Developing an asymmetric, stereodivergent route to selected 6-deoxy-6-fluoro-hexoses†

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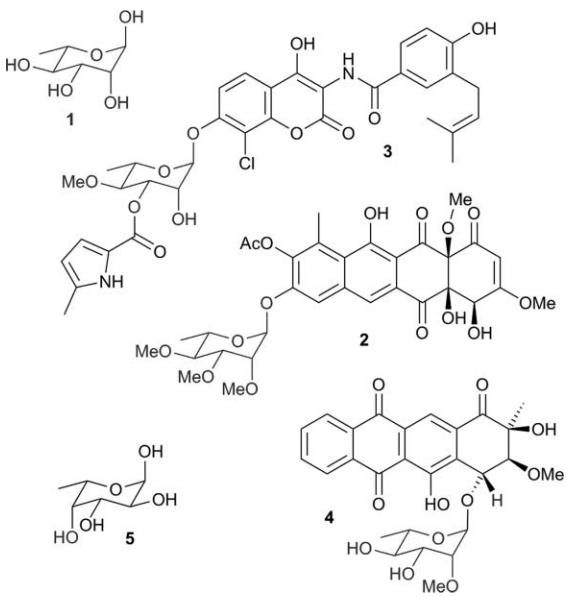
Free radical bromination and nucleophilic fluorination allows the conversion of methyl sorbate into the 6-fluoro analogue which undergoes sequential asymmetric dihydroxylation reactions. A range of 6-deoxy-6-fluorosugars were prepared by using different combinations of ligands. While the enantiomeric excesses obtained were comparable to those from other 6-substituted sorbates, the regioselectivity of dihydroxylation was moderate, with both 2,3- and 4,5-diols being obtained. A successful temporary persilylation strategy was evolved to convert the products of dihydroxylation rapidly to the fluorosugars 6-deoxy-6-fluoro-L-idose, 6-fluoro-L-fucose and 6-deoxy-6-fluoro-D-galactose, which were obtained in overall yields of 4%, 6% and 8% from methyl 6-fluoro-hexa-2*E*,4*E*-dienoate **6**.

Introduction

Fluorosugars are unknown in nature though fluoronucleoside natural products have been reported;[1,2] indeed, nature makes very few fluorinated compounds,[3] so selective fluorination represents an extremely useful strategy for locating molecules within the complex environments of cells or within the molecular diversity of the secondary metabolites. ^{19}F NMR can be used to locate fluorinated molecules and follow their transformations *in vitro* and potentially *in vivo*, and some valuable insights have been obtained in this way.[1,2] One of the most common biosynthetic modifications of the hexoses involves deoxygenation at the 6-position; this (and further deoxygenation at the 2- and 3-positions) is a characteristic feature of the sugars with which many macrolide antibiotics are embellished.

For example, rhamnose **1** is shown within the context of antibiotics elloramycin **2**,[4] novclobiocin 122 **3**,[5] and aranciamycin **4**.[6] In humans, fucose **5** is a common and critical sugar; many key cellular events, for example the inflammatory response and tumour metastasis, involve fucose-containing oligosaccharides, synthesised *via* the action of fucosyltransferase enzymes. The removal of fucosyl residues from the non-reducing end of glycoconjugates by fucosidases is also important; a clinical condition



(fucosidosis) arises from the accumulation of fucosylated glycolipids and glycoproteins in various tissues. Changes in fucosylation levels are also associated with certain carcinomas.[7] Fucose and other 6-deoxyhexoses are an interesting and important class of monosaccharide which are attracting the attention of a wide range of chemists.[8]

Significant differences between the ways in which the hexoses and their 6-deoxy analogues are recognised would be anticipated (Fig. 1).

Whereas in the former class of sugars C-6 bears an hydroxyl group which is capable of forming hydrogen bonds as both acceptor and donor, in the latter class C-6 is within a methyl group which cannot participate in this type of interaction. Though our ideas about sugar recognition are becoming more sophisticated as new types of binding are characterised and studied quantitatively,[9] recognition *via* the formation of networks of classical hydrogen bonds is still the most accepted model.[10] The most likely home

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† Electronic supplementary information (ESI) available: Details of HPLC procedures and chromatograms, Cartesian coordinates and energies from electronic structure calculations for **6** and **7**, details of T_1 determination for **37**, identification of pyranose and furanose forms and their anomers by ^{13}C and ^{1}H NMR, comparison of AD enantiomeric excesses with related systems from the literature, and characterisation spectra for **7**, **13**, **6**, **15a** and **16a**, **17a** and **18a**, **19** and **20**, **15b** and **16b**, **23**, **25**, **26**, **28**, **30**, **31**, **33**, **34**, **37**, **39** and **40**; crystal structure data. See DOI: 10.1039/b815342f

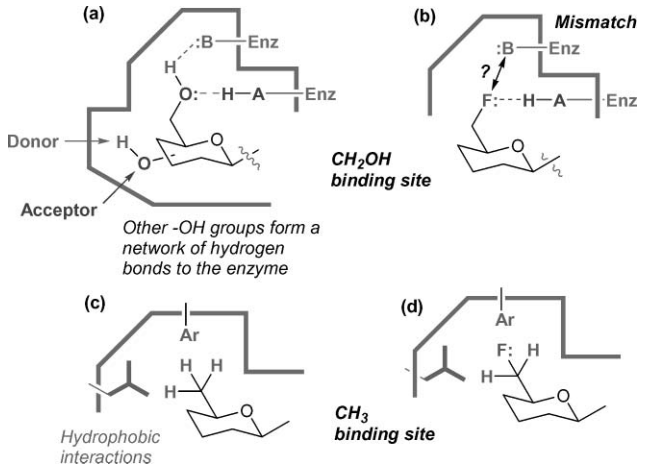
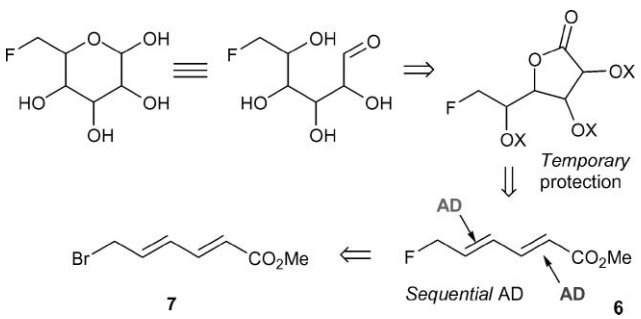


Fig. 1 Cartoon representations of features within the binding site of a sugar processing enzyme. (a) The C-6 hydroxyl group makes classical hydrogen bonding interations with the protein; (b) a weakly attractive interaction and a potential repulsive interaction with proximal basic broups on the enzyme arise when F replaces OH; (c) shows the likely arrangement within the CH_3 binding site for a 6-deoxysugar; (d) shows how F for H replacement may be less deleterious within the CH_3 binding site.

for the C-6 methyl group is a hydrophobic pocket (Fig. 1c), a favourable interaction making a modest additional contribution to the overall binding energy. As CH_3 and CH_2OH also differ in size, high selectivities for hexoses over 6-deoxyhexoses (or *vice versa*) could be contrived (and would be expected) in higher organisms, whereas species looking to maximise the diversity of their molecular production (such as *Streptomyces* species) may be more promiscuous[11] and use less structured binding domains. An enzyme which shows high affinity for galactosyl substrates, for example a galactosyltransferase (GalT), may not accept a 6-deoxy-6-fluorogalactose as a substrate if hydrogen bonding to the C-6 hydroxyl group is an important component of the recognition motif. The independent studies of Kodama[12] and Schengrund[13] would appear to support this idea. The former study showed that a GalT could catalyse the transfer of UDP-6-deoxy-6-fluoro-D-galactose and used the reaction in the synthesis of antennary oligosaccharides (albeit with sacrificial loading of enzyme), whereas the latter study showed the activated sugar was bound by two GalTs, neither of which could use UDP-6-fluoro-D-galactose as a substrate. While it is known that stabilising C–F···H–X interactions can be formed to allow other more favourable non-covalent bonding events to take place (Fig. 1b),[14,15] the interactions are relatively weak and unlikely to compensate for the loss of a C–O···H–X interaction. However, a fucosyltransferase (FucT) cannot use a hydrogen bond to recognise C-6, and we might expect a CH_2F group to fit reasonably well into the hydrophobic binding site for a CH_3, given that the monofluorination represents the minimal steric perturbation that we can make (Fig. 1d).

In order to appreciate the fine detail of the structure and mechanism of sugar nucleotide processing enzymes, including epimerases,[16] isomerases[17] and glycosyltransferases,[18,19] routine access to sugar nucleotides is required. In the case of D-galactose derivatives (and some other sugars), this is achieved practically through the concerted action of galactokinase and galactose-1-phosphate uridylyltransferase.[20] We sought a divergent route to 6-deoxy-6-fluoro sugars to feed through these activation methods, from readily-available and inexpensive starting materials.‡ We proposed a *de novo* route: Kirschning[21] has pointed out the advantages of total synthesis for the preparation of unusual sugars and has summarised developments in the area up to 2001.

The synthesis of deoxyfluorosugars from other carbohydrates usually requires extensive use of protecting group chemistry to expose a single hydroxyl group for nucleophilic fluorination. Withers *et al.*[22] and Schengrund *et al.*[13] *inter alia* synthesised 6-deoxy-6-fluorosugars in this way using nucleophilic fluorinating agent DAST.[23,24] Nucleophilic displacement of a good leaving group at C-6 by fluoride ion has also been used extremely successfully; 6-deoxy-6-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranoses[25] and 6-fluoro-D-olivose[26] *inter alia* were prepared in this way. However, because numerous protection and deprotection steps may be required to isolate the C-6 hydroxyl group, fluorination can be difficult, time consuming and inflexible, and is always subject to stereoelectronic effects exerted by the C(5)–O bond in the pyranose. A different synthesis may be required for each member of series of related hexose analogues and some may use scarce or expensive starting materials.[27] A strategically different approach would involve the introduction of fluorine early in the synthesis, to prepare an achiral but highly functionalised building block, which could be transformed into a range of different highly enantiomerically-enriched 6-deoxy-6-fluorosugars.[28] Scheme 1 shows a direct retrosynthetic analysis which raises two strategic issues.

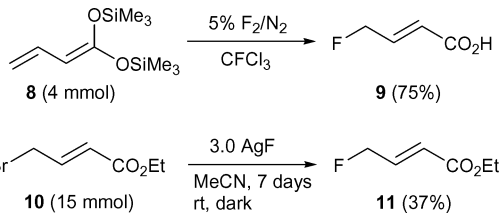


Scheme 1 Retrosynthetic analysis.

The first issue concerns the practicality of regioselective and sequential ADs of a fluorinated hexadienoate substrate. The Sharpless group's AD reactions of ethyl sorbate[29] indicate that multiple hydroxyl groups can be added to the hexadienoate template; maintaining C-1 at the carboxylic acid oxidation level could potentially save a number of oxidation/reduction steps. Corey and Guzmán-Pérez[30] showed how the first issue could be resolved (though no sugar syntheses were ever reported) with highly enantioselective and diastereoselective sequential dihydroxylations of protected sorbyl alcohols. The approach has more recently been developed to great effect by Somfai[31] and O'Doherty[32] in total syntheses of complex natural products.

‡ Racemic 6-deoxy-6-fluoro-galactose prepared in this manner proved to be an effective substrate for the enzymatic synthesis of UDP 6-deoxy-6-fluoro-galactose; see accompanying publication (DOI: 10.1039/b815549f).

The second issue concerns the preparation of the 6-fluorohexadienoate **6**. Fluorides of this structural type are uncommon in the literature; Purrington prepared 4-fluorobutenoate **9** by direct fluorination of silylketene acetal **8** with elemental fluorine (Scheme 2). Silver-mediated fluorinations of butenoyl bromide **10** are also known[33] delivering **11** in moderate yield but *via* a slow and expensive reaction. We decided to explore halogen exchange reactions of known[34] bromide **7** as an entry to **6**.[35]



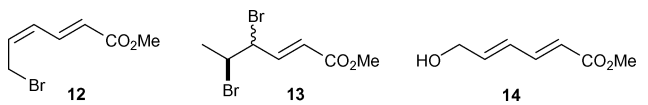
Scheme 2 Literature preparations of γ-fluorobutenoates.

