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# $\beta$ -Configured clickable [ $^{18}\text{F}$ ]FDGs as novel $^{18}\text{F}$ -fluoroglycosylation tools for PET†

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In oncology and neurology the  $^{18}\text{F}$ -radiolabeled glucose analogue 2-deoxy-2- $^{18}\text{F}$ fluoro-D-glucose ( $^{18}\text{F}$ FDG) is by far the most commonly employed metabolic imaging agent for positron emission tomography (PET). Herein, we report a novel synthetic route to  $\beta$ -configured mannopyranoside precursors and a chemoselective  $^{18}\text{F}$ -fluoroglycosylation method that employ two  $\beta$ -configured  $^{18}\text{F}$ FDG derivatives equipped with either a terminal azide or alkyne aglycon respectively, for use as a CuAAC clickable tool set for PET. The  $\beta$ -configured precursors provided the corresponding  $^{18}\text{F}$ FDGs in a radiochemical yield of 77–88%. Further, the clickability of these  $^{18}\text{F}$ FDGs was investigated by click coupling to the suitably functionalized Fmoc-protected amino acids, Fmoc-N-(propargyl)-glycine and Fmoc-3-azido-L-alanine, which provided the  $^{18}\text{F}$ -fluoroglycosylated amino acid conjugates in radiochemical yields of 75–83%. The  $^{18}\text{F}$ -fluoroglycosylated amino acids presented herein constitute a new and interesting class of metabolic PET radiotracers.

## Introduction

2-Deoxy-2- $^{18}\text{F}$ fluoro-D-glucose ( $^{18}\text{F}$ FDG) is often referred to as the golden standard in the field of positron emission tomography (PET), where approximately 90% of all PET scans are performed using  $^{18}\text{F}$ FDG.<sup>1</sup> As a glucose derivative,  $^{18}\text{F}$ FDG act as a biomarker of glucose metabolism and as such has found widespread use in oncology and neurology, both in clinic and in research.<sup>2</sup> When injected into the human body, it preferentially accumulates in tissue that exhibit an increase in glycolysis, *e.g.*, cancer cells. Conversely, diminished glucose consumption due to neuronal cell death in the brain inflicted by neurodegenerative disorders, *e.g.*, Alzheimer's disease, can also indirectly be probed using  $^{18}\text{F}$ FDG. However, despite its prominent role, one major drawback associated with using  $^{18}\text{F}$ FDG is that it suffers from poor tissue selectivity when distinguishing between malignant cells and benign cells that have a high metabolic rate, such as certain cells associated with inflammation or infection.<sup>3</sup> Furthermore, since  $^{18}\text{F}$ FDG is a metabolic imaging agent it is not sufficiently capable of detecting tumors found in most prostate cancers, bronchoalveolar-cell carcinoma or renal-cell carcinoma due to the fact that their metabolic rate is relatively low and therefore indistinguishable

from normal tissue.<sup>4</sup> Consequently, there is a great need for new PET tracers that exhibit both high affinity and selectivity towards a particular biomolecular target. In recent years, the concept of employing  $^{18}\text{F}$ FDG as a prosthetic group for the  $^{18}\text{F}$ -radiolabeling of ligands with defined molecular targets *in vivo* has received considerable attention.<sup>5</sup> The rationale is that glycoconjugates (*e.g.*, glycopeptides, glycoproteins) in general exhibit improved pharmacokinetic properties such as increased *in vivo* kinetics, higher metabolic stability and faster blood clearance compared to their non-glycosylated counterparts.<sup>6</sup> Furthermore, the relatively long half-life of  $^{18}\text{F}$  ( $t_{1/2} = 109.8$  min) provides a sufficient amount of time to perform multi-step radiosynthesis followed by a subsequent PET investigation.

