Efficient Synthesis of Glycosylated Asparaginic Acid Building Blocks via Click Chemistry

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Received 16 August 2007; revised 14 November 2007

Abstract: A series of per-*O*-acetyl-glycose-Fmoc-L-Asp(*O*-*t*-Bu) derivatives and *tert*-butyl per-*O*-acetyl-glycose-(*S*)-3-fluorenylmethyloxycarbamidobutyrates were prepared by copper-catalyzed 1,3-dipolar cycloaddition of fully acetylated propargyl 1-thioglycosides (gluco, galacto, manno and rhamno series) and Fmoc-L-Asp(*O*-*t*-Bu)propargyl amide with *tert*-butyl (*S*)-4-azido-3-fluorenylmethyloxycarbamidobutyrate, 2,3,4,6-tri-*O*-acetyl-glycosyl azides and ethyl 2,3,4-tri-*O*-acetyl-6-azido-6-deoxy-1-thioglycosides (gluco, galacto, manno series), respectively (click chemistry). Thus obtained orthogonally protected L-asparaginic and (*S*)-3-aminobutyric acids bearing an acetyl-protected glycose or glycoside moiety, linked through a triazole spacer, are suitable building blocks for combinatorial glycopeptide syntheses.

Key words: amino acids, azides, carbohydrates, 1,3-dipolar cycloadditions, glycosides, glycopeptides, heterocycles

Glycans and complex oligosaccharide structures play an important role in numerous biological processes. As integral constituents of most peptides, they contribute to the stability and proper folding of the latter and are involved in many highly specific biological recognition processes. In order to study those recognition processes on a molecular level, chemical synthesis of complex oligosaccharides is still the only means by which to provide sufficient amounts of pure material for this purpose. However, chemical oligosaccharide synthesis is still a challenge and usually very time consuming despite the great achievements made in this field during the past decades. It is therefore highly desirable to construct mimics of complex oligosaccharides which are easy to prepare in larger amounts, but which can still imitate the interaction of a given saccharide with its receptor. Recently, we have prepared combinatorial libraries of glycosylated glycopeptides which are thought to fulfill these requirements.[1–4]

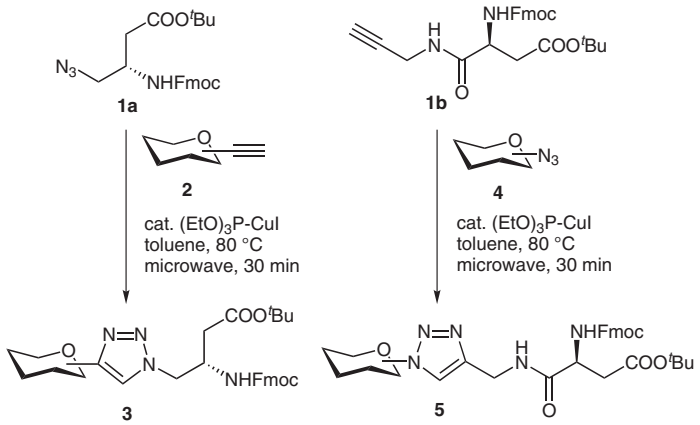
Our ongoing interest in constructing such combinatorial libraries of highly glycosylated beta-peptides that can mimic specific oligosaccharide–protein interactions, prompted us to further search for efficient routes toward glycosylated amino acid building blocks derived from asparaginic acid in which the glycon is bound to C-1 of the asparaginic acid through variable spacers. Previously, we have prepared a series of glycosylated asparaginic acid building blocks containing either simple alkyl chains[1] or amino alcohols as spacers.[2,3] Such building blocks have been shown to be well suited for combinatorial solid-phase or spot synthesis of libraries of highly glycosylated peptides, some members of which were indeed shown to behave like oligosaccharide mimics capable of specifically binding lectins.[1,4] Since mimics for complex oligosaccharides of biological origin would be ideal tools for studying carbohydrate–protein interactions, which play a major role in numerous vital biological processes, increasing the structural variability of the aforementioned glycosylated beta-peptides is desirable.

In order to achieve this goal, we wanted to further increase the structural variety of the glycosylated amino acid building blocks by introducing heterocyclic spacers that could be used in combinatorial spot syntheses of corresponding glycopeptides. We anticipated that such units would be ideal candidates provided that their synthesis and ability to link various sugar moieties with asparaginic acid and derivatives thereof was efficient and allows for a fast assembly of different sugars and linkage positions.

To this end, Huisgen's 1,3-dipolar cycloaddition of organic azides to alkynes giving 1,2,3-triazoles,[5] and its highly efficient copper-catalyzed variant (click reaction),[6–9] appeared to be promising because sugar derivatives bearing either an azido group or a terminal alkyne, as well as similarly derivatized asparaginic acids are easily accessible. Click reactions have also been widely applied to carbohydrate chemistry previously and have been shown to proceed efficiently with sugars bearing either azide or alkynyl groups.[10–18] Furthermore, 1,2,3-triazoles mimic amide moieties.[19] Thus, the efficient syntheses of suitable 1,2,3-triazole-containing glycosyl amino acid building blocks described here, is highly attractive for the preparation of glycopeptide libraries.

As asparaginic acid derivatives, we chose *tert*-butyl (*S*)-4-azido-3-fluoromethyloxycarbamidobutyrate (**1a**), which was conveniently prepared from Fmoc-Asp(*O*-*t*-Bu)OH in two steps,[20] and *tert*-butyl-protected Fmoc-asparaginic acid propargylamide **1b** (Scheme 1). The latter was prepared from Fmoc-Asp(*O*-*t*-Bu)*O*Pfp[1] and propargylamine in 98% yield.

SYNTHESIS 2008, No. 4, pp 0519–0526
Advanced online publication: 31.01.2008
DOI: 10.1055/s-2008-1032150; Art ID: T13107SS



