Chapter 6

Tuning the imidate leaving group of 2-deoxy-2-fluoro glycoside-based glycosidase inhibitors[1]

Introduction

Glycoconjugates are a highly diverse class of biomolecules, playing an important role in many biological processes.[2] The metabolism of glycoconjugates and the enzymes involved are extensively studied. Glycosidases, enzymes that hydrolyse glycosidic linkages, are engaged in a number of diseases, including metabolic storage disorders such as Gaucher's disease,[3,4] cancer,[5,6,7] HIV/AIDS,[8] Parkinson's disease,[9,10] Alzheimer's disease[11] and influenza.[12] Specific inhibitors of glycosidases are therefore interesting targets as potential therapeutics, as well as useful tools for structural and mechanistic characterisation of these enzymes.[13,14] In this framework attention has been focussed on the development of mechanism based covalent inhibitors and activity-based probes (ABPs), which are increasingly being used as research tools (see chapter 3 and 5).[15,16,17]

The classical Koshland double-replacement mechanism of retaining glycosidases operates in two steps, the first of which is the formation of a glycosyl-enzyme intermediate (the "glycosylation" step), which is hydrolysed in the second step (the "deglycosylation" step, Figure 1). In 1987

Withers *et al.* introduced the 2-deoxy-2-fluoroglucosides **1** and **2** (Figure 2) as mechanism based inhibitors for retaining β-glucosidases.[18] The design of inhibitors such as **1** and **2** is based on the stabilization of the inhibitor-enzyme intermediate by the introduction of an electron-withdrawing fluorine substituent at the C-2 position, which retards the deglycosylation step.[16]

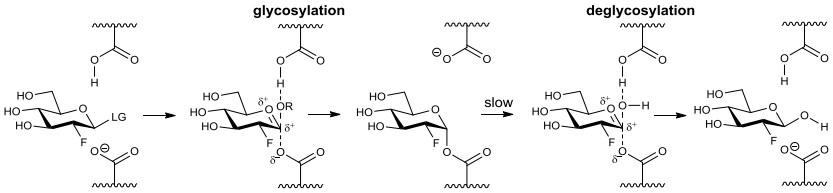


Figure 1: Mechanism-based inhibition of retaining beta-glucosidases with 2-deoxy-2-fluoroglucosides.

The electron-withdrawing fluorine substituent at the C-2 position of the inhibitor also reduces the rate of the formation of the inhibitor-enzyme intermediate. To counterbalance this effect, potent anomeric leaving groups are installed on the inhibitors. The 2-deoxy-2-fluoroglucosides **1** and **2**, provided with dinitrophenol or fluoride as leaving groups, were converted and evaluated as ABPs by Witte *et al.* (Figure 2a). Introduction of an azide at the C-6 of **1** and **2** gave two-step labelling probes **3** and **4**, which in turn were coupled to a BODIPY dye to give the fluorescent labelled ABPs **5** and **6**.[19] These labelled 2-deoxy-2-fluoroglucosides probes completely labelled the glucosidase GBA-1, provided that prolonged reaction times (6 h) and relatively high concentrations were used. Increasing the rate of formation of the inhibitor-enzyme intermediate can be achieved by tuning the ability of the leaving group on the anomeric position of the 2-deoxy-2-fluoro probes. Walvoort *et al*. investigated the influence of the leaving group at the anomeric centre by the synthesis and evaluation of APBs **7-10** (Figure 2b). It was shown that both phosphate probe **9** and imidate probe **10** label GBA-1 more efficiently than probes **5** and **6**. It was also shown that imidate probe **10** is more hydrolytic stabile than phosphate probe **9**.[20] Rempel *et al.* reported the synthesis and evaluation of various 2-deoxy-2-fluorinated glycosides

bearing an dialkyl phosphate or phosphonate as leaving group (**11**-**16**, Figure 2c).[21,22] In agreement with the pKa of the leaving groups it was shown that phosphate probes such as **14** are less hydrolytic stabile than phosphonate probes such as **15**. The β-D-gluco-, β-D-manno- and β-D-galacto-configured phosphonate derivatives function as efficient inhibitors of the corresponding β-D-gluco-, β-D-manno- and β-D-galactosidases. Contrary, the α-D-gluco- and α-D-manno-configured phosphonate derivatives proved to be less efficient covalent inhibitors. The finding that the inhibitory potency of a 2-fluoroglycoside based inhibitor can be fine tuned by varying the nature of the leaving group at the anomeric centre of the inhibitor and the activity of *N*-phenyl trifluoroacetimide imidate **10**, was an incentive to further explore *N*-phenyl trifluoroacetimide imidate ABPs.

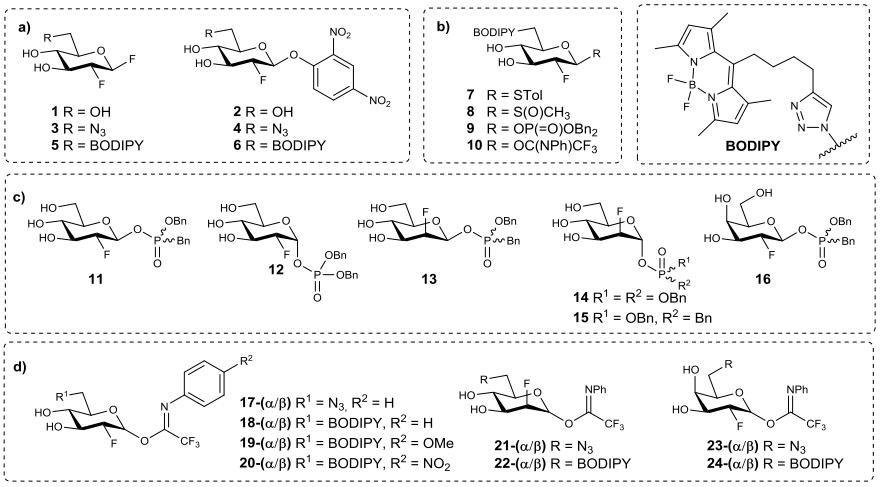


Figure 2: a) First generation 2-deoxy-2-fluoro glucosyl inhibitors **1-2**, modified 2-deoxy-2-fluoro glucosyl ABPs **3-6**. b) 2-Deoxy-2-fluoro glucosyl probes with varying leaving groups. c) Phosphate-/phosphonate- 2-deoxy-2-fluoro glucosyl **11-12**, mannosyl **13-15** and galactosyl **16** inhibitors. d) 2-Deoxy-2-fluoro glucosyl probes bearing various imidate leaving groups **17-20**, 2-deoxy-2-fluoro mannosyl ABPs **21-22**, 2-deoxy-2-fluoro galactosyl ABPs **23-24**.

Because several retaining glycosidases, processing different epimeric glycans following the same two-step mechanism described in Figure 1, are naturally occurring, stereoisomers of known 6-azido-β-D-gluco *N*-phenyl

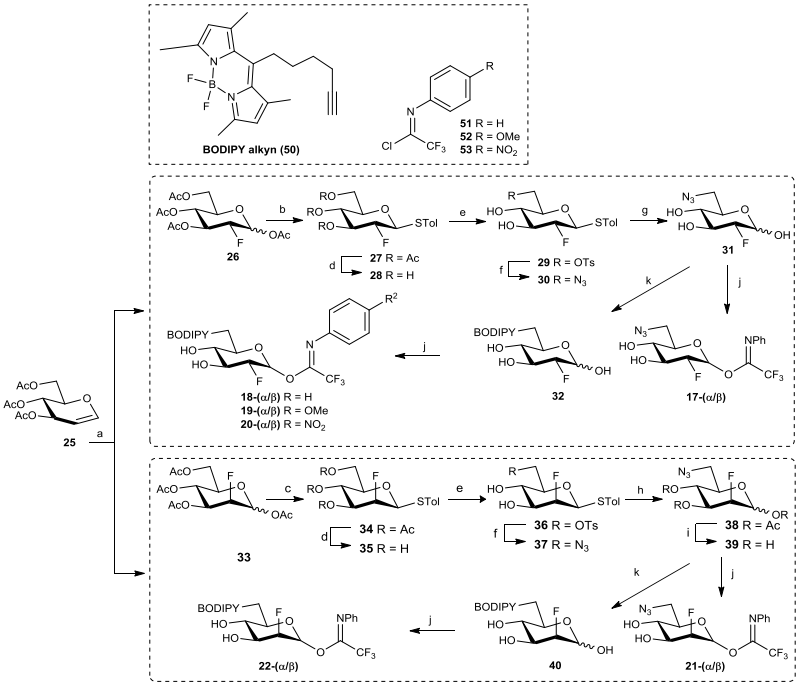
trifluoroacetimide probe **17-β** can potentially function as ABPs. Therefore this chapter describes a study to the synthesis of *N*-phenyl trifluoroacetimide imidate probes to give probes in the α- gluco- (**17-α**), the α-manno- (**21-α**) and the α- (**23-α**) and β-galacto (**23-β**) configuration (Figure 2d). Because the imidate substituent can also be readily adapted, thereby potentially further fine-tuning the reactivity of the probes, also different groups on the imidate nitrogen were explored. An electron donating methoxy substituent and an electron withdrawing nitro substituent were installed on the phenyl ring of the *N*-phenyl trifluoroacetimide imidate ABPs (**19-20**) having either an α- or β-gluco configuration. Some of the prepared 6-azido derivatives (**17**, **21** and **23**) were transformed in the corresponding fluorescently labelled ABPs (**18**, **22** and **24**) by the installation of a BODIPY group.

