Publication II

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Glycopolymers *via* catalytic chain transfer polymerisation (CCTP), Huisgens cycloaddition and thiol–ene double click reactions†

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CCTP has been used to give alkyne-functional macromonomers which are subsequently functionalised with sugar azides and thiols, using both CuAAC and thiol–ene Michael addition reactions, to yield end-functionalised glycopolymers in a convenient manner.

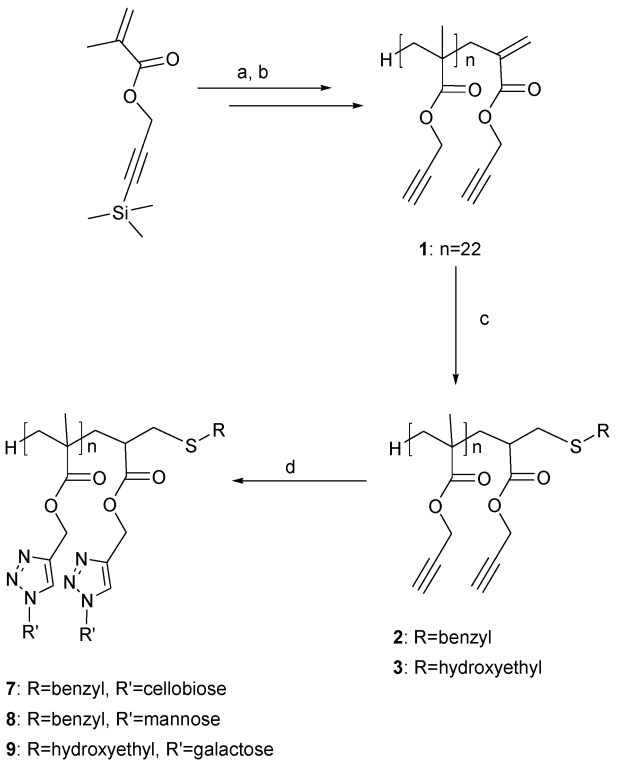
Click chemistry as a concept of simplifying synthesis is very useful in polymer science to produce complex macromolecular structures, functional polymers and protein conjugates. The Cu(I)-catalysed azide–alkyne cycloaddition (CuAAC) has been the most widely studied and employed of the available click reactions.[1–9] Recently, there has been an increasing interest in using the well-known addition of thiols to alkenes as a click process, so-called thiol–ene click chemistry.[10] Although thiol–ene click coupling has mainly been focused on a radical-mediated version to non-activated alkenes, this reaction can also proceed *via* Michael addition, especially when the vinyl group is alpha to an electron withdrawing moiety.[11–16] The use of thio-Michael addition as a click reaction was recently reported by Lowe *et al.* for the synthesis of star polymers.[17]

Synthetic glycopolymers containing pendent sugar moieties have been shown to interact multivalently with carbohydrate-binding proteins, lectins, in a similar manner to natural glycoproteins. These biomimetic properties have caused significant interest in the synthesis of glycopolymers, and a number of different strategies have been employed to obtain the required multivalent carbohydrate ligands.[18–20]

In our group, we have previously combined copper(I)-mediated living radical polymerisation (often called ATRP) and CuAAC to produce glycopolymers by post-functionalisation of well-defined "clickable" polyalkyne scaffolds with sugar azides.[21–25] An established, but dormant, method of obtaining end-functional polymers available for click reactions is catalytic chain transfer polymerisation (CCTP). This is an extremely efficient process to produce vinyl terminated methacrylic oligomers.[26–31]

In this present study we have used CCTP to give alkyne-functional oligomers available for both CuAAC and thio-Michael addition reactions. Post-functionalisation of the oligomers with these dual click reactions results in end-functionalised glycopolymers in a very convenient manner.