Several methods have been employed for the ligation of  $^{18}\text{F}$ FDG to a diverse set of ligands, for instance (i) *via* oxime formation,<sup>7</sup> (ii) chemoenzymatic approaches<sup>8</sup> as well as using (iii) thiol-selective S-glycosylation.<sup>9</sup> More importantly, one of the most established methods is by means of the CuAAC click reaction<sup>10,11</sup> which allows for a wide substrate scope using mild conditions.<sup>12</sup> Accordingly, in 2009, Maschauer *et al.*,<sup>13</sup> reported the synthesis of a set of 2-O-trifluoromethanesulfonyl-D-mannopyranosides, *i.e.*, precursors of  $^{18}\text{F}$ FDG analogs, that were equipped with either a  $\alpha$ -1-O-propargyl (**10 $\alpha$** ),  $\alpha$ -1-O-(2-azido)ethyl (**6 $\alpha$** ),  $\alpha$ - or  $\beta$ -azido aglycons (**16 $\alpha$**  and **16 $\beta$**  respectively, Scheme 1).

In their study, only minor amounts of the  $\alpha$ -configured precursors were radiolabeled ( $\leq 14\%$  radiochemical yield (RCY)) which rendered them inapplicable for PET. In contrast, the  $\beta$ -azide precursor (**16 $\beta$** ) gave a significantly higher RCY (71%) indicating that the  $\beta$ -anomeric configuration is a key criterion for a successful  $^{18}\text{F}$ -radiolabelling.

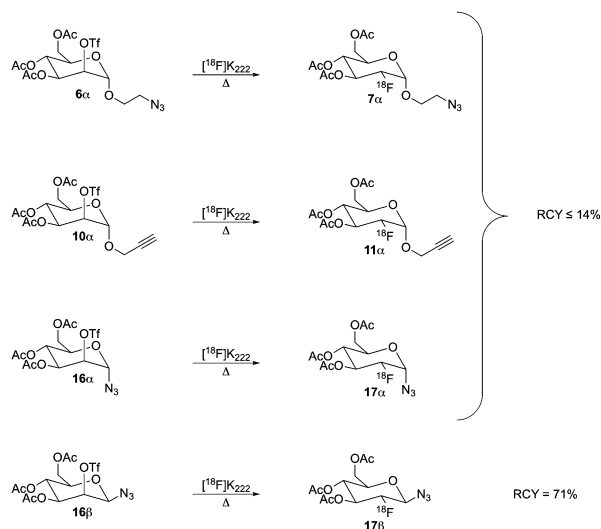
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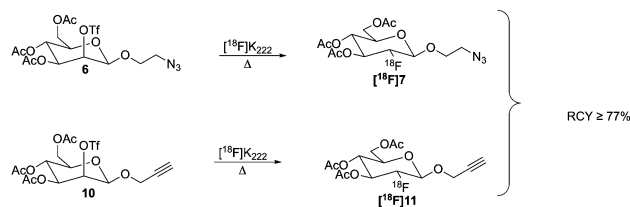
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c7nj00716g



## Previous work by Maschauer et al.



## Our work



**Scheme 1** (to the left) Previous work by Maschauer *et al.* on  $^{18}\text{F}$ -radiolabeling of clickable  $\alpha$  and  $\beta$  [ $^{18}\text{F}$ ]FDG precursors and (to the right) this work describing the high-yielding  $^{18}\text{F}$ -radiolabeling of  $\beta$ -D-mannopyranoside triflates equipped with both azide- and alkyne spacers.

The propensity of the precursors to undergo the displacement by  $^{18}\text{F}^-$  correlates well with the Richardson–Hough rules from 1967 that predict the  $\text{S}_{\text{N}}2$  displacement viability in carbohydrate sulfonate derivatives with external nucleophiles.<sup>14</sup> The outcome of the reaction is dictated by stereoelectronic effects but also accompanied by steric factors. This theory recently got extended by Hale *et al.* to encompass seemingly disallowed trifluoromethanesulfonate displacements.<sup>15</sup> Briefly, the theory predicts that 2-*O*-trifluoromethanesulfonyl- $\beta$ -D-mannopyranosides experience a significantly lower dipolar repulsion at the transition state and will therefore readily undergo the  $\text{S}_{\text{N}}2$  displacement while the corresponding  $\alpha$ -anomer should only give minor substitution or none at all.