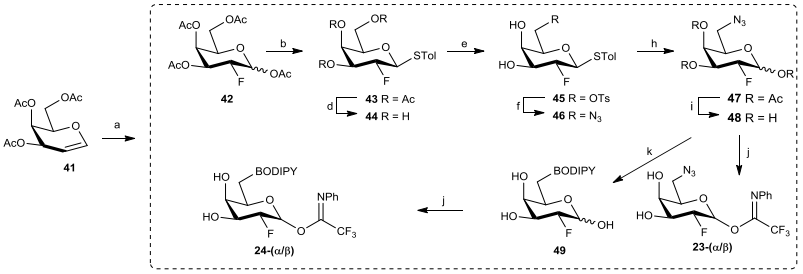
Results and discussion

All *N*-phenyl trifluoroacetimide imidate ABPs (**17-24**) were accessed through a similar route of synthesis, passing by the corresponding thioglycoside precursors (**28, 35** and **44**) as depicted in Scheme 1. Per-acetylated glucal **25** was used as a starting compound for both gluco- and manno-configured target compounds. Using the same procedure as described by Walvoort *et al.*[20] commercially available glucal **25** was treated with Selectfluor® to provide, after anomeric acetylation and column chromatography, 2-fluoro glucose **26** and 2-fluoro mannose **33** in 14% and 28% yield respectively (Scheme 1). The *p*-thiocresol was introduced at the anomeric centre of the gluco-configured **26** by preparing the anomeric bromide and subsequent treatment of this bromide with thiocresol under phase transfer conditions to give, after global deacetylation using NaOMe in MeOH, 2-fluoroglucoside **28**. Selective tosylation of the primairy hydroxyl followed by substitution of the tosylate with an azide yielded thioglucoside **30** in 88% over two steps. To access 2-fluoromannoside **34**, the anomeric acetate in 2-fluoro mannose **33** was first converted into the α-bromide,

which was treated with sodium *p*-thiocresolate to give β-thiomannoside **34**. Deacetylation, selective tosylation and azide substitution as described for the gluco-configured epimer, gave 6-azido thiomannoside **37** in 38% over five steps. The synthesis of 2-fluoro-6-azido thiogalactoside **46** starts from peracetylated galactal **41** and follows the same sequence of events as described for glucose epimer **30**. The reaction of galactal with Selectfluor® provided only the product with the galactose configuration, as formation of the talo-epimer was not observed. Having the three epimeric 2-fluoro-6-azido thioglycosides (**30**, **37** and **46**) in hand the syntheses of the respective two- step ABPs (**17**, **21** and **23**) and the BODIPY labelled ABPs (**18**-**20**, **22** and **24**) were undertaken.

Scheme 1: Synthesis of 2-deoxy-2-fluoro glycosyl ABPs **17-23**.





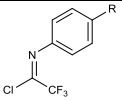
Reagents and conditions: (a) *i*. Selectfluor®, $MeNO_2/H_2O$, (5:1); *ii*. Ac_2O, pyridine 0 °C to rt **26**: 14%, **33**: 28%, **42**: 66%; (b) *i.* HBr (33% in AcOH), DCM, 0 °C to rt; *ii*. *P*-thiocresol, TBABr, KOH, $CHCl_3$, H_2O, 0 °C to rt, **27**: 82%, **43**: 68; (c) *i.* HBr (33% in AcOH), DCM, 0 °C to rt; *ii*. *p*-thiocresol, NaH (60%), DMF, 0 °C to rt, 79%; (d) NaOMe, MeOH, rt, **28**, **35** and **44** quantitatively; (e) TsCl, pyridine, 0 °C to rt, **29**: 88%, **36**: 63%, **45**: 83%; (f) NaN_3, DMF, 80 °C, **30** quantitatively, **37**: 76%, **46**: 74%; (g) NBS, acetone/H_2O (3:1), 0 °C to rt, 68%; (h) *i*. NBS, acetone/H_2O (3:1), 0 °C to rt; *ii*. Ac_2O, pyridine, 0 °C to rt, **38**: 51%, **47**: 32%; (i) NaOMe, MeOH, **39**, **48 (**quantitative); (j) Cs_2CO_3, imidate reagents, acetone, rt (results are summarized in Table 1); (k) 0.075M Sodium ascorbate (aq.), 0.05M $CuSO_4$ (aq.), DMF, **32**: 90%, **40**: 97%, **49**: 90%.

Treatment of 2-fluoro-6-azido thioglucoside **30** with NBS in a mixture of acetone and water gave the corresponding hemiacetal **31**. The same procedure was used to hydrolyse 2-fluoro-6-azido-mannoside **37** and 2-fluoro-6-azido galactoside **46** to their corresponding hemiacetals. Unfortunately the desired products could not be purified by column chromatography. After acetylation of the crude reaction products to give peracetylated 2-fluoro-6-azido mannoside **38** and peracetylated 2-fluoro-6-azido galactose purification could be accomplished. Saponification of **38** and **47** under Zémplen conditions provided 2-fluoro-6-azido mannoside **39** and 2-fluoro-6-azido galactoside **48** in 51% and 32%, respectively, starting from thiomannoside **37** and thiogalactoside **46**.

Next, the obtained 2-fluoro-6-azido glycosides **31**, **39** and **48** were subjected to a Cu-catalyzed azide alkyne cycloaddition with BODIPY alkyne **50**[23] giving 2-fluoro-6-BODIPY glucose **32** (90%), 2-fluoro-6-BODIPY mannose **40** (97%) and 2-fluoro-6-BODIPY galactose **49** (90%). Finally, the imidates were introduced on the 2-fluoro glycosides using the relevant

imidoylchloride reagents (**51-53**) in combination with Cs_2CO_3. The results are summarized in Table 1.

Table 1: Results imidate formation

Entry	Compound	 Imidate reagents	α-product	β-product
1	**31**	R = H (**51**)	3% (**17-α**)	2% (**17-β**)
2	**32**	R = H (**51**)	2% (**18-α**)	<1% (**18-β**)
3	**32**	R = OMe (**52**)	1% (**19-α**)	1% (**19-β**)
4	**32**	R = NO_2 (**53**)	2% (**20-α**)	3% (**20-β**)
5	**39**	R = H (**51**)	10% (**21-α**)	--- (**21-β**)
6	**40**	R = H (**51**)	6% (**22-α**)	--- (**22-β**)
7	**48**	R = H (**51**)	--- (**23-α**)	--- (**23-β**)
8	**49**	R = H (**51**)	--- (**24-α**)	--- (**24-β**)

[a] α/β-ratio determined by ^{1}H-NMR of the crude based on the anomeric signal of the α- and β-product.

The projected imidates prove to be unstable and very sensible towards acid. Purification by HPLC using 100 mM $(NH_4)_2CO_3$ (aq.) as eluens proceeded uneventful but decomposition of both the crude and purified products led to a dramatic loss of product. Decomposition of the purified products could be suppressed by cooling of the collected fractions to -80 °C and immediate lyophilisation. Following this procedure, the treatment of 2-fluoro-6-azido glucoside **31** with *N*-phenyl trifluoroacetimide **51** led to product **17**. The individual α- and β-products were separated by the aid of RP-HPLC yielding

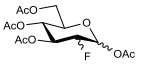
17-α in 3% and **17-β** in 2%. Three different imidates (**51**-**53**) were coupled to BODIPY glucoside **32** (Entry 2-4) leading to the individual α and β anomers (**18**-**20**). All glucosyl imidates were isolated in low yields, ranging from <1% for **18-β** (Entry 2) to 3% for **20-β** (Entry 4). 2-Fluoro-6-azido mannoside **21-α** was obtained as a single anomer from the reaction of **39** with imidate **51** in 10% after HPLC purification (Entry 5). A similar reaction using 2-fluoro-6-BODIPY mannoside **40** gave the α-product **22-α** in a somewhat lower yield of 6% (Entry 6). Finally, the 2-fluoro galactoside **48** and 2-fluoro-6-BODIPY galactoside **49** were subjected to a base mediated reaction with imidate reagent **51**. Unfortunately, TLC and HPLC analysis did not show the formation of the desired products (Entry 7-8). This can be explained by the relatively high instability/reactivity of galactosyl imidates.[24]

Conclusion

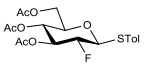
In summary, the synthesis of 2-deoxy-2-fluoro glycoside probes **17**-**22** is described. The probes turned out to be rather unstable and therefore purification was very difficult leading to poor overall yields. Nevertheless six new imidate probes were successfully prepared. In the glucose series, probes having the α- and β-anomeric configuration were obtained. In the manno series only the α-anomers were obtained. Unfortunately the corresponding galactosyl probes could not be obtained. Possibly this is the result of the higher reactivity of galactose probes with respect to the other epimers. The probes that were successfully synthesized can be evaluated for their inhibitory properties on relevant glycosidases (glucosidases, mannosidases) and be probed as possible chaperones, for example to stabilize glucosylcerebrosidase.[25,26,27]

