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Synthesis of fluoro- and seleno-containing D-lactose and D-galactose analogues†

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Synthetic deoxy-fluoro-carbohydrate derivatives and seleno-sugars are useful tools in protein–carbohydrate interaction studies using nuclear magnetic resonance spectroscopy because of the presence of the ^{19}F and ^{77}Se reporter nuclei. Seven saccharides containing both these atoms have been synthesized, three monosaccharides, methyl 6-deoxy-6-fluoro-1-seleno-β-D-galactopyranoside (**1**) and methyl 2-deoxy-2-fluoro-1-seleno-α/β-D-galactopyranoside (**2α** and **2β**), and four disaccharides, methyl 4-*O*-(β-D-galactopyranosyl)-2-deoxy-2-fluoro-1-seleno-β-D-glucopyranoside (**3**), methyl 4-Se-(β-D-galactopyranosyl)-2-deoxy-2-fluoro-4-seleno-β-D-glucopyranoside (**4**), and methyl 4-Se-(2-deoxy-2-fluoro-α/β-D-galactopyranosyl)-4-seleno-β-D-glucopyranoside (**5α** and **5β**), the three latter compounds with an interglycosidic selenium atom. Selenoglycosides **1** and **3** were obtained from the corresponding bromo sugar by treatment with dimethyl selenide and a reducing agent, while compounds **2α**/**2β**, **4**, and **5α**/**5β** were synthesized by the coupling of a D-galactosyl selenolate, obtained *in situ* from the corresponding isoselenouronium salt, with either methyl iodide or a 4-*O*-trifluoromethanesulfonyl D-galactosyl moiety. While benzyl ether protecting groups were found to be incompatible with the selenide linkage during deprotection, a change to acetyl esters afforded **4** in a 17% overall yield and over 9 steps from peracetylated D-galactosyl bromide. The synthesis of **5** was performed similarly, but the 2-fluoro substituent led to reduced stereoselectivity in the formation of the isoselenouronium salt (α/β ~ 1 : 2.3). However, the β-anomer of the uronium salt could be obtained almost pure (~98%) by precipitation from the reaction mixture. The following displacement reaction occurred without anomerisation, affording, after deacetylation, pure **5β**.

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Introduction

Unnatural modifications of carbohydrates, such as synthetic mono-deoxy-derivatives and mono-*O*-alkylated congeners, are excellent tools to elucidate the binding of glycans with proteins and chemically map their binding epitope.[1–4] In the same way, the introduction of fluorine atoms on carbohydrates, yielding deoxy-fluoro derivatives, has also been exploited in chemical mapping strategies. In fact, C–F and C–OH bonds are quite similar in terms of length and polarization, but they differ in their hydrogen bonding abilities. As the fluorine atom prevents hydrogen bond donation, while maintaining weak hydrogen bond acceptance properties, the OH → F substitution is a valid technique to probe hydrogen bond patterns involved in carbohydrate–protein interactions.[5,6] Thus, fluorinated carbohydrate derivatives have found application in the elucidation of the activity of enzymes involved in carbohydrate metabolism,[7,8] in the inhibition of glycosyltransferases involved in disease,[9,10] and in the detection of protein–carbohydrate interactions by ^{19}F NMR.[11–21] The ^{19}F nucleus is 100% abundant, naturally absent in biomolecules, and has a very similar sensitivity to the ^{1}H nucleus, with the plus of a broad ppm range (200 ppm) that lowers the chance of observing overlapping signals. This, in turn, leads to an overall simplification of the NMR spectrum, especially beneficial in studies with complex carbohydrate substrates[12,16] and/or cocktails of monosaccharide ligands for the detection of the binding preferences and modes of lectins.[17] Adding to the list of chemical modifications for the elucidation of carbohydrate–lectin interactions is the introduction of a selenium atom, which has also very favourable physical properties for structural analysis. Selenium derivatives of carbohydrate ligands, most often methyl selenoglycosides, have been used as substrates for glycosidase inhibition (similarly to S-linked carbohydrates[22]),[23] as ligands for plant and mammalian lectins,[24–26] in phasing crystal structures of carbohydrate-binding macromolecules, by virtue of the anomalous dispersion of selenium

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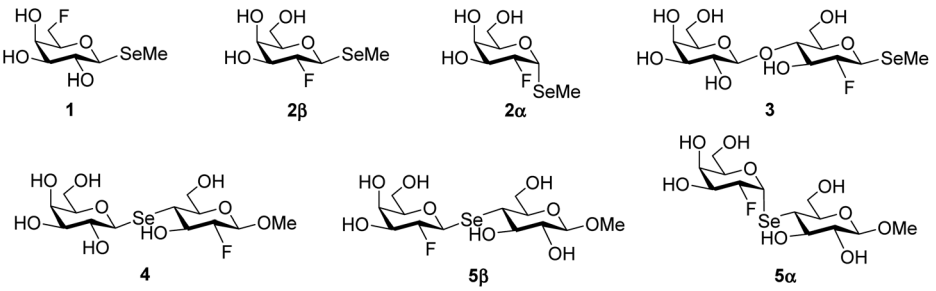


Fig. 1 Target F/Se saccharides **1–5**.

in response to X-ray irradiation,[27–29] and, in more recent years, have been employed in NMR studies with ^{77}Se as the reporting nucleus.[30–34] In fact, the ^{77}Se isotope has a $\frac{1}{2}$ spin, 7.6% natural abundance, and it is particularly sensitive to changes in its local environment, with a large chemical shift range around 3000 ppm. Synthetically, several strategies for the introduction of fluorine or selenium atoms in carbohydrates have been optimized over the years. Notably, preparations of deoxyfluoro carbohydrates can be roughly divided in nucleophilic (*e.g.* TASF, TBAF, DAST) and electrophilic approaches (*e.g.* SelectFluor™).[35,36] Generally, nucleophilic approaches are preferred for the synthesis of 3-, 4-, and 6-deoxy-fluoro compounds, while 2-deoxy-2-fluoro derivatives are obtained through electrophilic addition to the double bond of glycals. Selenium-containing derivatives are most commonly synthesised as glycosyl selenides *via* either Koenigs–Knorr type reactions[37,38] or *via* the formation of isoselenouronium salts.[39] Se-linked disaccharides, where the selenium atom is introduced at the interglycosidic linkage, have been synthesized either through the formation of suitable selenolates (usually generated *in situ*)[40,41] and selenouronium salts[39] or by intermolecular aglycon transfer between a glycosyl trichloroacetimidate and a mixed selenoacetal with TMSOTf activation,[42] to cite some of the most popular methodologies.

In the search for novel and diverse synthetic tools for probing protein–carbohydrate interactions, we have become interested in the simultaneous incorporation of both fluorine and selenium atoms in D-galactose and D-lactose scaffolds affording bi-functional carbohydrate mimetics to aid the structural analysis of galactose-binding lectins. The disaccharide β-D-Gal-(1→4)-D-Glc (Lac) and the closely related β-D-Gal-(1→4)-D-GlcNAc (LacNAc) are core motifs in mammalian *N*- and *O*-glycans, glycosphingolipids (GSLs), and human milk oligosaccharides, where they are found extended by other branching or capping saccharide moieties, and are recognized by a number of mammalian and plant lectins involved in several signalling pathways.[43–46] The designed Se/F-containing synthetic saccharides, represented in Fig. 1, are methyl 6-deoxy-6-fluoro-1-seleno-β-D-galactopyranoside (**1**), methyl 2-deoxy-2-fluoro-1-seleno-α/β-D-galactopyranoside (**2α**/**2β**), methyl (β-D-galactopyranosyl)-(1→4)-2-deoxy-2-fluoro-1-seleno-β-D-glucopyranoside (**3**), methyl (1-seleno-β-D-galactopyranosyl)-(1→4)-2-deoxy-2-fluoro-β-D-glucopyranoside (**4**), and methyl (2-deoxy-2-fluoro-1-seleno-α/β-D-galactopyranosyl)-(1→4)-β-D-glucopyranoside (**5α**/**5β**), the three latter with an interglycosidic selenium atom. This set of compounds maintains the natural anomeric β-configuration found in *N*- and *O*-glycans. Additionally, the selenium atom at the β-(1→4) interglycosidic linkage should not substantially affect the recognition process by lectins. In fact, the differences in the van der Waals radius (O 1.52 Å, Se 1.90 Å) and in the angle of the inter-glycosidic bond (C–O–C 112°, C–Se–C 96°) should be minimal.[29,32,47] Moreover, the fluorine atom, sitting at the C-2 of the D-glucopyranose ring or the C-2′ of the D-galactopyranose ring should not hinder the binding to galacto-specific lectins, *e.g.* galectins, but should be close enough to be able to experience variations in its local environment upon protein binding.[48] In return, both fluorine and selenium atoms can act as reporters in ^{19}F and ^{77}Se NMR studies, and also help in further structural analysis, *e.g.* crystallographic investigations.

