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Synthesis of triazole-linked *pseudo*-starch fragments

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Dedicated to the memory of Professor Nikolay K. Kochetkov

Abstract—Rapid assembly of starch fragment analogues was achieved using 'click chemistry'. Specifically, a pentadecasaccharide and two hexadecasaccharide mimics containing two parallel maltoheptaosyl chains linked *via* [1,2,3]-triazoles to glucose or maltose core were synthesised using Cu(I)-catalyzed [3+2] dipolar cycloaddition of azidosaccharides and 4,6-di-*O*-propargylated methyl α-D-glucopyranoside and 6,6′- and 4′,6′-di-*O*-propargylated *p*-methoxyphenyl β-maltoside.

Keywords: Dipolar cycloaddition; Amylopectin mimics

1. Introduction

Starch granules possess a well-organised physical structure that is characterised by repeating altered crystalline and amorphous regions.[1–3] It is believed that the semi-crystallinity of starch is a result of the specific arrangement of polysaccharide molecules of amylopectin, which comprises 70–80% of most starches. Highly branched amylopectin macromolecules consist of relatively short α-(1→4)-D-glucan chains forming clusters attached through α-(1→6)-linkages to α-(1→4)-D-glucan backbone. Theoretical models proposed for starch granule structure suggest that short glucan chains within clusters exist as double helices that are closely packed forming crystalline lamellae, whereas regions of the granule enriched with branch points are amorphous.[4–8] The branch points apparently play an important role in propagation of the double helices, thus influencing the whole granule structure. To gain insight into the structural features associated with branch points, computer modelling[9–11] and NMR spectroscopic studies[12] have been undertaken on amylopectin fragments. However, isolation of well-characterised amylopectin fragments incorporating branching points from natural starches is very difficult since they represent only a small fraction of the total polysaccharide material. Synthetic α-(1→4)-glucans incorporating α-(1→6)-branch points have been suggested as models of starch, which are useful tools for physicochemical and biochemical studies. Synthesis of oligosaccharides related to starch have been reported in the literature[13–19] but construction of challenging 1,2-*cis*-glucosidic linkages is known[20] to be a serious obstacle in the assembly of the large branched fragments. The synthesis may be considerably simplified if target structures are represented by *pseudo*-oligosaccharides or oligosaccharide mimics in which certain glycosidic bonds are substituted with non-glycosidic motifs. There are several approaches to synthetic *pseudo*-oligosaccharides including the construction of C-,[21] S-,[22] amide,[23,24] ureido and thioureido[25,26] linkages between monosaccharide residues. Recently, 1,2,3-triazole links have emerged as a popular bridging unit in carbohydrate chemistry because of the facile and efficient method of their introduction, which is referred to as

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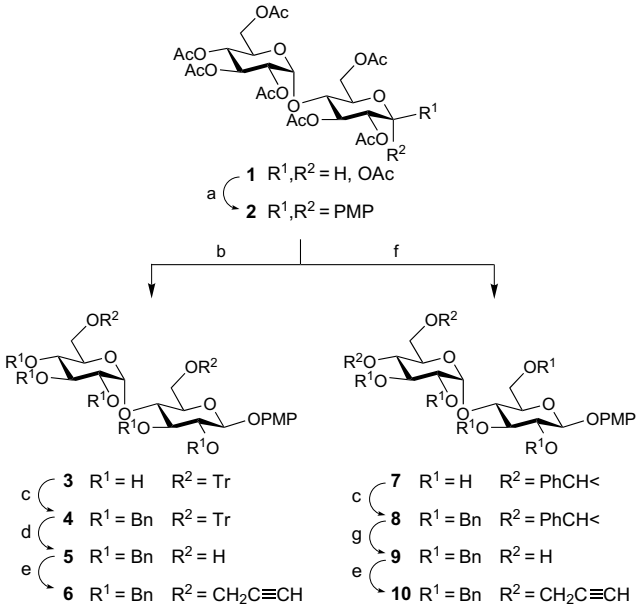
'click chemistry.'[27] The latter method is based on Cu(I)-catalyzed version[28,29] of Huisgen's 1,3-dipolar cycloaddition[30] of azides and terminal alkynes and it has been successfully applied for the synthesis of various glycoconjugates including multivalent glycosides,[31–34] cyclodextrin analogues,[35,36] glycopeptide mimetics[37,38] and glycosidase inhibitors.[39,40]

Continuing our efforts on generating synthetic amylopectin fragments,[20] we describe herein the application of 'click chemistry' to the construction of amylopectin analogues composed of two linear maltooligosaccharide chains attached to a maltose or glucose unit through heterocyclic bridges.[41] This type of oligosaccharide architecture is particularly interesting, given a potential for the formation of double helices, which are assumed to be crucial to starch granule organisation. The concept of enforced interaction of two parallel glucan chains through their attachment to a template was applied by Vasella and co-workers[42] in the construction of a cellulose II mimic. The branching templates chosen in our work were dipropargylated glucose and maltose derivative, whereas linear chains containing an azido group in the reducing terminal anomeric positions comprised the cycloaddition partner.

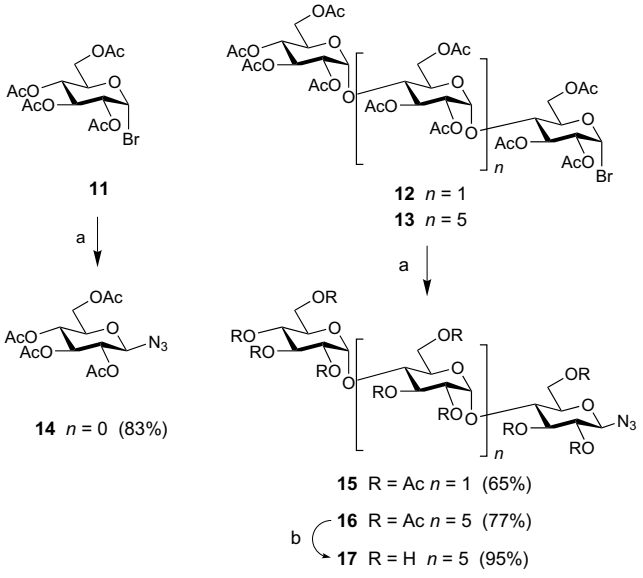


Scheme 1. Reagents and conditions: (a) *p*-methoxyphenol, CH_2Cl_2, $BF_3{\cdot}OEt_2$, 41%; (b) 1. MeOH, NaOMe, 2. TrCl, pyridine, 42%; (c) BnBr, NaH, 94% (for **3**), 92% (for **8**); (d) TsOH, MeOH, CH_2Cl_2, 90%; (e) $CH{\equiv}CCH_2Br$, NaH, THF, DMPU, 88% (for **6**), 93% (for **10**); (f) 1. NaOMe, MeOH, 2. $PhCH(OMe)_2$, TsOH, DMF, 65%; (g) 90% AcOH, 77%.

2. Results and discussion

Regioselectively propargylated maltose derivatives were synthesised in the form of their *p*-methoxyphenyl β maltosides, which were prepared starting from readily available maltose peracetate **1**.[43] Glycosidation of **1** with *p*-methoxyphenol in the presence of $BF_3{\cdot}OEt_2$ gave an α,β mixture of acetylated aryl glycosides from which pure β-anomer **2** was isolated by crystallisation in 41% yield (Scheme 1). Deacetylation of **2** followed by selective protection of primary positions with triphenylmethyl groups using excess TrCl in pyridine afforded 6,6′-di-*O*-trityl derivative **3** in 42% overall yield. For the introduction of temporary 4′,6′ protecting groups, *p*-methoxyphenyl maltoside was benzylidenated to produce acetal **7** in 65% yield starting from acetate **2**. The remaining hydroxy groups in **3** and **7** were benzylated to give derivatives **4** and **8** in high yield. Acid-labile triphenylmethyl and benzylidene groups were removed to give 6,6′-diol **5** and 4′,6′-diol **9** in 90% and 77% yield, respectively. The reactions of dialkoxides prepared in situ from diols **5** and **9** with propargyl bromide led to target di-*O*-propargyl maltosides **6** and **10** in 88% and 93% yield, respectively.

Peracetylated β-glycosyl azides of glucopyranose **14**,[44] maltotriose **15** and maltoheptaose **16** were synthesised in 65–83% yield by the reaction of the corresponding glycosyl bromides **11**, **12**[45] and **13**[45] with Me_3SiN_3 in the presence of Bu_4NF[44] (Scheme 2). Phase transfer catalyzed reaction[46] of **11**–**13** with NaN_3–Bu_4NHSO_4 in CH_2Cl_2–water mixture gave similar results.



