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A Convenient Strategy for Replacement of the Anomeric Hydroxyl Group by Difluoromethyl Functionality in Carbohydrate Derivatives†

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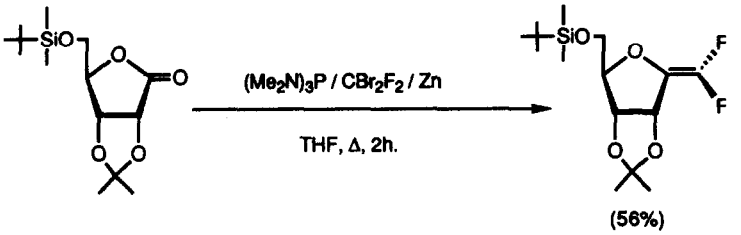
Abstract: *A series of carbohydrate gem-difluoroenol ethers are readily prepared by the reaction of the corresponding lactones with dibromodifluoromethane, tris(dimethylamino)phosphine and zinc. Subsequent catalytic hydrogenation provides difluoromethyl C-glycoside analogues in which the exocyclic oxygen atom has been replaced by a difluoromethylene unit.*

The enhancement of biological activity in many natural product classes by the selective introduction of one or more fluorine atoms is a proven cornerstone strategy of the medicinal and bioorganic chemist.[1,2] We were intrigued, however, by the possibility in C-glycoside chemistry that site specific replacement of an oxygen atom possessing stereochemically significant lone pairs by the larger difluoromethylene unit would provide compounds which retained hydrogen bonding potential. Although such an approach is not often considered, this principle has been exemplified recently in the case of difluoromethylene diphosphonic acids and related congeners as analogues of biological phosphoryl species.[3] We now report, in full detail, on the implementation of this transposition with particular reference to regiospecific replacement of the anomeric hydroxyl group in carbohydrates by the difluoromethyl moiety.[4]

The Difluoromethylenation of Carbohydrate Lactones

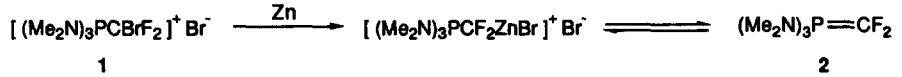
It was envisaged that a *gem*-difluoroenol ether would be an excellent starting point for the investigation of these and other fluorinated carbohydrate systems, as methyl-1-ene sugars are versatile intermediates in C-glycoside synthesis.[5] An added incentive for this approach was that, with the single exception of a report describing the photochemistry of a difluoroenol ether prepared from a formate ester,[6] the preparation and chemistry of this particular functional array had been little studied. To this end, a strategy was developed for the conversion of readily available sugar lactones to their difluoromethyl-1-ene derivatives.[4] In the event, we chose to adapt Burton's dibromodifluoromethane/tris(dimethylamino)phosphine (HMPT) ylid chemistry,[7] which has proven utility in the difluoromethylenation of relatively unreactive carbonyl compounds, as exemplified by the conversion shown in **Scheme 1.**

†Dedicated with admiration, respect and affection to Professor Sir Derek Barton on the occasion of his 75th birthday.



Scheme 1

The necessity for using the reactive HMPT based approach was borne out by the lack of success encountered in our attempts at difluoromethylenation with triphenylphosphine. A comparable procedure was employed by Chapleur in his dichloromethylenation of sugar lactones and acetates, although in addition to HMPT[8] triphenylphosphine has also proved to be effective.[9] From a practical point of view it is to be noted that THF can be substituted to great effect for the more usual high boiling glymes and amide solvents. In the case of carbohydrates this obviated problems associated with product isolation and the maintenance of rigorously anhydrous conditions. As originally reported, the reaction was performed using five equivalents each of dibromodifluoromethane, HMPT and zinc dust.[4] However, on extensive application of this procedure, we have found that the yields can be variable. We considered intuitively that problems of irreproducibility might well lie in the use of a heterogeneous system employing zinc, and this hypothesis, when taken in conjunction with the consideration of possible reaction pathways, eventually provided an experimentally convenient solution. Thus it has been shown in closely related systems that the initially formed phosphonium salt, such as (1), could be reduced by zinc to give an equilibrium mixture of zinc complexes and the ylid (2), which either then reacts with the sugar lactone or undergoes decomposition (**Scheme 2**).[10] The latter process may well be responsible for the required excess of fluorinating reagent and the dramatic darkening of colour that characterises this reaction.



1 2

Scheme 2

However, it is also known that debromination of the salt (1) can be effected, in the absence of zinc, by the addition of an equivalent of HMPT to give the ylid[7] and tris(dimethlyamino)phosphine dibromide. The toxicity of HMPT and its oxide (HMPA: CAUTION) generally make zinc the more practicable choice. We reasoned, however, that if the reaction of salt (1) with HMPT and reduction of the resultant tris(dimethylamino)phosphine dibromide by zinc were both more efficient than the direct zinc induced debromination of the salt, then HMPT could serve as the catalyst in this system.

In terms of experimental protocol the new procedure (Method B) was initially the same as previously reported (Method A),[4] with the phosphonium salt/sugar/THF mixture then being stirred vigorously at room temperature under a steady stream of argon for 30 minutes in order to evaporate all the excess dibromodifluoromethane, so that further phosphonium salt could not be formed on the addition of the excess phosphine. The zinc and 10 mol% phosphine were added, and the mixture heated to reflux. It was found that

the difluoroenol ethers were formed in generally improved yields. Method B is now used as the method of choice for the difluoromethylenation of all sugar lactones; it has proved to be considerably more reliable than the previous protocol, thereby lending tacit support to the idea that the phosphine is important in catalysis of the debromination step with zinc involved more crucially in the regeneration of phosphine. A comparison of the two methods is given in **Table 1** for a selection of typically protected carbohydrate lactones.

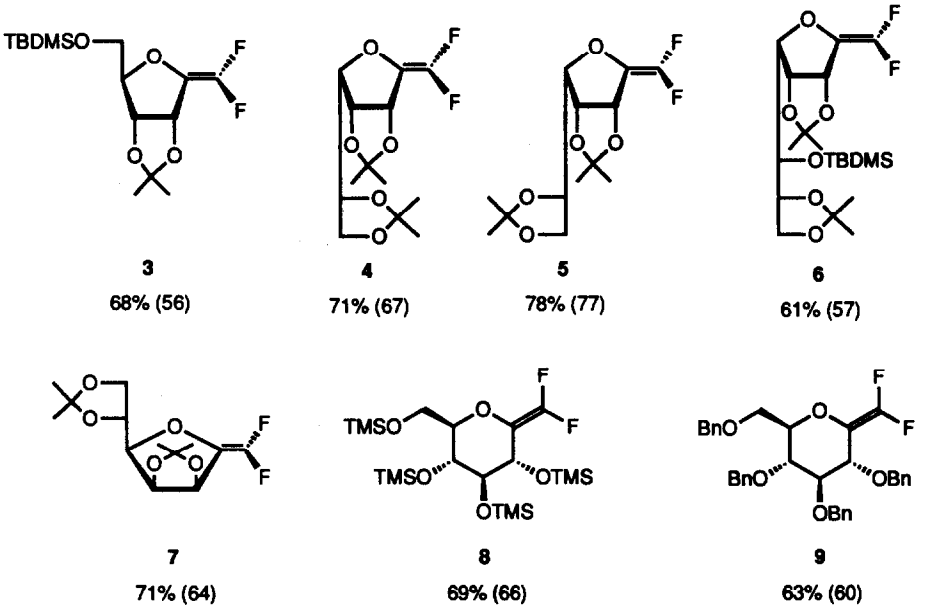
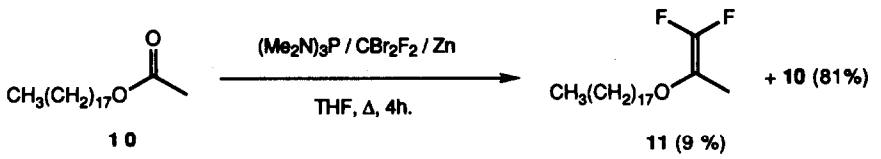


Table 1 *Difluoroenol Ethers from Carbohydrate Lactones*
(Yields are given for Method B with those for Method A in parentheses)

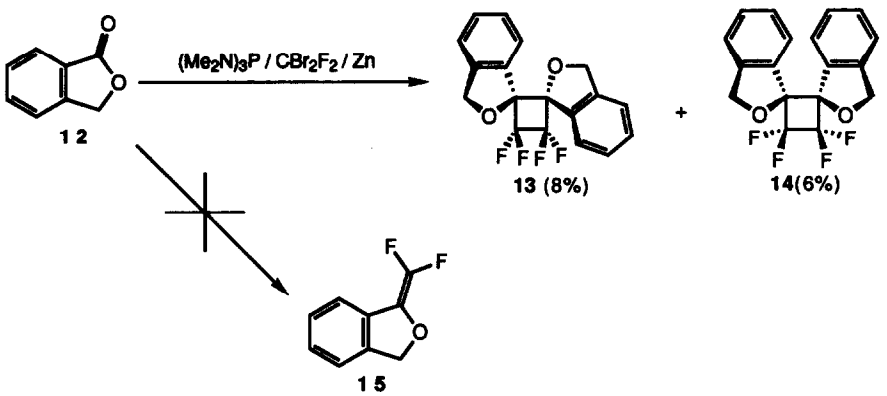
The successful conversion from the inherently less reactive δ-lactones of D-gluconolactone is particularly noteworthy, indicating not only the tolerance of the labile trimethylsilyl protecting groups, but also demonstrating that the presence of an isopropylidene group is not required to maintain the closed lactol structure in the initial intermediate formed by nucleophilic attack. Furthermore, in practical terms it is also worth noting that the trimethylsilyl protecting regime is compatible with the aqueous copper(II) sulphate wash used during the work up to remove HMPA.

With the success in the δ-lactone series, the reactivity of the system was explored further through the attempted difluoromethylenation of a less reactive acyclic ester (**10**) (**Scheme 3**). While the reduced reactivity of the substrate is apparent in the low conversion, the high recovery of starting material nevertheless indicates an absence of complicating side reactions.