Experimental

General: Traces of water in the starting materials were removed by co-evaporation with toluene for all moisture and oxygen sensitive reactions and the reactions were performed under an argon atmosphere. Dichloromethane was distilled over P_2O_5 and stored over activated 3 Å molecular sieves under an argon atmosphere. All other solvents and chemicals (Acros, Fluca, Merck) were of analytical grade and used as received. Column chromatography was performed on Screening Device silica gel 60 (0.040-0.063 mm). Size exclusion was performed on Sepadex LH20 (eluent DCM/MeOH, 1:1). TLC analysis was conducted on HPTLC aluminium sheet (Merck, TLC silica gel 60, F_{254}). Compounds were visualized by UV absorption (λ = 254 nm), staining with *p*-anisaldehyde (3.7 mL in 135 mL EtOH, 1.5 mL AcOH and 5 mL H_2SO_4), 20% H_2SO_4 in EtOH or with a solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (25g/L) in 10% H_2SO_4 in H_2O followed by charring at +/- 140 °C. ^1H and ^{13}C NMR were recorded on a Bruker DPX 300 (300 and 75 MHz respectively), Bruker AV 400 (400 and 100 MHz respectively), Bruker DMX 400 (400 and 100 MHz respectively) or Bruker DMX 600 (600 and 125 MHz respectively). Chemical shifts are given in ppm (δ) relative to the residual solvent peak or TMS (0 ppm) as internal standard. *J* couplings are given in Hz. Optical rotations were measured on a Propol automatic polarimeter. IR spectra (thin film) were conducted on a Perkin Elmer FTIR Spectrum Two UATR (Single reflection diamond). LC-MS measurements were conducted on a Thermo Finnigan LCQ Advantage MAX ion-trap mass spectrometer (ESI+) coupled to a Thermo Finnigan Surveyor HPLC system equipped with a standard C_{18} (Gemini, 4.6 mm x 50 mm, 5µm particle size, Phenomenex) analytical column and buffers A: H_2O, B: MeCN, C: 0.1% TFA (aq.). High resolution mass spectra were recorded on a LTQ Orbitrap (Thermo Finnigan) mass spectrometer.

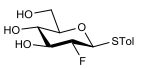


Acetyl 2-deoxy-2-fluoro-3,4,6-tri-*O*-acetyl-α/β-D-glucopyraniside (26) and Acetyl 2-deoxy-2-fluoro-3,4,6-tri-*O*-acetyl-α/β-D-mannopyraniside (33): To a 0 °C solution of acetylated glucal **25** (35.9 g, 131.9 mmol) in nitromethane/H_2O (5:1) (360 mL) was added Selectfluor® (59.8 g, 169 mmol) and the reaction mixture was allowed to warm to rt and stirred overnight. The mixture was heated to 100 °C for 1 h and concentrated *in vacuo*. The concentrate was dissolved in DCM and washed with sat. $NaHCO_3$ (1x), H_2O (1x), brine (1x), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was dissolved in pyridine (200 mL) and cooled to 0 °C. To the cooled solution was added dropwise Ac_2O (15 mL) and the mixture was allowed to rt. After completion the reaction was quenched with MeOH and the mixture was concentrated *in vacuo*. The product was dissolved in EtOAc, washed with 1M HCl (aq.) (3x), sat. $NaHCO_3$ (3x), H_2O (3x), brine (2x), dried over $MgSO_4$, filtered and concentrated *in vacuo* giving a mixture of 2-deoxy-2-fluoro-glucose **26** and 2-deoxy-2-fluoro-mannose **33**. Purification by column chromatography yielded 2-deoxy-2-fluoro-glucose **26** (6.3 g, 18.0 mmol, 14%) and 2-deoxy-2-fluoro-mannose **33** (10.7 g, 37.6 mmol, 28%) both as a colourless oil. Spectroscopic data were in accordance with known literature data for both compounds.[28]

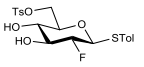


Tolyl 2-deoxy-2-fluoro-3,4,6-tri-*O*-acetyl-1-thio-β-D-glucopyranoside (27): To a 0 °C cooled solution of 2-deoxy-2-fluoro glucose **26** (3.26 g, 8.79 mmol) in DCM (6 mL) was added dropwise 33% HBr in AcOH (7.6 mL, 44.0 mmol) and the reaction was stirred at 4 °C overnight, followed by stirring for 2h at rt. The mixture was poured in ice-water and diluted with EtOAc. The two phases were separated and the organic phase was washed with H_2O (2x), brine (2x), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude bromide was taken up in $CHCl_3$ (10 mL) and to the solution was added *p*-thiocresol (1.64 g, 13.2 mmol) and a solution of TBABr (0.567 g, 1.76 mmol) in H_2O (11.9 mL). The mixture was cooled to 0 °C and under vigorous stirring was added

dropwise a KOH (1.0 g, 17.6 mmol) solution in H_2O (11.9 mL) over a period of 10 minutes. The reaction mixture was allowed to warm to rt and was vigorously stirred overnight. The two phases were separated and the organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography yielded peracetylated 2-deoxy-2-fluoro-thio glucoside **27** as a white amorphous solid (2.97 g, 7.17 mmol, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 5.31 (dt, , *J* = 14.0, 9.6 Hz, 1H), 4.93 (t, *J* = 10.0 Hz, 1H), 4.62 (dd, *J* = 9.6, 1.6 Hz, 1H), 4.16-4.22 (m, 2H), 4.11 (dt, *J* = 46.4, 9.6 Hz, 1H), 3.72 (ddd, *J* = 10.0, 4.4, 3.2 Hz, 1H), 2.38 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 170.1, 169.7, 139.5, 135.0, 129.9, 126.1, 87.0, 84.4, 75.9, 74.0 (d, *J* = 20 Hz), 68.1 (d, *J* = 7 Hz), 62.1, 21.4, 20.9, 20.8, 20.7; HRMS: $[M+H]^+$ calculated for $C_{19}H_{24}FO_7S$ 415.12213, found 415.12207.

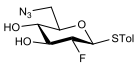


Tolyl 2-deoxy-2-fluoro-1-thio-β-D-glucopyranoside (28): To a solution of **27** (1.53 g, 3.70 mmol) in MeOH (30 mL) was added NaOMe (200 mg, 3.7 mmol) and stirred for 3 h. The reaction was quenched with Amberlite-H^+ IR-120 till pH≤7, filtered and concentrated *in vacuo* yielding 2-deoxy-2-fluoro thio glucose **28** as a white amorphous solid without further purification (1.07 g, 3.70 mmol, quantitatively). Spectroscopic data were in accordance with known literature data.[19]

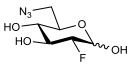


Tolyl 2-deoxy-2-fluoro-6-*O*-tosyl-1-thio-β-D-glucopyranoside (29): To a 0 °C cooled solution of 2-deoxy-2-fluoro thio glucose **28** (634 mg, 2.2 mmol) in pyridine (11 mL) was added TsCl (641 mg, 2.4 mmol), the mixture was allowed to warm to rt and stirred overnight. The reaction was quenched with MeOH and concentrated *in vacuo* followed by co-evaprated with toluene (3x) of the crude. Purification by column chromatography yielded tosylated 2-deoxy-2-fluoro thio glucose **29** as a white amorphous solid (859 mg, 1.94 mmol, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.4 Hz, 2H), 7.35-7.40 (m, 4H), 7.09 (d, *J* = 8.0

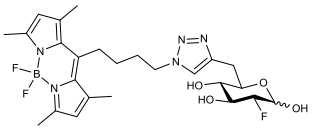
Hz, 2H), 4.53 (dd, *J* = 9.6, 1.6 Hz, 1H), 4.30 (s, 2H), 3.97 (dt, J = 49.6, 8.8 Hz, 1H), 3.70-3.78 (m, 1H), 3.49 (d, *J* = 4.8 Hz, 2H), 2.45 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.3, 139.1, 134.4, 132.7, 130.1, 129.9, 128.2, 126.9, 89.3 (d, *J* = 186 Hz), 84.5 (d, *J* = 24 Hz), 76.8, 76.4 (d, *J* = 19 Hz), 69.1 (d, *J* = 8 Hz), 68.3, 21.8, 21.4.



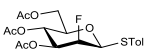
Tolyl 6-azido-2,6-di-deoxy-2-fluoro-1-thio-β-D-glucopyranoside (30): To a solution of tosylated glucose **29** (0.929 g, 2.1 mmol) in DMF (25 mL) was added NaN_3 (0.410 g, 6.3 mmol) and the mixture was stirred overnight at 80 °C. The reaction mixture was diluted with EtOAc and the product was washed with sat. $NaHCO_3$ (aq.) (2x), H_2O (2x), brine (2x), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography yielded 6-azido-2-deoxy-2-fluoro thio glucose **30** as a colourless amorphous solid (0.651 g, 2.1 mmol, quantitatively). Spectroscopic data were in accordance with known literature data.[19]



6-Azido-2,6-dideoxy-2-fluoro-α/β-D-glucopyranose (31): To a 0 °C cooled solution of 6-azido-2-deoxy-2-fluoro thio glucose **30** (0.392 g, 1.25 mmol) in a acetone/H_2O mixture (3:1, 12.5 mL) was added NBS (1.33 g, 7.5 mmol). The reaction mixture was allowed to warm to rt and was stirred overnight. During the reaction the mixture turned from orange to a colorless clear solution. The reaction was quenched with 10% $Na_2S_2O_3$ (aq.) and diluted with brine. The water layer was extracted with EtOAc (5x) and the combined organic layers were washed with brine (2x), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography yielded deprotected 6-azido-2-deoxy-2-fluoro glucose **31** as a white amorphous solid. Spectroscopic data were in accordance with known literature data.[19]