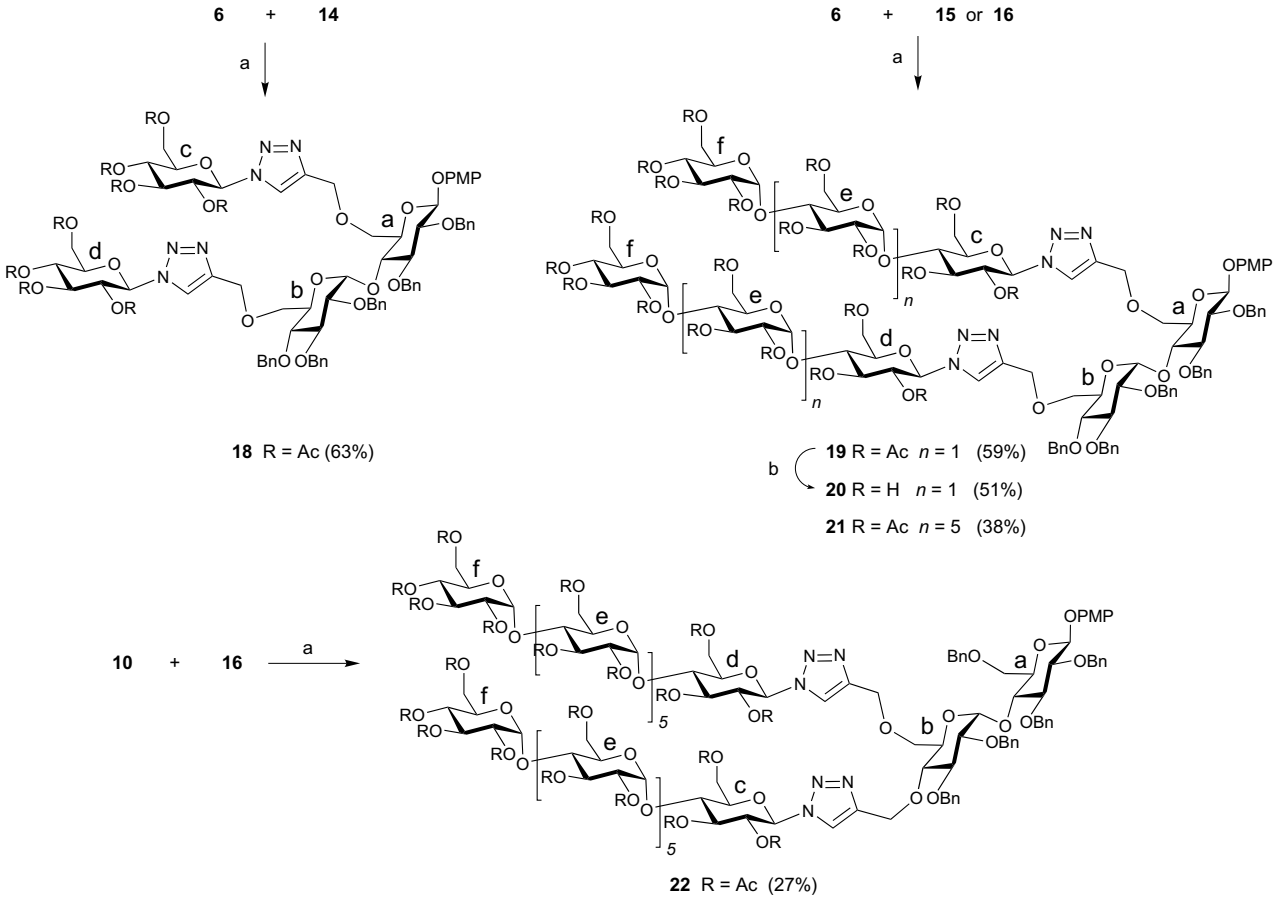
Scheme 2. Reagents and conditions: (a) Me_3SiN_3, Bu_4NF, THF; (b) NaOMe, MeOH then NaOH, water, 20 °C, 2 h.

Since Cu(I)-catalyzed cycloaddition of azides to alkynes was first developed,[28,29] a number of different Cu salts and a variation of conditions for this 'click reaction' have been suggested.[31,35,47–49] In the case of protected di-*O*-propargyl derivatives **6** and **10** and acetylated glycosyl azides **14**–**16**, we used $(Ph_3P)_3{\cdot}CuBr$

as a catalyst in the presence of DIPEA as a base[31,32] but instead of microwave irradiation a longer reaction time (12 h) was applied. The cycloaddition products were purified on silica gel where they were the slowest moving carbohydrate components of reaction mixtures. Thus, compounds **18**, **19**, **21** and **22** (Scheme 3) were obtained in yields ranging between 65% and 27%, with yields decreasing when increasing the length of the azidooligosaccharide chain.

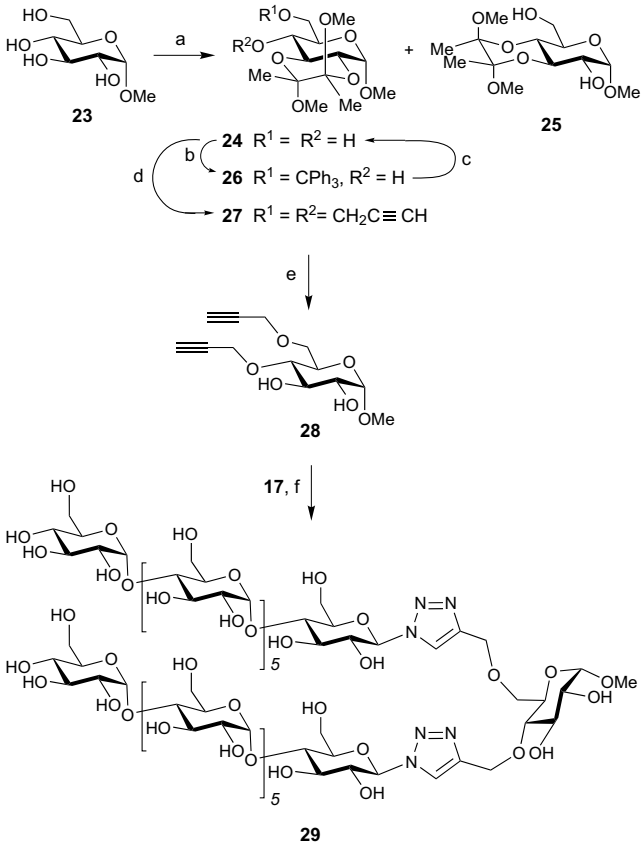
The formation of cycloaddition products was confirmed by MALDI-TOFMS, which clearly showed the presence of the expected sodium adducts of molecular ions: 1744.7 (**18**), 2897.1 (**19**), 5202.7 (**21**) and 5207.6 (**22**). The structure of these compounds was also confirmed by NMR spectroscopy. Both ^{1}H and ^{13}C NMR spectra of **18**, **19**, **21** and **22** revealed very close but distinguishable resonances ($\delta_H \sim 5.7$–5.9 and $\delta_C \sim 85$–86) corresponding to the anomeric centre of the glucopyranose residues attached to *N*-1 of the triazole unit. Characteristic signals of anomeric carbon atoms of the core maltoside unit ($\delta_{C\text{-}1} \sim 102$ and $\delta_{C-1'} \sim 97$) as well as resonances corresponding to *p*-methoxyphenyl group ($\delta_{OMe} \sim 55.5$, $\delta_C \sim 115$ and 118 for aromatics) were observed in the ^{13}C NMR spectra. The presence of two [1,2,3]-triazole rings in **18**, **19**, **21** and **22** followed from two separate triazole resonances of H-5 ($\delta_H \sim 7.7$) in ^{1}H NMR spectra and pairs of signals corresponding to C-4 ($\delta_C \sim 121.4$ and 121.8) and C-5 ($\delta_C \sim 145.5$, 145.9) in ^{13}C NMR spectra. From the rest of the considerably overlapping resonances of acetylated glucopyranose residues only clusters corresponding to signals of α-anomeric carbons of the core maltoside unit ($\delta_C \sim 95$–96) and C-6 ($\delta_C \sim 61.5$–62) carbon atoms were reliably distinguishable. Therefore, NMR data clearly indicated the formation of a single isomer in each case, which for the copper(I)-catalyzed cycloaddition reaction is known to be the 1,4-substituted [1,2,3]-triazole.[28] Regioselectivity of cycloaddition in the synthesis of 6,6′-di-substituted derivatives **18**–**20** also followed from the observation of only one pair of doublets of aromatic protons ($\delta_H \sim 6.9$ and $\delta_H \sim 7.0$) belonging to the anomeric *p*-methoxyphenyl group in the ^{1}H NMR spectra. We noted previously[20] that the chemical shifts of these signals are highly sensitive to the stereochemistry of a substituent at the 6 position of a *p*-methoxyphenyl β-maltoside unit.

It has been previously demonstrated[35] that protected *pseudo*-oligosaccharides incorporating [1,2,3]-triazole



Scheme 3. Reagents and conditions: (a) $(Ph_3P)_3CuBr$, *i*-Pr_2NEt, toluene, 20 °C, 12 h, (b) 1. H_2, Pd/C, 1:1 EtOAc–EtOH, 35 °C, 24 h, 2. NaOMe, MeOH then NaOH, water, 20 °C, 17 h.

bridges can be safely deprotected using conventional techniques. As an example, we performed a complete deprotection of *pseudo*-octasaccharide **19** using catalytic hydrogenolysis followed by two-step deacetylation, first with NaOMe in MeOH and then NaOH in water. After purification by gel-permeation chromatography, deprotected compound **20** was obtained in modest 51% yield. The protecting groups are currently necessary during the preparation of sugar components by cycloaddition 'click' reactions and are useful during the purification of protected *pseudo*-oligosaccharides. However, the protected carbohydrate hydroxyl groups are not essential for the cycloaddition reaction itself, which may be carried out in aqueous media and is not affected by the presence of alcohols. To investigate the possibility of direct synthesis of unprotected *pseudo*-oligosaccharides, we attempted 'click' reactions between unprotected maltoheptaosyl azide **17** and methyl 4,6-di-*O*-propargyl-α-D-glucopyranoside **28** (Scheme 4). Glycosyl azide **17** was readily available by deacetylation of compound **16** (Scheme 2). For the regioselective introduction of propargyl groups into positions 4 and 6 of methyl glucopyranoside **23**, the 2-OH and 3-OH groups were first protected as a temporary butanediacetal (BDA).[50] It is known that acetalation of **23** proceeds with the formation of an inseparable mixture of 2,3-diacetal **24** and 3,4-diacetal **25**.[51] In order to obtain pure 4,6-diol **24**, the mixture of products prepared by the reaction of **23** with butane-2,3-dione–$CH(OMe)_3$ in the presence of CSA was converted into a mixture of 6-*O*-trityl ethers by reaction with Ph_3CCl in pyridine and isomer **26** was isolated by chromatography in 38% overall yield. Removal of triphenylmethyl group in **26** with MeOH–C_5H_5N·TsOH led to diol **24** in 76% yield. Alkylation of **24** with propargyl bromide followed by hydrolysis of diacetal **27** with 90% CF_3CO_2H gave target 4,6-di-*O*-propargyl ether **28** in 68% yield over two steps. The position of propargyl groups was confirmed by the downfield shift of resonances of H-2 and H-3 in the ^1H NMR spectrum of an acetylated sample of **28** ($\delta_{H\text{-}2}$ 4.85, $\delta_{H\text{-}3}$ 5.46) compared to the corresponding resonances in the spectrum of diol **28** ($\delta_{H\text{-}2}$ 3.55, $\delta_{H\text{-}3} \sim 3.83$).