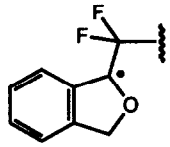
Scheme 3

However, as an extension to the chemistry of this fascinating system and by way of a caveat for the unwary practitioner, we would like to report two sets of reactions which can arise as potential complications. Firstly, as an adjunct to our central work we investigated the difluoromethylenation of phthalide (**12**), a non-carbohydrate γ-lactone. Rather than the expected difluoroenol ether (**15**), two tetrafluorocyclobutanes (**13**) and (**14**) were isolated in low yields along with unreacted phthalide (**Scheme 4**).



Scheme 4

Structural elucidation of (**13**) and (**14**) by X-ray crystallography revealed that the difluoroenol ether had dimerised and that of the four possible structures only those arising from "head-to-head" combinations were observed. Cyclobutane formation by thermal dimerisation or co-dimerisation is peculiarly facile among 1,1-difluoroalkenes[11] and it has been postulated that these reactions occur *via* radical intermediates as opposed to the thermally allowed ($\pi_{2s}+\pi_{2a}$) concerted process.[12] The relative stability of the radical intermediates has been proffered in explanation of the head-to-head regioselectivity. This is an attractive possibility in the case of phthalide since the intermediate radical (**16**) is stabilised both by the adjacent aromatic ring and the α-oxygen substituent. The additional stability of a benzylic radical is evident as dimerisation was not observed under the standard conditions with the carbohydrate lactones.



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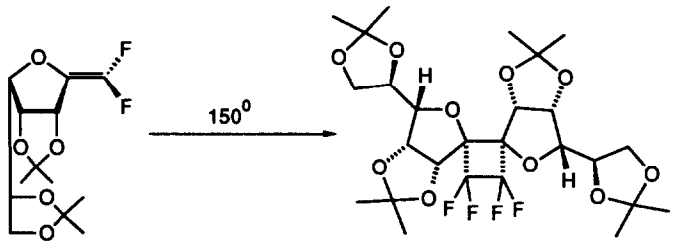
Indeed, it was found that a typical carbohydrate difluoroenol ether underwent only 40% dimerisation on heating at 150°C for 12 days (**Scheme 5**).



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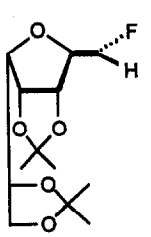
Scheme 5

Assignment of the anti arrangement of the carbohydrate ring oxygens about the tetrafluorocyclobutane was made through ^{19}F nmr correlation with (**13**). Inspection of molecular models suggests that it is reasonable to anticipate (**17**) as the sole or major dimer resulting as it does from the least sterically congested combination of two molecules of the difluoroenol ether.

Although the difluoromethylenation of phthalide remains anomalous among the lactones hitherto studied, it has revealed a process apparently general to difluoroenol ethers and typical of related 1,1-difluoroalkenes. Whilst it is worth noting the potential for dimerisation as an addition to the Arsenal of difluoroenol ether reactions and as a possible side reaction at elevated temperatures, it has not presented a problem in the carbohydrate series.

However, the second topic in our appendix to lactone difluoromethylenation has greater practical implications. During the current study we attempted to modify the difluoromethylenation procedure by isolating the initially formed phosphonium salt, to eliminate the need for its *in situ* preparation on every occasion. Thus, equal quantities of dibromodifluoromethane and HMPT were mixed in dry THF and the resultant precipitate collected by filtration. When the salt was treated with zinc and a THF solution of diisopropylidene D-gulonolactone, in addition to the expected difluoroenol ether (**4**) (30%) it also afforded a monofluoroenol ether (**18**) (29%).



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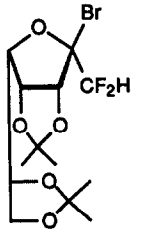

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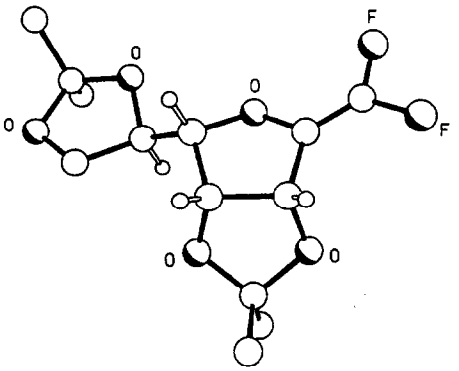

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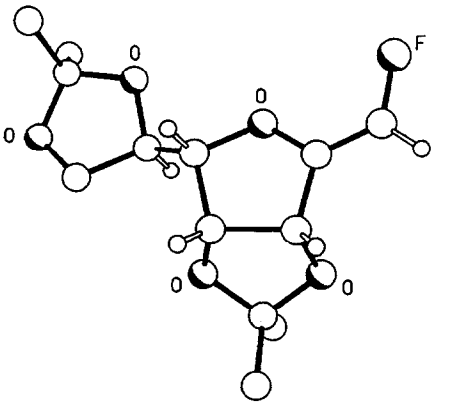

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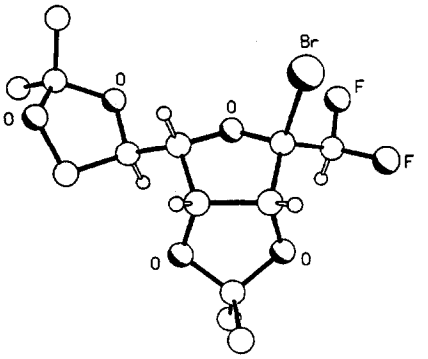

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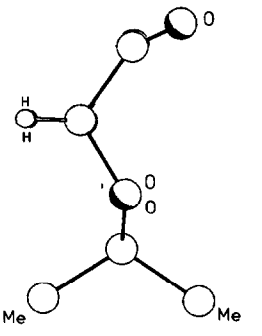
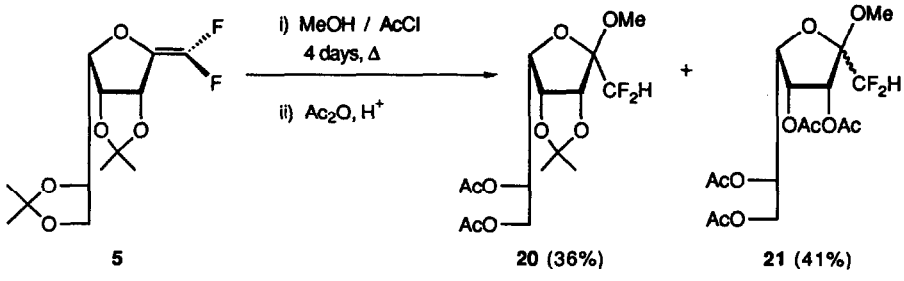


"S"

Figure

^1H and ^{19}F nmr spectra of (**18**) indicated a single double bond isomer, the stereochemistry of which was revealed by X-ray crystallography (Figure). A possible cause of this curious result appeared to be the presence of adventitious water arising from the isolation of the phosphonium salt. To test this hypothesis, a difluoromethylenation was performed in the presence of an equivalent of water subsequent to the *in situ* formation of the phosphonium salt. Mono- and difluoroenol ethers (**18** and **4**) were isolated in 24% and 11% yields respectively, but the major product was the anomeric bromide (**19**) (35%). The stereochemistry at the anomeric centre was determined by X-ray crystallography (Figure). Formally (**19**) may be regarded as a result of hydrogen bromide addition across the difluoroenol ether double bond with the observed anomeric stereochemistry corresponding to delivery of bromide from the least hindered β-face. The possibility of hydrogen bromide generation under the reaction conditions and its addition across a difluoroenol ether is supported by the report that bromodifluoromethyltriphenylphosphonium bromide is hydrolysed to hydrogen bromide[13] and by our own investigation of the reactivity of difluoroenol ethers under acidic conditions. When difluoroenol ether (**5**) was treated with acidic methanol followed by acetylation of deprotected hydroxyl groups two sets of products arose (**Scheme 6**).



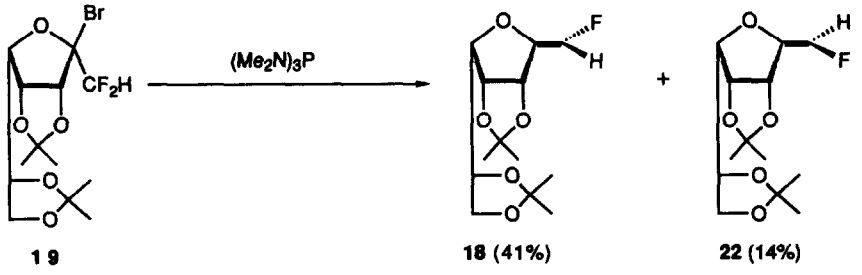
5 **20** (36%) **21** (41%)

Scheme 6

Adduct (**20**) resulted from the stereoselective addition of methanol to the enol ether and deprotection of the labile exocyclic isopropylidene unit. The importance of the ring isopropylidene group as an element of stereocontrol is evident from the mixture of anomers (**21**) obtained on complete deprotection. When the reaction is repeated at room temperature for a shorter period, the exocyclic diol can be isolated prior to the addition of methanol to the enol ether, thus establishing the sequence of events as initial deprotection of the exocyclic isopropylidene group followed by either methanol addition or ring isopropylidene deprotection.

Whereas the addition of a single equivalent of water to the difluoromethylenation of a lactone causes side reactions, the inclusion of two or more equivalents prevents reaction altogether, the reason for which is as yet unclear. It is noticeable that the addition of hydrogen bromide to the monofluoroenol ether was not observed indicating either that it is less reactive than the difluoroenol ether, or that the monofluoroenol ether is formed once the hydrogen bromide is consumed. In the event of the latter, the interesting possibility arises of bromide (**19**) being an intermediate of *in situ* conversion of di- to monofluoroenol ether. To test this (**19**) was reacted with zinc and HMPT, the two components of difluoromethylenation most probably capable of eliminating 'BrF'. It was found that (**19**) was unreactive towards zinc powder in THF heated to reflux. The reaction of (**19**) with HMPT furnished monofluoroenol ether (**18**) as the major product, but unexpectedly this was

accompanied by some of the other double bond isomer (22) (**Scheme 7**).