Scheme 1

Table 1 Copper-Catalyzed 1,3-Dipolar Cycloadditions

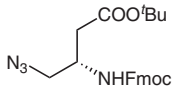
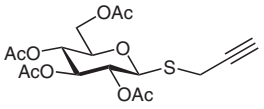
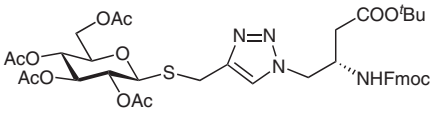
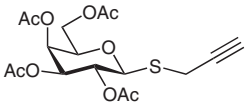
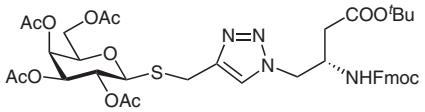
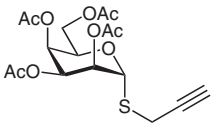
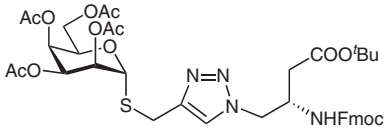
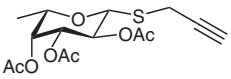
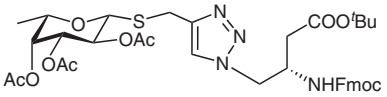
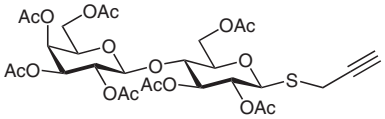
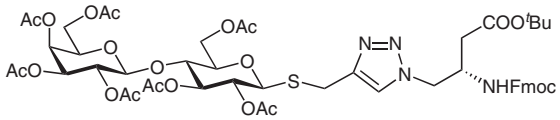
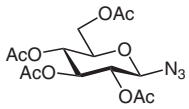
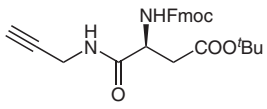
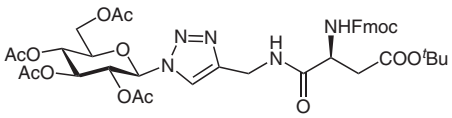
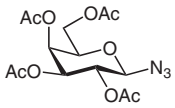
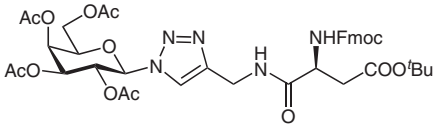
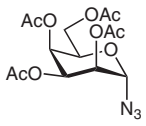
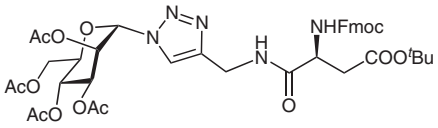
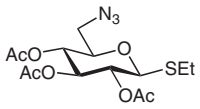
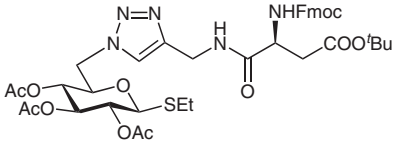
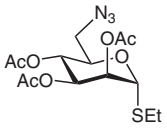
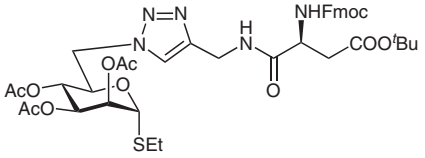
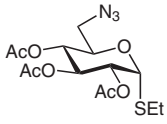
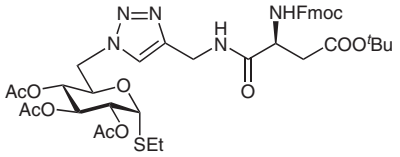
Entry	Azide	Alkyne	Product	Yield (%)
1	 **1a**	 **2a**	 **3a**	72
2	**1a**	 **2b**	 **3b**	69
3	**1a**	 **2c**	 **3c**	85
4	**1a**	 **2d**	 **3d**	76
5	**1a**	 **2e**	 **3e**	66
6	 **4a**	 **1b**	 **5a**	98
7	 **4b**	**1b**	 **5b**	94

Table 1 Copper-Catalyzed 1,3-Dipolar Cycloadditions (continued)

Entry	Azide	Alkyne	Product	Yield (%)
8	 **4c**	**1b**	 **5c**	65
9	 **4d**	**1b**	 **5d**	87
10	 **4e**	**1b**	 **5e**	91
11	 **4f**	**1b**	 **5f**	94

Both asparaginic derivatives **1** were chosen because they allow for a highly efficient strategy of automated beta-peptide preparation (Fmoc/*t*-Bu).[4] Butyrate **1a** was coupled to propargyl 1-thio-glycoside dipolarophiles **2**, affording triazole-linked glycosylated amino acids **3**, whereas asparaginic acid derivative **1b**, afforded glycosylated amino acids **5** upon copper-catalyzed coupling to glycosyl azides and 6-azido-6-deoxy-1-thioglycosides **4** (Scheme 1).

Proparyl 1-thioglycosides **2** were prepared from the corresponding per-*O*-acetylated 1-thioglycoses via alkylation of the latter with propargyl bromide. To this end, simple stirring of an equimolar amount of the corresponding acetyl-protected 1-thioglycose, propargyl bromide and diisopropylethylamine in dichloromethane afforded compounds **2** in 76–81% yield; this method was found to be superior to other procedures.[21,22] Glycosides **2**, thus prepared, were sufficiently pure to be used in the next step without further purification.

Glycosyl azides **4a**–**c** were prepared from the corresponding glycosyl bromides using standard procedures.[23] Compound **4d** has previously been prepared from 1,2,3,4-tetra-*O*-acetyl-6-azido-6-deoxy-D-glucopyranose by reacting the latter with (ethylthio)trimethylsilane (Me_3SiSEt) and zinc(II) chloride.[24] Here, we used another approach for the preparation of **4d**–**f**, starting from the corresponding ethyl 1-thioglycopyranosides in the gluco, galacto and manno series, which were first regioselectively tosylated at position 6 then acetylated.[25,26] Subsequent substitution of the tosyl group by azide in aqueous acetone, afforded compounds **4d**–**f**. However, prolonged heating of ethyl 2,3,4-tri-*O*-acetyl-6-*O*-tosyl-β-D-glucopyranoside under such conditions resulted in anomerization, giving mainly the α-linked glucoside **4f**. This anomerization during nucleophilic substitution with azide also occurred in the case of ethyl 2,3,4-tri-*O*-acetyl-6-*O*-tosyl-β-D-galactopyranoside but to a significantly lesser extent. Further investigation into the mechanism of this unusual anomerization is underway.

Table 1 summarizes the copper-catalyzed 1,3-dipolar cycloadditions between **1a** and **2** and between **1b** and **4**. All click reactions were performed at 80 °C in toluene under microwave irradiation (30 W) with 10 mol% of the $(EtO)_3PCuI$ complex as catalyst.[27] Yields of the cycloaddition were good to excellent. Microwave irradiation was necessary because reaction times were otherwise significantly longer and caused the formation of byproducts and decomposition of the educts.

All reagents were obtained commercially and were of the highest commercial quality and used without further purification. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 45 °C. Reactions were carried out under anhydrous conditions using dry glassware within an argon atmosphere in anhydrous, freshly distilled solvents, unless otherwise noted. Click reactions were performed in a microwave reactor CEM Discover at 80 °C and 20–30 W. Yields refer to chromatographically and spectroscopically (^1H NMR, ^{13}C NMR) homogeneous materials, unless otherwise stated. Analytical thin layer chromatography

(TLC) was performed on glass plates precoated with a 0.25 mm thickness of Macherey and Nagel POLYGRAM® SIL G/UV254 with UV light as the visualizing agent and 5% H_2SO_4 in EtOH solution and heat as detecting agents. Silica gel 60 (particle size 0.040–0.063 mm) was used for flash chromatography (PE = petroleum ether). NMR spectra were recorded on a Bruker Avance 400 spectrometer (400 MHz for ^{1}H, and 100 MHz for ^{13}C NMR spectra) and calibrated using the $CDCl_3$ as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, mc = centered multiplet, br = broad. Melting points were determined on a Büchi B-540 instrument and are uncorrected. Specific rotations were recorded with a Perkin–Elmer polarimeter model 341 at 589 nm and 20 °C in a quartz cuvette of 10 cm length. Elemental analysis was performed on Hekatech GmbH Euro EA 3000 analyzer.

tert-Butyl N^2-[(9*H*-Fluoren-9-ylmethoxy)carbonyl]-*N*-prop-2-yn-1-yl-L-asparaginate (1b)

tert-Butyl *N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-1-pentafluorophenyl L-aspartate[1] (2.9 g, 5.0 mmol) was dissolved in EtOAc (30 mL) and stirred with a slight excess of 2-propynylamine (0.39 g, 7.0 mmol) at 20 °C for 4 h. The mixture was concentrated and the residue was purified by column chromatography (EtOAc–PE, 1:3) to furnish **1b**.

Yield: 2.2 g (98%); colorless amorphous solid; $[\alpha]_D^{20}$ +16.5 (*c* 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 7.76 (d, 2 H, Fmoc), 7.58 (d, 2 H, Fmoc), 7.40 (dd, 2 H, Fmoc), 7.31 (dd, 2 H, Fmoc), 6.73 (s, 1 H, NH), 5.96 (d, 1 H, Fmoc-NH), 4.52 (s, 1 H, CH), 4.48–4.18 (m, 2 H, Fmoc-CH_2), 4.21 (t, 1 H, CH-Fmoc), 4.03 (dt, 2 H, CH_2), 2.90 (dd, 1 H, CH_2), 2.60 (dd, 1 H, CH_2), 2.20 (s, 1 H, CH), 1.45 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR ($CDCl_3$): δ = 171.1 (CONH), 170.2 (CO_2-*t*-Bu), 156.1 (Fmoc-CO), 143.7 (2 × C, Fmoc), 141.4 (2 × C, Fmoc), 127.8 (2 × C, Fmoc), 127.2, 127.1 (Fmoc), 125.0, 125.1 (Fmoc), 120.1 (2 × C, Fmoc), 82.1 [*C*(CH_3)$_3$], 79.1 (*C*≡CH), 71.8 (C≡*C*H), 67.2 (Fmoc-CH_2), 51.1 (CH), 47.2 (Fmoc-CH), 37.4 (CH_2), 29.4 (CH_2), 28.1 [C(*C*H_3)$_3$].