The "double clickable" alkyne-functional macromonomer **1** was prepared by CCTP of trimethylsilane-protected propargyl methacrylate using bis(boron difluorodimethylglyoximate) cobalt(II) (CoBF) as catalyst, followed by deprotection of the TMS groups (Scheme 1). The vinyl end group of propargyl methacrylate macromonomer **1** was reacted with benzyl mercaptan *via* a thio-Michael addition using dimethylphenylphosphine (DMPP) as catalyst. After conversion of the vinyl groups was achieved, the benzyl end-functionalised product, **2**, was isolated by precipitation. The success of the thio-Michael addition was confirmed by ^{1}H NMR with the disappearance of vinyl peaks at 5.7 ppm and 6.2 ppm and the appearance of a terminal benzyl at 7.2–7.4 ppm, Fig. 1a and 1b. To investigate the versatility of the thio-Michael addition to these oligomers, the vinyl end group of **1** was also reacted with



Scheme 1 Synthetic approach to end-functionalised glycopolymers. *Conditions*: (a) TMS-protected propargyl methacrylate, AIBN, CoBF, toluene, 60 °C; (b) TBAF, acetic acid, THF, ambient temperature (AT); (c) benzyl mercaptan or mercaptoethanol, **1**, DMPP, acetone, AT; (d) sugar azide **4**, **5** or **6**, polymer **2** or **3**, CuBr, bipy, TEA, DMSO, 60 °C.

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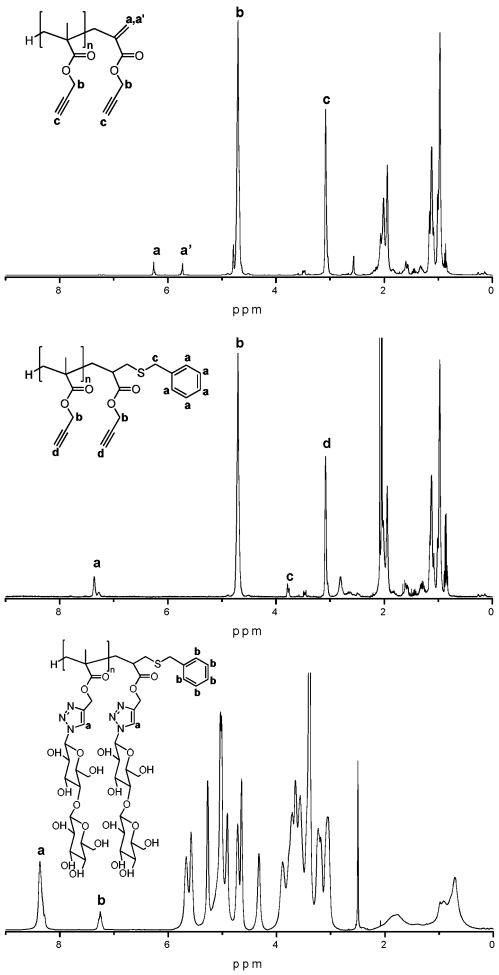

Fig. 1 ^{1}H NMR spectra of (a) **1** in acetone-d_6, (b) benzyl end-functionalised polymer **2** in acetone-d_6, and (c) benzyl end-functionalised cellobiose-functional glycopolymer **7** in DMSO-d_6.

mercaptoethanol (Scheme 1). The ^{1}H NMR spectrum of the purified hydroxyethyl-functional product **3** shows the disappearance of vinyl peaks and the appearance of peaks corresponding to the hydroxyethyl end group, indicating a successful reaction (see ESI†). MALDI-TOF analysis confirms the formation of the desired product (see ESI†). In addition, a by-product resulting from the conjugation of the DMPP to the polymer was visible in the MALDI-TOF spectrum. However, this by-product is cationic and is therefore expected to give disproportionately large peaks in this spectrum. It is noted that no peaks could be detected in the aromatic region of the ^{1}H NMR spectrum, or indeed no peaks could be detected in the ^{31}P NMR spectrum, from this by-product and thus the amount is assumed to be low.

Glycopolymers were synthesised by reacting the alkyne groups in the thiol-conjugated oligomers with sugar azides **4–6** (Chart 1) using CuAAC. Mannose azide and galactose azide were synthesised as described previously,[21] and cellobiose azide was synthesised using the same methodology, starting from the corresponding peracetylated sugar (see ESI†). The CuAAC reactions were catalysed by CuBr–bipyridine and performed in DMSO to ensure complete solubility of all reactants. Benzyl-functionalised oligomer **2**

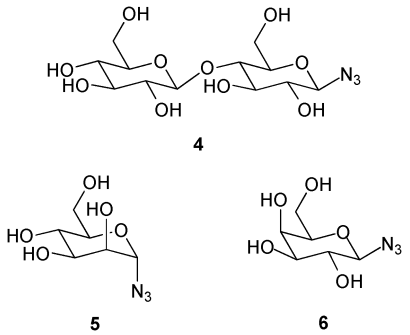

Chart 1 Sugar azides employed in the study: cellobiose azide (**4**), mannose azide (**5**) and galactose azide (**6**).

was reacted with cellobiose azide **4** to yield **7** (Scheme 1). The ^{1}H NMR spectrum of **7** shows the appearance of the triazole peak at 8.3 ppm, confirming the successful CuAAC reaction (Fig. 1c). It can also be seen that the benzyl end group is not affected by this reaction.