Scheme 7

Whilst providing a route from the di- to monofluoro systems, this reaction raises two further problems. Firstly, the formation of a monofluoroenol ether in the difluoromethylenation reaction always occurs stereoselectively, and secondly the presence of free phosphine would require reversible formation of either the phosphonium salt or the ylid. Dissociation of ylids to phosphine and difluorocarbene has precedence in the literature.[14] The matter of stereocontrol is important as there are few examples of stereoselective routes to monofluoroalkenes:[15] an attempt to synthesise directly analogous nucleotide monofluoroenol ethers through base induced elimination of HF from an anomeric difluoromethyl group gave a 2:1 mixture of isomers.[16] From comparison of the reactions responsible for monofluoroenol formation it is apparent that zinc bromide, generated *in situ* during difluoromethylenation, is present when the greatest stereoselectivity is observed. Whilst the detailed mechanism remains unknown we tentatively suggest that from what can currently be adduced the phosphine is responsible for the elimination of BrF from bromide (**19**) to form monofluoroenol ethers. It is conceivable that a Lewis acid such as zinc bromide could coordinate one of the fluorine atoms and the ring oxygen, thereby creating the fixed conformation required for selective debromofluorination. Further development work is currently in hand to establish this procedure as a preparatively useful route to monofluoroenol ethers. Monofluoroenol ethers have occasionally been observed during 'standard' difluoromethylenation reactions. It must therefore be emphasised that thorough drying of materials and reagents is necessary to ensure the success of difluoromethylenations.

Structural and Spectroscopic Features of the Carbohydrate gem*-Difluoroenol Ether Unit*

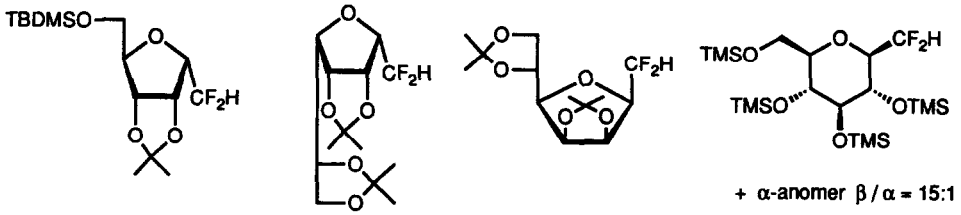
Within the series of carbohydrate *gem*-difluoroenol ethers thus far prepared, we were fortunate to obtain the derivative (**4**) in crystalline form which proved suitable for X-ray crystallographic diffraction studies (Figure), thereby allowing a detailed comparison of the gulose family to be made. This revealed a degree of congruency in the geometry of the trioxabicyclo[3.3.0] unit, which is surprising considering the very different nature of the substituents at the anomeric carbon centre. In all three cases the bicyclic unit adopts, when viewed 'side-on', an 'S'-like conformation, in which the fold angles display little variation as typified by the general structure "S" (Figure). Furthermore the length of the O-C bond between the furanyl oxygen and the anomeric carbon is unchanged regardless of whether the geometry is sp^3, as in the case of the bromide (**19**) (O-C = 1.368 (7) Å), or sp^2 as is present in the mono- and difluoro-analogues (O-C distances of 1.365(4) and 1.369(6)Å respectively). A possible explanation for this equivalence is that in the case of the bromide there is

internal compensation due to the oxygen lone pair donating into the antibonding orbital of the bromine. There is a pronounced double bond character in the C=CF_2 bond of (**4**), 1.290(6)Å, which is noticeably reduced in the monofluoroenol ether leading to an increase in bond length (1.317(5)Å). There is characteristic contraction from normal trigonal geometry of the F-C-F angle in (**4**) giving a value of 110.0(4)°, the other two C=C-F angles being equally enlarged to 125.0(4)°. In the monofluoroenol ether the geometry is trigonal, with all angles being 120°. The geometry about the bond linking the trioxabicyclo system and the exocyclic isopropylidene unit in all three structures is anti.

In terms of infrared spectroscopy, it was also of interest to note that in the furanose series the carbon-carbon double bond stretching frequency typically occurs at 1790 cm^{-1}, which is reminiscent of the parent γ-lactones, and as expected may be found at 1716 cm^{-1} in the case of the monofluoroenol ether (**18**).

Difluoromethyl C-Glycosides

With the development of an efficient and reproducible method for construction of exocyclic difluoroenol ethers in hand, our attention was then directed towards the preparation of difluoromethyl C-glycoside analogues, in which the anomeric hydroxyl group is replaced by a difluoromethyl group as a mimic. This was readily achieved by hydrogenation of the difluoroenol ether group using 10% palladium on carbon catalyst in either ethanol or ethyl acetate at ambient temperature (**Table 2**). In the case of the isopropylidene derivatives, hydrogenation occurred with stereospecific delivery from the convex face. Reduction of δ-lactone derivative (**8**) was complicated by extensive deprotection of the hydroxyl groups in ethanol and partial deprotection in ethyl acetate. Base washing materials and reagents offered no improvement and inclusion of a heterogeneous base such as sodium carbonate prevented reaction altogether. The most apposite solution to this problem was to perform the reaction in ethanol and resilylate the residue and the quoted yield includes the reprotection step. The predominance of the β-anomer is in accordance with literature precedent.[5] The conversion of the difluoroenol ether system to extended C-glycosides by radical addition has been reported in a preliminary communication,[17] and further studies in this area are currently under way.



23 95% from (**3**)

24 98% from (**4**)

25 98% from (**7**)

26 78% from (**8**)

Table 2 *The Hydrogenation of Difluoroenol Ethers*

Conclusions

In the present paper we have described a successful method for the preparation of exocyclic carbohydrate *gem*-difluoroenol ethers from readily available lactones through implementation of a Wittig-type strategy using dibromodifluoromethane, tris(dimethylamino)phosphine and zinc. Subsequent hydrogenation affords difluoromethyl C-glycoside derivatives. Considerable potential of course exists within this versatile enol ether unit for further controlled elaboration towards a variety of difluoromethylene mimics of biologically important carbohydrate classes.

Acknowledgements: We gratefully acknowledge the support of Glaxo Group Research for the award of Studentships to MJT and JSH.

Experimental

General: ^{1}H NMR spectra were recorded using residual protic solvent as the internal standard, at 90 MHz on a Jeol FX 90Q, at 270 MHz on a Jeol GSX 270 and at 500 MHz on a Bruker AM-500. ^{13}C NMR spectra were recorded at 67.9 MHz on a Jeol GSX 270 and at 125.8 MHz on a Bruker AM-500 with deuterated solvent as the internal standard. ^{19}F NMR spectra were recorded at 84.3 MHz on a Jeol FX 90Q with fluorotrichloromethane as the internal standard. Spectra were recorded in d-chloroform. Melting points were determined on a Kofler hot stage. Optical rotations were measured at 20°C on an Optical Activity AA1000 polarimeter; concentrations are expressed in grammes per 100 ml. Infra red spectra were recorded as thin films, unless otherwise stated, on a Perkin Elmer 983G grating machine. Mass spectra and accurate mass measurements were made at Imperial College on a VG 7070B instrument by E.I., or by the SERC mass spectrometry service on VG 12-253 and VG ZAB-E instruments by E.I. and C.I. with NH_3 carrier gas. Mass spectral data quoted were obtained by E.I. unless otherwise stated. Elemental analyses were performed by the staff of the Imperial College microanalytical laboratory. 'Petrol' refers to petroleum ether, boiling range 40-60°C, which was distilled prior to use, and 'ether' implies diethyl ether. Where used as reagents, diethyl ether and tetrahydrofuran were distilled from sodium-benzophenone ketyl, and dichloromethane from calcium hydride, all under argon, immediately prior to use. All other solvents and reagents were purified by standard means. All reactions were performed using oven dried glassware under an atmosphere of argon unless otherwise stated. Preparative column chromatography was performed at low positive pressure on Merck Kieselgel 60 (230-400 mesh).

Crystal Data: Data were collected on a Nicolet R3m diffractometer with Cu-Kα radiation (graphite monochromator) using ω-scans. In each case data were measured to $2\theta \leq 116°$. The data were corrected for Lorentz and polarisation factors and compound (**19**) was in addition corrected for absorption (numerical correction; maximum and minimum transmission factors 0.826 and 0.426). All structures were solved by direct methods and their non-hydrogen atoms were refined anisotropically. The positions of the hydrogen atoms were idealised, C-H=0.96Å, assigned isotropic thermal parameters, $U(H)=1.2U_{eq}(C)$, and allowed to ride on their parent carbon atoms. Methyl groups were refined as rigid bodies. A weighting scheme of the form $w^{-1}=\sigma^2(F)+gF^2$ was applied. All refinements converged to give shift errors of <0.16. The maximum residual electron density was $0.34eÅ^{-3}$. The absolute configuration of compound (**19**) was confirmed by an η

refinement. Computations were carried out on an Eclipse S140 computer using the SHELXT2 program system.

Preparation of 2,5-anhydro-6-*O*-(t-butyldimethylsilyl)-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*ribo*-hex-1-enitol (3). Method B: To a solution of 5-*O*-(t-butyldimethylsilyl)-2,3-*O*-isopropylidene-D-ribonolactone (2.0 g, 6.6 mmol) in tetrahydrofuran (65 ml), cooled to -20°C, was added dibromodifluoromethane (2.73 ml, 30.0 mmol) using a cooled syringe. To the vigorously stirred solution was added tris(dimethylamino)phosphine (6.50 ml, 30.0 mmol), and a dense white precipitate was formed immediately. The mixture was stirred at room temperature for 30 mins, and then zinc powder (1.95 g, 30.0 mmol) and tris(dimethylamino)phosphine (300 µl) were added and the mixture heated to reflux for 18 h. The dark brown reaction mixture was allowed to cool to room temperature and ether (20 ml) added. The ether layer was decanted and the residue washed with ether (10 ml). The combined ether extracts were washed with saturated copper sulphate solution until it remained blue, water (50 ml) and brine (50 ml), and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a yellow oil. Column chromatography (1:5 ether:petrol) afforded 2,5-anhydro-6-*O*-(t-butyldimethylsilyl)-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*ribo*-hex-1-enitol (3) as a colourless oil (1.50 g, 68%). δ_H (270 MHz; $CDCl_3$) 5.28 (1H, dd, J=6.1, 3.2 Hz, H-3), 4.81 (1H, ddd, J=6.1, 1.7, 1.0 Hz, H-4), 4.45 (1H, m, H-5), 3.77 (1H, dd, J=11.2, 2.7 Hz, H-6a), 3.72 (1H, dd, J=11.2, 2.4 Hz, H-6b), 1.50 (3H, s, MeC), 1.39 (3H, d, J=0.5 Hz, MeC), 0.87 (9H, s, Me_3CSi), 0.05 (3H, s, MeSi), 0.03 (3H, s, MeSi); δ_F (84.3 MHz; $CDCl_3$) -105.6 (1F, d, J=98 Hz), -122.6 (1F, d, J=98 Hz); δ_C (125.8 MHz; $CDCl_3$) 149.9 (dd, J=285, 270 Hz), 121.4 (dd, J=19, 13 Hz), 112.9, 87.2, 81.4, 78.3, 64.3, 26.6, 25.6, 18.1, -5.8, -5.9; ν_{max}=2934, 1792, 1471, 1383, 1214, 11164, 1087, 836 cm^{-1}; m/z 336 (M^+), 321 (M^+-Me), 279, 221; $[\alpha]_D$=-104.6° (c=1.03, $CHCl_3$). Found: C 53.28, H 7.83%; $C_{15}H_{26}F_2O_4Si$ requires: C 53.56, H 7.79%.