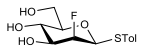


BODIPY 2-fluoro glucoside (32): Deprotected 6-azido-2-deoxy-2-fluoro glucose **31** (0.142 g, 0.687 mmol) was dissolved in DMF (55 mL) and the solution was purged with argon for 30 min. To the solution was added a 0.075 M sodium ascorbate solution (aq.) (6.87 mL, 0.52 mmol), a 0.05M $CuSO_4$ (aq.) (6.87 mL, 0.34 mmol) and the reaction was stirred for 2h. The mixture was taken up in brine and the product was extracted with EtOAc (2x). The combined organic layers were washed with brine (3x) dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography yielded 2-deoxy-2-fluoro BODIPY glucose **32** as an orange solid (0.332 g, 0.619 mmol, 90%). LC-MS: R_t 6.55 min (C_{18} column, linear gradient 10 → 90% B in 15 min). Spectroscopic data were in accordance with known literature data.[19]

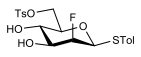


Tolyl 2-deoxy-2-fluoro-3,4,6-tri-*O*-acetyl-1-thio-β-D-mannopyranoside (34): To a 0 °C cooled solution of 2-deoxy-2-fluoro mannose **33** (7.32 g, 20.9 mmol) in dry DCM (14 mL) was added 33% HBr in AcOH (18 mL, 60 mmol) dropwise. Ac_2O (0.2 mL, 2.2 mmol) was added and the mixture was allowed to warm to rt and stirred overnight. The reaction was quenched with ice water and the product extracted with EtOAc (3x). The combined organic layers were washed with sat. $NaHCO_3$ (3x), H_2O (3x), brine (2x), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude bromide was dissolved in DMF (42 mL) and *p*-thiocresol (3.89 g, 31.45 mmol) was added to the solution. The mixture was cooled to 0 °C and to the cooled mixture was added 60% NaH (1.05 g, 26.13 mmol) in small portions. The mixture was allowed to warm to rt and stirred overnight. The reaction was quenched with 0.02M HCl (aq.) and taken up in EtOAc. The two phases were separated and the organic phase was washed with sat. $NaHCO_3$ (aq.) (1x), H_2O (3x), brine (2x), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography yielded 2-deoxy-2-fluoro-β-thio mannose **34** as a white

amorphous solid (6.9 g, 16.6 mmol, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.38 (t, *J* = 10.0 Hz, 1H), 5.06 (dd, *J* = 47.2, 2.4 Hz, 1H), 4.91-5.04 (m, 1H), 4.79 (d, *J* = 26.4 Hz, 1H), 4.27 (dd, *J* = 12.4, 5.6 Hz, 1H), 4.16 (dd, *J* = 12.4, 2.8 Hz, 1H), 3.64-3.69 (m, 1H), 2.35 (s, 3H), 2.03-2.12 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 170.5, 169.6, 138.7, 132.8, 130.0, 129.5, 89.0 (d, *J* = 186 Hz), 85.8 (d, *J* = 18 Hz), 76.4, 72.5 (d, *J* = 18 Hz), 65.7, 62.6, 21.3, 20.9, 20.9, 20.8; FT-IR: ν_{max} (neat)/cm^{-1} 1742, 1368, 1218, 1092, 1049, 960, 916, 834, 811, 776; HRMS: $[M+H]^+$ calculated for $C_{19}H_{24}FO_7S$ 415.12213, found 415.12281.

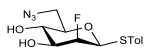


Tolyl 2-deoxy-2-fluoro-1-thio-β-D-mannopyranoside (35): To a solution of **34** (860 mg, 2.1 mmol) in MeOH (20 mL) was added NaOMe (0.108 g, 2.0 mmol) and stirred overnight. The reaction was quenched with Amberlite-H^+ IR-120 till pH≤7, filtered and concentrated *in vacuo* yielding 2-deoxy-2-fluoro thio mannose **35** as a white amorphous solid without further purification (606 mg, 2.1 mmol, quantitatively). ^{1}H NMR (400 MHz, MeOD): δ 4.99 (d, *J* = 28 Hz, 1H), 4.86 (dd, *J* = 49.2, 2.8 Hz, 1H), 3.89 (dd, *J* = 12.0, 2.4 Hz, 1H), 3.71 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.55-3.66 (m, 2H), 3.28-3.35 (m, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, MeOD): δ 138.6, 132.1, 130.8, 93.9 (d, *J* = 181 Hz), 86.7 (d, *J* = 18 Hz), 82.5, 74.8 (d, *J* = 18 Hz), 68.4 (d, *J* = 8 Hz), 62.8, 21.1; FT-IR: ν_{max} (neat)/cm^{-1} 3357, 1493, 1090, 1058, 1005, 849, 805, 766, 689, 487; HRMS: $[M+H]^+$ calculated for $C_{13}H_{18}FO_4S$: 289.34406, found 289.34409.

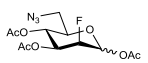


Tolyl 2-deoxy-2-fluoro-6-*O*-tosyl-1-thio-β-D-mannopyranoside (36): To a 0 °C cooled solution of 2-deoxy-2-fluoro thio mannose **35** (606 mg, 2.1 mmol) in pyridine (10.5 mL) was added TsCl (0.478 g, 2.51 mmol), the mixture was allowed to warm to rt and stirred overnight. The reaction was quenched with MeOH and concentrated *in vacuo* followed by co-evaprated with toluene (3x) of the crude. Purification by column chromatography yielded tosylated 2-deoxy-2-fluoro thio mannose **36** as a white amorphous solid (0.592 g, 1.34 mmol, 63%). ^{1}H

NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.0 Hz, 2H), 7.33-7.38 (m, 4H), 7.10 (d, *J* = 8.0 Hz, 2H), 4.94 (dd, *J* = 49.2, 2.4 Hz, 1H), 4.72 (d, *J* = 28.4 Hz, 1H), 4.37 (d, *J* = 11.2 Hz, 1H), 4.32 (dd, *J* = 11.2, 5.4 Hz, 1H), 3.78 (t, *J* = 9.4 Hz, 1H), 3.59 (ddd, *J* = 27.2, 9.6, 2.6 Hz, 1H), 3.45-3.48 (m, 1H), 2.43 (s, 3H,), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.3, 139.1, 134.4, 132.7, 130.1, 129.9, 128.2, 126.9, 89.3 (d, *J* = 186 Hz), 84.5 (d, *J* = 24 Hz), 76.8, 76.4 (d, *J* = 19 Hz), 69.1 (d, *J* = 8 Hz), 68.3, 21.8, 21.4. ;FT-IR: ν_{max} (neat)/cm^{-1} 3367, 1494, 1358, 1190, 1175, 1079, 983, 946, 810, 687, 760.

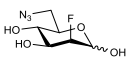


Tolyl 6-azido-2,6-di-deoxy-2-fluoro-1-thio-β-D-mannopyranoside (37): To a solution of tosylated mannose **36** (0.593 g, 1.34 mmol) in DMF (13.4 mL) was added NaN_3 (260 mg, 4.0 mmol) and the mixture was stirred overnight at 80 °C. The reaction mixture was diluted with EtOAc and the product was washed with sat. $NaHCO_3$ (aq.) (2x), H_2O (2x), brine (2x), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography yielded 6-azido-2-deoxy-2-fluoro thio mannose **37** as a colourless amorphous solid (318 mg, 1.0 mmol, 76%). ^1H NMR (400 MHz, MeOD): δ 7.42 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 4.97 (d, *J* = 28.0 Hz, 1H), 4.86 (dd, *J* = 50.0, 2.0 Hz, 1H), 3.37-3.64 (m, 5H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, MeOD): δ 139, 132.9, 131.8, 130.7, 93.7 (d, *J* = 181 Hz), 86.8 (d, *J* = 18 Hz), 80.8, 74.6 (d, *J* = 18 Hz), 69.1, 52.9, 21.1; FT-IR: ν_{max} (neat)/cm^{-1} 3356, 2093, 1493, 1278, 1060, 1018, 998, 982, 951, 869, 843, 807, 767, 689, 573; HRMS $[M+H]^+$ calculated for $C_6H_{10}FN_3O_3$ 191.07007, found 191.07010.



