Synthesis of the positron-emitting radiotracer [^{18}F]-2-fluoro-2-deoxy-D-glucose from resin-bound perfluoroalkylsulfonates†

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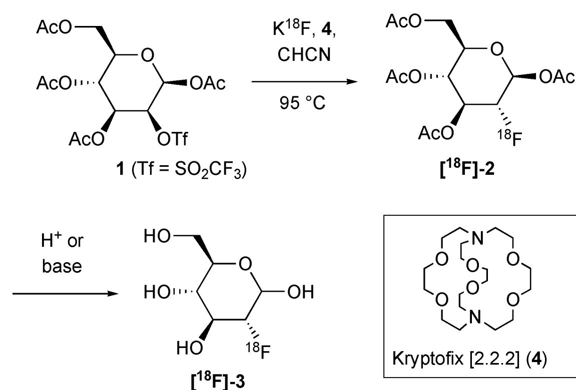
A new approach to the synthesis of 2-fluoro-2-deoxy-D-glucose (FDG, [$^{19/18}$F]-**3**) is described, which employs supported perfluoroalkylsulfonate precursors **33–36**, where the support consists of insoluble polystyrene resin beads. Treatment of these resins with [^{19}F]fluoride ion afforded protected FDG [^{19}F]-**18** as the major product, and the identities of the main byproducts were determined. Acidic removal of the acetal protecting groups from [^{19}F]-**18** was shown to produce [^{19}F]FDG. The method has been applied to the efficient radiosynthesis of the imaging agent [^{18}F]FDG, and was shown to produce the radiochemical tracer in good radiochemical yield (average 73%, decay corrected).

Introduction

Positron-emission-tomography (PET) is a powerful imaging tool,[1] which can be exploited clinically to locate and assess abnormalities in oncology,[2] neurology,[3] and cardiology.[4] Considerable additional interest in PET and microPET also emanates from applications of these techniques in drug discovery and development.[5] [^{18}F]2-Fluoro-2-deoxy-D-glucose ([^{18}F]FDG, [^{18}F]-**3**) is the most widely used radiochemical tracer in PET applications possessing the positron-emitting radionuclide ^{18}F (half-life ~ 110 min).[6,7] [^{18}F]FDG is used to measure glucose uptake into tissue, giving rise to real-time images that can assist in the diagnosis, management and study of diseases such as cancer. [^{18}F]FDG was originally synthesised in the late 1970's by electrophilic fluorination of glucal with $^{18}F_2$ in relatively low yields and limited stereoselectivity.[8] However, this early approach is not currently considered to be suitable for routine radiosynthesis and subsequently, various improved synthetic routes and modifications have been reported,[7,9–13] which are based on nucleophilic fluorination using [^{18}F]fluoride ion.[12]

The most important method is the one conventionally used in PET centres throughout the world, which involves the reaction of a large excess (100 000 fold) of tetra-*O*-acyel-2-*O*-trifluoromethanesulfonyl D-mannose (**1**) with [^{18}F]fluoride ion in the presence of the phase-transfer agent, Kryptofix [2.2.2] (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane, **4**) (Scheme 1).[11,12] Cleavage of the acetate protecting groups from the FDG precursor **2** thus obtained, under basic or acidic conditions produces [^{18}F]FDG.[7–13] Despite the very low chemical yields observed for the nucleophilic fluoridation reactions of triflate **1** (less than 5% based on **1** in the stoichiometric reaction), the use of massive excesses of triflate **1** and limiting [^{18}F]fluoride ion in the radiolabeling step ensures that radiochemical yields typically in excess of 60% are realised.



Scheme 1 Synthesis of [^{18}F]FDG ([^{18}F]-3) used in PET centres.

Reverse phase HPLC purification is impractical for commercial applications due to the short half-life of ^{18}F, which requires the radiotracer to be synthesised and purified as rapidly as possible, and ideally within one hour for clinical use. The methods routinely used for the radiosynthesis of [^{18}F]-FDG have the disadvantage that the protected FDG is produced as a mixture, with a large stoichiometric excess of **1** and other degradation products arising from side reactions of the starting material during fluoridation. This mixture, containing the excess triflate and any other by-products, is submitted to the deprotection conditions to give the desired [^{18}F]FDG, D-glucose and a variety of poorly characterised products.[14] The presence of the by-products is not considered to be detrimental to the patient or the efficacy of the injected product. However, we considered it advantageous to develop a method of synthesis that produced FDG containing reduced amounts of

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† Electronic supplementary information (ESI) available: General experimental procedures; preparations and characterization data for **8**, **9**, **11**; copies of ^{1}H spectra for **8**, **9**, **12**, **14**, **16**, **17**, **18**, **25**, **26**, **27**, **28**, **29**, **30**, **31**, **32**, **38**, crude [^{19}F]fluoridation reaction mixtures from **1** and resin **35**; copies of ^{19}F NMR spectra for **33**, **34**, **35**, **36** and crude [^{19}F]fluoridation reaction mixture from resin **35**; MAS ^{1}H and ^{13}C NMR spectra for **35**; HPLC chromatograms of [^{18}F]-**18**, [^{18}F]-**2**. See DOI: 10.1039/b816032e

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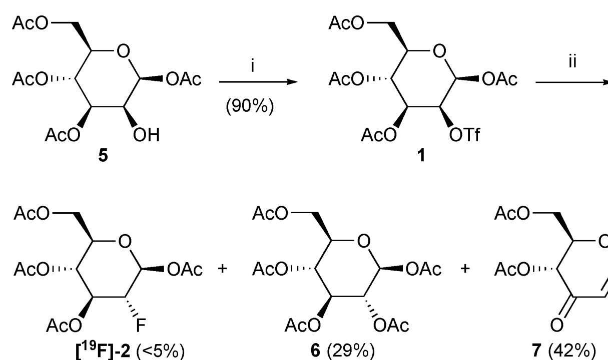
chemical impurity, which could also be applied to the production of other radiotracers containing ^{18}F. In this paper we describe an efficient process for the synthesis of FDG from novel resin-bound perfluoroalkylsulfonate precursors. We also report our studies on the purity profile of the protected product cleaved from the resin using [^{19}F]fluoride ion. In addition, we demonstrate that the methodology is suitable for radiosynthesis of [^{18}F]FDG with high radiochemical yield and improved chemical purity.[15]

Results and discussion

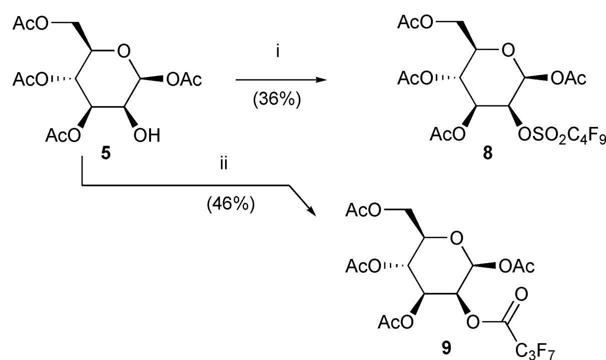
The objective of our research was to develop a platform technology based on solid-supported precursors that would allow the production of ^{18}F-labeled compounds, namely [^{18}F]FDG, by means of a nucleophilic cleavage reaction using [^{18}F]fluoride ion.[15,16] Solid-phase chemistry is readily amenable to automation and is used extensively for the efficient synthesis of oligopeptides, oligonucleotides, and other organic molecules on automated synthesisers.[17] Preparation of labeled radiopharmaceuticals by nucleophilic fluoridation-cleavage of precursors attached to a solid-phase would be advantageous in terms of the purity of the cleaved fluorinated products, whilst facilitating automation of the process and thus offering further protection from radiation exposure and increased reproducibility.[18] The new technology would produce ^{18}F-labeled tracers quickly and with high specific activity yet minimise time-consuming purification steps.

The targeted strategy involved immobilisation of FDG precursor on a solid-support through an highly activated sulfonate leaving group linker that would allow specific cleavage of the radiotracer into solution using [^{18}F]fluoride ion.[19] In principle, unreacted precursor should remain attached to the resin permitting its separation from the product by means of a simple filtration process, thus avoiding the presence of the excess reactive triflate in the deprotection step. Following removal of the protecting groups, the ^{18}F-containing tracer could be passed through disposable cartridges to remove Kryptofix [2.2.2] (**4**) and any residual [^{18}F]fluoride ion, leaving pure product ready for administration.

Preliminary studies concentrated on direct translation of the conventional FDG solution-phase chemistry onto the solid-phase to produce a supported analogue of the triflate **1**. However, progress along these lines was blocked due to limitations imposed by the presence of the base-sensitive acetyl protecting groups. Investigation of the solution reaction of triflate **1** with stoichiometric [^{19}F]fluoride yielded the desired fluoro-sugar [^{19}F]-**2** in less than 5% yield along with elimination product **7**, β-D-glucose pentaacetate (**6**) and some unreacted triflate **1** (Scheme 2).[20] This problem can be overcome in the radiosynthesis by simply employing a very large excess of the triflate **1**, although it would be highly desirable to start from a more chemically efficient fluoridation. However, more serious problems were associated with the preparation of nonaflate **8**, which was chosen as a representative model for more functionalised longer chain perfluoroalkylsulfonate esters (Scheme 3). Even though the triflate **1** can be prepared in good yields (90%) using triflic anhydride,[21] reaction of **4** with nonaflic anhydride led mainly to decomposition of the sugar with significantly reduced yields of the desired nonaflate **8** (36%).[22,23] This result was not encouraging with respect to the synthesis of more complex sugar–perfluoroalkylsulfonates.



Scheme 2 Synthesis of [^{19}F]FDG using stoichiometric fluoride. *Reagents and conditions:* (i) Tf_2O, pyridine, CH_2Cl_2, −15 °C to rt; (ii) $K^{19}F$, **4**, MeCN, 80 °C, 10 min.



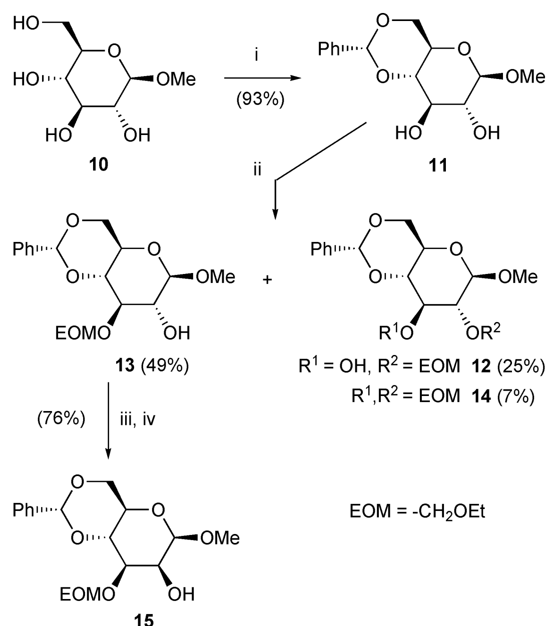
Scheme 3 Reactions of β-D-mannose tetraacetate **5** with nonafluorobutanesulfonyl chloride and nonafluorobutanesulfonic anhydride. *Reagents and conditions:* (i) $(C_4F_9SO_2)_2O$, pyridine, CH_2Cl_2; (ii) $C_4F_9SO_2Cl$, pyridine, AgOTf, THF.

