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Synthesis of Novel Types of Polyester Glycodendrimers as Potential Inhibitors of Urinary Tract Infections

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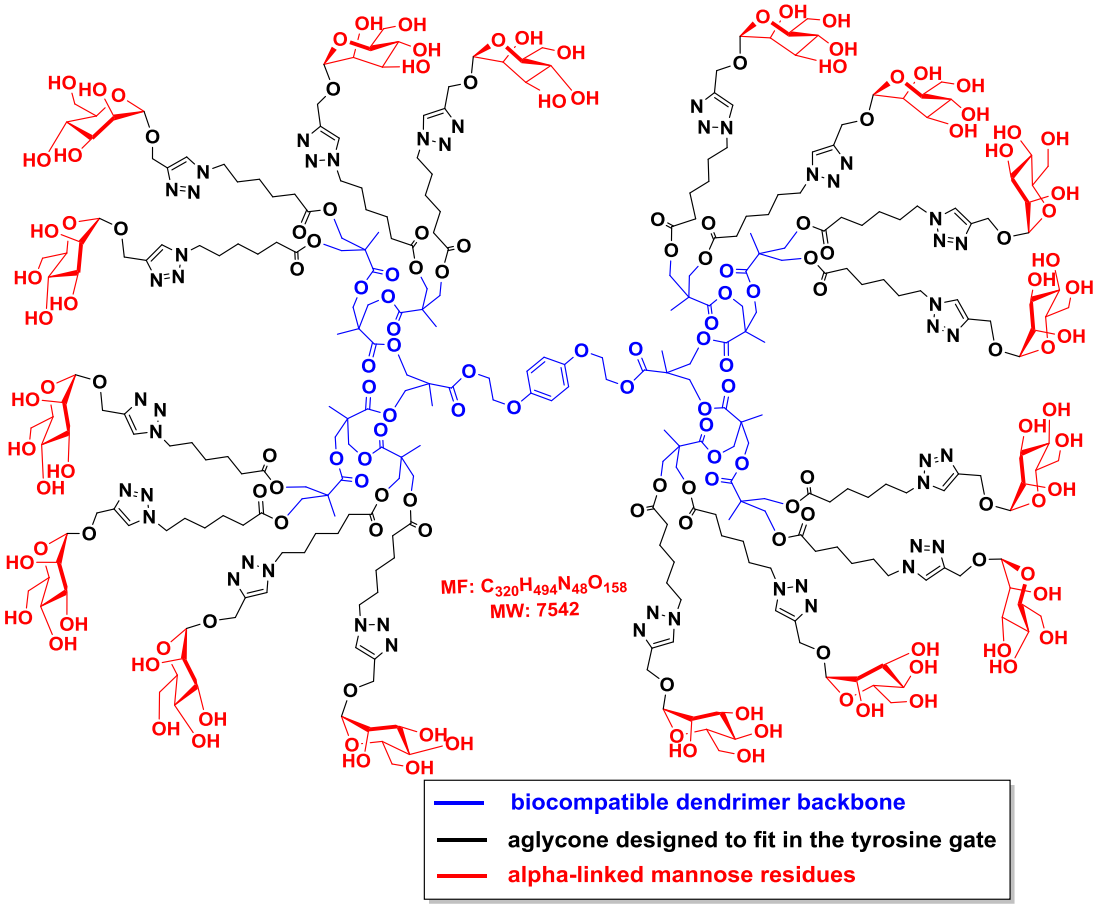
Abstract

Syntheses of highly mannosylated polyester dendrimers with 2, 4, 8, and 16 α-D-mannopyranose residues on their peripheries connected by different linker arms are presented. Attractive features of these systems as potential inhibitors of uropathogenic *Escherichia coli* (UPEC) include the use of non-toxic and biocompatible polyester dendrimer backbones, aglycones whose lengths are designed to fit in the tyrosine gate, and multiple copies of α-linked D-mannopyranose residues, capable of effectively binding to the exposed mannose-sensitive type 1 pili on UPEC's outer surface.



Key words: polyester glycodendrimers, urinary tract infections, click chemistry, mannosylated systems

INTRODUCTION

One of the medically most significant carbohydrate-protein interactions involves the initial attachment of pathogenic bacteria to target tissues and it has been suggested that this interaction will provide a source of alternative antibiotic targets, the anti-adhesion strategy.[1, 2] For Gram negative bacteria, these interactions often are between carbohydrate-binding proteins (lectins) called adhesions on fimbriae protruding from the bacterial surface and carbohydrates on the tissue surface.[3] Urinary tract infections (UTIs), which are mainly caused by strains of gram negative uropathogenic *Escherichia coli*,[4] are among the most frequently occurring bacterial diseases in humans.[5-7] The UPEC bind to the urinary tract endothelial surface through the 200 to 500 fimbriae which extend from the surface of each bacterial cell. At the tip of each fimbria there is a lectin, FimH, that recognizes terminal α-D-mannopyranoside residues of trimannose-terminated oligosaccharides[8] present on one of the proteins, uroplakin Ia (UPIa) on the endothelial surface.[9] The mannose-binding pocket of FimH is adjacent to a hydrophobic region known as the tyrosine gate that contains two tyrosines and an isoleucine,[10] that accommodates the non-polar faces of the non-terminal mannopyranoses of the UPIa oligosaccharides.[11, 12] The combination of a mannose-binding pocket with an adjacent extended hydrophobic region on FimH has resulted in compounds that are designed to bind to this site being poorly recognized by the many other mannose-binding receptors in humans.[13] Binding occurs by a catch-bond mechanism that is critical for attachment in the high-sheer environment of the urinary tract.[14, 15] Infection commences with FimH binding to UPIa that triggers a conformational change in the cell surfaces,[16] allowing the bacteria to enter and establish sub-surface colonies that are difficult to eradicate.

A number of compounds have been designed to evaluate the utility of anti-adhesion strategies against *E. coli*. Early on Firon et al. found that phenyl α-D-mannopyranosides, particularly the 2-chloro-4-nitro derivative, bound effectively,[17] and recently Hultgren and coworkers have shown that α-linked biphenyl derivatives are even more effective.[18] Other phenyl glycosides with planar substituents on the

phenyl ring have also proved to be quite effective,[19-21] and these compounds remain attached to FimH surface long enough to be clinically relevant.[22] Heptyl α-D-mannopyranoside was found to bind to FimH with strengths comparable to the better phenyl glycosides.[10]

Multivalent presentation of binding molecules to proteins has attracted considerable attention,[23] and many of these involve binding to FimH.[18, 23-25] Dendritic species are becoming increasingly important and are now used in a variety of applications.[26-35] The ability of dendrimers to present multiple copies of biologically active residues in a defined fashion has attracted attention because of the possibility to achieve reproducible results. In particular, polyester dendrimers are attractive as drug delivery carriers and numerous reports on their biomedical applications have appeared.[26, 27, 36-46]

Herein we report the syntheses of two higher generation polyester dendrimers bearing 8 and 16 mannose residues on their surfaces attached by different linker arms. As far as we are aware, the use of polyester dendrimers based on the 2,2-bis(hydroxymethyl) propanoic acid (bis-HMPA) monomer, in the preparation of mannosylated systems as potential inhibitors of urinary tract infections has not been explored. One concept that guided this work was that glycodendrimers based on a non-toxic core could combine effectiveness with the absence of side effects. Polyester dendrimers constitute an attractive class of polymers because they are biodegradable, biocompatible, and they have been found to have low toxicity in every reported study.[27, 36, 38, 47-49] Consequently, the polyester dendrimer scaffold is attractive for the preparation of biocompatible glycodendrimers.

RESULTS AND DISCUSSION

We are interested in the functionalization of polyester dendrimers to create highly mannosylated systems as potential therapeutics against urinary tract infections. Based on knowledge of the FimH binding site outlined in the introduction, two mannose residues (**7** and **10**) were prepared as shown in Scheme 1, in order to attach them to dendrimer surfaces using click chemistry. These particular

derivatives were selected for the following reasons. As shown in Figure 1, the original *p*-nitrophenyl glycoside[10, 17, 25] and the heptyl glycoside[10, 25] both had nM binding constants to FimH. The hexameric compound shown in Figure 2 had an even better K_d of 3 nM (that is a per mannose binding constant of 18 nM).[25] In view of the fact that the binding constant of the heptyl glycoside is considerably better than the butyl derivative, it was considered that the closeness of the branching point to the glycosidic centre of the derivative in Figure 2 considerably hindered its binding. This led to the first set of compounds (using **7**) which have a longer chain after the triazole ring. The second set of compounds (using **10**) was derived to more closely mimic heptyl α-D-mannopyranoside.[50] After this work was underway, Bouckaert et al. described how compounds having seven heptyl α-D-mannopyranosides grafted either onto the primary face of β-cyclodextrin or to short amylose chains bound FimH from *E. coli* well, and also reduced infection by the UTI89 strain in a mouse model.[24, 51] We hope that the less spatially defined nature of the current molecules will allow stronger binding because the complexes formed will be unhindered by adjacent strands and their higher valency will allow binding to greater numbers of bacterial cells.

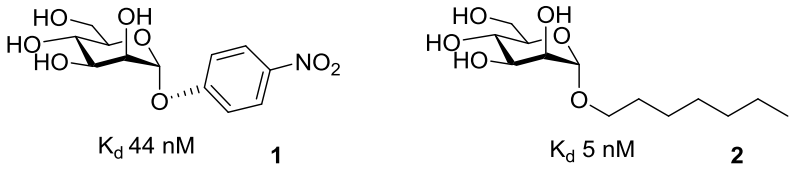


Figure 1 Binding constants of two monomeric mannosides with FimH[10, 25]

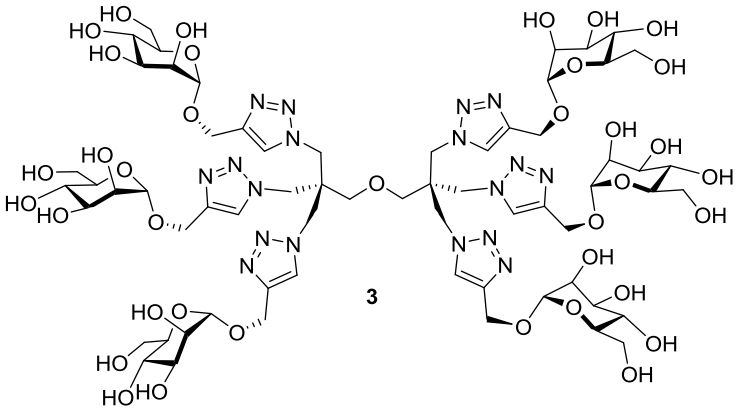
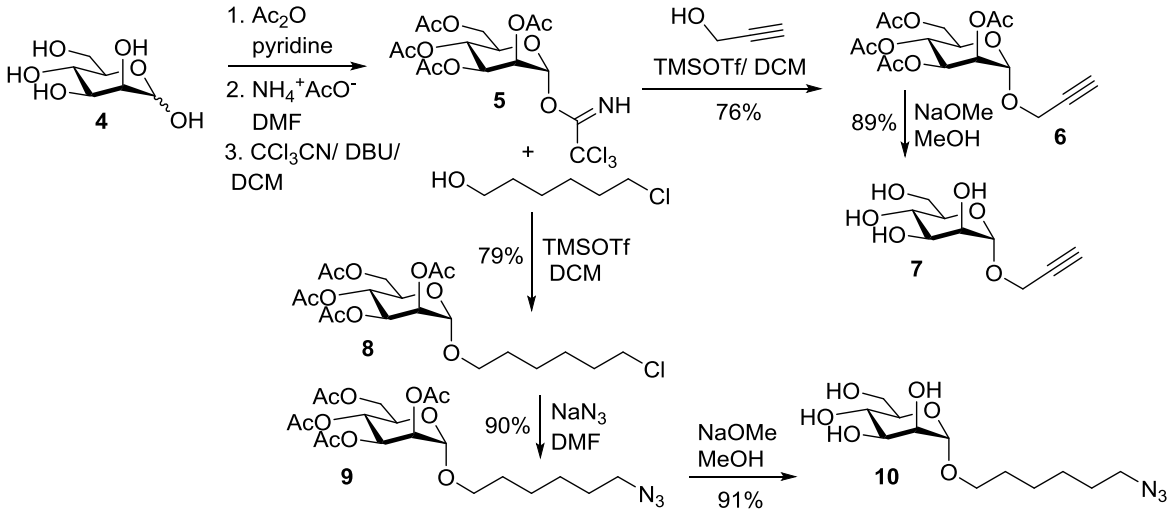
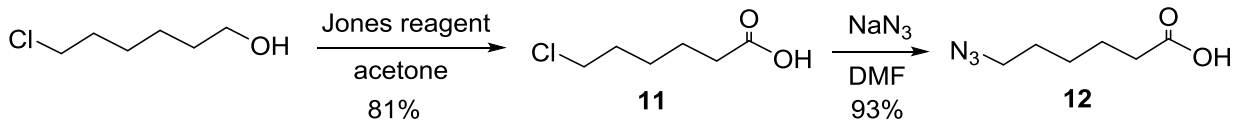