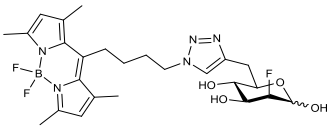
Acetyl 6-azido-2,6-dideoxy-2-fluoro-3,4-di-*O*-acetyl-α/β-D-mannopyraniside (38): To a 0 °C cooled solution of 6-azido-2-deoxy-2-fluoro thio mannose **37** (305 mg, 1.0 mmol) in a acetone/H_2O mixture (3:1, 12.5 mL) was added NBS (1.33 g, 7.5 mmol). The reaction mixture was allowed to warm to rt and was stirred overnight. During the reaction the mixture turned from orange to a colourless clear solution. The

reaction was quenched with 10% $Na_2S_2O_3$ (aq.) and diluted with brine. The product was extracted with EtOAc (5x) and the combined organic layers were washed with brine (2x), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The concentrate was taken up in pyridine (4 mL), cooled to 0 °C and Ac_2O (1.0 mL) was added to the cooled solution. The mixture was allowed to warm to rt and stirred overnight. The reaction was quenched with MeOH, concentrated *in vacuo* and dissolved in EtOAc. The product was washed with 1M HCl (aq.) (2x), sat. $NaHCO_3$(aq.) (1x), H_2O (3x), brine (2x), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography yielded acetylated 6-azido-2-deoxy-2-fluoro mannose **38** as a colourless oil (0.165 g, 0.495 mmol, 51%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.28 (d, *J* = 6.8 Hz, 1H), 5.36 (t, *J* = 10.0 Hz, 1H), 5.27 (ddd, *J* = 28.0, 10.0, 2.0 Hz, 1H), 4.77 (dd, *J* = 48.8, 1.8 Hz, 1H), 4.00-4.04 (m, 1H), 3.33-3.42 (m, 2H), 2.19 (s, 3H), 2.12 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 169.4, 168.0, 89.9 (d, *J* = 31 Hz), 86.0 (d, *J* = 181 Hz), 71.9, 69.3 (d, *J* = 16 Hz), 66.3, 50.8, 20.8, 20.7, 20.6; FT-IR: ν_{max} (neat)/cm^{-1} 2105, 1751, 1372, 1214, 1147, 1050 ,1021, 975, 927, 601; HRMS $[M+H]^+$ calculated for $C_{12}H_{17}FN_3O_7$ 334.10450, found 334.10476.

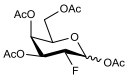


6-Azido-2,6-dideoxy-2-fluoro-α/β-D-mannopyranose (39): To a solution of acetylated 6-azido-2-deoxy-2-fluoro mannose **38** (0.143 g, 0.428 mmol) in MeOH (10 mL) was added NaOMe (4 mg, 0.04 mmol) and stirred overnight. The reaction was quenched with Amberlite-H^+ IR-120 till pH≤7, filtered and concentrated *in vacuo* yielding 6-azido-2-deoxy-2-fluoro mannose **39** as a colorless oil without further purification as an α/β mixture (α/β = 9:1, 87.4 mg, 0.422 mmol, quantitatively). ^{1}H NMR (400 MHz, MeOD): δ 5.22 (dd, *J* = 7.2, 2.0 Hz, 1H-α), 4.83 (d, *J* = 20.0 Hz, 1H-β), 4.60 (dd, *J* = 51.6, 2.2 Hz, 1H-β), 4.56 (dt, *J* = 50.4, 2.2 Hz, 1H-α), 3.87-3.91 (m, 1H, H-α), 3.79 (ddd, *J* = 30.8, 9.6, 2.4 Hz, 1H-α), 3.61 (td, *J* = 9.6, 0.8 Hz, 1H-α), 3.52 (dd, *J* = 13.2, 2.4 Hz, 1H-α), 3.41 (dd, *J* = 13.2, 6.0 Hz, 1H-α); ^{13}C NMR (100 MHz, MeOD): δ 94.3 (d, *J* = 16 Hz, C-β), 93.1 (d, *J* = 33 Hz, C-α), 92.7 (d, *J* = 182 Hz, C-β), 92.1 (d, *J* = 177 Hz, C-α), 73.1

(C-α), 71.2 (d, *J* = 17 Hz, C-α), 69.5 (C-α), 52.7 (C-α); FT-IR: ν_{max} (neat)/cm^{-1} 3354, 2107, 1283, 1064.

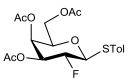


BODIPY 2-fluoro mannoside (40): Deprotected 6-azido-2-deoxy-2-fluoro mannose **39** (32.7 mg, 0.157 mmol) was dissolved in DMF (12 mL) and the solution was purged with argon for 30 min. To the solution was added a 0.075M sodium ascorbate solution (aq.) (1.50 mL, 0.113 mmol), a 0.05M $CuSO_4$ (aq.) (1.50 mL, 0.075 mmol) and the reaction was stirred for 2h. The mixture was taken up in brine and the product was extracted with EtOAc (2x). The combined organic layers were washed with brine (3x) dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography yielded BODIPY 2-deoxy-2-fluoro mannoside **40** as an orange solid (82.0 mg, 0.153 mmol, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (s, 1H), 7.70 (s, 1H), 6.07 (s, 2H), 5.17 (dd, *J* = 7.0, 1.4 Hz, 1H), 4.47-4.89 (m, 3H), 4.07 (ddd, *J* = 9.6, 9.6, 2.0 Hz, 1H), 3.83 (ddd, *J* = 30.8, 9.6, 2.4 Hz, 1H), 3.42 (t, *J* = 9.6 Hz, 1H), 2.80-2.85 (m, 2H), 2.68 (t, *J* = 7.6 Hz, 2H), 2.42 (s, 6H), 2.29 (s, 6H), 1.81 (p, *J* = 7.4 Hz, 2H), 1.56-1.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.8, 148.3, 147.9, 142.3, 132.6, 124.6, 122.6, 93.1 (d, *J* = 29 Hz), 91.9 (d, *J* = 174 Hz), 72.2, 71.1, 69.7, 52.3, 32.1, 30.8, 28.9, 25.8, 16.4, 14.5.



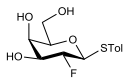
Acetyl 2-deoxy-2-fluoro-3,4,6-tri-*O*-acetyl-α/β-D-galactopyraniside (42): To a 0°C solution of acetylated galactal **41** (7.5 g, 27.5 mmol) in nitromethane/H_2O (5:1) (83 mL) was added Selectfluor® (11.7 g, 33 mmol) and the reaction mixture was allowed to warm to rt and stirred for 70 h. The mixture was heated to 100 °C for 30 min and cooled to rt. The mixture was diluted with brine and extracted with DCM (5x). The combined organic layers were washed with sat. $NaHCO_3$ (1x), H_2O (x), brine (1x), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was dissolved in DCM (65 mL) and cooled to 0 °C. To the

cooled solution was added pyridine (4.2 mL), Ac_2O (3.2 mL, 34 mmol) and the mixture was allowed to rt. After stirring overnight, the mixture was cooled to 0 °C and additionally pyridine (3 mL), Ac_2O (2 mL, 21 mmol) was added and the mixture was allowed to warm to rt. After 2 h the reaction was quenched with MeOH and the mixture was concentrated *in vacuo*. The product was dissolved in EtOAc, washed with 1M HCl (aq.) (3x), sat. $NaHCO_3$ (3x), H_2O (3x), brine (2x) dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography yielded 2-deoxy-2-fluoro galactoside **42** as a yellow oil (8.7 g, 18.0 mmol, 66%). Spectroscopic data were in accordance with known literature data.[29]

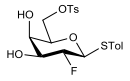


Tolyl 2-deoxy-2-fluoro-3,4,6-tri-*O*-acetyl-1-thio-β-D-galactopyranoside (43): To a 0 °C cooled solution of 2-deoxy-2-fluoro galactoside **42** (3.35 g, 9.56 mmol) in dry DCM (6.4 mL) was added 33% HBr in AcOH (8.2 mL, 9.6 mmol) dropwise. Ac_2O (0.1 mL, 1.1 mmol) was added and the mixture was allowed to warm to rt and stirred overnight. The reaction was quenched with ice water and the product extracted with EtOAc (3x). The combined organic layers were washed with sat. $NaHCO_3$ (3x), H_2O (3x), brine (2x), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude bromide was taken up in $CHCl_3$ (100 mL) and to the solution was added *p*-thiocresol (1.8 g, 14.3 mmol) and a solution of TBABr (0.616 g, 1.91 mmol) in H_2O (13.5 mL). The mixture was cooled to 0 °C and under vigorous stirring was added dropwise a KOH (1.1 g, 19.1 mmol) solution in H_2O (13.5 mL) over a period of 10 minutes. The reaction mixture was allowed to warm to rt and was vigorously stirred overnight. The two phases were separated and the organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography yielded peracetylated 2-deoxy-2-fluoro-thio galactoside **43** as a white amorphous solid (2.68 g, 6.46 mmol, 68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 7.6 Hz, 2H), 5.43 (s, 1H), 5.12 (ddd, *J* = 13.2, 9.2, 3.6 Hz, 1H), 4.68 (dd, *J* = 10.0, 2.6 Hz, 1H), 4.46 (dt, *J* = 49.6, 9.6 Hz, 1H), 4.18 (dd, *J* = 11.2, 6.8 Hz, 1H), 4.10 (dd, *J* = 11.2,

6.4 Hz, 1H), 2.36 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 170.1, 170.1, 170.1, 139.1, 134.2, 129.9, 127.4, 85.7 (d, *J* = 187 Hz), 85.6 (d, *J* = 24 Hz), 74.5, 72.2 (d, *J* = 20 Hz), 68.1 (d, *J* = 8 Hz), 61.5, 21.4, 20.8, 20.8, 20.6; HRMS: $[M+H]^+$ calculated for $C_{19}H_{24}FO_7S$ 415.12213, found 415.12222.



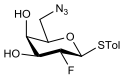
Tolyl 2-deoxy-2-fluoro-1-thio-β-D-galactopyranoside (44): To a solution of (860 mg, 2.1 mmol) in MeOH (20 mL) was added NaOMe (108 mg, 2.0 mmol) and stirred overnight. The reaction was quenched with Amberlite-H^+ IR-120 till pH≤7, filtered and concentrated *in vacuo* yielding 2-deoxy-2-fluoro thio mannose **44** as a white amorphous solid without further purification (597 mg, 2.1 mmol, quantitatively). ^{1}H NMR (400 MHz, MeOD): δ 7.45 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 4.66 (dd, *J* = 9.6, 2.0 Hz, 1H), 4.30 (dt, *J* = 50.8 Hz, 1H), 3.92 (t, *J* = 3.2 Hz, 1H), 3.68-3.78 (m, 3H), 3.58 (t, *J* = 6.0 Hz, 1H), 2.32 (s, 3H,); ^{13}C NMR (100 MHz, MeOD): δ 133.9, 130.6, 90.7, 86.7 (d, *J* = 24 Hz,), 80.8, 74.3, 62.4; HRMS: $[M+H]^+$ calculated for $C_{13}H_{18}FO_4S$: 289.34406, found 289.34461.