Preparation of 2,5-anhydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-D-*gulo*-hept-1-enitol (4). Method B: To a solution of 2,3;5,6-di-*O*-isopropylidene-D-gulono-1,4-lactone (1.00 g, 3.9 mmol) in tetrahydrofuran (40 ml), cooled to -20°C, was added dibromodifluoromethane (1.90 ml, 20.5 mmol) using a cooled syringe. To the vigorously stirred solution was added tris(dimethylamino)phosphine (4.40 ml, 20.5 mmol), and a dense white precipitate was formed immediately. The mixture was stirred at room temperature for 30 mins, and then zinc powder (1.31 g, 20.5 mmol) was added, along with a further portion of tris(dimethylamino)phosphine (200 µl), and the mixture was heated to reflux for 3 h. The dark brown reaction mixture was allowed to cool to room temperature and ether (150 ml) added. The ether layer was decanted and the residue washed with ether (100 ml). The combined ether extracts were washed with saturated copper sulphate solution until it remained blue, water (50 ml) and brine (50 ml), and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a yellow oil. Column chromatography (1:1 ether:petrol) afforded 2,5-anhydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-D-*gulo*-hept-1-enitol (4) (799 mg, 71%) as a yellow oil which crystallised on standing in the refrigerator; these crystals were of sufficient quality for the X-ray crystal structure to be determined without recrystallisation (m.p. 40-42°C). δ_H (270 MHz; $CDCl_3$) 5.34 (1H, dd, J=6.1, 3.2 Hz, H-3), 4.71 (1H, ddd, J=6.1, 4.2, 2.0 Hz, H-4), 4.42 (1H, dt, J=9.3, 6.8 Hz, H-6), 4.21 (1H, dd, J=8.7, 6.7 Hz, H-7a), 3.96 (1H, dd, J=8.4, 4.2 Hz, H-5), 3.71 (1H, dd, J=8.7, 7.0 Hz, H-7b), 1.45 (3H, s, Me), 1.43 (3H, s, Me), 1.37 (3H, s, Me), 1.33 (3H, s, Me); δ_F (84.3 MHz, $CDCl_3$) -100.4 (1F, d, J=83 Hz), -117.5 (1F, d, J=83 Hz); δ_C (67.9 MHz; $CDCl_3$) 150.4 (dd, J=290, 274 Hz), 118.8 (dd,

J=49, 14 Hz), 114.0, 110.2, 86.4, 79.4, 77.8, 75.6, 65.9, 26.7, 26.4, 25.5, 25.3; ν_{max}= 2989, 1787, 1373, 1286, 1265, 1213, 1161, 1107 cm^{-1}; m/z 292 (M^+), 277 (M^+-Me), 101, 43; $[\alpha]_D$=-117.4° (c=0.68, $CHCl_3$). Found: C 53.16, H 6.41%; $C_{13}H_{18}F_2O_5$ requires: C 53.41, H 6.21%.
Crystal Data (**4**): $C_{13}H_{18}F_2O_5$, M = 292.2, monoclinic, a = 5.440(2), b = 16.690(7), c = 8.242(3) Å, β = 95.60 (3)°, V = 745 $Å^3$, space group $P2_1$, Z = 2 D_c = 1.30 gcm^{-3}, Cu radiation, λ = 1.54178Å, μ(Cu-K_α) = 10cm^{-1}, F(000) = 308. 1020 Independent reflections were measured (2θ ≤ 116°), of which 962 had $|F_0| > 3\sigma(|F_0|)$ and were considered to be observed. The structure was refined to give R = 0.049, R_w = 0.055 [g=0.00191].

Preparation of 2,5-anhydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-L-*manno*-hept-1-enitol (5). Method B: To a solution of 2,3;5,6-di-*O*-isopropylidene-L-mannono-1,4-lactone (1.47 g, 5.69 mmol) in tetrahydrofuran (50 ml), cooled to -20°C, was added dibromodifluoromethane (2.23 ml, 24.3 mmol) using a cooled syringe. To the vigorously stirred solution was added tris(dimethylamino)phosphine (5.31 ml, 24.3 mmol), and a dense white precipitate was formed immediately. The mixture was stirred at room temperature for 30 mins, and then zinc powder (1.59 g, 24.3 mmol) and tris(dimethylamino)phosphine (300 μl) were added and the mixture heated to reflux for 3 h. The dark brown reaction mixture was allowed to cool to room temperature and ether (150 ml) added. The ether layer was decanted and the residue washed with ether (50 ml). The combined ether extracts were washed with saturated copper sulphate solution until it remained blue, water (50 ml) and brine (50 ml), and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a yellow oil. Column chromatography (1:3 ether:petrol) afforded 2,5-anhydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-L-*manno*-hept-1-enitol (**5**) as a yellow oil (1.29 g, 78%). δ_H (90 MHz; $CDCl_3$) 5.30 (1H, dd, J=6.0, 3.0 Hz, H-3), 4.80 (1H, ddd, J=5.8, 3.8, 2.0 Hz, H-4), 4.41 (1H, dt, J=7.9, 5.3 Hz, H-6), 4.05 (2H, d, J=5.3 Hz, H-7a, 7b), 3.87 (1H, dd, J=7.7, 3.7 Hz, H-5), 1.43 (3H, s, Me), 1.38 (3H, s, Me), 1.33 (6H, s, 2xMe); δ_F (84.3 MHz, $CDCl_3$) -102.0 (1F, d, J=83 Hz), -118.0 (1F, d, J=83 Hz); δ_C (67.9 MHz; $CDCl_3$) 150.5 (dd, J=288, 274 Hz), 118.8 (dd, J=49, 14 Hz), 113.6, 109.4, 83.9, 79.0, 77.4 (d, J=4 Hz), 72.7, 66.3, 26.7, 26.2, 25.2, 25.0; ν_{max}= 2989, 1788, 1373, 1262, 1213, 1160, 1120, 1107 cm^{-1}; m/z 292 (M^+), 277 (M^+-Me), 219, 159, 101, 43; Observed (M^+): 292.1122; $C_{13}H_{18}F_2O_5$ requires: 292.1122; $[\alpha]_D$=-108.2° (c=1.70, $CHCl_3$).

Preparation of 2,5-anhydro-6-*O*-(t-butyldimethylsilyl)-1-deoxy-1,1-difluoro-3,4;7,8-di-*O*-isopropylidene-D-*glycero*-D-*gulo*-oct-1-enitol (6). Method B: To a solution of 5-*O*-(t-butyldimethylsilyl)-2,3;6;7-di-*O*-isopropylidene-D-*glycero*-D-*gulo*-heptono-1,4-lactone (331 mg, 0.8 mmol) in tetrahydrofuran (8.0 ml), cooled to -20°C, was added dibromodifluoromethane (340 μl, 4.0 mmol) using a cooled syringe. To the vigorously stirred solution was added tris(dimethylamino)phosphine (811 μl, 4.0 mmol), and a dense white precipitate was formed immediately. The mixture was stirred at room temperature for 30 mins, and then zinc powder (243 mg, 4.0 mmol) and tris(dimethylamino)phosphine (40 μl) were added and the mixture heated to reflux for 3 h. The dark brown reaction mixture was allowed to cool to room temperature and ether (20 ml) added. The ether layer was decanted and the residue washed with ether (10 ml). The combined ether extracts were washed with saturated copper sulphate solution until it remained blue, water (10 ml) and brine (10 ml), and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a yellow oil. Column chromatography (1:3 ether:petrol) afforded 2,5-anhydro-6-*O*-(t-butyldimethylsilyl)-1-deoxy-1,1-difluoro-3,4;7,8-di-*O*-isopropylidene-D-*glycero*-D-*gulo*-oct-1-enitol (**6**) as a colourless oil (219 mg, 61%). δ_H (270 MHz; $CDCl_3$) 5.32 (1H, dd, J=5.6, 2.9 Hz, H-3), 4.72 (1H, ddd, J=5.6, 3.6, 2.2 Hz,

H-4), 4.25 (1H, dd, J=4.9, 4.8 Hz, H-6), 4.13 (1H, m, H-7), 3.97 (2H, m, H-8a, 8b), 3.66 (1H, dd, J=8.9, 3.3 Hz, H-5), 1.45 (3H, s, Me), 1.41 (3H, s, Me), 1.34 (6H, s, 2xMe), 0.88 (9H, s, Me_3CSi), 0.10 (3H, s, MeSi), 0.09 (3H, s, MeSi); δ_F (84.3 MHz, $CDCl_3$) -102.0 (1F, d, J=83 Hz), -118.6 (1F, d, J=83 Hz); δ_C (67.9 MHz; $CDCl_3$) 150.2 (dd, J=289, 273 Hz), 117.8 (dd, J=48, 13 Hz), 112.9, 108.8, 85.2, 78.8, 77.7 (m), 76.1, 70.7, 65.2, 26.4, 25.7, 25.5, 25.4, 24.9, -4.8, -4.9; ν_{max}= 2933, 1786, 1371, 1214, 1115 cm^{-1}; m/z 421 (M^+-Me), 379, 129, 101, 73, 59, 43; $[\alpha]_D$=-77.9° (c=1.20, $CHCl_3$). Found: C 55.08, H 7.52%; $C_{20}H_{34}F_2O_6Si$ requires: C 55.02, H 7.85%.