Scheme 4. Reagents and conditions: (a) 1,4-butanedione, $(MeO)_3CH$, CSA, reflux, 18 h; (b) TrCl, C_5H_5N, 40 °C, 18 h, 38% (steps a and b); (c) C_5H_5N·HOTs, MeOH, 37 °C, 72 h, 76%; (d) $HCCCH_2Br$, NaH, DMF; (e) 90% CF_3CO_2H, 20 °C, 1 h, 68% (steps d and c); (f) 0.2 equiv sodium ascorbate, 0.01 equiv $CuSO_4$, water, 70 °C, 2 h, 89%.

Cycloaddition ('click') reaction between maltoheptaosyl azide **17** and dialkyne **28** was carried out at 70 °C in water in the presence of cat. $CuSO_4$ and 0.1 equiv of sodium ascorbate.[28] Without any prior workup, the product was purified by aqueous gel-permeation chromatography to afford **29** in 89% yield. The elution volume of **29** on a GPC column was noticeably lower than that of one of the precursors, **17**, indicating the formation of a compound with much higher molecular mass. A peak at *m*/*z* 2648.8, present in the MALDI-TOF mass spectrum of the 'click' reaction product obtained from **17** and **28**, corresponded to an $[M+Na]^+$ adduct of **29**. In the ^{13}C NMR spectrum of **29**, intensive signals corresponding to C-1–C-6 of α-D-glucopyranose residues of maltoheptaosyl chains can be observed along with weaker resonances, which can be assigned to the core glucopyranose residue (δ 54.5, OMe), C-1 of glucopyranoses attached to triazole (δ 86.8, OMe) and triazole units (δ 123.9 and 124.0, C-5; δ 143.4 and 143.5, C-4).

To summarize, azide-alkyne 1,3-dipolar cycloaddition of protected saccharides proceeded in moderate to good yields. However, subsequent deprotection, which proved technically demanding, gave only modest yields of target *pseudo*-oligosaccharides. In contrast, saccharide deprotection prior to the key coupling 'click' reaction proved facile access to the ultimate deprotected target compound.

Detailed investigation of conformational properties of branch points of amylopectin by molecular modelling has shown[9,10] that strands of a double helix formed by two parallel α-(1→4)-glucan chains can be connected through an α-(1→6)-glucosidic linkage with minimal distortion of the original polysaccharide conformation. This suggests that the branch points might actually serve to initiate the organisation of glucan chains into double helices, leading to a crystalline arrangement. Clearly, the

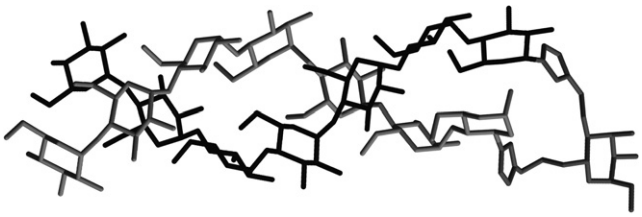


Figure 1. Molecular model of *pseudo*-pentadecasaccharide **29**.

introduction of an unnatural branch point may lead to more extensive disruption of the original double helix. In order to evaluate the potential or otherwise stability of the double helix in the 'click' product **29**, we carried out molecular mechanics optimisation of its structure using OPLS-AA force field.[52] An initial model of **29** was generated using crystallographic data[53] for A-amylose, the crystal lattice of which has α-(1→4)-linked glucan chains arranged in left-handed double helices. Crystallographic coordinates were taken for two heptasaccharide fragments of each parallel strand of the double helix of A-amylose and joined through the reducing ends of these heptasaccharides to a core bis(triazole)-glucopyranoside unit. It was found that the double helical conformation similar to that of the A-form of double helical amylose was preserved in an optimised structure of *pseudo*-starch fragment **29**. At least superficially, the bis(triazole)glycopyranoside unit appears to be suitable as a surrogate for branch points in amylopectin structure (Fig. 1).

3. Conclusion

In summary, we have described the first application of 'click chemistry' based on cycloaddition of substituted azide and alkynes to the synthesis of well-defined branched oligosaccharide mimics. Starting from dipropargylated maltosides and azido maltooligosaccharides, this modular approach allowed the construction of a number of [1,2,3]-triazole-based analogues of amylopectin fragments in one simple coupling step. As synthesis of starting glycosyl azides and propargyl ethers of maltose required the presence of protecting groups, the crucial cycloaddition step can also be carried out with protected carbohydrate components. The protecting groups can be removed after the isolation of a 'click' product or, alternatively, unprotected glycosyl azides and sugar propargyl ethers can be applied. The latter concept was demonstrated by the efficient synthesis of *pseudo*-pentadecasaccharide **29**. The analogues of starch fragments incorporating triazole bridges between two parallel maltoheptaosyl chains and branching maltose or glucose unit have potential for templating formation of double helices observed in crystalline regions of natural starches. Studies to investigate such assembly processes are ongoing.

4. Experimental

4.1. General methods

All solvents were dried and freshly distilled using standard procedures. The reactions were carried out at room temperature (22–24 °C) unless otherwise stated. Cation-exchange resin (Dowex 50WX8-200 (H^+) or Amberlite IR-120 (H^+) was pre-washed with water and dry MeOH before use. Solns of reaction products were dried with $MgSO_4$ or Na_2SO_4 before the solvents were removed by evaporation under was added slowly pressure at 25–40 °C. Thin-layer chromatography (TLC) was performed on aluminium-backed, pre-coated silica gel plates (Silica Gel 60 F_{254}, E. Merck). Spots were detected by immersion in a 5% ethanolic soln of H_2SO_4, followed by heating to 200 °C. Column chromatography was performed on a Biotage Horizon purification system using pre-packed silica gel cartridges. Evaporation of solvents was performed under was added slowly pressure at 25–40 °C. Reagents and dry solvents were added *via* syringes through septa. FT-IR spectra were recorded on a Perkin–Elmer 1720X spectrometer. Optical rotations were measured at 18 °C using a Perkin–Elmer 141 polarimeter. NMR spectra were recorded at 24 °C with a Varian Unity Plus spectrometer at 400 MHz (^1H) or 100.6 MHz (^{13}C) and Varian Gemini 2000 spectrometer at 75 MHz (^{13}C), respectively, using Me_4Si (for solns in $CDCl_3$) or MeOH (δ 49.9, for solns in D_2O) as internal standards. Resonance allocations were made with the aid of COSY and HSQC experiments when necessary. Signals corresponding to resonances of nuclei of aromatic fragments are generally not listed because of the complexity of the corresponding regions of NMR spectra. High resolution electrospray ionisation mass spectra (ESIMS) were obtained on Finnigan MAT 900 XLT mass spectrometer. For compounds with M_w >1000 mass spectra were recorded with an Applied Biosystems Voyager-DE-STR (MALDI-TOF) mass spectrometer or with a Waters ZQ4000 (ESIMS) mass spectrometer and experimental data were matched to theoretical isotope patterns.