In this manuscript, we describe the two-step preparation of **6** from methyl sorbate, sequential AD reactions and the synthetic endgame leading to the preparation of four 6-deoxy-6-fluorohexoses and a 2,3,6-trideoxy-6-fluorohexose. The scope and limitations of the route will be discussed.

Results and discussion

Hexadienoate synthesis and sequential (scalemic) dihydroxylation

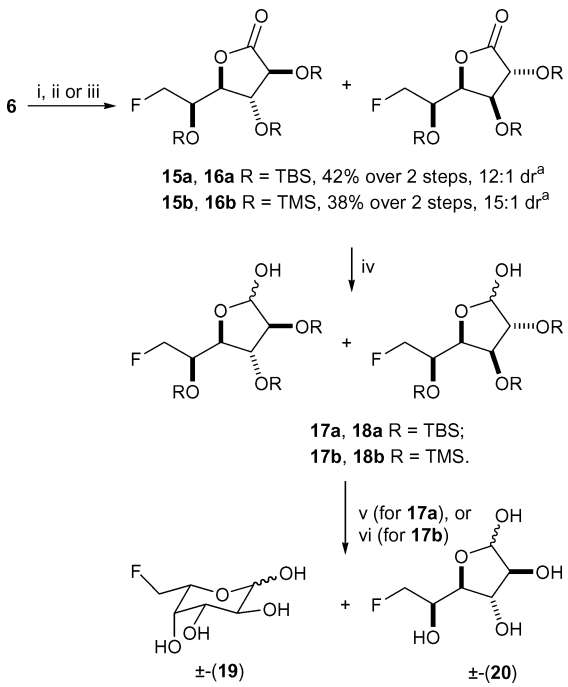
Methyl sorbate was converted to bromide **7** using the method of Green and co-workers.[34] However, we were not able to reproduce the high-yielding and selective reaction reported in the literature. Crude reaction mixtures also contained two side-products believed to be bromide **12** and dibromide **13** (characterised more fully as a 1:1 mixture of *syn*- and *anti*-diastereoisomers);[36] rigorous separation of these compounds from **7** resulted in significant yield loss. However, we note that Green and co-workers processed several moles of dienoate (400 g scale); it may be that the procedure is much more effective on the larger scale when fractional distillation may allow purer bromide **7** to be obtained.



Nucleophilic fluorination was attempted using a range of conditions; initially, we found that a fluorination using a mixture of TBAF trihydrate and KHF_2 mobilised with some hexane afforded **6** in useful yield, after numerous attempts to employ various forms (commercial "anhydrous" or the trihydrate) of TBAF alone had resulted in decomposition. We were also able to use the conditions described by Hou and co-workers (KF/TBAS in MeCN),[37] though the yield was lower using this method. The hexadienoate was obtained as a crystalline volatile solid which appeared to sublime close to 30 °C. The molecular structure in the crystal was determined by X-ray crystallographic analysis.

The purity of the bromide used in the fluorination reaction was critical; crude mixtures of products from the bromination reaction could not be used and material which had been purified by Kugelrohr failed to fluorinate cleanly, returning a complex mixture of products. We were not able to scale the fluorination beyond 12 mmol without the yield decreasing still further. Hydrolysis product **14** was also identifiable in the product mixture;[38] a significant amount of bromide is diverted to this side product (ratios of **6**:**14** of 2:1 to 3:1 were typical).

Hexadienoate **6** was then subject to sequential UpJohn dihydroxylations and the crude product was per-trialkylsilylated[39] and purified (Scheme 3). The products at this stage were inseparable furanolactones **15** (major) and **16** (minor); in the HMBC spectrum, a clear cross-peak connected the lactone carbonyl and H-4. We were able to determine the ratio of diastereoisomers by $\{^1H\}^{19}F$ NMR, measuring ratios of 15:1 (R = $SiMe_3$, 38% over 2 steps) and 12:1 (R = $SiMe_2t$-Bu, 42% over 2 steps). The mixtures were taken on and products arising from the minor diastereoisomer were removed in the final purification. Reduction with DIBAL-H was used to adjust the oxidation level at C-1; the tris(trimethylsilyl) species **15b** and **16b** were reduced and deprotected (3:6:1 HCOOH–THF–H_2O) directly to afford the racemic 6-deoxy-6-fluorogalactose as an 11:1 mixture of pyranose **19** and furanose **20** (58% over 2 steps). The data were identical with those reported by Schengrund and Kovac[13]§ and co-workers, so this represents a very direct preparation of a racemic 6-deoxy-6-fluorosugar.



Scheme 3 Racemic dihydroxylation sequences. *Reagents and conditions*: i, OsO_4, NMO, *t*-BuOH, acetone, H_2O, 20 °C; ii, TBSOTf, pyridine, dry DMF, 24 h, rt for **15a**, **16a**; or iii, TMSCl, pyridine, 15 h, 0 °C for **15b**, **16b**, iv, DIBAL-H, dry PhMe, 0 °C; v, $BF_3{\cdot}OEt_2$, CH_3CN, 0 °C, 1 h (73%) for **15a**; or vi, THF–HCOOH–H_2O (6:3:1), rt, 1 h (58%) for **15b**. [a] The diastereoisomeric ratio was determined by $\{^1H\}^{19}F$ NMR of the crude reaction mixture.

We were able to isolate and purify a mixture of **17a** and **18a** (the immediate products of DIBAL-H reduction) for characterisation. These tris-*O*-TBDMS species required more forcing deprotection

§ The anomer assignment in this paper appears to be incorrect; the anomers can be assigned with confidence from the HMBC spectrum using C_1–H_5 cross peaks, which are distinct for the two anomers.

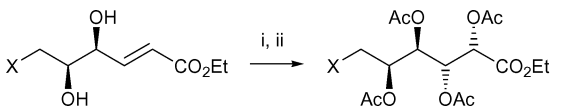
conditions after successful reduction. While treatment with TBAF was destructive,[40] ammonium fluoride (48 h in MeOH, rt) afforded **19** and **20** in moderate (49%) yield, exposure to boron trifluoride etherate in acetonitrile (1 h, 0 °C) was more effective,[41] and the free sugar was obtained in 80% yield. We were unable to detect significant side products, such as those arising from fluoride ion expulsion and epoxide formation, or dehydrofluorination and alkene formation, during the formation of **19** or **20**, or any of the other intermediates or final sugars synthesised in this study.

Though the overall yields are slightly higher when TBS protection is used, the use of TMS allows a facile deprotection after which no product purification is required. This is a distinct advantage when valuable products are being isolated. The sequence of events is likely to involve initial dihydroxylation across the C-4/C-5 alkenyl group on the basis of our asymmetric results (*vide infra*), and those of O'Doherty. If this is the correct sequence of events, the second UpJohn reaction is more stereoselective (and at a higher temperature) than the outcome reported by O'Doherty and co-workers for substrate-controlled UpJohn dihydroxylation of **21a** and **21b**.

Though the fluorine atom is remote, it appears to increase the effectiveness of the γ-hydroxyl group in exerting diastereofacial control.

Sequential asymmetric dihydroxylation of 6

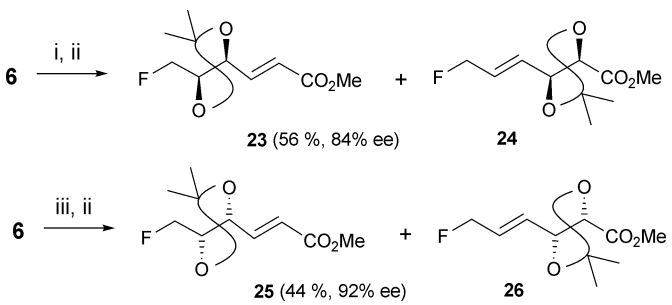
We exposed **6** to AD-mixes α and β at the osmate/ligand loadings described by O'Doherty (Scheme 4),[42] and converted the crude products directly to their acetonides (Scheme 5). The AD reactions were only moderately regioselective, affording 5:1 and 4:1 mixtures of acetonides **23** (56% over two steps, 84% ee) and **24**, and **25** (44% over two steps, 92% ee) and **26** respectively, but the products were separable. The minor regioisomers were characterised as



21a, X = H;
21b, X = OBn.

22a, X = H; 55%, 6 : 1 dr
22b, X = OBn, 60%, 5 : 1 dr

Scheme 4 Substrate-controlled racemic dihydroxylation sequences reported by O'Doherty. *Reagents and conditions*: i, OsO_4, NMO, *t*-BuOH, acetone, 0 °C; ii, Ac_2O, pyridine.



Scheme 5 *Reagents and conditions*: i, AD-mix-α: $K_2OsO_4{\cdot}2H_2O$, $(DHQ)_2PHAL$, $CH_3SO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH–H_2O (1:1), 24 h, 4 °C; ii, 2-methoxypropene, *p*-TsOH(cat.), DMF, 3 h, rt (**23**, 56% over 2 steps, ee = 84%); iii, AD-mix-β: $K_2OsO_4{\cdot}2H_2O$, $(DHQD)_2PHAL$, $CH_3SO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH–H_2O (1:1), 24 h, 4 °C (**25**, 44% over 2 steps, ee = 92%).

fully as possible. We did not find any products arising from dihydroxylation of both alkenyl groups.

The ADs which delivered **21a** and **21b** were much more regioselective, with only these diols being formed. O'Doherty explained these highly regioselective monodihydroxylation outcomes as arising from the electronic deactivation of the α,β-alkenyl group by the alkoxycarbonyl group. The potential second dihydroxylation is disfavoured strongly by a conflict between the directing effect of the γ-hydroxyl group and the facial preference of the ligand.

In our case, the presence of even a single fluorine atom appears to lower the reactivity of the γ,δ-alkenyl group of the diene as the rates of the two dihydroxylations are now more alike. The fluorine atom has a small effect on the diene HOMO energy, lowering it from –8.92 eV for methyl sorbate to –9.19 eV for **6** (calculated in Spartan06 at the MP2/6-311+G** level)[43,44] (though the patterns of Mulliken charges in the diene are very similar in fluorinated and non-fluorinated cases). Even such small differences in HOMO energy can affect dihydroxylation rates of alkenes significantly according to quantitative studies of permanganate and chromyl chloride-mediated dihydroxylations.[45] The regiochemistry of the dihydroxylation reaction of diene and polyene substrates has been reviewed recently; though dienes like **6** were explicitly excluded from consideration,[46] it is clear that the factors determining regioselectivity in diene dihydroxylation may be subtly balanced.

The ee values for our reactions were determined by chiral HPLC (Chiralcel ODH, eluting with 1% *i*-PrOH in hexane) and compare well with the values reported by O'Doherty for ethyl sorbate.[47] The second dihydroxylations revealed strong matched/mismatched effects, summarised in Table 1. Diastereoselectivities as low as 2:1 (measured from the ^{19}F NMR spectra of crude products) were obtained in the mismatched cases.

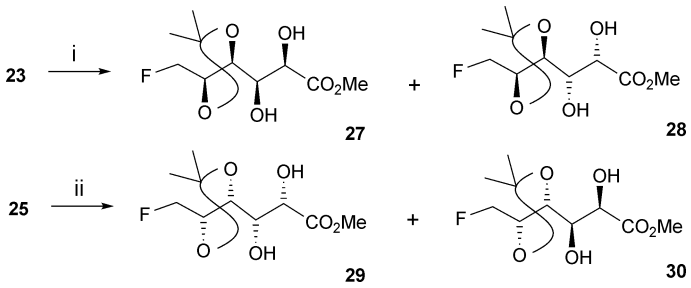
The matched cases give much higher diastereoselectivities, as expected from the results of O'Doherty *inter alia*. The protection strategy developed for the racemic syntheses was modified to deliver enantiomerically enriched 6-deoxy-6-fluorohexoses (Scheme 7). After acetonide removal, per-trimethylsilylation was achieved with *N*-methyl-*N*-trimethylsilyl trifluoroacetamide before DIBAL-H reduction (Scheme 6); we used the more reactive silylating reagent to shorten the reaction time with the enantiomerically-enriched species and minimise the risk of epimerisation. In the case of the major diastereoisomers **28** and **30** from the matched ADs, the per-trimethylsilylated furanolactols were characterised fully, then deprotected (3:6:1 HCOOH–THF–H_2O) to afford the sugars. The major product **27** from the mismatched AD of **23** was taken through to sugar **31** directly; **29** was converted to the bis-acetonide **34** and characterised at that stage.