It was clear that challenges associated with preparation of a highly reactive perfluoroalkylsulfonic anhydride linker that contained appropriate functionality to ultimately allow attachment to a solid-support were considerable, causing us to turn our attention to the use of less reactive perfluoroalklysulfonyl halides as sulfonate ester precursors. Accordingly, attempts were made to synthesise the model perfluoroalkylsulfonate **8** from the nonaflic fluoride and chloride in the presence of different bases.[22] The best result was a very disappointing 7% yield of nonaflate **8** when the reaction was carried out in CH_2Cl_2 in the presence of DMAP. Furthermore, most of the reactions conducted under basic conditions were complicated by migration of the acetyl group from the anomeric position to the C2 hydroxyl, which once again highlighted the limitations of the ester protecting group strategy. In an effort to enhance the reactivity of the sulfonyl chloride reagents, and to suppress any further reactions of the desired nonaflate **8** with liberated halide ion, AgOTf was added to the sulfonylation reaction. Surprisingly, the only isolated product was perfluorobutanoate **9** (Scheme 3).

The low reactivity of the perfluorosulfonyl halide reagents towards the alcohol hindered secondary alcohol nucleophile led us to reconsider the perfluorosulfonate formation conditions. It was believed that the sodium salt of a suitably protected mannose derivative would react more effectively with a perfluoroalkylsulfonyl halide to give the desired sulfonyl ester.[22,24] This would require a new protecting group strategy in order to accomplish

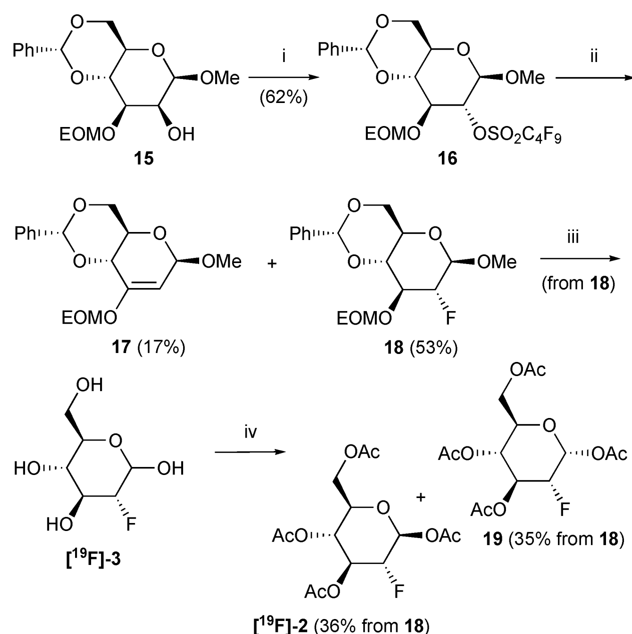
our overall aims. The protection chosen had to be stable to the conditions used to prepare a sugar sulfonate linkage, which would require strong base to deprotonate the secondary alcohol at the 2-position of the sugar. It would also be desirable if the revised protected mannose perfluoroalkylsulfonate could undergo a more efficient fluoridation than that of the tetraacetate **1**, which is a poor substrate. Finally, it was imperative that all of the protecting groups could be removed rapidly in one simple and efficient step that would cause negligible decomposition of FDG. Fortunately, literature precedent suggested that the use of a 4,6-benzylidene acetal in combination with acid-labile protection at the 1- and 3-positions might satisfy all of the above demands.[12c,25] The ethoxymethyl group was selected for protection of the C3 alcohol as it can be removed under similar conditions used to deblock the benzylidene and anomeric methoxy protecting groups.

Our synthetic approach began with the commercially available D-glucose derivative, methyl β-D-glucopyranoside (**10**), which was converted in near quantitative yield to its crystalline 4,6-benzylidene acetal **11**.[26] Reaction of the diol **11** with EOM-Cl gave a mixture of products, from which the desired C2-carbinol **13** was isolated in satisfactory yield (Scheme 4). Inversion of stereochemistry at the 2-position was achieved by means of a two-step sequence involving oxidation of **13** and subsequent stereoselective reduction of the resulting C2-carbonyl function using sodium borohydride to give the protected D-mannose derivative **15** in good yield.[25] The use of the β-anomer was required in order to direct the approach of the hydride reagent to the α-face of the ketone (isolated d.r. ~9 : 1), and to ultimately facilitate nucleophilic attack of fluoride ion at C2, which would also occur from the α-face of the sugar.



Scheme 4 Synthesis of the FDG precursor **15** with base-stable protecting groups. *Reagents and conditions:* (i) benzaldehyde dimethylacetal, CSA, MeCN, Et_3N, rt; (ii) chloromethylethyl ether, NaH, THF, rt; (iii) DMSO, Ac_2O, rt; (iv) $NaBH_4$, THF, CH_3OH, rt.

Following the protecting group switch, we were delighted to discover that the sodium alcoholate, obtained from treatment of alcohol **15** with NaH, reacted smoothly with nonafluorobutanesulfonyl fluoride in THF to give the desired nonaflate **16** (Scheme 5). Furthermore, the subsequent reaction of **16** with Kryptofix [2.2.2] and KF in CH_3CN afforded protected FDG **18** in a substantialy improved 53% yield along with a smaller quantity of an eliminated byproduct **17**. It is significant that similar preparative scale fluoridolysis carried out on the triflate **5** gave an amount of protected [^{19}F]FDG that was barely observable in the ^{1}H NMR spectrum of the crude reaction mixture,[20] thus indicating that **1** was not only less reactive than **16** towards nucleophilic displacement but also significantly more prone to give rise to byproducts. Heating **18** at reflux in 6 N HCl for 10 min resulted in removal of the protecting groups to afford unlabeled FDG [^{19}F]-**3**. The mixture of isomeric fluorosugars was peracetylated to give the α- and β-anomers of 2-deoxy-2-fluoro-β-D-glucopyranoside tetraacetate, which were separated and fully characterised as single compounds.[27] The structures were confirmed by comparison against authentic samples prepared from a commercial [^{19}F]FDG standard, under identical conditions. A more detailed optimization of the conditions for deprotection of **18** was postponed until the radiochemistry studies. These studies clearly showed that the acetal protected substrate **16** was a superior precursor to FDG in terms of the chemical synthesis.



Scheme 5 Synthesis of [^{19}F]FDG from a model for the solid-supported perfluoroalkylsulfonate. *Reagents and conditions:* (i) $C_4F_9SO_2F$, NaH, THF, rt; (ii) **4**, KF, MeCN, reflux, 10 min; (iii) 6 M HCl, reflux, 10 min; (iv) Ac_2O, pyridine.

Now that the viability of the overall approach had been demonstrated using the nonaflate **16** as a model for a perfluoroalkylsulfonate linker, we were able to turn our attention to the synthesis of a sugar-linker construct. Recent publications have described a perfluoroalkylsulfonyl fluoride linker, which when attached to a resin allows coupling of phenols and subsequent release of a range of substituted arenes, biaryls and biaryl amides into solution (Scheme 6).[28]

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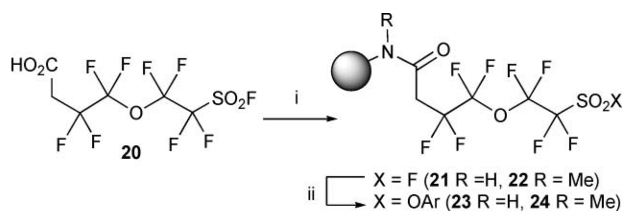


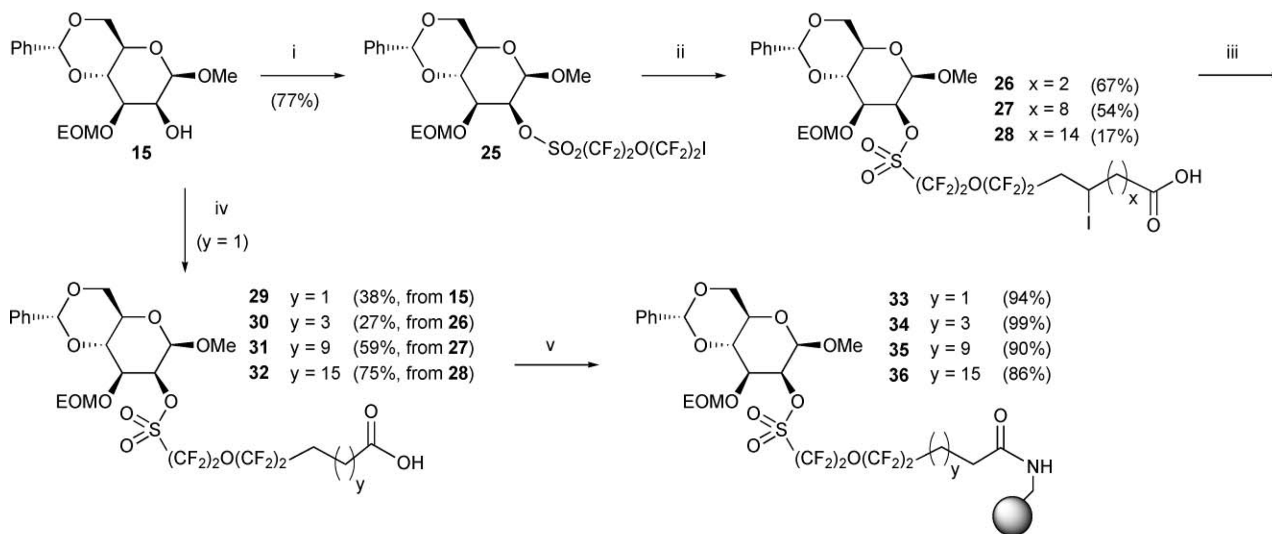
Scheme 6 Previously reported syntheses of perfluoroalkylsulfonate linkers.[28] *Reagents and conditions:* (i) (a) $(CO)_2Cl_2$, CH_2Cl_2, DMF; (b) amine resin, CH_2Cl_2, *i*-Pr_2NEt; (ii) ArOH, K_2CO_3, DMF.