Figure 2 A hexameric compound with a K_d per mannose residue of 18 nM[25]

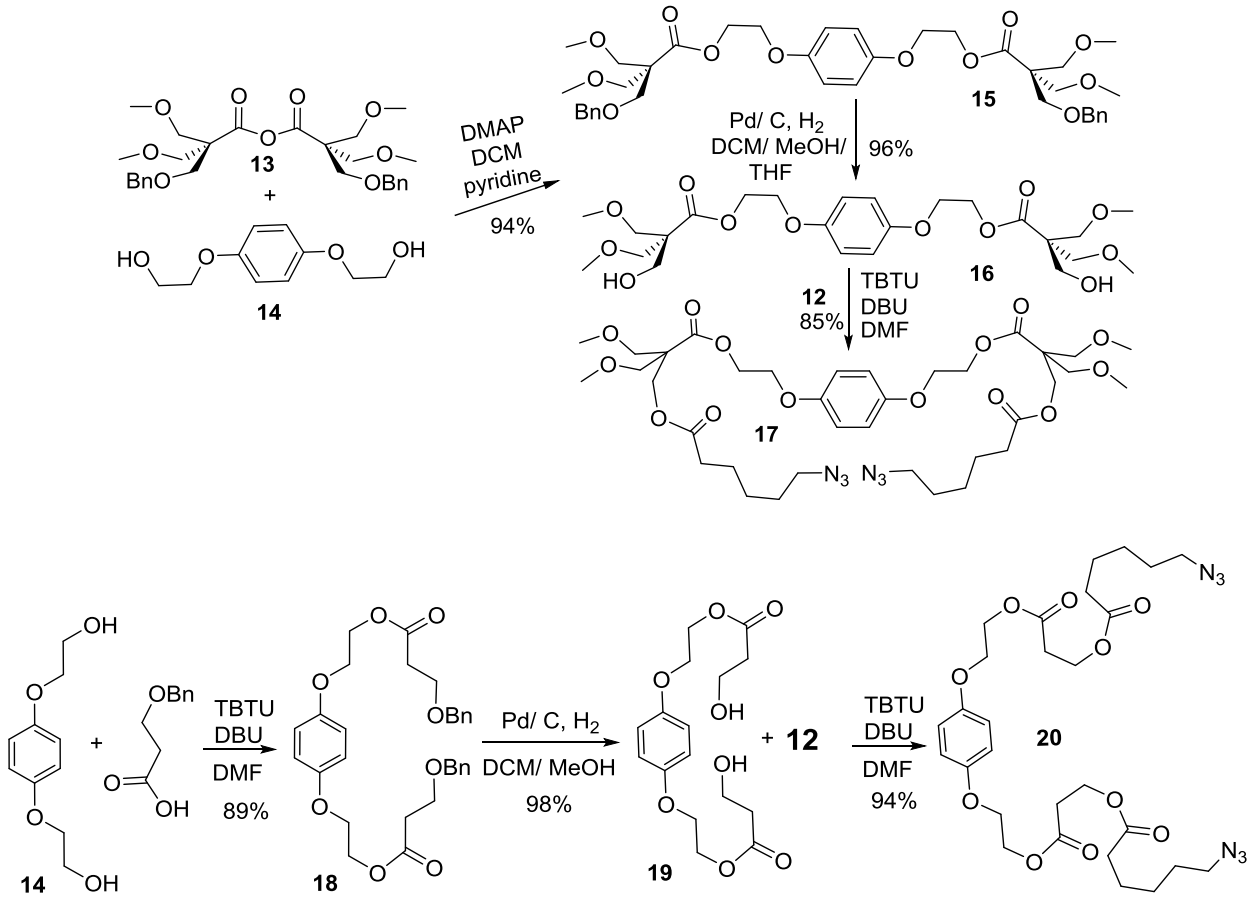


Scheme 1 Synthesis of mannoside residues **7** and **10**

Compounds **7**[60, 65] and **10**[52, 53] were made by literature methods as outlined in Scheme 1. We found it more efficient to make the 6-azido glycoside via the 6-chlorohexyl glycoside,[53] rather than make 6-azidohexanol first.[52] In other reactions, 6-azidohexanoic acid was prepared for attachment to click coupling partners of **7,** which must be azide-terminated. Accordingly, 6-chlorohexanol was oxidized to the corresponding acid using Jones reagent followed by an S_N2 displacement with sodium azide (Scheme 2).



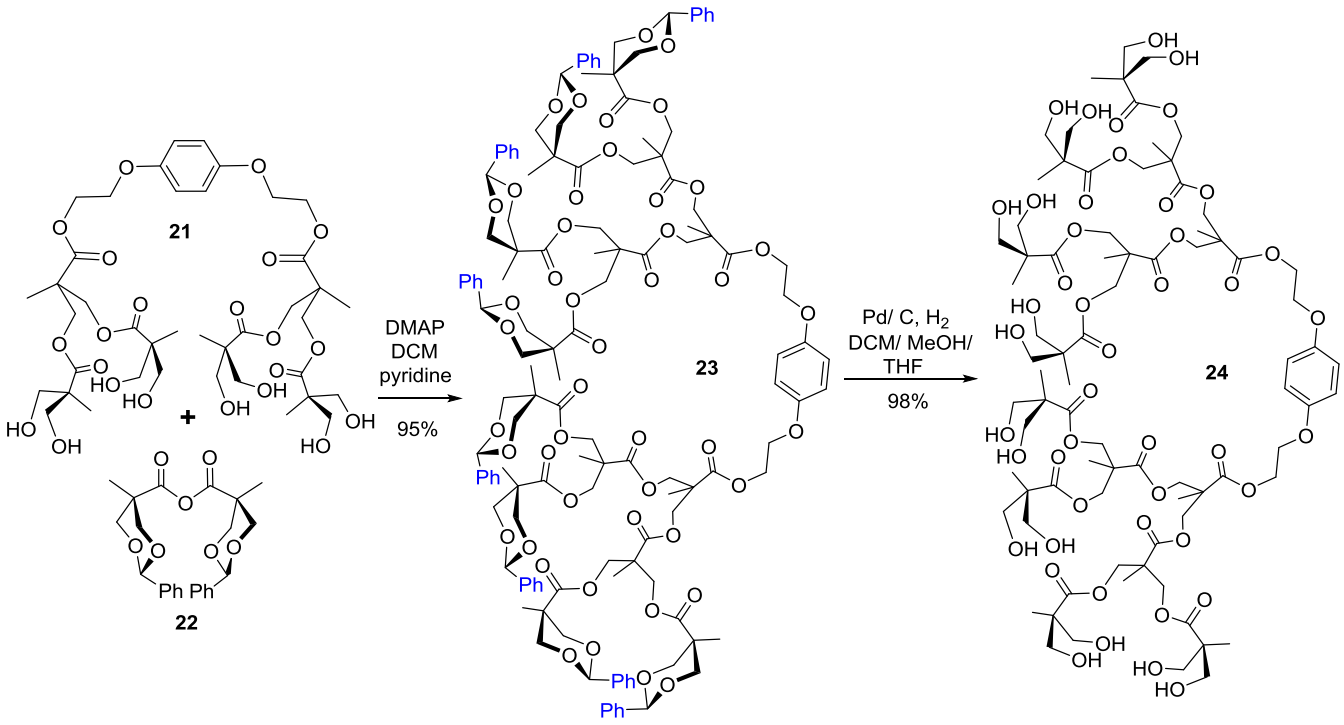
Scheme 2 Preparation of 6-azidohexanoic acid



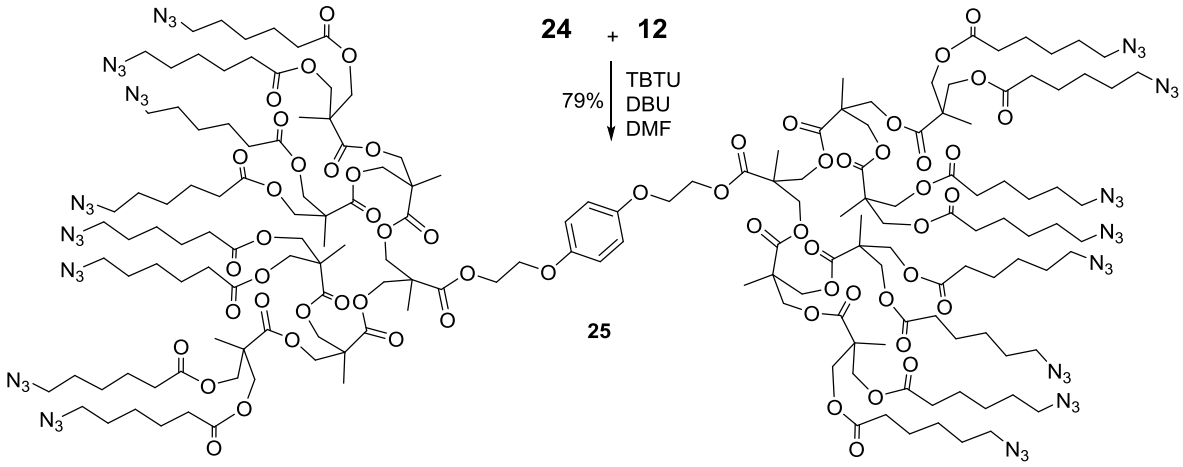
Scheme 3 Preparation of divalent azide compounds **17** and **20**

The TBTU-promoted esterification using 6-azidohexanoic acid for the preparation of azide-terminated species worked well in DMF. In the case of diols, reactions were high yielding with short reaction times as expected based on our previous studies.[54-56] As illustrated in Scheme 3, diol **16** reacted for 4 hours to afford the corresponding diazide **17** in 85% yield, while **19** yielded **20** in 94% yield after 2 hours. To obtain a highly mannosylated system, a third generation polyester dendrimer was divergently constructed. We have reported the preparation of second generation dendrimer **21.**[57] This octaol reacted

with a divalent anhydride (**22**) under standard conditions to give protected third generation dendrimer (**23**), which gave crystalline dendrimer **24** after hydrogenolysis (see Scheme 4). Third generation dendrimer **24** then afforded **25** in 79% yield after reacting with 6-azidohexanoic acid for 12 hours as shown in Scheme 5.

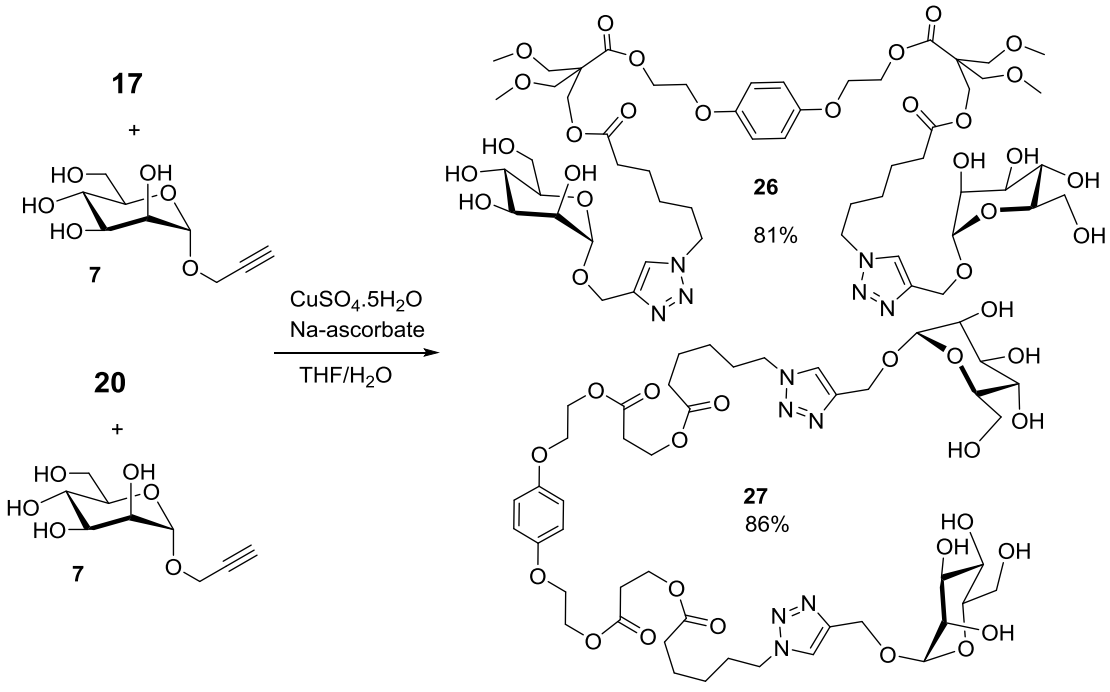


Scheme 4 Divergent synthesis of a third generation polyester dendrimer (**24**)