The  $\beta$ -azide equipped [ $^{18}\text{F}$ ]FDG (17 $\beta$ , Scheme 1) has successfully been utilized as a  $^{18}\text{F}$ -fluoroglycosylation tool to provide [ $^{18}\text{F}$ ]FDG conjugates with a diverse set of ligands, *e.g.*, the RGD peptide targeting the integrin receptor,<sup>16,17</sup> folic acid targeting the folate receptor,<sup>18</sup> and a diarylpyrazole targeting the NTS-1 neurotensin receptor.<sup>19</sup> However, the first generation of clickable [ $^{18}\text{F}$ ]FDGs is rather limited in scope. Ideally, a spacer between the FDG unit and the attached click functional group is desired to prevent any potential steric interference between the FDG unit and the ligand to which it will be attached. In fact, it has been shown that glucose derivatives bearing an anomeric 1,2,3-triazole, generated from the corresponding glucosyl azide, lack two key properties of [ $^{18}\text{F}$ ]FDG, *i.e.*, trapping *via* *O*-6 phosphorylation and cell uptake *via* GLUT-1 transporters.<sup>20</sup> This effect is most likely caused by the close proximity of the triazole. Moreover, ideally, in order to be able to radiolabel the full set of available click-enabled ligands, both azide- and alkyne equipped [ $^{18}\text{F}$ ]FDGs should be accessible. However, to date no alkyne equipped

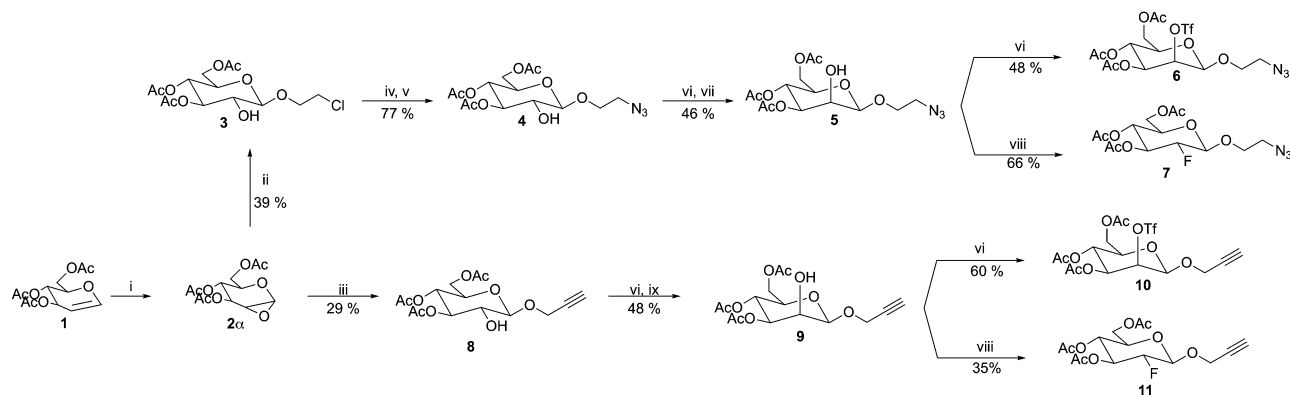
[ $^{18}\text{F}$ ]FDG that can be retrieved in a sufficient radiochemical yield is available.