Results and discussion

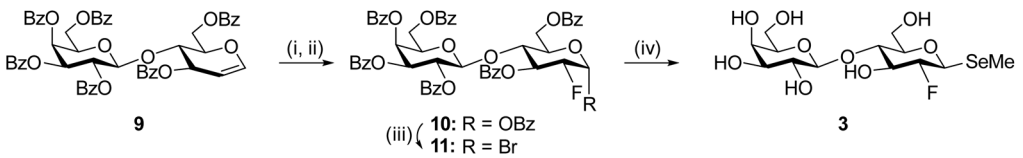
The synthesis of methyl selenoglycosides **1** and **3** utilizes the same method as we have used before, *i.e.*, treatment of a glycosyl bromide with methyl diselenide under reducing conditions to form the methyl selenolate *in situ*.[49] After the formation of the known 6-deoxy-6-fluoro-α-bromide **7**,[50] a 40% yield of the β-methyl selenoglycoside **8** was obtained, which was deprotected under Zemplén conditions to give **1** in 83% yield (Scheme 1). Lactal **9** [51] was treated with Selectfluor™ in nitro-

Scheme 1 Reagents and conditions: (i) HBr (33% in AcOH), CH_2Cl_2, RT, 2 h, 94%; (ii) $(CH_3)_2Se_2$, $NaBH_4$, EtOH/CH_3CN, RT, 22 h, 40%; (iii) NaOMe/MeOH, RT, 17 h, 83%.

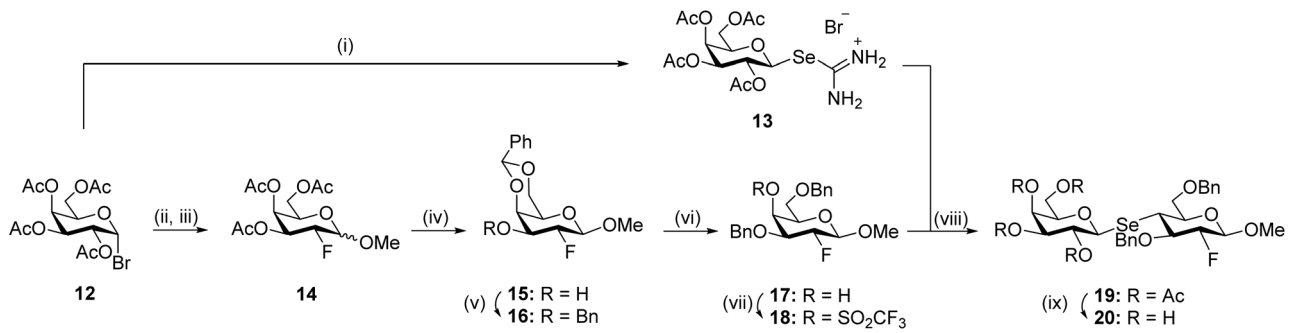
methane/water to give a mixture of α/β *gluco*-/*manno*-configurations from which, after benzoylation of the anomeric positions, compound **10** could be isolated in a 56% yield (Scheme 2). Treatment with HBr 33% in AcOH afforded the α-bromide (→**11**, 90%), which was converted to the β-methyl selenide and deprotected under standard conditions to afford target compound **3** in a 24% yield over two steps.

Differently from the synthesis of **1** and **3**, the preparation of lactose pseudo-disaccharides **4** and **5α**/**5β** included the coupling between D-galactopyranosyl isoselenouronium salts, as selenyl transfer reagents, and suitably protected methyl 4-*O*-trifluoromethanesulfonate D-galactopyranosides. For the synthesis of compound **4**, acetobromogalactose **12** was treated with selenourea in acetone under reflux, as described by Kumar *et al*. for D-glucopyranosyl bromide,[39] to form the corresponding D-galactosylselenyl transfer reagent **13** in 73% yield (Scheme 3).

The presence of a characteristic ^{13}C NMR peak at 165.0 ppm for the isoselenouronium carbon and the concurrent shift at 79.7 ppm of the C-1 signal, confirmed the formation of the desired selenouronium moiety. Treatment of galactosyl bromide **12** with activated Zn powder in acetic acid/water gave the corresponding D-galactal in a 69% yield *via* a reduction–elimination process.[52] The newly formed D-galactal was then reacted with SelectFluor™ in nitromethane/methanol to give derivative **14**[53] as a mixture of anomers (α/β = 1 : 2) in 84% yield. In particular, the reaction allows for the exclusive equatorial fluorination as a result of the directing properties of the acetate at C-4.[53] Although synthesised as a mixture of α/β anomers, the presence of ^{19}F–^{1}H and ^{19}F–^{13}C couplings in both ^{1}H and ^{13}C NMR, the low-field shift of the adjacent protons, and the ^{19}F NMR signals (−207.06, ddd, J = 52.7, 13.3, 2.5 Hz, F-2β and −208.89, ddd, J = 50.0, 10.8, 3.3 Hz, F-2α), confirmed the formation of the *galacto* 2-deoxy-2-fluoro derivative **14**. At this stage the anomers could not be separated and the subsequent reactions were carried out with the α/β mixture. D-Galactopyranoside **14** was readily deacetylated under Zemplén conditions, then reacted with benzaldehyde dimethyl acetal and catalytic amounts of *p*-toluenesulfonic acid to afford the corresponding 4,6-*O*-benzylidene acetal protected compound **15**, which was finally benzylated under standard conditions to afford a separable mixture of the desired β-anomer **16** and undesired **16α**, in 56% and 18% yield, respectively, over three steps. The 4,6-*O*-benzylidene acetal on **16** was then reductively opened with $NaCNBH_3$ and HCl/Et_2O,[54] affording the desired 6-*O*-benzyl product (→**17**, 91%). Finally, compound **17** was reacted with trifluoromethanesulfonic anhydride in pyridine at low temperature to give derivative **18** in 87% yield. D-Galactosyl isoselenouronium salt **13** and compound **18** were reacted under basic conditions to give the pseudo-lactoside **19** in 90% yield. The formation of the seleno pseudo-disaccharide derivative was confirmed by NMR; the ^{13}C signal at 77.8 ppm for C-1′ and, more interestingly, the upfield shift at 41.8 ppm for C-4, both confirmed the presence of the selenium atom at the interglycosidic linkage. In addition, the H-4 signal (^{1}H NMR 3.27 ppm) showed characteristic satellite peaks corresponding to $^{2}J_{Se,H}$ = 20.4 Hz. Finally, the large coupling constants observed for the signal at 3.27 ppm in ^{1}H NMR (*apparent* triplet, $J_{3,4} \sim J_{4,5} \sim$ 11.1 Hz, H-4) confirmed the inversion of configuration D-Gal → D-Glc.



Scheme 2 Reagents and conditions: (i) SelectFluor™, $MeNO_2/H_2O$, RT, 19 h (reflux 1 h); (ii) BzCl, Py, RT, 16 h, 56% (over 2 steps); (iii) HBr (33% in AcOH), RT, 22 h, 90%; (iv) (a) $(CH_3)_2Se_2$, $NaBH_4$, EtOH/CH_3CN, RT, 17 h, (b) NaOMe/MeOH, RT, 20 h, 24% over two steps.

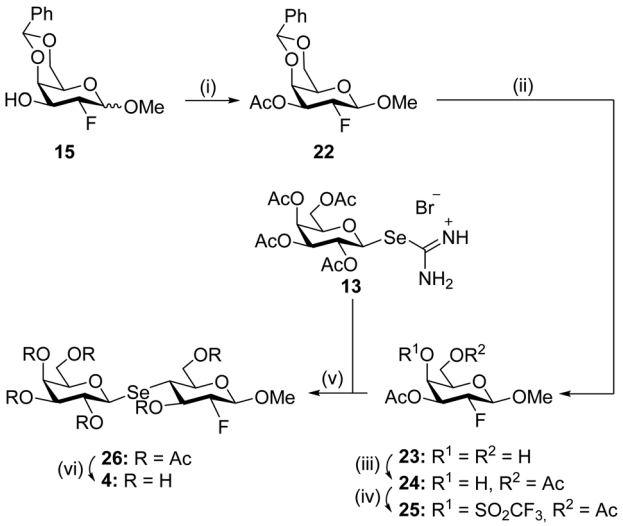


Scheme 3 Reagents and conditions: (i) selenourea, acetone, reflux, 1 h, 73%; (ii) Zn, AcOH/H_2O, RT, 17 h, 69%; (iii) SelectFluor™, $MeNO_2$/MeOH, RT, 4 h (then 1 h at 90 °C), 84% (α/β = 1 : 2); (iv) (a) NaOMe, MeOH, RT, 3 h, (b) $PhCH(OMe)_2$, *p*-TsOH, DMF, 50 °C, 4 h; (v) BnBr, NaH, DMF, 0 °C → RT, 1 h, 56% (over three steps, 74% overall yield; 56% for **16** and 18% for **16α**); (vi) $NaCNBH_3$, HCl (1 M in Et_2O), RT, 1 h, 91%; (vii) Tf_2O, pyridine, 0 °C → RT, 2 h, 87%; (viii) Et_3N, CH_3CN, RT, 1 h, 90%; (ix) NaOMe, MeOH, RT, 2 h, 90%.

Subsequently, deacetylation under Zemplén conditions (→**20**, 90%) was followed by benzyl ethers removal attempts as illustrated in Table 1.