However, this linker proved unsatisfactory for our application due to a number of significant shortcomings. Firstly, the yields obtained for the coupling of mannose derivative to the linker in solution or after attachment to the resin were poor, and we observed elimination of [19F]fluoride ion from the linker under basic conditions. In addition, when the coupling of the sugar is carried out on a resin-bound sulfonyl fluoride, any resin-bound sulfonyl [19F]fluoride **21** unreacted in the coupling could exchange with [18F]fluoride ion in the subsequent labeling studies, thereby producing unlabeled FDG and lowering the radiochemical yield and purity of the product. Potential for loss of [19F]fluoride ion from the linker was a major concern because limiting [18F]fluoride ion (<10 μmol) is used in the synthesis of [18F]FDG. It was therefore decided that a different linker was required, which would be less prone to elimination and that would be suitable for the formation of a sugar–linker conjugate in solution ready for coupling with the resin.

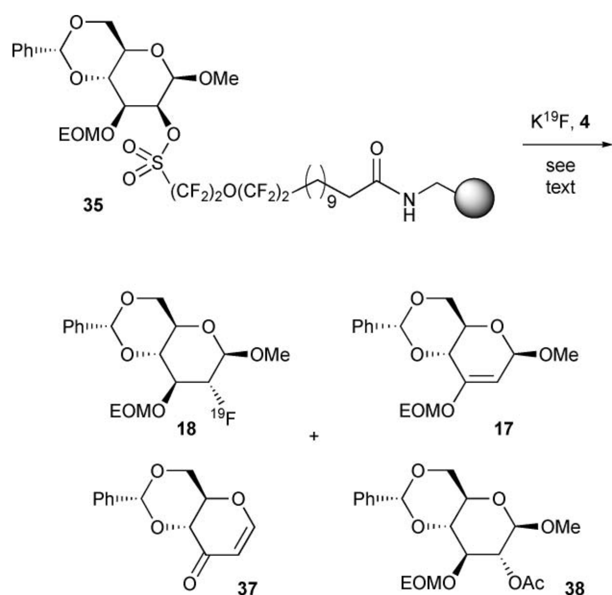
The strategy that ultimately proved to be successful involved preparation of the linker–sugar conjugate in solution and subsequent attachment to an amino resin (Scheme 7). Importantly, this approach should minimise the potential for release of [19F]fluoride ion from the linker, either due to E1cb elimination of $H^{19}F$ or through exchange with residual unreacted SO_2F groups present within the resin. A variety of different linker–sugar conjugates were prepared (**29–32**) by firstly coupling the alkoxide of the mannose derivative **15** to 5-iodooctafluoro-3-oxapentanesulfonyl fluoride. Initial formation of the sulfonate ester gave poor repeatability and yields using NaH as the base, but the results were dramatically improved by using NaHMDS to preform the alkoxide. With the iodide **25** in hand, radical-mediated coupling reactions were carried out with a series of enoic acids of varying chain lengths.[29] The lower yield observed using the l6-heptadecenoic acid was due to the poor solubility of this olefin in the reaction solvents. Reaction of acrylic acid with iodide **25** provided the reduced product **29** directly, whereas transfer of the iodine atom was observed in reactions of the longer alkenoic acids. The resulting iodoacids **26–28** were easily de-iodinated by refluxing in Et_2O–AcOH in the presence of zinc powder.[30] Gratifyingly, the protecting groups on the sugar and the perfluoroalkylsulfonate ester survived these acidic conditions by careful control of reaction time and temperature.

A range of different coupling agents and conditions were investigated for the attachment of acids **29–32** to aminomethyl polystyrene ($–NH_2$ = 1.5 mmol g^{-1}), and it was found that the resins **33–36** could be prepared in high yields (estimated from masses of dry resins) using diphenylphosphoryl chloride as the source of activation. Successful formation of the desired supported sulfonate esters was confirmed by on-bead IR, elemental analysis, ^{19}F NMR, MAS ^1H and ^{13}C NMR. With a view to reducing the ultimate cost of the resin for commercial application, resins **35** with lower loading levels were also synthesized by using limiting amounts of the acid **31**. Any unreacted aminomethyl groups were capped by treatment with Ac_2O and pyridine. The synthesis of one resin **35** (0.1 mmol g^{-1} by sulfur analysis) was conducted on a multi-kilogram scale.

Fluoridation experiments using [19F]fluoride ion were carried out in order to demonstrate that protected [19F]FDG could be released from the resin (Scheme 8). Replicating the radiochemical fluoridation conditions on a preparative scale is difficult to achieve due to the large ratio of FDG precursor to fluoride ion that is typically used in the radiosynthesis, so one would expect a significantly different product distribution. Nonetheless, these experiments would provide insight into the identity of any potential byproducts



Scheme 7 Preparation of the solid-supported FDG precursors **33–36**. *Reagents and conditions:* (i) $ICF_2CF_2OCF_2CF_2SO_2F$, NaHMDS (1.0 M in THF), THF, rt; (ii) $CH_2{=}CH(CH_2)_nCOOH$ where n = 2, 8 or 14; $NaHCO_3$, $Na_2S_2O_4$, MeCN, H_2O, rt; (iii) Zn, AcOH, Et_2O, reflux; (iv) $CH_2{=}CHCOOH$; $NaHCO_3$, $Na_2S_2O_4$, MeCN, H_2O, rt; (v) amino-methylated polystyrene, $(PhO)_2POCl$, *i*-Pr_2NEt, CH_2Cl_2, rt.



Scheme 8 [^{19}F]Fluoridation studies using resin **35**.

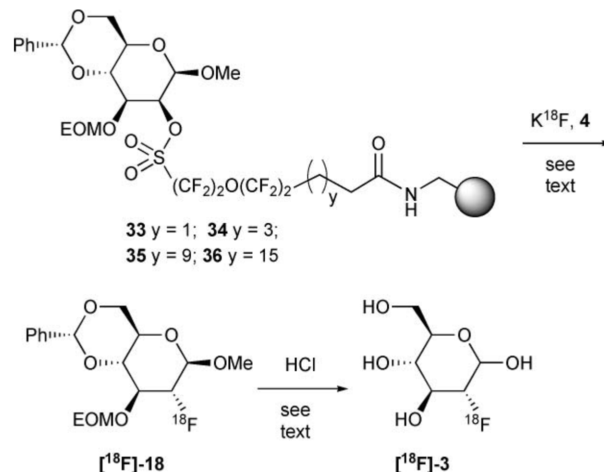
that could be generated during the radiochemistry. Fluoridolysis of the supported D-mannose derivative **35** (0.1 mmol g^{-1}) was explored by using excess [^{19}F]fluoride ion (10 equiv) in the first instance, in order to cleave all of the material from the solid-phase. The two expected major products **17** and **18** and two lesser ones **37** and **38** were released from the resin in ratios of 31 : 80 : 1 : 13 (**17** : **18** : **37** : **38**; estimated from ^{1}H NMR and HPLC analysis of the crude product). The NMR (^{1}H and ^{19}F) spectra also showed the presence of a large quantity of Kryptofix [2.2.2] (**4**) and complexed K^{19}F in the crude product. During the radiosynthesis of [^{18}F]FDG, these contaminants are removed by sequential elution through disposable cartridges (*e.g.* C18, alumina or ion exchange). For our purposes, passage through a short plug of silica gel served to remove the excess reagents, leaving only three significant components (**17**, **18** and **38**) observable by ^{1}H NMR and only one fluorinated product **18** (^{19}F NMR: $\delta = -37.30$ ppm, ref. C_6F_6). Complete cleavage of the sugar from the resin was confirmed by the loss of the ^{19}F NMR signal at –114 ppm (referenced to $CFCl_3$) due to the diastereotopic CF_2SO_3R fluorines, and the presence of an additional signal at –118 ppm due to the new CF_2SO_3K group.

Formation of eliminated byproduct **17** was expected from the fluoridation studies carried out on nonaflate **16**, and the minor byproduct **37** arises from further degradation of **17**. However, the observation of a new substitution product **38** resulting from acetate displacement of the sulfonate linker was not expected from earlier solution studies. The formation of the glucose derivative **38** could either be due to acetate present due to the capping step or from degradation of the acetonitrile solvent. In order to establish the origin of the acetate group, the reaction mixture from the fluoridation of nonaflate **16** was carefully reevaluated with the confirmation that acetate **38** was not formed in the solution reaction. This result strongly suggested that the acetate was coming from the capping step performed during the synthesis of the lower loading resin. The protected glucose derivative **38** is not considered to be harmful due to its conversion to D-glucose upon deprotection. However, these findings may be significant for the fluoridation of other substrates and the synthesis of lower loading resins should be modified to avoid the use of acetate capping. It is noteworthy that β-D-glucose pentaacetate (**6**) is a major side product from the fluoridation of the mannose triflate **1**, but in this case, the acetate comes from degradation of the starting material.

Fluoridolysis using limiting fluoride proceeded similarly to give **17** and **18** as the major products, and the recovered resin was shown to release further protected [^{19}F]FDG for up to four cycles. These conditions more closely resembled the proposed radiochemistry and clearly demonstrated that unreacted sulfonate ester remained attached to the solid-phase. Collectively, the above experiments showed that we had successfully developed a resin that was capable of releasing a protected FDG derivative **18** when exposed to [^{19}F]fluoride ion, and that the crude product was readily separated from any unreacted starting material and the reagents. Furthermore, the crude protected FDG prepared in this way was of vastly superior chemical purity compared to the corresponding crude tetraacetate [^{19}F]-**2** obtained using the conventional fluoridation procedure (see Scheme 2).[20] Finally, any concerns relating to the efficiency of nucleophilic cleavage due to poor swelling of the polystyrene resin in MeCN were allayed.

Radiochemical results

The excellent results obtained from the [^{19}F]fluoridolysis using the resin-bound D-mannose derivative **35** set the stage for the radiochemistry studies. Low activity labeling experiments were carried out manually using K^{18}F (185–350 MBq) and Kryptofix [2.2.2] (**4**) in CH_3CN, and radiochemical yields were established by reversed-phase HPLC analysis of the protected product [^{18}F]-**18** using UV and γ-detection (Scheme 9). Conventional solution-phase ^{18}F labeling typically results in 80–90% incorporation after 2 minutes at 86 °C in 1–2 mL reaction volumes.[9] In the present study involving heterogeneous reaction mixtures containing the solid-supported precursors **33–36**, advantage was gained from reducing the reaction volume to 0.2 mL to increase the concentration of the [^{18}F]fluoride ion solution. Using resin **35**, labeling times of 10–15 minutes were initially used to ensure maximum incorporation of ^{18}F into [^{18}F]-**18**. However, it transpired that even after 3–4 minutes, levels of [^{18}F] incorporation between 70–91% were achieved and no further improvement was obtained from longer reaction times (10–15 minutes). Incorporation gradually



Scheme 9 Synthesis of [^{18}F]-FDG from resin-bound precursors.