The sugars were characterised by the usual NMR methods and their rotations compared to those reported in the literature. The

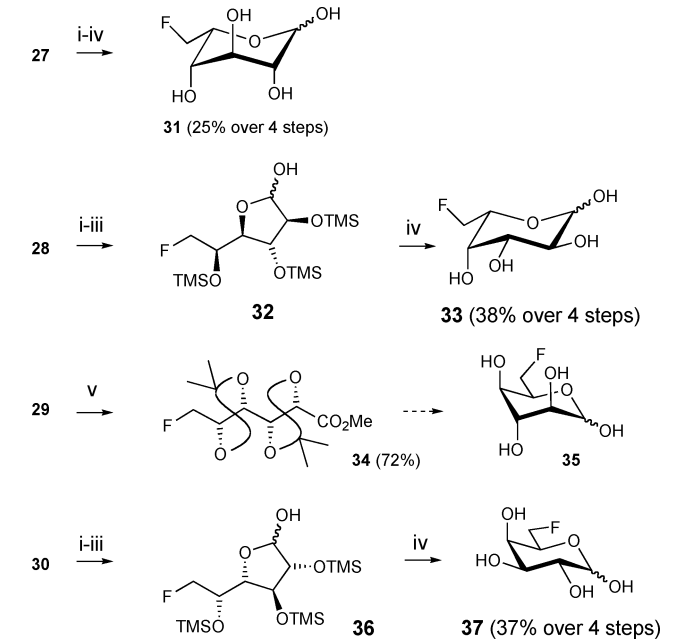
Table 1 AD reactions of **23** and **25**

	From **23**			From **25**		
AD mix	**27** (%)[a]	**28** (%)[a]	Ratio **27**:**28**[b]	**29** (%)[a]	**30** (%)[a]	Ratio **29**:**30**[b]
α	31	30	2:1	(–)	52 (99% ee)[c]	1:22
β	(–)	64 (96% ee)[c]	1:14	52	25	2:1

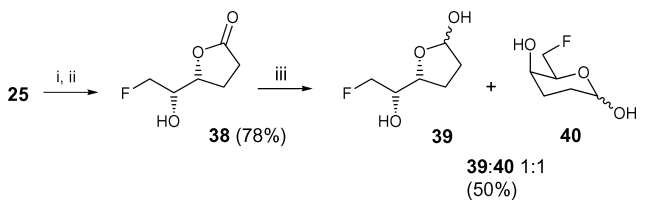
[a] Yields are isolated purified yields. [b] Ratios were determined by ^{19}F NMR of crude product mixtures. [c] ee determined by chiral HPLC.



Scheme 6 *Reagents and conditions*: i, AD-mix-α: $K_2OsO_4{\cdot}2H_2O$, $(DHQ)_2PHAL$, $CH_3SO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH–H_2O (1:1), 24 h, 4 °C; ii, AD-mix-β: $K_2OsO_4{\cdot}2H_2O$, $(DHQD)_2PHAL$, $CH_3SO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH–H_2O (1:1), 24 h, 4 °C.



Scheme 7 *Reagents and conditions*: i, 3 M HCl, MeOH, 24 h, rt; ii, $CF_3CON(Me)SiMe_3$, neat, 60 min, 60 °C; iii, DIBAL-H, dry PhMe, −78 °C, 30 min; iv, THF–HCOOH–H_2O (6:3:1) rt; v, 2-methoxypropene, *p*-TsOH (cat.), DMF, 3 h, rt.



Scheme 8 *Reagents and conditions*: i, H_2, 10% w/w Pd/C, EtOH; ii, HCl, MeOH, 18 h, rt; iii, DIBAL-H, dry PhMe, −78 °C.

rotations of the D-6-deoxy-6-fluorogalactose[48] and L-6-deoxy-6-fluorogalactose[49] were reported as $[\alpha]_D^{22} = +76.5$ (c 1.0, H_2O) and $[\alpha]_D^{22} = -76.5$ (c 0.23, H_2O) respectively; the rotations for our synthetic compounds were $[\alpha]_D^{18} = +64.0$ (c 0.5, H_2O) and $[\alpha]_D^{18} = -65.9$ (c 0.5, H_2O) respectively, confirming the authenticity of the final products and the sense of stereochemical assignment throughout the sequences.

The overall yields of sugars from our sequences all calculated from **6** are 4% for L-idose analogue **31**, 6% for L-fucose analogue **33** and 8% for D-galactose analogue **37**. The idose is a new compound but **33** and **37** have been synthesised before. The overall yields calculated using the methods of Kortynyk *et al.*[49] for these compounds are 8% for **33** from L-galactono-1,4-lactone and 32% for **37** from D-galactose respectively. As usual, the *de novo* syntheses of a carbohydrate is less efficient and attractive than a transformative method from a readily available precursor, but the potential for fully asymmetric and divergent methodology from an achiral precursor has been demonstrated.

Anomer ratios were assigned by comparison with literature data; C-1, C-2 and C-4 ^{13}C NMR chemical shifts are often diagnostic.[50] The studies of Serianni and co-workers were particularly useful for deconvolution of the idose spectra.[51]

One feature of the NMR behaviour requires comment. We were unable to obtain satisfactory integration of one of the H-2 protons in **33** and **37** despite repeated re-purification of the sample, so we measured the T_1 values for as many protons as possible, and found that the errant proton had a longer T_1 than expected (6.3 s). All the other T_1 values measured lay between 1.5 and 4 s, similar to the behaviour reported for galactose.[52] Recording the spectra with $D_1 = 30$ s allowed correct integration of this signal.

We also hydrogenated **25** to prepare 6-fluoro-D-rhodinose[53] *via* lactone **38** (Scheme 8), which could be reduced directly under the usual conditions to afford the 6-fluoro-2,3,6-trideoxysugar[54] as a complex mixture of furanoses **39** and pyranoses **40** (both anomers of each).

Conclusions

The route is most effective at delivering *syn*,*anti*,*syn* combinations of stereogenic centres with the all-*syn* diastereoisomers being more difficult to make because of the mismatch between the ligand and substrate-controlled selectivity.

The initial fluorination is difficult but our melt conditions and the phase-transfer protocol of Hou and co-workers allows gram quantities to be prepared. This study provides a valuable proof-of-concept that simple fluorinated building blocks can be deployed in effective stereodivergent syntheses of fluorinated sugars.

Experimental

NMR spectra were recorded on Bruker DPX-300, DRX-400, AV400, DPX-500 or AV-600 spectrometers. ^1H NMR spectra were recorded at 300, 400, 500 and 600 MHz, ^{13}C NMR spectra at 75 and 100 MHz, and ^{19}F spectra at 282 and 376 MHz. ^1H and ^{13}C NMR spectra were recorded using the deuterated solvent as the internal reference. ^{19}F NMR spectra were recorded relative to an external standard of fluorotrichloromethane. Unless otherwise stated, couplings, *J*, refer to $^3J_{H\text{-}H}$ couplings and are given in Hertz. Thin layer chromatography (TLC) was performed on precoated aluminium silica gel plated supplised by E. Merck, A. G. Darmstadt, Germany (silica gel 60 F254, thickness 0.2 mm, art. 1.05554) and compounds were visualised with UV light or a potassium permanganate stain. Solvents were dried using a Pure-Solv apparatus (Innovate Technology Inc). All other chemicals were used as received without any further purification.

GC analyses were carried out using a Perkin Elmer Autosystem XL instrument, using a standard PE-5 column (injector 250 °C, start temperature 40 °C, ramp rate 10 °C/min, end temperature

280 °C) or a Finnegan Pro GC-MS system, using the same temperature ramping programme, up to 320 °C Low resolution mass spectral data were collected either on a Finnegan Pro GC-MS system, using electron impact ionisation or on a Finnegan Pro electrospray system (by manual injection), using methanol or acetonitrile as solvents. High resolution mass spectra were recorded by the EPSRC Mass Spectrometry service by either electrospray or chemical ionisation, where polyethyleneimine was used as a reference compound. Infra-red analyses were carried out on a Perkin Elmer IR spectrometer, using KBr discs.

Crystals for X-ray analysis were grown by vapour diffusion.

Flash column chromatography was carried out on Biotage Horizon (with pre-packed cartridges) or Buchi Sepacore (with self-packed or Biotage Snap™ cartridges) instruments. Determination of enantiomeric excess by HPLC was carried out using a CHIRALCEL OD-H (25 × 0.46 cm ID) column with UV detection at 236 or 254 nm. Preparative HPLC was carried out on a Kromosil (10 μ × 100 Å, 250 × 10 mm ID) column with UV detection at 254 nm.

Methyl 6-bromohexa-2*E*,4*E*-dienoate, 7 and methyl-4,5-dibromohex-2*E*-enoate 13

A mixture of methyl sorbate (20.2 g, 160.1 mmol) and *N*-bromosuccinimide (29.93 g, 168.1 mmol) in dry chlorobenzene (140 mL) was heated to 100 °C over 1 hour; dibenzoylperoxide (1.75 g, 7.2 mmol) was then cautiously added in portions (0.10 g). **CAUTION**: the radical reaction can initiate violently; for effective containment, the reaction volume should be *no more than one third* of the volume of the reaction vessel). After the addition was complete, the reaction mixture was heated under reflux (130 °C) for 3 h, then cooled and the chlorobenzene was removed by evaporation under reduced pressure (15 mmHg). The residual paste was triturated with Et_2O (300 mL) and the ethereal extract was washed with sodium hydroxide (50 mL of a 5% aqueous solution) until the washings were colourless. The organic layer was then dried ($MgSO_4$), filtered and concentrated. The crude residue was purified first by distillation (Kugelrohr, bp 80–90 °C/0.06 mmHg) and then by chromatography on silica gel (0 to 10% ethyl acetate in hexane) to afford bromide **7** as a colourless oil (8.18 g, 25%, 97% by GC/MS); R_f (10% ethyl acetate in hexane) 0.48; υ_{max} (neat)/cm^{-1} 3000–2952 w, 1716 s, 1662w, 1645w, 1615w, 1435 m, 1250 m, 997 m, 977m; δ_H (300 MHz, $CDCl_3$) 7.24 (dd, 1H, *J* 15.4, 10.6, H-3), 6.34 (ddq, 1H, *J* 15.0, 10.6, ^4J 0.7, H-4), 6.24 (dt, 1H, *J* 15.0, 7.6, H-5), 5.92 (d, 1H, *J* 15.4, H-2), 4.01 (dd, 2H, *J* 7.6, ^4J 0.6, H-6), 3.73 (3H, OCH_3); δ_C (75 MHz, $CDCl_3$) 166.9, 142.8, 136.7, 131.8, 122.7, 51.7, 31.2. HRMS (EI) *m/z*: 203.97850 [M$^+$]; calc. for $C_7H_9{}^{79}BrO_2$:203.97859; *m/z* (EI) 204 (44%, M$^+$), 173 (29), 125 (100), 93 (71).

A small fraction of dibromides **13** (289 mg, 1%) was also isolated as an inseparable mixture of racemic *syn*- and *anti*-diastereoisomers: R_f (10% ethyl acetate in hexane) 0.42; υ_{max} (film)/cm^{-1} 3000–2952 w, 1728 s, 1659w, 1436 m; the diastereoisomers have the following distinct assignable signals:δ_H (400 MHz, $CDCl_3$) 6.99 (dd, 1H, *J* 15.4, *J* 9.1, H-3), 6.06 (dd, 1H, *J* 15.4, 0.8, H-2), 4.86 (ddd, 1H, *J* 9.1, 3.8, 0.8 H-4), 4.37 (qd, 1H, *J* 6.8, 3.8, H-5), 1.78 (d, 3H, *J* 6.8, CH_3); δ_C (100 MHz, $CDCl_3$) 141.0, 125.2, 53.8, 49.0, 20.9; and, 6.91 (dd, 1H, *J* 15.4, *J* 9.8, H-3), 5.97 (dd, 1H, *J* 15.4, 0.5, H-2), 4.64–4.58 (m, 1H, H-4), 4.20 (dq, 1H, *J* 8.8, 6.8, H-5), 1.86 (d, 3H, *J* 6.8, CH_3); δ_C (100 MHz, $CDCl_3$) 143.9 (C-3), 123.4 (C-2), 54.7 (C-4), 49.4 (C-5), 24.5 (CH_3).