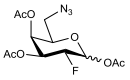
Tolyl 2-deoxy-2-fluoro-6-*O*-tosyl-1-thio-β-D-galactopyranoside (45):

To a 0 °C cooled solution of 2-deoxy-2-fluoro-thio galactoside **44** (0.591 g, 2.05 mmol) in pyridine (10 mL) was added TsCl (0.434 g, 2.25 mmol), the mixture was allowed to warm to rt and stirred overnight. The reaction was quenched with MeOH and concentrated *in vacuo* followed by co-evaprated with toluene (3x) of the crude. Purification by column chromatography yielded tosylated 2-deoxy-2-fluoro-thio galactoside **45** as a white amorphous solid (0.750 g, 1.369 mmol, 83%). ^{1}H NMR (400 MHz, MeOD): δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 4.61 (d, *J* = 9.2 Hz, 1H), 4.09-4.32 (m, 3H), 3.80-3.84 (m, 2H), 3.72 (ddd, *J* = 14.0, 8.8, 3.6 Hz, 1H), 2.43 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, MeOD): δ 146.6, 139.1, 133.8, 131.1, 130.6, 130.2, 129.1, 90.3

(d, *J* = 182 Hz), 86.1 (d, *J* = 25 Hz), 77.5, 73.9 (d, *J* = 18 Hz), 70.9, 70.9 (d, *J* = 6 Hz), 21.6, 21.1.

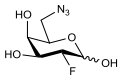


Tolyl 6-azido-2,6-di-deoxy-2-fluoro-1-thio-β-D-galactopyranoside (46): To a solution of tosylated galactoside **45** (650 mg, 1.5 mmol) in DMF (20 mL) was added NaN_3 (390 mg, 6.0 mmol) and the mixture was stirred overnight at 80 °C. The reaction mixture was diluted with EtOAc and the product was washed with sat. $NaHCO_3$ (aq.) (2x), H_2O (2x), brine (2x), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography yielded 6-azido-2-deoxy-2-fluoro-thio galactoside **46** as a colourless amorphous solid (342 mg, 1.1 mmol, 74%). ^{1}H NMR (400 MHz, MeOD): δ 7.45 (d, *J* = 8.0 Hz2H), 7.14 (d, *J* = 8.0 Hz, 2H), 4.68 (dd, *J* = 9.6, 2.0 Hz, 1H), 4.29 (dt, *J* = 50.4, 9.2 Hz, 1H), 3.69-3.83 (m, 3H), 3.60 (dd, *J* = 12.8, 8.8 Hz, 1H), 3.27-3.31 (m, 1H), 2.32 (s, 3H); ^{13}C- NMR (100 MHz, MeOD): δ 139.4, 134.3, 130.6, 130.1, 90.5 (d, *J* = 182 Hz), 86.8 (d, *J* = 24 Hz), 79.1 (C-5), 74.1 (d, *J* = 18 Hz), 71.4 (d, *J* = 9 Hz), 52.6, 21.1; HRMS: $[M+H]^+$ calculated for $C_{13}H_{17}FN_3O_3S$ 314.09692, found 314.09701.

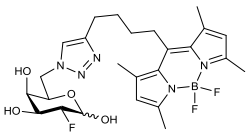


Acetyl 6-azido-2,6-dideoxy-2-fluoro-3,4-di-*O*-acetyl-α/β-D-galactopyraniside (47): To a 0 °C cooled solution of 6-azido-2-deoxy-2-fluoro thio galactoside **46** (325 mg, 1.0 mmol) in a acetone/H_2O mixture (3:1, 10.3 mL) was added NBS (1.1 g, 6.2 mmol). The reaction mixture was allowed to warm to rt and was stirred overnight. During the reaction the mixture turned from orange to a colourless clear solution. The reaction was quenched with 10% $Na_2S_2O_3$ (aq.) and diluted with brine. The product was extracted with EtOAc (5x) and the combined organic layers were washed with brine (2x), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The concentrate was taken up in pyridine (4 mL), cooled to 0 °C and Ac_2O (1.0 mL) was added to the cooled solution. The mixture was allowed to warm to rt and stirred overnight. The reaction was quenched with MeOH, concentrated *in vacuo* and dissolved in EtOAc. The product was washed

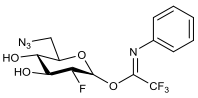
with 1M HCl (aq.) (2x), sat. $NaHCO_3$(aq.) (1x), H_2O (3x), brine (2x), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography yielded acetylated 6-azido-2-fluoro galactoside **47** as a colourless oil (0.110 g, 0.329 mmol, 32%). ^{1}H NMR (400 MHz, MeOD): δ 6.49 (d, *J* = 4.0 Hz, 1H-α), 5.83 (d, *J* = 8.0, 4.0 Hz, 1H-β), 5.51 (t, *J* = 3.0 Hz, 1H-α), 5.43-5.45 (m, 1H, H-β), 5.39 (dd, *J* = 10.8, 3.6 Hz, 1H-α), 5.20 (ddd, *J* = 13.4, 9.6, 3.6 Hz, 1H-β), 4.90 (ddd, *J* = 49.2, 10.4, 4.0 Hz, 1H-α), 4.66 (ddd, *J* = 51.6, 9.6, 8.0 Hz, 1H-β), 4.21 (t, *J* = 6.4 Hz,H-α), 4.00 (t, *J* = 6.4 Hz, 1H-β), 3.51 (dd, *J* = 12.8, 7.2 Hz, 1H-β), 3.43 (dd, *J* = 12.8, 7.2 Hz, 1H-α), 3.20-3.25 (m, 2H); ^{13}C NMR (100 MHz, MeOD): δ 170.1, 170.0, 169.8, 168.8, 168.8, 91.6 (d, *J* = 25 Hz), 88.9 (d, *J* = 23 Hz), 86.7 (d, *J* = 187 Hz), 84.1 (d, *J* = 190 Hz), 73.7, 71.0 (d, *J* = 27 Hz), 70.9, 68.2, 68.2, 50.2, 50.0, 20.9, 20.8, 20.7, 20.6, 20.6; HRMS $[M+H]^+$ calculated for $C_{12}H_{17}FN_3O_7$ 334.10450, found 334.10444.



6-Azido-2,6-dideoxy-2-fluoro-α/β-D-galactopyranose (48): To a solution of acetylated 6-azido-2-deoxy-2-fluoro galactoside **47** (0.110 g, 0.329 mmol) in MeOH (10 mL) was added NaOMe (3 mg, 0.06 mmol) and stirred overnight. The reaction was quenched with Amberlite-H^+ IR-120 till pH≤7, filtered and concentrated *in vacuo* yielding 6-azido-2-fluoro galactoside **48** as a colourless oil without further purification (68.1 mg, 0.33 mmol, quantitatively). ^{1}H NMR (400 MHz, MeOD): δ 5.32 (d, *J* = 4.0 Hz, 1H-α), 4.68 (dd, *J* = 7.6, 3.2 Hz, 1H-β), 4.65 (ddd, *J* = 50.4, 10.0, 4.0 Hz, 1H-α), 4.25 (ddd, *J* = 52.0, 9.2, 3.6 Hz, H-β), 4.13-4.17 (m, 1H), 3.98-4.05 (m, 1H-α), 3.86 (dt, *J* = 3.6, 1.2 Hz, 1H-α), 3.80 (dt, *J* = 3.8, 1.0 Hz, 1H-β), 3.68-3.76 (m, 2H), 3.49-3.60 (m, 2H), 3.29-3.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 96.1 (d, *J* = 24 Hz), 94.0 (d, *J* = 180 Hz), 91.8 (d, *J* = 22 Hz), 90.4 (d, *J* = 183 Hz), 75.2, 73.2 (d, *J* = 17 Hz), 72.0 (d, *J* = 8 Hz), 71.3 (d, *J* = 9 Hz), 70.4, 69.0 (d, *J* = 17 Hz), 52.4, 52.4.