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Table 1 Determination of optimum conditions for global deprotection of [^{18}F]-**18**

Entry	HCl (M)	Temp (°C)	Time (min)	% Cleavage[a]
1	6	110	10	90
2	6	110	5	52
3	6	125	10	97
4	6	125	5	97
5	5	125	5	81
6	4	125	5	52

[a] Determined by ion exchange HPLC measuring radioactivity.

improved with increasing temperature up to 86 °C; beyond this, there was no significant effect upon the radiochemical yield. High activity labeling studies (5.18–6.16 Ci) were also conducted, and excellent incorporation yields in the range of 68–77% were realised.

Five sequential labeling experiments re-using the same sample of resin **35** all led to the formation of protected [^{18}F]FDG with consistently high radiochemical yields. These experiments clearly demonstrate that the majority of the protected mannose derivative remains attached to the resin through the fluoroalkylsulfonyl linker during the [^{18}F]-labeling experiment, and that one batch of the resin could be used to generate multiple doses of the radiotracer.

To identify the optimum conditions required for removal of the protecting groups, a sample of the protected [^{18}F]fluoro-sugar [^{18}F]-**18** was subjected to a range of strongly acidic conditions (Table 1). Dionex anion exchange HPLC with γ-detection was used to quantify [^{18}F]FDG produced. Heating the protected product in 6 N HCl at 110 °C for ten minutes achieved a high percentage deprotection. However, reducing the heating time to five minutes resulted in a significant drop in the yield of [^{18}F]FDG.

In radiosynthesis using [^{18}F]fluoride ion, it is desirable to keep the reaction time as short as possible and the preferred conditions for the generation of [^{18}F]FDG required ^{18}F labeling at 86 °C for 4 minutes in CH_3CN followed by deprotection with 6 M HCl for five minutes at 125 °C. This produced an average radiochemical yield of 73% (decay corrected) and activity losses on the resin ranged between 3–8%, with 91–97% of the activity being collected. Deprotection of [^{18}F]-**18** using 6 M HCl, 125 °C for 5 minutes provided a radioactive ion-exchange chromatogram with one main peak ([^{18}F]FDG) and one small peak (<3%) corresponding to partially deprotected [^{18}F]FDG (Fig. 1). The major radioactive peak (black trace) was shown to co-elute with an authentic sample of [^{19}F]FDG (not shown) indicating that almost complete deprotection had occurred. The chromatogram from the electrochemical detector (grey trace) shows that the protected glucose formed as a side product in the initial fluoridation reaction to prepare [^{18}F]-**18** has been deprotected and some other decomposition products formed. The formation of these by-products are a consequence of residual water present in the [^{18}F]fluoride solution and elimination due to the use of excess base in the labeling process. Comparison of the chromatograms generated using electrochemical and γ-detectors indicates that [^{18}F]FDG was produced with high specific activity. The neutralized deprotection reaction mixture was analysed further for non-polar impurities by reversed phase HPLC, identifying benzaldehyde as the major non-polar impurity. Benzaldehyde was readily removed by passage of the reaction mixture through a C18 Sep-Pak® cartridge (benzaldehyde retained).

As a qualitative comparison of the chemical purity of the protected FDG [^{18}F]-**18** from the resin precursor **35** with the protected FDG product [^{18}F]-**2** obtained from the conventional solution synthesis method, HPLC analyses of the crude products were undertaken. As expected, both radioactivity traces indicated that the protected fluorinated sugars and [^{18}F]fluoride were the major [^{18}F]-containing compounds present. By contrast, the corresponding UV activity traces showed that the protected [^{18}F]-sugar obtained from the resin precursor **35** contained significantly reduced levels of chemical impurities.

We also investigated the effect of altering the linker chain length on the radiochemical yield for resins **33–36** (Table 2). Radiochemical yield improved with increasing alkyl chain length up to four methylene groups, after which it leveled off and then began to fall. Economically and synthetically, it was more practical to use the ten-carbon spacer, and given the high radiochemical yield achieved, immobilized sulfonate ester **35** ($y = 9$) contained the linker length of choice.

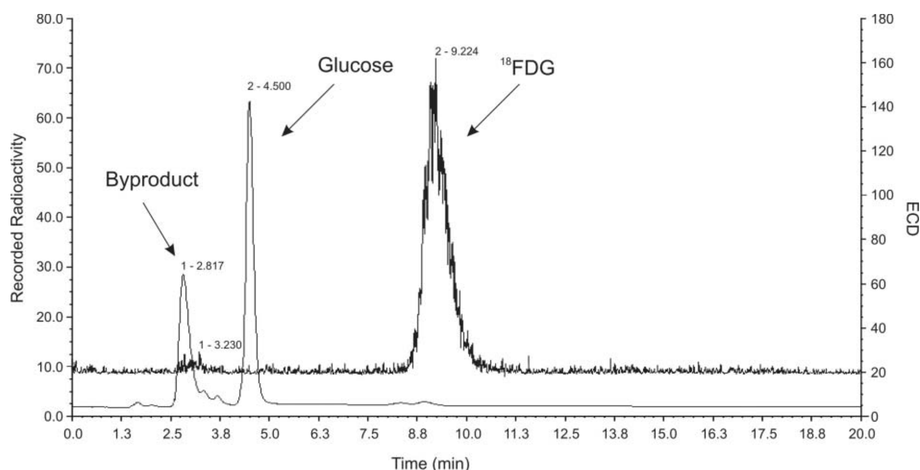

Fig. 1 Dionex anion exchange resin HPLC of the reaction mixture from entry 4, Table 1. Upper line; radioactivity trace. Lower line; electrochemical detector.

Table 2 Showing the effect of increasing linker chain length on the radiochemical yield of [^{18}F]-**18** and remaining [^{18}F]fluoride ion. (C_1 resin was synthesised by coupling methyl-4,6-*O*-benzylidene-3-*O*-ethoxymethyl-β-D-mannopyranoside (**15**) to resin **21**)

Entry	Linker length (*y*)	Radiochemical yield (%)[a]	[^{18}F]fluoride remaining (%)[a]
1	0	45–50	50–55
2	1	75	25
3	3	92	8
4	9	85–90	10–15
5	15	77	23

[a] Determined by HPLC with γ-detection (decay corrected).

Conclusions

We have described the synthesis of solid supports that liberate protected [^{18}F]FDG on treatment with [^{18}F]fluoride ion in high radiochemical yield, and we have shown that most of the unreacted precursor remains on the resin thereby avoiding the presence of excess triflate in subsequent deprotection steps. The product [^{18}F]-**18** can be easily and rapidly deprotected and purified to give the widely used radiotracer [^{18}F]FDG with high radiochemical purity. The general approach lends itself to automation of the radiosynthesis because the solid-supported precursor could be packaged in a suitable cartridge format. This new platform technology would be suited to the production of [^{18}F] radiopharmaceuticals where the presence of excess starting materials would have a deleterious effect on the efficacy of the product or the patient, particularly when purification of the radiotracer is impractical.

Experimental section

Methyl-4,6-*O*-benzylidene-3-*O*-ethoxymethyl-β-D-glucopyranoside (13)

To methyl-4,6-*O*-benzylidene-β-D-glucopyranoside (**11**, 847 mg, 3.0 mmol) in anhydrous THF (40 mL) was added NaH (60% in mineral oil, 192 mg, 4.8 mmol) and the mixture stirred, under argon, for 30 min. Chloromethylethyl ether (425 mg, 0.42 mL, 4.5 mmol) was added dropwise, and the reaction stirred at room temperature for 20 h. The reaction was quenched with methanol (0.5 mL) and concentrated *in vacuo.* The crude product was dissolved in CH_2Cl_2, washed with water and the aqueous phase extracted with CH_2Cl_2. The combined organic phase was washed with water, brine, dried (anhydrous Na_2SO_4) and concentrated *in vacuo.* Purification by silica gel column chromatography (hexane–EtOAc, 2 : 1) afforded three isolated products: compound **12** (white solid, 260 mg, 0.76 mmol, 25%), compound **13** (white solid, 500 mg, 49%) and compound **14** (white solid, 82 mg, 0.21 mmol, 7%). Data for **13**: mp 99–102 °C; $[\alpha]_D$ −11.3° ($c = 0.488$, $CHCl_3$); ν_{max} (neat, cm^{-1}) 3450, 2876, 1727, 1380, 1100, 1069, 1026; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.30 (5H, m), 5.53 (1H, s), 4.85 (1H, d, $J = 7.4$ Hz), 4.78 (1H, d, $J = 7.4$ Hz), 4.38 (1H, d, $J = 7.4$ Hz), 4.37 (1H, dd, $J = 5.2$, 10.3 Hz), 4.00 (1H, d, $J = 1.5$ Hz), 3.84–3.74 (2H, m), 3.66 (1H, t, $J = 8.1$ Hz), 3.62–3.56 (2H, m), 3.60 (3H, s), 3.58–3.40 (2H, m), 1.21 (3H, t, $J = 6.6$ Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 137.25, 129.28, 128.40, 126.33, 104.53, 101.77, 96.68, 82.17, 79.71, 74.09, 68.86, 66.55, 64.39, 57.67, 15.02; MS (ES$^+$) m/z 363.1 ([M + Na]$^+$); Anal. Calcd for $C_{17}H_{24}O_7$: C, 59.99; H, 7.11. Found: C, 59.83; H, 7.14.

Data for methyl-4,6-*O*-benzylidene-2-*O*-ethoxymethyl-β-D-glucopyranoside (12)

Mp 103–105 °C; $[\alpha]_D$ −20.8° ($c = 0.606$, $CHCl_3$); ν_{max} (neat, cm^{-1}) 3437, 2975, 2879, 1453, 1390, 1089, 1046, 1025; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51–7.30 (5H, m), 5.56 (1H, s), 4.89 (1H, d, $J = 6.6$ Hz), 4.79 (1H, d, $J = 7.4$ Hz), 4.38 (1H, d, $J = 7.4$ Hz), 4.36 (1H, dd, $J = 5.2$, 10.3 Hz), 4.02 (1H, s), 3.85–3.75 (3H, m), 3.62–3.55 (2H, m), 3.56 (3H, s), 3.46 (1H, ddd, $J = 4.4$, 9.5, 10.3 Hz), 3.34 (1H, t, $J = 8.1$ Hz), 1.21 (3H, t, $J = 6.6$ Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 137.08, 129.14, 128.26, 126.30, 103.47, 101.88, 96.67, 83.34, 80.59, 72.71, 68.70, 66.08, 64.33, 57.41, 15.01; MS (ES$^+$) m/z 363.3 ([M + Na]$^+$).