Standard hydrogenolysis of **20** with Pd/C (10 wt%) under H_2 atmosphere (20 bar) gave no conversion after 20 hours (entry 1). Instead, a 1 : 1 mixture of Pd/C (10 wt%) and $Pd(OH)_2/C$ (20 wt%) was tried under the same hydrogen atmosphere affording degradation of the starting material (entry 2). The obtained results are in line with previous reports[55] where the selenium atom is described to act as catalyst poison, similarly to sulphur.[56] At this point, alternative methodologies were screened to investigate their compatibility with the β-(1→4) Se-linkage. The biphasic oxidative cleavage with $NaBrO_3$/$Na_2S_2O_4$ [57] was deemed incompatible with the oxidation-sensitive selenium atom, and thus was not tested, Birch reduction conditions[58] were envisioned as a good methodology for the removal of the two benzyl ethers. Unexpectedly, when compound **20** was reacted with Na in liquid ammonia at −78 °C, and subsequently acetylated under standard conditions, diselenide **21** [59] was identified as the main reaction product (entry 3). Supposedly, the reaction conditions promoted the reductive cleavage of the C–Se bond forming a selenolate species prone to oxidation to the corresponding diselenide. Finally, also ferric(III) chloride promoted de-benzylation[60] failed to give the desired product (entry 4).

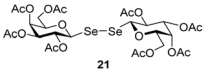
The presented difficulties in removing the benzyl ethers in a clean and efficient way forced a change of strategy, with the design of a differently protected D-galactose building block to couple with transfer reagent **13**. As Zemplén conditions are highly compatible with the presence of selenium and fluorine functionalities, it was decided to substitute the benzyl ether protecting groups with acetyl esters. Thus, compound **15** was acetylated instead of benzylated, to give the desired β-anomer (→**22**, 59%) and α-derivative (→**22α**, 26%) (Scheme 4). Subsequent cleavage of the 4,6-*O*-benzylidene acetal (→**23**, 78%), followed by selective acetylation of the primary C-6 hydroxyl with acetyl chloride and pyridine at low temperature, afforded **24** in 81% yield. Finally, trifluoromethanesulfonyl introduction gave building block **25** in 95% yield. Derivative **25** and isoselenouronium salt **13** were then coupled under basic conditions to give pseudo-disaccharide **26** in 91% yield. Gratifyingly, the substitution of the benzyl ethers for acetyl esters did not lower the reactivity of **25**, giving the pseudo-disaccharide **26** in the same yield as compound **19**. Again, NMR data confirmed the formation of the desired product: ^{13}C NMR signal at 77.3 ppm for the C-1′ and the upfield shift at 41.2 ppm for C-4 indicated the presence of the selenium atom at the interglycosidic linkage, the coupling pattern of the H-4 signal (^1H NMR 2.98 ppm, *apparent* triplet, $J_{3,4} \sim J_{4,5} \sim 11.2$ Hz) confirmed the inversion of configuration D-Gal → D-Glc, and this signal also showed the characteristic satellite peaks corresponding to $^2J_{Se,H}$ = 25.1 Hz. Finally, Zemplén global deacetylation of pseudo-disaccharide **26** gave target **4** in 86% yield.

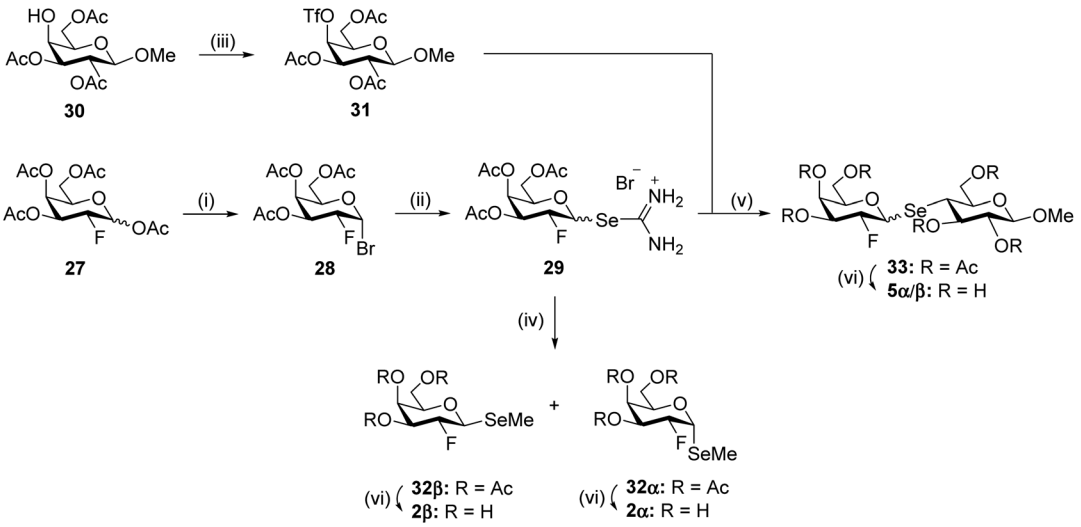


Scheme 4 Reagents and conditions: (i) Ac_2O, pyridine, RT, 18 h, 59% over three steps; (ii) 80% aq. AcOH, 80 °C, 3 h, 78%; (iii) AcCl, pyridine, CH_2Cl_2/CH_3CN, −30 °C → RT, 3 h, 81%; (iv) Tf_2O, pyridine, 0 °C → RT, 3 h, 95%; (v) Et_3N, CH_3CN, RT, 1 h, 91%; (vi) NaOMe, MeOH, RT, 4 h, 86%.

For the synthesis of target compound **5** the same approach was applied, with the 2-deoxy-2-fluoro selenouronium compound **29** formed from the 2-deoxy-2-fluoro galactosyl bromide **28**,[61] obtained from known compound **27** [18] (Scheme 5). However, here the 2-fluoro substituent affected the stereoselectivity and rate of the reaction and while selenourea **13** was obtained as the pure β-anomer after 1 hour, compound **29** was obtained as an α/β mixture in a 3 : 7 ratio in 87% yield after 3 hours. Several attempts to improve the β-selectivity were made but with no success, therefore it was decided to continue with the anomeric mixture of the selenourea salt and try to separate the anomers after the selenide formation. Model experiments were carried out with methyl iodide as the electrophile, instead of a glycosyl triflate, affording the 2-deoxy-2-fluoro methyl selenogalactoside **32** in 66% yield as an α/β mixture with about the same ratio as in **29**, which could be separated to give the pure anomers **32α** (15%) and **32β** (24%). Deprotection under Zemplén conditions gave target compounds **2α** and **2β**, both in an 87% yield. For the formation of the disaccharide **5**, compound **30** was synthesized and converted into the known 4-*O*-triflate derivative **31**.[62] The coupling between compound **29** and **31**, under basic conditions to form the selenolate from the selenourea salt, was less effective than the formation of **19** and **26** above (Schemes 3 and 4), affording

Table 1 Benzyl ether removal attempts on compound **20**

Entry	Conditions	Product/outcome
1	Pd/C (10 wt%), H_2 (20 bar)	No reaction
2	1 : 1 Pd/C (10 wt%) : $Pd(OH)_2/C$ (20 wt%), H_2 (20 bar)	Degradation
3	Na, NH_3(l), −78 °C then Ac_2O, pyridine	 **21**
4	$FeCl_3$, CH_2Cl_2, −30 °C	Degradation



Scheme 5 Reagents and conditions: (i) HBr (33% in AcOH), RT; 77% (ii) selenourea, acetone, reflux, 1 h, 87%, α/β = 3 : 7; (iii) Tf_2O, pyridine, 0 °C → RT, 2 h, 85%; (iv) Et_3N, MeI, CH_3CN, RT, 1 h, 66%, **32α**: 15%, **32β**: 24%; (v) Et_3N, CH_3CN, RT, 2 h, 61%, α/β = 0.3 : 1; (vi) NaOMe, MeOH, RT, 2 h, **2α**: 87%, **2β**: 87%, **5α**: quantitative, **5β**: 96%.

Table 2 Observed $^3J_{Se,F}$ coupling constants

	2α	**2β**	**3β**	**5a**	**5β**	**29α**	**29β**	**32α**	**32β**	**33α**	**33β**
$^3J_{Se,F}$ (Hz)	38	—	—	34	—	63	—	42	—	30	—

a 61% yield of **33** as an α/β mixture, again with the same α/β ratio as in **29**, indicating that there is no anomerisation taking place during the displacement reactions and that the reaction rate of the anomers is about the same. Separation of the anomers turned out to be quite difficult with major loss of material. Finally, employing a long thin silica gel column and slow elution, the anomers could be purified to give **33α** (7%) and **33β** (15%). Although low yielding, the easy access to the precursors made it possible to obtain good amounts (10–100 mg) of both anomers. However, we then found that if, in the preparation of the selenourea derivative, the product was not precipitated with ethyl ether, but the reaction mixture was allowed to stand and cool, a precipitate was formed, which was much enriched in the (desired) β-anomer, giving a 40–50% yield of almost pure **29β**. When this material was used in the formation of the pseudo-saccharide, the yield of **33β** was improved to 56%. Deacetylation of **33α** and **33β** then afforded target compounds **5α** and **5β** in quantitative yields (→**5α**, quantitative, →**5β**, 96%). Compounds **2**, **3**, **5**, **32**, and **33** are all containing a novel vicinal fluoro/seleno motif with possible $^3J_{F,Se}$ coupling constants, which are summarized in Table 2. Interestingly, only the α-*cis*-compounds show any coupling.