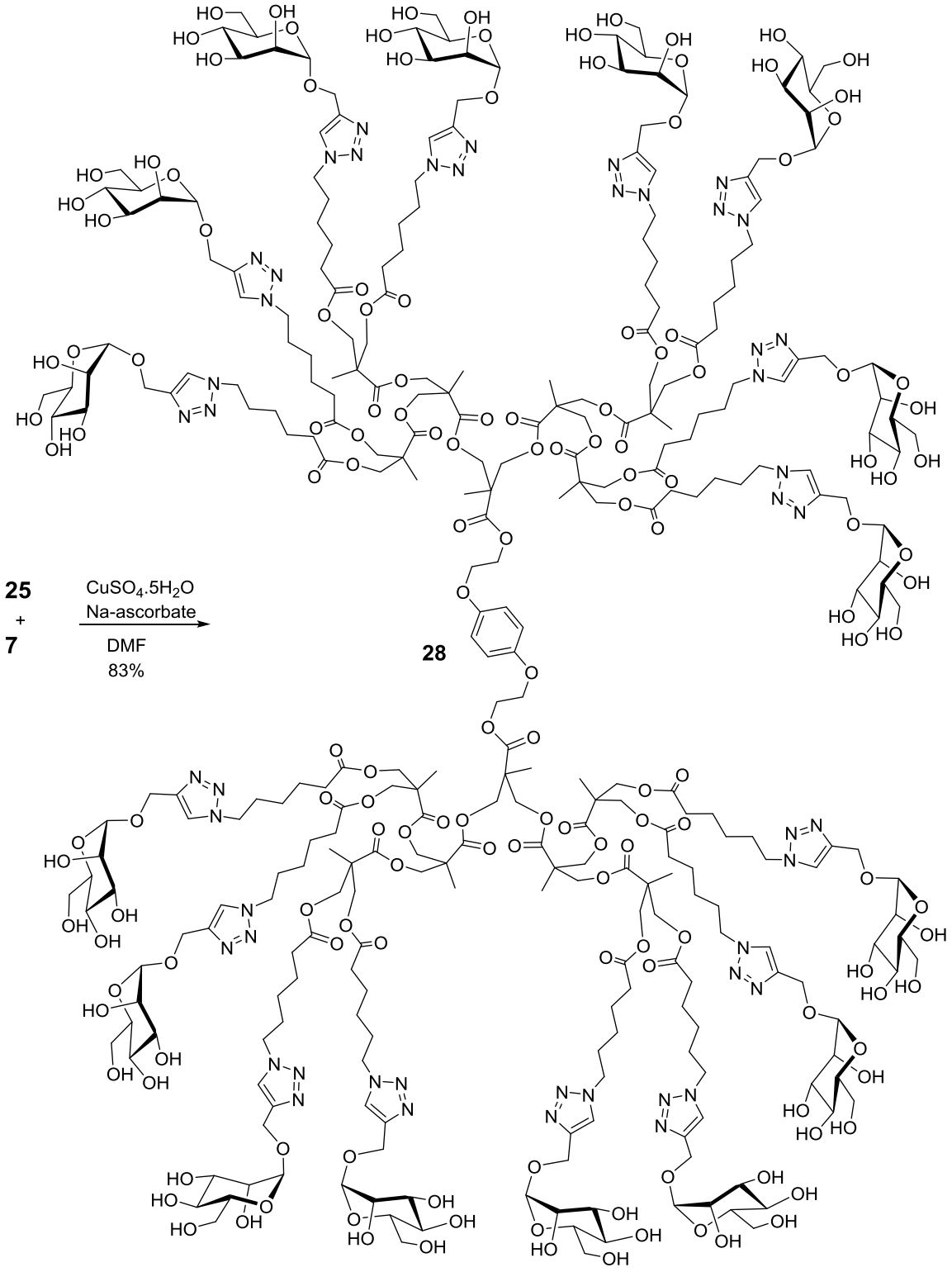


Scheme 5 Preparation of an azide-terminated third generation polyester dendrimer (**25**)

Having successfully prepared both the alkyne functionalized mannoside **7** and the azide terminated species; the next step was to connect them using a click reaction. Modified versions of the click reaction have been developed that do not require toxic copper (I) so that these reactions can even be used in living cells.[58-60] The reaction has also been used for the synthesis of monomers, dendrons and dendrimer skeletons.[61-64] Here, using the click reaction, **17** and **20** were reacted with mannoside **7** to give the corresponding divalent mannoside clusters **26** and **27**, respectively (Scheme 6). Most often, this reaction is carried out using a mixture of water and tetrahydrofuran and this system worked well for the preparation of divalent clusters. However, this solvent system did not work for the azide-terminated third generation polyester dendrimer **25**, which precipitated whenever water was introduced into the system. After a few trials, it was found that the reaction worked well in DMF. As shown in Scheme 7, dendrimer **25** reacted with mannoside **7** to give mannosylated system **28** with 16 mannose residues on its periphery.

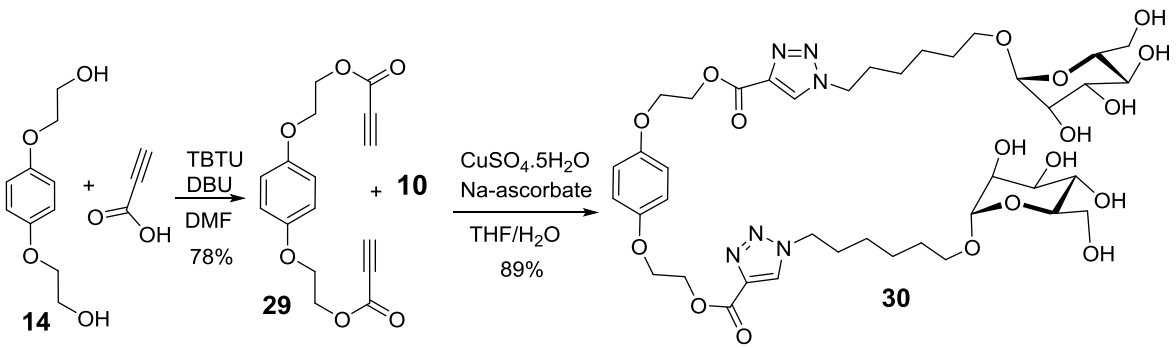


Scheme 6 Synthesis of divalent mannoside clusters **26** and **27**



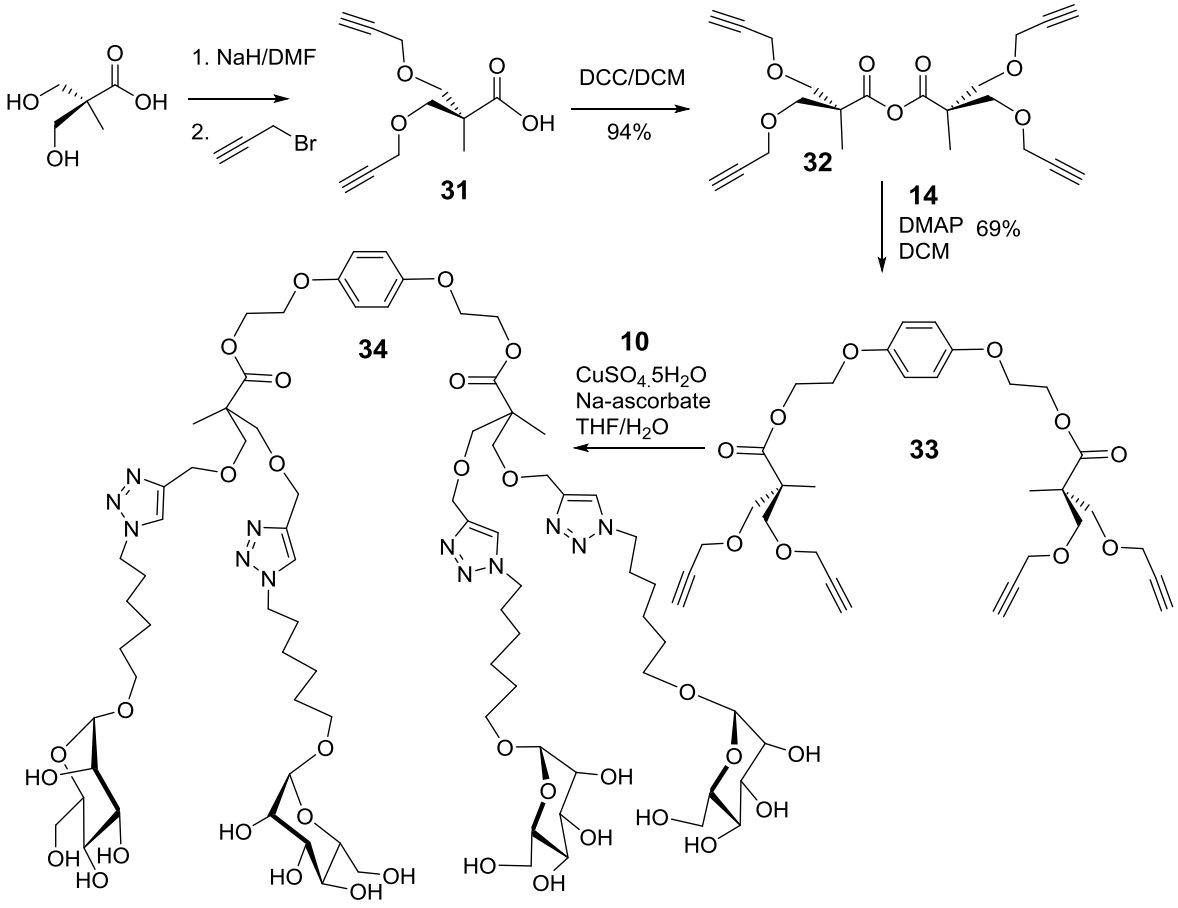
Scheme 7 Synthesis of a highly mannosylated system (**28**)

Mannoside **10** was used for the synthesis of glycodendrimers with linker arms more closely resembling heptyl α-D-mannopyranoside. Divalent glycodendrimer **30** was prepared by forming the bis ester of core molecule **14** with propynoic acid to give **29** that gave divalent glycodendrimer **30** after the click reaction with **10** in 89% yield (Scheme 8).



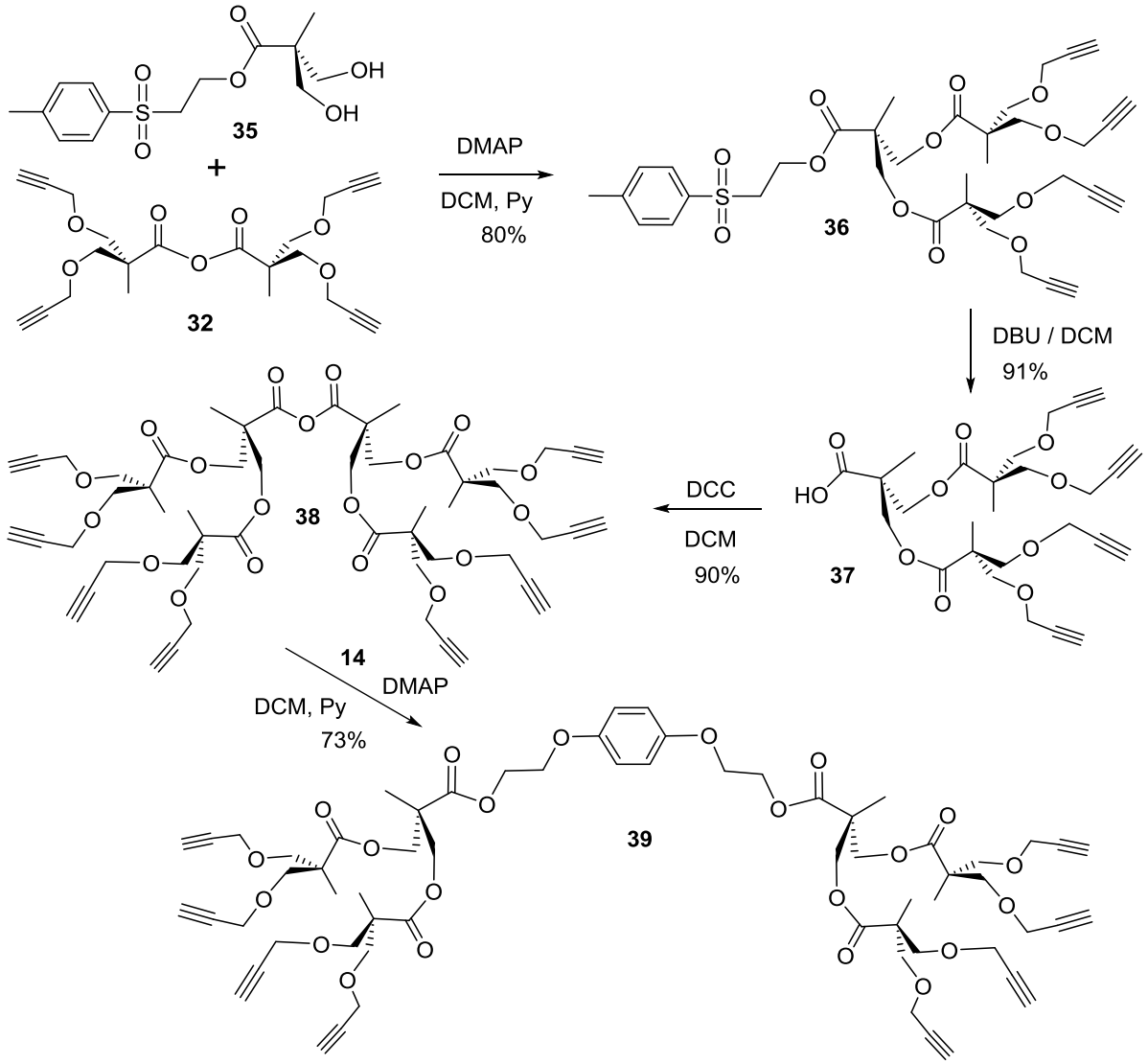
Scheme 8 Synthesis of divalent mannoside cluster **30**