Data for methyl-4,6-*O*-benzylidene-2,3-*O*-di(ethoxymethyl)-β-D-glucopyranoside (14)

Mp 73–75 °C; $[\alpha]_D$ −62.2° ($c = 0.475$, $CHCl_3$); ν_{max} (neat, cm^{-1}) 2975, 2880, 1455, 1390, 1095, 1046, 1028; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.30 (5H, m), 5.52 (1H, s), 4.90 (1H, d, $J = 6.6$ Hz), 4.89 (2H, s), 4.83 (1H, d, $J = 6.6$ Hz), 4.36 (1H, d, $J = 8.1$ Hz), 4.35 (1H, dd, $J = 4.4$, 10.3 Hz), 3.87 (1H, t, $J = 9.2$ Hz), 3.77 (1H, t, $J = 10.3$ Hz), 3.71–3.52 (6H, m), 3.54 (3H, s), 3.43 (1H, ddd, $J = 5.1$, 9.6, 10.3 Hz), 1.22 (3H, t, $J = 7.0$ Hz), 1.05 (3H, t, $J = 6.6$ Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 137.35, 129.18, 128.35, 126.29, 104.73, 101.65, 95.97, 80.89, 78.13, 76.89, 68.95, 66.23, 63.98, 63.75, 57.39, 15.13, 14.91; MS (ES$^+$) m/z 421.4 ([M + Na]$^+$).

Methyl-4,6-*O*-benzylidene-3-*O*-ethoxymethyl-β-D-mannopyranoside (15)

A solution methyl-4,6-*O*-benzylidene-3-*O*-ethoxymethyl-β-D-glucopyranoside (**13**, 14.0 g, 41.2 mmol) in DMSO (168 mL) and Ac_2O (84.5 mL, 0.943 mol) was stirred at room temperature for 24 h. The reaction was diluted with EtOAc (1 L) and washed with a saturated aqueous solution of K_2CO_3 (600 mL). The organic layer was separated, dried (Na_2SO_4) and concentrated to dryness *in vacuo* giving the crude ketone as a white solid (20 g). The crude ketone (20 g) was re-dissolved in MeOH (200 mL) and cooled to −20 °C before $NaBH_4$ (1.69 g, 44.4 mmol) was added slowly, with stirring. The reaction mixture was allowed to warm to 25 °C then stirred at this temperature for a further 48 h. The reaction was concentrated *in vacuo* to give a gum which was partitioned between EtOAc (250 mL) and saturated aqueous K_2CO_3. The organic layer was separated re-extracting the aqueous with EtOAc (2 × 100 mL). The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo.* Purification of the resulting off-white solid by silica gel column chromatography (hexane–EtOAc, 1 : 3) afforded the title compound as a white solid (**15**, 10.62 g, 31.2 mmol, 76%) in addition to some mixed fractions containing some of compound **15** (2.74 g) and pure **13** (1.54 g, 4.0 mmol, 10%). Data for **15**: mp 106–108 °C; $[\alpha]_D$ −38.7° ($c = 0.375$, $CHCl_3$); ν_{max} (neat, cm^{-1}) 3473, 2971, 2891, 1738, 1375, 1092, 1030; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.30 (5H, m), 5.56 (1H, s), 4.91 (1H, d, $J = 6.9$ Hz), 4.83 (1H, d, $J = 6.9$ Hz), 4.50 (1H, s), 4.34 (1H, dd, $J = 5.2$, 10.3 Hz), 4.17 (1H, dd, $J = 1.5$, 2.2 Hz), 4.06 (1H, t, $J = 9.6$ Hz), 3.91 (1H,

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dd, J = 2.9, 9.5 Hz), 3.88 (1H, t, J = 10.3 Hz), 3.73–3.60 (2H, m), 3.58 (3H, s), 3.40 (1H, ddd, J = 5.2, 9.6, 10.3 Hz), 2.59 (1H, d, J = 1.5 Hz), 1.17 (3H, t, J = 7.0 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 137.48, 129.15, 128.36, 126.25, 101.87, 101.50, 94.91, 77.65, 74.89, 70.56, 68.74, 67.13, 63.79, 57.50, 15.16; MS (ES$^+$) m/z 703.2 ([2M + Na]$^+$); HRMS (ES) Calcd for $C_{17}H_{24}O_7Na$: 363.1414. Found 363.1416; Anal. Calcd for $C_{17}H_{24}O_7$: C, 59.99; H, 7.11. Found: C, 59.90; H, 7.12.

Methyl-4,6-*O*-benzylidine-3-ethoxymethyl-2-(1,1,2,2,3,3,4,4,4-nonafluoro-butane-sulfonate)-β-D-mannopyranoside (16)

To a solution of **15** (204 mg, 0.6 mmol) in anhydrous THF (8 mL) was added NaH (60% in mineral oil, 43 mg, 1.1 mmol) and the reaction stirred, under argon, at room temperature for 30 min. Perfluoro-*n*-butylsulfonyl fluoride (290 mg, 0.1 mmol), was added, dropwise, and the reaction stirred for a further 1.5 h. The reaction was quenched with methanol and concentrated *in vacuo.* The crude product was dissolved in CH_2Cl_2, washed with water and the aqueous phase extracted with CH_2Cl_2. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated *in vacuo.* Purification by silica gel column chromatography (hexane–EtOAc, 2 : 1) afforded the title compound as a white solid (**16**, 233 mg, 62%). Mp 93–95 °C; $[\alpha]_D$ −56.7° (c = 0.425, $CHCl_3$); ν_{max} (film, cm^{-1}) 2944, 1714, 1410, 1353, 1197, 1143, 1078, 934; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.33 (5H, m), 5.59 (1H, s), 5.15 (1H, d, J = 3.0 Hz), 4.87 (1H, d, J = 6.9 Hz), 4.78 (1H, d, J = 7.4 Hz), 4.62 (1H, s), 4.36 (1H, dd, J = 5.0, 10.9 Hz), 4.15 (1H, dd, J = 3.0, 9.9 Hz), 3.91 (1H, t, J = 9.4 Hz), 3.90 (1H, t, J = 10.4 Hz), 3.74–3.59 (2H, m), 3.58 (3H, s), 3.46 (1H, ddd, J = 4.5, 9.5, 9.9 Hz), 1.15 (3H, t, J = 6.9 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 137.10, 129.29, 128.37, 126.19, 101.93, 99.15, 94.09, 83.83, 77.36, 71.01, 68.44, 67.59, 63.98, 57.49, 14.99; ^{19}F NMR (282 MHz, $CDCl_3$, ref. C_6F_6) δ 81.27, 52.03, 40.89, 35.83.

Solution-phase fluoridation: preparation of 17 and 18

A solution of **16** (124 mg, 0.20 mmol), 1,10-diaza-4,7,13,16,21,24-hexaoxabicyclo[8,8,8] hexacosan (90 mg, 0.24 mmol) and KF (14 mg, 0.24 mmol) in MeCN (4 mL) was vigorously refluxed, under argon, for 10 min. The reaction was cooled and concentrated *in vacuo.* The crude product was dissolved in CH_2Cl_2, washed with water and the aqueous phase re-extracted with CH_2Cl_2. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated *in vacuo.* Purification by silica gel column chromatography (hexane–Et_2O, 2 : 1) afforded compound **18** (36 mg, 53%) and compound **17** (11 mg, 17%). Data for methyl-4,6-*O*-benzylidene-3-*O*-ethoxymethyl-2-deoxy-2-fluoro-β-D-glucopyranoside (**18**): mp 44–46 °C; $[\alpha]_D$ −22.9° (c = 0.431, $CHCl_3$); ν_{max} (film, cm^{-1}) 2972, 2885, 1454, 1383, 1095, 1030; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.32 (5H, m), 5.53 (1H, s), 4.91 (1H, d, J = 6.6 Hz), 4.83 (1H, d, J = 6.6 Hz), 4.52 (1H, dd, J = 3.7, 7.7 Hz), 4.37 (1H, dd, J = 5.2, 10.3 Hz), 4.26 (1H, td, J = 7.7, 49.3 Hz), 4.09 (1H, td, J = 9.2, 15.4 Hz), 3.78 (1H, t, J = 10.3 Hz), 3.69–3.57 (3H, m), 3.60 (3H, s), 3.51–3.45 (1H, m), 1.12 (3H, t, J = 7.4 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 137.12, 129.29, 128.39, 126.25, 102.30 (d, J = 23.7 Hz), 101.68, 95.39, 92.55 (d, J = 186.8 Hz), 80.13 (d, J = 9.2 Hz), 75.15 (d, J = 18.8 Hz), 68.69, 66.38, 63.52, 57.61, 14.90; ^{19}F NMR (282 MHz, $CDCl_3$, ref. C_6F_6) δ −37.30 (ddd, J = 4.6, 16.2, 53.3 Hz); MS (ES$^+$) m/z 365.1 ([M + Na]$^+$); HRMS (ES) Calcd for $C_{17}H_{23}O_6FNa$: 365.1371. Found 365.1369.

Data for methyl-4,6-*O*-benzylidene-3-*O*-ethoxymethyl-2-deoxy-β-D-erythro-hex-2-enopyranoside (17)

Mp 77–79 °C; $[\alpha]_D$ +11.9° (c = 0.118, $CHCl_3$); ν_{max} (film, cm^{-1}) 2927, 2865, 1692, 1590, 1248, 1138, 1094; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.34 (5H, m), 5.61 (1H, s), 5.39 (1H, dd, J = 1.5, 2.2 Hz), 5.10 (2H, s), 4.99 (1H, t, J = 1.5 Hz), 4.40 (1H, dt, J = 2.2, 8.1 Hz), 4.32 (1H, dd, J = 4.4, 9.5 Hz), 3.90 (1H, t, J = 9.5 Hz), 3.80 (1H, ddd, J = 4.4, 8.1, 10.3 Hz), 3.68 (2H, q, J = 7.4 Hz), 3.47 (3H, s), 1.22 (3H, t, J = 7.4 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 153.03, 137.21, 129.15, 128.37, 126.42, 102.37, 100.06, 99.73, 92.86, 74.76, 69.19, 68.94, 64.73, 54.68, 15.11; MS (ES$^+$) m/z 255.0 ([M − C_6H_5CH + Na]$^+$), 233.1 ([M − C_6H_5CH]$^+$).

Preparation of FDG tetraacetates [^{19}F]2 and 19

A solution of **18** (59 mg, 0.17 mmol) in 6 N HCl (2 mL) was refluxed at 140 °C (bath) for 10 min. The reaction was concentrated *in vacuo* and Ac_2O (0.5 mL) and pyridine (1.0 mL) were added. The reaction was stirred at room temperature overnight, concentrated and purified by silica gel column chromatography (hexane–EtOAc 2 : 1) to afford compounds [^{19}F]**2** (22 mg, 36%) and **19** (21 mg, 35%).