Anal. Calcd for $C_{26}H_{28}N_2O_5$: C, 69.63; H, 6.29; N, 6.25. Found: C, 69.56; H, 6.49; N, 6.13.

Synthesis of Propargyl 1-Thioglycosides (2a–e); General Procedure

A solution of peracetylated 1-thioglycose (4.0 mmol), DIPEA (683 μL, 4.0 mmol) and 2-propynyl bromide (80% in toluene, 431 μL, 4.0 mmol) in CH_2Cl_2 (20 mL) was stirred at r.t. for 65 min. EtOAc (20 mL) was added and the precipitated salts were filtered off. The filtrate was concentrated and the residue was dried in vacuo.

Propargyl 2,3,4,6-Tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (2a)

According to the general procedure, 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose[28] (1.46 g) gave **2a** (1.33 g, 83%).

^{1}H NMR ($CDCl_3$): δ = 5.22 (t, *J* = 9.4 Hz, 1 H, H-3), 5.06–5.02 (m, 2 H, H-4, H-2), 4.73 (d, *J* = 10.1 Hz, 1 H, H-1), 4.22 (mc, 1 H, H-6a), 4.10 (mc, 1 H, H-6b), 3.71 (mc, 1 H, H-5), 3.52, 3.26 (2 × d, *J* = 16.7 Hz, 2 H, CH_2), 2.25 (t, 1 H, CH), 2.04, 2.02, 1.98, 1.97 (4 × s, 12 H, CH_3-Acetyl).

^{13}C NMR ($CDCl_3$): δ = 170.7, 170.2, 169.5, 169.4 (CH_3*C*O), 82.1 (C-1), 78.7 (CH_2-*C*), 76.0 (C-5), 73.8 (C-3), 72.0 (C-*C*H), 69.8 (C-4), 68.3 (C-2), 62.0 (C-6), 20.8, 20.7, 20.7, 20.6 (CH_3), 17.6 (SCH_2).

FAB MS: *m*/*z* = 403.1 [M + H]$^+$.

Propargyl 2,3,4,6-Tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (2b)

According to the general procedure, 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranose[28] (1.46 g) gave **2b** (1.22 g, 76%).

^{1}H NMR ($CDCl_3$): δ = 5.43 (d, *J* = 3.3 Hz, 1 H, H-4), 5.6 (t, *J* = 9.9 Hz, 1 H, H-2), 5.06 (mc, 1 H, H-3), 4.74 (d, *J* = 10.1 Hz, 1 H, H-1), 4.13 (mc, 2 H, H-6a, 6b), 3.95 (t, *J* = 6.6 Hz, 1 H, H-5), 3.56, 3.29 (2 × d, *J* = 16.7 Hz, 2 H, CH_2-C), 2.29 (t, 1 H, C-CH), 2.15, 2.06, 2.02, 1.98 (4 × s, 12 H, CH_3CO).

^{13}C NMR ($CDCl_3$): δ = 170.5, 170.3, 170.2, 169.8 (CH_3-*C*O), 82.6 (C-1), 78.8 (CH_2-*C*), 74.7 (C-3), 72.0 (C-*C*H), 71.9 (C-5), 67.3 (C-2), 67.2 (C-4), 61.4 (C-6), 20.9, 20.8, 20.7 (*C*H_3CO), 17.7 (SCH_2).

FAB MS: *m*/*z* = 403.0 [M + H]$^+$.

Propargyl 2,3,4,6-Tetra-*O*-acetyl-1-thio-α-D-mannopyranoside (2c)

According to the general procedure, 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranose[29] (1.46 g) gave **2c** (1.27 g, 79%).

^{1}H NMR (CDCl3): δ = 5.45, 5.38, 5.24 (3 × mc, 3 H, H-2, H-3, H-4), 5.20 (d, *J* = 6.1 Hz, 1 H, H-1), 4.34 (mc, 2 H, H-6), 4.10 (m, 1 H, H-5), 3.43, 3.25 (2 × d, *J* = 16.7 Hz, 2 H, CH_2-C), 2.26 (t, 1 H, C-CH), 2.04, 2.02, 1.98, 1.97 (4 × s, 12 H, CH_3CO).

^{13}C NMR ($CDCl_3$): δ = 170.7, 170.2, 169.5, 169.4 (CH_3-*C*O), 81.5 (C-1), 78.6 (CH_2-*C*), 72.0 (C-*C*H), 70.5 (C-5), 69.7 (C-4), 69.4 (C-2), 66.3 (C-3), 62.4 (C-6), 20.8, 20.7, 20.7, 20.6 (*C*H_3CO), 17.6 (SCH_2).

FAB MS: *m*/*z* = 403.3 [M + H]$^+$.

Propargyl 2,3,4-Tri-*O*-acetyl-1-thio-β-L-fucopyranoside (2d)

According to the general procedure, 2,3,4-tri-*O*-acetyl-1-thio-β-L-fucopyranose[30] (1.25 g) gave **2d** (1.20 g, 87%).

$[\alpha]_D^{20}$ –71.6 (*c* 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 5.25 (mc, 1 H, H-4), 5.18 (d, *J* = 10.1 Hz, 1 H, H-2), 5.06 (dd, *J* = 9.9, 3.3 Hz, 1 H, H-3), 4.68 (d, *J* = 9.8 Hz, 1 H, H-1), 3.83 (q, *J* = 6.5 Hz, 1 H, H-5), 3.54, 3.27 (2 × d, *J* = 16.6 Hz, 2 H, CH_2-C), 2.23 (t, *J* = 2.6 Hz, 1 H, C-CH), 2.14, 2.03, 1.95 (4 × s, 12 H, CH_3CO), 1.20 (m, 3 H, CH_3, H-6).

^{13}C NMR ($CDCl_3$): δ = 170.7, 170.1, 169.8 (CH_3*C*O), 82.3 (C-1), 79.1 (CH_2-*C*), 73.8 (C-3), 72.4 (C-*C*H), 71.7 (C-4), 70.5 (C-2), 67.3 (C-5), 20.8, 20.7, 20.6 (*C*H_3CO), 17.5 (SCH_2), 16.4 (C-6).

FAB MS: *m*/*z* = 345.1 [M + H]$^+$.

Anal. Calcd for $C_{15}H_{20}O_7S$: C, 52.31; H, 5.85; S, 9.31. Found: C, 52.29; H, 5.95; S, 8.76.

Propargyl 2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-1-thio-β-D-glucopyranoside (2e)

According to the general procedure, hepta-*O*-acetyl-1-thio-β-D-lactopyranose[31,32] (2.61 g) gave **2c** (2.24 g, 81%).

^{1}H NMR ($CDCl_3$): δ = 5.32 (s, 1 H, H-4′), 5.23 (t, *J* = 9.1 Hz, 1 H, H-2′), 5.08 (br t, *J* = 8.8 Hz, 1 H, H-3′), 4.94 (mc, 2 H, H-3, H-2), 4.74 (d, *J* = 10.1 Hz, 1 H, H-1′), 4.47 (mc, 2 H, H-1, H-6a), 4.10 (mc, 3 H, H-6a′, H-6b, H-6b′), 3.86 (br t, *J* = 6.6 Hz, 1 H, H-5′), 3.79 (br t, *J* = 9.6, 9.3 Hz, 1 H, H-4), 3.62 (mc, 1 H, H-5), 3.51, 3.24 (2 × d, *J* = 16.7 Hz, 2 H, CH_2-C), 2.25 (t, 1 H, C-C*H*), 2.13, 2.10, 2.04, 2.03, 2.02, 1.94 (6 × s, 21 H, CH_3CO).