Experimental

General methods

Unless noted, chemical reagents and solvents were used without further purification from commercial sources. Anhydrous solvents as CH_2Cl_2, Et_2O, and THF were obtained from a PureSolv-ENTM solvent purification system (Innovation Technology Inc). Concentration *in vacuo* was performed using a Buchi rotary evaporator. The $^1H/^{13}C/^{19}F$ NMR spectra (δ in ppm, relative to TMS in $CDCl_3$) were recorded with Varian spectrometers (Varian, Palo Alto, CA, USA) (400/101 MHz or 500/126 MHz) at 25 °C. Assignments were aided by $^1H–^1H$ and $^1H–^{13}C$ correlation experiments. HRMS spectra were recorded on a micromass LCT instrument from Waters and LaserToF LT3 *Plus* MALDI-TOF (DHAP Matrix). LRMS spectra were recorded on a Waters micromass Quattro Micro LC-MS/MS instrument using electrospray ionisation (ESI) in either positive or negative mode. Optical rotations were recorded on a PerkinElmer polarimeter (model 343) at the sodium D-line (589 nm) at 20 °C using a 1 dm cell and are not corrected. Silica gel chromatography was carried out using Davisil LC60A (Grace tech., Columbia, MD, USA) SiO_2 (40–63 μm) silica gel. All reactions were monitored by thin-layer chromatography (TLC). TLC was performed on Merck DC-Alufolien plates precoated with silica gel 60 F254. They were visualised with UV-light (254 nm) fluorescence quenching, and/or by charring with an 8% H_2SO_4 dip and/or ninhydrin dip. Deprotected sugars were lyophilised using a freeze-dryer Alpha 1-2 Ldplus (Christ Ltd), with a pressure of 0.035 mbar and ice condenser temperature −55 °C.

Selected procedures

Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-fluoro-1-seleno-β-D-galactopyranoside (8). A mixture of dimethyl diselenide (201 mg,

1.07 mmol) and sodium borohydride (81 mg, 2.14 mmol) in anhydrous EtOH (2 mL) was left stirring, under nitrogen, at room temperature until the yellow colour or the residual sodium borohydride had disappeared. The mixture was cooled to 0 °C and a solution of 2,3,4-tri-*O*-acetyl-6-deoxy-6-fluoro-D-galactopyranosyl bromide **7** (400 mg, 1.07 mmol) in anhydrous EtOH/CH_3CN (9 mL, 2 : 1, v/v) was added. The mixture was allowed to reach room temperature and left stirring for 22 hours. Afterwards it was neutralized with acetic acid (1 mL), stirred for an additional 10 minutes, and then concentrated *in vacuo*. The residue was taken up in EtOAc (20 mL), sequentially washed with water (2 × 10 mL), satd. aq. $NaHCO_3$ solution (2 × 10 mL), brine (1 × 10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by flash chromatography (toluene/EtOAc, 10 : 1 → 7 : 1, v/v) to give **8** (160 mg, 0.41 mmol, 39%) as a colourless amorphous solid. R_f 0.48, toluene/EtOAc, 3 : 1; $[\alpha_d^{20}]$ = −128 (*c* 0.5; $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.51 (dd, *J* = 3.3, 0.8 Hz, 1H, H-4), 5.31 (*a*t, *J* = 10.0 Hz, 1H, H-2), 5.06 (dd, *J* = 10.0, 3.4 Hz, 1H, H-3), 4.68 (dd, *J* = 30.6, 10.1 Hz, 1H, H-1), 4.59–4.29 (m, 2H; H-6a, H-6b), 3.99 (ddd, *J* = 11.9, 6.4, 1.0 Hz, 1H, H-5), 2.16, 2.14, 2.08, 2.00 (4s, 12H, 3 $COCH_3$, 1 $SeCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 170.2, 169.8 (3 $\underline{C}OCH_3$), 80.9 (d, *J* = 172.1 Hz, C-6), 77.5 (C-1), 76.4 (d, *J* = 23.1 Hz, C-5), 71.7 (C-3), 67.6 (C-2), 67.5 (d, *J* = 5.8 Hz, C-4), 21.0, 20.8, 20.8 (3 CO$\underline{C}H_3$), 2.7 ($SeCH_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ −230.78 (dd, *J* = 46.4, 11.9 Hz, F-6); HRMS (ESI$^+$) *m*/*z* calcd for $C_{13}H_{19}FO_7Se$: 409.0178 $[M + Na]^+$; found: 409.0197.

Methyl 6-deoxy-6-fluoro-1-seleno-β-D-galactopyranoside (1). A freshly prepared methanolic solution of NaOMe 1 M (200 μL) was added at room temperature to a solution of **8** (30 mg, 0.08 mmol) in anhydrous MeOH (2 mL). The mixture was left stirring for 15 hours, then it was neutralized by Dowex 50WX80 cation exchange resin, filtered, and evaporated *in vacuo* to give **1** (17 mg, 0.065 mmol, 83%) as a colourless amorphous solid. R_f 0.65, EtOAc/MeOH/H_2O, 7 : 2 : 1; $[\alpha_d^{20}]$ = −2.3 (*c* 0.3; H_2O). ^{1}H NMR (400 MHz, CD_3OD) δ 4.54 (dd, 2H, *J* = 47.3, 5.8 Hz, H-6a, H-6b), 4.54 (d, *J* = 9.7 Hz, 1H, H-1), 3.89 (dd, *J* = 3.3, 0.8 Hz, 1H, H-4), 3.84–3.75 (m, 1H; H-5), 3.65 (at, *J* = 9.7 Hz, 1H, H-2), 3.47 (dd, *J* = 9.2, 3.4 Hz, 1H, H-3), 2.09 (s, 3H; $SeCH_3$); ^{13}C NMR (101 MHz, CD_3OD) δ 83.8 (d, *J* = 167.6 Hz, C-6), 81.9 (C-1), 79.7 (d, *J* = 21.2 Hz, C-5), 75.7 (C-3), 71.7 (C-2), 70.3 (d, *J* = 6.6 Hz, C-4), 1.7 ($SeCH_3$). ^{19}F NMR (376 MHz, CD_3OD) δ −231.58 (ddd, *J* = 47.3, 14.0 Hz); HRMS (ESI$^+$): *m*/*z* calcd for $C_7H_{13}FO_5Se$: 282.9861 $[M + Na]^+$; found: 282.9869.

Methyl β-D-galactopyranosyl-(1→4)-2-deoxy-2-fluoro-1-seleno-α-D-glucopyranoside (3). A mixture of dimethyl diselenide (91 μL, 0.96 mmol) and sodium borohydride (36.31 mg, 0.96 mmol) in anhydrous EtOH (2 mL) was left stirring at room temperature until the yellow colour disappeared. The mixture was cooled to 0 °C and a solution of **11** (400 mg, 0.39 mmol) in anhydrous EtOH/CH_3CN (8 mL, 2 : 1, v/v) was added. The mixture was allowed to reach room temperature and left stirring for 22 hours, then it was neutralized by adding acetic acid (1 mL), left stirring for additional 10 minutes, and concentrated *in vacuo*. The residue was taken up in EtOAc (30 mL), sequentially washed with water (2 × 20 mL), satd. aq. $NaHCO_3$ solution (2 × 20 mL), brine (1 × 20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was dissolved in anhydrous MeOH (3 mL) and a freshly prepared methanolic solution of NaOMe 1 M (100 μL) was added. The mixture was left stirring at room temperature 17 hours, then it was neutralized with Dowex 50WX80 cationic resin, filtered, and concentrated *in vacuo*. The crude was purified by flash chromatography (EtOAc/MeOH/H_2O, 7 : 2 : 1, v/v) to give **3** (40 mg, 0.095 mmol, 24%) as a white amorphous solid. R_f 0.58 EtOAc/MeOH/H_2O, 7 : 2 : 1; $[\alpha_d^{20}]$ = +7.25 (*c* 0.4; H_2O). ^{1}H NMR (400 MHz, D_2O) δ 4.97 (d, *J* = 9.1 Hz, 1H, H-1), 4.50–4.25 (m, 2H, H-1′, H-2), 4.01–3.90 (m, 3H), 3.86–3.72 (m, 5H), 3.71–3.62 (m, 2H), 3.60–3.52 (m, 1H, H-2′), 2.17 (s, 3H; $SeCH_3$); ^{13}C NMR (101 MHz, D_2O) δ 102.7 (C-1′), 90.5 (d, *J* = 183.4 Hz, C-2), 79.8, 77.4 (d, *J* = 8.1 Hz, C-4), 75.7 (d, *J* = 25.7 Hz, C-1), 75.3, 73.9 (d, *J* = 18.4 Hz, C-3), 72.4, 70.8 (C-2′), 68.5, 60.9, 59.9, 1.8 ($SeCH_3$); ^{19}F NMR (376 MHz, D_2O) δ −188.19 (dd, *J* = 49.4, 15.4 Hz); HRMS (ESI$^+$) *m*/*z* calcd for $C_{13}H_{23}FO_9Se$: 445.0389 $[M + Na]^+$; found: 445.0384.