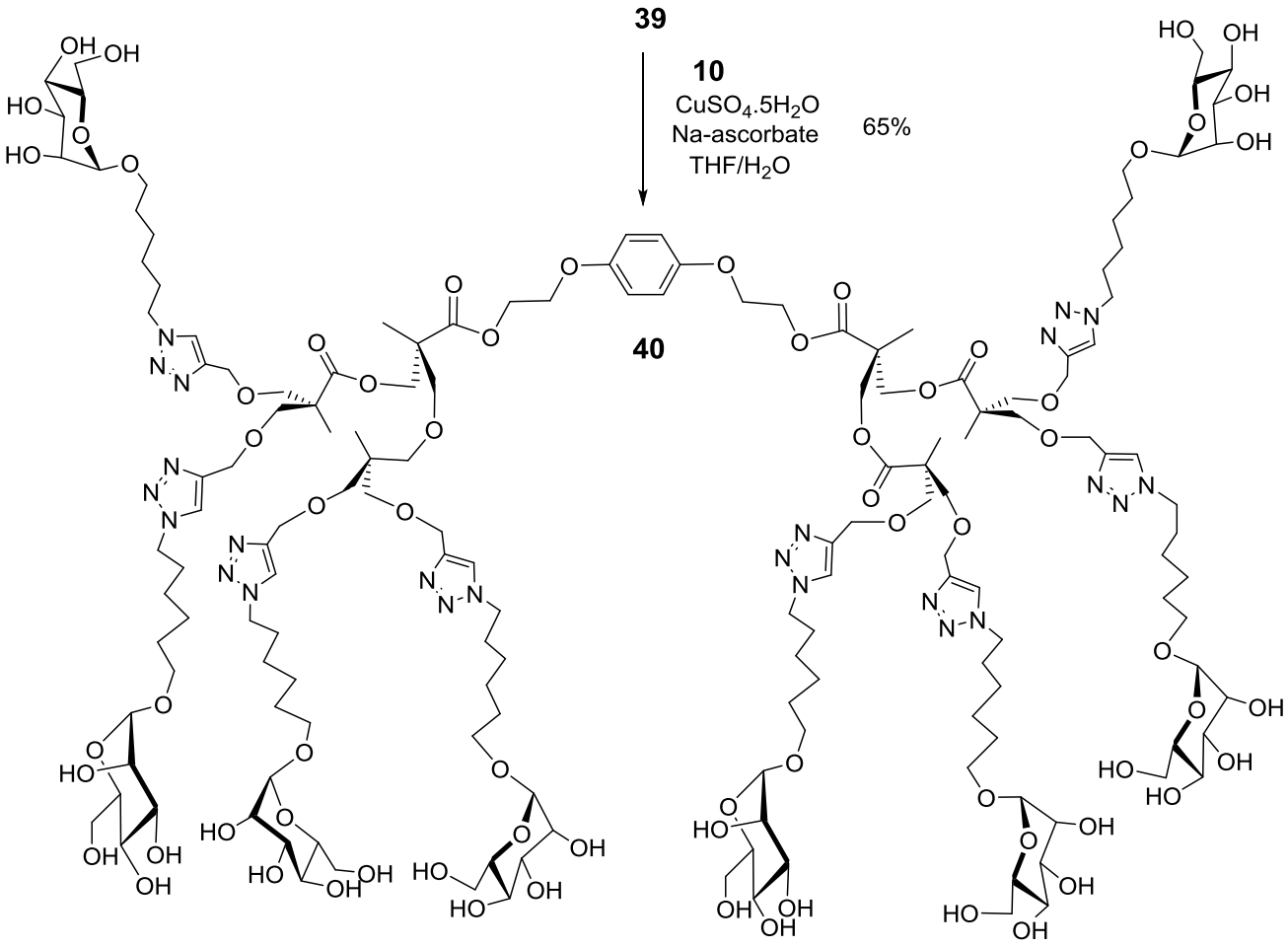
A partially convergent approach was used to prepare tetramannoside **34** as shown in Scheme 9. The bispropargyl ether of HMPA (**31**) was made by the method of Wu et al.[65] Characterization data for **31** are corrected in the experimental. This compound was converted to the anhydride (**32**), which was then reacted with core molecule **14** to form the tetrapropargyl ether. The copper-catalyzed click reaction with azide-terminated mannoside **10** gave the tetramannoside **34** in good yield.



Scheme 9 Synthesis of tetravalent mannoside cluster **34**

It was necessary to adopt a more convergent approach to prepare the third generation polyester glycodendrimer octamannoside **40** (Scheme 10). Adronov and coworkers prepared the 2-toluenesulfonylethyl ester of HMPA (**35**) and demonstrated that it could be used to prepare high generation HMPA dendrons.[66] We reacted compound **35** with the anhydride of propargylated HMPA to give the protected second generation dendron **36**. Removal of the carboxyl protecting group with DBU gave the second generation dendron **37**. Formation of its anhydride **38** with DCC gave a reactive intermediate that was converted into the propargylated third generation dendrimer **39** by reaction with core molecule **14**. The copper-catalysed click reaction with the azido-terminated mannoside **10** yielded the third generation octamannoside **40** in 65% yield.





Scheme 10 Synthesis of octavalent mannoside cluster **40**

CONCLUSIONS AND SUMMARY

A number of polyester glycodendrimers including compound **28** with 16 terminal mannose residues, and compound **40**, with eight terminal mannose residues, were efficiently prepared and characterized. Glycodendrimers **28** and **40** are highly mannosylated systems with non-toxic polyester backbones based on the bis-HMPA monomer. The lengths of the two aglycones were designed to present alternative approaches for fitting in the tyrosine gate. These polyester glycodendrimers will be evaluated against urinary tract infections in work to be presented later.

EXPERIMENTAL SECTION

General Methods

^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 500 or Bruker Avance 300 NMR spectrometers operating at 500.13 and 125.7 MHz or 300.15 and 75.5 MHz respectively using the solvent resonances as secondary chemical shift references. The carbon and hydrogen atoms were assigned following analysis of their one dimensional (^{1}H, ^{13}C) and two dimensional (COSY, HSQC, HMBC, and TOCSY) NMR spectral data. Coupling constant (*J)* values are reported in Hertz. Proton and carbon assignments shown with location numbers indicate their positions in 1,3-dioxane or mannose. High-resolution mass spectra were recorded on a Bruker Micro-TOF mass spectrometer using electrospray ionization. Melting points were determined on a Fisher-John's melting point apparatus and are uncorrected. Acetone was refluxed over K_2CO_3 and distilled over molecular sieves. Dichloromethane was refluxed over calcium hydride and distilled onto molecular sieves. Tetrahydrofuran was refluxed over $LiAlH_4$ and distilled over molecular sieves. Unless otherwise noted, non-aqueous reactions were carried out under a nitrogen atmosphere. Jones reagent (0.56 M) was prepared by dissolving sodium dichromate dihydrate ($Na_2Cr_2O_7.2H_2O$, 300 g, 1.01 mol) in 1.5 L of water followed by slowly adding conc. sulfuric acid (300 mL) to the cooled solution (0 ^{o}C). Compounds were visualized/ located by spraying the TLC plate with a solution of 2 % ceric ammonium sulfate in 0.5 M H_2SO_4 followed by heating on a hot plate until color developed. Solid compounds were purified on silica gel using flash column chromatography and specified eluents, or by crystallization. Liquids and oils were purified using flash column chromatography. Water soluble compounds were purified using size exclusion chromatography on a Sephadex LH-20 gel column with water as the eluent.

General procedures

Formation of dendritic esters (anhydride coupling): To an oven-dried round-bottomed flask equipped with a magnetic stir bar under nitrogen atmosphere, the anhydride, the hydroxyl-terminated dendrimer or

core, and *N*,*N*-dimethyl-4-aminopyridine (DMAP) were dissolved in a 3:1 mixture of CH_2Cl_2: pyridine (v/v). The reaction mixture was stirred at rt for 4 to 12 h and diluted with water (3 mL) in pyridine (3 mL). Stirring was continued overnight to quench the excess anhydride. The mixture was diluted with CH_2Cl_2 (150 mL) and washed using $NaHCO_3$ (1 M, 30 mL × 3), 10% aq. Na_2CO_3 (30 mL × 3), brine (30 mL × 2), and water (30 mL), then dried ($MgSO_4$), filtered, and concentrated. The crude product was then purified using precipitation out of hexanes/ EtOAc or column chromatography to give the desired product. The $NaHCO_3$ layers were combined, acidified (pH = 5 – 6), and the carboxylic acid by-product was recovered.

***Deprotection using hydrogenolysis*:** To an oven-dried round-bottomed flask equipped with a magnetic stir bar, the benzylidene or benzyl protected dendrimer was dissolved in a 1:2:1 mixture of CH_2Cl_2 : MeOH : THF (v/v/v) and a catalytic amount of Pd/C was added. The flask was evacuated and back-filled with hydrogen three times. After stirring the mixture overnight under a H_2 atmosphere, the catalyst was filtered off using celite and this celite was washed with MeOH. The filtrate was concentrated to dryness to afford the product as a colorless solid.

***Esterification procedure using TBTU*:** In an oven-dried round-bottomed flask equipped with a magnetic stir bar, an acid (1.20 mmol), TBTU (0.387 g, 1.20 mmol), and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.37 mL, 2.40 mmol) were dissolved in anhydrous DMF (3 mL) and the resulting mixture was stirred at rt for 30 min under a nitrogen atmosphere. An alcohol (1.00 mmol of hydroxyl groups) in DMF (1 mL) was then injected into the reaction mixture via syringe, and stirring was continued at rt until TLC confirmed the completion of the reaction (1 – 12 h). The reaction mixture was diluted with CH_2Cl_2 (15 mL) and the resulting mixture was washed with 5% HCl (2 x 3 mL), 1M $NaHCO_3$ (3 x 3 mL) and water (2 x 3 mL). The organic layer was collected, dried ($MgSO_4$), filtered and concentrated to give a crude ester product, which was purified using column chromatography and specified eluents.

Bis(2-(3-benzyloxy-2,2-bis-(methoxymethyl)propanoyloxy)ethoxy)benzene (15). Compound **15** was synthesized as described above in the general procedure for formation of dendritic esters. The core diol **14**[57] (0.500 g, 2.52 mmol), dry pyridine (5 mL), CH_2Cl_2 (15 mL), DMAP (0.185 g, 1.51 mmol) and anhydride **13**[67] (3.14 g, 6.05 mmol) were stirred at rt for 12 h under nitrogen. After work up and purification using column chromatography (hexanes/ EtOAc; 2:1; R_F 0.26), the product was obtained as colorless syrup (1.66 g, 94 % yield): ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 3.31 (s, 12H, $4OCH_3$), 3.62 (s, 8H, $4CH_2O$), 3.69 (s, 4H, $2CH_2O$), 4.09 (t, *J* = 5 Hz, 4H, $ArOCH_2$), 4.47 (t, *J* = 5 Hz, 4H, $2CH_2OC{=}O$), 4.52 (s, 4H, $2CH_2$ benzylic), 6.82 (s, 4H, PhH), 7.27 – 7.35 (m, 10H, PhH); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 172.4 (C=O), 153.0, 138.4, 128.2, 127.4, 127.2, 115.6 (PhC), 73.1 ($2CH_2$ benzylic), 70.2 ($4CH_2OMe$), 67.8 ($2CH_2OBn$), 66.5 (2PhO**C**), 62.9 (2**C**OC=O), 59.2 ($4OCH_3$), 53.5 ($2C_{quat}$). HR ESI MS: *m/z* calcd for $C_{38}H_{50}NaO_{12}$ 721.3194, found 721.3170.