^{13}C NMR ($CDCl_3$): δ = 170.4, 170.2, 170.1, 169.8, 169.2, 169.1(CH_3-*C*O), 101.1 (C-1′), 81.8 (C-1), 78.8 (CH_2-*C*), 76.4 (C-4), 76.2 (C-5), 73.7 (C-3), 72.0 (C-*C*H), 71.0 (C-3′), 70.8 (C-2), 70.2 (C-5′), 69.0 (C-2′), 66.7 (C-4′), 62.1 (C-6′), 61.0 (C-6), 21.2, 21.0, 20.9, 20.8, 20.7, 20.6 (*C*H_3CO), 17.6 (SCH_2).

FAB MS: *m*/*z* = 691.3 [M + H]$^+$.

Ethyl 2,3,4-Tri-*O*-acetyl-6-azido-6-deoxy-1-thio-β-D-glucopyranoside (4d)

Ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside[33] (3.9 g, 10.0 mmol) was deacetylated, regioselectively tosylated at position C-6 and reacetylated as previously described[23] to furnish ethyl 2,3,4-tri-*O*-acetyl-6-*O*-tosyl-1-thio-β-D-glucopyranoside[26] (3.8 g, 75%). The latter was dissolved in aq acetone (25 mL), NaN_3 (3.9 g, 60 mmol) was added and the mixture was stirred at 65 °C for 22 h. Column chromatography (EtOAc–PE, 1:3) afforded **4d** (1.54 g, 41%). Spectroscopic data were in accordance with those published.[24]

Ethyl 2,3,4-Tri-*O*-acetyl-6-azido-6-deoxy-1-thio-α-D-glucopyranoside (4f)

As described for **4d** above, treatment of ethyl 2,3,4-tri-*O*-acetyl-6-*O*-tosyl-1-thio-β-D-glucopyranoside (2.5 g, 5.0 mmol) with NaN_3 (3.9 g) in aq acetone (25 mL) at 65 °C for 3 d, afforded **4f** (1.1 g, 56%).

$[\alpha]_D^{20}$ +196.2 (*c* 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 5.69 (d, *J* = 5.8 Hz, 1 H, H-1), 5.35 (t, 1 H, H-3), 4.99 (dd, 1 H, H-2), 4.96 (t, 1 H, H-4), 4.42–4.36 (m, 1 H, H-5), 3.36 (dd, 1 H, H-6a), 3.28 (dd, 1 H, H-6b), 2.66–2.52 (m, 2 H, S*CH*$_2$CH$_3$), 2.05, 2.03, 2.00 (3 × s, 9 H, CH_3), 1.28 (t, 3 H, SCH$_2$*CH*$_3$).

^{13}C NMR ($CDCl_3$): δ = 169.8, 170.0 (3 × C, CH_3*C*O), 81.4 (C-1), 70.8 (C-5), 70.4 (C-3), 69.9 (C-2), 68.9 (C-4), 51.1 (C-6), 24.2 (S*C*H$_2$CH$_3$), 20.8, 20.7 (3 × C, CH_3), 14.6 (SCH$_2$*C*H$_3$).

Anal. Calcd for $C_{14}H_{21}N_3O_7S$: C, 44.79; H, 5.64; N, 11.19; S, 8.54. Found: C, 44.58; H, 5.99; N, 10.72; S, 8.43.

Ethyl 2,3,4-Tri-*O*-acetyl-6-azido-6-deoxy-1-thio-α-D-mannopyranoside (4e)

Ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranoside[34] (3.9 g, 10 mmol) was deacetylated, regioselectively tosylated at position C-6 and acetylated as described above (see **4d**), to furnish ethyl 2,3,4-tri-*O*-acetyl-6-*O*-tosyl-1-thio-α-D-mannopyranoside[25] (3.6 g, 72%). The latter was dissolved in aq acetone (25 mL), NaN_3 (3.9 g, 60 mmol) was added and the mixture was stirred at 65 °C for 48 h. Workup as described for compound **4d** afforded **4e** (1.73 g, 46%).

$[\alpha]_D^{20}$ +94.6 (*c* 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 5.31–5.29 (m, 1 H, H-3), 5.26 (s, 1 H, H-1), 5.23–5.21 (m, 2 H, H-4, H-2), 4.35–4.28 (m, 1 H, H-5), 3.37 (dd, 1 H, H-6a), 3.26 (dd, 1 H, H-6b), 2.73–2.57 (m, 2 H, S*CH*$_2$CH$_3$), 2.13, 2.02, 1.95 (3 × s, 9 H, CH_3), 1.29 (t, 3 H, SCH$_2$*CH*$_3$).

^{13}C NMR ($CDCl_3$): δ = 170.0, 169.7 (3 × C, CH_3*C*O), 81.9 (C-1), 71.1 (C-3), 70.4 (C-5), 69.3 (C-2), 67.4 (C-4), 51.1 (C-6), 25.4 (S*C*H$_2$CH$_3$), 20.9, 20.6 (3 × C, CH_3), 14.6 (SCH$_2$*C*H$_3$).

ESI MS: *m*/*z* = 376.4 $[M + H]^+$.

Click Reactions; General Procedure

Azide **1a** or **4** (1.0 equiv), alkyne **1b** or **2** (1.0 equiv), $(EtO)_3$PCuI (0.1 equiv) and diisopropyl ethyl amine (2.0 equiv) were dissolved in toluene, placed in a microwave vial and exposed to 20–30 W microwave irradiation at 80 °C for 30 min. After cooling to r.t., the solution was concentrated and the residue was purified by column chromatography (EtOAc) to afford the triazoles **3** and **5**.

***tert*-Butyl (3*S*)-3-{[(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino}-4-(4-{[(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thio]methyl}-1*H*-1,2,3-triazol-1-yl)butanoate (3a)**

According to the general procedure, **1a**[20] (250 mg, 0.6 mmol), **2a** (242 mg, 0.6 mmol), DIPEA (310 μL, 1.8 mmol), and $(EtO)_3$PCuI (24 mg, 0.06 mmol) in toluene (5 mL) afforded **3a**.

Yield: 0.36 g (72%); colorless amorphous solid; $[\alpha]_D^{20}$ –19.6 (*c* 3.5, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 7.73, 7.55 (2 × d, *J* = 7.1 Hz, 2 H, Fmoc-Ar), 7.41 (s, 1 H, CH-triazole), 7.37, 7.28 (2 × t, *J* = 7.3 Hz, 2 H, Fmoc-Ar), 5.67 (br d, *J* = 6.6 Hz, 1 H, NH), 5.20 (t, *J* = 9.4 Hz, 1 H, H-3), 5.09 (t, *J* = 9.6 Hz, 1 H, H-4), 5.00 (t, *J* = 9.6 Hz, 1 H, H-2), 4.60 (d, *J* = 10.1 Hz, 1 H, H-1), 4.57 (mc, 2 H, CH$_2$C*H*NH), 4.38 (mc, 2 H, CH_2-Fmoc), 4.20 (mc, 1 H, CH-Fmoc), 4.22 (mc, 1 H, H-6a), 4.10 (mc, 1 H, H-6b), 4.09 (mc, 2 H, C*H*$_2$CHNH), 4.04–3.84 (m, 2 H, SCH_2), 3.69 (mc, 1 H, H-5), 2.45 (br d, 2 H, C*H*$_2$CO$_2$-*t*-Bu), 2.06, 2.03, 1.98, 1.98 (4 × s, 12 H, CH_3CO), 1.45 [s, 9 H, $(CH_3)_3$C].