In the ^{1}H NMR the following signals were not assigned to one diastereoisomer: 3.74 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3) In the ^{13}C NMR, the following signals were not assigned to a single diastereoisomer: 165.5 (C=O), 165.4 (C=O) 51.7 (OCH_3),

Methyl 6-fluoro-hexa-2*E*,4*E*-dienoate, 6: method A

A mixture of tetrabutylammonium fluoride trihydrate (3.91 g, 12.39 mmol) and potassium hydrogen fluoride (3.87 g, 49.56 mmol) was melted at 100 °C with stirring. Hexane (5 mL) was added followed by bromide **7** (2.54 g, 12.39 mmol) and the viscous suspension was stirred vigorously for 30 minutes at 100 °C, then cooled to room temperature. The reaction mixture was diluted with Et_2O (25 mL) and H_2O (10 mL) was added to solubilise all the salts. The organic layer was separated and the aqueous layer was neutralized with solid $NaHCO_3$ (2 g) and extracted with Et_2O (3 × 50 mL). The combined original organic layer and extracts were dried ($MgSO_4$), filtered and concentrated. The crude product was purified by flash chromatography on silica gel (0–10% diethyl ether in hexane) to afford fluoride **6** (0.75 g, 42%, 98% by GC/MS) as a colourless solid (**CAUTION**: pure **6** is volatile, *P* >700 mmHg at 40 °C for evaporation of column fractions); mp 27–29 °C; R_f (10% ethyl acetate in hexane) 0.42; υ_{max} (neat)/cm^{-1} 3000–2952 w, 1716 s, 1647 m, 1622 m, 1435 m, 1267 s, 1235 s, 1141 s, 999 m, 977m; δ_H (400 MHz, $CDCl_3$) 7.28 (ddd, 1H, *J* 15.4, 11.0, ^4J 1.5, H-3), 6.43-6.37 (m, 1H, H-4), 6.17 (app. tt, 1H, *J* 16.8, $J_{H\text{-}F}$ 16.8, *J* 5.0, H-5), 5.94 (d, 1H, *J* 15.4, H-2), 4.97 (ddd, 2H, $^2J_{H\text{-}F}$ 46.2, *J* 5.0, ^4J 1.6, H-6), 3.74 (s, 3H, OCH_3); δ_C (75 MHz, $CDCl_3$) 167.1), 143.0, 135.5 (d, $^2J_{C\text{-}F}$ 15.7), 129.8 (d, $^3J_{C\text{-}F}$ 12.0), 122.5, 82.0 (d, $^1J_{C\text{-}F}$ 165.7), 51.7; δ_F (376 MHz, $CDCl_3$) –217.5 (app. tddt, $^2J_{F\text{-}H}$ 46.2, $J_{F\text{-}H}$ 16.8, $^4J_{F\text{-}H}$ 3.2, $^5J_{F\text{-}H}$ 1.5). HRMS (EI): *m/z* 144.05861 [M$^+$]; calc. for $C_7H_9FO_2$ 144.05866; *m/z* (EI) 144 (28%, M$^+$), 113 (53), 111 (100), 85 (70). Satisfactory microanalysis could not be obtained for this volatile solid, though the molecular structure in the crystal could be elucidated.¶

Methyl 6-fluoro-hexa-2*E*,4*E*-dienoate, 6: method B

Potassium fluoride dihydrate (32.3 mmol, 3.04 g), then tetrabutylammonium hydrogen sulfate (9.78 mmol, 3.32 g) were added to a solution of bromide **7** (8.08 mmol, 1.66 g) in acetonitrile (32 mL). The resulting suspension was stirred under reflux overnight. The reaction mixture was then diluted with Et_2O (300 mL) and the organic phase washed with water (3 × 100 mL), brine (100 mL) and dried ($MgSO_4$). After filtration and careful evaporation of the solvent (*P* >700 mmHg at 40 °C), the crude product was purified by flash chromatography on silica gel (0 to 10% gradient of diethyl ether in hexane) to afford **6** (0.41 g, 35%) as a colourless solid. The data were as reported previously.

¶ The identity of this product was confirmed by XRD analysis; $C_7H_9FO_2$, crystal size 0.23 × 0.16 × 0.15 mm^3, *M* = 144.14, crystal system monoclinic, unit cell dimensions *a* = 8.4625(16), *b* = 8.0276(16), *c* = 21.142(4) Å, *α* = 90°, *β* = 90.378(5)°, *γ* = 90°, *U* = 1436.2(5) Å^3, *T* = 150(2) K, space group *C*2/*c*, absorption coefficient *μ* (Mo-K*α*) = 0.113 mm^{-1}, 4948 reflections collected 1256 unique [*R*(int) = 0.0410], which were used in all calculations. Final *R* indices [$I > 2\sigma(I)$] *R*1 = 0.0455, *wR*2 = 0.1063; *R* indices (all data) *R*1 = 0.0535, *wR*2 = 0.1101. CCDC number 700908.

(3*S,4*R**,5*S**)-3,4-Bis(*tert*-butyldimethylsilyloxy)-5-((*R**)-1-(*tert*-butyldimethylsilyloxy)-2-fluoroethyl)dihydrofuran-2(3*H*)-one (±)-15a and (3*R**,4*S**,5*S**)-3,4-bis(*tert*-butyldimethylsilyloxy)-5-((*R**)-1-(*tert*-butyldimethyl-silyloxy)-2-fluoroethyl)dihydrofuran-2(3*H*)-one (±)-16a; preparation *via* racemic UpJohn dihydroxylation and protection**

Racemic UpJohn dihydroxylation, cyclisation and protection. A solution of NMO (463 mg, 3.95 mmol) in water (1 mL) was added to a stirred solution of dienoate **6** (285 mg, 1.98 mmol) in acetone (2.3 mL) and *t*-BuOH (2.3 mL) at room temperature. The mixture was stirred for 15 minutes then cooled to 0 °C, and OsO_4 (0.039 mmol, 2 mol%, 402 μL of a 2.5% solution in *t*-BuOH) was added dropwise. The mixture was warmed to room temperature slowly and stirred vigorously overnight, then quenched by the addition of solid sodium sulfite (2 g). After stirring for a further 30 min, the entire mixture was filtered through a pad of Celite and the filter pad washed with a mixture of EtOAc and MeOH (1:1 v/v, 50 mL). The filtrate was concentrated under reduced pressure and the crude product was dried under high vacuum and taken on without purification.

The crude tetrols were taken up in dry DMF (13 mL) and treated with pyridine (83 mmol, 6.7 mL) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (8.9 mmol, 2 mL) at 0 °C under an atmosphere of argon. The solution was then allowed to warm to room temperature and stirred for 24 h. The reaction mixture was evaporated to dryness *in vacuo* and the residue was taken up in CH_2Cl_2 (100 mL). The solution was washed with water (2 × 20 mL), dried ($MgSO_4$) and concentrated to afford a mixture of **15a** and **16a** (12:1 by ^{19}F NMR). The residue was purified by flash chromatography on silica gel (0–2% gradient of diethylether in hexane) to afford a mixture of inseparable protected furanolactones **15a** and **16a** (432 mg, 42% yield over two steps, 91% by GC/MS) as a colourless oil. R_f (5% ethyl acetate in hexane) 0.51; υ_{max} (neat)/cm^{-1} 2955–2858 w, 1801 s, 1472 w, 1464 w, 1252 m, 834 s, 777 s; δ_H (400 MHz, $CDCl_3$) 4.46 (dd, 2H, $^2J_{H\text{-}F}$ 46.4, *J* 6.0, H-6), 4.42 (t, 1H, *J* 6.0, H-3), 4.30 (d, 1H, *J* 5.6, H-2), 4.15 (ddd, 1H, *J* 5.6, *J* 2.8, $^4J_{H\text{-}F}$ 0.4, H-4), 4.09 (dtd, 1H, $^3J_{H\text{-}F}$ 12.4, *J* 6.0, *J* 2.8, H-5), 0.92 (s, 9H, $SiC(CH_3)_3$), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.20, 0.15, 0.13, 0.12, 0.10 (s, 18H, $Si(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 173.2, 83.7 (d, $^1J_{C\text{-}F}$ 172.1), 82.6 (d, $^3J_{C\text{-}F}$ 6.0), 76.7, 75.1, 69.6 (d, $^2J_{C\text{-}F}$ 22.1), 25.7, 25.6, 18.2, 17.8, –4.0, –4.2, –4.4, –4.8, –4.9; δ_F (376 MHz, $CDCl_3$) –223.86 (td, $^2J_{F\text{-}H}$ 46.4, $^3J_{F\text{-}H}$ 12.4, **15a**), –227.83 (td, $^2J_{F\text{-}H}$ 46.4, $^3J_{F\text{-}H}$ 16.0, **16a**). HRMS (FAB$^+$) 523.31051 [M + H$^+$]; calc. for $C_{24}H_{52}FO_5Si_3$ 523.31067; *m*/*z* (FAB$^+$) 523 (11%, M + H$^+$), 465 (35), 407 (6), 231 (100).

(3*S,4*R**,5*S**)-3,4-Bis(*tert*-butyldimethylsilyloxy)-5-((*R**)-1-(*tert*-butyldimethylsilyloxy)-2-fluoroethyl)dihydrofuran-2(3*H*)-ol (±)-17a and (3*R**,4*S**,5*S**)-3,4-bis(*tert*-butyldimethylsilyloxy)-5-((*R**)-1-(*tert*-butyldimethylsilyloxy)-2-fluoroethyl)dihydrofuran-2(3*H*)-ol (±)-18a *via* DIBAL-H reduction**

A solution of DIBAL in toluene (2 mL of a 1.5M solution, 3.04 mmol) was added very slowly to a solution of protected furanolactones **15a** and **16a** (794 mg, 1.52 mmol) in dry toluene (75 mL) under an atmosphere of argon at –78 °C. The reaction was stirred for 15 minutes at –78 °C, before being quenching by the dropwise addition of dry methanol (3 mL). The reaction was allowed to warm to about –20 °C (internal temperature), and then poured into a vigorously stirred solution of Rochelle salt (aqueous potassium sodium tartrate, 20 mL of a 1.2M solution). The viscous solution was stirred vigorously for 2 h, after which time it settled into two clear phases. The organic layer was separated and the aqueous layer was extracted three times with Et_2O (50 mL). The combined organic layers were dried ($MgSO_4$), evaporated *in vacuo* and purified by flash column chromatography on silica gel (0 to 3% gradient of ethyl acetate in hexane) to afford a mixture of protected lactols **17a** and **18a** (724 mg, 91%, 97% by GC/MS) as a colourless oil (**17a**:**18a** 8.9:1; α/β anomeric ratio for major diastereoisomer **17a**: 1:2.1 by ^{19}F NMR): δ_F (376 MHz, $CDCl_3$) –223.8 (td, $^2J_{F\text{-}H}$ 47.5, $^3J_{F\text{-}H}$ 14.1, **17a**, α anomer), –225.4 (td, $^2J_{F\text{-}H}$ 47.5, $^3J_{F\text{-}H}$ 17.2, **17a**, β anomer), –230.8 (td, $^2J_{F\text{-}H}$ 46.7, $^3J_{F\text{-}H}$ 20.6, **18a**), –231.8 (td, $^2J_{F\text{-}H}$ 46.7, $^3J_{F\text{-}H}$ 20.6, **18a**). A small pure fraction of major diastereoisomer **17a** was isolated and characterised: R_f (5% ethyl acetate in hexane) 0.30; υ_{max} (neat)/cm^{-1} 2954–2859 w, 1473 w, 1464 w, 1253 m, 1114 m, 1072 m, 834 s, 776 s; δ_H (400 MHz, $CDCl_3$)* 5.16 (dd, 1H, *J* 12.2, *J* 4.1, H-1α), 5.08 (d, 1H, *J* 11.8, H-1β), 4.56-4.23 (m, 4H, H-6α, H-6β), 4.22 (t, 1H, *J* 3.2, H-3α), 4.15-3.94 (m, 5H, H-2β, H-3β, H-4β, H-5α, H-5β), 3.93 (m, 1H, H-2α), 3.83 (dd, 1H, *J* 4.0, *J* 3.2, H-4α), 3.64 (d, 1H, *J* 12.2, OHα), 3.63 (d, 1H, *J* 11.8, OHβ), 0.93, 0.92, 0.90, 0.89, 0.88 (s, 27H, $SiC(CH_3)_3$), 0.17, 0.15, 0.14, 0.13, 0.12, 0.11, 0.10, 0.08 (s, 18H, $Si(CH_3)_2$). δ_C (100 MHz, $CDCl_3$) 103.4, 97.5, 89.7 (d, $^3J_{C\text{-}F}$ 6.4), 85.5 (d, $^3J_{C\text{-}F}$ 6.4), 85.0 (d, $^1J_{C\text{-}F}$ 171.0), 84.9 (d, $^1J_{C\text{-}F}$ 171.0), 81.2, 80.0, 77.2, 77.1 (d, $^4J_{C\text{-}F}$ 3.0), 71.6 (d, $^2J_{C\text{-}F}$ 19.2), 71.5 (d, $^2J_{C\text{-}F}$ 20.8), 25.9, 25.8, 25.7, 25.6, 18.3, 18.1, 18.0, 17.7, –4.3, –4.4, –4.5, –4.6, –4.7, –4.8, –5.0; HRMS (FAB$^-$); 523.31019 [M – H$^+$]; calc. for $C_{24}H_{52}FO_5Si_3$ 523.31067; *m*/*z* (FAB$^-$) 523 (6%, M – H$^+$), 467 (4), 260 (100).

