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First Synthesis of "Majoral-Type" Glycodendrimers Bearing Covalently Bound α-D-Mannopyranoside Residues onto a Hexachlocyclotriphosphazene Core

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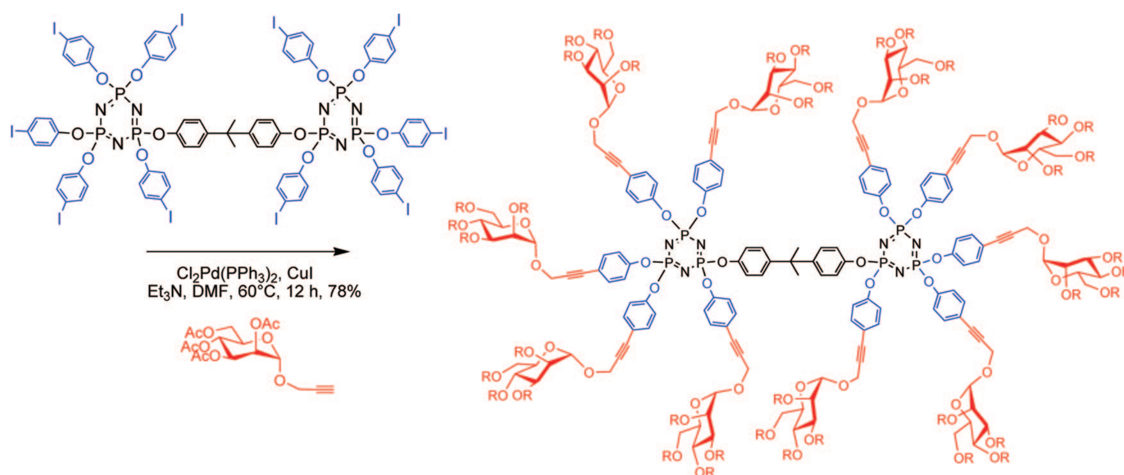

A short and efficient strategy for the first synthesis of "Majoral-Type" multivalent glycodendrimers bearing covalently bound α-D-mannopyranosides onto a cyclotriphosphazene scaffold assembled using single-step Sonogashira and click chemistry is reported. New glycoclusters with valencies ranging from 6 to 18 and different epitope spatial arrangements were obtained. Cross-linking abilities of this series of glycodendrimers were evaluated with the model lectin from *Canavalia ensiformis* (Concanavalin A). The decameric mannoside **23**, built around **19**, was shown to be much faster in cross-linking the tetravalent lectin Concanavalin A than the positive control, which is the polysaccharide mannan from yeast. The new glycoconjugates reported may be promising tools as probes or effectors of biological processes involving multivalent carbohydrate-binding proteins.

Introduction

The heavy use of antibiotics during the second half of the last century has resulted in widespread bacterial resistance.[1,2] Overcoming resistance requires the development of antibiotics aimed at new targets of microorganisms.[3] Bacteria such as fimbriated *Escherichia coli* produce proteins at the tip of their fimbriae (FimH) that recognize and bind to the mannosides of host human tissues as the premise for bacterial infections. *E. coli* is the main cause of urinary tract infections affecting the bladder (cystitis).[4,5] The importance of carbohydrate-binding proteins[6−9] or lectins in regulating biological systems is widely