4.2. *p*-Methoxyphenyl 2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-β-D-glucopyranoside (2)

Maltose octaacetate (**1**) (13.0 g, 19.1 mmol) was prepared by the reaction of maltose monohydrate (6.9 g, 19 mmol) with Ac_2O (70 mL) in the presence of iodine (500 mg) as described in lit.[43] To a stirred soln of **1** and *p*-methoxyphenol (10.85 g, 87 mmol) in dry CH_2Cl_2 (100 mL) $BF_3{\cdot}OEt_2$ (13.0 mL, 54.6 mmol) was added slowly at 0 °C. After stirring for 12 h at room temperature, the mixture was diluted with CH_2Cl_2 (150 mL), washed successively with water (2 × 80 mL), satd aq

$NaHCO_3$ (2 × 80 mL), water (2 × 80 mL) and dried. The solvent was evaporated and the residue was crystallised from Et_2O (250 mL) to give glycoside **2** (5.8 g, 41%); mp 130–132 °C; $[\alpha]_D$ +49 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 2.01, 2.03, 2.04, 2.05, 2.06, 2.11 (×2) (21H, 6 s, Ac), 3.78 (4H, m, OMe, H-5a), 3.97 (1H, m, H-5b), 4.01 (2H, m, H-4b, H-6), 4.26 (2H, m, 2 × H-6), 4.49 (1H, dd, $J_{5,6}$ 2.9 Hz, $J_{6,6'}$ 12.2 Hz, H-6), 4.87 (1H, dd, $J_{1,2}$ 3.9 Hz, $J_{2,3}$ 10.4 Hz, H-2b), 4.99 (1H, d, $J_{1,2}$ 7.6 Hz, H-1a), 5.06 (2H, m, H-2a, H-4a), 5.32 (1H, t, $J_{2,3} \approx J_{3,4}$ 8.8 Hz, H-3a), 5.37 (1H, t, $J_{2,3} \approx J_{3,4}$ 10.2 Hz, H-3b), 5.44 (1H, d, $J_{1,2}$ 3.9 Hz, H-1b), 6.82 (2H, J_{AB} 9.0 Hz, C_6H_4–OMe), 6.94 (2H, J_{AB} 9.0 Hz, C_6H_4–OMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.7 (×2), 20.8 (×2), 20.9, 21.0, 21.1 (×7, $CH_3C{=}O$), 55.8 (OMe), 61.7, 63.0 (C-6a, C-6b), 68.2, 68.7, 69.5, 70.2, 72.2, 72.4, 72.8, 75.5 (C-2a, C-2b, C-3a, C-3b, C-4a, C-4b, C-5a, C-5b), 95.7 (C-1a), 99.8 (C-1b), 114.7, 114.9, 116.1, 118.9 (C_6H_4–OMe), 150.9, 155.9 (quat. C of C_6H_4–OMe), 169.7, 169.9, 170.2, 170.5, 170.6, 170.5, 170.8 ($CH_3C{=}O$); HRESIMS: found *m/z* 760.2659 $[M+NH_4]^+$. Calcd for $C_{33}H_{42}O_{19}+NH_4$ 760.2659.

4.3. *p*-Methoxyphenyl 6-*O*-triphenylmethyl-4-*O*-(6-*O*-triphenylmethyl-α-D-glucopyranosyl)-β-D-glucopyranoside (3)

A soln of maltoside **2** (4.00 g, 5.27 mmol) in dry MeOH (40 mL) was treated with 0.2 M NaOMe in MeOH (10 mL) and the mixture was stirred until the reaction was complete (TLC). The mixture was neutralised with Dowex 50WX8-200 (H^+) resin, the resin was removed by filtration and the filtrate was concentrated and dried. The residue was dissolved in pyridine (30 mL), Ph_3CCl (5.80 g, 21.1 mmol) was added, the mixture was stirred for 2 days and pyridine was removed by evaporation. The residue was dissolved in CH_2Cl_2 (150 mL), successively washed with 1 M HCl (2 × 80 mL), $NaHCO_3$ (2 × 80 mL), water (80 mL) and the soln was dried and concentrated. The residue was purified by column chromatography (3:2 Me_2CO–CH_2Cl_2) to afford compound **3** (3.10 g, 42%) as amorphous white solid; $[\alpha]_D$ +21.5 (*c* 1.05, $CHCl_3$); ^1H NMR (400 MHz, CD_3OD): δ 2.86 (1H, dd, $J_{5,6'}$ 4 Hz, $J_{6,6'}$ 10.2 Hz, H-6), 2.97 (1H, dd, $J_{5,6}$ 8.4 Hz, $J_{6,6'}$, H-6), 3.21–3.30 (3H, m, H-6, H-5a, H-5b), 3.43–3.71 (13H, m, H-2, H-3, H-4, H-5, H-6, OMe), 4.80 (1H, d, $J_{1,2}$ 7.8 Hz, H-1a), 4.80 (1H, d, $J_{1,2}$ 2.9 Hz, H-1b), 6.83 (2H, d, J_{AB} 9.0 Hz, C_6H_4OMe), 7.06 (2H, d, J_{AB} 9.0 Hz, C_6H_4OMe); ^{13}C NMR (100 MHz, CD_3OD): δ 54.9 (OMe), 62.3, 63.8 (C-6a, C-6b), 69.9, 72.2, 72.8, 73.4, 73.9, 74.4, 77.4, 79.3, (C-2–C-5), 86.2, 86.8 (CPh_3), 100.9 (C-1b), 102.1 (C-1a), 114.3, 118.3 (2 × C_6H_4–OMe), 152.0, 155.4 (2 × quat. C_6H_4–OMe); HRESIMS: found *m/z* 950.4103 $[M+NH_4]^+$. Calcd for $C_{57}H_{56}O_{12}+NH_4$ 950.4110.

4.4. *p*-Methoxyphenyl 2,3-di-*O*-benzyl-6-*O*-triphenylmethyl-4-*O*-(2,3-di-*O*-benzyl-6-*O*-triphenylmethyl-α-D-glucopyranosyl)-β-D-glucopyranoside (4)

Benzylation of maltoside (**3**) (3.01 g, 3.22 mmol) was achieved by treatment of its soln in dry DMF (40 mL) with 60% suspension of NaH in mineral oil (1.28 g, 32.2 mmol) followed by addition of BnBr (3.80 mL, 32.2 mmol) at 0 °C and stirring the mixture at room temperature for 17 h. After careful addition of MeOH (10 mL) at 0–10 °C and concentration, the mixture was diluted with CH_2Cl_2 (200 mL), washed with water (3 × 80 mL), dried and concentrated again. The product was purified by chromatography (toluene/EtOAc, 10:0→9:1) to **4** as a white foam (3.21 g, 94%); $[\alpha]_D$ +16.5 (*c* 1.05, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 3.03 (1H, dd, $J_{5,6}$ 4.7 Hz, $J_{6,6'}$ 9.7 Hz, H-6a), 3.21–3.30 (2H, m, H-5, H-6′a), 3.36–3.41 (2H, m, H-3b, H-6b), 3.45–3.53 (3H, m, H-2b, H-4b, H-6′b), 3.72 (3H, s, OMe), 3.86–3.97 (3H, m, H-2a, H-3a, H-5a), 4.15–5.13 (10H, H-1a, H-4a, CH_2Ph), 5.78 (1H, d, $J_{1,2}$ 3.5 Hz, H-1b), 6.79 (2H, d, J_{AB} 8.9 Hz, C_6H_4OMe), 6.98 (2H, d, J_{AB} 8.9 Hz, C_6H_4OMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.6 (OMe), 62.2 (C6a), 63.9 (C-6b), 70.6 (C-4a), 71.2 (C-5b), 73.1, 73.2 (2 × CH_2Ph), 74.6 (C-5a), 74.9, 75.1, 75.9 (3 × CH_2Ph), 78.1, 79.7 (C-2b, C-4b), 82.1 (C-3b), 82.3 (C-3a), 85.4 (C-3a), 86.3, 86.8 (2 × CPh_3), 95.0 (C-1b), 102.9 (C-1a), 114.8, 118.6 (2 × C_6H_4–OMe), 151.9, 155.5 (2 × quat. C_6H_4–OMe); ESIMS: *m/z* 1406.8 $[M+Na]^+$.

4.5. *p*-Methoxyphenyl 2,3-di-*O*-benzyl-4-*O*-(2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl)-β-D-glucopyranoside (5)

Detritylation of **4** (2.55 g, 1.84 mmol) was carried out in the presence of TsOH (2.0 g) in 1:1 MeOH–$CHCl_3$ (40 mL) for 5 h. Then the mixture was neutralised with a satd aq $NaHCO_3$ soln, concentrated to a half of the volume, diluted in CH_2Cl_2 (100 mL), washed with water (2 × 40 mL) and the organic layer was dried. The product was purified by chromatography (25:75→3:7 toluene–EtOAc) to give diol **5** as a white amorphous solid (1.49 g, 90%); $[\alpha]_D$ +27 (*c* 1.16, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 3.39–3.49 (2H, m, H-2b, H-4b), 3.57–3.65 (2H, m, H-6, H-5a), 3.69–3.96 (5H, m, H-2a, H-5b, OMe), 3.86–3.96 (5H, m, 3 × H-6, H-4a, H-3b), 4.15 (1H, t, $J_{3,4} \approx J_{4,5}$ 8.8 Hz, H-4a), 4.49–5.02 (11H, m, H-1a, CH_2Ph), 5.75 (1H, d, $J_{1,2}$ 3.8 Hz, H-1b), 6.84 (2H, d, J_{AB} 9.6 Hz, C_6H_4OMe), 6.98 (2H, d, J_{AB} 9.6 Hz, C_6H_4OMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.9 (OMe), 61.6, 62.3 (C-6a, C-6b), 71.5 (C-3a), 72.6 (C-2a), 73.7, 74.3 (CH_2Ph), 75.0 (C-5a), 75.2, 75.5,

75.8 (3 × CH_2Ph), 78.4, 79.5 (C-2b, C-4b), 82.1, 82.3 (C-3b, C-5b), 84.9 (C-4a), 97.1 (C-1b), 102.8 (C-1a), 115.0, 118.5 (2 × C_6H_4–OMe), 150.9, 155.9 (2 × quat. C_6H_4–OMe); HRESIMS: found *m/z* 916.4269 $[M+NH_4]^+$. Calcd for $C_{54}H_{58}O_{12}+NH_4$ 916.4269.