*The α and β suffixes refer to the pyranose anomer to which the signal belongs.

Racemic 6-deoxy-6-fluoro galactose (±)-19 and (±)-20

Deprotection with boron trifluoride. BF_3 etherate (102 μL, 0.80 mmol) was added to a solution of protected lactols **17a** and **18b** (140 mg, 0.268 mmol) in dry acetonitrile (4 mL) at 0 °C under an argon atmosphere. The mixture was stirred for 1 h at 0 °C, then neutralised with a saturated solution of $NaHCO_3$ and concentrated *in vacuo*. The crude residue was purified by chromatography on silica gel (0 to 20% gradient of MeOH in CH_2Cl_2) to afford (±)-6-deoxy-6-fluoro-galactose as a mixture of pyranose **19** and furanose **20** (39 mg, 80%) as a hygroscopic solid; by ^1H NMR, the product is a 10.9:1 mixture of pyranoses and furanoses; the anomeric ratio of pyranoses is α:β = 1:1.8 and the anomeric ratio of furanoses is α:β = 1:1.5.

R_f (20% MeOH in CH_2Cl_2) 0.29; υ_{max} (neat)/cm^{-1} 3342br, 2498 m, 1408 m, 1360 m, 1253 m, 1147 m, 1070 s, 1024 s, 997 s, 782m; δ_H (400 MHz, D_2O)* 5.34 (d, 1H, *J* 3.7, H-1α), 4.82–4.50 (m, 4H, H-6α, H-6β), 4.66 (d, 1H, *J* 7.8, H-1β), 4.41 (ddd, 1H, $^3J_{H\text{-}F}$ 16.6, *J* 7.2, *J* 3.8, H-5α), 4.09 (dd, 1H, *J* 3.2, *J* 0.9, H-4α), 4.08-3.98 (m, 1H, H-5β), 4.02 (d, 1H, *J* 3.7, H-4β), 3.92 (dd, 1H, *J* 10.3, *J* 3.2, H-3α), 3.86 (dd, 1H, *J* 10.3, *J* 3.7, H-2α), 3.71 (dd, 1H, *J* 9.9, *J* 3.5, H-3β), 3.55 (dd, 1H, *J* 9.9, *J* 7.9, H-2β); δ_C (100 MHz, D_2O) 96.4, 92.4, 83.5 (d, $^1J_{C\text{-}F}$ 164.6), 83.2 (d, $^1J_{C\text{-}F}$ 166.2), 73.4 (d, $^2J_{C\text{-}F}$ 20.8), 72.5, 71.7, 69.0 (d, $^3J_{C\text{-}F}$ 7.9), 69.0 (d, $^2J_{C\text{-}F}$ 22.4), 68.9, 68.4 (d, $^3J_{C\text{-}F}$ 8.0), 68.2; δ_F (376 MHz, D_2O) –229.2 (td, $^2J_{F\text{-}H}$

47.3, $^{3}J_{F-H}$ 19.1, **20**), –229.6 (ddd, $^{2}J_{F-H}$ 48.1, $^{2}J_{F-H}$ 45.6, $^{3}J_{F-H}$ 15.5, **19**, β anomer), –229.7 (ddd, $^{2}J_{F-H}$ 48.1, $^{2}J_{F-H}$ 45.6, $^{3}J_{F-H}$ 16.6, **19**, α anomer), –230.7 (td, $^{2}J_{F-H}$ 47.0, $^{3}J_{F-H}$ 20.7, **20**); HRMS (ES^{+}): 200.0930 [M + NH_4^+]; calc. for $C_6H_{15}FNO_5$ 200.0929; *m*/*z* (ES^{-}) 181 (29%, M – H^{+}), 59 (100). The data were in agreement with those reported by Schengrund and Kovac.[13]

* The α and β suffixes refer to the pyranose anomer to which the signal belongs. Signals from the furanose are too weak to be reported and assigned.

Deprotection with ammonium fluoride. A mixture of **17a** and **18a** (85.8 mg, 0.16 mmol) was suspended in a NH_4F (14.7 mL of 0.5M solution in methanol, 7.35 mmol) under an argon atmosphere and stirred for 2 days at room temperature. Silica gel (2.8 g) was then added and the resulting suspension was evaporated to dryness (until the silica was free flowing). The dry silica gel was then washed at the pump with a solution of CH_2Cl_2/MeOH (4:12, 50 mL) and the filtrate was concentrated to give the racemic galactose as a mixture of pyranose **19** and furanose **20** (14.3 mg, 49%) as a hygroscopic solid. The data were in agreement with those reported previously.

Racemic 6-deoxy-6-fluoro galactose (±)-19 and (±)-20 *via* temporary protection

Dihydroxylation/temporary protection. A solution of NMO (811 mg, 6.92 mmol) in water (1 mL) was added to a stirred solution of **6** (499 mg, 3.46 mmol) in acetone (4 mL) and ^{t}BuOH (4 mL) at room temperature. After stirring for 15 min, the mixture was cooled to 0 °C, and OsO_4 (1.05 mL, 0.01 mmol, 3 mol% of 2.5% solution in *t*-BuOH) was added dropwise over 5 minutes. The mixture was allowed to warm to room temperature and stirred vigorously overnight. The reaction mixture was quenched by the addition of solid sodium sulfite (5 g) and stirred for 30 min. The mixture was filtered through a pad of Celite and washed at the pump with a mixture of EtOAc–MeOH (1:1, 50 mL). The filtrate was concentrated *in vacuo* and the residue was dried *in vacuo* and taken up in dry pyridine (15 mL).

Chlorotrimethylsilane (2 mL, 15.57 mmol, 1.5 eq per OH group) was added to the stirred solution at 0 °C. After 15 h, pentane (200 mL) was added and the mixture was washed with cold water (6 × 30 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography on silica gel (0 to 10% gradient of ethyl acetate in hexane) to afford an inseparable mixture of lactones **15b** and **16b** (15:1 by ^{19}F NMR) (524 mg, 38% yield over two steps, 98% by GC/MS) as a colourless oil; R_f (4% ethyl acetate in hexane) 0.26; υ_{max} (neat)/cm^{-1} 2958–2850 w, 1800 m, 1251 s, 1138 s, 1066 ws, 837 s; δ_H (400 MHz, $CDCl_3$) 4.47 (part of an ABMX system, 1H, $^{2}J_{H-F}$ 46.4, *J* 9.4, *J* 5.0, H-6), 4.45 (part of an ABMX system, 1H, $^{2}J_{H-F}$ 46.4, *J* 9.4, *J* 6.6, H-6), 4.36-4.30 (m, 2H, H-2, H-3), 4.13-4.05 (m, 2H, H-4, H-5), 0.23, 0.18, 0.16 (s, 27H); δ_C (100 MHz, $CDCl_3$) 172.8, 83.8 (d, ^{1}JC-F 172.6), 80.1 (d, $^{3}J_{C-F}$ 8.0), 76.1, 74.5, 68.8 (d, $^{2}J_{C-F}$ 22.4), 0.4; δ_F (376 MHz, $CDCl_3$) –224.1 (td, $^{2}J_{F-H}$ 46.4, $^{3}J_{F-H}$ 12.2, **15b**), –225.7 (td, $^{2}J_{F-H}$ 46.4, $^{3}J_{F-H}$ 15.5, **16b**); HRMS (EI): 396.16190 [M^{+}] calc. for $C_{15}H_{33}FO_5Si_3$ 396.16199; *m*/*z* (EI) 396 (53%, M^{+}), 381 (25), 73 (100).

Reduction. A solution of DIBAL in toluene (0.81 mL of a 1.5M solution, 1.22 mmol) was added over 10 minutes to a solution of **15b** and **16b** (268 mg, 0.68 mmol) in dry toluene (10 mL) under an atmosphere of argon at –78 °C. The reaction was stirred for 20 minutes at –78 °C, then quenched by the dropwise addition of dry methanol (300 μL). The reaction was allowed to warm to about –20 °C (internal temperature), then poured into water (5 mL). The viscous solution was stirred vigorously for 10 minutes, after which time it formed two clear phases. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The original organic layer and combined extracts were dried ($MgSO_4$), evaporated and the mixture of **17b** and **18b** was taken on without purification.

Deprotection. The crude residue from the previous step was taken up in a mixture of THF, HCOOH and H_2O (5:0.5:1, 3 mL) and the solution was stirred 1 hour at room temperature. The mixture was evaporated to dryness *in vacuo*. For full characterisation, the residue was purified by chromatography on silica gel (0 to 20% gradient of MeOH in CH_2Cl_2) to afford an 11:1 mixture of (±)-**19** (anomer ratio α/β: 1:1.8) and (±)-**20** (71 mg, 58% over 2 steps) as a hygroscopic solid. The data were in agreement with those reported previously.

Methyl 4*S*,5*R*-dihydroxy-6-fluoro-4,5-*O*-isopropylidene-hex-2*E*-enoate 23 and methyl 2*S*,3*R*-dihydroxy-6-fluoro-2,3-*O*-isopropylidene-hex-4*E*-enoate 24: representative asymmetric dihydroxylation procedure

$(DHQ)_2PHAL$ (120 mg, 0.15 mmol, 2.1 mol%) and $K_2OsO_4{\cdot}2H_2O$ (54 mg, 0.15 mmol, 2 mol%) were added to a mixture of, $K_3Fe(CN)_6$ (7.24 g, 21.98 mmol), K_2CO_3 (3.04 g, 21.98 mmol), and $MeSO_2NH_2$ (697 mg, 7.33 mmol) in *t*-BuOH (26 mL) and water (26 mL), and the mixture was stirred at room temperature for about 15 minutes and then cooled to 0 °C. Dienoate **6** (1.06 g, 7.35 mmol) was added to this solution and the reaction was stirred vigorously at 0 °C for 24 h. The reaction was then quenched with solid sodium sulfite (11 g) at room temperature. Ethyl acetate (200 mL) was added to the reaction mixture, and (after separation of the layers) the aqueous phase was further extracted with ethyl acetate (2 × 100 mL). The combined original organic layer and extracts were dried ($MgSO_4$) and evaporated to dryness *in vacuo*.