Preparation of 2,5-anhydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-D-*manno*-hept-1-enitol (7). Method B: To a solution of 2,3;5,6-di-*O*-isopropylidene-D-mannono-1,4-lactone (5.66 g, 21.9 mmol) in tetrahydrofuran (200 ml), cooled to -20°C, was added dibromodifluoromethane (8.59 ml, 94.0 mmol) using a cooled syringe. To the vigorously stirred solution was added tris(dimethylamino)-phosphine (20.5 ml, 94.0 mmol), and a dense white precipitate was formed immediately. The mixture was stirred at room temperature for 30 mins, and then zinc powder (6.12 g, 94.0 mmol) and tris(dimethylamino)-phosphine (2 ml) were added and the mixture heated to reflux for 2.5 h. The dark brown reaction mixture was allowed to cool to room temperature and ether (500 ml) added. The ether layer was decanted and the residue washed with ether (100 ml). The combined ether extracts were washed with saturated copper sulphate solution until it remained blue, water (150 ml) and brine (150 ml), and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a yellow oil. Column chromatography (1:3 ether:petrol) afforded 2,5-anhydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-D-*manno*-hept-1-enitol (7) as a pale yellow oil (4.52g, 71%). δ_H (270 MHz; $CDCl_3$) 5.35 (1H, dd, J=6.0, 3.1 Hz, H-3), 4.86 (1H, ddd, J=5.9, 3.8, 2.1 Hz, H-4), 4.46 (1H, ddd, J=7.8, 5.6, 4.9 Hz, H-6), 4.14 (1H, dd, J=8.8, 5.9 Hz, H-7a), 4.10 (1H, dd, J=8.8, 4.6 Hz, H-7b), 3.92 (1H, dd, J=7.8, 3.7 Hz, H-5), 1.49 (3H, s, Me), 1.45 (3H, s, Me), 1.40 (3H, s, Me), 1.39 (3H, s, Me); δ_F (84.3 MHz, $CDCl_3$) -102.0 (1F, d, J=83 Hz), -118.0 (1F, d, J=83 Hz); δ_C (67.9 MHz; $CDCl_3$) 150.4 (dd, J=288, 274 Hz), 118.8 (dd, J=49, 14 Hz), 113.7, 109.4, 83.9, 79.0, 77.4 (d, J=4 Hz), 72.7, 66.4, 26.7, 26.3, 25.2, 25.0; ν_{max}= 2989, 1787, 1454, 1373, 1213, 1107 cm^{-1}; m/z 292 (M^+), 277 (M^+-Me), 219, 159, 101, 43; $[\alpha]_D$=+112.5° (c=1.10, $CHCl_3$). Found: C 53.25, H 6.13%; $C_{13}H_{18}F_2O_5$ requires: C 53.41, H 6.21%.

Preparation of 2,6-anhydro-1-deoxy-1,1-difluoro-3,4,5,7-tetrakis-*O*-(trimethylsilyl)-D-*gluco*-hept-1-enitol (8). Method B: To a solution of 2,3,4,6-tetra-*O*-(trimethylsilyl)glucono-1,5-lactone (4.33 g, 9.3 mmol) in tetrahydrofuran (90 ml), cooled to -20°C, was added dibromodifluoromethane (3.90 ml, 43.0 mmol) using a cooled syringe. To the vigorously stirred solution was added tris(dimethylamino)-phosphine (9.21 ml, 43.0 mmol), and a dense white precipitate was formed immediately. The mixture was stirred at room temperature for 30 mins, and then zinc powder (2.81 g, 43.0 mmol) added, along with a further portion of tris(dimethylamino)phosphine (500 µl) and the mixture heated to reflux for 18 h. The dark brown reaction mixture was allowed to cool to room temperature and ether (100 ml) added. The ether layer was decanted and the residue washed with ether (50 ml). The combined ether extracts were washed with saturated copper sulphate solution until it remained blue and brine (50 ml), and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a yellow oil. Column chromatography (1:1 ether:petrol) afforded 2,6-anhydro-1-deoxy-1,1-difluoro-3,4,5,7-tetrakis-*O*-(trimethylsilyl)-D-*gluco*-hept-1-enitol (8) as a colourless oil (3.17g, 69%). δ_H (500 MHz; $CDCl_3$) 4.15 (1H, t, J=3.6 Hz, H-3), 3.86 (1H, ddd, J=8.4, 4.2, 2.4 Hz, H-

6), 3.82 (1H, dd, J=11.7, 2.4 Hz, H-7a), 3.74 (1H, dd, J=11.7, 4.3 Hz, H-7b), 3.68 (1H, ddd, J=5.2, 3.7, 1.5 Hz, H-4), 3.65 (1H, dd, J=8.5, 5.6 Hz, H-5), 0.16 (9H, s, Me_3Si), 0.15 (9H, s, Me_3Si), 0.13 (9H, s, Me_3Si), 0.12 (9H, s, Me_3Si); δ_F (84.3 MHz, $CDCl_3$) -102.0 (1F, d, J=78 Hz), -118.0 (1F, d, J=78 Hz); δ_C (67.9 MHz; $CDCl_3$) 152.3 (dd, J=289, 276 Hz), 114.8 (dd, J=18, 13 Hz), 78.9, 78.8, 72.2, 69.1 (d, J=2 Hz), 61.8, 0.54, 0.49, -0.1, -0.4; ν_{max}= 2957, 1765, 1251, 1143, 1091, 1017, 841 cm^{-1}; m/z 500 (M^+), 321, 217, 191, 73; Observed (M^+): 500.2077; $C_{19}H_{42}F_2O_5Si_4$ requires: 500.2077; $[\alpha]_D$=+25.1° (c=1.02, $CHCl_3$).

Preparation of 2,6-anhydro-1-deoxy-1,1-difluoro-3,4,5,7-tetrakis-*O*-benzyl-D-*gluco*-hept-1-enitol (9). Method B: To a solution of 2,3,4,6-tetra-*O*-benzylglucono-1,5-lactone (4.83 g, 8.93 mmol) in tetrahydrofuran (100 ml), cooled to -20°C, was added dibromodifluoromethane (4.08 ml, 44.6 mmol) using a cooled syringe. To the vigorously stirred solution was added tris(dimethylamino)phosphine (10.0 ml, 44.6 mmol), and a dense white precipitate was formed immediately. The mixture was stirred at room temperature for 30 mins, and then zinc powder (2.92 g, 44.6 mmol) was added, along with a further portion of tris(dimethylamino)phosphine (700 µl) and the mixture was heated to reflux for 4 h. The dark brown reaction mixture was allowed to cool to room temperature and ether (100 ml) added. The ether layer was decanted and the residue washed with ether (50 ml). The combined ether extracts were washed with saturated copper sulphate solution until it remained blue and brine (50 ml), and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a yellow oil. Column chromatography (1:1 ether:petrol) afforded 2,6-anhydro-1-deoxy-1,1-difluoro-3,4,5,7-tetrakis-*O*-benzyl-D-*gluco*-hept-1-enitol (**9**) as a yellow oil (3.20 g, 63%). δ_H (500 MHz; $CDCl_3$) 7.38-7.25 (20H, m, Ph), 4.71-4.43 (8H, m, $C\underline{H}_2Ph$), 4.25 (1H, t, J=3.8 Hz, H-3), 4.07 (1H, ddd, J=9.5, 4.0, 2.5 Hz, H-6), 3.87 (1H, ddd, J=5.6, 4.3, 1.4 Hz, H-4), 3.76 (2H, m, H-5, 7a), 3.72 (1H, dd, J=11.1, 4.1 Hz, H-7b); δ_F (84.3 MHz, $CDCl_3$) -100.0 (1F, d, J=78 Hz), -116.9 (1F, d, J=78 Hz); δ_C (67.9 MHz; $CDCl_3$) 153.5 (dd, J=291, 278 Hz), 128.4-127.5 (Ph), 112.3 (dd, J=38, 13 Hz), 82.2, 77.1, 76.7, 73.6, 73.3, 72.9 (d, J=2 Hz), 72.8, 71.1, 68.6; ν_{max}= 2865, 1763, 1461, 1250, 1207, 1092, 736 cm^{-1}; m/z 572 (M^+), 481, 306, 181, 108, 91, 79; Observed (M^+): 572.2374; $C_{35}H_{34}F_2O_5$ requires: 572.2374; $[\alpha]_D$=+46.7° (c=0.88, $CHCl_3$).

Preparation of 1-(1,1-difluoro-1-propen-2-yloxy) octadecane (11). Method A: To a solution of octadecyl acetate (**10**) (1.56 g, 5 mmol) in tetrahydrofuran (50 ml), cooled to -20°C, was added dibromodifluoromethane (2.47 ml, 27 mmol) and tris(dimethylamino)phosphine (5.77 ml, 27 mmol). The mixture was allowed to warm to room temperature with continuous stirring. Zinc powder (1.77 g, 27 mmol) was added and the mixture heated at reflux for 4 h. Ether (250 ml) was added to the dark brown reaction mixture. The ethereal solution was washed with water (4 x 50 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a yellow oil. Column chromatography (1:4 ether:petrol) afforded starting material (**10**) (1.27 g, 81%) and 1-(1,1-difluoro-1-propen-2-yloxy) octadecane (**11**) (0.15 g, 9%) as a yellow oil. δ_H (270 MHz; $CDCl_3$) 3.68 (2H, br t, J=6.5 Hz, CH_2O), 1.75 (3H, dd, J=4.4, 3.9 Hz, CH_3C), 1.60 (2H, m, $C\underline{H}_2CH_2O$), 1.40-1.25 (CH_2 envelope), 0.88 (3H, t, J=6.7 Hz, $C\underline{H}_3CH_2$); δ_F (84.3 MHz; $CDCl_3$) -105.0 (1F, d, J=83 Hz), -117.5 (1F, d, J=78 Hz); ν_{max} 2922, 1767,1465, 1246, 1141, 1040 cm^{-1}; m/z 346 (M^+), 295, 85, 71, 57, 43; Observed (M^+): 346.3054; $C_{21}H_{40}F_2O$ requires: 346.3047.

