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A series of 2-*O*-trifluoromethylsulfonyl-D-mannopyranosides as precursors for concomitant ^{18}F-labeling and glycosylation by click chemistry

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ABSTRACT

A series of 'clickable' mannopyranosides bearing a triflate leaving group at C-2 position were synthesized and tested for their potential as ^{18}F-labeling precursors. 3,4,6-Tri-*O*-acetyl-2-*O*-trifluoromethanesulfonyl-β-D-mannopyranosyl azide (**2β**) was the most convenient precursor for a site-specific and reliable click chemistry-based three-step, two-pot concomitant ^{18}F-labeling and glycosylation of an alkyne-functionalized amino acid derivative.

1. Introduction

Twenty-four years ago, the synthesis of 1,3,4,6-tetra-*O*-acetyl-2-*O*-trifluoromethanesulfonyl-β-D-mannopyranose (**1**, Fig. 1) was published by Hamacher.[1] The application of **1** for the highly reliable and efficient radiosynthesis of 2-deoxy-2-[^{18}F]fluoroglucose (FDG)[2] was one of the most important driving forces in the fast-growing field of positron emission tomography (PET) technology. Today, FDG represents by far the most frequently used oncological PET radiopharmaceutical for imaging studies in both nuclear medicine and radiopharmaceutical sciences.[3,4] Moreover, the commercial availability of the FDG precursor **1** has essentially driven the exponentially growing number of clinical studies with FDG-PET worldwide.

In the field of PET chemistry, the positron emitter F-18 is a superior PET radionuclide with excellent physical characteristics ($E_{\beta+}$ = 635 keV, $t_{1/2}$ = 109.7 min) allowing for extended and multi-step radiochemical syntheses, when compared to alternative positron emitters such as C-11 ($t_{1/2}$ = 20.3 min) and N-13 ($t_{1/2}$ = 10 min). In recent years, strategies for the synthesis of PET radiopharmaceuticals have been improved, especially due to the development of various ^{18}F-labeled prosthetic groups,[5,6] designed mainly for the chemoselective labeling of peptides. Moreover, the use of 1,3-dipolar cycloaddition by the Huisgen reaction in the presence of Cu(I) (click chemistry)[7,8] has been successfully demonstrated in the field of PET chemistry.[9–14] The major disadvantage of most ^{18}F-labeling strategies is a limited uncorrected radiochemical yield of the short-lived radioactive end-product, due to the required laborious multiple-step syntheses.

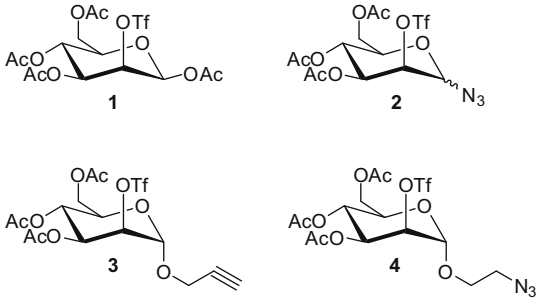

Figure 1. Structures of carbohydrate-based ^{18}F-labeling precursors.

Glycosylation of peptides has often been shown to enhance the biokinetics and in vivo clearance properties of peptides;[15–17] however, only a few approaches toward the glycoconjugation of an ^{18}F-labeled glycosyl donor with target compounds have been described.[18–23] Herein, we present the synthesis of a series of 'clickable' mannosides and study their potential as ^{18}F-labeling precursors in order to develop an efficient concomitant ^{18}F-labeling and glycosylation strategy for the synthesis of ^{18}F-peptides that function as PET tracers with improved biokinetics. This leads us to the straightforward synthesis of 3,4,6-tri-*O*-acetyl-2-*O*-trifluoro-

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methanesulfonyl-β-D-mannopyranosyl azide (**2β**), representing an optimized ^{18}F-labeling glycosyl precursor suitable for a click chemistry-based glycosylation strategy.

2. Results and discussion

Aiming at the synthesis of the azido- or propargyl-bearing mannosyl triflates **2**, **3**, and **4** that would serve as suitable precursors for ^{18}F-labeling by nucleophilic ^{18}F-for-OTf substitution (Fig. 1), we started with 1,3,4,6-tetra-*O*-acetyl-β-D-mannopyranose **5**, which was synthesized following the procedure described by Deferrari et al.,[24] with modifications[25] (Scheme 1). Choosing a protecting group for the 2-hydroxy group that was stable under the acidic conditions used for the bromination of **5** was essential. Therefore, according to the methods described by Takatani et al.,[26] we used pentafluoropropionyl (Pfp) as a protecting group for the synthesis of **6**. However, unlike Takatani's observations, the bromination of **6** using acetic anhydride in HBr–AcOH afforded several by-products. Therefore, we changed the procedure to use the commonly used bromination conditions, applying HBr–AcOH in dichloromethane at room temperature. This synthesis step proceeded quantitatively.

Glycosylation of 2-propargyl alcohol or 2-bromoethanol with bromide **7** proceeded under standard conditions to afford **8** or **10** in yields of 65% and 68%, respectively, as pure α-anomers (Scheme 1). Prior to cleavage of Pfp with pyridine in ethanol,[26] which proceeded quantitatively to give **9** and **12**, Br-for-N_3 exchange of **10** was realized using sodium azide in dimethylformamide to yield **11** in 39% yield. A suitable leaving group for nucleophilic ^{18}F-fluorination, the triflate group was introduced at position 2 of **9** and **12** using trifluoromethanesulfonic anhydride in dichloromethane to yield the target compounds **3** and **4** as pure α-anomers (Scheme 1, Fig. 2). For the synthesis of triflate **2**, compound **7** was reacted with sodium azide in dimethylformamide (Scheme 1). The TLC analysis of this reaction mixture revealed four different products,

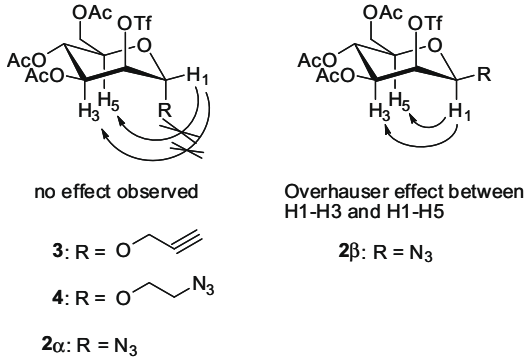
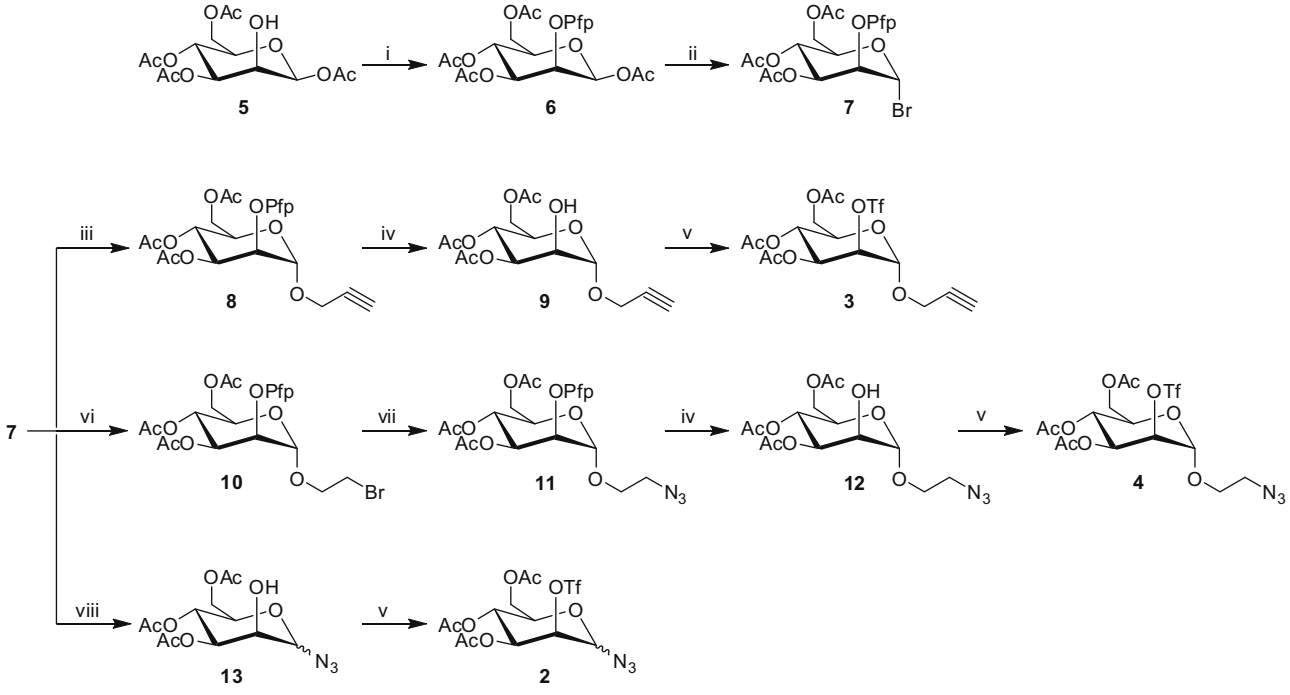