Oligomer **2** was reacted with mannose azide **5**, and hydroxyethyl-functionalised macromer **6** was reacted with galactose azide **7**, to yield end-functionalised glycopolymers **8** and **9**, respectively (Scheme 1). The CuAAC reactions with mannose azide and galactose azide required less catalyst and shorter reaction times than for cellobiose azide. This is in accordance with our previous results for the CuAAC reaction using lactose azide,[21] and may be explained by increased steric demands of the disaccharide cellobiose rendering the unreacted alkyne functionalities in the partly clicked polymer less accessible to further functionalisation.

Although in this study we have chosen to functionalise the oligomer end group prior to reacting the alkyne groups, it may for some applications be preferable to change the order of the reactions. To ensure that the vinyl end groups in the oligomer would not be affected by the CuAAC reaction of the alkyne side groups, unfunctionalised oligomer was also reacted with cellobiose azide. The click reaction could be confirmed by ^{1}H NMR by the appearance of a triazole peak at 8.3 ppm, and it could further be seen that the vinyl end group was retained after this reaction (see ESI†).

The potential of the end-functionalised mannose- and galactose-functional glycopolymers **8** and **9** to be recognised by different lectins was investigated. For the mannose-functional glycopolymer **8**, turbidimetry was used to study the rate of the binding of the sugar epitopes to the mannose-specific lectin concanavalin A (con A). Absorbance changes at 420 nm were measured over time in a solution of con A and **8** in HEPES buffer at pH 7.4. When the glycopolymer binds to the lectin, the formation of precipitating clusters changes the absorbance in the solution.[32] It could be seen that upon mixing **8** and the lectin con A, the absorbance initially quickly increased, then reached a plateau, indicating that most of the polymer was able to rapidly interact with the lectin, forming stable clusters (see ESI†).

For the polymer **9**, the interaction with the galactose selective lectin *Ricinus communis* agglutinin I (RCA I) was studied by affinity chromatography analysed by HPLC. A solution of **9** was injected into a column packed with immobilised RCA I. The glycopolymer is retained by the column as the sugar

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moieties are recognised by the lectin. Using a mobile phase containing galactose as a competing ligand, the polymer is released from the column and can be detected by UV absorbance.[33] By increasing the concentration of galactose in the mobile phase, the amount of eluted glycopolymer increased, indicating that the retention of the polymer in the column was indeed due to the sugar–lectin interaction.

In summary, we have used CCTP to synthesise polymers containing two different clickable groups, which can be functionalised using two different click reactions. The polymer end group has been reacted using Michael addition with different thiols to obtain end-funtionalised polymers, and glycopolymers have been produced by clicking sugar moieties to the side chain of these polymers by CuAAC. The ability of the resulting end-functionalised glycopolymers to be recognised by lectins has been investigated. The results from this study indicate that the mannose- and galactose-containing glycopolymers prepared with the method described herein are able to function as multivalent ligands for the recognition of the lectins con A and RCA I, respectively.

Thus, CCTP in combination with thio-Michael addition and CuAAC is a useful synthetic approach not only to glycopolymers but also to many different types of functional polymers and conjugates.

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Supplementary Material (ESI) for Chemical Communications
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Supporting Information

Glycopolymers via catalytic chain transfer polymerisation (CCTP), Huisgens cycloaddition and thiol-ene double click reactions

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1. Experimental

1.1 Materials

Copper(I) bromide (Aldrich, 98%) was purified according to the method of Keller and Wycoff.[1] α-Azido-D-mannose and β-azido-D-galactose were prepared as previously described[2] starting from peracetylated sugars prepared by slight modification of a known general protocol.[3] Trimethylsilyl-protected propargyl methacrylate was synthesised as previously described[4] starting from 3-(trimethylsilyl) propargyl alcohol (Alfa Aesar, 98%). Dimethylphenylphosphine (DMPP, Aldrich, 97%) was stored under nitrogen. Amberlite IR-120 (PLUS) ion-exchange resin was washed several times with methanol. All other reagents and solvents were obtained at the highest purity available from Sigma-Aldrich Chemical Company and used without further purification unless stated.