^{13}C NMR ($CDCl_3$): δ = 170.8, 170.2, 169.6, 169.5 (CH_3*C*O), 155.7 (NHCOO), 143.8, 141.4, 127.9, 127.2, 125.1, 120.1 (Fmoc-Ar), 144.9 (triazole), 123.4 (triazole-CH), 82.7 [*C*(CH$_3$)$_3$], 82.1 (C-1), 76.0 (C-5), 73.9 (C-3), 70.2 (C-4), 68.3 (C-2), 66.9 (CH_2-Fmoc), 61.9 (C-6), 52.2 (CH*C*H$_2$), 48.6 (CHNH), 47.3 (CH-Fmoc), 37.0 (*C*H$_2$COO-*t*-Bu), 28.2 [C(*C*H$_3$)$_3$], 24.3 (CH_2S), 20.9, 20.8, 20.7, 20.7 (*C*H$_3$CO).

Anal. Calcd for $C_{40}H_{48}N_4O_{13}S$: C, 58.24; H, 5.87; N, 6.79; S, 3.89. Found: C, 58.21; H, 5.90; N, 6.68; S, 3.58.

***tert*-Butyl (3*S*)-3-{[(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino}-4-(4-{[(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)thio]methyl}-1*H*-1,2,3-triazol-1-yl)butanoate (3b)**

According to the general procedure, **1a**[20] (250 mg, 0.6 mmol), **2b** (242 mg, 0.6 mmol), DIPEA (310 μL, 1.8 mmol) and $(EtO)_3$PCuI (24 mg, 0.06 mmol) in toluene (5 mL) afforded **3b**.

Yield: 0.34 g (69%); colorless amorphous solid; $[\alpha]_D^{20}$ –19.2 (*c* 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 7.76, 7.56 (2 × d, *J* = 7.1 Hz, 2 H, Fmoc-Ar), 7.40 (s, 1 H, CH-triazole), 7.37–7.32 (m, 2 H, Fmoc-Ar), 5.62 (br d, *J* = 6.6 Hz, 1 H, NH), 5.42 (br d, *J* = 3.3 Hz, 1 H, H-4), 5.24 (t, *J* = 9.9 Hz, 1 H, H-2), 5.04 (mc, 1 H, H-3), 4.58 (mc, 2 H, H-1, CH$_2$C*H*NH), 4.41 (mc, 2 H, CH_2-Fmoc), 4.35 (mc, 1 H, CH-Fmoc), 4.21 (mc, 1 H, H-6a), 4.11 (mc, 1 H, H-6b), 4.09 (mc, 2 H, CH_2-triazole), 4.04–3.92 (m, 3 H, SCH_2), 3.88 (mc, 1 H, H-5), 2.46 (br d, 2 H, C*H*$_2$COO-*t*-Bu), 2.15, 2.06, 2.02, 1.98 (4 × s, 12 H, CH_3CO), 1.45 [s, 9 H, $(CH_3)_3$C].

^{13}C NMR ($CDCl_3$): δ = 170.8, 170.2, 169.6 (CH_3*C*O), 155.7 (NHCOO), 145.1, 143.8, 127.9, 127.2, 125.1, 120.2 (Fmoc-Ar), 141.4 (triazole-Ar), 123.3 (triazole-Ar-CH), 82.5 [*C*(CH$_3$)$_3$], 82.0 (C-1), 77.3 (CH_2), 73.3 (C-3), 72.3 (C-5), 70.5 (C-2), 67.6 (C-4), 66.9 (CH_2-Fmoc), 61.4 (C-6), 52.3 (CH_2-triazole), 48.6 (CHNH), 47.3 (CH-Fmoc), 37.0 (*C*H$_2$COO-*t*-Bu), 28.2 [C(*C*H$_3$)$_3$], 24.0 (CH_2S), 21.2, 20.8, 20.7 (*C*H$_3$CO).

Anal. Calcd for $C_{40}H_{48}N_4O_{13}S$: C, 58.24; H, 5.87; N, 6.79; S, 3.89. Found: C, 58.13; H, 5.99; N, 6.43; S, 3.64.

***tert*-Butyl (3*S*)-3-{[(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino}-4-(4-{[(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)thio]methyl}-1*H*-1,2,3-triazol-1-yl)butanoate (3c)**

According to the general procedure, **1a**[20] (250 mg, 0.6 mmol), **2c** (242 mg, 0.6 mmol), DIPEA (310 μL, 1.8 mmol) and $(EtO)_3$PCuI (24 mg, 0.06 mmol) in toluene (5 mL) afforded **3c**.

Yield: 0.42 g (85%); colorless oil; $[\alpha]_D^{20}$ +70.9 (*c* 7.2, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 7.73, 7.55 (2 × d, 2 H, *J* = 7.1 Hz, Fmoc-Ar), 7.41 (s, 1 H, triazole), 7.37, 7.28 (2 × t, *J* = 7.3 Hz, 2 H, Fmoc-Ar), 5.67 (br d, *J* = 6.6 Hz, 1 H, NH), 5.32 (t, *J* = 9.4 Hz, 1 H, H-2), 5.24–5.22 (m, 2 H, H-3, H-4), 4.57 (mc, 2 H, CH$_2$C*H*NH), 4.38–4.25 (m, 4 H, CH_2-Fmoc, H-1, H-6a), 4.18 (mc, 1 H, CH-Fmoc), 4.10 (mc, 1 H, H-6b), 4.09 (mc, 2 H, CH_2-triazole), 4.04–3.84 (m, 3 H, SCH_2), 3.69 (mc, 1 H, H-5), 2.45 (br d, 2 H, C*H*$_2$COO-*t*-Bu), 2.06, 2.03, 1.98, 1.98 (4 × s, 12 H, CH_3CO), 1.45 [s, 9 H, $(CH_3)_3$C].

^{13}C NMR ($CDCl_3$): δ = 170.8, 170.2, 169.6, 169.5 (CH_3CO), 155.7 (NHCOO), 143.8, 141.4, 127.9, 127.2, 125.1, 120.1 (Fmoc-Ar), 144.9 (triazole), 123.4 (triazole-CH), 81.9 [$C(CH_3)_3$], 81.5 (C-1), 71.4 (C-5), 69.6 (C-3), 69.5 (CH_2-Fmoc), 66.3 (C-2), 62.4 (C-6), 52.3 (CHCH_2-triazole), 48.5 (CHNH), 47.4 (CH-Fmoc), 36.8 (CH_2COO-*t*-Bu), 28.2 [C(CH_3)$_3$], 25.0 (CH_2S), 20.9, 20.8, 20.7, 20.7 (CH_3CO).

Anal. Calcd for $C_{40}H_{48}N_4O_{13}S$: C, 58.24; H, 5.87; N, 6.79; S, 3.89. Found: C, 57.81; H, 5.89; N, 6.40; S, 3.78.

***tert*-Butyl (3*S*)-3-{[(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino}-4-(4-{[(2,3,4,6-tetra-*O*-acetyl-β-L-fucopyranosyl)thio]methyl}-1*H*-1,2,3-triazol-1-yl)butanoate (3d)**

According to the general procedure, **1a**[20] (250 mg, 0.6 mmol), **2d** (207 mg, 0.6 mmol), DIPEA (310 μL, 1.8 mmol) and $(EtO)_3PCuI$ (24 mg, 0.06 mmol) in toluene (5 mL) afforded **3d**.