4.6. *p*-Methoxyphenyl 2,3-di-*O*-benzyl-6-*O*-(prop-2-ynyl)-4-*O*-(2,3,4-tri-*O*-benzyl-6-*O*-(prop-2-ynyl)-α-D-glucopyranosyl)-β-D-glucopyranoside (6)

A mixture of maltoside **5** (500 mg, 0.556 mmol) and propargyl bromide (2.22 mmol, 200 μL) was dried by evaporation of its toluene soln (three times) and then dissolved in 3:1 THF–DMPU (5 mL). The soln was cooled to 0 °C and 60% suspension of NaH in mineral oil (90 mg, 2.22 mmol) was added slowly under nitrogen. The reaction mixture was stirred at room temperature for 6 h, carefully treated with water (10 mL) and diluted with EtOAc (100 mL). The organic phase was washed with brine (3 × 30 mL), water (2 × 30 mL) and dried (Na_2SO_4). The product was purified by chromatography (4:1 hexane–EtOAc) affording **6** (478 mg, 88%) as a syrup; $[\alpha]_D$ +23 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.30–2.37 (2H, m, $CH_2C{\equiv}CH$), 3.52 (1H, dd, $J_{1,2}$ 3.6 Hz, $J_{2,3}$ 9.8 Hz, H-2b), 3.62–3.95 (13H, m, OMe, H-2a, H-3a, H-3b, H-4b, H-5a, H-5b, 4 × H-6), 4.10 (1H, t, $J_{3,4} \approx J_{4,5}$ 9.5 Hz, H-4a), 4.11–4.26 (4H, m, $CH_2C{\equiv}CH$), 4.52 (1H, d, *J* 11.6 Hz, CH_2Ph), 4.60 (1H, d, *J* 11.6 Hz, CH_2Ph), 4.69 (2H, d, *J* 11.5 Hz, CH_2Ph), 4.76–5.01 (7H, m, H-1b, CH_2Ph), 5.69 (1H, d, $J_{1,2}$ 3.6 Hz, H-1b), 6.84 (2H, d, J_{AB} 9.2 Hz, C_6H_4OMe), 7.02 (2H, d, J_{AB} 9.2 Hz, C_6H_4OMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.6 (OMe), 58.5, 58.8 ($CH_2C{\equiv}CH$), 68.0, 68.5 (2 × C-6), 70.8, 72.3, 73.3, 73.9, 74.3, 74.7, 74.8 (×2), 74.9, 75.0, 75.4, 79.2, 79.3, 79.5, 82.0 (×2), 84.6 (C-2a, C-2b, C-3a, C-3b, C-4a, C-4b, C-5a, C-5b, 5 × CH_2Ph, 2 × $CH_2C{\equiv}CH$), 96.9 (C-1b), 102.7 (C-1a), 114.6, 118.5 (2 × C_6H_4–OMe), 151.5, 155.5 (2 × quat. C_6H_4–OMe); HRESIMS: found *m/z* 992.4583 $[M+NH_4]^+$. Calcd for $C_{60}H_{62}O_{12}+NH_4$ 992.4580.

4.7. *p*-Methoxyphenyl 4-*O*-(4,6-*O*-benzylidene-α-D-glucopyranosyl)-β-D-glucopyranoside (7)

Maltoside **2** (2.94 g, 3.88 mmol) was deacetylated with 0.04 M NaOMe in MeOH (38 mL) as described in the preparation of **3**. Deprotected maltoside was dissolved in DMF (20 mL) and $PhCH(OMe)_2$ (1.16 mL, 7.76 mmol) and $TsOH{\cdot}H_2O$ (50 mg) were added. The mixture was stirred for 12 h, neutralised with Et_3N and concentrated. The resulting residue was purified by column chromatography (7:3 Me_2CO–CH_2Cl_2) to give **7** (1.30 g, 65%); $[\alpha]_D$ +27 (*c* 0.9, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 3.91–4.22 (15H, m, H-2–H-6, OMe), 4.79 (1H, d, $J_{1,2}$ 7.7 Hz, H-1a), 4.86 (1H, s, C*H*Ph), 5.22 (1H, d, $J_{1,2}$ 3.7 Hz, H-1b), 6.83 (2H, d, J_{AB} 9.2 Hz, C_6H_4OMe), 7.05 (2H, d, J_{AB} 9.2 Hz, C_6H_4–OMe), 6.71 (2H, d, J_{AB} 9.0 Hz, C_6H_4OMe), 6.96 (2H, d, J_{AB} 9.0 Hz, C_6H_4–OMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.7 (OMe), 61.2, 63.8 (C-6a, C-6b), 68.7, 7.90, 73.1, 73.3, 74.8, 76.0, 79.8, 80.7 (C-2–C-5), 101.8, 102.0 (C-1a, C-1b), 102.2 (*C*HPh), 115.6, 119.4 (2 × C_6H_4–OMe), 153.3, 158.95 (2 × quat. C_6H_4OMe); HRESIMS: found *m/z* 554.2230 $[M+NH_4]^+$. Calcd for $C_{26}H_{32}O_{12}+NH_4$ 554.2232.

4.8. *p*-Methoxyphenyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranosyl)-β-D-glucopyranoside (8)

To a soln of maltoside **7** (334 mg, 0.62 mmol) in dry DMF (5 mL), a 60% suspension of NaH in mineral oil (186 mg, 4.65 mmol) was added slowly followed by the addition of BnBr (550 μL, 4.65 mmol) at 0 °C. The mixture was then stirred for 12 h at room temperature, carefully treated with MeOH (1 mL) and concentrated. The residue was mixed with CH_2Cl_2 (100 mL), the organic soln was washed with water (3 × 30 mL), dried and concentrated again. The product was purified by chromatography (0:10→4:1 EtOAc–hexane) to give **8** (560 mg, 92%) as an amorphous solid; $[\alpha]_D$ +3.8 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.60 (1H, dd, $J_{1,2}$ 3.8 Hz, $J_{2,3}$ 9.4 Hz, H-2b), 3.66–3.98 (10H, m, OMe, H-3a, H-4b, H-5a, H-5b, 3 × H-6), 4.08 (1H, t, $J_{2,3} \approx J_{3,4}$ 9.4 Hz, H-3b), 4.25 (2H, m, H-4a, H-6), 4.62–5.12 (11H, m, H-1a, CH_2Ph), 5.62 (1H, s, C*H*Ph), 5.80 (1H, d, $J_{1,2}$, H-1b), 6.89 (2H, d, J_{AB} 9.1 Hz, C_6H_4OMe), 7.13 (2H, d, J_{AB} 9.1 Hz, C_6H_4–OMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.6 (OMe), 63.3, 68.8, 68.9, 72.1, 74.0, 74.5, 78.7 (×2), 82.2, 82.3, 84.9 (C-2–C-6), 73.5 (×2), 73.8, 74.9, 75.3, (5 × CH_2–Ph), 97.5 (C-1b), 101.2 (C-1a), 102.9 (*C*H–Ph), 114.7, 118.8 (2 × C_6H_4–OMe), 151.6, 155.65 (2 × quat. C_6H_4OMe); HRESIMS: found *m/z* 1004.4588 $[M+NH_4]^+$. Calcd for $C_{61}H_{64}O_{12}+NH_4$ 1004.4580.

4.9. *p*-Methoxyphenyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3-di-*O*-benzyl-α-D-glucopyranosyl)-β-D-glucopyranoside (9)

A soln of the benzylidene derivative **8** (548 mg, 0.55 mmol) in 1:10 AcOH–water (11 mL) was heated at 80 °C for 4 h. After concentration, the residue was purified by chromatography (4:1 hexane–EtOAc) affording **9** (381 mg, 77%) as a syrup; $[\alpha]_D$ +16 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.40 (1H, dd, $J_{1,2}$ 3.6 Hz, $J_{2,3}$ 9.5 Hz, H-2b), 3.50 (1H, t, $J_{3,4} \approx J_{4,5}$ 8.8 Hz, H-4b), 3.64–3.87 (10H, m, H-3b, H-5, H-6, OMe), 3.86 (1H, t, $J_{2,3} \approx J_{3,4}$ 8.8 Hz, H-3a), 4.12 (1H, t, $J_{3,4} \approx J_{4,5}$ 8.9 Hz, H-4a), 4.53–5.04 (11H, m, H-1a,

CH_2Ph), 5.66 (1H, d, $J_{1,2}$, H-1b), 6.81 (2H, d, J_{AB} 8.8 Hz, C$_6H_4$OMe), 7.20 (2H, d, J_{AB} 8.8 Hz, C$_6H_4$OMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.5 (OMe), 62.2, 70.3, 71.9, 72.3, 73.0 (×2), 73.4, 73.9, 74.7 (×2), 75.1, 79.0, 81.0, 81.9, 84.7 (C-2–C-6, 5 × CH_2Ph), 96.5 (C-1b), 102.7 (C-1a), 114.6, 118.6 (2 × C$_6$H$_4$–OMe), 151.5, 155.5 (2 × quat. C$_6$H$_4$OMe); HRESIMS: found m/z 916.4266 $[M+NH_4]^+$. Calcd for $C_{54}H_{58}O_{12}$+NH_4 916.4267.