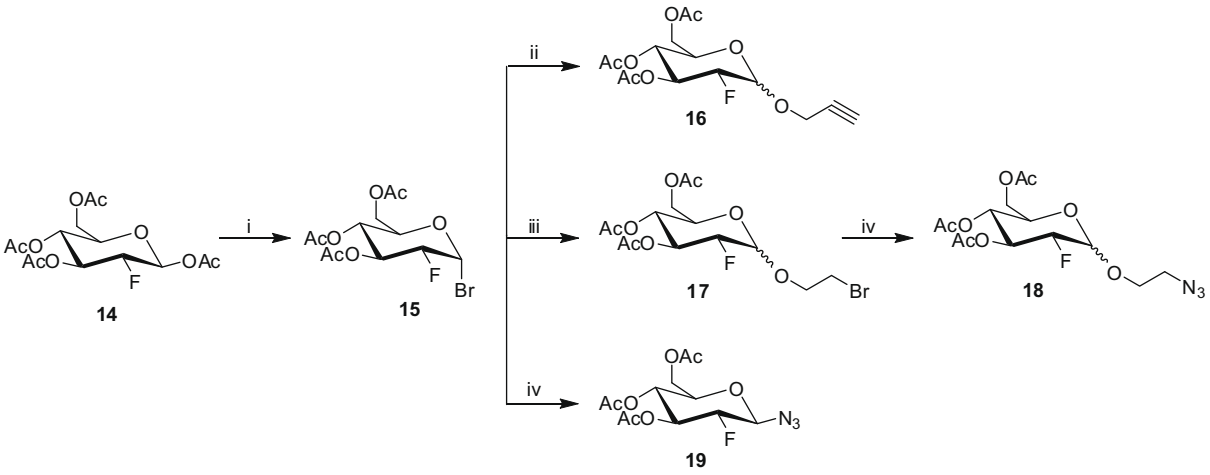
Figure 2. Selective NOE experiments for the determination of the anomeric configuration of precursor compounds.

including the β-anomer of acetylated mannopyranosyl azide bearing the Pfp-group (see Section 3) and the Pfp-cleaved mannopyranosyl azide **13** as a mixture of anomers. In order to simplify the synthesis of **13**, we performed a one-pot procedure by adding ethanol and pyridine to the reaction mixture of **7** and NaN_3, initiating complete Pfp-deprotection in situ. Following this procedure, compound **13** was obtained as a mixture of anomers (α:β ~ 1:1) in an increased yield of 79%. Introduction of the triflate leaving group was achieved as described for compounds **3** and **4**, to give **2** as α/β-anomers, which were subsequently separated by column chromatography. The anomeric β-configuration of **2β** was proven by selective NOE experiments, indicating coupling between protons H-1 and H-3, as well as between H-1 and H-5 (Fig. 2).

The syntheses of the 2-fluorinated reference compounds **16**, **18**, and **19** were realized analogously (Scheme 2). Peracetylated 2-deoxy-2-fluoro-glucopyranose **14** was brominated to obtain **15**, which was used as a glycosyl donor for the AgOTf-promoted Koenigs–Knorr glycosylation of 2-bromoethanol and 2-propargyl



Scheme 1. Reagents and conditions: (i) Pfp_2O, py, CH_2Cl_2, 1 h, 0 °C, quant.; (ii) HBr–AcOH, CH_2Cl_2, 0 °C to rt, 20 h, 90%; (iii) AgOTf, propargyl alcohol, CH_2Cl_2, rt, 40 min, 65%; (iv) EtOH, py, rt, 2 h, quant.; (v) Tf_2O, py, CH_2Cl_2, −20 °C to 0 °C, 1 h, 74% for **3**, 36% for **4**, 40% for **2β**, 55% for **2α**; (vi) AgOTf, 2-bromoethanol, CH_2Cl_2, rt, 40 min, 68%; (vii) NaN_3, DMF, rt, 20 h, 39%; (viii) NaN_3, DMF, rt, 20 h, then EtOH, py, rt, 1 h, 79%.



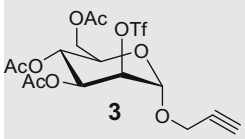
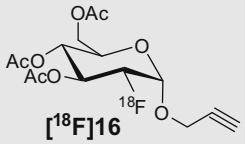
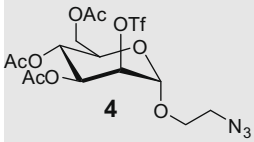
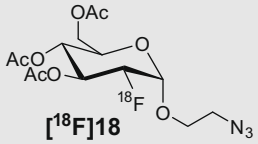
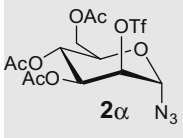
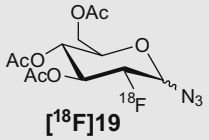
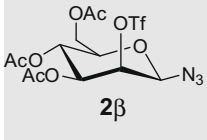
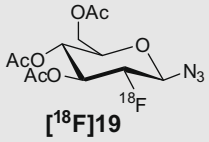
Scheme 2. Reagents and conditions: (i) HBr–AcOH, CH_2Cl_2, 0 °C to rt, 20 h, 90%; (ii) AgOTf, propargyl alcohol, CH_2Cl_2, rt, 1 h, 84%; (iii) AgOTf, 2-bromoethanol, CH_2Cl_2, rt, 40 min, 93%; (iv) NaN_3, DMF, rt, 4 h, 47% for **18**, 1 h, 74% for **19**.

alcohol. After reaction of **17** with sodium azide in DMF, the obtained products **16** and **18** were both identified to be mixtures of anomers in a ratio of 3:2 (α:β). The poor selectivity of glycosylations using bromide **15** as the glycosyl donor and strong nucleophiles is well known.[27] Both anomeric mixtures of **16** and **18** appeared to be inseparable by common column chromatography on silica gel; however, HPLC analysis revealed two separate peaks. The preparation of 2-deoxy-2-fluoro glycosyl azide **19** was easily achieved by azide-for-bromo exchange using standard conditions to yield the pure β-anomer (Scheme 2).

The commonly used ^{18}F-labeling conditions for nucleophilic ^{18}F-for-X substitution involve use of aminopolyether (Kryptofix 2.2.2) in combination with K_2CO_3 to generate the cryptate complex [K ⊂ 2.2.2]^{18}F of high nucleophilicity in aprotic solvents.[2,28] Due to the basic reaction medium, these reaction conditions often lead to elimination reactions and accelerated degradation of the labeling precursors. After applying the cryptate–carbonate system, the triflate precursors **2α**, **2β**, **3**, and **4** were insufficiently stable. Therefore, we investigated mild ^{18}F-labeling conditions[29] for the 'clickable' precursors **2α**, **2β**, **3**, and **4**. The use of a cryptate complex obtained from a mixture of K_2CO_3/KH_2PO_4 proved to be ideal, both for adequate stability of the precursors during the radiolabeling reaction and for easy separation from the ^{18}F-labeled product by semipreparative HPLC. Interestingly, only the ^{18}F-synthesis of [^{18}F]**19** using mannosyl triflate **2β** gave a high radiochemical yield of 71% in 5 min (Table 1). The alternative ^{18}F-labeling of precursors **2α**, **3**, and **4**, all of them α-anomers, showed only poor radiochemical yields for [^{18}F]**19**, [^{18}F]**16**, or [^{18}F]**18**, respectively (Table 1). We assume that efficient ^{18}F-for-triflate exchange in α-mannosyl compounds **2α**, **3**, and **4** could be restricted by steric hindrance or electronic effects, induced by the α-anomeric substituent, that impair nucleophilic attack of fluoride at C-2. The optimal amount of **2β** for ^{18}F-labeling was determined to be 15 μmol (7.3 mg). Even though **2β** was isolated as an oil, we determined that this compound was stable in acetonitrile for at least 4 months when stored in aliquots (7.3 mg in 50 μL CH_3CN) in airtight reaction vessels at −20 °C by observing that the ^{18}F-labeling reaction worked reliably using these aliquots.

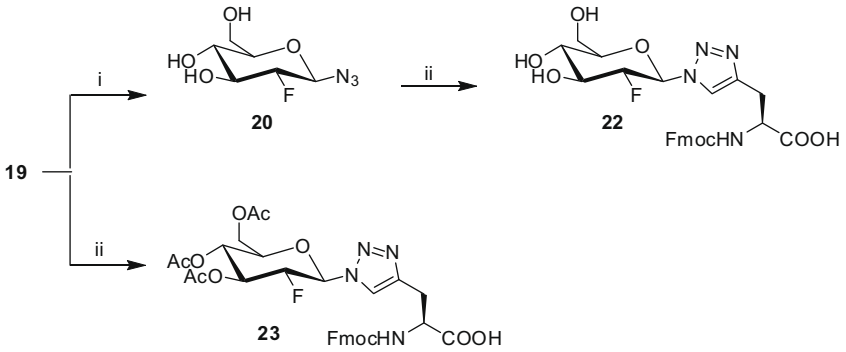
Due to the convenient and high-yielding radiosynthesis of [^{18}F]**19** starting from the mannosyl azide precursor **2β** (Table 1), we chose to study this ^{18}F-labeled glycosyl azide to determine its feasibility in a subsequent click reaction with a model compound (N^{α}-(9-fluorenylmethyloxycarbonyl)-L-2-propargylglycine, **21**), representing a potential bioactive derivative.