CAUTION! Although we have never experienced any adverse event when working with these products, organic azides are potentially explosive compounds which should be handled with utmost care!

1.2 Characterisation

All reactions were carried out using standard Schlenk techniques under an inert atmosphere of oxygen-free nitrogen, unless otherwise stated. NMR spectra were obtained on a Bruker DPX-400 and Bruker AV-400 spectrometer. All chemical shifts are reported in ppm (d) relative to tetramethylsilane, referenced to the chemical shifts of residual solvent resonances (^{1}H and ^{13}C). The following abbreviations were used to explain the multiplicities: d=doublet, m=multiplet, t=triplet. The degree of polymerisation of the oligomers $DP_{(NMR)}$ were calculated by comparing the integrals of the vinyl bond chain-end signals and appropriate peaks related to the polymer backbone. Molar mass distributions of oligomers **1a** and **1b** were measured using Size Exclusion Chromatography (SEC), on a system equipped with two PL gel 5 µm mixed D columns (300 x 7.5 mm) and one PL gel 5 µm guard column (50 x 7.5 mm; Polymer Laboratories, suitable for molecular weights between 200 and 400000 g/mol) with a differential refractive index detector calibrated with linear poly(methyl methacrylate) standards (200 – 3 x 10^5 g mol^{-1}). The system was eluted at 1.0 ml min^{-1} with a solution of chloroform/triethylamine 95:5 v/v. Analyte samples contained (0.5% volume) toluene as the flow rate marker.

Infrared absorption spectra were recorded on a Bruker VECTOR-22 FTIR spectrometer using a Golden Gate diamond attenuated total reflection cell.

Mass spectra were recorded using a Micromass Autospec apparatus.

MALDI-TOF analysis was performed with a Bruker Ultraflex III equipped with a neodymium-doped yttrium aluminium garnet laser (Nd:YAG). The matrix solution was prepared by dissolving 0.1 g of 2,4-dihydroxybenzoic acid in a 10 mL mixture of equal volumes of ethanol and water. Trifluoroacetic acid was added was added in 0.1 % overall concentration and the polymer dissolved to a concentration of 1 mg cm^{-3}.

The matrix solution (0.5µl) was applied to the stainless steel side and the solvent allowed to evaporate. The same volume of polymer sample solution was applied on top of the dried matrix, and the overall mixture allowed to dry. The sample was irradiated with 500 pulsed laser shots at a 37% laser power. Calibration was performed with various linear poly(ethylene glycol) standards.

RCA I recognition experiments were performed using an HPLC system equipped with a Shodex AFpak ARC-894 column, a Dionex P680 HPLC pump and a Gilson UV–Vis-55 detector. Turbidimetry was performed as described by Kiessling and coworkers[5] using a Varian Cary 50 Bio UV–Vis spectrometer, using 2 mL volume polycarbonate cuvettes (1 cm pathlength). Absorbance data was recorded at 420 nm for 10 min at 0.125 s. The steepest part of the initial aggregation was fit to determine the rate of aggregation.

1.3 Synthetic procedures

1.3.1 Azidation of cellobiose octaacetate: β-azido-D-cellobiose heptaacetate.

Trimethylsilyl azide (5.8 ml, 44 mmol) was added under nitrogen to a solution of D-cellobiose octaacetate (15 g, 22 mmol) in anhydrous CH_2Cl_2 (200 mL), followed by tin(IV) chloride (1.6 mL, 13 mmol). The mixture was stirred at ambient temperature for 12 h, then the solvent was removed under reduced pressure and the crude residue was purified by flash chromatography (CC, SiO_2, ethyl acetate/petroleum ether 1:1