Bis(2-(3-hydroxy-2,2-bis-(methoxymethyl)propanoyloxy)ethoxy)benzene (16). Using the general procedure for hydrogenolysis described above, compound **15** (1.45 g, 2.08 mmol), dissolved in dry CH_2Cl_2 (10 mL), dry MeOH (30 mL), and dry THF (15 mL) afforded **16** as a colorless syrup (1.05 g, 98% yield): ^{1}H NMR (500.13 MHz, acetone-d_6) δ 3.24 (s, 12H, $4OCH_3$), 3.51 – 3.55 (m, 8H, $4CH_2O$), 3.73 (d, *J* = 6 Hz, 4H, $2CH_2O$), 3.80 (t, *J* = 6 Hz, 2H, OH), 4.14 (t, *J* = 5 Hz, 4H, $ArOCH_2$), 4.39 (t, *J* = 5 Hz, 4H, $2CH_2OC{=}O$), 6.90 (s, 4H, PhH); ^{13}C NMR (125.7 MHz, acetone-d_6) δ 173.0 (2C=O), 153.9, 116.4 (PhC), 71.0 (4**C**H_2OMe), 67.3 (2PhO**C**), 63.4 (2**C**OC=O), 61.0 ($2CH_2OH$), 59.3 ($4OCH_3$), 54.9 ($2C_{quat}$). HR ESI MS: *m/z* calcd for $C_{24}H_{38}NaO_{12}$ 541.2255, found 541.2254.

Bis(2-(3-(6-azidohexanoyloxy)-2,2-bis-(methoxymethyl)propanoyloxy)ethoxy)benzene (17). Compound **17** was synthesized using the general esterification procedure using TBTU. 6-Azidohexanoic acid **12** (0.190 g, 1.20 mmol) and diol **16** (0.260 g, 1.00 mmol (OH)) were reacted for 4 h to give **17** (0.34 g, 85% yield) as a colorless syrup after purification using column chromatography (hexanes/ EtOAc; 3:2; R_F 0.36): ^{1}H NMR (300.15 MHz, $CDCl_3$) δ 1.28 – 1.35, 1.47 – 1.59 (2 m, 12H, 3 CH_2),

2.21 (t, *J* = 7 Hz, 4H, O=CCH$_2$), 3.19 (t, *J* = 7 Hz, 4H, CH$_2$N), 3.24 (s, 12H, 4OCH$_3$), 3.50 (s, 8H, 2 C$_{quat}$2CH$_2$O), 4.05 (t, *J* = 4.5 Hz, 4H, ArOCH$_2$), 4.23 (s, 4H, C$_{quat}$CH$_2$OC=O), 4.39 (t, *J* = 4.5 Hz, 4H, CH$_2$OC=O), 6.77 (s, 4H, PhH); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 172.6, 171.5 (C=O), 153.0, 115.7 (PhC), 70.2 (4**C**H$_2$OMe), 66.5 (ArOCH$_2$), 63.1 (OCH$_2$***C***H$_2$O), 62.0 (***C***H$_2$OC=O), 59.3 (4OCH$_3$), 52.4 (2C$_{quat}$), 51.1 (CH$_2$N$_3$), 33.8 (CH$_2$C=O), 28.4, 26.1, 24.3 (CH$_2$). HR ESI MS: *m/z* calcd for C$_{36}$H$_{56}$N$_6$NaO$_{14}$ 819.3747, found 819.3743.

Bis((3-benzyloxypropanoyloxy)ethoxy)benzene (18). Compound **18** was synthesized using the general esterification procedure using TBTU. 3-Benzyloxypropanoic acid (0.216 g, 1.20 mmol) and diol **14**[57] (0.100 g, 1.00 mmol (OH)) were reacted for 1.5 h to give **18** (0.23 g, 89% yield) as a colorless solid after purification using column chromatography (hexanes/ EtOAc; 2:1; R$_F$ 0.29): mp 105 – 107 °C; ^{1}H NMR (500.13 MHz, CDCl$_3$) δ 2.69 (t, *J* = 6.5 Hz, 4H, CH$_2$C=O), 3.78 (t, *J* = 6.5 Hz, 4H, CH$_2$OBn), 4.12 (t, *J* = 4.5 Hz, 4H, PhOCH$_2$), 4.44 (t, *J* = 4.5 Hz, 4H, CH$_2$OC=O), 4.54 (s, 4H, benzylic), 6.85 (s, 4H, PhH), 7.29 – 7.35 (m, 10H, PhH); ^{13}C NMR (125.7 MHz, CDCl$_3$) δ 171.5 (C=O), 153.0, 138.0, 128.4, 127.6, 115.6 (PhC), 73.0 (CH$_2$, benzylic), 66.5 (PhOCH$_2$), 65.5 (CH$_2$OBn), 62.9 (CH$_2$OC=O), 35.0 (CH$_2$C=O). HR ESI MS: *m/z* calculated for C$_{30}$H$_{34}$NaO$_8$ 545.2146, found 545.2139.

Bis((3-hydroxypropanoyloxy)ethoxy)benzene (19). Using the general procedure for hydrogenolysis described above, compound **19** (0.750 g, 1.44 mmol), dissolved in dry CH$_2$Cl$_2$ (5 mL), dry MeOH (10 mL), and dry THF (5 mL) afforded **19** as a colorless crystalline solid (0.48 g, 98% yield): mp 118 – 120 °C ^{1}H NMR (500.13 MHz, methanol-*d*$_4$) δ 2.56 (t, *J* = 6.5 Hz, 4H, CH$_2$C=O), 3.82 (t, *J* = 6.5 Hz, 4H, C**H$_2$**OH), 4.13 (t, *J* = 4.5 Hz, 4H, PhOCH$_2$), 4.40 (t, *J* = 4.5 Hz, 4H, CH$_2$C=O), 6.87 (s, 4H, PhH); ^{13}C NMR (125.7 MHz, methanol-*d*$_4$) δ 173.5 (C=O), 154.5, 116.7 (PhC), 67.7 (PhOCH$_2$), 64.2 (CH$_2$OC=O), 58.7 (CH$_2$OH), 38.4 (CH$_2$C=O). HR ESI MS: *m/z* calcd for C$_{16}$H$_{22}$NaO$_8$ 365.1207, found 365.1205.

Bis((3-(6-azidohexanoyloxy)-propanoyloxy)ethoxy)benzene (20). Compound **20** was synthesized using the general esterification procedure using TBTU. 6-Azidohexanoic acid **12** (0.190 g, 1.20 mmol)

and diol **19** (0.170 g, 1.00 mmol (OH)) reacted for 2 h to give **20** (0.29 g, 94% yield) as a colorless solid after purification using precipitation from diethyl ether. Purification was also achieved using column chromatography (hexanes/ EtOAc; 1:1; R_F 0.53): mp 102 – 105 °C; ^{1}H NMR (300.15 MHz, $CDCl_3$) δ 1.36 – 1.40, 1.51 – 1.65 (2 m, 12H, 2 x 3 CH_2), 2.27 (t, *J* = 7.4 Hz, 4H, O=CC**H$_2$**CH_2C), 2.69 (t, *J* = 6.2 Hz, 4H, O=CC**H$_2$**CH_2O) 3.23 (t, *J* = 6.8 Hz, 4H, CH_2N), 4.10 (t, *J* = 4.5 Hz, 4H, PhOCH_2), 4.33 (t, *J* = 6.2 Hz, 4H, O=CCH_2C**H$_2$**O), 4.42 (t, *J* = 4.5 Hz, 4H, PhOCH_2C**H$_2$**), 6.82 (s, 4H, PhH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.1, 170.7 (C=O), 153.1, 115.8 (PhC), 66.6 (PhOCH_2), 63.2 (PhOCH_2**C**H_2), 59.7 (O=COCH_2), 51.2 (CH_2N_3), 33.9 (2 CH_2C=O), 28.6, 26.2, 24.4 (C**C**H2C). HR ESI MS: *m/z* calcd for $C_{28}H_{40}N_6NaO_{10}$ 643.2696, found 643.2701.

Benzylidene-protected hydroquinone-cored third-generation dendrimer (23). Compound **23** was synthesized as described above in the general procedure for dendritic ester synthesis. Compound **21**[57] (1.01 g, 1.13 mmol), dry pyridine (5 mL), CH_2Cl_2 (15 mL), DMAP (0.330 g, 2.71 mmol) and anhydride **22**[57] (4.81 g, 11.3 mmol) were stirred at rt for 10 h under nitrogen. After work up and purification as described above, the product was obtained as a colorless solid (2.71 g, 95% yield): mp 112 – 114 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 0.92 (s, 24H, 8CH_3), 1.04 (s, 6H, 2CH_3), 1.19 (s, 12H, 4CH_3), 3.57 (d, *J* = 11.5 Hz, 16H, H-4$_{ax}$, H-6$_{ax}$), 3.97 (t, *J* = 5 Hz, 4H, ArOCH_2), 4.07 (AB q, $\Delta\nu_{AB}$ = 11 Hz, J_{AB} = 11 Hz, 8H, 4C*H$_2$*OC=O), 4.31 – 4.37 (m, 20H, 8CH_2OC=O, 2CH_2OC=O), 4.55 – 4.57 (m, 16H, H-4$_{eq}$, H-6$_{eq}$), 5.39 (s, 8H, H-2), 6.75 (s, 4H, PhH), 7.27 – 7.40 (m, 40H, PhH); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 173.3, 172.3, 172.0 (C=O), 153.0, 137.9, 129.0, 128.3, 126.3, 115.8 (PhC), 101.8 (C-2), 73.63, 73.56 (C-4, C-6), 66.3 (ArO***C***H_2), 66.0 (4CH_2OC=O), 65.3 (8CH_2OC=O), 63.8 (OCH_2***C***H_2O), 47.0 (4C_{quat}), 46.6 (2C_{quat}), 42.7 (C-5), 17.82 (8CH_3), 17.78 (4CH_3), 17.4 (2CH_3). HR ESI MS: *m/z* calcd for $C_{136}H_{158}Na_2O_{46}$/2 1286.4904, found 1286.4887.

Third generation hydroquinone-cored dendrimer (24). Using the general procedure for hydrogenolysis described above, protected third generation dendrimer **23** (1.55 g, 0.613 mmol)

dissolved in dry CH_2Cl_2 (15 mL), dry methanol (30 mL), and dry THF (15 mL) afforded **24** as a colorless solid (1.10 g, 98% yield): mp 109 – 111 °C; ^{1}H NMR (500.13 MHz, DMSO-d_6) δ 1.00 (s, 24H, 8CH_3), 1.14 (s, 12H, 4CH_3), 1.20 (s, 6H, CH_3), 3.39 – 3.46 (m, 32H, 16CH_2OH), 4.08 – 4.23 (m, 28H, 8CH_2O, 4CH_2O, 2ArOCH_2), 4.36 (br, 4H, $OCH_2C\boldsymbol{H_2}O$), 4.66 (br, 16H, OH), 4.86 (s, PhH); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 174.1 (6C=O), 172.1 (2C=O), 171.9 (4C=O), 152.5, 115.6 (PhC), 66.0 (OCH_2CH_2O), 65.8, 64.5 (4, 8 CH_2OC=O), 63.7 (CH_2OH, PhOCH_2O), 50.3 (8C_{quat}), 46.4 (4C_{quat}), 46.2 (2C_{quat}), 17.2 (4CH_3), 17.0 (2CH_3), 16.8 (8CH_3). HR ESI MS: *m/z* calcd for $C_{80}H_{126}Na_2O_{46}$/2 934.3652, found 934.3654.