In this work, we report the detailed synthesis of the CuAAC clickable  $\beta$ -configured [ $^{18}\text{F}$ ]FDGs (Scheme 1). In order to evaluate their clickability, the [ $^{18}\text{F}$ ]FDGs were chemically ligated to the suitably functionalized Fmoc-protected amino acids Fmoc-*N*-(propargyl)-glycine **12** and Fmoc-3-azido-L-alanine **14** by means of the click reaction which successfully provided the expected [ $^{18}\text{F}$ ]FDG conjugates, both rapidly and in good radiochemical yield. Due to the increased cell proliferation of most cancers, protein synthesis is up-regulated and, as a natural consequence, the amino acid uptake is usually significantly increased. The synthesized [ $^{18}\text{F}$ ]FDG amino acid conjugates will therefore serve as the basis for a new class of highly promising metabolic imaging agents. Furthermore, the described  $^{18}\text{F}$ -fluoroglycosylation method may well be extended to encompass the radiolabeling of, not only amino acids, but also peptides and proteins.

## Results and discussion

Since the fluorination step required to obtain the  $\beta$ -configured [ $^{18}\text{F}$ ]FDG ([ $^{18}\text{F}$ ]7, [ $^{18}\text{F}$ ]11), is accompanied by an  $\text{S}_{\text{N}}2$  inversion, the triflate precursors (**6**, **10**) are by necessity  $\beta$ -D-mannopyranosides. Unfortunately,  $\beta$ -D-mannopyranosides are well-known to be challenging to synthesize due to the inherently strong preference of conventional mannosyl donors to form  $\alpha$ -D-mannopyranosides. This is a result of the simultaneous occurrence of both the  $\alpha$ -directing anomeric effect and repulsion between the axial C-2 substituent and the approaching nucleophile.<sup>21</sup> Moreover, neighboring group participation of a 2-acyl mannosyl donor





**Scheme 2** General conditions and reagents: (i) oxone, acetone, TBAHSO<sub>4</sub>, DCM, satd. aq. NaHCO<sub>3</sub>, 0 °C to rt. (ii) Cl(CH<sub>2</sub>)<sub>2</sub>OH, ZnCl<sub>2</sub>, DCM, 0 °C to rt. (iii) Propargyl alcohol, ZnCl<sub>2</sub>, DCM, 0 °C to rt. (iv) NaI, acetone, 70 °C (v) NaN<sub>3</sub>, DMF, rt. (vi) Tf<sub>2</sub>O, py, DCM, −15 to 10 °C. (vii) TBANO<sub>2</sub>, toluene, 50 °C. (viii) DAST, diglyme, 100 °C, 10 min. (ix) TBANO<sub>2</sub>, toluene, rt.

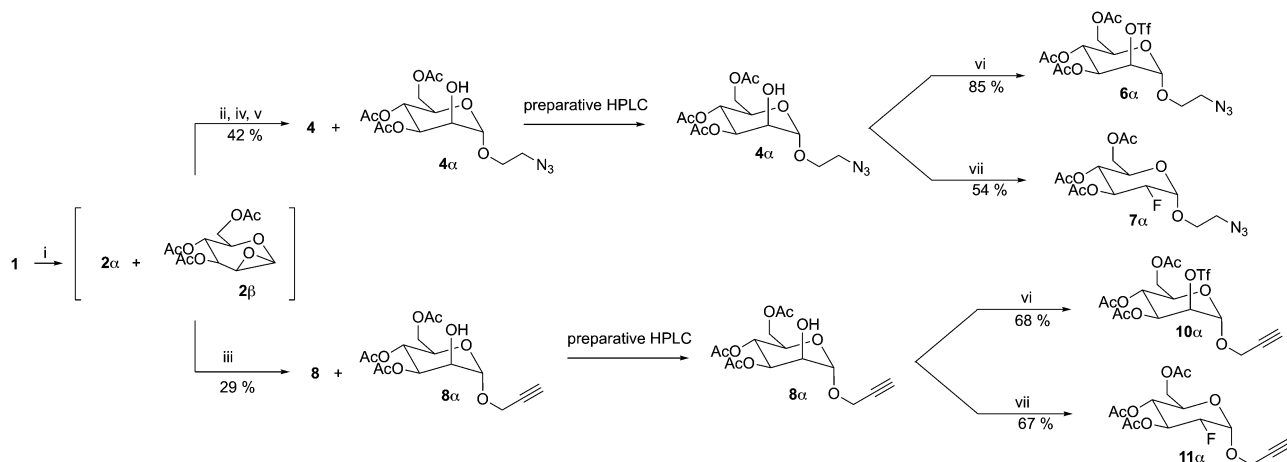
also leads to  $\alpha$ -mannopyranosides. Fortunately, several ingenious synthetic approaches to circumvent these obstacles have already been devised.