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recognized and has inspired numerous efforts to understand and manipulate these processes. However, carbohydrate−protein interactions often occur with low-monomeric-binding affinities.[10−14] Consequently, biologically relevant interactions involve multivalent interactions between the lectin and the multiple carbohydrate ligands.[15−25] Moreover, these multivalent interactions have several advantages over monomeric ones and are used often by nature to control a wide variety of cellular processes.[10,18,19] From these observations, glycodendrimers[16,17,19−25] were synthesized to address fundamental aspects in multivalent carbohydrate−protein interactions using well-defined and monodispersed chemical entities. The "glycoside cluster effect" of glycodendrimers is now firmly accepted and corresponds to an affinity enhancement that is much greater than that expected from a single binding event at a multiple-carbohydrate-recognition domain (CRD).[11,12,14,25] Although several attempts to quantify the effects of a multivalent presentation have been reported,[10−14,26−28] the detailed mechanism at the molecular level still remains unclear, but a recent paper nicely described the potential source of the increased binding using entropic arguments and the "bind and slide" model.[29] Thus, the design of various types of clusters that can serve as inhibitors of biological systems for medical use is still carried out on a very empirical basis. A wide variety of dendrimers that is peripherally functionalized with mannose units has been studied toward these ends.[16,21,22,24,25]

In previous communications, we described our findings on several families of mannosylated dendrimers.[25,30] Pentaerythritol and bis-pentaerythritol scaffolds were used for the preparation of first-generation glycodendrimers bearing aryl α-D-mannopyranoside residues assembled using single-step Sonogashira and "click chemistry". These glycodendrimers were found to be excellent model ligands for the *Canavalia ensiformis* lectin (Concanavalin A) and to be the best ligands known to date toward *E. coli* K12 FimH with subnanomolar affinities.[30,31]

For high versatility and efficiency, the development of a general approach to dendrimer functionalization should, therefore, employ a reaction that occurs with high yields, proceeds under mild reaction conditions, and is compatible with essentially all potential surface functional groups and internal dendritic repeat units. The divergent method for dendrimer-containing triazole unit(s) at the periphery can be facilitated by fewer coupling reaction(s) between a terminal azide-functionalized core and alkynes. In addition, the concept of click chemistry has received enormous attention and has generated considerable impact in organic synthesis since its simplification in 2001[32−36] because of the high yields and the lack of byproducts provided by click chemistry for "stitching" together alkynes and azide cores. There have been ample examples since of applications of click chemistry in the field of carbohydrate chemistry.[37]

Because of our interest in developing new mannosylated dendrimers as potential drug candidates for gastrointestinal and urinary tract infections caused by *E. coli*,[25,30] we became involved in exploring an efficient cycloaddition reaction that provides easy access to glycodendrimers. Here, we present the syntheses of representative members of a new class of glycodendrimers that are built on nontoxic cyclotriphosphazene cores. Cyclophosphazene derivatives and polyorganophosphazenes are encountered frequently in inorganic, organic, and high-polymer chemistry.[38] Allcock et al.[39] reported that the syntheses of polyphosphazene can be used as carriers for drug delivery systems owing to their prominent biodegradability and biocompatibility. Cyclotriphosphazenes exhibit useful thermal and chemical properties such as flame retardancy, oil repellance, and biocompatibility. Inoue et al.[40,41] reported the syntheses of star-shaped amino acids with cyclotriphosphazene cores. Aziri-