Table 1
Radiochemical yield (RCY) of the ^{18}F-for-OTf substitution using **3**, **4**, **2α**, or **2β**

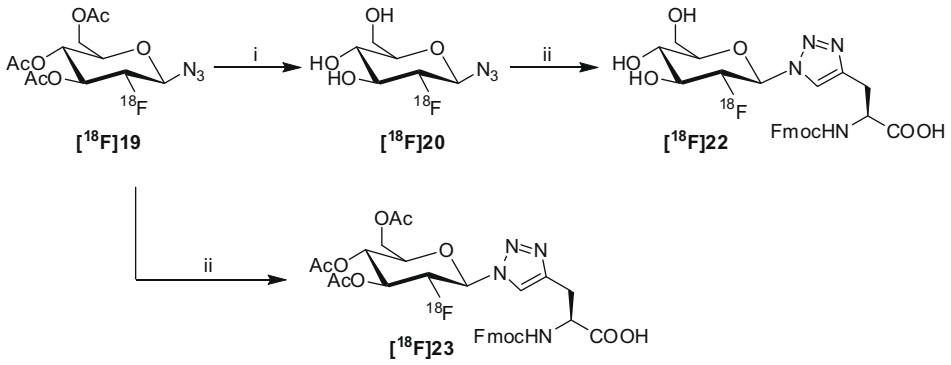
Mannosyl precursor	^{18}F-Labeled glucoside	RCY[a,b]
 **3**	 [^{18}F]**16**	7%
 **4**	 [^{18}F]**18**	8–9% (n = 2)
 **2α**	 [^{18}F]**19**	14%[c]
 **2β**	 [^{18}F]**19**	71 ± 10% (n = 11)

[a] 15 μmol precursor, [^{18}F]F^-, Kryptofix® 2.2.2 (10 mg), K_2CO_3 (1.75 μmol), KH_2PO_4 (1.75 μmol), anhydrous acetonitrile (450 μL), 85 °C, t = 5 min.
[b] Decay-corrected radiochemical yields, determined by analytical radio-HPLC from a sample withdrawn from the reaction mixture.
[c] Sum of yield of [^{18}F]**19** (β-anomer) and an unidentified radiolabeled product, presumably the α-anomer.

First, for identification and characterization of ^{18}F-labeled compounds, we synthesized the corresponding ^{19}F-substituted reference compounds **20**, **22** and **23** (Scheme 3). Copper(I)-catalyzed 1,3-dipolar cycloaddition was carried out under standard conditions ($CuSO_4$, Na-ascorbate using ethanol or *tert*-butanol as the solvent)[30] with either acetylated glucosyl azide **19** or deacetylated glucosyl azide **20** and Fmoc-protected propargylglycine **21**. It is noteworthy that the click reaction with glucosyl azide **20** proceeded more smoothly than that with the peracetylated glucosyl azide **19**, yielding **22** (91%) and **23** (50%), respectively (Scheme 3). The triazole-linked glycosylated amino acids **22** and **23** were



Scheme 3. Reagents and conditions: (i) MeONa–MeOH, rt, 1 h, 97%; (ii) **21**, $CuSO_4$, sodium ascorbate, ethanol, rt, 20 h, 91% for **22**, 50% for **23**.



Scheme 4. Reagents and conditions: (i) 60 mM NaOH, 60 °C, 5 min, quant., then 0.1 M HCl; (ii) **21**, $CuSO_4$, sodium ascorbate, *tert*-butanol, 60 °C, 10 min, 60% for [^{18}F]**22**, 76% for [^{18}F]**23**.

obtained as pure β-anomers, as indicated by ^{19}F NMR. Hence, as expected, the anomeric stereochemistry was retained during the glycosylation process, consistent with reports for similar examples for the synthesis of triazole-linked glycoamino acids.[31,32]

Second, for glycosylation with the ^{18}F-labeled glycosyl donor [^{18}F]**19** using click chemistry, we first attempted a one-pot approach, beginning with ^{18}F-fluorination of **2β** (Table 1). After the evaporation of acetonitrile, **21**, as well as $CuSO_4$ and sodium ascorbate in a mixture of water and *tert*-butanol in a total volume of 0.3 mL, were directly added to the reaction vial containing [^{18}F]**19** and the reaction was stirred at 60 °C (Scheme 4). This one-pot approach successfully provided the 1,2,3-triazole-linked glyco-amino acid [^{18}F]**23** in a radiochemical yield of >90% (based on [^{18}F]**19**) within a reaction time of 10 min. Unfortunately, due to the presence of the azide-bearing labeling precursor **2β**, this procedure required rather large amounts of the alkyne **21** (10 μmol, 33 mM), rendering it unsuitable for radiolabeling of peptides. Using HPLC-purified [^{18}F]**19**, the click reaction of **21** with peracetylated ^{18}F-labeled glycosyl azide [^{18}F]**19** only required 0.3 μmol of the alkyne and proceeded satisfactorily, yielding about 76% of [^{18}F]**23** in a reaction time of 10 min (Scheme 4). A comparable radiochemical yield of about 60% was achieved for deacetylated [^{18}F]**22** by performing the deacetylation with 60 mM NaOH at 60 °C for 5 min, followed by subsequent neutralization and Cu^1-catalyzed 1,3-dipolar cycloaddition under optimized reaction conditions (Scheme 4).

In conclusion, a new mannosyl azide precursor was successfully synthesized for the radiosynthesis of a 'clickable' ^{18}F-glycosyl donor as a hydrophilic prosthetic group. With this precursor (**2β**), a simple and reliable click chemistry-based three-step, two-pot concomitant ^{18}F-labeling and glycosylation of alkyne-functionalized molecules in high radiochemical yields has been established. The described procedure for the introduction of an ^{18}F-glucopyranoside label is unique due to (1) the durability of the precursor **2β**, which is stable for months at −20 °C, (2) the hydrophilic nature of the ^{18}F-labeled prosthetic group, (3) its high-yielding and reliable radiochemistry, and (4) its general applicability for concomitant ^{18}F-labeling and glycosylation of alkyne-bearing molecules. Using this strategy, work is in progress in our laboratory toward the development of ^{18}F-labeled glycopeptides that will serve as radiopharmaceuticals, whose biokinetics will be explored in vivo by PET.

3. Experimental

3.1. General methods

All chemicals and reagents were of analytical grade and were obtained from commercial sources if not stated otherwise. *N,N'*-Dimethylformamide (DMF), dichloromethane (CH_2Cl_2), and acetonitrile were obtained from Fluka as SureSeal bottles. [^{18}F]Fluoride was obtained from PET Net GmbH (Erlangen, Germany). Radio-thin layer chromatography (radio-TLC) was carried out on plastic sheets using ethyl acetate/*n*-hexane (1:1, v/v) as eluent (Polygram, Sil G/UV254, Macherey Nagel). Electronic autoradiography (Instant Imager, Canberra Packard) was used to analyze radio-TLC data. Analytical HPLC was performed on an Agilent 1100 system with a quarternary pump and variable wavelength detector and radio-HPLC detector D505TR (Canberra Packard). Computer analysis of the HPLC data was performed using FLO One software (Canberra Packard). Optical rotations were measured for solutions in $CHCl_3$ or methanol with a Perkin–Elmer automatic polarimeter, Model 241. Electron-spray-ionization (ESI) mass spectrometry analysis was performed using a Bruker esquire 2000 instrument. High resolution matrix-assisted laser desorption ionization time of flight mass spectrometry (HRMALDI-ToF-MS) analysis was performed on a Shimadzu Biotech Axima Confidence instrument (R = 5000), using cesium iodide as calibrating reference. NMR spectra were

recorded on a Varian Gemini-300 system for ^{19}F NMR (Deutero GmbH, Germany) and on a Bruker Avance 600 system for ^{1}H NMR, ^{13}C NMR, and selective NOE experiments. NOE experiments were performed for all mannosides when the anomeric configuration could not be undoubtedly assigned from $^{3}J_{1,2}$ values. Elemental analysis was performed by Mikroanalytisches Labor Pascher (Remagen, Germany). Reactions were monitored by thin-layer-chromatography (TLC) performed on precoated plates (Alugram Sil G/UV254, Macherey Nagel, 4 × 8 cm); zones were visualized by spraying with a solution of 97:2:1 (v/v/v) acetic acid–sulfuric acid–anisaldehyde with heating at 120 °C for about 0.5 min. 1,3,4,6-Tetra-*O*-acetyl-β-D-mannopyranose (**5**),[24] 1,3,4,6-tetra-*O*-acetyl-2-*O*-pentafluoropropionyl-β-D-mannopyranose (**6**),[26] 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-β-D-glucopyranose (**14**),[19] and 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-glucopyranosyl bromide (**15**)[27] were synthesized as described previously.

3.2. Propargyl 3,4,6-tri-*O*-acetyl-2-*O*-trifluoromethanesulfonyl-α-D-mannopyranoside (3)

3.2.1. 3,4,6-Tri-*O*-acetyl-2-*O*-pentafluoropropionyl-α-D-mannopyranosyl bromide (7)

A solution of **6** (1 g, 2 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C and HBr (33%) in acetic acid (4 mL) was added in a dropwise manner. The solution was allowed to warm to room temperature and stirred overnight. The solution was diluted with CH_2Cl_2 and washed with $NaHCO_3$ (satd) and water. The organic layer was dried over $NaSO_4$ and concentrated in vacuo. The crude product was purified by silica gel chromatography (1:1 hexane–EtOAc) to yield **7** (925 mg, 90%) as a yellow oil. R_f (2:1 hexane–EtOAc) = 0.7; ^{1}H NMR ($CDCl_3$, 600 MHz): 1.99 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.09 (s, 3H, OAc), 4.19 (dd, 1H, H-6b), 4.24 (ddd, 1H, $J_{5,6a}$ 3.9 Hz, $J_{5,6b}$ 2.1 Hz, H-5), 4.30 (dd, 1H, $J_{6a,6b}$ 12.6 Hz, H-6a), 5.39 (dd (t), 1H, $J_{4,5}$ 10.2 Hz, H-4), 5.66 (dd, 1H, $J_{2,3}$ 3.2 Hz, H-2), 5.79 (dd, 1H, $J_{3,4}$ 10.2 Hz, H-3), 6.36 (d, 1H, $J_{1,2}$ 1.2 Hz, H-1).