The residue was taken up in DMF (73 mL) and 2-methoxypropene (2.8 mL, 29.3 mmol) and a few crystals of *p*-TsOH monohydrate (139 mg, 0.73 mmol) were added. The mixture was stirred 3 h at room temperature, then poured into Et_2O (300 mL) and washed with water (2 × 50 mL), then brine (50 mL). The organic phase was dried ($MgSO_4$), filtered, concentrated *in vacuo*, then purified by flash chromatography (silica gel, 2 to 10% gradient of ethyl acetate in hexane) to afford acetonide **23** (884 mg, 56% over 2 steps, 99% by GC/MS, 84% ee) as a colourless oil; $[\alpha]_D^{21}$ = +8.4 (c 1.0, $CHCl_3$); R_f (10% ethyl acetate in hexane) 0.28; υ_{max} (neat)/cm^{-1} 2989–2850 w, 1725 s, 1664 w, 1457 w, 1438 m, 1374 m, 1306 m, 1258 m, 1165 s, 1026 s; δ_H (300 MHz, $CDCl_3$) 6.90 (dd, 1H, *J* 15.5, *J* 5.8, H-3), 6.15 (dd, 1H, *J* 15.5, *J* 1.5, H-2), 4.58 (part of an ABMX system, 1H, $^{2}J_{H-F}$ 46.8, *J* 10.5, 3.5, H-6), 4.51 (m, 1H, H-4), 4.44 (part of an ABMX system, 1H, $^{2}J_{H-F}$ 46.8, *J* 10.5, 4.0, H-6), 3.96 (app. ddt, 1H, $^{3}J_{H-F}$ 20.7, *J* 8.4, 3.7, H-5), 3.75 (s, 3H, OCH_3), 1.45 (s, 3H, CH_3), 1.44 (s, 3H, CH_3); δ_C (75 MHz, $CDCl_3$) 166.2, 143.4, 122.8, 110.7, 81.1 (d, $^{1}J_{C-F}$ 174.7), 79.0 (d, $^{2}J_{C-F}$ 20.3), 75.8 (d, $^{3}J_{C-F}$ 7.2), 51.8, 26.7, 26.6; δ_F (282 MHz, $CDCl_3$) –231.1 (td, $^{2}J_{F-H}$ 46.4, $^{3}J_{F-H}$ 20.6); HRMS (EI): 217.08757

[M − H$^+$]: calc. for $C_{10}H_{14}FO_4$ 217.08761; *m/z* (EI) 217 (2%, M − H$^+$), 203 (14); 187 (2), 145 (11), 113 (79), 99 (91), 84 (100). HPLC: Chiralcel ODH column, 1% *i*-PrOH in hexane eluant, 1 mL/min flow rate, 254 nm detection; t_R (major) = 12.5 min; t_R (minor) = 8.4 min.

From a mixed column fraction, **24** was isolated and purified by preparative HPLC, eluting with 10% ethyl acetate in hexane; δ_H (400 MHz, $CDCl_3$) 6.05 (ttd, 1H, $^3J_{H\text{-}F}$ 15.3, *J* 15.3, *J* 5.0, 1.0, H-5), 5.95-5.88 (m, 1H, H-4), 4.91 (dddd, 2H, $^2J_{H\text{-}F}$ 46.5, *J* 5.0, *J* 1.4, *J* 0.8, H-6), 4.65-4.58 (m, 1H, H-3), 4.23 (d, 1H, *J* 7.7, H-2), 3.80 (s, 3H, OCH_3), 1.49 s, (3H, CH_3), 1.48 (s, 3 H, CH_3); δ_C (100 MHz, $CDCl_3$) 170.3, 129.5 (d, $^3J_{C\text{-}F}$ 11.7), 128.9 (d, $^2J_{C\text{-}F}$ 16.9), 111.5, 82.1 (d, $^2J_{C\text{-}F}$ 165.6), 79.0 (d, $^5J_{C\text{-}F}$ 1.9), 78.6, 52.6, 25.9, 26.9; δ_F (376 MHz, $CDCl_3$) −216.5 (tdt, $^2J_{F\text{-}H}$ 46.5, $^3J_{F\text{-}H}$ 15.3, $^4J_{F\text{-}H}$ 3.0, $^5J_{F\text{-}H}$ 3.0); HRMS (ES$^+$): 236.1290 [M + NH_4^+]; calcd for $C_{10}H_{19}FNO_4$: 236.1293; *m/z* (EI) 203 (16); 161 (24), 141 (70), 81 (58), 73 (100). This minor regioisomer was not characterised further and the enantiomeric purity was not determined.

Methyl 4*R*,5*S*-dihydroxy-6-fluoro-4,5-*O*-isopropylidene-hex-2*E*-enoate 25 and methyl 2*R*,3*S*-dihydroxy-6-fluoro-2,3-*O*-isopropylidene-hex-4*E*-enoate 26

From $(DHQD)_2PHAL$ (130 mg, 0.17 mmol, 2.1 mol%), $K_2OsO_4{\cdot}2H_2O$ (59 mg, 0.16 mmol, 2 mol%), $K_3Fe(CN)_6$ (7.88 g, 23.93 mmol), K_2CO_3 (3.31 g, 23.93 mmol), $MeSO_2NH_2$ (0.76 g, 7.97 mmol) and **6** (1.15 g, 7.97 mmol) in *t*-BuOH (30 mL) and water (30 mL), according to the previous procedure, work up and isolation.

The residue was protected in DMF (80 mL) containing 2-methoxypropene (3.0 mL, 31.88 mmol) and a few crystals of *p*-TsOH monohydrate (152 mg, 0.80 mmol) according to the previous procedure, work up and isolation. Flash chromatography (silica gel, 2 to 10% gradient of ethyl acetate in hexane) afforded acetonide **25** (783 mg, 44% over two steps, 94% by GC/MS, 92% ee) as a colourless oil; $[\alpha]_D^{24}$ = −8.7 (c 1.0, $CHCl_3$); HPLC: Chiralcel ODH, 1% *i*-PrOH in hexane, 1 mL/min, 254 nm; t_R (major) = 8.4 min; t_R (minor) = 12.5 min. The rest of the data were in agreement with those reported for **23**.

The presence of **26** was also detected in the ^{19}F NMR spectrum but the second regioisomer was not isolated in this case.

Methyl 6-fluoro-2*R*,3*R*,4*S*,5*R*-tetrahydroxy-4,5-*O*-isopropylidene-hexanoate 27 and methyl 6-fluoro-2*S*,3*S*,4*S*,5*R*-tetrahydroxy-4,5-*O*-isopropylidene-hexanoate 28

Mismatched asymmetric dihydroxylation affording 27. $(DHQ)_2PHAL$ (44 mg, 0.057 mmol, 2.1 mol%) and $K_2OsO_4{\cdot}2H_2O$ (20 mg, 0.054 mmol, 2 mol%) were added to a solution of $K_3Fe(CN)_6$ (2.69 g, 8.16 mmol), K_2CO_3 (1.13 g, 8.16 mmol), $MeSO_2NH_2$ (259 mg, 2.72 mmol) in *t*-BuOH (10 mL) and water (10 mL) and the mixture was stirred at room temperature for about 15 minutes and then cooled to 0 °C. Acetonide **23** (593 mg, 2.72 mmol) was added to this solution and the reaction was stirred vigorously at 0 °C for 24 h. The reaction was then quenched with solid sodium sulfite (5.5 g) at room temperature. Ethyl acetate (150 mL) was added to the reaction mixture, and (after separation of the layers) the aqueous phase was further extracted with ethyl acetate (2 × 50 mL). The original organic layer and the combined extracts were dried ($MgSO_4$) and evaporated to dryness *in vacuo*. The residue (a 2.1:1 mixture of diastereoisomers by $\{^1H\}^{19}F$ NMR) was purified by chromatography on silica gel (12 to 50% gradient of ethyl acetate in hexane) to afford diol **27** (213 mg, 31%) $[\alpha]_D^{18}$ = −21.6 (c 1.0, $CHCl_3$); R_f (50% ethyl acetate in hexane) 0.28; υ_{max} (neat)/cm^{-1} 3461br, 2989–2957 w, 1740 s, 1440, 1374, 1214 s, 1167 m, 1102 s, 1048 s; δ_H (400 MHz, $CDCl_3$) 4.60 (part of an ABMX system, 1H, $^2J_{H\text{-}F}$ 47.2, *J* 10.2, 3.5, H-6), 4.52 (part of an ABMX system, 1H, $^2J_{H\text{-}F}$ 47.2, *J* 10.2, 4.1, H-6), 4.31 (d, 1H, *J* 2.6, H-2), 4.28 (app. ddt, 1H, *J* 20.6, 8.0, 3.8 H-5), 4.16 (dd, 1H, *J* 8.0, 3.5, H-4), 3.95 (app. t, 1H, *J* 3.0, H-3), 3.84 (s, 3H, OCH_3), 1.45 (s, 3H, CH_3), 1.44 (s, 3H, CH_3); δ_C (100 MHz, $CDCl_3$) 172.7, 110.5, 82.0 (d, $^1J_{C\text{-}F}$ 172.6), 77.1 (d, $^3J_{C\text{-}F}$ 4.8), 76.1 (d, $^2J_{C\text{-}F}$ 19.2), 71.7, 70.8, 52.9, 26.8; δ_F (376 MHz, $CDCl_3$) −229.7 (td, $^2J_{F\text{-}H}$ 47.2, $^3J_{F\text{-}H}$ 20.6); HRMS (EI): 253.10869 [M + H$^+$]; calc. for $C_{10}H_{18}FO_6$ 253.10874; *m/z* (EI) 253 (1%, M + H$^+$), 237 (75), 221 (17), 193 (24), 177 (64), 163 (72), 133 (81), 59 (100). and **28** (206 mg, 30%); the data for diastereoisomer **28** are reported in the next experiment.

Matched asymmetric dihydroxylation affording 28. From $(DHQD)_2PHAL$ (39 mg, 0.05 mmol, 2.1 mol%), $K_2OsO_4{\cdot}2H_2O$ (17.5 mg, 0.047 mmol, 2 mol%), $K_3Fe(CN)_6$ (2.36 g, 7.15 mmol), K_2CO_3 (989 mg, 7.15 mmol), $MeSO_2NH_2$ (227 mg, 2.38 mmol), and acetonide **23** (520 mg, 2.38 mmol) in *t*-BuOH (8.5 mL) and water (8.5 mL), according to the previous procedure, work up and isolation. The residue was purified by chromatography on silica gel (12 to 50% gradient of ethyl acetate in hexane) to afford diols **27** and **28** (385 mg, 64%, 1:14.5 by ^{19}F NMR, 99% by GC/MS): for **28**; $[\alpha]_D^{18}$ = +13.3 (c 1.0, $CHCl_3$); mp 56–57 °C; found: C, 47.69; H, 6.89; $C_{10}H_{17}FO_6$ requires: C, 47.62; H, 6.79%; R_f (50% ethyl acetate in hexane) 0.34; υ_{max} (neat)/cm^{-1} 3286br, 2986–2949 w, 1748 s, 1458 w, 1379 m, 1371 m, 1252 m, 1207 m, 1136 m, 1105 s, 1048 s; δ_H (400 MHz, $CDCl_3$) 4.66 (ABMX system, 1H, $^2J_{H\text{-}F}$ 47.2, *J* 9.9, 2.6, H-6), 4.52 (part of an ABMX system, 1H, $^2J_{H\text{-}F}$ 47.2, *J* 9.9, 4.7, H-6), 4.48 (d, 1H, *J* 1.2, H-2), 4.33-4.17 (m, 1H, H-5), 4.04-3.95 (m, 2H, H-3, H-4), 3.85 (s, 3H, OCH_3), 1.44 (s, 3H, CH_3), 1.43 (s, 3H, CH_3); δ_C (100 MHz, $CDCl_3$) 173.6, 110.2, 83.1 (d, $^1J_{C\text{-}F}$ 172.6), 79.1 (d, $^2J_{C\text{-}F}$ 17.6), 74.8 (d, $^3J_{C\text{-}F}$ 6.4), 73.8, 70.7, 53.0, 27.1, 26.8; δ_F (376 MHz, $CDCl_3$) −228.9 (td, $^2J_{F\text{-}H}$ 47.2, $^3J_{F\text{-}H}$ 22.1); HRMS (EI): 253.10878 [M + H$^+$]; calc. for $C_{10}H_{18}FO_6$ 253.10874; *m/z* (EI) 253 (2%, M + H$^+$), 237 (71), 219 (64), 195 (47), 177 (63), 163 (65), 133 (79), 59 (100). The data for minor diastereoisomer **27** were reported in the previous experiment.

