mixture was quenched with sodium sulfite (11 g) and the reaction stirred for 1 h. DCM (30 mL) was added and the organic layer separated. The aqueous phase was extracted with DCM (3 × 30 mL). The combined organic extracts were dried and concentrated under reduced pressure to afford a pale yellow oil (950 mg). Purification by column chromatography over silica gel (40% ethyl acetate in light petroleum ⇒ 100% ethyl acetate in light petroleum) afforded diol **40** as a colourless oil (145 mg, 10%); $R_f$ (80% ethyl acetate in light petroleum) 0.13; $\nu$ (film/$cm^{-1}$) 3414 bd s (OH), 1767 s, 1709 w, 1643 w, 1457 m, 1368 m, 1274 s, 1241 s, 1202 s, 1113 bd s, 1027 s, 963 s, 889 m, 850 m, 769 w; $\delta_H$ (300 MHz, $CDCl_3$) 4.92 (2H, s, $OCH_2O$), 3.97–3.88 (1H, m), 3.82–3.78 (2H, m), 3.65 (1H, dd, *one half of an ABX*, $^2J$ 11.2, $^3J$ 2.9), 3.58–3.54 (2H, m), 3.50 (1H, dd, *one half of an ABX*, $^2J$ 11.2, $^3J$ 6.6), 3.39 (3H, s), 3.17–3.02 (1H, bd s), 2.57–2.42 (1H, bd s), 2.37–2.30 (2H, m); $\delta_C$ (75 MHz, $CDCl_3$) 155.2 (dd, $^1J_{CF}$ 287.7, 280.9), 113.1 (dd, $^2J_{CF}$ 41.3, 14.1), 95.6 (t, $^4J_{CF}$ 2.8), 71.6, 69.3 (dd, $^4J_{CF}$ 3.4, 2.3), [68.2, 68.2], 66.0, 59.1, 30.6 (d, $^3J_{CF}$ 2.8); $\delta_F$ (282 MHz, $CDCl_3$) −100.24 (1F, d, $^2J$ 68.6), −112.31 (1F, dt, $^2J$ 68.6, $^4J_{HF}$ 4.4); [HRMS (ES-TOF, M+Na) Found: 265.0865; Calcd for $C_9H_{16}O_5F_2Na$: 265.0864]; *m/z* (ES-TOF) 265.1 (100%, M+Na). The configuration is assigned on the basis of the Sharpless model. The extent of enantiomeric enrichment has not been determined.

**4.7.10. 1,3-Dideoxy-1,1-difluoro-α-D-*glycero*-pent-2-ulofuranose and 1,3-dideoxy-1,1-difluoro-β-D-*glycero*-pent-2-ulofuranose 41.** Chlorotrimethylsilane (63 μL, 0.5 mmol) was added dropwise to a solution of diol **40** (145 mg, 0.5 mmol) in methanol (5 mL) at 0 °C. The resulting colourless solution was allowed to warm to ambient temperature and stirred for 18 h. The reaction mixture was concentrated under reduced pressure to afford a pale yellow oil. Acetone (5 mL) was added and the solution concentrated onto silica gel to afford a pale yellow powder. Purification by column chromatography over silica gel (60% ethyl acetate in hexanes) afforded pentuloses **41** as clear oils (50 mg, 65%, ∼1:1 α:β); $R_f$ (60% ethyl acetate in hexanes) 0.31; $\nu$ (film/$cm^{-1}$) 3400 bd s, 2963 m, 2894 m, 2520 bd s, 1704 w, 1471 w, 1437 m, 1372 w, 1076 s; $\delta_H$ (300 MHz, $CD_3OD$) 5.68 (0.5H, t, $^2J_{HF}$ 55.9), 5.59 (0.5H, t, $^2J_{HF}$ 56.3), 4.58–4.50 (0.5H, m), 4.44–4.37 (0.5H, m), 4.11 (0.5H, dd, $^2J$ 9.4, $^3J$ 4.8), 3.96–3.93 (1H, m, envelope), 3.75 (0.5H, dd, $^2J$ 9.3, $^3J$ 3.1), 2.43–2.36 (0.5H, m), 2.17–2.11 (1H, m, envelope), 1.92–1.85 (0.5H, m); $\delta_C$ (126 MHz, $CD_3OD$) 115.4 (t, $^1J_{CF}$ 246.0), 104.8–104.2 (m), 76.8, 76.0, 71.2, 42.6, 41.1; $\delta_F$ (282 MHz, $CD_3OD$) −130.22 (dd, $^2J$ 283.7, $^3J_{HF}$ 56.1), −134.01 (dd, $^2J$ 283.7, $^3J_{HF}$ 55.8), −132.10 (apparent d, 55.9 Hz separation, highly distorted ABX), (1.05:1 α:β after 24 h in $CD_3OD$;

1.35:1 α:β after two months in $CD_3OD$); *m/z* (CI) 308 (52%, 2M or $2M-H_2O+NH_4$), 290 (28%, $2M-H_2O$), 194 (29%), 172 (81%, $M+NH_4$), 154 (100%, $M^+$).

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