Azide-functionalized hydroquinone-cored third-generation dendrimer (25). Compound **25** was synthesized using the general esterification procedure using TBTU. 6-Azidohexanoic acid **12** (0.190 g, 1.20 mmol) and dendrimer **24** (0.114 g, 1.00 mmol (OH)) were reacted for 12 h to give **25** (0.20 g, 79% yield) as a colorless syrup after purification using column chromatography (hexanes/ EtOAc; 3:2; R_F 0.16): ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 1.20 (s, 24H, 8CH_3), 1.21 (s, 12H, 4CH_3), 1.28 (s, 6H, 2CH_3), 1.33 - 1.40, 1.55 - 1.63 (2 m, 96 H, 16 x 3 CH_2), 2.30 (t, *J* = 7.5 Hz, 32H, CH_2C=O), 3.25 (t, *J* = 6.9 Hz, 32H, CH_2N), 4.11 - 4.28 (m, 60H, 30 x CH_2OC=O), 4.42 (t, *J* = 4.5 Hz, 4H, 2 x Ph$OCH_2C\mathbf{H_2}$), 6.81 (s, 4H, PhH); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 172.8, 172.03, 172.01, 171.5 (C=O), 153.0, 115.7 (PhC), 66.3 (PhOCH_2), 66.1, 65.2, 64.9 (CH_2OC=O), 63.9 (Ph$OCH_2\mathbf{C}H_2$), 51.2 (CH_2N_3), 46.7, 46.6, 46.4 (C_q), 33.8 ($\mathbf{C}H_2C$=O), 28.6, 26.2, 24.4 ($C\mathbf{C}H_2C$), 17.8, 17.6, 17.5 (CH_3). HR ESI MS: *m/z* calcd for $C_{176}H_{270}Na_3N_{48}O_{62}$/3 1372.6356, found 1372.6389.

Divalent α-D-mannopyranoside-terminated dendrimer (26). The azide-functionalized divalent dendrimer **17** (0.440 g, 0.552 mmol) and known propargyl α-D-mannopyranoside **7**[62, 68] (0.280 g, 1.28 mmol) were dissolved in THF (15 mL). To the clear solution was added sodium ascorbate (0.060 g, 0.303 mmol) and a solution of copper(II) sulfate pentahydrate (0.030 g, 0.120 mmol) in water (15 mL). The mixture was then vigorously stirred overnight and concentrated under reduced pressure. Purification

using size exclusion chromatography on Sephadex LH-20 column gave the product as a thick colorless syrup (0.55 g, 81% yield). ^{1}H NMR (500.13 MHz, D_2O) δ 1.14 (br, 4H, 2 CH_2), 1.44 (br, 4H, 2 CH_2), 1.60 – 1.80 (br, m, 4H, 2 CH_2), 2.18 (br, 4H, CH_2C=O), 3.17 – 4.92 (complex m, 54H), 6.88 (s, 4H, PhH), 8.05 (br, 2H, Triaz CH). HR ESI MS: *m/z* calcd for $C_{54}H_{84}N_6Na_2O_{26}/2$ 639.2610, found 639.2628.

Extended α-D-mannopyranoside-terminated dendrimer (27). The azide functionalized divalent dendrimer **20** (0.700 g, 1.13 mmol) and propargyl α-D-mannopyranoside **7** (0.570 g, 2.61 mmol) were dissolved in THF (20 ml). To the clear solution was added sodium ascorbate (0.120 g, 0.606 mmol) and a solution of copper(II) sulfate pentahydrate (0.060 g, 0.240 mmol) in water (15 mL). The mixture was then vigorously stirred overnight and concentrated under reduced pressure. Purification using size exclusion chromatography on Sephadex LH-20 column gave the product (**27**) as a thick colorless syrup (1.03 g, 86% yield): ^{1}H NMR (500.13 MHz, methanol-d_4) δ 1.25 (pentet (p), J = 7.5 Hz, 4H, CH_2), 1.58 (p, J = 7.5 Hz, 4H, O=CCH_2C**H$_2$**), 1.86 (p, J = 7.5 Hz, 4H, NCH_2C**H$_2$**), 2.25 (t, J = 7.5 Hz, 4H, O=CC**H$_2$**CH_2C), 2.69 (t, J = 6 Hz, 4H, O=CC**H$_2$**CH_2O), 3.55 – 3.89 (m, 12H, H-2, H-3, H-4, H-5, H-6), 4.23 (t, J = 4.5 Hz, 4H, PhOCH_2), 4.30 (t, J = 6 Hz, 4H, CH_2OC=O), 4.37 (t, J = 7 Hz, 4H, CH_2N), 4.41 (t, J = 4.5 Hz, 4H, PhOCH_2C**H$_2$**), 4.64 (d, J = 12.5 Hz, 2H, =CCHOC-1), 4.79 (d, J = 12.5 Hz, 2H, =CCH'OC-1), 4.86 (br, 2H, H-1), 6.86 (s, 4H, PhH), 8.00 (s, 2H, triazCH, triaz); ^{13}C NMR (125.7 MHz, methanol-d_4) δ 174.8, 172.5 (C=O), 154.4 (PhCq), 145.2 (triaz Cq), 125.3 (triaz CH), 116.6 (PhC), 100.7 (C-1), 74.9 (C-5), 72.5 (C-3), 71.9 (C-2), 68.5 (C-4), 67.8 (PhOCH_2), 64.5 (C-6), 62.9 (PhOCH_2CH_2), 61.1 (OCH_2Triaz), 60.7 (CH_2OC=O), 51.1 (CH_2N), 34.6, 34.5 (CH_2C=O), 30.8, 26.8, 25.2 (C**C**H_2C). HR ESI MS: *m/z* calcd for $C_{46}H_{68}N_6NaO_{22}$ 1079.4279, found 1079.4246.

Third generation dendrimer bearing 16 mannose residues (28). The azide functionalized dendrimer **25** (1.40 g, 0.346 mmol) and propargyl α-D-mannopyranoside **7** (1.51 g, 6.92 mmol) were dissolved in DMF (35 ml). To the clear solution was added sodium ascorbate (0.290 g, 1.46 mmol) and a solution of

copper(II) sulfate pentahydrate (0.145 g, 0.581 mmol) in water (3 mL). The mixture was then vigorously stirred overnight and concentrated under reduced pressure. Purification using size exclusion chromatography on Sephadex LH-20 column gave the product as a thick colorless syrup (2.16 g, 83% yield): ^{1}H NMR (500.13 MHz, D_2O) δ 1.09 – 1.30 (br, 74H, 14CH_3, 16CH_2), 1.50 (br, 32H, 16CH_2), 1.79 (br, 32H, 16CH_2), 2.25 (br, 32H, 16CH_2), 3.57 – 4.89 ((br, m, 240H (32H, 16CH_2, CH_2N), (32H, 16CH_2, CH_2OC-1), (112H, 16sugar x 7H), (8H, OCH_2CH_2O), (8H, 2C_{quat}2CH_2O), (16H, 4C_{quat}2CH_2O), (32H, 8C_{quat}2CH_2O)), 6.82 (br, 4H, PhH), 8.04 (br, 16H, H_g); ^{13}C NMR (125.7 MHz, D_2O) δ 174.0, 172.7, 172.0 (C=O), 152.8 (PhC), 144.1 (triaz Cq), 125.1 (triaz CH), 115.9 (PhC), 99.4 (C-1), 73.0 (C-5), 70.6 (C-3), 70.0 (C-2), 66.6 (C-4), 65.3 (O**C**H_2**C**H_2O), 60.8 (C-6), 59.7 (Triaz CH_2O), 50.1 (CH_2N), 46.5, 46.3 (C_{quat}), 33.3 (CH_2C=O), 29.3, 25.4, 23.8 (CCH_2C), 17.3, 17.2, 17.1 (Me). HR ESI MS: *m/z* calcd for $C_{320}H_{494}N_{48}Na_6O_{158}$/6 1279.6901, found 1279.6411.

Bis(2-(2-propynyloxy)ethoxy)benzene (29). Compound **29** was synthesized using the general esterification procedure using TBTU. Propynoic acid (0.084 g, 1.20 mmol) and diol **14** (0.099 g, 1.00 mmol (OH)) were reacted for 1 h to give the title compound (0.12 g, 78% yield) as a colorless solid after purification using column chromatography (hexanes/ EtOAc; 3:1; R_F 0.18): mp 99 – 102 °C; ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 2.92 (s, 2H, CCH), 4.16 (t, *J* = 4.5 Hz, 4H, PhOCH_2), 4.52 (t, *J* = 4.5 Hz, 4H, CH_2OC=O), 6.85 (s, 4H, PhH); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 153.1 (C=O), 152.7, 115.9 (PhC), 75.5 (acetylene CH), 74.5 (acetylene O=C**C**), 66.2 (PhOCH_2), 64.6 (CH_2OC=O). HR ESI MS: *m/z* calcd for $C_{16}H_{14}NaO_6$ 325.0683, found 325.0678.

Divalent α-D-mannopyranoside-terminated dendrimer with a hexyl linker (30). Dialkyne **29** (0.260 g, 0.860 mmol) and 6-azidohexyl α-D-mannopyranoside **10**[52] (0.550 g, 1.80) were dissolved in THF (15 ml). To the clear solution was added sodium ascorbate (0.090 g, 0.454) and a solution of copper(II) sulfate pentahydrate (0.045 g, 0.180 mmol) in water (15 mL). The mixture was then vigorously stirred overnight and concentrated under reduced pressure. Purification using size exclusion chromatography on

Sephadex LH-20 column gave the product as a colorless solid (0.72 g, 89% yield): mp 132 – 134 °C ^{1}H NMR (500.13 MHz, DMSO-d_6/ methanol-d_4) δ 1.11 – 1.40 (m, 8H, 4 CH_2), 1.41 – 1.50 (m, 4H, C**H$_2$**CH_2OC-1), 1.82 (p, *J* = 7 Hz, 4H, NCH_2CH_2), 3.26 – 3.67 (m, 16H, CH_2OC-1, H-2, H-3, H-4, H-5, H-6), 4.18 (br, 4H, $PhOCH_2$), 4.36 (t, *J* = 7 Hz, CH_2N), 4.54 (br, 4H, $PhOCH_2C$**H$_2$**), 4.58 (br, 2H, H-1), 6.85 (s, 4H, PhH), 8.58 (s, 2H, H_c); ^{13}C NMR (125.7 MHz, DMSO-d_6/ methanol-d_4) δ 161.9 (C=O), 154.2 (PhC), 140.2 (triaz Cq), 130.2 (triaz CH), 116.9 (PhC), 101.4 (C-1), 75.0 (C-5), 72.5 (C-3), 72.0 (C-2), 68.5 (C-4), 67.9 (CH_2OC-1), 67.7 ($PhOCH_2$), 64.7 ($PhOCH_2$**C**H_2), 62.8 (C-6), 51.4 (CH_2N), 31.0, 30.3, 27.1, 26.7 (CH_2). HR ESI MS: *m/z* calcd for $C_{40}H_{60}N_6NaO_{18}$ 935.3856, found 935.3848.

2,2'-Bis-(2-propynyloxymethy)propanoic acid (31). Compound was synthesized by the method of Wu et al.[65] in 48 % yield: ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 1.25 (s, 3H, CH_3), 2.42 (t, *J* = 2.1 Hz, 2H, acetylenic H), 3.65 (AB q, Δν 0.179 ppm, *J* = 8.9 Hz, 4H, OCH_2C), 4.14 (AB part of ABX pattern, J_{AX} = J_{BX} = 2.3 Hz, J_{AB} = 16.3 Hz, 2H, CH_2CCH); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 180.3 (CO), 79.6 (**C**CH), 74.7 (H**C**C), 71.7 (OCH_2CCH), 58.9 (CH_2O), 48.0 (C_q), 17.9 (CH_3). HR ESI MS: *m/z* calcd for $C_{11}H_{14}NaO_4$ 233.0784, found 233.0794.

2,2'-Bis-(2-propynyloxymethyl)propanoyl anhydride (32). Acid **31** (1.00 g, 4.80 mmol) was added to a stirred solution of DCC (0.530 g, 2.60 mmol) at rt and reaction mixture was stirred for overnight. The mixture was filtered to remove *N*,*N*'-dicyclohexylurea and the filtrate was concentrated to give **32** as a light reddish liquid (1.8 g, 94 % yield): ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 1.28 (s, 3H, CH_3), 2.46 (t, *J* = 2.2 Hz, 2H, acetylenic H), 3.71 (AB q, Δυ = 0.149 ppm, *J* = 9.0 Hz, 4H, OCH_2C), 4.14 (d, *J* = 2.3 Hz, 2H, CH_2CCH); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 169.1 (CO), 79.6 (**C**CH), 74.8 (H**C**C), 71.2 (OCH_2CCH), 58.9 (CH_2O), 49.6 (Cq), 17.4 (CH_3). HR ESI MS: *m/z* calcd for $C_{22}H26Na_1O_7$ 425.1571, found 425.1571.