Methyl 6-fluoro-2*S*,3*S*,4*R*,5*S*-tetrahydroxy-4,5-*O*-isopropylidene-hexanoate 29 and methyl 6-fluoro-2*R*,3*R*,4*R*,5*S*-tetrahydroxy-4,5-*O*-isopropylidene-hexanoate 30

Mismatched asymmetric dihydroxylation affording 29. From $(DHQ)_2PHAL$ (34.2 mg, 0.044 mmol, 2.1 mol%), $K_2OsO_4{\cdot}2H_2O$ (15.4 mg, 0.042 mmol, 2 mol%), $K_3Fe(CN)_6$ (2.07 g, 6.28 mmol), K_2CO_3 (868 mg, 6.28 mmol), $MeSO_2NH_2$ (199 mg, 2.09 mmol) and acetonide **25** (456 mg, 2.09 mmol) in *t*-BuOH (11.5 mL) and water (11.5 mL), according to the previous procedure, work up and isolation. The residue (a 2.1:1 mixture of diastereoisomers by $\{^1H\}^{19}F$ NMR) was purified by flash column chromatography on silica gel (12 to 50% gradient of ethyl acetate in hexane) afforded diol **29** (275 mg, 52%, 90% by GC/MS), $[\alpha]_D^{18}$ = +21.8 (c 1.0, $CHCl_3$) as a colourless oil and diol **30** (131 mg, 25%, 99% by

GC/MS) as a colourless solid. The rest of the data for **29** and **30** were in agreement with those reported for **27** and **28** respectively.

Matched asymmetric dihydroxylation affording 30. From $(DHQD)_2PHAL$ (24 mg, 0.030 mmol, 2.1 mol%; 130 mg, 0.17 mmol, 2.1 mol%), $K_2OsO_4{\cdot}2H_2O$ (11 mg, 0.029 mmol, 2 mol%; 59 mg, 0.16 mmol, 2 mol%), $K_3Fe(CN)_6$ (1.42 g, 4.32 mmol; 7.88 g, 23.93 mmol), K_2CO_3 (597 mg, 4.32 mmol; 3.31 g, 23.93 mmol), $MeSO_2NH_2$ (137 mg, 1.44 mmol; 0.76 g, 7.97 mmol) and acetonide **25** (476 mg, 2.18 mmol) in *t*-BuOH (5 mL; 30 mL) and water (5 mL; 30 mL), according to the previous procedure, work up and isolation.

The residue (a 48:1 mixture of diastereoisomers by $\{^1H\}^{19}F$ NMR) was purified by flash column chromatography on silica gel (12 to 50% gradient of ethyl acetate in hexane) to afford diol **30** (285 mg, 52%) as a colourless solid; $[\alpha]_D^{18} = -13.3$ (c 1.0, $CHCl_3$). The rest of the data were in agreement with those reported for **28**.

6-Deoxy-6-fluoro-L-idose 31

Four-step deprotection/reduction procedure. Hydrochloric acid (675 μL of a 3M aqueous solution, 2.02 mmol) was added to a stirred solution of diol **27** (170 mg, 0.67 mmol) in MeOH (2.5 mL) at room temperature and the mixture was stirred for 1 day at that temperature. The MeOH was removed *in vacuo* and the residue was washed through a pad of Celite mixed with silica gel, with a mixture of ethyl acetate and MeOH (7:3, 15 mL). The solvent was removed *in vacuo* and the residue was dried under vacuum overnight. the residue was taken up in *N*-methyl-*N*-(trimethylsilyl)-trifluoroacetamide (525 μL, 2.83 mmol, 1.4 eq. per OH group) was added and the mixture was heated to 60 °C and stirred vigorously for 1 hour, then dried for 24 h *in vacuo*.

A solution of the residue in dry toluene (6.7 mL) was cooled under an atmosphere of argon to −78 °C. DIBAL-H (0.9 mL of a 1.5M solution in toluene, 1.76 mmol) was added very slowly and the reaction was stirred for 30 minutes at −78 °C, then quenched by the dropwise addition of methanol (250 μL). The reaction was allowed to warm to about −20 °C (internal temperature) and then water (4.5 mL) was added. The viscous solution was stirred vigorously for 30 minutes, after which two clear phases formed. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The original organic layer and combined extracts were dried ($MgSO_4$), evaporated *in vacuo* and purified by flash chromatography on silica gel (2 to 10% gradient of ethyl acetate in hexane) to afford a colourless oil (89 mg, 33% over 3 steps, 90% by GC/MS); R_f (10% ethyl acetate in hexane) 0.4; the two anomers are separable in GC-MS: *m/z* (EI): 217 (15%), 173 (19%), 147 (12%), 145 (12%), 145 (22%), 129 (15%), 77 (30%), 75 (80%), 73 (100%) and 217 (13%), 147 (15%), 129 (13%), 77 (20%), 75 (38%), 73 (100%).

The oil (89 mg, 0.226 mmol) was taken up in a mixture of THF, HCOOH and H_2O (3:0.2:1, 2.5 mL) and the solution was stirred 1 hour at room temperature. The solvents were removed *in vacuo* and the residue was purified by chromatography on silica gel (0 to 15% of MeOH in CH_2Cl_2) to give 6-deoxy-6-fluoro-L-idose **31** (30 mg, 25% over 4 steps) as a white hydroscopic solid. By ^1H NMR, the product is a 2.6:1 mixture of pyranoses and furanoses; the anomeric ratio of pyranoses is α:β = 1.6:1 and the anomeric ratio of furanoses is α:β = 1:1.5.

For **31**: $[\alpha]_D^{18} = -6.0$ (c 0.5, H_2O); R_f (20% MeOH in CH_2Cl_2) 0.34; υ_{max} (neat)/cm^{-1} 3337br, 2494br, 1408 m, 1355 m, 1254 m, 1147 m, 1072 s, 1025 s, 998 s, 784m; δ_H (300 MHz, D_2O) 5.48 (d, 1H, *J* 4.3, H-1β furanose), 5.27 (d, 1H, *J* 1.2, H-1α furanose), 5.15 (d, 1H, *J* 1.6, H-1β pyranose), 5.07 (dd, 1H, *J* 6.6, 1.6, H-1α pyranose), 4.99-4.46 (m, 8H, H-6), 4.38-4.09 (m, 11H,H-2, H-3, H-4, H-5 α and β furanose, H-5α, H-3β, H-5β pyranoses), 3.91 (dd, 1H, *J* 8.3, 5.8, H-4α pyranose), 3.79 (td, 1H, *J* 8.3, 1.7, H-3α pyranose), 3.76-3.73 (m, 2H, H-2β, H-4β, pyranoses), 3.40 (m, 1H, H-2α, pyranoses); δ_C (100 MHz, D_2O) 101.8, 95.6 93.9 (d, $^4J_{C\text{-}F}$ 3.4), 92.4, 84.8 (d, $^1J_{C\text{-}F}$ 165.7), 84.7 (d, $^1J_{C\text{-}F}$ 166.0), 83.7 (d, $^1J_{C\text{-}F}$ 164.5), 83.2 (d, $^1J_{C\text{-}F}$ 167.0), 80.7, 80.6 (d, $^3J_{C\text{-}F}$ 8.1), 77.2 (d, $^3J_{C\text{-}F}$ 7.6), 76.0, 74.9, 74.7, 73.3, 73.2 (d, $^2J_{C\text{-}F}$ 19.8), 72.5 (d, $^4J_{C\text{-}F}$ 3.4), 72.1 (d, $^2J_{C\text{-}F}$ 18.0) 69.9 (d, $^2J_{C\text{-}F}$ 4.0), 69.8, 69.6, 69.5 (d, $^2J_{C\text{-}F}$ 18.3), 68.5 (d, $^2J_{C\text{-}F}$ 18.8), 67.7 (d, $^3J_{C\text{-}F}$ 7.5); δ_F (282 MHz, D_2O) −225.4 (td, $^2J_{F\text{-}H}$ 47.3, $^3J_{F\text{-}H}$ 31.6), (−228.3)-(−229.0) (m), −230.34 (td, $^2J_{F\text{-}H}$ 47.2, $^3J_{F\text{-}H}$ 20.8), −231.9 (td, $^2J_{F\text{-}H}$ 47.2, $^3J_{F\text{-}H}$ 24.8); HRMS (FAB^-): 181.05116 [M − H^+]; calc. for $C_6H_{10}FO_5$ 181.05123; *m/z* (FAB^-) 181 (73%, M − H^+), 168 (100), 122 (94).

*The α and β suffixes refer to the anomer to which the signal belongs.

6-Fluoro-2,3,5-tri-*O*-trimethylsilyl-L-fucofuranose 32

Three-step preparation from 28. From diol **28** (220 mg, 0.87 mmol), hydrochloric acid (873 μL of a 3M aqueous solution, 2.62 mmol) and MeOH (4 mL) according to the previous procedure, work up and isolation. The residue was taken up in *N*-methyl-*N*-(trimethylsilyl)-trifluoroacetamide (558 μL, 3.0 mmol, 1.15 eq. per OH group) and treated according to the previous procedure, work up and isolation. The residue was reduced in dry toluene (8.7 mL) with DIBAl-H (1.16 mL of a 1.5M solution in toluene, 1.76 mmol) quenched with methanol (400 μL) according to the previous procedure, work up and isolation. Flash chromatography of the residue on silica gel (3 to 10% gradient of ethyl acetate in hexane) afforded protected lactol **32** as a 1:1 mixture of anomers (by ^{19}F NMR) (133 mg, 38% over 3 steps, 92% by GC/MS,) as a colourless oil, R_f (10% ethyl acetate in hexane) 0.30; υ_{max} (neat)/cm^{-1} 3498w, 2959–2906 w, 1400 w, 1250 s, 1115 m, 964 s, 876 s, 837 s; δ_H (300 MHz, $CDCl_3$) 5.10 (dd, 1H, *J* 11.1, 4.1, H-1α), 5.06 (d, 1H, *J* 9.6, H-1β), 4.57-4.17 (m, 4H, H-6, α and β anomers), 4.13-3.78 (m, 8H, H-2, H-3, H-4, H-5, α and β anomers), 3.62 (d, 1H, *J* 11.1, OH α), 3.59 (d, 1H, *J* 9.6, OHβ), 0.22-0.12 (m, 54H, OTMS); δ_C (75 MHz, $CDCl_3$) 102.9, 96.7, 87.0 (d, $^3J_{C\text{-}F}$ 7.5), 84.9 (d, $^1J_{C\text{-}F}$ 168.7), 84.5 (d, $^1J_{C\text{-}F}$ 169.8), 83.6 (d, $^3J_{C\text{-}F}$ 7.2), 80.9, 79.3, 76.9 (d, $^4J_{C\text{-}F}$ 1.1), 76.8 (d, $^4J_{C\text{-}F}$ 1.7), 70.8 (d, $^2J_{C\text{-}F}$ 19.6), 70.6 (d, $^2J_{C\text{-}F}$ 19.4), 0.2, 0.0 (2 signals), −0.1, −0.2, −0.3; δ_F (282 MHz, $CDCl_3$) −224.9 (td, $^2J_{F\text{-}H}$ 47.4, $^3J_{F\text{-}H}$ 14.9), −225.7 (td, $^2J_{F\text{-}H}$ 47.8, $^3J_{F\text{-}H}$ 19.2); HRMS (EI): 398.17766 [M^+]; calc. for $C_{15}H_{35}FO_5Si_3$ 398.17764; *m/z* (EI) 398 (1%, M^+), 383 (1), 233 (4), 217 (44), 145 (75), 73 (100).

6-Fluoro-L-fucose 33

From **32** (100 mg, 0.25 mmol) in THF, HCOOH and H_2O (3:0.2:1, 3 mL) according to the previous procedure, work up and isolation; 6-fluoro-α,β-L-fucose **33** (46 mg, 38% over 4 steps) was obtained as a white hygroscopic solid. By ^1H NMR, the product is a 10.9:1 mixture of pyranoses and furanoses; the anomeric ratio

of pyranoses is α:β = 1:1.8 and the anomeric ratio of furanoses is α:β = 1:1.5.