3.2.2. Propargyl 3,4,6-tri-*O*-acetyl-2-*O*-pentafluoropropionyl-α-D-mannopyranoside (8)

To a solution of **7** (800 mg, 1.55 mmol) in CH_2Cl_2 (10 mL) were added silver triflate (400 mg, 1.55 mmol) and propargyl alcohol (90 μL, 1.55 mmol). The mixture was stirred at room temperature in the dark and the reaction was monitored (TLC) until completion (40 min). After filtration of the suspension, the organic layer was washed with water, dried over $NaSO_4$, and concentrated in vacuo. The crude product was purified by silica gel chromatography (1:1 hexane–EtOAc) to afford **8** (490 mg, 65%) as a colorless oil. $[\alpha]_D^{20}$ +10.0 (*c* 1.2, $CHCl_3$); R_f (1:1 hexane–EtOAc) = 0.8; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 1.97 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.09 (s, 3H, OAc), 2.52 (t, 1H, *J* 2.4 Hz, CH), 4.05 (ddd, 1H, $J_{5,6a}$ 4.3 Hz, $J_{5,6b}$ 2.4 Hz, H-5), 4.16 (dd, 1H, H-6b), 4.26 (dd, 1H, $J_{6a,6b}$ 12.4 Hz, H-6a), 4.32 (d, 2H, *J* 2.4 Hz, CH_2), 5.14 (d, 1H, $J_{1,2}$ 1.8 Hz, H-1), 5.31 (dd (t), 1H, $J_{4,5}$ 9.9 Hz, H-4), 5.42 (dd, 1H, $J_{3,4}$ 9.9 Hz, H-3), 5.49 (dd, 1H, $J_{2,3}$ 3.2 Hz, H-2); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 20.31 (CH_3), 20.51 (CH_3), 20.58 (CH_3), 55.25 (*C*H_2C≡CH), 61.68 (C-4), 65.18, 68.56, 69.14, 73.14, 76.08 (CH_2C≡*C*H), 77.49 (CH_2*C*≡CH), 95.10 (C-1), 105.86 (tq, *J* 266 Hz, *J* 40 Hz, CF_3), 117.57 (qt, *J* 118 Hz, *J* 34 Hz, CF_2), 157.55 (t, *J* 30 Hz, *C*=OCF_2), 169.25 (C=O), 169.63 (C=O), 170.63 (C=O).

3.2.3. Propargyl 3,4,6-tri-*O*-acetyl-α-D-mannopyranoside (9)

Compound **8** (475 mg, 970 μmol) was dissolved in ethanol (48.5 mL) and pyridine (779 μL, 9.7 mmol) was added and the solution was stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo to afford **9** (333 mg, quant.), which was used without further purification for the subsequent reaction.

3.2.4. Propargyl 3,4,6-tri-*O*-acetyl-2-*O*-trifluoromethanesulfonyl-α-D-mannopyranoside (3)

A solution of **9** (334 mg, 970 μmol) in CH_2Cl_2 (8 mL) and anhydrous pyridine (183 μL) was cooled to −20 °C, and trifluoromethanesulfonic anhydride (183 μL) was added dropwise. After stirring for 1 h at 0 °C, the mixture was diluted with CH_2Cl_2 and washed with cold H_2O. The organic layer was dried over $NaSO_4$ and concentrated in vacuo. The crude product was purified by silica gel chromatography (1:1 hexane–EtOAc) to afford **3** (340 mg, 74%) as a colorless oil. $[\alpha]_D^{20}$ +57.4 (*c* 1.2, $CHCl_3$); R_f (1:1 hexane–EtOAc) = 0.7; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 2.05 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.11 (s, 3H, OAc), 2.53 (t, 1H, *J* 2.4 Hz, CH), 4.04 (ddd, 1H, $J_{5,6a}$ 4.8 Hz, $J_{5,6b}$ 2.6 Hz, H-5), 4.17 (dd, 1H, H-6b), 4.24 (dd, 1H, $J_{6a,6b}$ 12.4 Hz, H-6a), 4.32 (d, *J* 2.4 Hz, 2H, CH_2), 5.06 (dd, 1H, $J_{2,3}$ 2.6 Hz, H-2), 5.24 (d, 1H, $J_{1,2}$ 1.8 Hz, H-1), 5.31 (dd (t), 1H, $J_{4,5}$ 10.0 Hz, H-4), 5.39 (dd, 1H, $J_{3,4}$ 10.1 Hz, H-3); ^{13}C NMR ($CDCl_3$, 90 MHz,) δ 20.48 (CH_3), 20.56 (CH_3), 20.68 (CH_3), 55.52 (*C*H_2C≡CH), 61.88 (C-4), 65.18, 67.80, 69.27, 76.31, 77.13 (CH_2C≡*C*H), 81.54 (CH_2*C*≡CH), 95.29 (C-1), 118.49 (q, *J* 319.5 Hz, CF_3), 169.23 (C=O), 169.74 (C=O), 170.59 (C=O); ESI-MS *m*/*z* 499.1 $[M+Na]^+$, 515.0 $[M+K]^+$. Anal. Calcd for $C_{16}H_{19}F_3O_{11}S$: C, 40.34; H, 4.02. Found: C, 40.37; H, 3.97.

3.3. Azidoethyl 3,4,6-tri-*O*-acetyl-2-*O*-trifluoromethanesulfonyl-α-D-mannopyranoside (4)

3.3.1. Bromoethyl 3,4,6-tri-*O*-acetyl-2-*O*-pentafluoropropionyl-α-D-mannopyranoside (10)

A solution of **7** (800 mg, 1.55 mmol) in CH_2Cl_2 (10 mL), silver triflate (400 mg, 1.55 mmol), and 2-bromoethanol (111 μL, 1.55 mmol) was stirred at room temperature in the dark. The progress of the reaction was monitored by TLC and after disappearance of **7** (40 min), the suspension was filtered. The organic layer was washed with water, dried over $NaSO_4$, and concentrated in vacuo. The crude product was purified by silica gel chromatography (1:1 hexane–EtOAc) to yield **10** (585 mg, 68%) as a colorless oil. R_f (1:1 hexane–EtOAc) = 0.8; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 1.98 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.10 (s, 3H, OAc), 3.54 (t, 2H, *J* 5.8 Hz, CH_2), 3.93 (dt, 1H, *J* 11.4 Hz, *J* 5.6 Hz, CH_2), 4.04 (dt, 1H, *J* 11.4 Hz, *J* 5.6 Hz, CH_2), 4.16 (ddd, 1H, $J_{5,6a}$ 4.5, $J_{5,6b}$ 2.4 Hz, H-5), 4.19 (dd, 1H, H-6b), 4.24 (dd, 1H, $J_{6a,6b}$ 12.3 Hz, H-6a), 4.98 (d, 1H, $J_{1,2}$ 1.8 Hz, H-1), 5.30 (dd (t), 1H, $J_{4,5}$ 10.0 Hz, H-4), 5.42 (dd, 1H, $J_{3,4}$ 10.0 Hz, H-3), 5.48 (dd, 1H, $J_{2,3}$ 3.3 Hz, H-2); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 20.33 (CH_3), 20.53 (CH_3), 20.60 (CH_3), 29.50 (CH_2Br), 61.78 (C-4), 65.17, 68.59, 68.69, 69.17, 73.10 (*C*$H_2$$CH_2$Br), 96.67 (C-1), 105.83 (tq, *J* 265 Hz, *J* 40 Hz, CF_3), 117.56 (qt, *J* 287 Hz, *J* 34 Hz, CF_2), 157.58 (t, *J* 30 Hz, *C*=OCF_2), 169.32 (C=O), 169.65 (C=O), 170.61 (C=O).

3.3.2. Azidoethyl 3,4,6-tri-*O*-acetyl-2-*O*-pentafluoropropionyl-α-D-mannopyranoside (11)

Compound **10** (550 mg, 987 μmol) was dissolved in DMF (4.5 mL) and sodium azide (64 mg, 987 μmol) was added. After stirring overnight at room temperature, the mixture was concentrated in vacuo and redissolved in CH_2Cl_2. The organic layer was washed with H_2O, dried over $NaSO_4$, and concentrated in vacuo. The crude product was purified by silica gel chromatography (1:1 hexane–EtOAc) to afford **11** (200 mg, 39%) as a colorless oil. R_f (1:1 hexane–EtOAc) = 0.7; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 1.98 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.09 (s, 3H, OAc), 3.44–3.53 (m, 2H, CH_2), 3.72 (ddd, 1H, *J* 10.6 Hz, *J* 5.9 Hz, *J* 3.8 Hz, CH_2), 3.92 (ddd, 1H, *J* 10.5 Hz, *J* 6.4 Hz, *J* 4.1 Hz, CH_2), 4.07 (ddd, 1H, $J_{5,6a}$ 4.5 Hz, $J_{5,6b}$ 2.5 Hz, H-5), 4.18 (dd, 1H, H-6b), 4.26 (dd, 1H, $J_{6a,6b}$ 12.4 Hz, H-6a), 4.97 (d, 1H, $J_{1,2}$ 1.8 Hz, H-1), 5.31 (dd (t), 1H, $J_{4,5}$ 10.0 Hz, H-4), 5.43 (dd, 1H, $J_{3,4}$ 9.9 Hz, H-3), 5.48 (dd, 1H, $J_{2,3}$ 3.2 Hz, H-2);

^{13}C NMR ($CDCl_3$, 151 MHz) δ 20.31 (CH_3), 20.50 (CH_3), 20.59 (CH_3), 50.34 (CH_2N_3), 61.83 (C-4), 65.18 ($CH_2CH_2N_3$), 67.31, 68.51, 69.02, 73.08, 96.70 (C-1), 157.58 (t, *J* 31 Hz, *C*=OCF_2), 169.31 (C=O), 169.60 (C=O), 170.60 (C=O).

3.3.3. Azidoethyl 3,4,6-tri-*O*-acetyl-α-D-mannopyranoside (12)

Compound **11** (505 mg, 970 μmol) was dissolved in ethanol (48.5 mL), pyridine (779 μL, 9.7 mmol) was added and the solution was stirred at room temperature. TLC analysis showed complete cleavage of Pfp after 2 h. The reaction mixture was concentrated in vacuo to afford **12** (364 mg, quant.), which was used without further purification for the subsequent reaction.