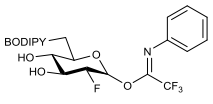


BODIPY 2-fluoro galactoside (49): Deprotected 6-azido-2-deoxy-2-fluoro galactoside **48** (33.6 mg, 0.16 mmol) was dissolved in DMF (12 mL) and the solution was purged with argon for 30 min. To the solution was added a 0.075M sodium ascorbate solution (aq.) (1.5 mL, 0.11 mmol), a 0.05M $CuSO_4$ (aq.) (1.5 mL, 0.075 mmol) and the reaction was stirred for 1h. The mixture was taken up in brine and the product was extracted with EtOAc (2x). The combined organic layers were washed with brine (3x) dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography yielded BODIPY 2-deoxy-2-fluoro galactoside **49** as an orange solid (85.3 mg, 0.16 mmol, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (s, 1H), 7.69 (s, 1H), 6.07 (s, 4H), 5.26 (d, *J* = 3.6 Hz, 1H-α), 4.42-4.68 (m, 6H), 4.40 (t, *J* = 6.8 Hz, 1H-β), 4.30 (ddd, *J* = 52, 9.2, 8.0 Hz, 1H-β), 3.96-4.06 (m, 2H), 3.90 (t, *J* = 3.0 Hz, 1H-α), 3.83 (t, *J* = 2.8 Hz, 1H-β), 3.71-3.77 (m, 1H), 2.80-2.84 (m, 4H), 2.68 (t, *J* = 7.4 Hz, 2H), 2.41 (s, 12H), 2.28 (s, 12H), 1.81 (p, *J* = 7.5 Hz, 4H), 1.52-1.60 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.8, 148.4, 147.9, 142.3, 132.6, 124.3, 124.2, 122.6, 96.0 (d, *J* = 23 Hz), 93.8 (d, *J* = 179 Hz), 91.8 (d, *J* = 22 Hz), 90.3 (d, *J* = 183 Hz), 74.8, 72.9 (d, *J* = 17 Hz), 71.9 (d, *J* = 8 Hz), 71.3 (d, *J* = 9 Hz), 70.2, 68.9 (d, *J* = 18 Hz), 52.1, 52.0, 32.1, 30.8, 28.9, 25.8, 16.4, 14.5.



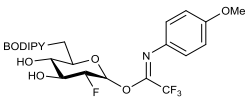
α/β-6-Azido-2-fluoro-glucosyl imidate (17): To a 0 °C cooled solution of 6-azido-2-deoxy-2-fluoro glucosyl **31** (26.2 mg, 126 µmol) in acetone (6 mL) was added trifluoro aniline imidate **51** (52.5 mg, 253 µmol) and Cs_2CO_3 (100 mg, 280 µmol). The reaction was gradually warmed to rt and stirred overnight. The solids were filtered and the filtrate was concentrated *in vacuo* Purificaton by column chromatography yielded glucose aniline imidate **17** as a α/β mixture (α/β = 3:2, 1.08 mg, 2.86 µmol, 2%). Spectroscopic data for the α-anomer **17-α**: ^{1}H NMR (CD_3CN, 600 MHz): δ 7.31 (t, 2H, *J* = 7.8 Hz), 7.12 (t, 1H, *J* = 7.2 Hz), 6.85 (d, 2H, *J* = 7.2 Hz), 6.41 (bs, 1H), 4.50 (d, 1H, *J* = 48.0 Hz), 3.77-3.82 (m, 2H), 3.51-3.58 (m, 1H), 3.36-3.41 (m, 2H); LC-MS: R_t 7.68

min (C18 column, linear gradient 10 → 90% B in 15 min); FT-IR: ν_{max} (neat)/cm^{-1} 3352, 2104, 1720, 1312, 1211, 1155, 1116, 1031, 117, 695.
Spectroscopic data for the β-anomer **17-β**: ^{1}H NMR (CD_3CN, 850 MHz): δ 7.31 (t, 2H, *J* = 7.7 Hz), 7.13 (t, 1H, *J* = 7.2 Hz), 6.87 (bs, 2H), 5.92 (bs, 1H), 4.31(d, 1H, *J* = 50.2 Hz), 3.50-3.75 (m, 2H), 3.41-3.44 (m, 2H), 3.33-3.39 (m, 1H); LC-MS: R_t 8.18 min (C18 column, linear gradient 10 → 90% B in 15 min); FT-IR: ν_{max} (neat)/cm^{-1} 3356, 2103, 1721, 1316, 1212, 1163, 1001, 695.



α/β-2-Fluoro-BODIPY-glucosyl imidate (18): To a 0 °C cooled solution of BODIPY 2-deoxy-2-fluoro glucosyl **32** (51.1 mg, 95.4 µmol) in acetone (6 mL) was added trifluoro aniline imidate **51** (39.6 mg, 191 µmol) and Cs_2CO_3 (47.0 mg, 140 µmol). The reaction was gradually warmed to rt and stirred overnight. The solids were filtered and the filtrate was concentrated *in vacuo* Purificaton by column chromatography yielded glucose aniline imidate **18** as a α/β mixture (α/β = 1:2, 22.3 mg, 31.6 µmol, 33%) . Purification by RP-HPLC followed by lyophilisation yielded α-2-deoxy-2-fluoro-BODIPY-glucosyl-aniline-imidate **18-α** (1.63 mg, 2.30 µmol, 2%) and β-2-deoxy-2-fluoro-BODIPY-glucosyl-aniline imidate **18-β** (97 µg, 0.14 µmol, 0.1%) both as an orange powder. Spectroscopic data for the α-anomer **18-α**: ^{1}H NMR (CD_3CN, 600 MHz): δ 7.50 (s, 1H, CH_{arom} triazole), 7.27 (t, 2H, *J* = 8.1 Hz, CH_{arom} phenyl), 7.09 (t, 1H, *J* = 7.5 Hz, CH_{arom} phenyl), 6.55 (d, 2H, *J* = 7.2 Hz, CH_{arom} phenyl), 6.26 (bs, 1H, H-1), 6.14 (s, 2H, CH_{arom} pyrrole), 4.72 (d, 1H, *J* = 13.8 Hz, H-6), 4.40-4.48 (m, 2H, H-2, H-6), 3.87-4.01 (m, 4H, H-3, H-5, OH), 3.26 (bs, 1H, H-4), 2.97 (t, 2H, *J* = 8.7 Hz, CH_2), 2.67-2.77 (m, 2H, CH_2), 2.43 (s, 6H, CH_3), 2.37 (s, 6H, CH_3), 1.81-1.84 (m, 2H, CH_2), 1.52-1.76 (m, 2H, CH_2); LC-MS: R_t 9.80 min (C18 column, linear gradient 10 → 90% B in 15 min); FT-IR: ν_{max} (neat)/cm^{-1} 3383, 1719, 1550, 1510, 1310, 1203, 1159, 1075, 986. HRMS $[M + H]^+$ calculated for $C_{33}H_{37}BF_6N_6O_4$: 707.29463, found 707.29547.

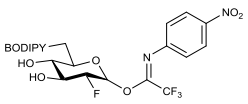
Spectroscopic data for the β-anomer **18-β**: NMR (CD_3CN, 600 MHz): δ 7.57 (s, 1H, CH_{arom} triazole), 7.26 (t, 2H, J = 7.8 Hz, CH_{arom} phenyl), 7.08 (t, 1H, J = 7.5 Hz, CH_{arom} phenyl), 6.70 (t, 2H, J = 7.2 Hz, CH_{arom} phenyl), 6.15 (s, 2H, CH_{arom} pyrrole), 5.66 (bs, 1H, C-1), 4.79 (d, 1H, J = 14.4 Hz, H-6), 4.32-4.36 (m, 2H, H-2, H-6), 4.06 (bs, 1H, OH), 3.96 (bs, 1H, OH), 3.71 (bs, 2H, H-3, H-5), 3.33 (bs, 1H, H-4), 2.92 (t, 2H, J = 8.4 Hz, CH_2), 2.54-2.61 (m, 2H, CH_2), 2.44 (s, 6H, CH_3), 2.34 (s, 6H, CH_3), 1.70-1.75 (m, 2H, CH_2), 1.52-1.54 (m, 2H, CH_2); HRMS $[M + H]^+$ calculated for $C_{33}H_{37}BF_6N_6O_4$: 707.29463, found 707.29547.



α/β-2-Flouro-BODIPY-glucosyl imidate (19): To a 0 °C cooled solution of 2-deoxy-2-fluoro BODIPY glucose **32** (53.2 mg, 99.4 µmol) in acetone (6 mL) was added trifluoro *p*OMe-aniline imidate reagens **52** (47.2 mg, 199 µmol) and Cs_2CO_3 (48.9 mg, 150 µmol). The reaction was gradually warmed to rt and stirred overnight. The solids were filtered and the filtrate was concentrated *in vacuo* Purificaton by column chromatography yielded *p*OMe-aniline imidate glucosyl **19** as a α/β mixture (α/β = 1:2, 19.8 mg, 26.7 µmol, 27%). Purification by RP- followed by lyophilisation yielded α-2-fluoro-BODIPY-glucose-*p*OMe-aniline-imidate **19-α** (0.374 mg, 0.51 µmol, 0.5%) and β-2-fluoro-BODIPYglucose-*p*OMe-aniline imidate **19-b** (1.03 mg, 1.4 µmol, 1.4%) both as an orange powder. Spectroscopic data for the α-anomer **19-α**: ^{1}H NMR (600 MHz, CD_3CN): δ 7.49 (s, 1H), 6.82 (d, J = 9.0 Hz, 2H), 6.60 (bs, 2H), 6.23 (bs, 1H), 6.14 (s, 2H), 4.71 (d, J = 14.4 Hz, 1H), 4.37-4.46 (m, 2H), 3.88-3.95 (m, 4H), 3.71 (s, 3H), 3.26 (bs, 1H), 2.97 (t, J = 8.7 Hz, 2H), 2.66-2.78 (m, 2H), 2.43 (s, 6H), 2.37 (s, 6H), 1.80-1.85 (m, 2H), 1.52-1.59 (m, 2H); LC-MS: R_t 3.92 min (C18 column, linear gradient 50 → 90% B in 15 min); FT-IR: ν_{max} (neat)/cm^{-1} 3356, 2925, 1551, 1508, 1203, 1159, 1067; HRMS $[M + H]^+$ calculated for $C_{34}H_{39}BF_6N_6O_5$: 737.30519, found 737.30615.