A particularly elegant approach was developed by the Danishefsky group during the 1990's, where epoxidation of *per*-benzylated D-glucal using DMDO, conveniently provided the corresponding 1,2- $\alpha$ -anhydrosugar that subsequently during glycosylation stereoselectively produced the corresponding  $\beta$ -D-glucoside – and simultaneously generated an unprotected hydroxyl group in the 2-position. Subsequent epimerization of this site, following an oxidation–reduction sequence generated the  $\beta$ -D-mannopyranoside.<sup>22</sup> In this report we employ a similar synthetic approach which is depicted in Scheme 2. The chosen route requires access to multi-gram quantities of 1,2-anhydrosugar **2 $\alpha$**  from tri-acetyl-D-glucal **1**. While this transformation is commonly achieved using a dilute solution of DMDO in acetone,<sup>23</sup> performing this reaction on a large scale poses several practical issues. For instance, the DMDO solution has to be kept rigorously dry, only dilute solutions can be produced (*ca.* 0.1 M) and furthermore, the scale-up of organic peroxy compounds is potentially hazardous.

To circumvent these drawbacks, the Dondoni group, in 2006, developed an epoxidation method for glycals where DMDO is formed *in situ* from a biphasic buffered solution containing oxone, acetone, satd. NaHCO<sub>3</sub> and DCM.<sup>24</sup> This protocol was further elaborated on by Lafont *et al.* in 2011 by the addition of the phase transfer catalyst, tetrabutylammonium hydrogen sulphate (TBAHSO<sub>4</sub>) that significantly increased the reaction speed as well as the reproducibility.<sup>25</sup> By employing the oxone-acetone-TBAHSO<sub>4</sub> epoxidation protocol, we conveniently prepared the 1,2-anhydrosugar **2 $\alpha$**  which was then directly used in the subsequent glycosylation. The glycosylation of 2-chloroethanol or propargyl alcohol, promoted by ZnCl<sub>2</sub> in DCM, provided the corresponding  $\beta$ -D-glucosides **3** and **8** in 39% and 29%, respectively over two steps. The predominant by-product formed was the corresponding 1,2-diol hydrolysis product. Converting the 2-chloroethyl glucoside **3** to the corresponding 2-azidoethyl glucoside **4** proved to be a major challenge. Standard conditions for azidation, *i.e.*, NaN<sub>3</sub> in DMF at elevated temperatures (80 °C or 110 °C), with or without the additives TBAI or TBAB,