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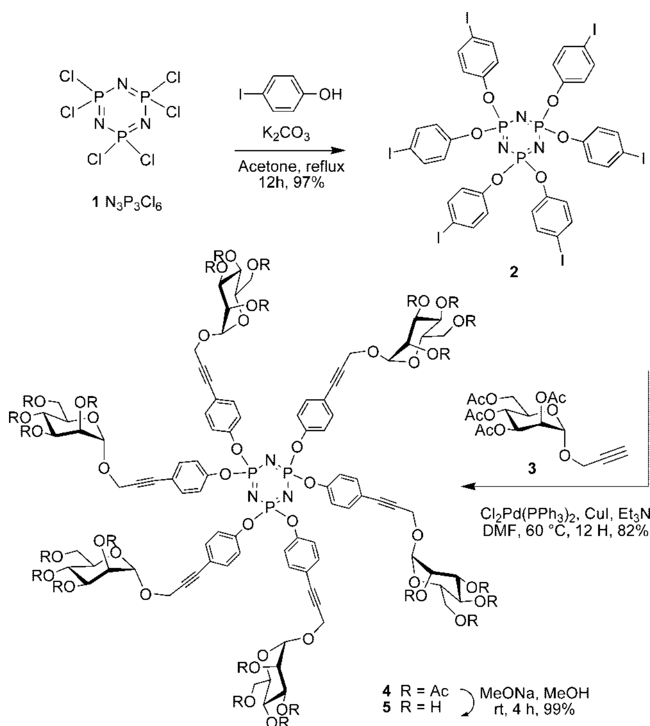
dine group-substituted cyclophosphazenes were investigated as biomedical products because of their strong antitumor activity.[42] The antimicrobial and biological effects of some phosphazenes on bacterial and yeast cells have been studied.[43−45] A hexavalent core has obvious advantages because it can accommodate a greater number of dendrons and, hence, more functional groups for a given dendrimer generation. Cyclotriphosphazene-centered dendrimers are the landmark of the Majoral's group[46−50] and are pioneers in cyclotriphosphazene core use in material chemistry; however, to the best of our knowledge, those having peripheral covalently bound sugar units are not described yet. Taking advantage of the click ligation technique, we were able to use terminal azide-functionalized hexachlorocyclotriphosphazene cores to introduce mannosides into dendrimers in a "clicked" divergent fashion. In systematic QSAR studies using panels of mannoside-binding proteins, the above family of novel glycodendrimers should complement nicely our understanding of multivalent binding interactions.

Results and Discussion

Click chemistry has attracted much attention recently because of its high specificity, quantitative yield, and tolerance to various functional groups. Several papers have been published about the synthesis of dendrimers through the click reaction in either a convergent or a divergent manner.[16,25,37] Moreover, transition metal-catalyzed cross-couplings have proven to be powerful tools for mild, highly efficient, carbon−carbon bond formations. Among these processes, those involving palladium catalysis, especially Sonogashira coupling of aryl halides,[51] are particularly useful for the syntheses of complex molecules owing to their excellent levels of selectivity and high functional group compatibility. Consequently, and on the basis of previous expertise,[19,20,25,30] the efficient and systematic synthesis of a family of glycodendrimers bearing mannopyranoside residues using multiple 1,3-cycloadditions and Sonogashira coupling is described herein.

The target hexamer **5** was synthesized as depicted in Scheme 1. Treatment of $N_3P_3Cl_6$ (**1**) with iodophenol under basic conditions (K_2CO_3, acetone, 97%) afforded $N_3P_3(O\text{-}C_6H_4\text{-}p\text{-}I)_6$ (**2**). Compound **2** is the primary starting material for the assembly of the α-D-mannopyranosides, as it possesses six reactive iodo aryl groups. The reaction of **2** with propargyl α-D-mannopyranoside under Sonogashira coupling conditions affords hexamannosylated product **4** in good yield. Deacetylation under Zemplén conditions (NaOMe, MeOH) gave unprotected hexamer **5** in a quantitative yield as shown in Scheme 1. The ^{31}P NMR of **5** shows that the phosphorus chemical shifts corresponding to the cyclophosphazene skeleton are isochronous and resonate at δ 11.75.

SCHEME 1



Trimethylsilylacetylene was next coupled to known **2** under Sonogashira conditions[52] to afford a 4-trimethylsilylethynylphenyl-substituted core (**6**) in 96% yield. The acetylene was easily deprotected by treatment with aqueous potassium hydroxide in a methanol/ether mixture to afford **7** in 90% yield (Scheme 2). Treatment of (4-acetylenylphenyl)cyclotriphosphazene **7** in $CuSO_4$-catalyzed click reaction conditions with 2-azidoethyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside **8**[53,54] provided hexamer **10** in good yields after deacetylation (NaOMe, MeOH) (Scheme 2).