2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosylisoselenouronium bromide (13). 2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl bromide **12** [63] (700 mg, 1.70 mmol) was dissolved in acetone (1.7 mL), then selenourea (209 mg, 1.70 mmol) was added and the mixture was heated to reflux for 1 hour. The formed white precipitate was filtered out, washed with acetone, and dried to give **13** (665 mg, 1.24 mmol, 73%) as a white powder. $[\alpha_d^{20}]$ = +11.5 (*c* 1.0, H_2O) ^{1}H NMR (500 MHz, D_2O) δ 5.63 (*a*d, *J* = 3.2 Hz, 1H, H-4), 5.58–5.54 (m, 2H, H-1, H-2), 5.35 (dd, *J* = 8.2, 3.2 Hz, 1H, H-3), 4.42 (*a*t, *J* = 6.0 Hz, 1H, H-5), 4.35–4.26 (m, 2H, H-6a, H-6b), 2.26 (s, 3H, $OCOCH_3$), 2.18 (s, 3H, $OCOCH_3$), 2.13 (s, 3H, $OCOCH_3$), 2.08–2.05 (m, 3H, $OCOCH_3$); ^{13}C NMR (126 MHz, D_2O) δ 173.4, 172.9, 172.8, 172.4 (4 O$\underline{C}OCH_3$), 165.0 (SeC═N), 79.7 (C-1), 76.2 (C-5), 71.4 (C-3), 68.0 (C-4), 67.7 (C-2), 62.1 (C-6), 20.1, 20.0, 19.9 (4 OCO$\underline{C}H_3$); HRMS (ESI$^+$): *m*/*z* calcd for $C_{15}H_{23}BrN_2O_9Se$: 455.0569 $[M - Br]^+$; found: 455.0552.

Methyl 4-Se-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-3,6-di-*O*-benzyl-2-deoxy-2-fluoro-4-seleno-β-D-glucopyranoside (19). Isoselenouronium salt **13** (115 mg, 0.21 mmol) and triflate derivative **18** (175 mg, 0.34 mmol) were dissolved in CH_3CN (4.3 mL) and Et_3N (51 μL, 0.36 mmol) was added. After 1 hour, the solvent was evaporated *in vacuo* and crude was purified by flash column chromatography (toluene/EtOAc, 9 : 1 → 8 : 2, v/v) to give **19** (150 mg, 0.19 mmol, 90%) as a white foam. R_f = 0.60, toluene/EtOAc 7 : 3; $[\alpha_d^{20}]$ = −19.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.43 (m, 2H, H_{Ar}), 7.39–7.27 (m, 8H, H_{Ar}), 5.31 (dd, *J* = 3.5, 1.1 Hz, 1H, H-4′), 5.21 (*a*t, *J* = 10.1 Hz, 1H, H-2′), 4.92–4.77 (m, 4H, H-3′, CH_2Ph, H-1′), 4.66 (d, *J* = 11.9 Hz, 1H, CH$\underline{H}$Ph), 4.53 (d, *J* = 11.9 Hz, 1H, C$\underline{H}$HPh), 4.47–4.28 (m, 2H, H-1, H-2), 4.08–3.87 (m, 4H, H-6a, H-6b, H-6′a, H-6′b), 3.71–3.65 (m, 1H, H-5), 3.65–3.59 (m, 1H, H-3), 3.57 (s, 3H, OCH_3), 3.45 (*a*td, *J* = 6.5, 6.1, 1.2 Hz, 1H, H-5′), 3.27 (*a*t, *J* = 11.1 Hz, 1H, H-4), 2.14 (s, 3H, $OCOCH_3$), 2.00 (s, 3H, $OCOCH_3$), 1.98–1.96 (m, 6H, 2 $OCOCH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.34, 170.33, 170.1, 169.6 (4 O$\underline{C}OCH_3$), 138.2 (C_{Ar}),

137.9 (C_{Ar}), 128.6, 128.5, 128.4, 128.3, 128.1, 127.9, 127.8 (10 C_{Ar}), 101.4 (d, J = 23.0 Hz, C-1), 94.2 (d, J = 188.1 Hz, C-2), 79.0 (d, J = 17.9 Hz, C-3), 77.8 (under $CDCl_3$ peak, C-1′), 76.4 (C-5), 75.5 (C-5′), 74.2 (CH_2Ph), 73.6 (CH_2Ph), 71.60 (C-3′), 70.1 (C-6), 68.5 (C-2′), 67.4 (C-4′), 61.8 (C-6′), 57.0 (OCH_3), 41.9 (d, J = 6.8 Hz, C-4), 20.9, 20.8, 20.74, 20.72 (4 $OCO\underline{C}H_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ −192.30 (*a*dd, J = 52.7, 14.5 Hz, F-2); HRMS (ESI^+): m/z calcd for $C_{35}H_{43}FO_{13}Se$: 793.1751 $[M + Na]^+$; found: 793.1728.

Methyl 4-Se-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-3,6-di-*O*-acetyl-2-deoxy-2-fluoro-4-seleno-β-D-glucopyranoside (26). Isoselenouronium salt **13** (52 mg, 97 μmol) and derivative **25** (100 mg, 0.24 mmol) were dissolved in CH_3CN (2 mL) and Et_3N (30 μL, 0.24 mmol) was subsequently added. After 1 hour, the solvent was evaporated *in vacuo* and crude was purified by flash column chromatography (toluene/acetone, 9 : 1, v/v) to give **26** (59 mg, 88 μmol, 91%) as a white foam. R_f = 0.39, toluene/acetone 9 : 1; $[\alpha_d^{20}]$ = −3.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.45 (dd, J = 3.4, 1.1 Hz, 1H, H-4′), 5.29 (ddd, J = 13.3, 11.5, 8.7 Hz, 1H, H-3), 5.18 (*a*t, J = 9.9 Hz, 1H, H-2′), 5.10–4.99 (m, 2H, H-1′, H-3′), 4.59 (dd, J = 12.0, 2.1 Hz, 1H, H-6a), 4.51 (dd, J = 12.0, 4.9 Hz, 1H, H-6b), 4.44 (dd, J = 7.7, 2.6 Hz, 1H, H-1), 4.33–4.02 (m, 3H, H-2, H-6′a, H-6′b), 3.99–3.88 (m, 2H, H-5, H-5′), 3.56 (s, 3H, OCH_3), 2.98 (*a*t, J = 11.2 Hz, 1H, H-4), 2.17 (s, 3H, $OCOCH_3$), 2.13 (s, 3H, $OCOCH_3$), 2.09 (s, 3H, $OCOCH_3$), 2.07 (s, 3H, $OCOCH_3$), 2.03 (s, 3H, $OCOCH_3$), 1.97 (s, 3H, $OCOCH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 170.30, 170.27, 169.94, 169.89, 169.86 (6 $O\underline{C}OCH_3$), 101.4 (d, J = 22.3 Hz, C-1), 90.9 (d, J = 192.2 Hz, C-2), 77.3 (C-1′), 75.8 (C-5′), 73.8 (C-5), 71.6 (C-3′), 70.6 (d, J = 19.4 Hz, C-3), 67.9 (C-2′), 67.4 (C-4′), 64.5 (C-6), 62.4 (C-6′), 57.2 (OCH_3), 41.2 (d, J = 4.9 Hz, C-4), 21.0, 20.9, 20.8, 20.74, 20.66 (6 $OCO\underline{C}H_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ −196.30 (ddd, J = 51.0, 13.4, 2.6 Hz, F-2); HRMS (ESI^+): m/z calcd for $C_{25}H_{35}FO_{15}Se$: 697.1023 $[M + Na]^+$; found: 697.1003.