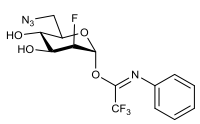
Spectroscopic data for the β-anomer **19-β**: NMR (600 MHz, CD_3CN): δ 7.55 (s, 1H,), 6.81 (d, J = 6.6 Hz, 2H), 6.67 (bs, 2H), 6.15 (s, 2H), 5.65 (bs, 1H),

4.79 (d, *J* = 14.4 Hz, 1H), 4.31-4.35 (m, 2H), 4.05 (bs, 1H), 3.94 (bs), 3.68 (bs 5H), 3.32 (bs, 1H), 2.91 (t, *J* = 8.4 Hz, 2H), 2.54-2.59 (m, 2H), 2.44 (s, 6H), 2.34 (s, 6H), 1.74 (bs, 2H), 1.51-1.54 (m, 2H); LC-MS: R_t 4.14 min (C18 column, linear gradient 50 → 90% B in 15 min); LC-MS: R_t 9.73 min (C18 column, linear gradient 10 → 90% B in 15 min); FT-IR: ν_{max} (neat)/cm^{-1} 3356, 2971, 1551, 1508, 1409, 1310, 1203, 1160, 1080, 986, 836; HRMS $[M + H]^+$ calculated for $C_{34}H_{39}BF_6N_6O_5$: 737.30519, found 737.30613.

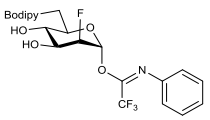


α/β-2-Fluoro-BODIPY-glucosyl imidate (20): To a 0 °C cooled solution of 2-deoxy-2-fluoro BODIPY glucose **32** (75.1 mg, 140 µmol) in acetone (6 mL) was added trifluoro *p*NO_2 aniline imidate **53** (70.7 mg, 240 µmol) and Cs_2CO_3 (68.2 mg, 210 µmol). The reaction was gradually warmed to rt and stirred overnight. The solids were filtered and the filtrate was concentrated *in vacuo*. Purification by column chromatography yielded glucosyl *p*OMe-aniline imidate **20** as an α/β mixture (α/β = 2:3, 47.5 mg, 63.2 µmol, 45%) . Purification by RP-HPLC followed by lyophilisation yielded α-2-deoxy-2-fluoro-BODIPY-glucosyl-*p*NO_2-aniline-imidate **20-α** (2.52 mg, 3.35 µmol, 2%) and β-2-deoxy-2-fluoro-BODIPY-glucosyl-*p*NO_2-aniline imidate **20-β** (3.03 mg, 4.03 µmol, 2.9%) both as an orange powder. Spectroscopic data for the α-anomer **20-α**: NMR (CD_3CN, 600 MHz): δ 8.06 (dd, 2H, *J* = 6.9, 2.1 Hz), 7.50 (s, 1H), 6.73 (dd, 2H, *J* = 6.9, 2.1 Hz), 6.15 (s, 1H), 6.12 (s, 2H), 4.75 (dd, 1H, *J* = 14.4, 2.4 Hz), 4.49 (ddd, 1H, *J* = 48 Hz), 4.39 (dd, 1H, *J* = 14.4, 3.0 Hz), 4.10 (dt, 1H, *J* = 9.6, 2.4 Hz), 3.40 (bs, 1H), 3.90-3.93 (m, 1H) 3.31-3.33 (m, 1H), 2.87-2.90 (m, 2H), 2.68-2.80 (m, 2H), 2.43 (s, 6H), 2.32 (s, 6H), 1.80-1.83 (m, 2H), 1.45-1.47 (m, 2H); LC-MS: R_t 3.57 min (C18 column, linear gradient 50 → 90% B in 15 min); LC-MS: R_t 9.36 min (C18 column, linear gradient 10 → 90% B in 15 min); FT-IR: ν_{max} (neat)/cm^{-1} 3360, 2972, 1551, 1511, 1408, 1343, 1311, 1203, 1161, 1066, 986; HRMS $[M + H]^+$ calculated for $C_{33}H_{36}BF_6N_7O_6$: 752.27971, found 752.28037.

Spectroscopic data for the β-anomer **20-β**: NMR (CD3CN, 600 MHz): δ 8.09 (dt, 2H, J = 9.0, 2.7 Hz), 7.58 (s, 1H), 6.83 (dt, 2H, J = 9.0, 2.4 Hz), 6.14 (s, 2H), 5.59 (bs, 1H), 4.80 (dd, 1H, J = 14.7, 1.5 Hz), 4.30-4.43 (m, 2H), 4.08 (bs, 1H), 4.00 (bs, 1H), 3.62-3.76 (m, 2H), H-52.84-2.88 (m, 2H), 2.52-2.69 (m, 2H), 2.43 (s, 6H), 2.29 (s, 6H), 1.85-1.98 (m, 2H), 1.63-1.80 (m, 2H); LC-MS: Rt 3.95 min (C18 column, linear gradient 50 → 90% B in 15 min); LC-MS: Rt 9.55 min (C18 column, linear gradient 10 → 90% B in 15 min); FT-IR: ν_{max} (neat)/cm^{-1} 3360, 2972, 1551, 1511, 1408, 1311, 1202, 1161, 1079, 986. HRMS [M + H]$^+$ calculated for $C_{33}H_{36}BF_6N_7O_6$: 752.27971, found 752.28052.



α-6-Azido-2-Flouro-mannosyl imidate (21): To a 0 °C cooled solution of 2-deoxy-2-fluoro azido mannose **39** (27.5 mg, 133 µmol) in acetone (6 mL) was added trifluoro aniline imidate **51** (55.0 mg, 265 µmol) and Cs_2CO_3 (67.0 mg, 0.2 mmol). The reaction was gradually warmed to rt and stirred overnight. The solids were filtered and the filtrate was concentrated *in vacuo*. Purificaton by column chromatography yielded α-glucose aniline imidate **21** (α/β = 1:0, 18.0 mg, 47.5 µmol, 36%). Purification by RP-HPLC followed by lyophilisation yielded α-6-azido-2-deoxy-2-fluoro-mannosyl-aniline-imidate **21** as an orange powder (5.25 mg, 13.9 µmol, 10%). LC-MS: Rt 7.64 min (C18 column, linear gradient 10 → 90% B in 15 min); Spectroscopic data for the α-anomer **21-α:** ^{1}H NMR (CD_3CN, 600 MHz): δ 7.36-7.30 (m, 2H), 7.12 (t, 1H, *J* = 7.5 Hz), 6.86 (d, 2H, *J* = 7.2 Hz), 6.25 (bs, 1H), 4.82 (d, 1H, *J* = 46.2 Hz), 3.73-3.83 (m, 2H), 3.60-3.65 (m, 1H), 3.51-3.56 (m, 2H), 3.36-3.45 (m, 2H); R_t 7.64 min (C18 column, linear gradient 10 → 90% B in 15 min); FT-IR: ν_{max} (neat)/cm^{-1} 3369, 2103, 1717, 1307, 1211, 1165, 1111, 951, 755, 694; HRMS [M + H]$^+$ calculated for $C_{14}H_{14}F_4N_4O_4$: 455.14225, found 455.15176.



α-2-Flouro-BODIPY-mannosyl imidate (22): To a 0 °C cooled solution of 2-deoxy-2-fluoro BODIPY mannose **40** (59.6 mg, 111 µmol) in acetone (6 mL) was added trifluoro aniline imidate **51** (46.2 mg, 223 µmol) and Cs_2CO_3 (55.9 mg, 0.167 mmol). The reaction was gradually warmed to rt and stirred overnight. The solids were filtered and the filtrate was concentrated *in vacuo* Purificaton by column chromatography yielded α-mannose-BODIPY aniline imidate **22-α** (α/β = 1:0, 16.8 mg, 23.8 µmol, 21%). Purification by RP-HPLC (linear gradient 50 → 90 % MeCN in 12min) followed by lyophilisation yielded α-2-deoxy-2-fluoro-BODIPY-mannose-aniline-imidate **22-α** as an orange powder (4.33 mg, 6.13 µmol, 5.5%). ^{1}H NMR (600 MHz, CD_3CN): δ 7.53 (s, 1H), 7.27 (t, *J* = 8.1 Hz, 2H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.68 (d, *J* = 7.2 Hz, 2H), 6.15 (bs, 1H), 6.14 (s, 2H), 4.80 (d, *J* = 48.0 Hz, 1H), 4.4.74 (d, *J* = 14.4 Hz, 1H), 4.48 (dd, J = 14.4, 7.8 Hz, 1H), 4.00 (bs, 1H), 3.70-3.84 (m, 3H), 2.97 (t, J = 8.7 Hz, 2H), 2.68-2.77 (m, 2H), 2.43 (s, 6H), 2.38 (s, 6H), 1.80-1.85 (m, 2H), 1.54-1.66 (m, 2H); Rt 9.96 min (C18 column, linear gradient 10 → 90% B in 15 min); FT-IR: ν_{max} (neat)/cm-1 3368, 2972, 1550, 1510, 1409, 1309, 1202, 1161, 1117, 1079, 985.; HRMS $[M + H]^+$ calculated for $C_{33}H_{37}BF_6N_6O_4$: 707.29463, found 707.29553.

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