4.10. *p*-Methoxyphenyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3-di-*O*-benzyl-4,6-di-*O*-(prop-2-ynyl)-α-D-glucopyranosyl)-β-D-glucopyranoside (10)

Diol **8** (368 mg, 0.410 mmol) and propargyl bromide (1.64 mmol, 146 μL) were dried by concentration (three times) of their soln in dry toluene, then dissolved in 3:1 THF-DMPU (4 mL) and the soln was cooled to 0 °C. A 60% suspension of NaH in mineral oil (66 mg, 1.64) was added slowly to the mixture which was stirred for 6 h at room temperature. After careful addition of water (10 mL), the mixture was diluted with EtOAc (100 mL) and the organic phase was washed with brine (3 × 30 mL), water (2 × 30 mL) and dried with Na_2SO_4. The crude product was purified by chromatography (9:1→4:1 hexane–EtOAc) affording **10** (370 mg, 93%) as a gum; $[\alpha]_D$ +25 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41–2.45 (2H, m, 2 × CH_2C≡C*H*), 3.43 (1H, dd, $J_{1,2}$ 3.6 Hz, $J_{2,3}$ 9.8 Hz, H-2b), 3.46–3.53 (2H, m, H-4b, H-6), 3.67–3.89 (11H, m, H-2a, H-3b, H-4a, H-5a, H-5b, 3 × H-6, OMe), 4.02 (1H, dd, *J* 2.2 Hz, *J* 16 Hz, CH_2C≡CH), 4.10 (1H, t, $J_{2,3}$ 8.6 Hz, H-4a), 4.18 (1H, dd, *J* 2.2 Hz, *J* 16 Hz, CH_2C≡CH), 4.38 (2H, m, CH_2C≡CH), 4.74–5.02 (11H, m, H-1a, CH_2Ph), 5.66 (1H, d, $J_{1,2}$ 3.6 Hz, H-1b), 6.80 (2H, d, J_{AB} 9.0 Hz, C$_6H_4$OMe), 7.04 (2H, d, J_{AB} 9.0 Hz, C$_6H_4$OMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.5 (OMe), 58.4 (*C*H$_2$C≡CH), 60.0 (*C*H$_2$C≡CH), 67.7 (C-6), 68.9 (C-6), 70.4, 72.7, 73.2, 73.4, 73.9, 74.1 (×2), 74.7, 74.8, 75.4, 77.2, 78.9, 79.3, 80.0, 81.5, 82.0, 84.6 (C-2–C5, 5 × *C*H$_2$–Ph, 2 × *C*H$_2$*C*≡CH), 96.8 (C-1a), 102.7 (C-1b), 114.6, 118.5 (2 × C$_6$H$_4$–OMe), 151.5, 155.4 (2 × quat. C$_6$H$_4$OMe); HRESIMS: found m/z 992.4585 $[M+NH_4]^+$. Calcd for $C_{60}H_{66}O_{12}$+NH_4 992.4585.

4.11. (2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl)-(1→4)-(2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl azide (15)

To a soln of bromide[45] **2** (1 g, 1.01 mmol) and Me_3SiN_3 (174 μL, 1.31 mmol) in dry THF (10 mL), a 1 M soln of TBAF in THF (1.31 mL) previously dried over activated 4 Å molecular sieves was added. The soln was stirred for 4 h, filtered through a plug of silica gel, dried over Na_2SO_4 and concentrated. The crude product was purified by chromatography (3:2→1:1 hexane–EtOAc) affording azide **15** (630 mg, 65%) as a white amorphous solid; ν_{max} 2119 cm^{-1} (N_3); $[\alpha]_D$ +65 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.00 (×2), 2.01, 2.02, 2.04 (×2), 2.06 (×2), 2.11, 2.17 (10 × Ac), 3.83 (1H, m, H-5), 3.92–4.07 (5H, m, H-4a, H-4b, H-5b, H-5c, H-6), 4.17–4.53 (5H, m, 5 × H-6), 4.71–4.80 (3H, m, H-1a, H-2a, H-2b), 4.86 (1H, dd, $J_{1,2}$ 4.0 Hz, $J_{2,3}$ 10.6 Hz, H-2c), 5.08 (1H, t, $J_{3,4} \approx J_{4,5}$ 10.1 Hz, H-4c), 5.24–5.30 (2H, m, H-1b, H-1c, H-3c), 5.33–5.43 (3H, m, H-1b, H-3b, H-3c); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.2–20.5 (*C*H$_3$C=O), 61.15, 62.1, 62.5 (3 × C-6), 67.6, 68.3, 69.8, 70.2, 71.2, 71.4, 72.3, 73.3, 73.9, 74.6 (C-2–C-5), 87.1 (C-1a), 95.5, 95.7 (C-1b, C-1c), 169.3–170.5 (CH$_3$*C*=O); HRESIMS: found m/z 972.2704 $[M+Na]^+$. Calcd for $C_{38}H_{51}N_3O_{25}$+Na 972.2693.

4.12. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl-{(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl}$_5$-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl azide (16)

Peracetylated maltoheptaose **13**[45] (1.08 g, 0.505 mmol) was dissolved in dry CH_2Cl_2 (6 mL), the soln was cooled with an ice bath and 33% HBr in AcOH (2 mL) was added. After 2 h at room temperature the soln was diluted with CH_2Cl_2 (100 mL) and washed successively with ice-water (2 × 30 mL), cold satd aq $NaHCO_3$ (3 × 30 mL) and water (30 mL). The organic phase was separated, concentrated and crystallised (Et_2O–hexane) affording α-maltoheptaosyl bromide **13** (1.00 g, 96%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.86–4.28 (22H, m), 4.43–4.60 (6H, m), 4.65–4.75 (5H, m), 4.83 (1H, *J* 3.8 Hz, *J* 10.2 Hz), 5.05 (1H, t, *J* 9.8 Hz), 5.24–5.42 (10H, m, H-1b-g), 5.58 (1H, t, *J* 9.5 Hz), 6.48 (1H, d, $J_{1,2}$ 3.8 Hz, H-1a); ^{13}C NMR (75 MHz, $CDCl_3$): δ 86.0 (C-1a), 95.6, 95.7 (5 × C-1); MALDI-TOFMS m/z found: 2163.6 $[M+Na]^+$. Calcd for $C_{86}H_{115}O_{57}Br$+Na 2163.5. To a soln of **13** (1.00 g, 0.46 mmol), Bu_4NHSO_4 (340 mg, 0.50 mmol) and NaN_3 (260 mg, 2.00 mmol) in CH_2Cl_2 (10.0 mL) was added satd aq $NaHCO_3$ (10.0 mL). The mixture was stirred for 2 h and diluted with EtOAc (100 mL). The organic phase was separated, washed successively with satd aq $NaHCO_3$ (40 mL) and water (2 × 40 mL), dried and concentrated. After purification by chromatography (85:15→75:25 toluene–Me_2CO), the crude product was crystallised from EtOH affording azide **16** (740 mg, 77%); mp 127–130 °C; ν_{max} 2119 cm^{-1} (N_3); $[\alpha]_D$ +159 (*c* 1.0, $CHCl_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.3, 20.6 (*C*H$_3$C=O), 61.3, 62.1, 62.3, 62.4, 62.5 (C-6), 67.9, 68.3, 68.8, 68.9, 69.0, 69.2, 69.9, 70.3, 70.4, 71.4, 71.5, 72.4, 73.3, 73.4, 73.5, 74.1, 74.8 (C-2–C-5), 87.3 (C-1a), 95.5, 95.6 (C-1), 169.4–170.7 (CH$_3$*C*=O). MALDI-TOFMS: m/z 2124.5 $[M+Na]^+$.

4.13. α-D-Glucopyranosyl-{(1→4)-α-D-glucopyranosyl}$_5$-(1→4)-β-D-glucopyranosyl azide (17)

To a soln of acetate **16** in THF/MeOH (4:1, 5 mL), 0.1 M NaOMe in MeOH (0.5 mL) was added and the mixture was stirred at room temperature. After 10 min a white precipitate formed, the mixture was stirred for 1 h and concentrated to dryness. The residue was dissolved in water (5 mL), stirred for 2 h and neutralised with Amberlite IRA-120 (H^+). The resin was filtered off and the filtrate was freeze-dried to give **17** (95%) as a white powder, $[\alpha]_D$ +160 (*c* 1.0, H_2O); ^{13}C NMR (75 MHz, D_2O, signal intensity is not indicated): δ 59.9 (C-6), 68.7, 70.6, 70.9, 71.0, 72.1, 72.3, 75.6, 75.8, 75.9, 76.2, 76.3 (C-2–C-5), 89.4 (C-1x), 99.0–99.2 (C-1); MALDI-TOFMS: *m*/*z* 1200.5 $[M+Na]^+$.

4.14. General procedure for the synthesis of 18, 19, 21 and 22 by 1,3-dipolar cycloaddition using protected carbohydrates

A mixture of a di-*O*-propargylated maltoside (1.0 equiv), a glycosyl azide (2.2 equiv), *i*-Pr_2NEt (3.0 equiv) and $(Ph_3P)_3CuBr$ (0.11 equiv) in dry toluene (5.0 mL) was stirred for 12 h. The mixture was concentrated and the product was purified by chromatography.