Methyl 4-Se-(β-D-galactopyranosyl)-2-deoxy-2-fluoro-4-seleno-β-D-glucopyranoside (4). Compound **26** (30 mg, 44 μmol) was dissolved in MeOH (900 μL) and stirred at room temperature with solid NaOMe at pH = 10. The reaction was neutralized, after 4 hours, by the addition of Dowex 50WX8 H^+ resin. After filtration and solvent evaporation *in vacuo*, the crude residue was purified by flash column chromatography (CH_2Cl_2/MeOH, 9 : 1, v/v) to afford **4** (16 mg, 38 μmol, 86%) as a white powder. R_f = 0.22, CH_2Cl_2/MeOH 9 : 1; $[\alpha_d^{20}]$ = −31.8 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 4.78 (d, J = 9.8 Hz, 1H, H-1′), 4.44 (dd, J = 7.7, 2.3 Hz, 1H, H-1), 4.10 (dd, J = 12.2, 2.0 Hz, 1H, H-6a), 3.98 (ddd, J = 51.5, 8.6, 7.7 Hz, 1H, H-2), 3.97 (dd, J = 12.2, 4.8 Hz, 1H, H-6b), 3.87 (dd, J = 3.4, 1.1 Hz, 1H, H-4′), 3.83–3.69 (m, 3H, H-3, H-6′a, H-2′), 3.69–3.61 (m, 2H, H-6′b, H-5), 3.56 (ddd, J = 7.4, 4.4, 1.1 Hz, 1H, H-5′), 3.53 (s, 3H, OCH_3), 3.47 (dd, J = 9.2, 3.4 Hz, 1H, H-3′), 2.98 (*a*t, J = 11.0 Hz, 1H, H-4); ^{13}C NMR (101 MHz, CD_3OD) δ 101.0 (d, J = 22.8 Hz, C-1), 92.9 (d, J = 187.4 Hz, C-2), 80.7 (C-5′), 80.4 (C-1′), 76.7 (C-5), 74.4 (C-3′), 72.3 (d, J = 18.4 Hz, C-3), 70.4 (C-2), 69.3 (C-4′), 62.3 (C-6), 61.4 (C-6′), 55.6 (OCH_3), 41.9 (d, J = 5.7 Hz, C-4); ^{19}F NMR (376 MHz, CD_3OD) δ −197.77 (ddd, J = 51.5, 14.7, 2.3 Hz, F-2); HRMS (ESI^+): m/z calcd for $C_{13}H_{23}FO_9Se$: 445.0389 $[M + Na]^+$; found: 445.0397.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-fluoro-α/β-D-galactopyranosylisoselenuronium bromide (29α/β)

Procedure for α : β = 3 : 7. Acetone (920 μL) was added to a vial containing **28** (340 mg, 916 μmol) and selenourea (113 mg, 916 μmol). The reaction mixture was heated to 65 °C for 3 hours before adding Et_2O (5 mL). Collection of the white precipitate formed gave **29** (385 mg, 779 μmol, 87%) as an amorphous solid (α/β = 3 : 7). R_f = 0.71, MeCN/H_2O 85 : 15; ^{1}H NMR (500 MHz, D_2O) δ 6.99 (dd, J = 5.6, 1.8 Hz, 1H, H-1α), δ 5.71 (dd, J = 10.0, 3.4 Hz, 1H, H-1β), 5.66 (td, J = 3.2, 1.2 Hz, 1H, H-4α), 5.64 (td, J = 3.2, 1.0 Hz, 1H, H-4β), 5.49–5.32 (m, 2H, H-2α, H-3α), 5.41 (ddd, J = 13.5, 9.2, 3.4 Hz, 1H, H-3β), 5.12 (ddd, J = 49.1, 9.8, 9.2 Hz, 1H, H-2β), 4.82–4.80 (m, 1H, H-5α), 4.43 (ddd, J = 6.5, 5.4, 1.1 Hz, 1H, H-5β), 4.36–4.25 (m, 4H, H-6aα, H-6bα, H-6aβ, H-6bβ), 2.25 (s, 3H, $OCOCH_3$α), 2.24 (s, 3H, $OCOCH_3$β), 2.14 (s, 6H, 2× $OCOCH_3$β), 2.13 (s, 3H, $OCOCH_3$α), 2.12 (s, 3H, $OCOCH_3$α); ^{13}C NMR (126 MHz, D_2O) δ 173.4 ($O\underline{C}OCH_3$β), 173.3 ($O\underline{C}OCH_3$α), 172.9 ($O\underline{C}OCH_3$α), 172.8 ($O\underline{C}OCH_3$β), 172.6 ($O\underline{C}OCH_3$β), 172.5 ($O\underline{C}OCH_3$α), 164.20 (SeC═Nα), 164.24 (SeC═Nβ), 86.7 (d, J = 186.4 Hz, C-2β), 85.3 (d, J = 187.3 Hz, C-2α), 83.0 (d, J = 24.6 Hz, C-1α), 78.5 (d, J = 26.9 Hz, C-1β), 76.1 (C-5β), 71.7 (d, J = 19.1 Hz, C-3β), 70.7 (C-5α), 69.9 (d, J = 19.0 Hz, C-3α), 68.5 (d, J = 8.7 Hz, C-4β), 68.0 (d, J = 8.6 Hz, C-4α), 62.0 (C-6α), 20.1 ($OCO\underline{C}H_3$β), 20.0 ($OCO\underline{C}H_3$α), 20.03 ($OCO\underline{C}H_3$α), 20.00 ($OCO\underline{C}H_3$β), 19.9 ($OCO\underline{C}H_3$β), 19.8 ($OCO\underline{C}H_3$α); ^{19}F NMR (470 MHz, D_2O) δ −194.73 (dd, J = 48.1, 14.3 Hz, F-2α), −196.45 (dd, J = 48.5, 12.1 Hz, F-2β). HRMS (ESI^+): m/z calcd for $C_{13}H_{20}BrFN_2O_7Se$: 415.0415 $[M - Br]^+$; found: 415.0416.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-fluoro-β-D-galactopyranosylisoselenuronium bromide (29β)

Procedure for α : β = 1 : 99. Acetone (1 mL) was added to a vial containing **28** (367 mg, 989 μmol) and selenourea (122 mg, 989 μmol). The reaction mixture was heated to 65 °C for 3 hours, and was left for 90 minutes at room temperature, before collection of the white precipitate formed to give **29β** (234 mg, 474 μmol, 48%, 96% purity) as an amorphous solid.

Procedure for α : β = 2 : 98. Acetone (1.22 mL) was added to a vial containing **28** (367 mg, 989 μmol) and selenourea (122 mg, 989 μmol). The reaction mixture was heated to 65 °C for 3 hours, and was left for 3 days at room temperature, before filtration to give **29β** (218 mg, 440 μmol, 44%, 98% purity) as a white crystalline solid. $[\alpha_d^{20}]$ = +12.5 (*c* 1.0; H_2O); m.p. (°C): 168–168.5.

Methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-1-seleno-β-D-galactopyranoside (32β) and methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-1-seleno-α-D-galactopyranoside (32α). Triethylamine (164 μL, 1.17 mmol) was added to a solution of **29** (387 mg, 783 μmol) and methyl iodide (146 μL, 2.35 mmol) in acetonitrile (3.7 mL) and the mixture was stirred at room temperature for 90 min before removal of solvents under reduced pressure. Purification by flash column chromatography (cyclohexane/EtOAc, 8 : 2 → 1 : 1, v/v) gave **32** (198 mg, 515 μmol, 66%,) as an anomeric mix. Purification by flash column

chromatography (cyclohexane/Et_2O, 6 : 4, v/v) gave **32α** (45 mg, 117 μmol, 15%) and **32β** (73 mg, 190 μmol 24%) as transparent oils. **32α**: R_f = 0.18, cyclohexane/Et_2O 6 : 4; $[\alpha_d^{20}]$ = +222 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (dd, *J* = 5.8, 2.2 Hz, 1H, H-1), 5.48 (td, *J* = 3.1, 1.2 Hz, 1H, H-4), 5.25 (ddd, *J* = 12.2, 10.0, 3.5 Hz, 1H, H-3), 4.95 (ddd, *J* = 51.2, 9.9, 5.7 Hz, 1H, H-2), 4.54 (td, *J* = 6.4, 1.3 Hz, 1H, H-5), 4.12 (app. dd, *J* = 6.6, 1.7 Hz, 2H, H-6a, H-6b), 2.14 (s, 3H, $OCOCH_3$), 2.05 (s, 3H, $OCOCH_3$), 2.04 (s, 3H, $OCOCH_3$), 2.02 (s, 3H, $SeCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 170.1, 170.0 (3 O$\underline{C}$OCH$_3$), 85.9 (d, *J* = 187.8 Hz, C-2), 79.2 (d, *J* = 25.1 Hz, C-1), 70.0 (d, *J* = 18.8 Hz, C-3), 68.6 (C-5), 68.4 (d, *J* = 8.3 Hz, C-4), 61.7 (C-6), 20.82, 20.75, 20.7 (3 OCO$\underline{C}$H$_3$); ^{19}F NMR (470 MHz, $CDCl_3$) δ −196.01 (ddt, *J* = 51.0, 12.1, 2.5 Hz, F-2); HRMS (ESI^+): *m*/*z* calcd for $C_{13}H_{19}FO_7Se$: 409.0173 $[M + Na]^+$; found: 409.0171. **32β**: R_f = 0.14, cyclohexane/Et_2O 6 : 4; $[\alpha_d^{20}]$ = +17.1 (*c* 2.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.53–5.40 (m, 1H, H-4), 5.09 (ddd, *J* = 13.0, 9.3, 3.5 Hz, 1H, H-3), 4.76 (dd, *J* = 9.8, 2.8 Hz, 1H, H-1), 4.60 (dt, *J* = 49.6, 9.6 Hz, 1H, H-2), 4.12 (dd, *J* = 11.4, 6.8 Hz, 1H, H-6a), 4.07 (dd, *J* = 11.3, 6.5 Hz, 1H, H-6b), 3.93 (td, *J* = 6.8, 1.2 Hz, 1H, H-5), 2.15 (s, 3H, $SeCH_3$), 2.11 (s, 3H, $OCOCH_3$), 2.03 (s, 3H, $OCOCH_3$), 2.02 (s, 3H, $OCOCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 170.1, 170.0 (3 O$\underline{C}$OCH$_3$), 87.3 (d, *J* = 186.1 Hz, C-2), 76.3 (d, *J* = 26.0 Hz, C-1), 75.6 (C-5), 71.9 (d, *J* = 19.8 Hz, C-3), 68.1 (d, *J* = 8.4 Hz, C-4), 61.4 (C-6), 20.74, 20.69, 20.6 (3 OCO$\underline{C}$H$_3$), 2.74 ($SeCH_3$); ^{19}F NMR (470 MHz, $CDCl_3$) δ −196.28 (ddt, *J* = 49.6, 13.2, 2.9 Hz, F-2); HRMS (ESI^+): *m*/*z* calcd for $C_{13}H_{19}FO_7Se$: 409.0173 $[M + Na]^+$; found: 409.0171.