Data for 2-fluoro-2-deoxy-β-D-glucopyranoside tetraacetate [^{19}F]2

$[\alpha]_D$ +43° (c = 0.41, CH_2Cl_2), lit.[31] $[\alpha]_D$ +50°; ν_{max} (film, cm^{-1}) 2957, 1748, 1434, 1369, 1212, 1072, 1035; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (1H, dd, J = 3.2, 8.1 Hz), 5.38 (1H, td, J = 9.6, 15.5 Hz), 5.08 (1H, t, J = 9.6 Hz), 4.45 (1H, ddd, J = 8.1, 9.6, 51 Hz), 4.30 (1H, dd, J = 4.4, 12.5 Hz), 4.10 (1H, dd, J = 2.0, 12.5 Hz), 3.87 (1H, ddd, J = 2.0, 4.4, 9.6 Hz), 2.19 (3H, s), 2.10 (3H, s), 2.09 (3H, s), 2.05 (3H, s); ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.72, 170.04, 169.70, 168.99, 91.65 (d, J = 24 Hz), 88.60 (d, J = 192 Hz), 73.17, 73.12 (d, J = 19 Hz), 68.03 (d, J = 8 Hz), 61.75, 20.98, 20.86, 20.80, 20.71; ^{19}F NMR (282 MHz, $CDCl_3$, ref. C_6F_6) δ −39.05 (m). Spectroscopic data consistent with those reported previously in the literature.[20a]

Data for 2-deoxy-2-fluoro-α-D-glucopyranoside tetraacetate (19)

$[\alpha]_D$ +119° (c = 0.53, CH_2Cl_2), lit.[32] $[\alpha]_D$ +147° (c = 1.0, $CHCl_3$); ν_{max} (film, cm^{-1}) 2963, 1746, 1434, 1370, 1213, 1078, 1036; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.44 (1H, d, J = 4.4 Hz), 5.50 (1H, td, J = 9.6, 12.5 Hz), 5.08 (1H, t, J = 9.6 Hz), 4.66 (1H, ddd, J = 4.4, 9.6, 49 Hz), 4.30 (1H, dd, J = 4.4, 12.5 Hz), 4.13–4.00 (2H, m), 2.21 (3H, s), 2.10 (3H, s), 2.09 (3H, s), 2.05 (3H, s); ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.59, 170.17, 169.50, 168.70, 88.72 (d, J = 22 Hz), 86.60 (d, J = 195 Hz), 70.97 (d, J = 19 Hz), 69.96, 67.83 (d, J = 8 Hz), 61.76, 20.88, 20.70, 20.56; ^{19}F NMR (282 MHz, $CDCl_3$, ref. C_6F_6) δ −40.64 (dd, J = 10, 48 Hz). Spectroscopic data consistent with those reported previously in the literature.[32]

Methyl-4,6-*O*-benzylidine-3-ethoxymethyl-2-(5-iodooctafluoro-3-oxapentane sulfonate)-β-D-mannopyranoside (25)

To methyl-4,6-*O*-benzylidene-3-*O*-ethoxy methyl-β-D-mannopyranoside (**15**, 315 mg, 0.93 mmol) in anhydrous THF (10 mL) was added NaHMDS (1.0 M solution in THF, 1.1 mL, 1.1 mmol) and the reaction stirred, under argon, at room temperature for 20 min. 5-Iodooctafluoro-3-oxapentanesulfonyl fluoride (437 mg, 1.11 mmol), was added, dropwise, and the reaction stirred for a further 45 min. The reaction was concentrated *in vacuo*, dissolved in Et_2O, washed with saturated K_2CO_3 solution and water and the aqueous phase re-extracted with Et_2O. The combined organic phase was washed with brine, dried (anhydrous $MgSO_4$) and concentrated *in vacuo.* Purification by silica gel column chromatography (hexane–EtOAc, 3 : 1) afforded the desired product **25** as a white solid (540 mg, 77%). $[\alpha]_D$ −4.0° (c = 0.028, $CHCl_3$); ν_{max} (film, cm^{-1}) 2971, 2890, 1738, 1411, 1380, 1208, 1146, 1092, 1025, 915; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.30 (5H, m), 5.57 (1H, s), 5.13 (1H, d, J = 2.9 Hz), 4.86 (1H, d, J = 7.4 Hz), 4.78 (1H, d, J = 7.4 Hz), 4.57 (1H, s), 4.34 (1H, dd, J = 5.1, 10.3 Hz), 4.12 (1H, dd, J = 2.9, 9.6 Hz), 3.94–3.82 (2H, m), 3.74–3.55 (2H, m), 3.56 (3H, s), 3.44 (1H, ddd, J = 4.4, 9.5, 10.3 Hz), 1.13 (3H, t, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.13, 129.28, 128.37, 126.19, 101.92, 99.16, 94.07, 83.61, 77.32, 71.04, 68.44, 67.58, 63.96, 57.50, 15.01; ^{19}F NMR (282 MHz, $CDCl_3$, ref. C_6F_6) δ 96.98, 79.97, 76.42, 48.24; MS (ES$^+$) m/z 769.1 ([M + Na]$^+$); Anal. Calcd for $C_{21}H_{23}O_{10}F_8IS$: C, 33.79; H, 3.11. Found: C, 33.86; H, 3.13.

General procedure A: the alkylation of iodide 25 to provide acids 26–29

To the iodide **25** and the carboxylic acid (1.2 equiv) in MeCN was added H_2O followed by $NaHCO_3$ (1.2 equiv) and $Na_2S_2O_4$ (85%, 1.2 equiv) and the reaction stirred at room temperature for 30 min. The reaction was concentrated *in vacuo*, dissolved in Et_2O (100 mL), washed with water (100 mL) and the aqueous phase re-extracted with Et_2O (50 mL). The combined organic phase was washed with brine (100 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified as described.

Methyl-4,6-*O*-benzylidine-3-ethoxymethyl-2-(3-oxa-6,6,7,7,9,9,10,10-octafluoro-4-iodo-decanoic acid-10-sulfonate)-β-D-mannopyranoside (26)

Using the general procedure A with the following amounts: iodide **25** (400 mg, 0.54 mmol) and 4-pentenoic acid (56 mg, 0.56 mmol) in CH_3CN (4 mL), H_2O (2 mL) with $NaHCO_3$ (59 mg, 0.70 mol) and $Na_2S_2O_4$ (85%, 140 mg, 0.70 mmol). Purification by silica gel column chromatography eluting with EtOAc–hexane (1 : 2) afforded the desired product **26** as a colourless oil (305 mg, 67%). ν_{max} (film, cm^{-1}) 2975, 2878, 1714, 1410, 1192, 1148, 1093, 1025, 920; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.25 (5H, m), 5.52 (1H, s), 5.17 (1H, d, J = 2.9 Hz), 4.86 (1H, d, J = 7.4 Hz), 4.80 (1H, d, J = 7.4 Hz), 4.60 (1H, s), 4.34–4.24 (2H, m), 4.09 (1H, dd, J = 2.9 Hz), 3.90–3.77 (2H, m), 3.70–3.50 (2H, m), 3.50 (3H, s), 3.45–3.32 (1H, m), 2.98–2.28 (4H, m), 2.18–1.90 (2H, m), 1.05 (3H, t, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.32, 137.12, 129.28, 128.36, 126.20, 101.93, 99.19, 94.02, 83.66, 77.28, 71.10, 68.43, 67.61, 64.01, 57.54, 41.37, 35.14, 34.21, 19.09, 14.98; ^{19}F NMR (282 MHz, $CDCl_3$, ref. C_6F_6) δ 79.74, 72.97, 47.56, 43.89; MS (ES$^-$) m/z 844.7 ([M]$^-$).

Methyl-4,6-*O*-benzylidine-3-ethoxymethyl-2-(3-oxa-12,12,13,13,15,15,16,16-octa fluoro-10-iodo-hexadecanoic acid-16-sulfonate)-β-D-mannopyranoside (27)

Using the general procedure A with the following amounts: iodide **25** (300 mg, 0.40 mmol) and undecylenic acid (89 mg, 0.48 mmol) in CH_3CN (2 mL), H_2O (1 mL) with $NaHCO_3$ (41 mg, 0.48 mmol) and $Na_2S_2O_4$ (85%, 97 mg, 0.48 mmol). Purification by silica gel column chromatography twice, first eluting with CH_2Cl_2–CH_3OH (98 : 2), secondly eluting with CH_2Cl_2–CH_3OH (99 : 1) afforded the desired product **27** as a colourless oil (200 mg, 54%). ν_{max} (film, cm^{-1}) 2931, 2858, 1709, 1410, 1192, 1147, 1093, 1025, 919; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.31 (5H, m), 5.58 (1H, s), 5.15 (1H, d, J = 2.9 Hz), 4.85 (1H, d, J = 7.4 Hz), 4.79 (1H, d, J = 7.4 Hz), 4.61 (1H, s), 4.40–4.25 (2H, m), 4.17 (1H, dd, J = 2.9, 10.3 Hz), 3.95–3.85 (2H, m), 3.75–3.60 (2H, m), 3.58 (3H, s), 3.51–3.42 (1H, m), 3.00–2.65 (2H, m), 2.35 (2H, t, J = 7.4 Hz), 1.90–1.30 (14H, m), 1.15 (3H, t, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.22, 136.01, 128.10, 128.18, 126.46, 102.20, 99.47, 94.26, 83.84, 77.58, 71.39, 68.71, 67.90, 64.25, 57.73, 41.65, 40.69, 34.31, 29.86, 29.53, 29.49, 29.37, 28.82, 25.04, 21.48, 15.23; ^{19}F NMR (282 MHz, $CDCl_3$, ref. C_6F_6) δ 79.78, 74.37, 47.92, 43.70; MS (ES$^-$) m/z 929.3 ([M]$^-$); HRMS (ES$^+$) Calcd for $C_{32}H_{43}O_{12}F_8ISNa$: 953.1284. Found 953.1266.