Preparation of *trans*- and *cis*-3, 3, 4, 4-tetrafluorodispirocyclobutane-1,1' (3'H):2,1" (3"H)bisisobenzofuran (13) and (14). Method A: To a solution of phthalide (2.68 g, 20 mmol) in

tetrahydrofuran (60 ml), cooled to -30°C, was added dibromodifluoromethane (5.48 ml, 60 mmol) and tris(dimethylamino)phosphine (12.8 ml, 60 mmol). The mixture was allowed to warm to room temperature, zinc powder (3.92 g, 60 mmol) was added and the mixture heated at reflux for 6 h. The dark brown reaction mixture was poured into ether (250 ml), the solution washed with water (5 x 50 ml) and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave a yellow oil. Column chromatography (1:1 ether:petrol) afforded phthalide (1.20 g, 45%) and two other products: *trans*-3, 3, 4, 4-tetrafluorodispirocyclobutane-1,1' (3'H):2,1" (3"H)-bisisobenzofuran (**13**) (260 mg, 8%) as a colourless crystalline solid (m.p. 151-155°C); δ_H (270 MHz; $CDCl_3$) 7.72 (1H, m, aromatic), 7.35 (2H, m, aromatic), 7.16 (1H, m, aromatic), 5.20 (1H, d, J=12.4 Hz, H_a-3'), 4.92 (1H, d, J=12.4 Hz, H_b-3'); δ_F (84.3 MHz; $CDCl_3$) -129.3 (m); ν_{max} (film) 2874, 1608, 1461, 1377, 1355, 1166, 1056, 1036, 1024, 862 cm^{-1}; m/z 336 (M^+), 236, 168, 137, 118, 90; found: C 63.99, H 3.52%; $C_{18}H_{12}F_4O_2$ requires: C 64.29, H 3.60%; and *cis*-3, 3, 4, 4-tetrafluorodispirocyclobutane-1,1' (3'H):2,1" (3"H)-bisisobenzofuran (**14**) (220 mg, 6%) as a colourless crystalline solid (m.p. 147-148°C); δ_H (500 MHz; $CDCl_3$) 7.47 (1H, d, J=7.3 Hz, aromatic), 7.31 (1H, t, J=7.4 Hz, aromatic), 7.25 (1H, m, aromatic), 7.19 (1H, d, J=7.5 Hz, aromatic), 5.25 (1H, d, J=12.5 Hz, H_a-3'), 4.15 (1H, d, J=12.5 Hz, H_b-3'); δ_F (84.3 MHz; $CDCl_3$) -126.8 (d, J=220 Hz), -132.4 (d, J=220 Hz); ν_{max} 2871, 1608, 1460, 1373, 1352, 1171, 1159, 1049, 1034, 1024, 997 cm^{-1}; m/z 336 (M^+), 168, 137, 118, 90; found: C 64.25, H 3.59%; $C_{18}H_{12}F_4O_2$ requires: C 64.29, H 3.60%.

Crystal Data (**13**): $C_{18}H_{12}F_4O_2$, M = 336.3, monoclinic, a = 6.859(4), b = 16.795(11), c = 12.924(8) Å, β = 95.76 (5)°, U = 1481Å^3, space group $P2_1/c$, Z = 4, D_c = 1.50 gcm^{-3}, Cu radiation, λ = 1.54178Å, μ(Cu-K_α) = 11 cm^{-1}, F(000) = 680. 1985 Independent reflections were measured (2θ ≤ 116°), of which 1832 had $|F_0| > 3\sigma(|F_0|)$ and were considered to be observed. Refinement was by block-cascade, full-matrix, least-squares to R = 0.046, R_w = 0.053 [g=0.00047]. Crystal Data (**14**): $C_{18}H_{12}F_4O_2$, M = 336.3, monoclinic, a = 11.537(5), b = 9.756(4), c = 13.180(4) Å, β = 96.16(3)°, U = 1475Å^3, space group $P2_1/n$, Z = 4, D_c = 1.51 gcm^{-3}, Cu radiation, λ = 1.54178Å, μ(Cu-K_α) = 11 cm^{-1}, F(000) = 680. 1986 Independent reflections were measured (2θ ≤ 116°), of which 1913 had $|F_0| > 3\sigma(|F_0|)$ and were considered to be observed. The structure was refined R = 0.047, R_w = 0.065 [g=0.00023].

Preparation of 3,3,4,4-tetrafluoro-2',3';5',6';2",3";5",6"-tetra-*O*-isopropylidenedispirocyclobutane-1,1':2,1"-bi-(1,4-anhydro-D-gulitol) (17). 2,5-Anhydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-D-*gulo*-hept-1-enitol (**4**) (200 mg, 0.68 mmol) was sealed in an NMR tube (5 mm) under argon with a little d_6-benzene and heated at 150°C for 12 days, after which no starting material was apparent by ^{19}F NMR. Column chromatography (1:1 ether:petrol) afforded 3,3,4,4-tetrafluoro-2',3';5',6';2",3";5",6"-tetra-*O*-isopropylidenedispirocyclobutane-1,1':2,1"-bi-(1,4-anhydro-D-gulitol) (**17**) (80 mg, 40%) as a colourless oil. δ_H (270 MHz; $CDCl_3$) 5.06 (1H, d, J=6.1 Hz, H-2'), 4.59 (1H, dd, J=5.9, 4.4 Hz, H-3'), 4.44 (1H, dt, J=7.8, 6.8 Hz, H-5'), 4.21 (1H, dd, J=8.9, 7.0 Hz, H-6'a), 3.76 (1H, dd, J=8.9, 6.0 Hz, H-6'b), 3.27 (1H, dd, J=7.8, 4.4 Hz, H-4'), 1.46 (3H, s, MeC), 1.43 (3H, s, MeC), 1.38 (3H, s, MeC), 1.27 (3H, s, MeC); δ_F (84.3 MHz; $CDCl_3$) -125.4 (m); ν_{max} 2876, 1375, 1211, 1176, 1109, 1066 cm^{-1}; m/z 584 (M^+), 569 (M^+-Me), 101, 84, 43; Observed (M^+): 584.2245; $C_{26}H_{36}F_4O_{10}$ requires: 584.2245.

Preparation of bromodifluoromethyl[tris(dimethylamino)]phosphonium bromide. To a solution of dibromodifluoromethane (10.0 ml, 109 mmol) in tetrahydrofuran (10 ml), cooled to -20°C, was

added tris(dimethylamino)phosphine (20.7 ml, 97 mmol).and, with vigorous stirring, the mixture was allowed to warm to room temperature. The white precipitate was filtered and washed with anhydrous ether. Residual solvent was removed giving bromodifluoromethyl[tris(dimethylamino)]phosphonium bromide (32.0 g, 86%), which was stored over silica gel drying crystals in a desiccator.

Preparation of (*Z*)-2,5-anhydro-1-deoxy-1-fluoro-3,4;6,7-di-*O*-isopropylidene-D-*gulo*-hept-1-enitol (18). To a mixture of 2,3;5,6-di-*O*-isopropylidene-D-gulonolactone (0.258 g, 1.0 mmol), bromodifluoromethyl[tris(dimethylamino)]phosphonium bromide (1.12 g, 3.0 mmol) and zinc dust (0.20 g, 3.0 mmol) was added tetrahydrofuran (30 ml). The resultant grey suspension was heated at reflux for 2 h. The dark brown solution was allowed to cool to room temperature and poured into ether (30 ml). The ethereal solution was washed with water (4 x 20 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a yellow oil, which was adsorbed onto silica. Column chromatography (1:1 ether:petrol) afforded difluoromethylene compound (**4**) (87 mg, 30 %) as a yellow oil and (*Z*)-2,5-anhydro-1-deoxy-1-fluoro-3,4;6,7-di-*O*-isopropylidene-D-*gulo*-hept-1-enitol (**18**) (80 mg, 29%) as a colourless crystalline solid (m.p. 71-75°C). δ_H (270 MHz; $CDCl_3$) 6.37 (1H, dd, J=74.7, 0.7 Hz, H-1), 5.10 (1H, d, J=6.1 Hz, H-3), 4.69 (1H, ddd, J=6.2, 4.4, 1.8 Hz, H-4), 4.42 (1H, dt, J=8.3, 6.8 Hz, H-6), 4.20 (1H, dd, J=8.7, 6.7 Hz, H-7a), 4.07 (1H, dd, J=8.3, 4.4 Hz, H-5), 3.72 (1H, dd, J=8.7, 6.7 Hz, H-7b), 1.45 (3H, s, Me), 1.44 (3H, s, Me) 1.37 (3H, s, Me), 1.31 (3H, s, Me); δ_F (84.3 MHz; $CDCl_3$) -160.0 (d, J=78 Hz); ν_{max} 2935, 1716, 1373, 1212, 1106, 1071, 1042, 1015, 906 cm^{-1}; m/z 274 (M^+), 259 (M^+-Me), 201, 143, 141, 101, 43; $[\alpha]_D$= -84.9° (c = 0.97, $CHCl_3$). Found: C 56.72, H 6.98%; $C_{13}H_{19}FO_5$ requires: C 56.92, H 6.98%. Crystal Data (**18**): $C_{13}H_{19}FO_5$, M = 274.3, monoclinic, a = 5.325(3), b = 8.081(4), c = 16.303(6) Å, β = 95.82 (4)°, U = 698$Å^3$, space group $P2_1$, Z = 2, D_c = 1.31 gcm^{-3}, Cu radiation, λ = 1.54178Å, μ(Cu-K_α) = 9cm^{-1}, F(000) = 292. 1023 Independent reflections were measured (2θ ≤ 116°), of which 1002 had $|F_0| > 3\sigma(|F_0|)$ and were considered to be observed. The structure was refined to give R = 0.045, R_w = 0.047 [g=0.00050].