consistently resulted in a complex mixture of products due to acetate migration to the unprotected 2-OH, whereas no reaction occurred at ambient temperature. We therefore reasoned that installing a better leaving group might make the reaction proceed more smoothly and thus avoid the accompanying acetate migration. This was realized by converting the 2-chloro compound **3** to the corresponding iodo compound by means of the classical Finkelstein reaction utilizing NaI (2 eq.) in acetone at 70 °C for 48 h. The azidation of the iodoethyl glucoside using NaN<sub>3</sub> in DMF now proceeded cleanly at ambient temperature to afford the azidoethyl glucoside **4** in good yield (77%) over two steps. Next, we decided to use the nitrite-mediated Lattrell–Dax inversion for the pending epimerization. The Lattrell–Dax inversion has been extensively studied by the Ramström group<sup>26</sup> who concluded that the inversion proceeds reliably – and even stereospecifically – if and only if a vicinal equatorial ester is present. This criterion is suitably met for the glucosides **4** and **8**. Standard triflation of glucoside **4** using triflic anhydride followed by inversion using TBANO<sub>2</sub> in toluene at ambient temperature over night yielded the  $\beta$ -D-mannopyranosides **5** and **9** cleanly albeit in a moderate yield of 46% and 48% respectively. The  $\beta$ -anomeric configuration was confirmed by evaluating the  $J_{C-1,H-1}$  coupling constant in a coupled <sup>1</sup>H–<sup>13</sup>C NMR experiment and was found to be 157.6 Hz and 159.0 Hz respectively for  $\beta$ -D-mannopyranosides **5** and **9**.<sup>27</sup> With the desired  $\beta$ -D-mannopyranosides at hand, standard triflation afforded the  $\beta$ -D-mannosyl triflates, *i.e.*, the [<sup>18</sup>F]FDG precursors **6** and **10** in 48% and 60%, respectively after silica gel chromatography. Subsequently, to afford the FDG analogs as a non-radioactive reference, a typical fluorination protocol using potassium fluoride and the cryptand kryptofix (K[2.2.2]) in MeCN at 85 °C was attempted. Unfortunately, only trace amount of the expected fluorosugar could be observed, most likely as a result of the known poor nucleophilicity of the fluoride ion. Instead, we choose to directly fluorinate the  $\beta$ -D-mannopyranosides bearing a free hydroxyl-group in the second position, **5** and **9**, using the common fluorination agent, DAST.<sup>28</sup> At first, the reaction was run in DCM at −25 °C to rt over night to give the fluorosugars **7** and **11** in 31% and 19% respectively. The poor yield rendered us to instead perform the





**Scheme 3** General conditions and reagents: (i) oxone, acetone, TBAHSO<sub>4</sub>, DCM, satd. aq. NaHCO<sub>3</sub>, 0 °C to rt. (ii) Cl(CH<sub>2</sub>)<sub>2</sub>OH, ZnCl<sub>2</sub>, DCM, 0 °C to rt. (iii) Propargyl alcohol, ZnCl<sub>2</sub>, DCM, 0 °C to rt. (iv) NaI, acetone, 70 °C. (v) NaN<sub>3</sub>, DMF, rt. (vi) Tf<sub>2</sub>O, py, DCM, −15 to 10 °C. (vii) DAST, diglyme, 100 °C, 10 min.

reaction in diglyme at 100 °C for 10 min which afforded the fluorosugars **7** and **11** in a significantly increased yield of 66% and 35% respectively. The fluorination proceeded as expected with inversion of configuration, as proven by the characteristic  $J_{H-1,H-2}$  coupling constant of 7.6 Hz for **7** and 7.7 Hz for **11**, confirming the *gluco*-configuration. Furthermore, 1D <sup>19</sup>F-NMR revealed a characteristic FDG signal for fluorosugar **7** at −199.7 ppm (ddd,  $^2J_{H-2,F-2} = 50.5$  Hz,  $^3J_{H-3,F-2} = 14.3$  Hz,  $^3J_{H-1,F-2} = 2.7$  Hz), and a similar signal for **11** (ESI,† page 35 and 50 respectively).

To test our hypothesis that a β-configured FDG precursor is radiolabeled to a greater extent than its α-anomeric counterpart, we decided to synthesize the α-FDGs reported by Maschauer *et al.* to make a direct side-by-side comparison using the same <sup>18</sup>F-fluorination set-up. On closer inspection of our devised synthetic route to the β-FDGs we realized that since the epoxidation step is only moderately stereoselective on acetylated glycals (α/β approx., 7 : 1),<sup>24</sup> as a consequence, the minor β-1,2-anhydrosugar (**2β**) would then upon glycosylation stereoselectively be ring-opened to give the sought α-D-mannopyranosides, **4α** and **8α**, with the second hydroxyl group exposed.

As predicted, the glycosylations outlined in Scheme 3 resulted in a diastereomeric mixture of the glycosides **4** and **4α**, and **8** and **8α**, (dr ~ 9 : 1 *gluco/manno* in both cases) that were separated using preparative HPLC. Spectroscopic data for the α-mannopyranosides was in good agreement with the data reported by Maschauer *et al.*<sup>29</sup> Triflation or fluorination (*vide supra*) of the isolated α-mannopyranosides then furnished the required precursors (**6α** and **10α**) and the α-configured FDGs (**7α** and **11α**) respectively.