3.3.4. Azidoethyl 3,4,6-tri-*O*-acetyl-2-*O*-trifluoromethanesulfonyl-α-D-mannopyranoside (4)

A solution of **12** (365 mg, 970 μmol) in CH_2Cl_2 (8 mL) and anhydrous pyridine (183 μL) was cooled to −20 °C and trifluoromethanesulfonic anhydride (183 μL) was added dropwise. After stirring for 1 h at 0 °C, the mixture was diluted with CH_2Cl_2 and washed with cold H_2O. The organic layer was dried over $NaSO_4$ and concentrated in vacuo. The crude product was purified by silica gel chromatography (1:1 hexane–EtOAc) to afford **4** (166 mg, 36%) as a colorless oil. $[\alpha]_D^{20}$ +30.8 (*c* 1.0, $CHCl_3$); R_f (1:1 hexane–EtOAc) = 0.7; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 2.06 (s, 3H, OAc), 2.09 (s, 3H, OAc), 2.10 (s, 3H, OAc), 3.47–3.54 (m, 2H, CH_2), 3.74 (ddd, 1H, *J* 10.7 Hz, *J* 5.9 Hz, *J* 3.9 Hz, CH_2), 3.91 (ddd, 1H, *J* 10.5 Hz, *J* 6.5 Hz, *J* 3.9 Hz, CH_2), 4.07 (ddd, 1H, $J_{5,6a}$ 4.9 Hz, $J_{5,6b}$ 3.0 Hz, H-5), 4.19 (dd, 1H, H-6b), 4.24 (dd, 1H, $J_{6a,6b}$ 12.4 Hz, H-6a), 5.07 (dd, 1H, $J_{2,3}$ 3.1 Hz, H-2), 5.09 (d, 1H, $J_{1,2}$ 1.9 Hz, H-1), 5.30 (dd (t), 1H, $J_{4,5}$ 10.0 Hz, H-4), 5.41 (dd, 1H, $J_{3,4}$ 10.1 Hz, H-3); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 20.47 (CH_3), 20.58 (CH_3), 20.67 (CH_3), 50.32 (CH_2N_3), 62.00 (C-4), 65.15 ($CH_2CH_2N_3$), 67.46, 67.79, 69.11, 81.38, 96.98 (C-1), 118.48 (q, *J* 319 Hz, CF_3), 169.30 (C=O), 169.71 (C=O), 170.56 (C=O); ESI-MS *m*/*z* 530.1 $[M+Na]^+$. Anal. Calcd for $C_{15}H_{20}F_3N_3O_{11}S$: C, 35.51; H, 3.97; N, 8.28. Found: C, 35.09; H, 3.98; N, 8.10.

3.4. 3,4,6-Tri-*O*-acetyl-2-*O*-trifluoromethanesulfonyl-D-mannopyranosyl azide (2)

3.4.1. 3,4,6-Tri-*O*-acetyl-2-*O*-pentafluoropropionyl-β-D-mannopyranosyl azide

Compound **7** (800 mg, 1.55 mmol) was dissolved in DMF (7 mL) and sodium azide (100 mg, 1.55 mmol) was added. After stirring overnight, the mixture was concentrated in vacuo, redissolved in CH_2Cl_2, and filtered. The organic layer was washed with H_2O, dried over $NaSO_4$, and concentrated in vacuo. The crude product was purified by silica gel chromatography (1:1 hexane–EtOAc) to afford the title compound as a colorless oil (274 mg, 37%): R_f (1:1 hexane–EtOAc) = 0.6; ^{1}H NMR ($CDCl_3$, 600 MHz): 1.99 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.11 (s, 3H, OAc), 3.83 (ddd, 1H, $J_{5,6a}$ 4.3 Hz, $J_{5,6a}$ 2.8 Hz, H-5), 4.26 (m, 2H, H-6a, H-6b), 4.97 (d, 1H, $J_{1,2}$ 1.1 Hz, H-1), 5.15 (dd, 1H, $J_{3,4}$ 10.1 Hz, H-3), 5.29 (t, 1H, $J_{4,5}$ 10.1 Hz, H-4), 5.52 (dd, 1H, $J_{2,3}$ 3.1 Hz, H-2); ^{13}C NMR ($CDCl_3$, 91 MHz) δ 20.18 (CH_3), 20.50 (CH_3), 20.54 (CH_3), 61.60 (C-4), 64.64, 70.38, 73.12, 74.62, 84.45 (C-1), 157.75 (t, *J* 31 Hz, *C*=OCF_2), 169.68 (C=O), 169.10 (C=O), 170.58 (C=O).

3.4.2. 3,4,6-Tri-*O*-acetyl-D-mannopyranosyl azide (13)

Compound **7** (800 mg, 1.55 mmol) was dissolved in DMF (7 mL) and sodium azide (100 mg, 1.55 mmol) was added. After stirring overnight, ethanol (10 mL) and pyridine (1 mL) were added, and the solution was stirred for 1 h at room temperature. Subsequently, the mixture was concentrated in vacuo and redissolved in CH_2Cl_2. The organic layer was washed with H_2O, dried over $NaSO_4$, and concentrated in vacuo. The crude product was purified by silica gel chromatography (1:1 hexane–EtOAc) to afford **13** as a mixture of anomers (406 mg, 79%, α:β ~ 1:1) as a colorless oil. β-anomer: R_f (1:1 hexane–EtOAc) = 0.5; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.05 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.11 (s, 3H, OAc), 3.74 (ddd, 1H, $J_{5,6a}$ 5.3 Hz, $J_{5,6a}$ 2.4 Hz, H-5), 4.12 (1H, dd, $J_{2,3}$ 2.6 Hz, H-2), 4.19 (dd, 1H, H-6b), 4.30 (dd, 1H, $J_{6a,6b}$ 12.4 Hz, H-6a), 4.80 (d, 1H, $J_{1,2}$ 1.0 Hz, H-1), 4.97 (dd, 1H, $J_{3,4}$ 9.9 Hz, H-3), 5.38 (t, 1H, $J_{4,5}$ 9.9 Hz, H-4); ^{13}C NMR ($CDCl_3$, 91 MHz) δ 20.65 (CH_3), 20.74 (CH_3), 20.79 (CH_3), 62.20 (C-4), 65.37, 69.39, 72.94, 74.45, 87.12 (C-1), 169.48 (C=O), 170.10 (C=O), 170.69 (C=O); α-anomer: R_f (1:1 hexane–EtOAc) = 0.4; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 2.05 (s, 3H), 2.09 (s, 3H, OAc), 2.10 (s, 3H, OAc), 3.99 (ddd, 1H, $J_{2,3}$ 3.1, Hz, H-2), 4.08–4.16 (m, 1H, H-5), 4.17 (dd, 1H, $J_{6b,5}$ 2.3 Hz, H-6b), 4.31 (dd, 1H, $J_{6a,6b}$ 12.4 Hz, $J_{6a,5}$ 5.3 Hz, H-6a), 5.18 (dd, 1H, $J_{3,4}$ 9.8 Hz, H-3), 5.34 (t, 1H, $J_{4,5}$ 9.9 Hz, H-4), 5.43 (d, $J_{1,2}$ 2.0 Hz, 1H, H-1); ^{13}C NMR ($CDCl_3$, 91 MHz) δ 20.66 (CH_3), 20.72 (CH_3), 20.80 (CH_3), 62.14 (C-4), 65.73, 69.07, 70.59, 70.86, 89.31 (C-1), 169.70 (C=O), 169.77 (C=O), 170.72 (C=O).

3.4.3. 3,4,6-Tri-*O*-acetyl-2-*O*-trifluoromethanesulfonyl-D-mannopyranosyl azide (2)

A solution of 3,4,6-tri-*O*-acetyl-D-mannopyranosyl azide **13** (150 mg, 453 μmol) in CH_2Cl_2 (5 mL) and anhydrous pyridine (85 μL) was cooled to −20 °C and trifluoromethanesulfonic anhydride (85 μL) was added dropwise. After stirring for 1 h at 0 °C, the mixture was diluted with CH_2Cl_2 and washed with cold H_2O. The organic layer was dried over $NaSO_4$ and concentrated in vacuo. The crude product was purified by silica gel chromatography (1:1 hexane–EtOAc) to yield **2β** (84 mg, 40%) and **2α** (115 mg, 55%) as colorless oils. β-anomer: $[\alpha]_D^{20}$ −63.5 (*c* 1.0, $CHCl_3$); R_f (1:1 hexane–EtOAc) = 0.6; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 2.07 (s, 3H, OAc), 2.11 (s, 6H, 2 × OAc), 3.83 (ddd, 1H, $J_{5,6a}$ 4.9, $J_{5,6b}$ 3.1 Hz, H-5), 4.27–4.24 (m, 2H, H-6a, H-6b), 5.04 (dd, 1H, $J_{2,3}$ 3.0 Hz, H-2), 5.03 (d, 1H, $J_{1,2}$ 0.8 Hz, H-1), 5.11 (dd, 1H, $J_{3,4}$ 10.1 Hz, H-3), 5.29 (dd (t), 1H, $J_{4,5}$ 10.0 Hz, H-4); ^{13}C NMR ($CDCl_3$, 151 MHz,) δ 19.42 (CH_3), 19.51 (CH_3), 19.63 (CH_3), 60.82 (C-4), 63.55, 68.78, 73.93, 80.09, 83.39 (C-1), 117.34 (q, *J* 319.6 Hz, CF_3), 168.05 (C=O), 168.90 (C=O), 169.54 (C=O); ESI-MS *m*/*z* 486.0 $[M+Na]^+$. Anal. Calcd for $C_{13}H_{16}F_3N_3O_{10}S$: C, 33.70; H, 3.48; N, 9.07. Found: C, 34.03; H, 3.41; N, 9.02. The β-configuration was confirmed by selective NOE experiments showing a coupling between the protons H-1, H-3, and H-5. The purity of **2β** was determined by gradient HPLC (Kromasil C8, 250 × 4.6 mm, 40–100% acetonitrile (0.1% TFA) in water (0.1% TFA) in a linear gradient over 50 min, 1.5 mL/min, t_R = 15.8 min). α-anomer: $[\alpha]_D^{20}$ +94.4 (*c* 1.2, $CHCl_3$); R_f (1:1 hexane–EtOAc) = 0.8; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 2.07 (s, 3H, OAc), 2.09 (s, 3H, OAc), 2.11 (s, 3H, OAc), 4.15–4.26 (m, 3H, H-5m H-6a, H-6b), 4.97 (br s, 1H, H-1), 5.27–5.31 (m, 2H, H-3, H-4), 5.56 (br d, 1H, $J_{2,3}$ 1.9 Hz, H-2); ^{13}C NMR ($CDCl_3$, 151 MHz,) δ 20.38 (CH_3), 20.50 (CH_3), 20.59 (CH_3), 61.67 (C-4), 64.76, 67.21, 70.76, 81.05, 86.79 (C-1), 118.43 (q, *J* 319.7 Hz, CF_3), 169.15 (C=O), 169.61 (C=O), 170.52 (C=O); ESI-MS *m*/*z* 486.0 $[M+H]^+$. Anal. Calcd for $C_{13}H_{16}F_3N_3O_{10}S$: C, 33.70; H, 3.48. Found: C, 33.86; H, 3.51.