Methyl-4,6-*O*-benzylidine-3-ethoxymethyl-2-(3-oxa-18,18,19,19,21,21,22,22-octafluoro-16-iodo-docosanoic acid-22-sulfonate)-β-D-mannopyranoside (28)

Using the general procedure A with the following amounts: iodide **25** (1.0 g, 1.34 mmol) and 16-heptadecenoic acid (378 mg, 1.41 mmol) in CH_3CN (60 mL), H_2O (30 mL) with $NaHCO_3$ (135 mg, 1.61 mmol) and $Na_2S_2O_4$ (85%, 322 mg, 1.61 mmol). The reaction remained cloudy and was stirred at room temperature for 1 h. Purification by silica gel column chromatography, eluting with EtOAc–hexane (1 : 3) afforded the desired product **28** as a colourless oil (230 mg, 17%). ν_{max} (film, cm^{-1}) 2927, 2855, 1725, 1412, 1194, 1149, 1096, 1026, 921; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.31 (5H, m), 5.58 (1H, s), 5.15 (1H, d, J = 2.9 Hz), 4.86 (1H, d, J = 7.4 Hz), 4.80 (1H, d, J = 7.4 Hz), 4.63 (1H, s), 4.40–4.28 (2H, m), 4.17 (1H, dd, J = 2.9, 10.3 Hz), 3.97–3.87 (2H, m), 3.75–3.62 (2H, m), 3.60 (3H, s), 3.52–3.42 (1H, m), 3.00–2.70 (2H, m), 2.37 (2H, t, J = 7.4 Hz), 1.85–1.40 (4H, m), 1.30–1.10 (22H, m), 1.15 (3H, t, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.04, 137.56, 129.67, 128.76, 126.62, 102.36, 99.64, 94.47, 84.00, 77.59, 71.55, 68.87, 68.06, 64.41, 57.91, 42.02, 41.82, 41.62, 40.91, 34.48, 30.17, 30.14, 30.10, 29.99, 29.93, 29.81, 29.65, 29.10, 25.32, 21.79, 15.40; ^{19}F NMR (282 MHz, $CDCl_3$, ref. C_6F_6) δ 80.20, 73.14, 47.87, 43.76; MS (ES$^-$) m/z 1013.1 ([M]$^-$), 1127.5 ([M + TFA]$^-$).

Methyl-4,6-*O*-benzylidine-3-ethoxymethyl-2-(3-oxa-4,4,5,5,7,7,8,8-octafluoro-octanoic acid-8-sulfonate)-β-D-mannopyranoside (29)

Using the general procedure A with the following amounts: iodide **25** (1.0 g, 1.34 mmol) and acrylic acid (101 mg, 1.41 mmol) in CH_3CN (8 mL), H_2O (4 mL) with $NaHCO_3$ (135 mg, 1.61 mmol)

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and $Na_2S_2O_4$ (85%, 322 mg, 1.61 mmol). Purification by silica gel column chromatography, eluting with EtOAc–hexane (1 : 4) to EtOAc–hexane (1 : 0) afforded the desired product **29** as a colourless oil (419 mg, 38%). ν_{max} (film, cm^{-1}) 2972, 1722, 1412, 1193, 1148, 1096, 1026, 921; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52–7.32 (5H, m), 5.58 (1H, s), 5.15 (1H, d, J = 2.9 Hz), 4.85 (1H, d, J = 7.4 Hz), 4.80 (1H, d, J = 7.4 Hz), 4.61 (1H, s), 4.30 (1H, q, J = 5.2 Hz), 4.16 (1H, dd, J = 2.9, 10.3 Hz), 3.90–3.78 (2H, m), 3.75–3.62 (2H, m), 3.58 (3H, s), 3.51–3.42 (1H, m), 2.68 (2H, t, J = 7.4 Hz), 2.55–2.36 (2H, m), 1.65–1.15 (3H, t, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.63, 137.11, 129.31, 128.38, 126.20, 101.92, 99.19, 93.93, 83.61, 77.23, 71.09, 68.41, 67.58, 64.01, 57.54, 25.97, 25.69, 14.94; ^{19}F NMR (282 MHz, $CDCl_3$, ref. C_6F_6) δ 79.82, 73.56, 47.73, 43.27; MS (ES^-) m/z 804.8 ($[M + TFA]^-$); HRMS (ES^+) Calcd for $C_{24}H_{28}O_{12}F_8IS$ Na: 715.1066. Found 715.1068.

General procedure B: the reduction of acids 26–28 to provide acids 30–32

To acid (**26–28**) in Et_2O was added zinc (99.998%, 100 mesh, 6 equiv) and AcOH and the reaction heated at reflux, under argon, for 3 h (bath temp = 80 °C). The reaction was allowed to cool to room temperature and filtered through celite, washing with Et_2O (3 × 30 mL). The filtrate and combined washings were concentrated to dryness *in vacuo* and purified as described.

Methyl-4,6-*O*-benzylidine-3-ethoxymethyl-2-(3-oxa-6,6,7,7,9,9,10,10-octafluoro-decanoic acid-10-sulfonate)-β-D-mannopyranoside (30)

Using the general procedure B with the following amounts: acid **26** (300 mg, 0.36 mmol), zinc (93 mg, 1.42 mmol) in Et_2O (2 mL) and AcOH (1 mL). Purification by silica gel column chromatography, eluting with EtOAc–hexane (1 : 3) afforded the desired product **30** as a colourless oil (70 mg, 27%). ν_{max} (film, cm^{-1}) 2932, 1723, 1410, 1192, 1149, 1115, 1027, 922; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50–7.31 (5H, m), 5.58 (1H, s), 5.15 (1H, d, J = 2.9 Hz), 4.87 (1H, d, J = 7.4 Hz), 4.79 (1H, d, J = 7.4 Hz), 4.63 (1H, s), 4.36 (1H, q, J = 5.2 Hz), 4.17 (1H, dd, J = 2.9, 10.3 Hz), 3.95–3.86 (2H, m), 3.75–3.60 (2H, m), 3.58 (3H, s), 3.52–3.43 (1H, m), 2.42 (2H, t, J = 7.4 Hz), 2.20–2.00 (2H, m), 1.80–1.60 (4H, m), 1.15 (3H, t, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.65, 137.11, 129.29, 128.37, 126.20, 101.92, 99.19, 93.99, 83.50, 77.27, 71.08, 68.42, 67.60, 64.00, 57.54, 33.55, 30.29, 24.16, 20.07, 14.97; ^{19}F NMR (282 MHz, $CDCl_3$, ref. C_6F_6) δ 79.72, 73.61, 47.91, 43.70; MS (ES^-) m/z 719.0 ($[M]^-$), 832.9 ($[M + TFA]^-$); HRMS (ES^+) Calcd for $C_{26}H_{32}O_{12}F_8SNa$: 743.1379. Found 743.1365.

Methyl-4,6-*O*-benzylidine-3-ethoxymethyl-2-(3-oxa-12,12,13,13,15,15,16,16-octafluoro-hexadecanoic acid-16-sulfonate)-β-D-mannopyranoside (31)

Using the general procedure B with the following amounts: acid **27** (190 mg, 0.20 mmol), zinc (41 mg, 0.61 mmol) in Et_2O (2 mL) and AcOH (1 mL). Purification by silica gel column chromatography, eluting with EtOAc–hexane (1 : 3) afforded the desired product **31** as a colourless oil (97 mg, 59%). ν_{max} (film, cm^{-1}) 2929, 2858, 2858, 1710, 1411, 1147, 1093, 1025, 994, 918; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50–7.31 (5H, m), 5.58 (1H, s), 5.15 (1H, d, J = 2.9 Hz), 4.85 (1H, d, J = 7.4 Hz), 4.79 (1H, d, J = 7.4 Hz), 4.63 (1H, s), 4.35–4.25 (1H, q, J = 5.8 Hz), 4.17 (1H, dd, J = 2.9, 10.3 Hz), 3.95–3.86 (2H, m), 3.75–3.60 (2H, m), 3.58 (3H, s), 3.51–3.42 (1H, m), 2.35 (2H, t, J = 7.4 Hz), 2.15–1.90 (2H, m), 1.65–1.25 (14H, m), 1.10 (3H, t, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.34, 129.39, 128.48, 126.34, 102.08, 99.38, 94.14, 83.57, 77.46, 71.31, 68.59, 67.78, 64.11, 57.58, 34.22, 30.89, 30.67, 30.45, 29.57, 29.45, 29.36, 29.30, 24.95, 20.56, 15.09; ^{19}F NMR (282 MHz, $CDCl_3$, ref. C_6F_6) δ 79.8, 74.2, 47.9, 43.5; MS (ES^-) m/z 803.3 ($[M]^-$); HRMS (ES^+) Calcd for $C_{32}H_{44}O_{12}F_8SNa$: 827.2318. Found 827.2299.

Methyl-4,6-*O*-benzylidine-3-ethoxymethyl-2-(3-oxa-18,18,19,19,21,21,22,22-octafluoro-docosanoic acid-22-sulfonate)-β-D-mannopyranoside (32)

Using the general procedure B with the following amounts: acid **28** (200 mg, 0.20 mmol), zinc (80 mg, 1.23 mmol) in Et_2O (4 mL) and AcOH (2 mL). Purification by silica gel column chromatography, eluting with EtOAc–hexane (1 : 3) afforded the desired product **32** as a colourless oil (132 mg, 75%). ν_{max} (film, cm^{-1}) 2926, 2854, 1711, 1412, 1191, 1149, 1096, 1027, 920; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50–7.35 (5H, m), 5.60 (1H, s), 5.15 (1H, d, J = 2.9 Hz), 4.86 (1H, d, J = 7.4 Hz), 4.79 (1H, d, J = 7.4 Hz), 4.61 (1H, s), 4.36 (1H, q, J = 5.1 Hz), 4.20–4.12 (1H, m), 3.95–3.85 (2H, m), 3.75–3.60 (2H, m), 3.58 (3H, s), 3.51–3.42 (1H, m), 2.37 (2H, t, J = 7.4 Hz), 1.70–1.55 (4H, m), 1.40–1.20 (26H, m), 1.15 (3H, t, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.40, 137.07, 129.51, 128.60, 126.45, 102.19, 99.49, 94.28, 83.70, 77.58, 71.43, 68.71, 67.89, 64.29, 57.78, 34.46, 31.02, 30.80, 30.58, 30.04, 29.99, 29.84, 29.80, 29.65, 29.49, 25.17, 21.43, 20.70, 15.21; ^{19}F NMR (282 MHz, $CDCl_3$, ref. C_6F_6) δ 80.01, 74.08, 47.96, 43.34; MS (ES^-) m/z 887.1 ($[M]^-$); HRMS (ES^+) Calcd for $C_{38}H_{56}O_{12}F_8SNa$: 911.3257. Found 911.3275.

General procedure C: coupling of acids 29–32 to provide resins 33–36

To amino-methylated polystyrene (NovaBiochem, 50–100 mesh, loading: 1.5 mmol g^{-1}) and acid (**29–32**, 1.3 equiv) in anhydrous CH_2Cl_2 was added *N,N*-diisopropylethylamine (2.6 equiv) followed by diphenylphosphoryl chloride (1.3 equiv). The reaction was stirred gently, under argon, at room temperature for 18 h. The resin was removed by filtration, washed with CH_2Cl_2 (3 × 10 mL), CH_3OH (3 × 10 mL), Et_2O (3 × 10 mL) and dried *in vacuo*, at 40 °C for 48 h.