### <sup>18</sup>F-Radiolabeling

<sup>18</sup>F was produced using the <sup>18</sup>O(p,n)<sup>18</sup>F reaction using a scan-ditronix MC-17 cyclotron. The water was transported to the hot cell and trapped on a QMA which was flushed with MeCN. [<sup>18</sup>F]Fluoride was eluted using a kryptofix 2.2.2/K<sub>2</sub>CO<sub>3</sub> solution. After azeotropic distillation with MeCN the precursor (**6**, **6α**, **10** or **10α**) in dry MeCN was added to the vial which was heated to 85 °C for 30 minutes. After the reaction was finished, an aliquot was taken and analysed by radio-HPLC to determine the non-isolated

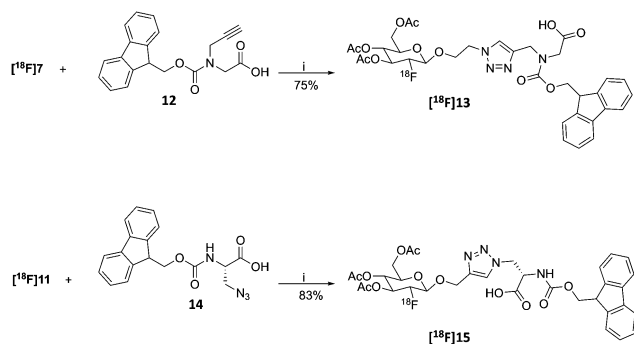
**Table 1** <sup>18</sup>F-Radiolabeling of α- and β-D-mannopyranoside precursors (0.2 μmol) to yield the corresponding [<sup>18</sup>F]FDGs

Entry	Precursor	Product	RCY (%)
1	<b>6</b>	<b>[<sup>18</sup>F]7</b>	77 ± 2
2	<b>6α</b>	<b>[<sup>18</sup>F]7α</b>	0
3	<b>10</b>	<b>[<sup>18</sup>F]11</b>	88 ± 5
4	<b>10α</b>	<b>[<sup>18</sup>F]11α</b>	0

RCY of the reaction (Table 1). Both β-mannopyranosides **6** and **10** performed well under these conditions and gave RCY of 77 ± 2% and 88 ± 5% for [<sup>18</sup>F]**7** and [<sup>18</sup>F]**11**, respectively ( $n = 2$  for both compounds) (Scheme 4). Unfortunately the α-precursors gave no results (0% RCY) using these conditions as only unreacted <sup>18</sup>F<sup>−</sup> could be identified using analytical radio-HPLC.‡

‡ In the original radiolabelling procedure by Maschauer *et al.* an optimized kryptofix 2.2.2 buffer (K<sub>2</sub>CO<sub>3</sub>/KH<sub>2</sub>PO<sub>4</sub>) was necessary in order to keep the precursors intact and obtain a RCY. In addition, the precursor load was 15 μM compared to 2 μM used herein. These differences may explain the failed radiolabelling of the α-precursors in our hands.





**Scheme 4**  $^{18}\text{F}$ -Fluoroglycosylation of amino acids **12** and **14**. General conditions and reagents: (i) amino acid (0.25  $\mu\text{mol}$ ) aq.,  $\text{CuSO}_4$  (50  $\mu\text{L}$ , 0.20 M), aq., (+)-sodium L-ascorbate (50  $\mu\text{L}$ , 0.60 M), 60  $^\circ\text{C}$ , 20 min, DMF.