Yield: 0.35 g (76%); colorless oil; $[\alpha]_D^{20}$ +18.3 (*c* 3.2, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 7.76, 7.57 (2 × d, *J* = 7.1 Hz, 2 H, Fmoc-Ar), 7.40 (s, 1 H, triazole), 7.38, 7.31 (2 × t, *J* = 7.3 Hz, 2 H, Fmoc-Ar), 5.63 (br d, *J* = 6.6 Hz, 1 H, NH), 5.26 (mc, 1 H, H-4), 5.18 (d, *J* = 10.1 Hz, 1 H, H-2), 5.03 (dd, *J* = 9.9, 3.3 Hz, 1 H, H-3), 4.54 (d, *J* = 9.8 Hz, 1 H, H-1), 4.54 (mc, 2 H, CH_2CHNH), 4.40 (mc, 2 H, CH_2-Fmoc), 4.19 (mc, 1 H, CH-Fmoc), 3.94 (d, *J* = 16.6 Hz, 2 H, CH_2S), 3.83 (q, *J* = 6.5 Hz, 1 H, H-5), 2.43 (br d, 2 H, CH_2COO-*t*-Bu), 2.17, 2.03, 1.95 (3 × s, 12 H, CH_3CO), 1.45 [s, 9 H, $(CH_3)_3C$], 1.20 (s, 3 H, H-6).

^{13}C NMR ($CDCl_3$): δ = 170.8, 170.2, 169.9 (CH_3CO), 155.7 (NHCOO), 145.1, 143.8, 127.9, 127.2, 125.1, 120.2 (Fmoc-Ar), 141.4 (triazole-Ar), 123.3 (triazole-Ar-CH), 82.5 [$C(CH_3)_3$], 82.1 (C-1), 73.8 (C-3), 72.4 (C-4), 70.6 (C-2), 67.6 (C-5), 66.9 (CH_2-Fmoc), 52.3 (CHCH_2-triazole), 48.4 (CHNH), 47.3 (CH-Fmoc), 37.0 (CH_2COO-*t*-Bu), 28.2 [C(CH_3)$_3$], 24.0 (CH_2S), 21.2, 20.9, 20.7 (CH_3CO), 16.5 (C-6).

Anal. Calcd for $C_{38}H_{46}N_4O_{11}S$: C, 59.52; H, 6.05; N, 7.31; S, 4.18. Found: C, 59.25; H, 6.07; N, 7.12; S, 3.98.

***tert*-Butyl (3*S*)-3-{[(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino}-4-[(4-{[2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl]thio}methyl)-1*H*-1,2,3-triazol-1-yl]butanoate (3e)**

According to the general procedure, **1a**[20] (250 mg, 0.6 mmol), **2e** (415 mg, 0.6 mmol), DIPEA (310 μL, 1.8 mmol) and $(EtO)_3PCuI$ (24 mg, 0.06 mmol) in toluene (5 mL) afforded **3e**.

Yield: 0.44 g (66%); colorless amorphous solid; $[\alpha]_D^{20}$ +55.3 (*c* 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 7.76, 7.57 (2 × d, *J* = 7.1 Hz, 2 H, Fmoc-Ar), 7.40 (s, 1 H, CH-triazole), 7.38, 7.31 (2 × t, *J* = 7.3 Hz, 2 H, Fmoc-Ar), 5.70 (br d, *J* = 6.6 Hz, 1 H, NH), 5.33 (br s, 1 H, H-4′), 5.20 (t, *J* = 9.1 Hz, 1 H, H-2′), 5.09 (br t, *J* = 8.8 Hz, 1 H, H-3′), 4.92 (mc, 2 H, H-3, H-2), 4.57 (mc, 3 H, H-1′, CH_2CHNH), 4.47 (mc, 2 H, H-1, H-6a), 4.40 (mc, 2 H, CH_2-Fmoc), 4.19 (mc, 1 H, CH-Fmoc), 4.10 (mc, 3 H, H-6a′, H-6b, H-6b′), 3.85 (mc, 2 H, CH_2S), 3.82 (mc, 1 H, H-5′), 3.79 (mc, 1 H, H-4), 3.62 (mc, 1 H, H-5), 2.47 (br d, 2 H, CH_2COO-*t*-Bu), 2.15, 2.13, 2.11, 2.04, 2.02, 1.98, 1.96 (7 × s, 21 H, CH_3CO), 1.44 [s, 9 H, $(CH_3)_3C$].

^{13}C NMR ($CDCl_3$): δ = 170.6, 170.4, 170.3, 170.2, 169.9, 169.8, 169.1 (CH_3CO), 155.7 (NHCOO), 143.8, 141.4, 127.9, 127.2, 125.1, 120.2 (Fmoc-Ar), 141.4 (triazole-*C*), 123.3 (triazole-*C*H), 101.2 (C-1′), 82.5 [$C(CH_3)_3$], 82.0 (C-1), 77.3 (CH_2), 76.6 (C-4), 76.1 (C-5), 73.8 (C-3), 72.0 (CH), 71.0 (C-3′), 70.8 (C-2), 70.2 (C-5′), 69.1 (C-2′), 66.9 (CH_2-Fmoc), 66.7 (C-4′), 62.0 (C-6′), 60.9 (C-6), 52.2 (CHCH_2-triazole), 48.4 (CHNH), 47.3 (CH-Fmoc), 37.0 (CH_2COO-*t*-Bu), 28.2 [C(CH_3)$_3$], 24.0 (CH_2S), 21.2, 21.0, 20.9, 20.8, 20.7, 20.6 (CH_3CO).

Anal. Calcd for $C_{52}H_{64}N_4O_{21}S$: C, 56.11; H, 5.80; N, 5.03; S, 2.88. Found: C, 56.11; H, 5.83; N, 5.58; S, 2.89.

***tert*-Butyl N^2-[(9*H*-Fluoren-9-ylmethoxy)carbonyl]-*N*-{[1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}-L-α-asparaginate (5a)**

According to the general procedure, **4a**[23] (224 mg, 0.6 mmol), **1b** (269 mg, 0.6 mmol), DIPEA (310 μL, 1.8 mmol) and $(EtO)_3PCuI$ (24 mg, 0.06 mmol) in toluene (5 mL) afforded **5a**.

Yield: 482 mg (98%); amorphous colorless solid; $[\alpha]_D^{20}$ –13.6 (*c* 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 7.79 (s, 1 H, triazole), 7.76–7.74 (d, 2 H, Fmoc), 7.58–7.56 (d, 2 H, Fmoc), 7.41–7.37 (t, 2 H, Fmoc), 7.32–7.29 (m, 2 H, Fmoc), 7.04 (s, 1 H, CH_2N*H*), 5.94–5.92 (d, 1 H, Fmoc-NH), 5.82–5.80 (d, *J* = 5.8 Hz, 1 H, H-1), 5.40–5.39 (d, 2 H, H-3, H-2), 5.23–5.21 (d, 1 H, H-4), 4.53 (s, 3 H, CH, triazole-CH_2), 4.42 (s, 2 H, Fmoc-CH_2), 4.20 (t, 1 H, Fmoc-CH), 4.26 (dd, 1 H, H-6b), 4.12 (d, 1 H, H-6a), 3.97 (d, 1 H, H-5), 2.91 (d, 1 H, CH_2), 2.63 (dd, 1 H, CH_2), 2.05 (s, 6 H, CH_3CO), 1.99 (s, 3 H, CH_3CO), 1.83 (s, 3 H, CH_3CO), 1.42 [s, 9 H, $(CH_3)_3C$].

^{13}C NMR ($CDCl_3$): δ = 171.1 (CONH), 170.7 (*C*OO-*t*-Bu), 170.6, 168.9 (4 × C, COO), 156.1 (Fmoc-CO), 143.7 (2 × C, Fmoc), 141.4 (triazole), 141.4 (2 × C, Fmoc), 127.1, 127.8 (4 × C, Fmoc), 125.1 (2 × C, Fmoc), 125.1 (triazole), 120.1 (2 × C, Fmoc), 85.8 (C-1), 82.0 [$C(CH_3)_3$], 75.2 (C-5), 72.6 (C-3), 70.4 (C-2), 67.7 (C-4), 67.2 (Fmoc-CH_2), 61.6 (C-6), 51.2 (CH), 47.2 (Fmoc-CH), 37.4 (CH_2), 35.2 (triazol-CH_2), 28.1 [C(CH_3)$_3$], 20.2, 20.7 (4 × C, CH_3).