Difluoromethylenation of 2,3;5,6-di-*O*-isopropylidene-D-gulono-1,4-lactone in the presence of water. To a cooled solution of dibromodifluoromethane (0.46 ml, 5.0 mmol) in tetrahydrofuran (10 ml) was added tris(dimethylamino)phosphine (1.07 ml, 5.0 mmol), which resulted in the immediate formation of a dense white precipitate. Water (0.018 ml, 1 mmol) was added and the mixture allowed to warm to room temperature. 2,3;5,6-di-*O*-isopropylidene-D-gulono-1,4-lactone (0.258 g, 1.0 mmol) and zinc dust (0.32 g, 5.0 mmol) were added and the mixture heated at reflux for 2 h. The dark brown solution was allowed to cool to room temperature and poured into ether (50 ml). The ethereal solution was washed with water (6 x 10 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a yellow oil, which was adsorbed onto silica. Column chromatography (1:4 ether:petrol) afforded: (**4**) (70 mg, 24%) and (**18**) (30 mg, 11%) as colourless oils, for which ^1H and ^{19}F NMR data were in agreement with those of independently prepared samples; and 2,5-anhydro-2-bromo-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-D-*glycero*-L-*galacto*-heptitol (**19**) (130 mg, 35%) as a colourless crystalline solid (m.p. 91-95°C). δ_H (270 MHz; $CDCl_3$) 5.88 (1H, dd, J=56.9, 53.7 Hz, H-1), 5.22 (1H, d, J=5.6 Hz, H-3), 4.86 (1H, ddd, J = 5.9, 4.2, 1.2 Hz, H-4), 4.45 (1H, dt, J=8.3, 6.6 Hz, H-6), 4.29 (1H, dd, J=8.3, 4.2 Hz, H-5), 4.23 (1H, dd, J=8.8, 6.6 Hz, H-7a), 3.78 (1H, dd, J=8.6, 6.6 Hz, H-7b), 1.46 (3H, s, MeC), 1.39 (3H, s, MeC), 1.38 (3H, s, MeC), 1.29 (3H, s, MeC); δ_F (84.3 MHz; $CDCl_3$) -123.8 (1F, dd, J=293, 54 Hz), -129.6 (1F, dd, J=293, 59 Hz); δ_C (67.9 MHz; $CDCl_3$) 114.3, 110.9 (dd, J=250, 244 Hz), 110.4, 103.6 (dd,

J=35, 22 Hz), 89.8 (d, J=2 Hz), 86.6, 78.9, 74.1, 65.9, 26.7, 25.6, 25.3, 24.4; ν_{max} 2937, 1317, 1212, 1163, 1110, 1069, 944, 847 cm^{-1}; m/z 359, 357 (M^+-Me), 293 (M^+-Br), 159, 101, 43; $[\alpha]_D$= -94.7° (c=0.75, $CHCl_3$). Found: C 41.91, H 4.94%; $C_{13}H_{19}BrF_2O_5$ requires: C 41.84, H 5.13%.
Crystal Data (**19**): $C_{13}H_{19}BrF_2O_5$, M = 373.2, orthorhombic, a = 10.104(2), b = 10.199(1), c = 15.798(3) Å, V = 1628 $Å^3$, space group $P2_12_12_1$, Z = 4, D_c = 1.52 gcm^{-3}, Cu radiation, λ = 1.54178Å, μ(Cu-K_α) = 38 cm^{-1}, F(000) = 760. 1281 Independent reflections were measured ($2\theta \leq 116°$), of which 1196 had $|F_0| > 3\sigma(|F_0|)$ and were considered to be observed. The structure was refined to give R = 0.043, R_w = 0.045 [g=0.00020].

Reaction of 2,5-anhydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-L-*manno*-hept-1-enitol (5) with acidic methanol. A solution of 2,5-anhydro-1-deoxy-1,1-difluoro-3,4;6,7-di*O*-isopropylidene-L-*manno*-hept-1-enitol (**5**) (404 mg, 1.4 mmol) and acetyl chloride (0.5 ml) in methanol (10 ml) was heated at reflux for 4 days, after which time the solvent was removed under reduced pressure. To the residue was added acidic acetic anhydride [5 ml of a solution of 1 drop of perchloric acid in acetic anhydride (10 ml)] and the solution stirred at room temperature for 30 min. Ice/water was added, the mixture stirred for a further 30 min and then the mixture was extracted with dichloromethane (50 ml). The dichloromethane extract was washed three times with water and dried over $MgSO_4$. The solvent was removed *in vacuo* to give a yellow oil. Column chromatography afforded 6,7-di-*O*-acetyl-2,5-anhydro-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-L-*glycero*-L-*galacto*-heptitol (**20**) (185 mg, 36%) as a colourless oil. δ_H (270 MHz; $CDCl_3$) 5.87 (1H, dd, J=55.2, 52.5 Hz, H-1), 5.30 (1H, ddd, J=8.6, 4.6, 2.4 Hz, H-6), 4.78 (1H, ddd, J=5.7, 3.9, 1.8 Hz, H-4), 4.62 (1H, dd, J=12.4, 2.4 Hz, H-7a), 4.52 (1H, d, J=5.9 Hz, H-3), 4.22 (1H, dd, J=12.2, 4.6 Hz, H-7b), 4.12 (1H, dd, J=8.8, 3.9 Hz, H-5), 3.60 (3H, d, J=2.9 Hz, OMe), 2.25 (6H, s, 2xMeCO), 1.64 (3H, s, MeC), 1.47 (3H, s, MeC); δ_F (84.3 MHz; $CDCl_3$) -129.7 (1F, dd, J=298, 54 Hz), -137.1 (1F, dd, J=298, 59 Hz); δ_C (67.9 MHz; $CDCl_3$) 170.6, 169.5, 113.9 (t, J=243 Hz), 113.8, 85.4 (d, J=4 Hz), 79.7, 78.3,77.6, 68.7, 63.0, 51.4 (d, J=6 Hz), 25.8, 24.5, 21.0, 20.8; ν_{max} 2987, 1748, 1375, 1220, 1093, 1051 cm^{-1}; m/z 353 (M^+-Me), 233, 200, 191, 98, 43; Observed (M^+-Me): 353.1042; $C_{14}H_{19}F_2O_8$ requires: 353.104.

Reaction of 2,5-anhydro-2-bromo-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-D-*glycero*-L-*galacto*-heptitol (19) with tris(dimethylamino)phosphine. To a solution of 2,5-anhydro-2-bromo-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-D-*glycero*-L-*galacto*-heptitol (**19**) (100 mg, 0.27 mmol) in tetrahydrofuran (3ml) was added tris(dimethylamino)phosphine (300 μl, 1.40 mmol). The solution was heated at reflux for 3h and poured into ether (20 ml). The ethereal solution was washed with 10% HCl (10 ml) and water (2 x 10 ml), and dried over $MgSO_4$. The solvent was removed *in vacuo* to give a yellow oil. Column chromatography afforded (**18**) (30 mg, 41%) as a colourless oil and (*E*)-2,5-anhydro-1-deoxy-1-fluoro-3,4;6,7-di-*O*-isopropylidene-D-*gulo*-hept-1-enitol (**22**) (10 mg, 14%) as a colourless oil. δ_H (270 MHz; $CDCl_3$) 7.00 (1H, dd, J=88.2, 1.0 Hz, H-1), 5.47 (1H, m, H-3), 4.69 (1H, dd, J=6.4, 4.4 Hz, H-4), 4.44 (1H, dt, J=8.3, 6.9 Hz, H-6), 4.24 (1H, dd, J=8.8, 6.8 Hz, H-7a), 3.94 (1H, dd, J=8.3, 3.9 Hz, H-5), 3.74 (1H, dd, J=8.8, 7.8 Hz, H-7b), 1.49 (3H, s, Me), 1.46 (3H, s, Me) 1.40 (3H, s, Me), 1.37 (3H, s, Me); δ_F (84.3 MHz; $CDCl_3$) -177.4 (d, J=82 Hz); ν_{max} 2932, 1719, 1210, 1045, 910 cm^{-1}; m/z 274 (M^+), 259 (M^+-Me), 159, 141, 101, 43; $[\alpha]_D$= -81.0° (c = 0.61, $CHCl_3$).

Preparation of 2,5-anhydro-6-*O*-(t-butyldimethylsilyl)-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-altritol (23). To a solution of 2,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-1,1-difluoro-3,4-*O*-isopropylidene-D-*ribo*-hex-1-enitol (3) (180 mg, 0.53 mmol) in ethyl acetate (5 ml) was added 10% palladium on charcoal (0.15 g, 0.14 mmol). The apparatus was evacuated and flushed with hydrogen three times. The solution was then stirred under an atmosphere of hydrogen for 18 h. The reaction mixture was filtered through a pad of Celite® and the solvent removed under reduced pressure to give a colourless oil. Column chromatography (1:4 ether:petrol) furnished 2,5-anhydro-6-*O*-(t-butyldimethylsilyl)-1-deoxy-1, 1-difluoro-3,4-*O*-isopropylidene-D-altritol (23) (170 mg, 95%) as a colourless crystalline solid (m.p. 65-67°C). δ_H (500 MHz; $CDCl_3$) 5.84 (1H, ddd, J=57.7, 53.9, 6.7 Hz, H-1), 4.87 (1H, d, J=6.1 Hz, H-4), 4.84 (1H, dd, J=6.1, 4.2 Hz, H-3), 4.26 (1H, m, H-2), 4.20 (1H, m, H-5), 3.82 (1H, dd, J=11.1, 2.9 Hz, H-6a), 3.72 (1H, dd, J=11.1, 2.6 Hz, H-6b),1.50 (3H, s, MeC), 1.34 (3H, s, MeC) 0.89 (9H, s, Me_3CSi), 0.06 (6H, s, Me_2Si); δ_F (84.3 MHz; $CDCl_3$) -127.8 (m); δ_C (67.9 MHz; $CDCl_3$) 115.0 (dd, J=242, 239 Hz), 113.0, 85.6, 83.2, 81.5 (dd, J=30, 24 Hz), 81.3 (d, J= 5 Hz), 65.5, 26.2, 25.9, 25.4, 18.1, -5.6, -5.7; ν_{max} 2931, 1381, 1218, 1162, 1130, 1094 cm^{-1}; m/z 323 (M^+-Me), 281, 167, 77, 73, 59, 43; $[\alpha]_D$= -13.9° (c = 1.01, $CHCl_3$). Found: C 53.16, H 8.39%; $C_{15}H_{28}F_2O_4Si$ requires: C 53.23, H 8.34%.