3.5. 2-Azidoethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-D-glucopyranoside (18)

3.5.1. 2-Bromoethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-D-glucopyranoside (17)

Compound **15** (148 mg, 400 μmol) was dissolved in CH_2Cl_2 (2–3 mL) and AgOTf (102 mg, 400 μmol) and 2-bromoethanol (29 μL, 400 μmol) was added. The solution was stirred at room temperature in the dark until TLC showed complete conversion (40 min).

After filtration of the suspension, the organic layer was washed with water, dried over $NaSO_4$ and concentrated in vacuo to afford the crude product **17** as a reddish oil (155 mg, 93%, R_f (1:1 hexane–EtOAc) = 0.7), which was used for the subsequent reaction without further purification.

3.5.2. 2-Azidoethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-D-glucopyranoside (18)

A solution of **17** (106 mg, 255 μmol) in DMF (2 mL) and sodium azide (16.6 mg, 255 μmol) was stirred for 4 h. The mixture was concentrated under reduced pressure and the residue was taken up in CH_2Cl_2. After filtration of the suspension, the organic layer was washed with water, dried over $NaSO_4$, and concentrated in vacuo. The crude product was purified by silica gel chromatography (1:1 hexane–EtOAc) to afford **18** as a mixture of anomers (45 mg, 47%, α:β = 3:2), as a colorless oil. R_f (1:1 hexane–EtOAc) = 0.6; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 2.04 (s, 1.8H, OAc, β), 2.04 (s, 3H, OAc, α), 2.07 (s, 3H, OAc, α), 2.08 (s, 1.8H, OAc, β), 2.09 (s, 1.8H, OAc, β), 2.09 (s, 3H, OAc, α), 3.42 (ddd, 0.6H, *J* 13.3 Hz, *J* 5.8 Hz, *J* 3.8 Hz, CH_2, β-anomer), 3.49 (ddd, 0.6H, *J* 13.3 Hz, *J* 5.9 Hz, *J* 3.7 Hz, CH_2, β-anomer), 3.51 (ddd, 1H, *J* 9.8 Hz, *J* 6.5 Hz, *J* 3.7 Hz, CH_2, α-anomer), 3.54 (ddd, 1H, *J* 13.3 Hz, *J* 7.0 Hz, *J* 3.6 Hz, CH_2, α-anomer), 3.71–3.77 (m, 1.6H, CH_2 α+β-anomer), 3.80 (ddd, 0.6H, $J_{5,6a}$ 7.3 Hz, $J_{5,6b}$ 3.8 Hz, H-5, β-anomer), 3.91 (ddd, 1H, $J_{5,6a}$ 7.0 Hz, $J_{5,6b}$ 3.7 Hz, H-5, α-anomer), 4.05 (ddd, 0.6H, *J* 10.5 Hz, *J* 5.8 Hz, *J* 3.8 Hz, CH_2, β-anomer), 4.11 (dd, 2H, $J_{6a,6b}$ 11.3 Hz, H-6a α-anomer, CH_2, α-anomer), 4.16 (dd, 0.6H, $J_{6a,6b}$ 12.4 Hz, H-6a β-anomer), 4.23–4.29 (m, 1H, H-6b α, 0.6H, H-6b β-anomer), 4.33 (ddd, 0.6H, $J_{2,F}$ 50.6 Hz, $J_{2,3}$ 9.1 Hz, H-2, β-anomer), 4.52 (ddd, 1H, $J_{2,F}$ 49.1 Hz, $J_{2,3}$ 9.6 Hz, H-2, α-anomer), 4.64 (dd, 0.6H, $J_{1,2}$ 7.7 Hz, $J_{1,F}$ 2.8 Hz, H-1, β-anomer), 5.03 (t (dd), 1H, $J_{4,5}$ 9.7 Hz, H-4, α-anomer), 5.04 (t (dd), 0.6H, $J_{4,5}$ 9.7 Hz, H-4, β-anomer), 5.11 (d, 1H, $J_{1,2}$ 3.9 Hz, H-1, α-anomer), 5.33 (dt, 0.6 H, $J_{3,F}$ 14.6 Hz, $J_{3,4}$ 9.3 Hz, H-3, β-anomer), 5.57 (dt, 1H, $J_{3,F}$ 11.9 Hz, $J_{3,4}$ 9.5 Hz, H-3, α-anomer); ^{13}C NMR ($CDCl_3$, 91 MHz,) δ 20.57 (β-anomer), 20.60 (α-anomer), 20.66 (β-anomer), 20.71 (α+β-anomer), 20.72 (α-anomer), 50.51 (CH_2N_3, α-anomer), 50.62 (CH_2N_3, β-anomer), 61.75 (C-6, β-anomer), 61.77 (d, C-6, $J_{6,F}$ 0.8 Hz, α-anomer), 67.67 (OCH_2, α-anomer), 67.71 (d, C-5, $J_{5,F}$ 1.0 Hz, α-anomer), 67.98 (d, C-4, $J_{4,F}$ 7.3 Hz, α-anomer), 68.12 (d, C-4, $J_{4,F}$ 7.3 Hz, β-anomer), 68.96 (OCH_2, β-anomer), 70.52 (d, C-3, $J_{3,F}$ 19.5 Hz, α-anomer), 71.92 (d, C-5, $J_{5,F}$ 0.6 Hz, β-anomer), 72.72 (d, C-3, $J_{3,F}$ 20.0 Hz, β-anomer), 87.60 (d, C-2, $J_{2,F}$ 191.5 Hz, α-anomer), 89.80 (d, C-2, $J_{2,F}$ 191.3 Hz, β-anomer), 96.31 (d, C-1, $J_{1,F}$ 20.7 Hz, α-anomer), 100.56 (d, C-1, $J_{1,F}$ 22.8 Hz, β-anomer), 169.48 (β-anomer), 169.67 (α-anomer), 169.95 (β-anomer), 170.03 (α-anomer), 170.54 (β-anomer), 170.57 (α-anomer); ESI-MS *m*/*z* 400.1 $[M+Na]^+$. Anal. Calcd for $C_{14}H_{20}FN_3O_8$: C, 44.56; H, 5.34. Found: C, 44.67; H, 5.26.