Anal. Calcd for $C_{40}H_{47}N_5O_{14}$: C, 58.46; H, 5.76; N, 8.52. Found: C, 58.54; H, 5.73; N, 8.34.

FAB MS: *m*/*z* = 822.3 $[M + H]^+$.

***tert*-Butyl N^2-[(9*H*-Fluoren-9-ylmethoxy)carbonyl]-*N*-{[1-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}-L-α-asparaginate (5b)**

According to the general procedure, **4a**[23] (224 mg, 0.6 mmol), **1b** (269 mg, 0.6 mmol), DIPEA (310 μL, 1.8 mmol) and $(EtO)_3PCuI$ (24 mg, 0.06 mmol) in toluene (5 mL) afforded **5a**.

Yield: 463 mg (94%); amorphous colorless solid; $[\alpha]_D^{20}$ +21 (*c* 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 7.83 (s, 1 H, triazole), 7.75 (d, 2 H, Fmoc), 7.57 (d, 2 H, Fmoc), 7.39 (dd, 2 H, Fmoc), 7.31–7.27 (m, 2 H, Fmoc), 7.11 (s, 1 H, CH_2N*H*), 5.97 (d, 1 H, Fmoc-NH), 5.79 (d, *J* = 9.0 Hz, 1 H, H-1), 5.54–5.50 (m, 2 H, H-4, H-2), 5.24 (dd, 1 H, H-3), 4.54 (d, 3 H, CH, triazole-CH_2), 4.42 (d, 2 H, Fmoc-CH_2), 4.22–4.16 (m, 3 H, H-6b, H-5, Fmoc-CH), 4.12–4.08 (m, 1 H, H-6a), 2.91 (dd, 1 H, CH_2), 2.65 (dd, 1 H, CH_2), 2.21 (s, 3 H, CH_3), 2.02 (s, 3 H, CH_3), 1.99 (s, 3 H, CH_3), 1.84 (s, 3 H, CH_3), 1.42 [s, 9 H, $(CH_3)_3C$].

^{13}C NMR ($CDCl_3$): δ = 171.0 (CONH), 170.6 (*C*OO-*t*-Bu), 170.3, 169.0 (4 × C, COO), 156.1 (Fmoc-CO), 145.2 (triazole), 143.7 (2 × C, Fmoc), 141.3 (2 × C, Fmoc), 127.8, 127.1 (4 × C, Fmoc), 125.1, 125.0 (2 × C, Fmoc), 121.1 (CH-triazol), 120.1 (2 × C, Fmoc), 86.3 (C-1), 81.9 [$C(CH_3)_3$], 74.0 (C-5), 70.8 (C-3), 67.9 (C-4), 67.2 (Fmoc-CH_2), 66.8 (C-2), 61.2 (C-6), 51.2 (CH), 47.2 (Fmoc-CH), 37.4 (CH_2), 35.1 (triazole-CH_2), 28.0 [C(CH_3)$_3$], 20.7, 20.2 (4 × C, CH_3).

Anal. Calcd for $C_{40}H_{47}N_5O_{14}$: C, 58.46; H, 5.76; N, 8.52. Found: C, 58.29; H, 5.59; N, 8.84.

FAB MS: *m*/*z* = 822.6 $[M + H]^+$.

***tert*-Butyl N^2-[(9*H*-Fluoren-9-ylmethoxy)carbonyl]-*N*-{[1-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}-L-α-asparaginate (5c)**

According to the general procedure, **4a**[23] (224 mg, 0.6 mmol), **1b** (269 mg, 0.6 mmol), DIPEA (310 μL, 1.8 mmol) and $(EtO)_3PCuI$ (24 mg, 0.06 mmol) in toluene (5 mL) afforded **5a**.

Yield: 320 mg (65%); amorphous colorless solid; $[\alpha]_D^{20}$ –9.1 (*c* 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 7.81 (s, 1 H, triazole), 7.74 (d, 2 H, Fmoc), 7.56–7.55 (m, 2 H, Fmoc), 7.38 (dd, 2 H, Fmoc), 7.28 (t, 3 H, CH_2NH, Fmoc), 6.19 (s, 1 H, H-1), 5.98 (d, 1 H, Fmoc-NH), 5.68 (s, 1 H, H-2), 5.33–5.32 (m, 2 H, H-3, H-4), 4.50 (d, 3 H, CH, triazole-CH_2), 4.40 (d, 2 H, Fmoc-CH_2), 4.27 (dd, 1 H, H-6a), 4.19–4.16 (m, 2 H, H-6b, Fmoc-CH), 3.97 (s, 1 H, H-5), 2.86 (dd, 1 H, CH_2), 2.65–2.59 (dd, 1 H, CH_2), 2.09 (s, 3 H, CH_3), 2.07 (s, 6 H, CH_3), 1.98 (s, 3 H, CH_3), 1.41 [s, 9 H, $(CH_3)_3C$].

^{13}C NMR ($CDCl_3$): δ = 170.8 (CONH), 170.7 (*C*OO-*t*-Bu), 170.6, 169.3 (4 × C, CH_3CO), 156.0 (Fmoc-CO), 144.7 (triazole), 143.6 (2 × C, Fmoc), 141.3 (2 × C, Fmoc), 127.7, 127.1 (4 × C, Fmoc), 125.0 (2 × C, Fmoc), 121.8 (triazole), 120.0 (2 × C, Fmoc), 84.7 (C-1), 81.8 [$C(CH_3)_3$], 75.5 (C-5), 70.7 (C-3), 68.8 (C-2), 67.1 (Fmoc-CH_2), 65.0 (C-4), 62.2 (C-6), 51.3 (CH), 47.1 (Fmoc-CH), 37.4 (CH_2), 35.0 (triazole-CH_2), 28.0 [$C(CH_3)_3$], 21.0, 20.8, 20.6, 20.5 (CH_3).

Anal. Calcd for $C_{40}H_{47}N_5O_{14}$: C, 58.46; H, 5.76; N, 8.52. Found: C, 58.55; H, 5.69; N, 8.46.

***tert*-Butyl N^2-[(9*H*-Fluoren-9-ylmethoxy)carbonyl]-*N*-{[1-(2,3,4-tri-*O*-acetyl-6-deoxy-6-ethylsufanyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}-L-α-asparaginate (5d)**

According to the general procedure, **4d**[23] (225 mg, 0.6 mmol), **1b** (269 mg, 0.6 mmol), DIPEA (310 μL, 1.8 mmol) and $(EtO)_3PCuI$ (24 mg, 0.06 mmol) in toluene (5 mL) afforded **5d**.

Yield: 430 mg (87%); amorphous colorless solid; $[\alpha]_D^{20}$ +1.1 (*c* 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 7.75 (d, 3 H, Fmoc, triazole), 7.56 (d, 2 H, Fmoc), 7.39 (t, 2 H, Fmoc), 7.30 (t, 2 H, Fmoc), 7.11 (s, 1 H, CH_2NH), 5.92 (s, 1 H, Fmoc-NH), 5.19 (t, 1 H, H-3), 4.96 (t, 1 H, H-2), 4.85 (t, 1 H, H-4), 4.51 (s, 3 H, H-6a, triazole-CH_2), 4.46–4.37 (m, 4 H, Fmoc-CH_2, CH, H-1), 4.28 (mc, 1 H, H-6b), 4.18 (s, 1 H, Fmoc-CH), 3.85 (s, 1 H, H-5), 2.91 (d, 1 H, CH_2), 2.62 (dd, 1 H, CH_2), 2.54–2.52 (m, 2 H, SCH_2), 2.07 (s, 3 H, CH_3), 2.02 (s, 3 H, CH_3), 1.99 (s, 3 H, CH_3), 1.42 [s, 9 H, $(CH_3)_3C$], 1.13 (t, 3 H, SCH_2CH_3).