Methyl 2-deoxy-2-fluoro-1-seleno-β-D-galactopyranoside (2β). NaOMe (1 M in MeOH, 44 μL) was added to a solution of **32β** (56 mg, 146 μmol) in MeOH (1.5 mL). After 26 hours Amberlite IR120 H^+ resin was added. The solution was filtered before removal of solvents under reduced pressure to give **2β** (33 mg, 127 μmol, 87%) as an amorphous solid. R_f = 0.69, MeCN/H_2O 95 : 05; $[\alpha_d^{20}]$ = +28 (*c* 1.0; H_2O); ^{1}H NMR (400 MHz, D_2O) δ 4.90 (dd, *J* = 10.0, 2.1 Hz, 1H, H-1), 4.56 (dt, *J* = 49.8, 9.5 Hz, 1H, H-2), 4.09 (t, *J* = 3.5 Hz, 1H, H-4), 3.96 (ddd, *J* = 14.6, 9.1, 3.5 Hz, 1H, H-3), 3.85–3.68 (m, 3H, H-5, H-6a, H-6b), 2.19 (s, 3H, $SeCH_3$); ^{13}C NMR (101 MHz, D_2O) δ 90.2 (d, *J* = 179.2 Hz, C-2), 80.2 (C-5), 76.4 (d, *J* = 26.0 Hz, C-1), 72.0 (d, *J* = 18.3 Hz, C-3), 69.4 (d, *J* = 9.2 Hz, C-4), 60.8 (C-6), 1.9 ($SeCH_3$); ^{19}F NMR (376 MHz, D_2O) δ −196.07 (ddt, *J* = 49.8, 14.7, 2.7 Hz, F-2); HRMS (ESI^+): *m*/*z* calcd for $C_7H_{13}FO_4Se$: 282.9856 $[M + Na]^+$; found: 282.9859.

Methyl 2-deoxy-2-fluoro-1-seleno-α-D-galactopyranoside (2α). NaOMe (1 M in MeOH, 30 μL) was added to a solution of **32α** (39 mg, 101 μmol) in MeOH (1 mL). After 26 hours Amberlite IR120 H^+ resin was added. The solution was filtered before removal of solvents under reduced pressure to give **2α** (23 mg, 88 μmol, 87%) as an amorphous solid. R_f = 0.71, MeCN/H_2O 95 : 05; $[\alpha_d^{20}]$ = +269 (*c* 1.0; H_2O); ^{1}H NMR (400 MHz, D_2O) δ 5.96 (dd, *J* = 5.7, 2.1 Hz, 1H, H-1), 4.88 (ddd, *J* = 51.5, 9.7, 5.8 Hz, 1H, H-2), 4.25 (ddd, *J* = 6.6, 5.1, 1.1 Hz, 1H, H-5), 4.07 (td, *J* = 3.5, 1.1 Hz, 1H, H-4), 4.01 (ddd, *J* = 13.5, 9.8, 3.5 Hz, 1H, H-3), 3.81–3.77 (m, 2H, H-6a, H-6b), 2.07 (s, 3H, $SeCH_3$); ^{13}C NMR (101 MHz, D_2O) δ 89.2 (d, *J* = 180.9 Hz, C-2), 79.6 (d, *J* = 24.6 Hz, C-1), 73.1 (C-5), 69.6 (d, *J* = 16.8 Hz, C-3), 69.4 (d, *J* = 9.2 Hz, C-4), 60.8 (C-6), 2.3 ($Se–CH_3$); ^{19}F NMR (376 MHz, D_2O) δ −195.48 (ddt, *J* = 51.1, 13.3, 2.7 Hz, F-2); HRMS (ESI^+): *m*/*z* calcd for $C_7H_{13}FO_4Se$: 282.9856 $[M + Na]^+$; found: 282.9856.

Methyl 4-Se-(3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-β-D-galactopyranosyl)-2,3,6-tri-*O*-acetyl-4-seleno-β-D-glucopyranoside (33β) and methyl 4-Se-(3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-galactopyranosyl)-2,3,6-tri-*O*-acetyl-4-seleno-β-D-glucopyranoside (33α). Triflic anhydride (298 μL, 1.8 mmol) was added over 12 minutes to a stirred solution of **30** [64] (284 mg, 886 μmol) in pyridine (4.4 mL) at 0 °C. The reaction mixture was left to reach room temperature. After 2 hours CH_2Cl_2 (50 mL) was added, and the mixture was washed with satd. aq. $NaHCO_3$/ice (50 mL). The organic phase was dried before removal of solvents under reduced pressure to give crude **31** [62] (361 mg, 90% crude weight, 92% pure by NMR). Triethylamine (90 μL, 666 μmol) was added to a stirred solution of **31** (216 mg, 476 μmol) and **29α/β** (165 mg, 333 μmol) in anhydrous CH_3CN (5.6 mL) at room temperature, and the mixture was stirred for 90 minutes before removal of solvents under reduced pressure. Purification by flash column chromatography (cyclohexane/EtOAc, 1 : 1, v/v) gave **33** (137 mg, 203 μmol, 61%, α/β = 0.28 : 1) as a transparent oil. Purification by flash column chromatography (cyclohexane/Et_2O, 6 : 4 → 4 : 6, v/v) gave **33α** (15 mg, 22 μmol, 7%) as a transparent oil, and **33β** (33 mg, 49 μmol, 15%) as a transparent amorphous solid. **33α**: R_f = 0.43, cyclohexane/EtOAc 1 : 1; $[\alpha_d^{20}]$ = +70.4 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (dd, *J* = 5.5, 1.6 Hz, 1H, H-1′), 5.45 (td, *J* = 3.3, 1.3 Hz, 1H, H-4′), 5.21 (dd, *J* = 11.3, 9.4 Hz, 1H, H-3), 5.04–4.84 (m, 2H, H-3′, H-2′), 4.84 (dd, *J* = 9.4, 8.0 Hz, 1H, H-2), 4.69 (dd, *J* = 11.9, 2.2 Hz, 1H, H-6b), 4.41 (td, *J* = 6.3, 1.3 Hz, 1H, H-5′), 4.40 (d, *J* = 7.9 Hz, 1H, H-1), 4.32 (dd, *J* = 12.0, 5.9 Hz, 1H, H-6a), 4.14 (dd, *J* = 11.4, 6.5 Hz, 1H, H-6b′), 4.09 (dd, *J* = 11.4, 6.6 Hz, 1H, H-6a′), 3.76 (ddd, *J* = 11.2, 5.8, 2.2 Hz, 1H, H-5), 3.48 (s, 3H, OCH_3), 3.10 (t, *J* = 11.3 Hz, 1H, H-4), 2.13 (s, 3H, $OCOCH_3$), 2.09 (s, 3H, $OCOCH_3$), 2.06 (s, 3H, $OCOCH_3$), 2.05 (s, 3H, $OCOCH_3$), 2.03 (s, 3H, $OCOCH_3$), 2.02 (s, 3H, $OCOCH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 170.5, 170.0, 169.93, 169.89, 169.8 (6 O$\underline{C}$OCH$_3$), 101.5 (C-1), 84.9 (d, *J* 191.2 Hz, C-2′), 83.3 (d, *J* = 24.7 Hz, C-1′), 74.4 (C-3), 73.4 (C-5), 72.9 (C-2), 69.7 (C-5′), 69.6 (C-3′), 67.9 (d, *J* = 6.9 Hz, C-4′), 64.7 (C-6), 61.1 (C-6′), 57.1 (OCH_3), 42.5 (C-4), 21.0, 20.9, 20.8, 20.70, 20.68, 20.66 (6 OCO$\underline{C}$H$_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ −192.76–−193.15 (m, F-2′); HRMS (ESI^+): *m*/*z* calcd for $C_{25}H_{35}FO_{15}Se$: 697.1020 $[M + Na]^+$; found: 697.1018. **33β**: R_f = 0.42, cyclohexane/EtOAc 1 : 1; $[\alpha_d^{20}]$ = −16.4 (*c* 1.0, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.47 (ddd, *J* = 3.7, 2.7, 1.1 Hz, 1H, H-4′), 5.17 (dd, *J* = 11.5, 9.3 Hz, 1H, H-3), 5.08 (ddd, *J* = 13.0, 9.4, 3.5 Hz, 1H, H-3′), 4.93 (dd, *J* = 9.7, 2.8 Hz, 1H, H-1′), 4.90 (dd, *J* = 9.3, 8.0 Hz, 1H, H-2), 4.71 (dd, *J* = 12.1, 2.1 Hz, 1H, H-6b), 4.59 (dt, *J* = 49.4, 9.6 Hz, 1H, H-2′), 4.39 (d, *J* = 7.9 Hz, 1H, H-1), 4.35 (dd, *J* = 12.1, 6.0 Hz, 1H, H-6a), 4.11 (m, 1H, H-6a′), 4.09 (dd, *J* = 12.1, 6.0 Hz, 1H, H-6b′), 3.97 (td, *J* = 6.4, 1.2 Hz, 1H, H-5′), 3.83 (ddd, *J* = 11.2, 6.0, 2.1 Hz, 1H, H-5), 3.49 (s, 3H, OCH_3), 3.06 (t, *J* = 11.3 Hz, 1H, H-4), 2.17 (s, 3H, $OCOCH_3$), 2.08 (s, 3H, $OCOCH_3$), 2.07 (s, 3H, $OCOCH_3$), 2.06