vol/vol). The relevant fractions were collected, combined and concentrated to dryness under reduced pressure. Obtained 13.8 g (94%) of β-azido-D-cellobiose heptaacetate as a white solid. ^{1}H NMR (400.03 MHz, DMSO-d_6, 298 K) δ = 1.91 (s, 3H, CH_3); 1.96 (6H, 2xCH_3); 1.98 (s, 3H, CH_3); 2.00 (s, 3H, CH_3); 2.02 (s, 3H, CH_3); 2.09 (s, 3H, CH_3); 3.79-3.88 (m, 1H); 3.90-4.10 (m, 4H); 4.20-4.28 (m, 1H); 4.33-4.40 (m, 1H); 4.61-4.68 (m, 1H); 4.69-4.75 (m, 1H); 4.79-4.85 (m, 1H); 4.85-4.92 (m, 1H); 5.02-5.07 (m, 1H); 5.17-5.30 (m, 2H). ^{13}C{^{1}H} NMR (100.59 MHz, $CDCl_3$, 298 K) δ = 20.06 (1H, CH_3); 20.07 (1H, CH_3); 20.15 (1H, CH_3); 20.22 (1H, CH_3); 20.25 (1H, CH_3); 20.33 (1H, CH_3); 20.52 (1H, CH_3); 61,38 (1H, CH_2); 62.00 (1H, CH_2); 67,58 (1H, CH); 70.34 (1H, CH); 70.40 (1H, CH); 71.08 (1H, CH); 71.61 (1H, CH); 72.10 (1H, CH); 73.81 (1H, CH); 75.94 (1H, CH); 85.97 (1H, CHN_3); 99.45 (1H, CH); 168.94 (1C, CH_2OAc); 169.12 (1C, CH_2OAc); 169.15 (1C, CH_2OAc); 169.31 (1C, CH_2OAc); 169.52 (1C, CH_2OAc); 169.95 (1C, CH_2OAc); 170.20 (1C, CH_2OAc). FTIR (neat): $\tilde{\nu}$ = 2119, 1734, 1427, 1365, 1213, 1165, 1032, 950, 898 cm^{-1}.

1.3.2. Deprotection of cellobiose heptaacetate azide: β-azido-D-cellobiose.

Sodium methoxide (25% w/w solution in methanol, 24.2 mL, 106 mmol) was added to a dispersion of β-azido-D-cellobiose heptaacetate (10.0 g, 15.1 mmol) in methanol (550 mL). The mixture was stirred at ambient temperature for 3h. The mixture turned into a clear solution. Amberlite IR-120 (PLUS) ion-exchange resin was added and the reaction mixture was stirred for further 30 min. The resin was then removed by filteration and the resulting solution concentrated under reduced pressure. The crude product was purified by flash chromatography (CC, SiO_2, methanol/CH_2Cl_2 1:3, vol/vol). The relevant fractions were collected, combined and concentrated to dryness under reduced pressure. Obtained 3.02 g (54%, not optimized) of β-azido-D-cellobiose

as a white solid. ^{1}H NMR (400.03 MHz, DMSO-d_6, 298 K) δ = 2.95-3.01 (m, 1H); 3.01-3.09 (m, 2H); 3.11-3.22 (m, 2H); 3.30-3.45 (m, 4H); 3.58-3.66 (m, 1H); 3.66-3.77 (m, 2H); 4.25 (d, *J*=8.2Hz, 1H, CH); 4,56 (d, *J*=9.1Hz, 1H, CH). ^{13}C{^{1}H} NMR (100.59 MHz, DMSO, 298 K) δ = 59.93 (1H, CH_2); 60.97 (1H, CH_2); 69.97 (1H, CH); 73.04 (1H, CH); 73.23 (1H, CH); 74.79 (1H, CH); 76.40 (1H, CH); 76.74 (1H, CH); 76.96 (1H, CH); 79.54 (1H, CH); 89.65 (1H, CHN_3); 103.01 (1H, CH).

1.3.2 CCTP of TMS-protected propargyl methacrylate

A solution of TMS-protected propargyl methacrylate (2.00 g, 10.2 mmol), AIBN (10.0 mg 0.5 wt%) and mesitylene (100 μL, internal standard) in toluene (1.6 mL) was deoxygenated by 4 freeze-pump-thaw cycles. A deoxygenated solution of CoBF in toluene (392 μL, 1.30 mM) was subsequently added under nitrogen. The reaction was allowed to proceed at 60 °C for 19 h. After completion of the reaction, the crude polymerisation mixture was passed through a column of basic alumina to remove CoBF. The oligomer was isolated by precipitation into cold petroleum ether.

1.3.3 Deprotection of TMS-protected oligomer

Trimethylsilyl-protected oligomer (2.00 g, 10.2 mmol of trimethylsilyl groups) and acetic acid (875 μL, 1.5 equiv. mol/mol with respect to the alkyne-trimethylsilyl groups) were dissolved in THF (10 mL). Nitrogen was bubbled (ca. 10 min) and the solution was cooled to -20 °C. A 1.0 M solution of TBAF in THF (15.3 mL, 1.5 equiv. mol/mol with respect to the alkyne-trimethylsilyl groups) was added slowly via syringe. The resulting mixture was stirred at -20 °C for 30 min and then at ambient temperature overnight. The reaction solution was passed through a short silica pad in order to remove the excess of TBAF and the pad was subsequently washed with

additional THF. The resulting solution was then concentrated under reduced pressure and the **1** was recovered by precipitation in petroleum ether.