3.6. Propargyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-D-glucopyranoside (16)

To a solution of **15** (212 mg, 571 μmol) in CH_2Cl_2 (3 mL) was added AgOTf (146 mg, 571 μmol) and propargyl alcohol (33 μL, 571 μmol). The solution was stirred for 1 h at room temperature in the dark. After filtration of the suspension, the organic layer was washed with water, dried over $NaSO_4$, and concentrated in vacuo. The crude product was purified by silica gel chromatography (1:1 hexane–EtOAc) to afford **16** as a mixture of anomers (yellow oil, 165 mg, 84%, α:β ~ 3:2). R_f (1:1 hexane–EtOAc) = 0.6; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 2.04 (s, 4.8H, OAc, α- and β-anomers), 2.07 (s, 3H, OAc, α-anomer), 2.09 (s, 3.6H, 2 × OAc, β-anomer), 2.09 (s, 3H, OAc, α-anomer), 2.50 (t, 1H, *J* 2.4 Hz, CH, α-anomer), 2.52 (t, 0.6H, *J* 2.4 Hz, CH, β-anomer), 3.75 (ddd, 0.6H, $J_{5,4}$ 10.0 Hz, $J_{5,6a}$ 4.7 Hz, $J_{5,6b}$ 2.4 Hz, H-5, β-anomer), 4.07–4.11 (m, 2H, H-6 α-anomer, H-5 α-anomer), 4.14 (dd, 0.6H, $J_{6b,6a}$ 12.4 Hz, $J_{6b,5}$ 2.4 Hz, H-6b, β-anomer), 4.25–4.46 (m, 5.4H, H-2 β-anomer, H-6 α-anomer, H-6 β-anomer, CH_2 α-anomer, CH_2 β-anomer), 4.54 (ddd, 1H, $J_{2,F}$ 49.0 Hz, $J_{2,3}$ 9.7 Hz, $J_{2,1}$ 3.9 Hz, H-2, α-anomer), 4.86 (dd, 0.6H, $J_{1,2}$ 7.7 Hz, $J_{1,F}$ 2.7 Hz, H-1, β-anomer), 5.05 (t, 1.6H, $J_{4,5}$ 9.7 Hz, H-4, α- and β-anomers), 5.29 (d, 1H, $J_{1,2}$ 3.9 Hz, H-1 α-anomer), 5.35 (td, 0.6H, $J_{3,F}$ 14.6 Hz, $J_{3,4}$ 9.2 Hz, H-3 β-anomer), 5.56 (td, 1H, $J_{3,F}$ 11.9 Hz, $J_{3,4}$ 9.6 Hz, H-3 α-anomer); ^{13}C NMR (151 MHz, $CDCl_3$) δ 20.57, 20.58, 20.68, 20.70, 20.72, 55.63 ($OCH_2C{\equiv}CH$, α-anomer), 56.13 ($OCH_2C{\equiv}CH$, β-anomer), 61.59 $OCH_2C{\equiv}CH$, α-anomer), 61.66 $OCH_2C{\equiv}CH$, β-anomer), 67.85 (C-6, α-anomer), 67.99 (d, *J* 7.2 Hz, C-4, α-anomer), 68.09 (d, *J* 7.4 Hz, C-4, β-anomer), 70.55 (d, *J* 19.5 Hz, C-3, α-anomer), 71.95 (C-6, β-anomer), 72.81 (d, *J* 20.0 Hz, C-3, β-anomer), 75.63 (C-5, α-anomer), 75.96 (C-5, β-anomer), 77.73 ($OCH_2C{\equiv}CH$, β-anomer), 77.95 ($OCH_2C{\equiv}CH$, α-anomer), 86.95 (d, *J* 195.9 Hz, C-2, α-anomer), 89.06 (d, *J* 191.7 Hz, C-2, β-anomer), 94.85 (d, *J* 20.5 Hz, C-1, α-anomer), 97.79 (d, *J* 22.8 Hz, C-1, β-anomer), 169.50, 169.61, 169.98, 170.01, 170.56; ESI-MS *m*/*z* 360.1 $[M+Na]^+$. Anal. Calcd for $C_{15}H_{19}FO_8$: C, 52.02; H, 5.53. Found: C, 51.66; H, 5.56.

3.7. 3,4,6-Tri-*O*-acetyl-2-deoxy-2-fluoro-β-D-glucopyranosyl azide (19)

Compound **15** (140 mg, 377 μmol) was dissolved in DMF (3 mL) and sodium azide (25 mg, 377 μmol) was added. After stirring for 1 h, the solution was concentrated in vacuo and the residue was taken up in CH_2Cl_2. After filtration of the suspension, the organic layer was washed with water, dried over $NaSO_4$, and concentrated. The crude product was purified by silica gel chromatography (1:1 hexane–EtOAc) to afford **19** (93 mg, 74%) as a white amorphous solid. $[\alpha]_D^{20}$ +26.7 (*c* 0.3, $CHCl_3$); R_f (1:1 hexane–EtOAc) = 0.7; ^{1}H NMR (600 MHz, $CDCl_3$ δ 2.04 (s, 3H), 2.09 (s, 3H), 2.10 (s, 3H), 3.81 (ddd, 1H, $J_{5,6a}$ 4.9 Hz, $J_{5,6a}$ 2.3 Hz, H-5), 4.16 (dd, 1H, $J_{6a,6b}$ 12.5 Hz, H-6b), 4.21 (dt, 1H, $J_{2,F}$ 50.2 Hz, $J_{2,3}$ 8.8 Hz, H-2), 4.28 (dd, 1H, H-6a), 4.82 (dd, 1H, $J_{1,2}$ 8.5 Hz, $J_{1,F}$ 3.0 Hz, H-1), 5.36–5.30 (t, 1H, $J_{4,5}$ 9.8 Hz H-4), 5.05 (t, 1H, $J_{3,F}$ 14.1 Hz, $J_{3,4}$ 9.8 Hz, H-3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 20.52, 20.61, 20.68, 61.55 (C-6), 67.63 (d, *J* 7.4 Hz, C-4), 72.60 (d, *J* 19.6 Hz, C-3), 73.99 (C-5), 87.78 (d, *J* 22.8 Hz, C-1), 88.91 (d, *J* 192.7 Hz, C-2), 169.40, 169.89, 170.52; ^{19}F NMR (282 MHz, $CDCl_3$): δ *−199.18* (ddd, $J_{F,2}$ 50.5 Hz, $J_{F,3}$ 14.1 Hz, $J_{F,1}$ 3.0 Hz); ESI-MS *m*/*z* 356.1 $[M+Na]^+$. Anal. Calcd for $C_{12}H_{16}FN_3O_7$: C, 43.25; H, 4.84; N, 12.61. Found: C, 43.28; H, 4.82; N, 12.7.

3.8. (*S*)-2-{[(9*H*-Fluoren-9-yl)methoxy]carbonylamino}-3-(1-(2-deoxy-2-fluoro-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl)propanoic acid (22)

3.8.1. 2-Deoxy-2-fluoro-β-D-glucopyranosyl azide (20)

A solution of **19** (100 mg, 300 μmol) and sodium methoxide in methanol (10 mM) was stirred at room temperature for 1 h. Subsequently, the solution was neutralized with Amberlite 120 H^+, the resin was filtered off, and the solvent was removed under reduced pressure. After lyophilization, **20** was obtained as a white amorphous solid (60 mg, 97%). $[\alpha]_D^{20}$ −15.5 (*c* 1.0, methanol); ^{1}H NMR (360 MHz, DMSO-d_6: δ 3.16 (t, 1H, $J_{4,5}$ 9.3 Hz, H-4), 3.34 (ddd, 1H, $J_{5,6a}$ 5.7 Hz, $J_{5,6b}$ 1.9 Hz, H-5), 3.47 (dd, 1H, $J_{6a,6b}$ 11.9 Hz, H-6a), 3.50 (ddd, 1H, $J_{3,F}$ 16.4 Hz, $J_{3,4}$ 8.3 Hz, H-3), 3.70 (dd, 1H, H-6b), 3.83 (t, 1H, $J_{2,F}$ 51.3 Hz, $J_{2,3}$ 8.8 Hz, H-2), 4.98 (dd, $J_{1,2}$ 8.6 Hz, $J_{1,F}$ 2.6 Hz, 1H, H-1); ^{13}C NMR (151 MHz, DMSO-d_6): δ 60.37 (C-6), 69.28 (d, *J* 8.1 Hz, C-4), 74.16 (d, *J* 16.1 Hz, C-3), 79.08 (C-5), 86.58 (d, *J* 23.0 Hz, C-1), 92.06 (d, *J* 185.7 Hz, C-2); ^{19}F NMR (282 MHz, DMSO-d_6): δ *−196.30* (ddd, $J_{F,2}$ 51.7 Hz, $J_{F,3}$ 16.0 Hz, $J_{F,1}$ 2.3 Hz).

3.8.2. (*S*)-2-{[(9*H*-Fluoren-9-yl)methoxy]carbonylamino}-3-(1-(2-deoxy-2-fluoro-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl)propanoic acid (22)

To a solution of 2-deoxy-2-fluoro-D-glucopyranosyl azide (**20**) (5 mg, 24 μmol) and N^{α}-(9-fluorenylmethyloxycarbonyl)-L-2-propargylglycine (**21**) (8 mg, 24 μmol) in water/ethanol (1:2, 1.5 mL) was added a solution of copper(II)sulfate pentahydrate (0.2 M, 24 μL) and sodium ascorbate (0.6 M, 24 μL). The mixture was stirred at room temperature overnight, then diluted with water (10 mL), and passed through a RP-18 cartridge (SepPak® Plus Environmental, Waters). The cartridge was washed with water (20 mL), and the product was eluted with ethanol (5 mL). The solvent was evaporated in vacuo and **22** was isolated using semipreparative RP-HPLC (Kromasil C8, 125 × 8 mm, 30–70% acetonitrile (0.1% TFA) in water (0.1% TFA) in a linear gradient over 30 min, 4 mL/min, t_R = 5.8 min)). The product fraction was lyophilized to yield **22** as a white solid (11.8 mg, 91%). ^{1}H NMR (360 MHz, DMSO-d_6: δ 3.04 (dd, 1H, $J_{6a,6b}$ 15.0 Hz, $J_{6a,5}$ 9.4 Hz, H-6a), 3.07 (dd, $J_{6b,6a}$ 15.0 Hz, $J_{6b,5}$ 5.9 Hz, H-6b), 3.32 (t, 1H, $J_{4,5}$ 9.3 Hz, H-4), 3.46 (dd, 1H, *J* 12.1 Hz, *J* 5.8 Hz), 3.56 (ddd, 1H, $J_{5,6a}$ 9.7 Hz, $J_{5,6b}$ 5.6 Hz, H-5), 3.73 (dt, 1H, $J_{3,F}$ 15.9 Hz, $J_{3,4}$ 8.9 Hz, H-3), 3.65–3.72 (m, 1H), 4.16–4.36 (m, 4H), 4.80 (dt, 1H, $J_{2,F}$ 50.9 Hz, $J_{2,3}$ 9.0 Hz, H-2), 5.99 (dd, 1H, $J_{1,2}$ 9.1 Hz, $J_{1,F}$ 2.2 Hz, H-1), 7.29–7.36 (m, 2H), 7.39–7.44 (m, 2H), 7.66–7.79 (m, 3H), 7.85–7.92 (m, 2H), 8.19 (s, 1H); ^{13}C NMR (151 MHz, DMSO-d_6): δ 27.02 (CH_2, β-Gly), 46.47 (CH, Fmoc), 53.60 (CH, α-Gly), 60.23 (C-6), 65.67 (CH_2, Fmoc), 69.2 (d, *J* 8.0 Hz, C-4), 74.31 (d, *J* 16.1 Hz, C-3), 79.78 (C-5), 83.83 (d, *J* 24.0 Hz, C-1), 91.31 (d, *J* 186.0 Hz, C-2), 120.00 (4C, Fmoc), 122.39 (CH, triazole), 125.17 (C, triazole), 127.01 (2C, Fmoc), 127.54 (2C, Fmoc), 140.58 (2C, Fmoc), 143.41 (1C, Fmoc), 143.70 (1C, Fmoc), 155.90 (C=O, Fmoc), 172.77 (COOH); ^{19}F NMR (282 MHz, DMSO-d_6) *δ −197.63* (ddd, $J_{F,2}$ 51.5 Hz, $J_{F,3}$ 16.3 Hz, $J_{F,1}$ 2.5 Hz); HRMALDI-ToF-MS: calcd for $[M+H]^+$: 543.1891. Found: *m*/*z* 543.1695; calcd for $[M+Na]^+$: 565.1711. Found: *m*/*z* 565.1719.