Lower loading resins **35** were synthesised using reduced amounts of the acid **31**. Residual aminomethyl groups were capped using excess Ac_2O and pyridine. A Kaiser test was carried out for qualitative detection of amino groups. If the test was positive, the capping process was repeated.

Methyl-4,6-*O*-benzylidine-3-ethoxymethyl-2-(3-oxa-4,4,5,5,7,7,8,8-octafluoro-octanoic acid-8-sulfonate)-β-D-mannopyranoside polystyryl amide (33)

Using general procedure C with the following amounts: amino-methylated polystyrene (145 mg, 0.218 mmol), acid **29** (200 mg, 0.289 mmol) in CH_2Cl_2 (2 mL), *N,N*-diisopropylethylamine (75 mg, 100 μL, 0.579 mmol) and diphenylphosphoryl chloride (68 mg, 55 μL, 0.289 mmol). This gave the title resin **33** as a pale yellow solid (283 mg, 94%). ν_{max} (on-bead, cm^{-1}) 2970, 1739, 1418, 1366, 1216, 1093; ^{19}F NMR (282 MHz, $CDCl_3$, ref. $CFCl_3$)

δ −81.84, −87.79, −113.67, −117.96; Loading Calcd: 0.75 mmol g^{-1}. Found (F elemental analysis) 0.80 mmol g^{-1}.

Methyl-4,6-*O*-benzylidine-3-ethoxymethyl-2-(3-oxa-6,6,7,7,9,9,10,10-octafluoro-decanoic acid-10-sulfonate)-β-D-mannopyranoside polystyryl amide (34)

Using general procedure C with the following amounts: amino-methylated polystyrene (45 mg, 0.067 mmol), acid **30** (58 mg, 0.289 mmol) in CH_2Cl_2 (1 mL), *N,N*-diisopropylethylamine (21 mg, 28 μL, 0.162 mmol) and diphenylphosphoryl chloride (19 mg, 16 μL, 0.081 mmol). This gave the title resin **34** as a pale yellow solid (87 mg, 99%). ν_{max} (on-bead, cm^{-1}) 2931, 1662, 1493, 1452, 1410, 1275, 1146, 1094, 1025, 919; ^{19}F NMR (282 MHz, $CDCl_3$, ref. $CFCl_3$) δ −82.01, −88.13, −113.86, −118.23; Loading Calcd: 0.73 mmol g^{-1}. Found (F elemental analysis) 0.55 mmol g^{-1}.

Methyl-4,6-*O*-benzylidine-3-ethoxymethyl-2-(3-oxa-12,12,13,13,15,15,16,16-octafluoro-hexadecanoic acid-16-sulfonate)-β-D-mannopyranoside polystyryl amide (35)

Using general procedure C with the following amounts: amino-methylated polystyrene (50 mg, 0.07 mmol), acid **31** (80 mg, 0.10 mmol) in CH_2Cl_2 (1 mL), *N,N*-diisopropylethylamine (35 μL, 0.20 mmol) and diphenylphosphoryl chloride (24 mg, 0.10 mmol). This gave the title resin **35** as a pale yellow solid (103 mg, 90%). ν_{max} (on-bead, cm^{-1}) 2925, 1662, 1493, 1453, 1411, 1146, 1095, 1025; ^{19}F NMR (282 MHz, $CDCl_3$, ref. $CFCl_3$) δ −82.1, −88.1, −113.9, −118.3; Theoretical loading calcd: 0.69 mmol g^{-1}. Found (F elemental analysis) 0.59 mmol g^{-1}.

A lower loading resin **35**, capped with Ac_2O, gave the following data: ^{19}F NMR (282 MHz, $CDCl_3$, ref. $CFCl_3$) δ −82.0, −88.1, −113.8, −118.2; Loading (S elemental analysis) 0.1 mmol g^{-1}.

Methyl-4,6-*O*-benzylidine-3-ethoxymethyl-2-(3-oxa-18,18,19,19,21,21,22,22-octafluoro-docosanoic acid-22-sulfonate)-β-D-mannopyranoside polystyryl amide (36)

Using general procedure C with the following amounts: amino-methylated polystyrene (62 mg, 0.093 mmol), acid **32** (108 mg, 0.121 mmol) in CH_2Cl_2 (3 mL), *N,N*-diisopropylethylamine (42 μL, 0.243 mmol) and diphenylphosphoryl chloride (29 mg, 0.121 mmol). This gave the title resin as a pale yellow solid (**36**, 136 mg, 86%). ν_{max} (on-bead, cm^{-1}) 2925, 1662, 1493, 1453, 1411, 1146, 1095, 1025; ^{19}F NMR (282 MHz, $CDCl_3$, ref. $CFCl_3$) δ −82.06, −88.14, −113.93, −118.34; Theoretical loading calcd: 0.65 mmol g^{-1}. Found (F elemental analysis) 0.52 mmol g^{-1}.

Solid-phase fluoridation using $K^{19}F$: preparation of [^{19}F]-18

To a solution of KF (14 mg, 0.25 mmol) and 1,10-diaza-4,7,13,16,21,24-hexaoxabicyclo[8,8,8] hexacosan (94 mg, 0.25 mmol) in MeCN (15 mL) in a standard glass reaction vessel, was added resin **35** (5.0 g, 0.1 mmol g^{-1}, 0.5 mmol) and the suspension was refluxed at 86 °C, under nitrogen, for 1 h. The cooled reaction mixture was filtered and the resin washed with CH_2Cl_2 (30 mL). The combined filtrate and washing were concentrated *in vacuo.* The crude product was passed through a short plug of silica gel eluting with EtOAc–hexane (4 : 6) to give a mixture of products (31 mg) which were subsequently purified by preparative HPLC on a silica gel column eluting with hexane–*i*-PrOH (9 : 1 → 7 : 3) to afford compound [^{19}F]-**18** (13 mg, 0.04 mmol, 16% based on KF). Compounds **17**, **37** and **38** were also present in the crude isolated reaction mixture. For ^{1}H and ^{19}F NMR spectra of the crude reaction mixture, see ESI.† Data for compound **38**: ν_{max} (neat, cm^{-1}) 2975, 2884, 1751; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.33 (5H, m), 5.54 (1H, s), 5.00 (1H, dd, J = 8.0, 9.3 Hz), 4.85 (1H, d, J = 7.0 Hz), 4.67 (1H, d, J = 7.0), 4.43 (1H, d, J = 8.0 Hz), 4.37 (1H, dd, J = 5.0, 9.3 Hz), 3.97 (1H, t, J = 9.3 Hz), 3.80 (1H, t, J = 10.3 Hz), 3.69 (1H, t, J = 9.3 Hz), 3.62–3.45 (3H, m), 3.51 (3H, s), 2.12 (3H, s), 1.12 (3H, t, J = 7.1 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.43, 137.05, 129.05, 128.20, 126.07, 102.46, 101.57, 94.34, 80.96, 75.48, 72.78, 68.68, 66.25, 63.39, 57.00, 20.90, 14.80; MS (ES^+) m/z 405 ($[M + Na]^+$).

Procedure for the manual radiosynthesis of [^{18}F]-2-fluoro-2-deoxy-D-glucose ([^{18}F]-3) from a resin-bound β-D-mannose derivative 35

Labeling. A carbon glass reaction vessel was placed in a brass heater and the pot lid (with three lines attached to allow evaporation, nitrogen flow, and addition of reagents) tightened down and the whole system leak tested. Kryptofix [2.2.2] (22 mg) in CH_3CN (300 μL) and K_2CO_3 (8 mg) in water (300 μL) were transferred using a plastic syringe (1 mL) into the carbon glass reaction vessel. The [^{18}F]fluoride ion (185–370 MBq) in water (0.5–2 mL) was added and heated to 125 °C. After 15 min, three aliquots of CH_3CN (0.5 mL) were added at 1 min intervals. [^{18}F]Fluoride ion was dried up to 40 min in total. The heater was cooled to room temperature, the pot lid removed and CH_3CN (0.2 mL) was added. The pot lid was replaced and the lines were capped off with stoppers. The heater was set at 100 °C for 10 min and the [^{18}F]fluoride ion redissolved. After cooling to room temperature, the [^{18}F]fluoride ion solution (0.2 mL) was transferred to a second carbon glass reaction vessel containing the resin (20–25 mg) using a plastic syringe (1 mL). This carbon glass vessel was transferred to an ion chamber and the labeling activity measured. The carbon glass vessel was replaced in the brass heater and the capped pot lid tightened. The reaction was heated to 86 °C for 4 min before cooling with compressed air. The pot lid was removed, CH_3CN (1.0 mL) was added and the activity in the reaction vessel was measured. The resin was mixed and drawn up into a plastic syringe and then passed through a sintered syringe and into a collection vial. The reaction vessel was washed with a further volume of CH_3CN (0.5 mL) and passed through the sintered syringe. The activity in the collection vial, on the resin and of the sintered syringe was measured. The reaction mixture was diluted with water (1 mL), passed through a C_{18} Sep-Pak (Waters) that had been pre-conditioned with EtOH (5 mL) and water (10 mL). This solution was then passed through a silica Sep-Pak (Waters) that had been pre-conditioned with Et_2O (5 mL). The activities of all solutions were measured at each stage.

Deprotection. The solution of [^{18}F]-**18** after treatment through the Sep-Pak cartridges was transferred into a third carbon glass reaction vessel and the activity measured. The reaction vessel was placed in the brass heater and the pot lid was tightened. Lines from the pot were connected to the nitrogen supply and waste vial and then the solution heated at 100 °C for 10 min to evaporate the solvent. The vessel was cooled with compressed air before removal of the pot lid and addition of HCl (6 M, 0.5 mL). A second pot lid

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was secured with no lines to enable heating under pressure. The heater was set at 120 °C and left for 5 min. After cooling to rt, the pot lid was removed, water (1 mL) was added and the activity in the reaction vessel measured. The reaction mixture was transferred to a collection vial and once again activity in the new vial and empty reaction vessel was measured. Reaction mixture (100 µL) was added to the Dionex eluent [NaOH (50–52%)–water (600 mL)] (4–5 mL) to give a solution with a pH of 7 ±2 ready for ion exchange and reverse phase HPLC analysis. For further purification, the neutralised solution was flushed through a conditioned C18 Sep-Pak and the eluate analysed by reverse phase HPLC.

Labeling the resin **35** using the manual protocol described above, incorporation yields were consistently in the range 73–91% (reverse phase HPLC, average 80–85%), and deprotection proceeded in 91–97% (ion exchange HPLC).

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