^{13}C NMR ($CDCl_3$): δ = 171.0 (CONH), 170.6 (*C*OO-*t*-Bu), 170.1, 170.0, 169.7 (CH_3CO), 156.2 (Fmoc-CO), 143.7 (triazole), 141.4 (2 × C, Fmoc), 127.9 (2 × C, Fmoc), 127.2 (2 × C, Fmoc), 125.2, 125.1 (3 × C, Fmoc, triazole), 120.1 (2 × C, Fmoc), 83.6 (C-1), 82.0 [$C(CH_3)_3$], 76.2 (C-5), 73.5 (C-3), 69.8 (2 × C, C-4, C-2), 67.3 (Fmoc-CH_2), 53.5 (C-6), 51.4 (CH), 47.2 (Fmoc-CH), 37.3 (CH_2), 29.8 (triazole-CH_2), 28.1 [$C(CH_3)_3$], 24.5 (SCH_2), 20.7, 20.6 (3 × C, CH_3), 14.9 (SCH_2CH_3).

Anal. Calcd for $C_{40}H_{49}N_5O_{12}S{\cdot}H_2O$: C, 58.31; H, 5.99; N, 8.50; S, 3.89. Found: C, 58.08; H, 5.92; N, 8.33; S, 3.73.

***tert*-Butyl N^2-[(9*H*-Fluoren-9-ylmethoxy)carbonyl]-*N*-{[1-(2,3,4-tri-*O*-acetyl-6-deoxy-6-ethylsufanyl-α-D-mannopyranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}-L-α-asparaginate (5e)**

According to the general procedure, **4e**[23] (225 mg, 0.6 mmol), **1b** (269 mg, 0.6 mmol), DIPEA (310 μL, 1.8 mmol) and $(EtO)_3PCuI$ (24 mg, 0.06 mmol) in toluene (5 mL) afforded **5e**.

Yield: 450 mg (91%); amorphous colorless solid which slowly decomposed upon drying; $[\alpha]_D^{20}$ +32.2 (*c* 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 7.74 (d, 2 H, Fmoc), 7.61 (s, 1 H, triazole), 7.54 (d, 2 H, Fmoc), 7.40–7.34 (m, 2 H, Fmoc), 7.29 (t, 2 H, Fmoc), 7.06 (s, 1 H, CH_2NH), 5.90 (d, 1 H, Fmoc-NH), 5.30–5.09 (m, 3 H, H-1, H-2, H-3), 5.06–5.05 (m, 1 H, H-4), 4.52–4.40 (m, 7 H, Fmoc-CH_2, H-6a, CH, triazole-CH_2, H-5), 4.36–4.29 (m, 1 H, H-6b), 4.18 (t, 1 H, Fmoc-CH), 2.88 (d, 1 H, CH_2), 2.59 (dd, 1 H, CH_2), 2.23–2.16 (m, 2 H, SCH_2), 2.13 (s, 3 H, CH_3), 2.09 (s, 3 H, CH_3), 1.97 (s, 3 H, CH_3), 1.41 [s, 9 H, $(CH_3)_3C$], 1.02 (t, 3 H, SCH_2CH_3).

^{13}C NMR ($CDCl_3$): δ = 171.0 (CONH), 170.6 (*C*OO-*t*-Bu), 170.1, 170.0, 169.7 (3 × C, CH_3CO), 156.1 (Fmoc-CO), 145.5 (triazole), 143.7 (Fmoc), 141.3 (Fmoc), 127.9 (CH), 127.8 (2 × C, Fmoc), 127.1 (2 × C, Fmoc), 125.0 (2 × C, Fmoc), 120.1 (2 × C, Fmoc), 81.9 [2 × C, C-1, $C(CH_3)_3$], 71.0 (C-3), 69.5 (C-5), 69.2 (C-2), 67.7 (C-4), 67.2 (Fmoc-CH_2), 51.3 (CH), 51.0 (C-6), 47.2 (Fmoc-CH), 37.3 (CH_2), 35.1 (triazole-CH_2), 28.1 [$C(CH_3)_3$], 25.0 (SCH_2), 20.9, 20.7, 20.6 (CH_3), 14.4 (SCH_2CH_3).

ESI MS: m/z = 824.0 $[M + H]^+$.

***tert*-Butyl N^2-[(9*H*-Fluoren-9-ylmethoxy)carbonyl]-*N*-{[1-(2,3,4-tri-*O*-acetyl-6-deoxy-6-ethylsufanyl-α-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methyl}-L-α-asparaginate (5f)**

According to the general procedure, **4f**[23] (225 mg, 0.6 mmol), **1b** (269 mg, 0.6 mmol), DIPEA (310 μL, 1.8 mmol) and $(EtO)_3PCuI$ (24 mg, 0.06 mmol) in toluene (5 mL) afforded **5f**.

Yield: 464 mg (94%); amorphous colorless solid; $[\alpha]_D^{20}$ +89 (*c* 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 7.75 (d, 2 H, Fmoc), 7.55 (d, 3 H, Fmoc, triazole), 7.39 (t, 2 H, Fmoc), 7.31–7.27 (m, 2 H, Fmoc), 7.03 (s, 1 H, CH_2NH), 5.90 (d, 1 H, Fmoc-NH), 5.58 (d, J = 5.31 Hz, 1 H, H-1), 5.34 (t, 1 H, H-3), 4.93 (dd, 1 H, H-2), 4.77 (t, 1 H, H-4), 4.69–4.55 (m, 1 H, H-5), 4.51–4.48 (m, 4 H, H-6a, CH, triazole-CH_2), 4.43–4.40 (m, 2 H, Fmoc-CH_2), 4.34–4.28 (m, 1 H, H-6b), 4.19 (t, 1 H, Fmoc-CH), 2.90 (d, 1 H, CH_2), 2.59 (dd, 1 H, CH_2), 2.15–2.13 (m, 2 H, SCH_2), 2.08 (s, 6 H, CH_3), 2.03 (s, 3 H, CH_3), 1.99 (s, 3 H, CH_3), 1.42 [s, 9 H, $(CH_3)_3C$], 1.02 (t, 3 H, SCH_2CH_3).

^{13}C NMR ($CDCl_3$): δ = 171.4 (CONH), 171.0 (*C*OO-*t*-Bu), 170.2 (3 × C, CH_3CO), 156.4 (Fmoc-CO), 145.1 (triazole), 141.7, 141.6 (Fmoc), 128.2 (2 × C, Fmoc), 127.5, 127.4 (Fmoc), 125.4, 125.3 (Fmoc), 124.2 (triazole), 120.4 (2 × C, Fmoc), 82.3 [$C(CH_3)_3$], 81.7 (C-1), 70.9 (C-2), 70.5 (C-3), 70.4 (C-4), 68.4 (C-5), 67.5 (Fmoc-CH_2), 51.5 (CH), 51.0 (C-6), 47.5 (Fmoc-CH), 37.6 (CH_2), 35.5 (triazole-CH_2), 28.4 [$C(CH_3)_3$], 24.1 (SCH_2), 21.1, 21.0 (3 × C, CH_3), 14.6 (SCH_2CH_3).

Anal. Calcd for $C_{40}H_{49}N_5O_{12}S$: C, 58.31; H, 5.99; N, 8.50; S, 3.89. Found: C, 58.32; H, 6.18; N, 7.94; S, 3.68.

Acknowledgment

We thank Professor K. Albert and his group for measuring the NMR spectra, Professor K. P. Zeller and his group for performing the mass spectrometry and A. Vogel for doing the elemental analyses. This work was financially supported by the Fonds der Chemischen Industrie.

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