3.9. (*S*)-2-{[(9*H*-Fluoren-9-yl)methoxy]carbonylamino}-3-(1-(3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl)propanoic acid (23)

To a solution of **19** (15 mg, 45 μmol) and N^{α}-(9-fluorenylmethyloxycarbonyl)-L-2-propargylglycine (**21**) (15 mg, 45 μmol) in ethanol (1.5 mL) was added a solution of copper(II)sulfate pentahydrate (0.2 M, 45 μL) and sodium ascorbate (0.6 M, 45 μL). The mixture was stirred at room temperature overnight, then diluted with CH_2Cl_2, and washed with water. The organic layer was dried over $NaSO_4$ and concentrated in vacuo. The crude product was purified by semipreparative RP-HPLC (Kromasil C8, 125 × 8 mm, 40–80% acetonitrile (0.1% TFA) in water (0.1% TFA) in a linear gradient over 30 min, 4 mL/min, t_R = 6.8 min)). The product fraction was lyophilized to yield **23** as a white solid (15 mg, 50%). ^{1}H NMR (360 MHz, $CDCl_3$ δ 2.00 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.08 (s, 3H, OAc), 3.44–3.35 (m, 2H), 3.93–4.02 (m, 1H, H-5), 4.07 (d, 1H, $J_{6a,6b}$ 12.5 Hz, H-6b), 4.20 (t, 1H, *J* 6.9 Hz), 4.23 (dd, 1H, $J_{6a,6b}$ 12.9 Hz, $J_{6a,5}$ 5.0 Hz, H-6a), 4.39 (m, 2H), 4.65–4.75 (m, 1H), 5.05 (dt, 1H, $J_{2,F}$ 50.0 Hz, $J_{2,3}$ 9.1 Hz, $J_{2,1}$ 9.0 Hz, H-2), 5.16 (t, 1H, $J_{4,5}$ 9.8 Hz, H-4), 5.33 (dt, 1H, $J_{3,F}$ 13.8 Hz, $J_{3,4}$ 9.3 Hz, H-3), 5.84 (dd, 1H, $J_{1,2}$ 9.0 Hz, $J_{1,F}$ 2.0 Hz, H-1), 5.96 (m, 1H), 7.27–7.34 (m, 2H), 7.36–7.42 (m, 2H), 7.54–7.60 (m, 2H), 7.65 (s, 1H), 7.72–7.78 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 20.49, 20.56, 20.61, 27.75, 47.13, 53.21, 61.38 (C-6), 67.28, 67.45 (d, *J* 7.1 Hz, C-4), 72.70 (d, *J* 19.1 Hz, C-3), 75.08 (C-5), 85.00 (d, *J* 24.3 Hz, C-1), 87.81 (d, *J* 194.1 Hz, C-2), 120.03, 122.30 (CH, triazole), 125.17 (C, triazole), 127.15, 127.80, 141.30, 143.69, 156.51, 169.43, 169.88, 170.55, 172.98; ^{19}F NMR (282 MHz, $CDCl_3$): *δ −199.84* (ddd, $J_{F,2}$ 50.4 Hz, $J_{F,3}$ 13.8 Hz, $J_{F,1}$ 2.4 Hz), ESI-MS *m*/*z* 669.2 $[M+H]^+$, 691.3 $[M+Na]^+$; HRMALDI-ToF-MS: calcd for $[M+H]^+$: 669.2208, found: *m*/*z* 669.2213; calcd for $[M+Na]^+$: 691.2028, found: *m*/*z* 691.2186.

3.10. Radiochemistry

Each ^{18}F-labeled compound was identified by retention time (t_R) on the radio-HPLC system and by co-injection of the corresponding reference compound.

3.10.1. Propargyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[^{18}F]fluoroglucopyranoside ([^{18}F]16), 2-azidoethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[^{18}F]fluoroglucopyranoside ([^{18}F]18) and 3,4,6-tri-*O*-acetyl-2-deoxy-2-[^{18}F]fluoroglucopyranosyl azide ([^{18}F]19)

For the preparation of [^{18}F]**16**, [^{18}F]**18**, or [^{18}F]**19**, respectively, a QMA-cartridge with [^{18}F]fluoride was eluted with a solution of 10 mg Kryptofix® 2.2.2, 0.1 M K_2CO_3 (17.5 μL) and 0.1 M KH_2PO_4 (17.5 μL) in 1 mL acetonitrile/water (8:2). The solution was evaporated using a stream of nitrogen at 85 °C and co-evaporated to dryness with CH_3CN (2 × 200 μL). The labeling precursor (15 μmol of **3**, **4**, **2α**, or **2β**, respectively) in anhydrous acetonitrile (450 μL) was added. This mixture was stirred for 5 min at 85 °C. The radiochemical yields of ^{18}F-labeled glucosides were determined by analytical HPLC from a sample withdrawn from the reaction mixture. t_R ([^{18}F]**16**) = 8.58 min; t_R ([^{18}F]**18**) = 9.22 min, t_R ([^{18}F]**19**) = 9.27 min (radio-HPLC: Kromasil C8, 250 × 4.6 mm, 1.5 mL/min, linear gradient from 40% to 100% acetonitrile in water (0.1% TFA) over 50 min).

For isolation of [^{18}F]**19**, the solvent was evaporated in a stream of nitrogen and the residue was re-dissolved with 500 μL acetonitrile/water (30:70) and submitted to semipreparative HPLC (Kromasil C8, 125 × 8, 4 mL/min, acetonitrile/water 30:70). The product fraction was diluted with water (1:10) and passed through a C18-cartridge (Merck, 100 mg). The cartridge was washed with water (2 mL), dried in a stream of nitrogen, and eluted with ethanol (1 mL). Starting from 370 MBq [^{18}F]fluoride, this procedure yielded 250 MBq [^{18}F]**19** after a total synthesis time of 30 min.

3.10.2. 2-Deoxy-2-[^{18}F]fluoroglucopyranosyl azide ([^{18}F]20) and (*S*)-2-{[(9*H*-Fluoren-9-yl)methoxy]carbonylamino}-3-(1-(2-deoxy-2-[^{18}F]fluoroglucopyranosyl)-1*H*-1,2,3-triazol-4-yl)propanoic acid ([^{18}F]22)

[^{18}F]**19** was dried at 60 °C in a stream of nitrogen. Subsequently, NaOH (60 mM in water containing 10% ethanol, 0.25 mL) was added. After stirring for 5 min at 60 °C, deacetylation of [^{18}F]**19** was complete and product [^{18}F]**20** was used for the click reaction in a one-pot-procedure. The solution was neutralized by addition of HCl (0.1 M, 13.5 μL), followed by addition of N^{α}-(9-fluorenylmethyloxycarbonyl)-L-2-propargylglycine (**21**, 0.2 mg, 0.6 μmol) dissolved in *tert*-butanol (200 μL), $CuSO_4$ (0.2 M, 10 μL), and sodium ascorbate (0.6 M, 10 μL). The reaction mixture was stirred for 10 min at 60 °C. The radiochemical yield of [^{18}F]**22** was 60% as determined by analytical HPLC from a sample withdrawn from the reaction mixture. t_R ([^{18}F]**20**) = 8.18 min (radio-HPLC: Rezex 8μ 8% H. Monos., 300 × 7.8 mm, 1 mL/min, methanol–water 2:98); t_R ([^{18}F]**22**) = 4.35 min (radio-HPLC: Kromasil C8, 250 × 4.6 mm, 1.5 mL/min, linear gradient from 40% to 100% acetonitrile in water (0.1% TFA) over 50 min).

3.10.3. (*S*)-2-{[(9*H*-Fluoren-9-yl)methoxy]carbonylamino}-3-(1-(3,4,6-tri-*O*-acetyl-2-deoxy-2-[^{18}F]fluoroglucopyranosyl)-1*H*-1,2,3-triazol-4-yl)propanoic acid ([^{18}F]23)

[^{18}F]**19** was dried at 60 °C in a stream of nitrogen and N^{α}-(9-fluorenylmethyloxycarbonyl)-L-2-propargylglycine (**21**, 0.2 mg, 0.6 μmol) in a 1:1 mixture of *tert*-butanol and water (200 μL) was added, followed by $CuSO_4$ (0.2 M, 10 μL) and sodium ascorbate

(0.6 M, 10 μL). The reaction mixture was stirred for 10 min at 60 °C. The radiochemical yield of [**^{18}F**]**23** was 76% as determined by analytical HPLC from a sample withdrawn from the reaction mixture. t_R ([**^{18}F**]**23**) = 13.73 min (radio-HPLC: Kromasil C8, 250 × 4.6 mm, 1.5 mL/min, linear gradient from 40% to 100% acetonitrile in water (0.1% TFA) over 50 min).

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