For **33**: $[\alpha]_D^{18} = -65.9$ (c 0.5, H_2O); R_f (20% MeOH in CH_2Cl_2) 0.29; υ_{max} (neat)/cm^{-1} 3333br, 2494br, 1408 m, 1353 m, 1254 m, 1147 m, 1071 s, 1025 s, 999 s, 783m; δ_H (400 MHz, D_2O) 5.34 (d, 1H, *J* 3.7, H-1α), 4.82-4.50 (m, 4H, H-6α, H-6β), 4.66 (d, 1H, *J* 7.8, H-1β), 4.41 (ddd, 1H, $^3J_{H\text{-}F}$ 16.6, *J* 7.2, *J* 3.8, H-5α), 4.09 (dd, 1H, *J* 3.2, *J* 0.9, H-4α), 4.08-3.98 (m, 1H, H-5β), 4.02 (d, 1H, *J* 3.7, H-4β), 3.92 (dd, 1H, *J* 10.3, *J* 3.2, H-3α), 3.86 (dd, 1H, *J* 10.3, *J* 3.7, H-2α), 3.71 (dd, 1H, *J* 9.9, *J* 3.5, H-3β), 3.55 (dd, 1H, *J* 9.9, *J* 7.9, H-2β); δ_C (100 MHz, D_2O) 96.4, 92.4, 83.5 (d, $^1J_{C\text{-}F}$ 164.6), 83.2 (d, $^1J_{C\text{-}F}$ 166.2), 73.4 (d, $^2J_{C\text{-}F}$ 20.8), 72.5, 71.7, 69.0 (d, $^3J_{C\text{-}F}$ 7.9), 69.0 (d, $^2J_{C\text{-}F}$ 22.4), 68.9, 68.4 (d, $^3J_{C\text{-}F}$ 8.0), 68.2; δ_F (376 MHz, D_2O) –229.2 (td, $^2J_{F\text{-}H}$ 47.3, $^3J_{F\text{-}H}$ 19.1, furanose), –229.6 (ddd, $^2J_{F\text{-}H}$ 48.1, $^2J_{F\text{-}H}$ 45.6, $^3J_{F\text{-}H}$ 15.5, pyranose β anomer), –229.7 (ddd, $^2J_{F\text{-}H}$ 48.1, $^2J_{F\text{-}H}$ 45.6, $^3J_{F\text{-}H}$ 16.6, pyranose α anomer), –230.7 (td, $^2J_{F\text{-}H}$ 47.0, $^3J_{F\text{-}H}$ 20.7, furanose); HRMS (ES^+): 200.0929 [M + NH_4^+]; calc. for $C_6H_{15}FNO_5$ 200.0929.

*The α and β suffixes refer to the anomer to which the signal belongs. Signals from the furanose are too weak to be reported and assigned.

Methyl 6-fluoro-2*S*,3*R*,4*R*,5*S*-2,3:4,5-bis(isopropylidene) hexanoate 34

From diol **29** (256 mg, 1.01 mmol), 2-methoxypropene (390 μL, 4.06 mmol), *p*-TsOH monohydrate (19 mg, 0.1 mmol) in DMF (10 mL) according to the previous procedure, work up and isolation.

Flash chromatography (silica gel, 0 to 10% gradient of ethyl acetate in hexane) to afford bis-acetonide **34** (213 mg, 72%, 99% by GC/MS) as a colourless oil; $[\alpha]_D^{18} = +21.4$ (c 1.0, $CHCl_3$); R_f (10% ethyl acetate in hexane) 0.17; υ_{max} (neat)/cm^{-1} 2990–2840 w, 1762 s, 1456 w, 1439w, 1382 m, 1372 m, 1249 m, 1209 s, 1165 s; δ_H (400 MHz, $CDCl_3$) 4.61 (d, 1H, *J* 7.6, H-2), 4.59 (part of an ABMX system, 1H, $^2J_{H\text{-}F}$ 47.2, *J* 10.2, 4.0, H-6), 4.54 (part of an ABMX system, 1H, $^2J_{H\text{-}F}$ 47.2, *J* 10.2, 4.0, H-6), 4.34 (ddt, 1H, $^3J_{H\text{-}F}$ 20.4, *J* 8.2, 4.0, H-5), 4.23 (dd, 1H, *J* 7.6, 3.2, H-3), 4.15 (dd, 1H, *J* 8.2, 3.2, H-4), 3.82 (s, 3H, OCH_3), 1.49 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.45 (s, 6H, CH_3); δ_C (100 MHz, $CDCl_3$) 170.8, 111.7, 110.4, 82.1 (d, $^1J_{C\text{-}F}$ 172.6), 77.5, 75.8 (d, $^3J_{C\text{-}F}$ 6.4), 75.6 (d, $^2J_{C\text{-}F}$ 20.8), 75.4, 52.6, 27.0, 26.7, 26.5, 26.0; δ_F (282 MHz, $CDCl_3$) –230.2 (td, $^2J_{F\text{-}H}$ 47.4, $^3J_{F\text{-}H}$ 20.0); HRMS (EI): 293.14010 [M + H^+]; calc. for $C_{13}H_{22}FO_6$ 293.14004; *m/z* (EI) 293 (1%, M + H^+), 277 (62), 159 (57), 133 (52), 59 (100). This product was not progressed to sugar **35**.

6-Deoxy-6-fluoro-2,3,5-tri-*O*-trimethylsilyl-D-galactofuranose 36

From hydrochloric acid (790 μL of a 3M aqueous solution, 2.36 mmol), diol **30** (198 mg, 0.79 mmol 220 mg, 0.87 mmol) in MeOH (2.6 mL 4 mL) according to the previous procedure, work up and isolation.

The residue was silylated with *N*-methyl-*N*-(trimethylsilyl)-trifluoroacetamide (502 μL, 2.7 mmol, 558 μL, 3.0 mmol, 1.15 eq. per OH group) according to the previous procedure, work up and isolation.

The reduction was effected in dry toluene (8.7 mL) with DIBAL-H (1.05 mL of a 1.5M solution, 1.57 mmol 1.16 mL of a 1.5M solution in toluene, 1.76 mmol) and quenched with methanol (300 μL 400 μL) according to the previous procedure, work up and isolation. Flash chromatography on silica gel (3 to 10% gradient of ethyl acetate in hexane) afforded **36** (117 mg, 37%) as a colourless oil (ratio α/β = 1/1.3 by ^1H NMR) (93% by GC/MS). The rest of the data were in agreement with those reported for **32**.

6-Deoxy-6-fluoro-D-galactopyranose 37

A solution of lactol **36** (100 mg, 0.25 mmol) in a mixture of THF, HCOOH and H_2O (3:0.2:1, 2 mL) was stirred for 1 hour at room temperature. The solvents were removed under reduced pressure and 6-deoxy-6-fluoro-D-galactose **37** (45 mg, *ca.* 100%) was obtained as a white hygroscopic solid. $[\alpha]_D^{18} = +64.0$ (c 0.5, H_2O). The rest of the data (including the furanose:pyranose and anomer ratios) were in agreement with those reported for **33**.

2,3,6-Trideoxy-6-fluoro-D-galactono-1,4-lactone 38

A solution of **25** (178 mg, 0.82 mmol) in absolute EtOH (15 mL) containing palladium-on-carbon (10% w/w, 72 mg) was stirred vigorously overnight at room temperature under an atmosphere of hydrogen (1 bar). The suspension was then filtered through a pad of Celite™ and the filtrate was concentrated to a colourless oil. The residue was taken up in MeOH (2.4 mL) and HCl (0.8 mL of a 3 M aqueous solution, 2.45 mmol) was added. The resulting solution was stirred overnight, then concentrated *in vacuo*. The residue was purified by chromatography on silica gel (60% ethyl acetate in hexane) to afford lactone **38** (94 mg, 77% over two steps, 99% by GC/MS) (CAUTION: the lactone is volatile) as a colourless oil; $[\alpha]_D^{23} = -48.5$ (c 1.0, $CHCl_3$); R_f (60% ethyl acetate in hexane) 0.27; υ_{max} (neat)/cm^{-1} 3421br, 2961–2920 w, 1755 s, 1462 w, 1419 w, 1189 s; δ_H (400 MHz, $CDCl_3$) 4.63 (ddd, 1H, *J* 7.5, 6.9, 3.3, H-4), 4.52 (part of an ABMX system, 1H, $^2J_{H\text{-}F}$ 47.0, *J* 9.7, 5.6, H-6), 4.51 (part of an ABMX system, 1H, $^2J_{H\text{-}F}$ 47.0, *J* 9.7, 5.6, H-6), 3.90 (dtd, 1H, $^3J_{H\text{-}F}$ 15.1, *J* 5.6, 3.3, H-5), 3.16 (br, 1H, OH), 2.62 (part of an ABMN system, 1H, *J* 17.8, 9.8, 6.0, H-2), 2.53 (part of an ABMN system, 1H, *J* 17.8, 9.6, 8.2, H-2), 2.37-2.20 (2H, m, H-3); δ_C (100 MHz, $CDCl_3$) 177.8, 83.4 (d, $^1J_{C\text{-}F}$ 169.5), 79.3 (d, $^3J_{C\text{-}F}$ 5.8), 71.6 (d, $^2J_{C\text{-}F}$ 21.0), 28.3, 23.5; δ_F (376 MHz, $CDCl_3$) –223.0 (td, $^2J_{F\text{-}H}$ 47.0, $^3J_{F\text{-}H}$ 15.1); HRMS (EI): 147.04578 [M – H^+]; calc. for $C_6H_8FO_3$ 147.04575; *m/z* (EI) 147 (1%, M – H^+), 128 (7), 115 (73), 97 (12), 85 (100).

6-Fluoro-D-rhodinose (2,3,6-trideoxy-6-fluoro-D-galactose) 39 and 40

From lactone **38** (31 mg, 0.21 mmol) in dry toluene (2 mL), and DIBAL-H (276 μL of a 1.5M solution in toluene, 0.42 mmol) according to the previous procedure, work up and isolation. Flash chromatography on silica gel (60 to 90% gradient of ethyl acetate in hexane) afforded 6-fluoro-D-rhodinose (16 mg, 51%). By ^1H NMR, the product is a 1:1:1 mixture of furanoses **39** and pyranoses **40**; the anomeric ratio of pyranoses is α:β = 1:1.4 and the anomeric ratio of furanoses is α:β = 1:1.1.

R_f (90% ethyl acetate in hexane) 0.36; υ_{max} (neat)/cm^{-1} 3362br, 2956w, 1443w, 1256w, 1199 m, 1111 m, 1000s; δ_H (500 MHz, D_2O) 5.59 (dd, 1H, *J* 2.1, 4.2, H-1), 5.53 (d, 1H, *J* 4.3, H-1), 5.37 (br s, 1H, H-1α), 4.91 (dd, 1H, *J* 2.6, 9.5, H-1β, pyranose), 4.74-4.42 (m, 12H, H-6), 4.36-4.26 (m, 2H, H-5α pyranose, H-4), 4.15 (m, 1H,

H-4), 3.99 (dddd, 1H, $^{3}J_{H\text{-}F}$ 16.4, J 7.4, 3.7, 1.3, H-5β), 3.97-3.94 (m, 1H, H-4α), 3.94-3.82 (m, 3H, H-4β, H-5, H-5), 2.29-1.51 (m, 12H, H-2 and H-3); δ_C (100 MHz, D_2O) 98.6, 97.8, 95.8, 90.9, 85.0 (d, $^{1}J_{C\text{-}F}$ 164.6), 84.9 (d, $^{1}J_{C\text{-}F}$ 166.2), 84.5 (d, $^{1}J_{C\text{-}F}$ 164.6), 83.9 (d, $^{1}J_{C\text{-}F}$ 164.6), 79.9 (d, $^{3}J_{C\text{-}F}$ 8.0), 77.7 (d, $^{3}J_{C\text{-}F}$ 8.0), 76.6 (d, $^{2}J_{C\text{-}F}$ 19.2), 72.8 (d, $^{2}J_{C\text{-}F}$ 17.6), 71.7 (d, $^{2}J_{C\text{-}F}$ 19.2), 69.3 (d, $^{2}J_{C\text{-}F}$ 19.2), 63.8 (d, $^{3}J_{C\text{-}F}$ 8.0), 62.9 (d, $^{3}J_{C\text{-}F}$ 8.0), 33.3, 32.5, 28.6, 26.3, 25.2, 24.6, 23.8, 23.4; δ_F (376 MHz, D_2O) –229.8 (td, $^{2}J_{F\text{-}H}$ 47.8, $^{3}J_{F\text{-}H}$ 20.2), –229.9 (td, $^{2}J_{F\text{-}H}$ 46.0, $^{3}J_{F\text{-}H}$ 16.5), –230.48 (td, $^{2}J_{F\text{-}H}$ 47.8, $^{3}J_{F\text{-}H}$ 18.4), –231.5 (td, $^{2}J_{F\text{-}H}$ 46.0, $^{3}J_{F\text{-}H}$ 22.1); HRMS (ES^+): 168.1031 [M + NH_4^+]; calc. for $C_6H_{15}FNO_3$ 168.1030; m/z (ES^-) 149 (100%, M – H^+), 129 (21).

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