$DP_{(NMR)} = 23$, $M_{n(SEC)} = 2200$ g mol^{-1}, $M_w/M_n = 1.5$

1.3.4 Thiol-conjugation to propargyl methacrylate oligomer, general procedure

Propargyl methacrylate oligomer **1** (140 mg, 50 μmol of vinyl end groups) were dissolved into *d*-acetone (1.00 mL) in an NMR tube. Benzyl mercaptan was added (9.3 mg, 75 μmol). Finally, DMPP was added (6.9 mg, 50 μmol). The reaction was carried out overnight. The final benzyl-functionalised product **2** was precipitated from petroleum ether several times and dried under vacuum.

1.3.5 Reaction of end group functionalized poly(propargyl methacrylate) with sugar azide, general procedure

A solution of mannose azide, **5,** (58 mg, 0.28 mmol), benzyl-functionalised poly(propargyl methacrylate), **2**, (29 mg, 0.23 mmol of alkyne groups), bipyridine (7.0 mg, 47 μmol), triethylamine (5.0 mg, 47 μmol) and mesitylene (8.0 mg, internal standard) in DMSO (6.0 mL) was deoxygenated by three freeze-pump-thaw cycles. This solution was then transferred via cannula under nitrogen into a Schlenk tube, previously evacuated and filled with nitrogen, containing CuBr (3.0 mg, 23 μmol). The resulting solution was stirred overnight at 60 °C. When the reaction was completed, the reaction mixture was diluted with water and then dialysed against water for several days after which the product (**8**) could be recovered by freeze-drying.