4.15. *p*-Methoxyphenyl (1-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-1*H*-[1,2,3]triazol-4-ylmethyl)-(4→6)-(2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-[(1-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-1*H*-[1,2,3]triazol-4-ylmethyl)-(4→6)]-2,3-di-*O*-benzyl-β-D-glucopyranoside (18)

This was synthesised from **6** (138 mg, 0.14 mmol) and **14** (116 mg, 0.31 mmol) and purified by chromatography (6:4 EtOAc–hexane) to give **8** (153 mg, 63%) as a white foam; $[\alpha]_D$ −5.4 (*c* 1.06, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.79, 1.62, 1.95, 2.02 (×2), 2.03, 2.07 (24H, s, Ac), 3.50 (1H, dd, $J_{1,2}$ 3.5 Hz, $J_{2,3}$ 9.7, H-2b), 3.59 (1H, t, $J_{3,4} \approx J_{4,5}$ 9.5 Hz, H-4b), 3.64–4.32 (16H, m, H-3a, H-3b, H-4a, 4 × H-5, 8 × H-6, OMe), 4.50–5.00 (15H, m, H-1a, 10 × CH_2Ph, 2 × CH_2 triazole), 5.27–5.58 (7H, m, H-1b, H-2c, H-2d, H-3c, H-3d, H-4c, H-4d), 5.87 (1H, d, $J_{1,2}$ 3.3 Hz, H-1c or H-1d), 5.91 (1H, d, $J_{1,2}$ 3.1 Hz, H-1d or H-1c), 6.85 (2H, J_{AB} 9.0 Hz, C_6H_4OMe), 7.00 (2H, J_{AB} 9.0 Hz, C_6H_4OMe), 7.7 (1H, s, triazole), 8.02 (1H, s, triazole), δ_C (75 MHz, $CDCl_3$): δ 19.9, 20.4, 20.45 (8 × CH_3C=O), 55.5 (OMe), 60.5 (×2, C-6c, C-6d), 63.9, 64.0 (CH_2 triazole), 68.4 (×2, C-6a, C-6b), 85.5, 85.7 (C-1c, C-1d), 97.6 (C-1b), 102.2 (C-1a), 113.8, 117.3 (C_6H_4–OMe), 120.8 (C-5 triazole), 144.8, 144.9 (C-4 triazole), 151.4, 155.4 (C_6H_4–OMe); MALDI-TOFMS: *m*/*z* 1744.7 $[M+Na]^+$.

4.16. *p*-Methoxyphenyl (2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-(1→4)-(2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl)-(1→4)-(1-(2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl)-1*H*-[1,2,3]triazol-4-ylmethyl)-(4→6)-(2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-[(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-(1→4)-(2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl)-(1→4)-(1-(2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl)-1*H*-[1,2,3]triazol-4-ylmethyl)-(4→6)]-2,3-di-*O*-benzyl-β-D-glucopyranoside (19)

This was synthesised following the general procedure using *p*-methoxyphenyl maltoside **6** (111 mg, 0.11 mmol) and maltotriosyl azide **15** (235 mg, 0.31 mmol). The residue was purified by chromatography (7:3 EtOAc–hexane) to give **19** (207 mg, 65%) as a white solid; $[\alpha]_D$ +61 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): 1.77–2.16 (60H, s, CH_3–C=O), 3.50 (1H, dd, $J_{1,2}$ 3.6 Hz, $J_{2,3}$ 9.8 Hz, H-2b), 4.93 (1H, d, $J_{1,2}$ 9.0 Hz, H-1a), 5.30–5.48 (8H, m, 4 × H-1e,f, H-2c, H-2d, H-3c, H-3d), 5.61 (1H, d, $J_{1,2}$ 3.6 Hz, H-1b), 5.75 (1H, d, $J_{1,2}$ 8.8 Hz, H-1c or H-1d), 5.85 (1H, d, $J_{1,2}$ 9.1 Hz, H-1d or H-1c), 6.87 (2H, J_{AB} 9.1 Hz, C_6H_4OMe), 7.02 (2H, J_{AB} 9 Hz, C_6H_4OMe), 7.69 (1H, s, triazole), 7.72 (1H, s, triazole); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.6 (OMe), 85.0, 85.1 (C-1c, C-1d), 95.7 (×2), 96.1 (×2) (C-1e–C-1h), 97.1 (C-1b), 102.3 (C-1a), 114.7, 118.2 (C_6H_4–OMe), 121.4, 121.8 (C-5 triazole), 145.5, 145.9 (C-4 triazole), 151.4, 155.4 (C_6H_4–OMe); MALDI-TOFMS: *m*/*z* 2897.1 $[M+Na]^+$.

4.17. Deprotection of 19

Compound **19** (90 mg, 0.031 mmol) was dissolved in 1:1 EtOAc–EtOH (12 mL) and hydrogenated in the presence of cat. 10% Pd/C for 24 h at 35 °C. The catalyst was removed by filtration, the filtrate was concentrated and the residue was dissolved in CH_2Cl_2/MeOH mixture (1:4, 5 mL). NaOMe (1 M) in MeOH (0.5 mL) was added to the mixture, which was then stirred for 2 h and concentrated. The residue was dissolved in water (5 mL) and the soln was stirred for 17 h. The soln was diluted with water, neutralised with Amberlite IRA-120 (H^+), the resin was filtered off, washed with water and combined aqueous filtrates were concentrated. The product was purified by gel chromatography (TSK gel Toyopearl HW 40S, 1.5 × 85 cm) in 0.1% CF_3CO_2H. The target product was collected in fractions eluted with 85–110 mL with a peak maximum at 100 mL; maltotriose was eluted with a peak maximum at 111 mL. Deprotected compound **20** (25 mg, 51%), ESIMS: *m*/*z* 1583.1 $[M+H]^+$.

4.18. *p*-Methoxyphenyl (2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-(1→4)-{2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl)-(1→4)}$_5$-(2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-1*H*-[1,2,3]triazol-4-ylmethyl)-(4→6)-(2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→4)-[(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-(1→4)-{(2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl)-(1→4)}$_5$-(2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-1*H*-[1,2,3]triazol-4-ylmethyl)-(4→6)]-2,3-di-*O*-benzyl-β-D-glucopyranoside (21)

This was synthesised following the general procedure from **6** (60 mg, 0.061 mmol) and **16** (280 mg, 0.13 mmol). The product was purified by chromatography (6:3→9:1 EtOAc–hexane) to give the title compound (121 mg, 38%) as a white foam; $[\alpha]_D$ +108 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.62 (1H, d, $J_{1,2}$ 3.6 Hz, H1-b), 5.73 (1H, d, $J_{1,2}$ 8.8 Hz, H1-d), 5.84 (1H, d, $J_{1,2}$ 9.2 Hz, H1-c), 6.88 (2H, d, J_{AB} 9.2 Hz, C_6H_4OMe), 7.01 (2H, d, J_{AB} 9.0 Hz, C_6H_4OMe), 7.67 (1H, s, triazole), 7.71 (1H, s, triazole); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.6 (OMe) 84.7, 85.0 (C-1c, C-1d), 95.6, 95.7, 96.1 (C-1e, C-1f), 97.1 (C-1b), 102.2 (C-1a), 114.8, 118.2 (C_6H_4–OMe), 121.4, 121.8 (C-5 triazole), 145.5, 145.9 (C-4 triazole), 151.4, 155.3 (C_6H_4–OMe); MALDI-TOFMS: *m*/*z* 5202.7 $[M+Na]^+$.

4.19. *p*-Methoxyphenyl (2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-(1→4)-{2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl)-(1→4)}$_5$-(2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-1*H*-[1,2,3]triazol-4-ylmethyl)-(4→4)-[(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-(1→4)-{(2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl)-(1→4)}$_5$-(2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl-1*H*-[1,2,3]triazol-4-ylmethyl)-(4→6)]-2,3-di-*O*-benzyl-β-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (22)

This was synthesised from maltoside **10** (60 mg, 0.061 mmol) and maltoheptaosyl azide **16** (280 mg, 0.13 mmol) as described in the general procedure. Purification of the product by chromatography (3:2→9:1 EtOAc–hexane) gave the title compound as a white foam (85.5 mg, 27%); $[\alpha]_D$ +126 (*c* 1.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.64 (1H, d, $J_{1,2}$ 3.3 Hz, H1-b), 5.82 (1H, d, $J_{1,2}$ 8.8 Hz, H1-c/d), 5.87 (1H, d, $J_{1,2}$ 9.0 Hz, H1-c/d), 6.81 (2H, d, J_{AB} 9.0 Hz, C_6H_4OMe), 7.03 (2H, d, J_{AB} 9.0 Hz, C_6H_4OMe), 7.60 (1H, s, triazole), 7.74 (1H, s, triazole);^{13}C NMR (100 MHz, $CDCl_3$): 85.5 (C-1c, C-1d), 95.2–96.2 (C-1e, C-1f), 97.1 (C-1b), 103.0 (C-1a), 114.8, 118.2 (C_6H_4–OMe), 121.4, 121.8 (C-5 triazole), 151.4, 155.3 (C_6H_4–OMe); MALDI-TOFMS: *m*/*z* 5202.7 $[M+Na]^+$.