1,4-Bis-2-(2,2'-bis-(2-propynyloxy)methyl)propanoyloxy)ethoxy)benzene (33). Core diol **14**[57] (0.300 g, 2.52 mmol), dry pyridine (5 mL), CH_2Cl_2 (15 mL), DMAP (0.036 g, 0.30 mmol) and the anhydride **32**

(1.52 g, 3.78 mmol) were stirred at rt for 12 h under nitrogen. After work up and purification using column chromatography (hexanes/ EtOAc; 2:1; R_F 0.36), the product was obtained as a light brownish liquid (0.60 g, 69 % yield): ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 1.22 (s, 6H, $2CH_3$), 2.37 (t, *J* = 2.3 Hz, 4H, acetylenic H), 3.64 (AB q, *J* = 9.6 Hz, 8H, OCH_2C), 4.11-4.13 (complex m, 12H, CH_2CCH and OCH_2), 4.42 (t, *J* = 4.8 Hz, 4H, $PhOCH_2C\mathbf{H_2}$), 6.83 (s, 4H, Ar); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 174.2 (CO), 153.3 (C-Ar), 116.0 (CH-Ar), 79.8 (CCH), 74.5 (HCC), 71.9 (OCH_2CCH), 66.9 ($PhOCH_2$), 63.2 ($PhOCH_2\mathbf{C}CH_2$), 58.8 (CH_2O), 48.3 (C_q), 18.0 (CH_3). HR ESI MS: *m/z* calcd for $C_{32}H_{38}NaO_{10}$ 605.2357, found 605.2374.

Tetramannoside polyester dendrimer 34. **T**etraalkyne **33** (0.150 g, 0.257 mmol) and 6-azidohexyl α-D-mannopyranoside **10** (0.393 g, 1.28) were dissolved in THF (15 mL). To the clear solution was added sodium ascorbate (0.026 g, 0.134 mmol) and a solution of copper(II) sulfate pentahydrate (0.012 g, 0.052 mmol) in water (15 mL). The mixture was then vigorously stirred overnight and concentrated under reduced pressure. Purification using size exclusion chromatography on a Sephadex LH-20 column gave the product as an fluffy solid (yield 0.34 g, 73%): mp 122-124 ^{o}C; ^{1}H NMR (500.13 MHz, DMSO-d_6) δ 1.06 (s, 6H, $2CH_3$), 1.22 (m, 8H, $N(CH_2)_2\mathit{CH_2}$), 1.24 (m, 8H, $O(CH_2)_2\mathit{CH_2}$), 1.46 (m, 8 H, $OCH_2\mathit{CH_2}$), 1.78 (p, 8H, *J* = 7.2 Hz, $NCH_2\mathit{CH_2}$), 3.25-3.66 (complex m, 32 H, H-2, H-3, H-4, H-5, H-6, H-6', $OCH_2CC{=}O$), 4.06 (m, 4H, $PhOCH_2$), 4.26 (m, 4H, $O{=}CO\text{-}CH_2$), 4.29 (t, *J* = 7.1 Hz, 8H, NCH_2),4.39 (t, 4H, J = 6.0.3 Hz, OH-6), 4.46 (br s, 8H, $CH_2CN{=}N$), 4.49 (d, 4H, J = 6.0 Hz, OH), 4.57 (s, 4H, H-1), 4.63 (d, 4H, J = 4.4 Hz, OH), 4.67 (d, 4H, J = 5.3 Hz, OH), 6.86 (s, 4H, Ar), 8.00 (s, 4H, triazole H); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 174.2 (CO), 153.3 (C-Ar), 145.0 (triaz Cq), 123.6 (triazole CH), 115.7 (CH-Ar), 99.7 (C-1), 73.9 (C-5), 71.0 (C-3), 70.4 (C-2), 66.0 (C-4), 71.6, 66.0, 64.1, 61.3 (4 x OCH_2), 66.2 (2 x CH_2OPh), 62.6 (2 x $CH_2OC{=}O$), 49.2 (NCH_2), 29.6, 28.8, 25.6, 25.1 (4 x CH_2), 17.5 (2 x CH_3). HR ESI MS: *m/z* calcd for $C_{80}H_{130}Na_2O_{34}/2$ 924.4298, found 924.4295.

2-(p-Toluenesulfonyl)ethyl 2,2'-bis(2,2'-bis-(2-propynyloxymethyl)propanoyloxymethyl)-propanoate (36) Compound **36** was synthesized as described above in the general procedure for formation of dendritic esters, using 2-toluenesulfonylethyl 2,2-bis(hydroxylmethylpropanoate (**35**)[66] (1.00 g, 3.20 mmol), and anhydride **32** (3.18 g, 7.91 mmol) in dry pyridine (5 mL), and dichloromethane (15 mL) containing DMAP (0.038 g, 0.320 mmol) at rt for 12 h. After work up and purification using column chromatography (hexanes/ EtOAc; 2:1; RF 0.36), the product was obtained as a colorless syrup (1.84 g, 80 % yield): ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 1.13 (s, 3H, CH_3), 1.18 (s, 6H, 2 x CH_3), 2.42 (br s, 4H, 4 x CCH), 2.46 (s, 3H, $PhCH_3$), 3.44 (t, 2H, J = 6.3 Hz, SCH_2), 3.53-3.62 (m, 8H, 4 x $OCH_2CC(C=O)Me$), 4.08-4.15 (m, 12H, 4 x CH_2CCH, and 2 x $CH_2OC=O$), 4.44 (t, 2H, J = 6.3 Hz, $CH_2OC=O$), 7.39 (d, 2H, J = 8.1 Hz, PhH), 7.80 (d, J = 8.2 Hz, 2H, PhH); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 173.5 (C=O), 172.3 (C=O), 145.5, 136.5, 130.4, 128.3 (PhC), 79.8 (CCH), 74.9 (HCC), 71.9 (OCH_2CCH), 65.3 ($O=COCH_2$), 58.8 (4 Cq**C**H_2O), 58.4 (2 Cq**C**H_2O), 55.2 (CH_2S), 48.3 (2 Cq), 46.8 (Cq), 21.8 ($PhCH_3$), 18.1 (2 CH_3), 17.6 (CH_3). HR ESI MS: m/z calcd for $C_{36}H_{44}NaO_{12}S$ 723.2446, found 723.2437.

2,2'-Bis(2,2'-bis-(2-propynyloxymethyl)propanoyloxymethyl)propanoic acid (37) Compound **36** (1.70 g, 2.42 mmol) was dissolved in CH_2Cl_2 (15 mL) in a flame-dried round-bottom flask equipped with a magnetic stir bar, and 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) (200 μL, 1.3 x 10^{-8} mmol) was added. The reaction was vigorously stirred for 12 h, then the solution was concentrated to a syrup. The product was then washed three times with 9:1 hexanes: ethyl acetate (v/v) and residual solvent was removed by concentration to yield a gummy syrup (1.14 g, 91 % yield): ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 1.18 (s, 6H, 2xCH_3), 1.32 (s, 3H, CH_3), 2.45 (br s, 4H, 4 x CCH), 3.62-3.68 (m, 8H, 4 x OCH_2Cq), 4.12-4.18 (m, 8H, CH_2CCH), 4.32 (AB q, 4H, J =11.4 Hz, Δν = 0.013 ppm, $CH_2OC=O$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 177.2 (C=OOH), 173.6 (C=O), 79.7 (**C**CH), 74.8 (H**C**C), 71.8 (O**C**H_2CCH),

65.3 (**C**H_2OC=O), 58.7 (Cq**C**H_2O), 48.3 (2 Cq), 46.9 (Cq), 18.0 (2 CH_3), 17.8 (CH_3). HR ESI MS: *m/z* calcd for $C_{27}H_{34}NaO_{10}$ 541.2044, found 541.2033.

2,2'-Bis(2,2'-bis-(2-propynyloxymethyl)propanoyloxymethyl)propanoic anhydride (38) A solution of acid **37** (1.10 g, 2.10 mmol) and DCC (0.240 g, 1.10 mmol) in dichloromethane (15 mL) was stirred at rt for 12 h under nitrogen. The resulting mixture was filtered to remove *N*, *N*'-dicyclohexylurea and the filtrate was concentrated to a colorless gummy solid (**38**) (1.0 g, 90 % yield): ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 1.23 (s, 12H, 4 x CH_3), 1.36 (s, 6H, 2 x CH_3), 2.46 (br s, 8H, 8 x HCC), 3.62-3.68 (m, 16H, 8 x OCH_2C), 4.15-4.17 (m, 16H, 8 x CH_2CCH), 4.35 (AB q, 8H, J = 11.3 Hz, Δν = 0.023 ppm, 4 x CCH_2OC=O); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 173.4 (C=O), 167.6 (O=COC=O), 79.7 (**C**CH), 74.8 (H*C*C), 71.8 (O**C**H_2CCH), 64.7 (**C**H_2OC=O), 58.8 (Cq**C**H_2O), 48.42 (Cq), 48.36 (Cq), 18.0 (4 CH_3), 17.3 (2 CH_3). HR ESI MS: m/z calcd for $C_{54}H_{66}NaO_{19}$ 1041.4091, found 1041.4101.

Octapropargylated polyester dendrimer (39). Core molecule **14** (0.090 g, 0.450 mmol) and anhydride **38** (1.00 g, 0.980 mmol) dissolved in dry pyridine (5 mL), and dichloromethane (15 mL) containing DMAP (0.038 g, 0.320 mmol) were stirred at rt for 12 h under nitrogen under the conditions for formation of dendritic esters. After work up and purification using column chromatography (hexanes/ EtOAc; 1:1; RF 0.45), the product (**39**) was obtained as colorless syrup (0.40 g, 73 % yield): ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 1.18 (s, 12H, 4 x CH_3), 1.26 (s, 6H, 2 x CH_3), 2.40 (td, 8H, J = 0.8, 2.3 Hz, 8 x CCH), 3.56-3.63 (m, 16H, 8 x OCH_2Cq), 4.11 (d, 16H, J = 2.3 Hz, 8 x OCH_2CCH), 4, 12-4.14 (m, 4H, 2 x $PhOCH_2$), 4.28 (s, 8H, 4 x CH_2OC=O), 4.43 (1/2 AA'XX' pattern, 4H, 2 x O=$COCH_2$), 6.83 (s, 4H, PhH); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 173.6 (C=O), 153.2 (PhC), 116.0 (PhCH), 79.7 (**C**CH), 74.7 (H**C**C), 71.9 (OCH_2CCH), 66.6 ($PhOCH_2$), 65.6 (**C**H_2OC=O), 63.7 ($PhOCH_2$**C**H_2), 58.8 (Cq**C**H_2O), 48.3 (4 Cq), 46.9 (2 Cq), 18.0 (4 CH_3), 17.8 (2 CH_3). HR ESI MS: m/z calcd for $C_{64}H_{78}NaO_{22}$ 1221.4877, found 1221.4860.

Octavalent mannose-terminated polyester dendrimer (40) 6-Azidohexyl α-D-mannopyranoside (**10**) (0.611 g, 2.00 mmol) and octapropargylated polyester dendrimer (**39**) (0.200 g, 0.160 mmol) were dissolved in THF (15 mL) and sodium ascorbate (0.016 g, 0. 080 mmol) and a solution of copper (II) sulfate pentahydrate (0.002 g, 0.008 mmol) in water (5 mL) were added. The mixture was stirred vigorously for 12 h, then concentrated to a syrup. Purification using size exclusion chromatography on Sephadex LH-20 column gave the product as light yellow fluffy solid (0.40 g, 65% yield): mp became transparent at 85 ^{o}C, then decomposed at 200-205 ^{o}C; ^{1}H NMR (500.13 MHz, D_2O) δ 1.10 (br s, 18H, 6x CH_3), 1.24– 1.34 (br s, m, 32H, CH_2CH_2 CH_2), 1.53 (br s, 16H, CH_2CH_2O), 1.84 (br s, 16H, CH_2CH_2N), 3.42 – 3.96 (m, 80H, Sugar- H-2, H-3, H-4, H-5, H-6, OCH_2), 4.16 (br s, 16H, OCH_2C), 4.37 (br s, 16H, OCH_2C), 4.16 (br s, 16H, OCH_2NNC), 4.55 (br s, 16H, OCH_2C-N), 4.16 (br s, 8H, Sugar- H-1), 6.86 (s, 4H, PhH), 7.93 (br, 8H, H-triazole); ^{13}C NMR (125.7 MHz, CDCl3) δ 174.6, 173.4 (C=O), 152.8 (PhC), 143.6 (triaz Cq), 124.6 (Triaz CH), 116.5 (PhCH), 99.8 (C-1), 72.8 (C-5), 71.8 (OCH_2), 70.8 (C-3) 70.3 (C-2), 67.6 (OCH_2), 66.8 (C-4), 66.0 ($PhOCH_2$), 65.3, 64.2, 64.0, 60.9 (CH_2O), 60.9 (CH_2OC=O), 50.3 (NCH_2), 48.4, 46.7 (Cq), 29.5, 28.5, 25.6, 25.0 (CH_2), 17.4 (4 x CH_3), 17.1 (2 x CH_3). HR ESI MS: m/z calcd for $C_{160}H_{262}Na_3O_{70}$/3 1236.2452, found 1236.2432.