2. Thio-Michael addition

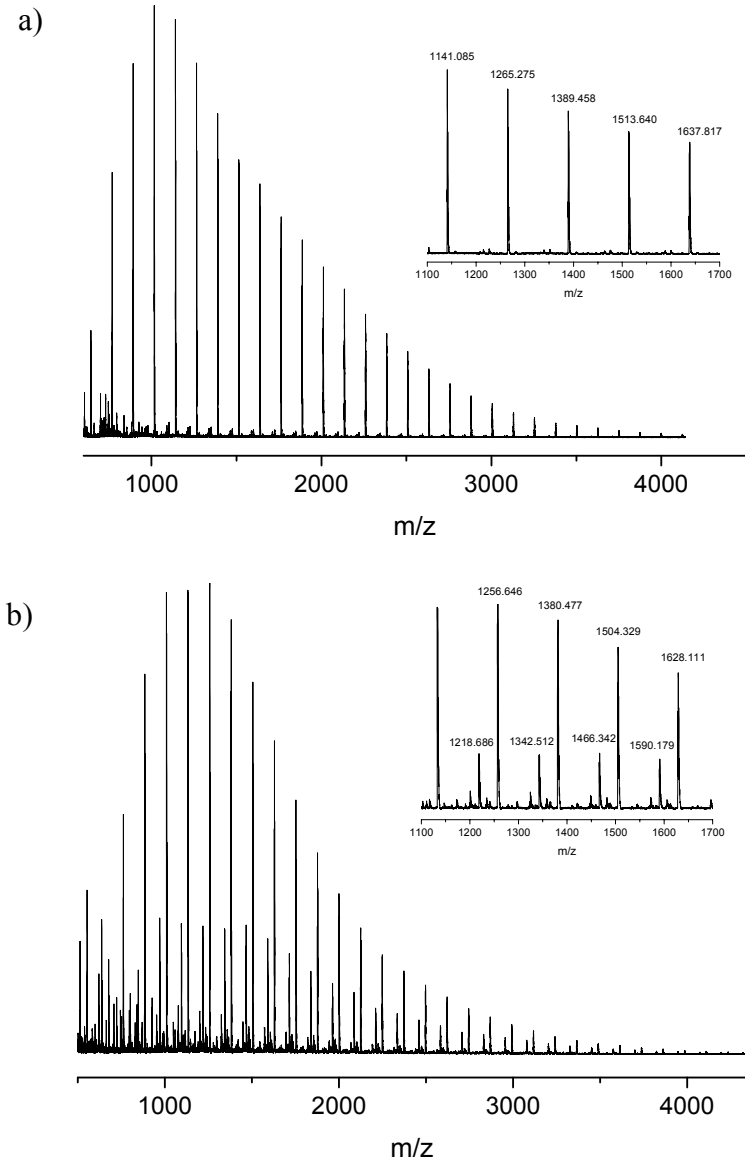

Fig. S1 MALDI-TOF traces for a) propargyl methacrylate oligomer **1**, and b) product after reaction with mercaptoethanol. The main distribution corresponds to the DMPP-conjugated oligomer, and the smaller distribution corresponds to the desired hydroxyethyl-functionalised product (**3**). The insets show an expansion of the same traces.

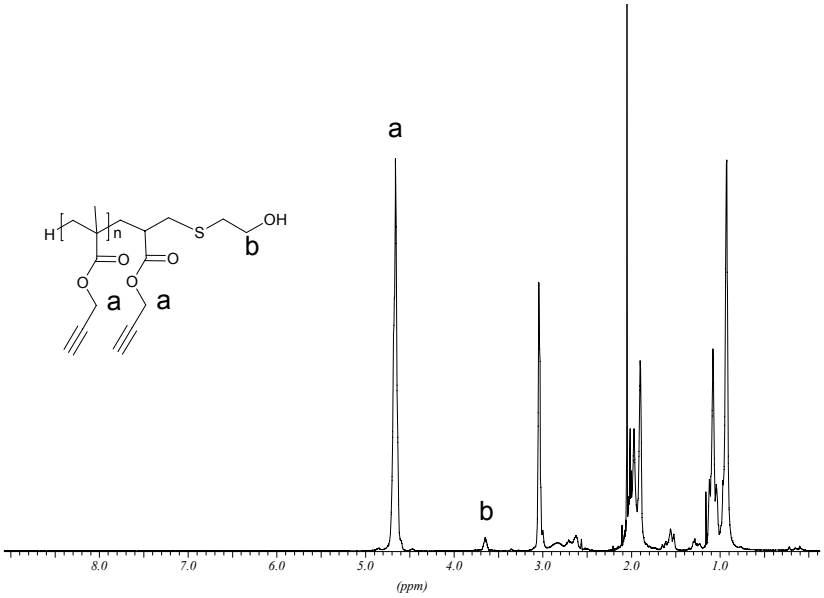

Fig. S2 ^{1}H NMR spectrum of hydroxyethyl-functionalised poly(propargyl methacrylate) **3.**