4.20. Methyl [(2′*R*,3′*R*)-2,3-dimethoxybutane-2′,3′-diyl]-6-*O*-triphenylmethyl-α-D-glucopyranoside (26)

Camphorsulfonic acid (230 mg, 1.00 mmol) was added to a soln of **23** (2.00 g, 10.31 mmol), $(MeO)_3CH$ (12.4 mL, 11.4 mmol) and 1,4-butanedione (2.0 mL, 23 mmol) in dry MeOH (40 mL). After refluxing for 18 h, the mixture was neutralised by the addition of Et_3N and concentrated to give a dark brown syrup. The syrup was dissolved in 2:1 CH_2Cl_2–hexane (200 mL) and the products were extracted with water (6 × 50 mL). The combined aqueous extracts were concentrated and the residual water was removed by repeated evaporation of the solvent from a toluene soln of the products. After drying the residue, a crude mixture of **24** and **25** (3.1 g, 97%) was obtained as a yellow syrup. ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.4, 17.5 (4 × acetal C*Me*), 47.6, 47.7 (×2), 47.8 (4 × acetal OMe), 54.9, 55.1 (2 × anomeric OMe), 60.8, 61.6 (2 × C-6), 65.8, 67.6, 68.1, 69.3, 69.7 (×2), 69.9, 71.8 (C-2–C-5), 98.0, 99.4, 99.5, 99.6 (×2), 99.8 (2 × C-1, 4 × acetal $C_{quat.}$). The crude mixture was dissolved in pyridine, Ph_3CCl (2.79 g, 10.0 mmol) was added and the mixture was stirred for 18 h at 40 °C. CH_2Cl_2 (150 mL) was added, the mixture was washed with water (50 mL), dried and concentrated. The residue was purified by chromatography (pet. ether/EtOAc, 8:2→1:1) to afford trityl ether **26** (2.15 g, 38%), which was eluted first. Compound **26**, $[\alpha]_D$ −48 (*c* 1.8, $CHCl_3$); δ ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (3H, s, acetal CMe), 1.36 (3H, s, acetal CMe), 3.28, 3.29 (6H, 2 × s, acetal OMe), 3.39 (2H, m, H-6, H-6′), 3.42 (3H, s, anomeric OMe), 3.70–3.82 (3H, H-2, H-4, H-5), 4.20 (1H, t, $J_{2,3} \approx J_{3,4}$ 9.0 Hz, H-3), 4.67 (1H, d, *J* 3.5 Hz, H-1), 7.22–7.33 (9H, m, Ph), 7.46–7.48 (6H, m, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.7, 17.6 (2 × acetal C*Me*), 47.7, 47.9 (2 × acetal OMe), 54.8 (anomeric OMe), 63.8 (C-6), 68.1, 69.2, 69.6, 70.5 (C-2–C-5), 87.0 (*C*Ph_3), 97.9 (C-1), 99.4, 99.9 (acetal $C_{quat.}$), 127.1, 127.9, 128.7, 143.8 (Ph); HRESIMS: found *m*/*z* 573.2465. Calcd for $C_{32}H_{38}O_8$+Na 573.2459. Acetylation of a small sample of **26** gave its 4-acetate, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (3H, s, acetal CMe), 1.34 (3H, s, acetal CMe), 1.73 (Ac), 3.08–3.18 (2H, m, H-6, H-6′), 3.20, (3H, s, acetal OMe), 3.26 (3H, s, acetal OMe), 3.52 (3H, s, anomeric OMe), 3.86 (1H, dd, $J_{1,2}$ 3.5, $J_{2,3}$ 10.2 Hz, H-2), 4.08 (1H, t, $J_{2,3} \approx J_{3,4}$ 10.2 Hz, H-3), 4.67 (1H, d, H-1), 4.99 (1H, t, $J_{3,4} \approx J_{4,5}$ 10.2 Hz, H-4), 7.14–7.33 (9H, m, Ph), 7.40–7.48 (6H, m, Ph).

4.21. Methyl [(2′*R*,3′*R*)-2,3-dimethoxybutane-2′,3′-diyl]-α-D-glucopyranoside (24)

To a soln of trityl ether **26** (2.00 g, 3.64 mmol) in dry MeOH (40 mL), pyridinium *p*-toluenesulfonate (1.00 g,

3.98 mmol) was added and the mixture was heated at 37 °C for 72 h. The mixture was concentrated, CH_2Cl_2 (100 mL) was added and the soln was washed with water (2 × 50 mL). The organic phase was dried and concentrated. The product was purified by column chromatography (1:1→3:7 toluene–EtOAc) followed by crystallisation from Et_2O to afford diol **24** (850 mg, 76%), mp 136.5–137.5 °C; $[\alpha]_D$ −58 (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.33, 1.36 (6H, 2 × s, acetal CMe), 2.82 (1H, br s, OH), 3.27, 3.30 (2H, 2 × s, acetal OMe), 3.41 (3H, s, anomeric OMe), 3.52 (1H, br s, OH), 3.65 (1H, m, H-5), 3.75–3.90 (3H, m, H-2, H-6, H-6′), 4.04 (1H, t, $J_{3,4} \approx J_{4,5}$ 10.3 Hz, H-3), 4.75 (1H, d, J 3.5 Hz, H-1); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.7 (2 × acetal C*Me*), 47.9, 48.1 (2 × acetal OMe), 55.1 (anomeric OMe), 61.7 (C-6), 67.6 (C-4), 68.3 (C-2), 69.4 (C-3), 71.9 (C-5), 98.1 (C-1), 99.5, 99.95 (acetal $C_{quat.}$); HRESIMS: found *m*/*z* 326.1809 $[M+NH_4]^+$. Calcd for $C_{13}H_{24}O_8+NH_4$ 326.1809.

4.22. Methyl 4,6-di-*O*-(prop-2-ynyl)-α-D-glucopyranoside (28)

To a soln of diacetal **24** (350 mg, 1.14 mmol) in dry DMF (5 mL) was added a 60% suspension of NaH in mineral oil (100 mg, 2.5 mmol) and the mixture was stirred for 1 h under nitrogen. Then it was cooled to 0 °C, $HC{\equiv}CCH_2Br$ (0.31 mL, 3.44 mmol) was added and stirring was continued for 2 h at this temperature before the reaction was quenched with MeOH. The mixture was diluted with EtOAc (50 mL), washed with water (4 × 10 mL) and the solvent was evaporated. The product was purified by chromatography (4:1 toluene–EtOAc) to give a brown syrup, which was taken up in CF_3CO_2H (0.9 mL) and water (0.1 mL). After stirring the mixture for 1 h it was diluted with toluene and concentrated. The procedure was repeated several times until complete removal of CF_3CO_2H. The product was purified by reverse phase (C-18) column chromatography (H_2O/MeCN, 92:8→80:20) to afford compound **28** (68%), mp 68–71 °C (Et_2O/pet. ether), $[\alpha]_D$ +146 (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 2.48, 2.51 (2H, 2s, $CH_2C{\equiv}CH$), 3.41 (3H, s, OMe), 3.46 (1H, t, $J_{3,4} \approx J_{4,5}$ 9 Hz, H-4), 3.55 (1H, dd, $J_{1,2}$ 3.7 Hz, $J_{2,3}$ 9.2 Hz, H-2), 3.69 (1H, m, H-5), 3.73–3.86 (3H, m, H-3, H-6, H-6′), 4.20 (1H, AB, J_{AB} 3.7 Hz, $CH_2C{\equiv}CH$), 4.45 (2H, s, $CH_2C{\equiv}CH$), 4.78 (1H, d, $J_{1,2}$ 3.7 Hz, H-1); HRESIMS: found *m*/*z* 288.1445 $[M+NH_4]^+$. Calcd for $C_{13}H_{24}O_8+NH_4$ 288.1448. A small sample of **28** was acetylated to give 2,3-di-*O*-acetyl derivative, ^1H NMR (400 MHz, $CDCl_3$): δ 2,07, 2.10 (6H, 2s, Ac), 2.43, 2.46 (2H, 2s, $CH_2C{\equiv}CH$), 3.39 (3H, s, OMe), 3.70–3.90 (4H, m, H-4, H-5, H-6, H-6′), 4.20–4.37 (m, 4H, $CH_2C{\equiv}CH$), 4.85 (1H, dd, $J_{1,2}$ 3.6 Hz, $J_{2,3}$ 10.3 Hz, H-2), 4.91 (1H, d, $J_{1,2}$ 3.6 Hz, H-1), 5.46 (1H, t, 1H, $J_{3,4} \approx J_{4,5}$ 10 Hz, H-3).

4.23. Methyl α-D-glucopyranosyl-(1→4)-{α-D-glucopyranosyl)-(1→4)}$_5$-(α-D-glucopyranosyl-1*H*-[1,2,3]triazole-4-ylmethyl)-(4→4)-[α-D-glucopyranosyl-(1→4)-{(α-D-glucopyranosyl)-(1→4)}$_5$-(α-D-glucopyranosyl-1*H*-[1,2,3]triazole-4-ylmethyl)-(4→6)]-α-D-glucopyranoside (29)

A soln of azide **17** (140 mg, 0.120 mmol), di-*O*-propargyl derivative **28** (16 mg, 0.060 mmol), sodium ascorbate (2.4 mg, 0.012 mmol) and $CuSO_4{\cdot}5H_2O$ (0.6 mg) in water (0.65 mL) was heated at 70 °C for 2 h. The soln was diluted with water (1.35 mL) and subjected to gel permeation chromatography (TSK gel Toyopearl HW 40S, 1.5 × 85 cm) in 0.1% CF_3CO_2H in water in four separate injections. The target product was collected in fractions eluted with 70–84 mL (peak maximum at 76 mL), the maltoheptaosyl azide **17** had a maximum of elution peak at 86 mL on the same column. The combined fractions were concentrated and the residual soln was freeze-dried to give *pseudo*-pentadecasaccharide **28** as a white powder, yield 140 mg (89%), $[\alpha]_D$ +155 (*c* 1.3, H_2O); ^{13}C NMR (75 MHz, D_2O): δ 54.5, 59.8 (high intensity), 62.4, 63.7, 67.5, 68.5, 70.6 (high intensity), 70.95 (high intensity), 71.2, 71,5, 72.1, 72.3, 72.7 (high intensity), 75.7–79.9 (high intensity), 86.8, 98.6, 99.2 (high intensity), 124.0, 124.1, 143.4, 143.5; MALDI-TOFMS: *m*/*z* 2648.8 $[M + NH_4]^+$.

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