Preparation of 2,5-anhydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-D-*glycero*-L-*galacto*-heptitol (24). To a solution of 2,5-anhydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-D-*gulo*-hept-1-enitol (4) (570 mg, 1.95 mmol) in absolute ethanol (30 ml) was added 5% palladium on charcoal (437 mg). The apparatus was evacuated and flushed with hydrogen three times. The solution was then stirred under an atmosphere of hydrogen for 1 h. The reaction mixture was filtered through a pad of Celite® and the solvent removed under reduced pressure to give a colourless oil. Column chromatography (1:1 ether:petrol) furnished 2,5-anhydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-D-*glycero*-L-*galacto*-heptitol (24) (561 mg, 98%) as a colourless crystalline solid (m.p. 68°C). δ_H (270 MHz; $CDCl_3$) 5.90 (1H, ddd, J=55.4, 53.2, 6.6 Hz, H-1), 4.77 (1H, dd, J=6.1, 3.7 Hz, H-3), 4.63 (1H, ddd, J=5.8, 4.0, 1.8 Hz, H-4), 4.33 (1H, br dd, J=14.8, 7.2 Hz, H-6), 4.15 (1H, dd, J=8.6, 6.6 Hz, H-7a), 3.69 (1H, m, H-2), 3.65 (1H, dd, J=8.4, 7.4 Hz, H-7b), 3.59 (1H, dd, J=8.1, 3.9 Hz, H-5), 1.48 (3H, s, MeC), 1.44 (3H, s, MeC), 1.34 (3H, s, MeC), 1.22 (3H, s, MeC); δ_F (84.3 MHz; $CDCl_3$) -127.0 (m); δ_C (67.9 MHz $CDCl_3$) 113.6 (dd, J=244, 236 Hz), 112.7, 109.1, 83.7, 80.3 (d, J=7 Hz), 80.0 (dd, J=34, 23 Hz), 79.9, 74.4, 65.1, 25.8, 24.8, 24.5, 23.5; ν_{max} 2937, 1380, 1218, 1162, 1130, 1094, 1070, 975 cm^{-1}; m/z 279 (M^+-Me), 219, 161, 109, 101; Observed (M^+-Me): 279.1038; $C_{12}H_{17}F_2O_5$ requires: 279.1044; $[\alpha]_D$ = +13.6° (c=0.87, $CHCl_3$). Found: C 53.09, H 6.87%; $C_{13}H_{20}F_2O_5$ requires: C 53.05, H 6.85%.

Preparation of 2,5-anhydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-D-*glycero*-D-*galacto*-heptitol (25). To a solution of 2,5-anhydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-D-*glycero*-D-*galacto*-heptitol (7) (290 mg, 1.0 mmol) in ethyl acetate (10 ml) was added 10% palladium on charcoal (250 mg). The apparatus was evacuated and flushed with hydrogen three times. The solution was then stirred under an atmosphere of hydrogen for 14 h. The reaction mixture was filtered through a pad of Celite® and the solvent removed under reduced pressure to give a colourless oil. Column chromatography (1:1 ether:petrol) furnished 2,5-anhydro-1-deoxy-1,1-difluoro-3,4;6,7-di-*O*-isopropylidene-D-*manno*-hept-1-enitol (25) (288 mg, 98%) as a colourless crystalline solid (m.p. 61-64°C). δ_H (270 MHz; $CDCl_3$) 5.90 (1H, ddd, J=57.4, 53.5, 6.6 Hz, H-1), 4.83 (2H, m, H-3, 4), 4.41 (1H, ddd, J=7.8, 5.6, 4.6 Hz, H-6), 4.10 (1H, dd, J=8.8, 5.8 Hz, H-7a), 4.06 (1H, dd, J=8.8, 4.6 Hz, H-7b), 3.69 (1H, m, H-2),

3.60 (1H, dd, J=7.8, 3.2 Hz, H-5), 1.49 (3H, s, MeC), 1.44 (3H, s, MeC), 1.37 (3H, s, MeC), 1.33 (3H, s, MeC); δ_F (84.3 MHz; $CDCl_3$) -127.8 (m); δ_C (67.9 MHz; $CDCl_3$) 114.5 (dd, J=243, 238 Hz), 113.4, 109.4, 82.7, 80.6, 80.5, 80.1 (t, J=23 Hz), 72.8, 66.9, 27.0, 25.6, 25.3, 24.3; ν_{max} (dichloromethane) 2938, 1372, 1116, 1093, 1073, 974 cm^{-1}; m/z 279 (M^+-Me), 221, 165, 119, 101, 43; $[\alpha]_D$= -18.3° (c = 0.78 in $CHCl_3$). Found: C 53.06, H 6.66%; $C_{13}H_{20}F_2O_5$ requires: C 53.05, H 6.85%;.

Preparation of 2, 6-anhydro-1-deoxy-1,1-difluoro-3,4,5,7-tetrakis-*O*-(trimethylsilyl)-D-*glycero*-D-*gulo*-heptitol (26). To a solution of 2, 6-anhydro-1-deoxy-1,1-difluoro-3,4, 5,7-tetrakis-*O*-(trimethylsilyl)-D-*glycero*-D-*gulo*-hept-1-enitol (**8**) (750 mg, 1.50 mmol) in absolute ethanol (10 ml) was added 10% palladium on charcoal (500 mg). The apparatus was evacuated and flushed with hydrogen three times. The solution was then stirred under an atmosphere of hydrogen for 17 h. The reaction mixture was filtered through a pad of Celite® and the solvent removed under reduced pressure. To a solution of the crude residue in dichloromethane (1.5 ml), pyridine (1.5 ml) and diisopropylethylamine (0.26 ml) were added, and freshly distilled chlorotrimethylsilane was added (1.125 ml) dropwise. The mixture was stirred at room temperature for 24 h. Petrol (15 ml) was added and the resultant solution washed with saturated potassium dihydrogen phosphate solution (4.5 ml) and water (1.5 ml). The combined aqueous washings were extracted with petrol (2 x 4 ml). The combined organic phases were washed with saturated sodium bicarbonate (8 ml) and water (8 ml) and dried over Na_2SO_4. Column chromatography (5% ether/petrol) furnished 2,6-anhydro-1-deoxy-1,1-difluoro-3,4,5,7-tetrakis-*O*-(trimethylsilyl)-D-*gluco*-hept-1-enitol (**26**) (595 mg, 78%) as a white solid (m.p. 57-60°C). δ_H (270 MHz; $CDCl_3$) 5.83 (1H, dt, J=52.5, 1.2 Hz, H-1), 3.78 (2H, m, H-7a, 7b), 3.66 (1H, t, J=8.8 Hz, H-5), 3.60 (1H, t, J=8.8 Hz, H-3), 3.42 (1H, t, J=8.6 Hz, H-4), 3.26 (1H, m, H-2), 3.10 (1H, dt, J=9.0, 2.8 Hz, H-6), 0.28 (9H, s, Me_3Si), 0.24 (9H, s, Me_3Si), 0.21 (9H, s, Me_3Si), 0.11 (9H, s, Me_3Si); δ_F (84.3 MHz; $CDCl_3$) -133.0 (m); δ_C (67.9 MHz; $CDCl_3$) 113.5 (t, J=244 Hz), 81.3, 79.0, 78.1 (t, J=20 Hz), 71.2, 71.0 (d, J=3 Hz), 62.3, 1.4, 1.0, 0.8, -0.2; ν_{max} (dichloromethane) 2952, 1165, 1101, 1051, 1028, 867, 846 cm^{-1}; m/z 502 (M^+), 487 (M^+-Me), 412, 399, 332, 147, 73; $[\alpha]_D$= +12.6° (c = 1.36 in $CHCl_3$). Found: C 45.32, H 9.11%; $C_{19}H_{44}F_2O_5Si_4$ requires: C 45.38, H 8.82%.

References

1. Welch, J.T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley and Sons, Inc.: New York, 1991.
2. Welch, J.T., Ed. *Effects of Fluorination on Reactivity*; ACS Symposium Series **456**; American Chemical Society: Washington, DC, 1991.
3. Chambers, R.D.; Jaouhari, R.; O'Hagan, D. *Tetrahedron* **1989**, *45*, 5101.
4. Motherwell, W.B.; Ross, B.C.; Tozer, M.J. *J. Chem. Soc., Chem. Commun.* **1989**, 1437.
5. RajanBabu, T.V.; Reddy, G.S. *J. Org. Chem.* **1986**, *51*, 5458.
6. Fried, J.; Kittisopikul, S.; Hallinan, E.A. *Tetrahedron Lett.* **1984**, *25*, 4329.
7. Hayashi, S.-i.; Nakai, T.; Ishikawa, N.; Burton, D.J.; Naae, D.G.; Kesling, H.S. *Chem. Lett.* **1979**, 983 and references cited therein.
8 Chapleur, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 449.
9. Chapleur, Y. *Synlett* **1991**, 583.

10. Tyuleneva, V.V.; Rokhlin, E.M.; Knunyants, I.L. *Russ. Chem. Rev.* **1981**, *50*, 522.
11. Chambers, R.D. *Fluorine in Organic Chemistry*; John Wiley and Sons, Inc.: New York, 1973.
12. Roberts, J.D.; Sharts, C.M. *Org. Reactions* **1962**, *12*, 1.
13. Flynn, R.M.; Manning, R.G.; Kessler, R.M.; Burton, D.J.; Hansen, S.W. *J. Fluorine Chem.* **1981**, *18*, 525.
14. Burton, D.J.; Naae, D.G.; Flynn, R.M.; Smart, B.E.; Brittelli, D.R. *J. Org. Chem.* **1983**, *48*, 3616.
15. McCarthy, J.R.; Matthews, D.P.; Stemerick, D.M.; Huber, E.W.; Bey, P.; Lippert, B.J.; Snyder, R.D.; Sunkara, P.S. *J. Am. Chem. Soc.* **1991**, *113*, 7439.
16 McCarthy, J.R.; Jarvi, E.T.; Matthews, D.P.; Edwards, M.L.; Prakash, N.J.; Bowlin, T.L.; Mehdi, S; Sunkara, P.S.; Bey, P. *J. Am. Chem. Soc.* **1989**, *111*, 1127.
17. Motherwell, W.B.; Ross, B.C.; Tozer, M.J. *Synlett* **1989**, 68.