3. CuAAC reactions

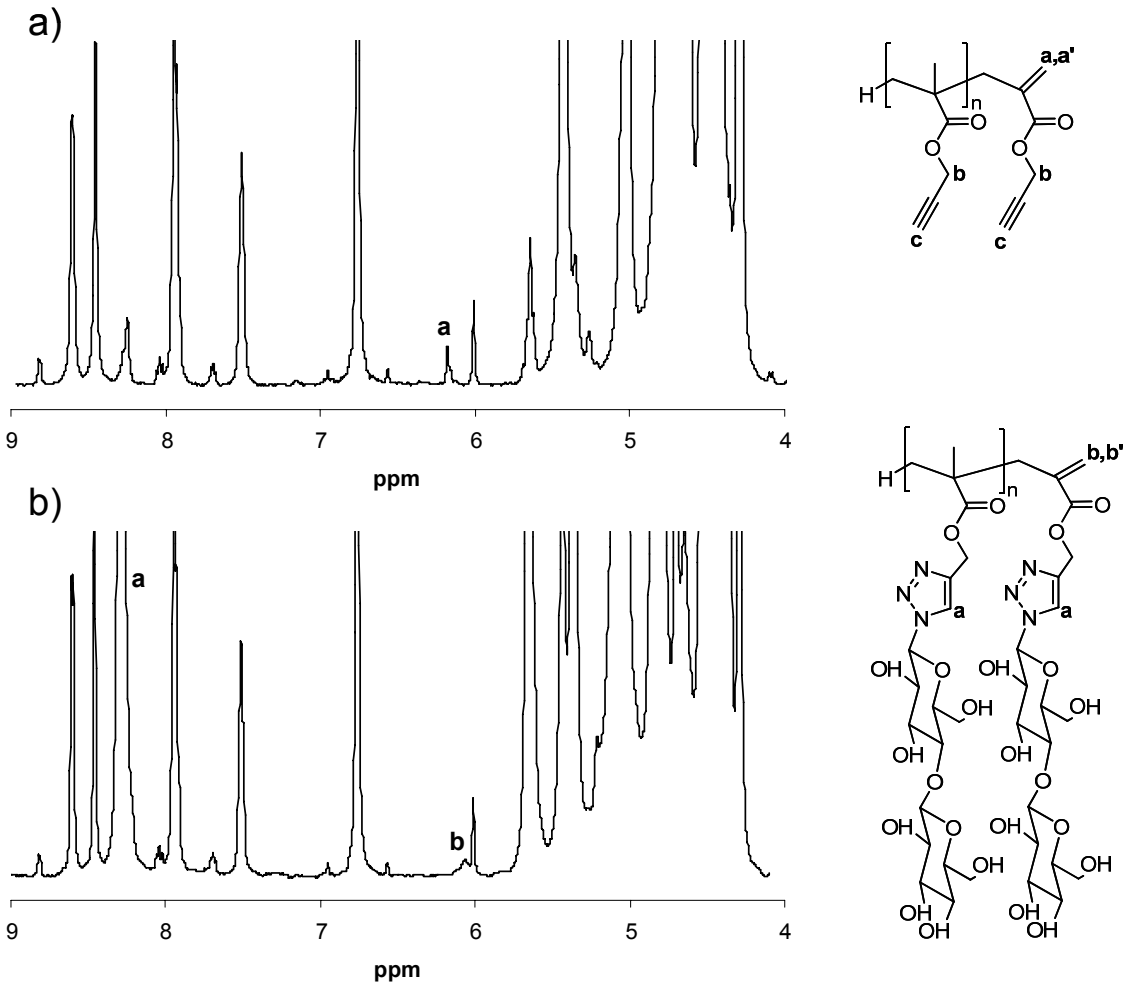

Fig. S3 The vinyl end group is retained in CuAAC. ^{1}H NMR spectra of the reaction mixtures for CuAAC side-chain functionalization a) before reaction b) after reaction. Poly(propargyl methacrylate) was reacted with cellobiose azide. The vinyl end group proton in poly(propargyl methacrylate) at 6.18 ppm shifts to 6.06 ppm as reaction proceeds.

4. Lectin recognition studies

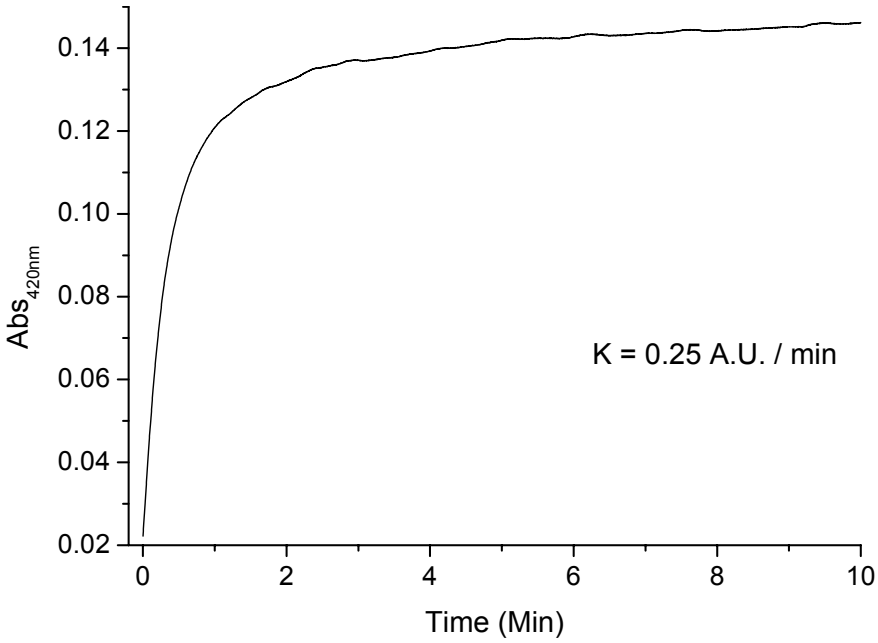

Fig. S4 Turbidimetry results for glycopolymer **8** in the presence of mannose-selective lectin Con A. The curve shown is an average of three separate runs. The aggregation rate constant K is calculated from the initial clustering rate (error +/- 5%).

5. References

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