SUPPORTING INFORMATION AVAILABLE

^{1}H and ^{13}C NMR spectra of all compounds prepared.

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References

1. C. K. Cusumano and S. J. Hultgren, *Idrugs*, 2009, **12**, 699-705.
2. N. Sharon, *Biochim. Biophys. Acta, Gen. Subj.*, 2006, **1760**, 527-537.
3. H. Remaut and G. Waksman, *Curr. Opin. Struct. Biol.*, 2004, **14**, 161-170.
4. T. J. Hannan, M. Totsika, K. J. Mansfield, K. H. Moore, M. A. Schembri and S. J. Hultgren, *Fems Microbiol. Rev.*, 2012, **36**, 616-648.
5. T. M. Hooton and W. E. Stamm, *Infect. Dis. Clin. N. Am.*, 1997, **11**, 551-581.
6. B. Foxman and P. Brown, *Infect. Dis. Clin. N. Am.*, 2003, **17**, 227-241.
7. B. Foxman, *Infect. Dis. Clin. N. Am.*, 2014, **28**, 1-13.
8. B. Xie, G. Zhou, S. Y. Chan, E. Shapiro, X. P. Kong, X. R. Wu, T. T. Sun and C. E. Costello, *J. Biol. Chem.*, 2006, **281**, 14644-14653.
9. G. R. Nielubowicz and H. L. T. Mobley, *Nature Rev. Urol.*, 2010, **7**, 430-441.
10. J. Bouckaert, J. Berglund, M. Schembri, E. De Genst, L. Cools, M. Wuhrer, C. S. Hung, J. Pinkner, R. Slättegård, A. Zavialov, D. Choudhury, S. Langermann, S. J. Hultgren, L. Wyns, P. Klemm, S. Oscarson, S. D. Knight and H. De Greve, *Mol. Microbiol.*, 2005, **55**, 441-455.
11. R. U. Lemieux, *Chem. Soc. Rev.*, 1989, **18**, 347-374.
12. G. Roos, A. Wellens, M. Touaibia, N. Yamakawa, P. Geerlings, R. Roy, L. Wyns and J. Bouckaert, *ACS Med. Chem. Lett.*, 2013, **4**, 1085-1090.
13. M. Scharenberg, O. Schwardt, S. Rabbani and B. Ernst, *J. Med. Chem.*, 2012, **55**, 9810-9816.
14. L. M. Nilsson, W. E. Thomas, E. Trintchina, V. Vogel and E. V. Sokurenko, *J. Biol. Chem.*, 2006, **281**, 16656-16663.
15. I. Le Trong, P. Aprikian, B. A. Kidd, M. Forero-Shelton, V. Tchesnokova, P. Rajagopal, V. Rodriguez, G. Interlandi, R. Klevit, V. Vogel, R. E. Stenkamp, E. V. Sokurenko and W. E. Thomas, *Cell*, 2010, **141**, 645-655.
16. H. Wang, G. Min, R. Glockshuber, T. T. Sun and X. P. Kong, *J. Mol. Biol.*, 2009, **392**, 352-361.
17. N. Firon, S. Ashkenazi, D. Mirelman, I. Ofek and N. Sharon, *Infect. Immun.*, 1987, **55**, 472-476.
18. Z. F. Han, J. S. Pinkner, B. Ford, R. Obermann, W. Nolan, S. A. Wildman, D. Hobbs, T. Ellenberger, C. K. Cusumano, S. J. Hultgren and J. W. Janetka, *J. Med. Chem.*, 2010, **53**, 4779-4792.
19. O. Sperling, A. Fuchs and T. K. Lindhorst, *Org. Biomol. Chem.*, 2006, **4**, 3913-3922.
20. L. Pang, S. Kleeb, K. Lemme, S. Rabbani, M. Scharenberg, A. Zalewski, F. Schaedler, O. Schwardt and B. Ernst, *ChemMedChem*, 2012, **7**, 1404-1422.
21. X. Jiang, D. Abgottspon, S. Kleeb, S. Rabbani, M. Scharenberg, M. Wittwer, M. Haug, O. Schwardt and B. Ernst, *J. Med. Chem.*, 2012, **55**, 4700-4713.
22. M. Scharenberg, X. H. Jiang, L. J. Pang, G. Navarra, S. Rabbani, F. Binder, O. Schwardt and B. Ernst, *ChemMedChem*, 2014, **9**, 78-83.
23. A. Bernardi, J. Jiménez-Barbero, A. Casnati, C. De Castro, T. Darbre, F. Fieschi, J. Finne, H. Funken, K. E. Jaeger, M. Lahmann, T. K. Lindhorst, M. Marradi, P. Messner, A. Molinaro, P. V. Murphy, C. Nativi, S. Oscarson, S. Penadés, F. Peri, R. J. Pieters, O. Renaudet, J. L. Reymond, B. Richichi, J. Rojo, F. Sansone, C. Schäffer, W. B. Turnbull, T. Velasco-Torrijos, S. Vidal, S. Vincent, T. Wennekes, H. Zuilhof and A. Imberty, *Chem. Soc. Rev.*, 2013, **42**, 4709-4727.
24. J. Bouckaert, Z. Li, C. Xavier, M. Almant, V. Caveliers, T. Lahoutte, S. D. Weeks, J. Kovensky and S. G. Gouin, *Chem.-Eur. J.*, 2013, **19**, 7847-7855.
25. M. Touaibia, A. Wellens, T. C. Shiao, Q. Wang, S. Sirois, J. Bouckaert and R. Roy, *ChemMedChem*, 2007, **2**, 1190-1201.
26. A. Adronov and J. M. J. Fréchet, *Chem. Commun.*, 2000, 1701-1710.
27. J. K. Twibanire and T. B. Grindley, *Polymers*, 2014, **6**, 179-213.
28. T. Dutta, N. K. Jain, N. A. J. McMillan and H. S. Parekh, *Nanomed.-Nanotechnol.*, 2010, **6**, 815-815.

29. T. Dutta, N. K. Jain, N. A. J. McMillan and H. S. Parekh, *Nanomed.-Nanotechnol.*, 2010, **6**, 25-34.
30. P. M. H. Heegaard, U. Boas and N. S. Sorensen, *Bioconjugate Chem.*, 2010, **21**, 405-418.
31. L. G. Weaver, Y. Singh, G. Vamvounis, M. F. Wyatt, P. L. Burn and J. T. Blanchfield, *Polymer Chem.*, 2014, **5**, 1173-1179.
32. T. K. Lindhorst, C. Kieburg and U. Krallmann-Wenzel, *Glycoconjugate J.*, 1998, **15**, 605-613.
33. M. Hartmann and T. K. Lindhorst, *Eur. J. Org. Chem.*, 2011, 3583-3609.
34. T. K. Lindhorst, M. Dubber, U. Krallmann-Wenzel and S. Ehlers, *Eur. J. Org. Chem.*, 2000, 2027-2034.
35. T. K. Lindhorst, S. Kötter, U. Krallmann-Wenzel and S. Ehlers, *J. Chem. Soc., Perkin Trans. 1*, 2001, 823-831.
36. J. K. Twibanire and T. B. Grindley, *Polymers*, 2012, **4**, 794-879.
37. E. R. Gillies and J. M. J. Fréchet, *Drug Discov. Today*, 2005, **10**, 35-43.
38. E. R. Gillies, E. Dy, J. M. J. Fréchet and F. C. Szoka, *Mol. Pharmaceut.*, 2005, **2**, 129-138.
39. C. C. Lee, E. R. Gillies, M. E. Fox, S. J. Guillaudeu, J. M. J. Fréchet, E. E. Dy and F. C. Szoka, *Proc. Nat. Acad. Sci. U.S.A.*, 2006, **103**, 16649-16654.
40. M. R. Bryce, P. de Miguel and W. Devonport, *Chem. Commun.*, 1998, 2565-2566.
41. R. S. Dhanikula, A. Argaw, J. F. Bouchard and P. Hildgen, *Mol. Pharmaceut.*, 2008, **5**, 105-116.
42. D. G. Barrett, T. J. Merkel, J. C. Luft and M. N. Yousaf, *Macromolecules*, 2010, **43**, 9660-9667.
43. M. T. Morgan, Y. Nakanishi, D. J. Kroll, A. P. Griset, M. A. Carnahan, M. Wathier, N. H. Oberlies, G. Manikumar, M. C. Wani and M. W. Grinstaff, *Cancer Res.*, 2006, **66**, 11913-11921.
44. R. S. Dhanikula and P. Hildgen, *Bioconjugate Chem.*, 2006, **17**, 29-41.
45. R. S. Dhanikula and P. Hildgen, *Biomaterials*, 2007, **28**, 3140-3152.
46. D. G. van der Poll, H. M. Kieler-Ferguson, W. C. Floyd, S. J. Guillaudeu, K. Jerger, F. C. Szoka and J. M. Fréchet, *Bioconjugate Chem.*, 2010, **21**, 764-773.
47. S. H. Medina and M. E. H. El-Sayed, *Chem. Rev.*, 2009, **109**, 3141-3157.
48. M. T. Morgan, M. A. Carnahan, C. E. Immoos, A. A. Ribeiro, S. Finkelstein, S. J. Lee and M. W. Grinstaff, *J. Am. Chem. Soc.*, 2003, **125**, 15485-15489.
49. P. Antoni, Y. Hed, A. Nordberg, D. Nyström, H. von Holst, A. Hult and M. Malkoch, *Angew. Chem. Int. Ed.*, 2009, **48**, 2126-2130.
50. M. Touaibia and R. Roy, *Mini-Rev. Med. Chem.*, 2007, **7**, 1270-1283.
51. M. Almant, V. Moreau, J. Kovensky, J. Bouckaert and S. G. Gouin, *Chem.-Eur. J.*, 2011, **17**, 10029-10038.
52. E. Kaya, K. Gutsmiedl, M. Vrabel, M. Mueller, P. Thumbs and T. Carell, *ChemBioChem*, 2009, **10**, 2858-2861.
53. K. Öberg, J. Ropponen, J. Kelly, P. Löwenhielm, M. Berglin and M. Malkoch, *Langmuir*, 2013, **29**, 456-465.
54. J. K. Twibanire and T. B. Grindley, *Org. Lett.*, 2011, **13**, 2988-2991.
55. N. K. Paul, J. D. K. Twibanire and T. B. Grindley, *J. Org. Chem.*, 2013, **78**, 363-369.
56. J. K. Twibanire, R. P. Omran and T. B. Grindley, *Org. Lett.*, 2012, **14**, 3909-3911.
57. J. K. Twibanire, H. Al-Mughaid and T. B. Grindley, *Tetrahedron*, 2010, **66**, 9602-9609.
58. X. H. Ning, J. Guo, M. A. Wolfert and G. J. Boons, *Angew. Chem. Int. Ed.*, 2008, **47**, 2253-2255.
59. E. M. Sletten and C. R. Bertozzi, *Org. Lett.*, 2008, **10**, 3097-3099.
60. J. A. Johnson, J. M. Baskin, C. R. Bertozzi, J. T. Koberstein and N. J. Turro, *Chem. Commun.*, 2008, 3064-3066.
61. M. Malkoch, K. Schleicher, E. Drockenmuller, C. J. Hawker, T. P. Russell, P. Wu and V. V. Fokin, *Macromolecules*, 2005, **38**, 3663-3678.
62. E. Fernandez-Megia, J. Correa, I. Rodríguez-Meizoso and R. Riguera, *Macromolecules*, 2006, **39**, 2113-2120.
63. M. J. Joralemon, R. K. O'Reilly, J. B. Matson, A. K. Nugent, C. J. Hawker and K. L. Wooley, *Macromolecules*, 2005, **38**, 5436-5443.
64. Z. Huang, Y. Peng, H. Chen, Q. Xue and H. Li, *Design. Mon. Polym.*, 2014, **17**, 601-609.

65. W. Wu, W. Driessen and X. Jiang, *J. Am. Chem. Soc.*, 2014, **136**, 3145-3155.
66. M. C. Parrott, S. R. Benhabbour, C. Saab, J. A. Lemon, S. Parker, J. F. Valliant and A. Adronov, *J. Am. Chem. Soc.*, 2009, **131**, 2906-2916.
67. J. K. Twibanire, M. P. Huestis and T. B. Grindley, *Tetrahedron Lett.*, 2014, **55**, 3436-3439.
68. P. van der Peet, C. T. Gannon, I. Walker, Z. Dinev, M. Angelin, S. Tam, J. E. Ralton, M. J. McConville and S. J. Williams, *ChemBioChem*, 2006, **7**, 1384-1391.