(s, 3H, $OCOCH_3$), 2.05 (s, 3H, $OCOCH_3$), 2.04 (s, 3H, $OCOCH_3$); ^{13}C-NMR (101 MHz, $CDCl_3$) δ 170.7, 170.4, 170.3, 170.1, 169.9, 169.8 (6 $O\underline{C}OCH_3$), 101.5 (C-1), 87.0 (d, J 187.2 Hz, C-2′), 76.1 (d, J 26.2 Hz, C-1′), 76.0 (C-5′), 74.1 (C-5), 72.9 (C-2), 71.7 (d, J 19.7 Hz, C-3′), 71.7 (C-3), 68.0 (d, J 8.2 Hz, C-4′), 64.8 (C-6), 61.7 (C-6′), 57.0 (OCH_3, 40.5 (C-4), 21.2, 21.0, 20.9, 20.8, 20.73, 20.69 (6 $OCO\underline{C}H_3$); ^{19}F-NMR (376 MHz, $CDCl_3$) δ −195.79 (ddt, J = 49.4, 13.1, 2.7 Hz, F-2′); HRMS (ESI^+): m/z calcd for $C_{25}H_{35}FO_{15}Se$: 697.1020 $[M + Na]^+$; found: 697.1017.

Methyl 4-Se-(3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-β-D-galactopyranosyl)-2,3,6-tri-*O*-acetyl-4-seleno-β-D-glucopyranoside (33β). Triethylamine (83 μL, 592 μmol) was added to a stirred solution of **31** (255 mg, 561 μmol), and **29β** (171 mg, 346 μmol) in CH_3CN (7.1 mL), and was left for 1 hour before removal of solvents under reduced pressure. Purification by flash column chromatography (cyclohexane/Et_2O, 2 : 8, v/v) gave **33β** (132 mg, 20 μmol, 56%) as a white amorphous solid.

Methyl 4-Se-(2-deoxy-2-fluoro-β-D-galactopyranosyl)-4-seleno-β-D-glucopyranoside (5β). NaOMe (1 M in MeOH, 28 μL) was added to a solution of **33β** (31 mg, 46 μmol) in MeOH (930 μL). After 23 hours Amberlite IR120 H^+ resin was added. The solution was filtered before removal of solvents under reduced pressure to give **5β** (19 mg, 44 μmol 96%) as an amorphous solid. R_f = 0.51, MeCN/H_2O 85 : 15; $[\alpha_d^{20}]$ = −22.2 (c 1.0; H_2O); ^{1}H NMR (400 MHz, D_2O) δ 5.11 (dd, J = 10.0, 2.2 Hz, 1H, H-1′), 4.55 (dt, J = 50.0, 9.5 Hz, 1H, H-2′), 4.38 (d, J = 8.1 Hz, 1H, H-1), 4.20 (dd, J = 12.5, 2.1 Hz, 1H, H-6b), 4.07 (t, J = 3.3 Hz, 1H, H-4′), 4.00–3.91 (m, 2H, H-6a, H-3′), 3.83–3.78 (m, 1H, H-5), 3.79–3.70 (m, 3H, H-5′, H-6a′, H-6b′), 3.65 (dd, J = 10.9, 8.9 Hz, 1H, H-3), 3.58 (s, 3H, OCH_3), 3.31 (t, J = 8.4 Hz, 1H, H-2), 3.02 (t, J = 11.1 Hz, 1H, H-4); ^{13}C NMR (101 MHz, D_2O) δ 102.9 (C-1), 90.7 (d, J = 180.6 Hz, C-2′), 80.3 (C-5′), 76.4 (C-5), 76.0 (d, J = 25.9 Hz, C-1′), 74.4 (C-2), 73.2 (C-3), 72.1 (d, J = 18.3 Hz, C-3′), 69.3 (d, J = 9.2 Hz, C-4′), 62.1 (C-6), 61.0 (C-6′), 57.0 (OCH_3), 43.4 (C-4); ^{19}F NMR (376 MHz, D_2O) δ −195.71 (ddt, J = 49.9, 14.9, 2.8 Hz, F-2′). HRMS (ESI^+): m/z calcd for $C_{13}H_{23}FO_9Se$: 445.0384 $[M + Na]^+$; found: 445.0383.

Methyl 4-Se-(2-deoxy-2-fluoro-α-D-galactopyranosyl)-4-seleno-β-D-glucopyranoside (5α). NaOMe (1 M in MeOH, 11 μL) was added to a solution of **33α** (12 mg, 18 μmol) in MeOH (360 μL). After 24 hours Amberlite IR120 H^+ resin was added. The solution was filtered before removal of solvents under reduced pressure to give **5α** (8 mg, 18 μmol, quantitative) as an amorphous solid. R_f = 0.54, MeCN/H_2O 85 : 15; $[\alpha_d^{20}]$ = +224 (c 1.0; H_2O); ^{1}H NMR (500 MHz, D_2O) δ 6.27 (dd, J = 5.9, 1.8 Hz, 1H, H-1′), 4.86 (ddd, J = 51.7, 10.2, 6.0 Hz, 1H, H-2′), 4.38 (d, J = 8.0 Hz, 1H, H-1), 4.25 (ddd, J = 6.7, 5.1, 1.2 Hz, 1H, H-5′), 4.18 (dd, J = 12.2, 2.2 Hz, 1H, H-6b), 4.08 (td, J = 3.4, 1.1 Hz, 1H, H-4′), 3.96 (ddd, J = 12.6, 10, 3.5 Hz, 1H, H-3′), 3.92 (dd, J = 12.3, 6.0 Hz, 1H, H-6a), 3.84–3.69 (m, 4H, H-3, H-5, H-6a′, H-6b′), 3.58 (s, 3H, OCH_3), 3.26 (dd, J = 9.1, 8.0 Hz, 1H, H-2), 2.91 (t, J = 11.0 Hz, 1H, H-4); ^{13}C NMR (126 MHz, D_2O) δ 102.9 (C-1), 88.5 (d, J 183.2 Hz, C-2′), 80.4 (d, J 24.7 Hz, C-1′), 75.8 (C-3), 75.4 (C-5), 74.4 (C-2), 73.7 (C-5′), 69.5 (d, J 17.1 Hz, C-3′), 69.3 (d, J 9.3 Hz, C-4′), 62.4 (C-6), 60.7 (C-6′), 57.0 (OCH_3), 42.6 (C-4); ^{19}F NMR (376 MHz, D_2O) δ −193.87 (app. dd, J = 50.8, 12.3 Hz, F-2′). HRMS (ESI^+): m/z calcd for $C_{13}H_{23}FO_9Se$: 445.0384 $[M + Na]^+$; found: 445.0386.

Conclusions

In summary, a set of ^{19}F and ^{77}Se substituted saccharides (**1–5**) has been synthesized. While selenoglycosides **1** and **3** were prepared by reacting the corresponding glycosyl bromides with methyl diselenide under reducing conditions, compounds **2**, **4**, and **5** were synthesized *via* the formation of the corresponding isoselenouronium salts as selenyl transfer reagents. The proposed approach for the synthesis of pseudo-lactosides **4** and **5** allowed for the efficient introduction of a selenium atom at the interglycosidic linkage and a fluorine at C-2, either on the D-glucose or the D-galactose moiety. In the case of the preparation of pseudo-lactoside **5β** and selenogalactoside **2α/β**, the 2′-F substituent complicated the synthesis, yielding an α/β mixture in the formation of the selenourea salt **29**. However, the almost pure β-form could be obtained by fractional precipitation directly from the reaction mixture and the following displacement reactions were found to be stereospecific and with no anomerisation occurring. To the best of our knowledge, the synthesised compounds represent the first example of a set of small carbohydrates functionalised with both selenium and fluorine, constituting valuable tools for structural elucidations of protein–carbohydrate interactions exploiting the complementary reporting abilities of the two unnatural substitutions.

Author contributions

Conceptualization: S. O.; synthesis and characterization: C. R., D. B., A. S. I.; writing original draft: C. R.; manuscript review & editing: S. O., C. R., D. B.

Conflicts of interest

There are no conflicts to declare.

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