Having established a synthetic protocol to acquire the  $^{18}\text{F}$ FDGs we then turned to investigate their performance in the click reaction. We choose to use the appropriately functionalized Fmoc-protected amino acids, Fmoc-*N*-(propargyl)-glycine (**12**) and Fmoc-3-azido-*L*-alanine (**14**) as a model system to show the proof of concept. The click reaction was performed in a one pot, two-step process starting from  $^{18}\text{F}^-$  and **6** or **10**. After the reaction, the MeCN was evaporated with a stream of helium after which the protected  $^{18}\text{F}$ **7** or  $^{18}\text{F}$ **11** was subsequently dissolved in dry DMF, where to the Cu(i) catalyst, prepared *in situ* by the addition of aq.  $\text{CuSO}_4$  (50  $\mu\text{L}$ , 0.20 M) and aq. (+)-*L*-sodium ascorbate (50  $\mu\text{L}$ , 0.60 M) along with amino acid **12** or **14** (2.5  $\mu\text{mol}$ ) were added. The reaction was then heated to 60  $^\circ\text{C}$  for 20 min. The RCY of  $^{18}\text{F}$ **13** was  $75 \pm 2\%$  and for  $^{18}\text{F}$ **15**  $83 \pm 2\%$  as deduced by analytical-HPLC ( $n = 2$  for each compound). In preparative runs starting with 3 GBq (81 mCi) of fluoride, 820 MBq (22 mCi) of  $^{18}\text{F}$ **13** (55% RCY) and 990 MBq (27 mCi) of  $^{18}\text{F}$ **15** (66%) was obtained, respectively. Both compounds were pure (RCP > 99%) as deduced by HPLC. The RCY was decay corrected to end of bombardment (EOB) and the total synthesis time was 2 hours. The corresponding non-radioactive FDG amino acid conjugates was synthesized using microwave irradiation at 80  $^\circ\text{C}$  for 5 min (ESI,† Scheme S2, page 3). The click reaction between FDG **7** (1.2 eq.) and amino acid **12** (1.0 eq.) and between FDG **11** (1.2 eq.) and amino acid **14** (1.0 eq.) yielded FDG conjugates **13** and **15** in 64% and 86% respectively.

## Conclusions

We have developed a chemoselective  $^{18}\text{F}$ -fluoroglycosylation method for PET *in vivo* imaging that employ the  $\beta$ -configured  $^{18}\text{F}$ FDGs,  $^{18}\text{F}$ **7** and  $^{18}\text{F}$ **11**, as CuAAC clickable prosthetic groups for  $^{18}\text{F}$ -labeling. These clickable  $^{18}\text{F}$ FDGs may in principle be readily attached to any click functionalized ligand and thus provide access to a diverse set of  $^{18}\text{F}$ -fluoroglycosylated PET radiotracers. We have also demonstrated that the anomeric configuration of the  $^{18}\text{F}$ FDG precursors has a great impact on the radiochemical yield, where the  $\beta$ -configuration is superior to the  $\alpha$ -configuration. Furthermore, the clickability of these

$^{18}\text{F}$ FDGs was demonstrated by click coupling to the suitably functionalized Fmoc-protected amino acids, Fmoc-*N*-(propargyl)-glycine (**12**) and Fmoc-3-azido-*L*-alanine (**14**) in near quantitative RCY, using a simple two-step one-pot protocol. The  $^{18}\text{F}$ -fluoroglycosylated amino acids,  $^{18}\text{F}$ **13**,  $^{18}\text{F}$ **15**, constitute a new and interesting class of metabolic oncological PET radiotracers. We also recognize that while  $^{18}\text{F}$  is excellently suited for PET imaging, the natural isotope,  $^{19}\text{F}$ , has almost optimal properties for  $^{19}\text{F}$ -NMR, a technique that in recent years has received considerable attention as a means to probe biological mechanisms.<sup>30</sup> The developed  $^{18}\text{F}$ -fluoroglycosylation method at hand may thus equally well serve as a means to provide novel  $^{19}\text{F}$ -NMR probes. Our lab is currently engaged in synthesizing  $^{18}\text{F}$ FDG conjugates targeting cancer and disease associated protein aggregates that will be reported in due course.

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