As shown in Scheme 3, treatment of (4-acetylenylphenyl)-cyclotriphosphazene **7** under Sonogashira coupling conditions with 4-iodophenyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside **11**[55] provided a hexamer bearing aromatic aglycones **13** in good yields after deacetylation (NaOMe, MeOH).

All attempts to prepare a uniform hexakis arylmethyl azide intermediate from $N_3P_3Cl_6$ (**1**) and the corresponding *p*-azidomethyl phenol under various basic conditions (K_2CO_3, Na_2CO_3, NaOH, NaH, etc.) failed, with the ^{31}P NMR of **5** showing systematically more than one resonance. The reaction mixtures resulted in inseparable mono- and polysubstituted

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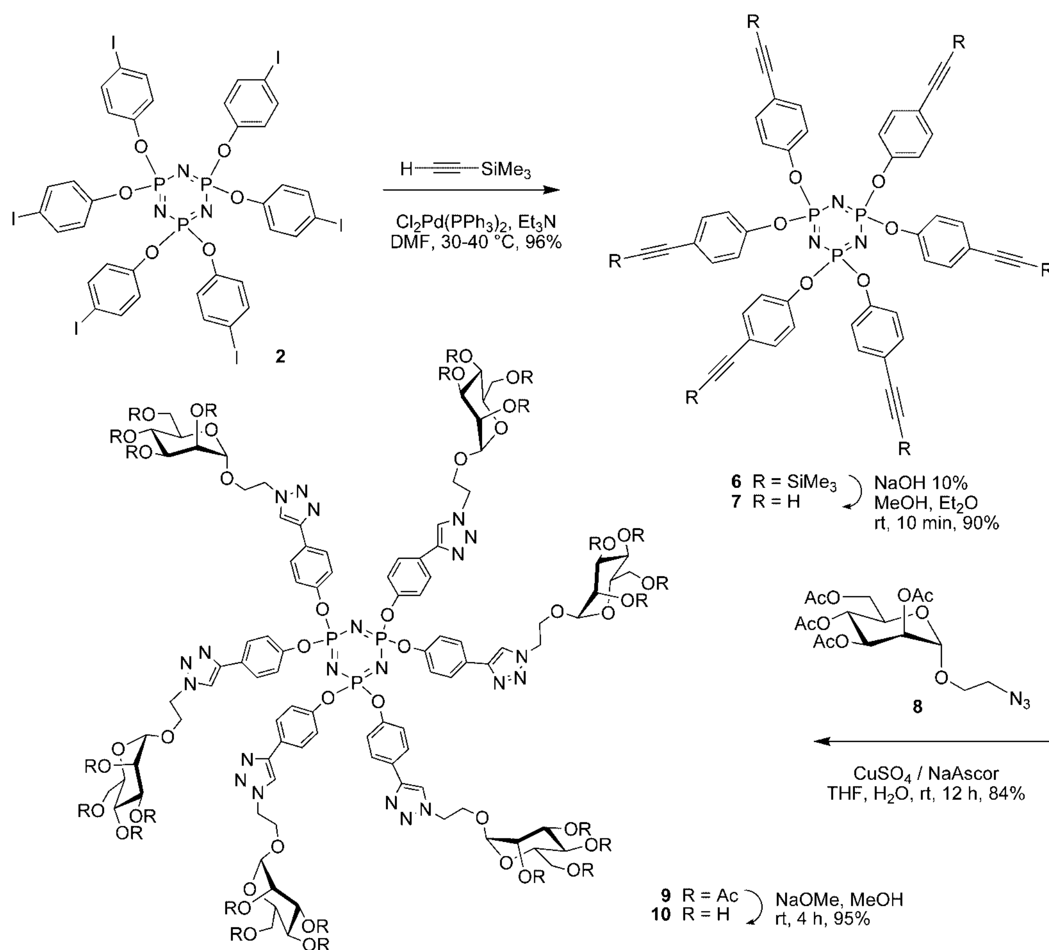
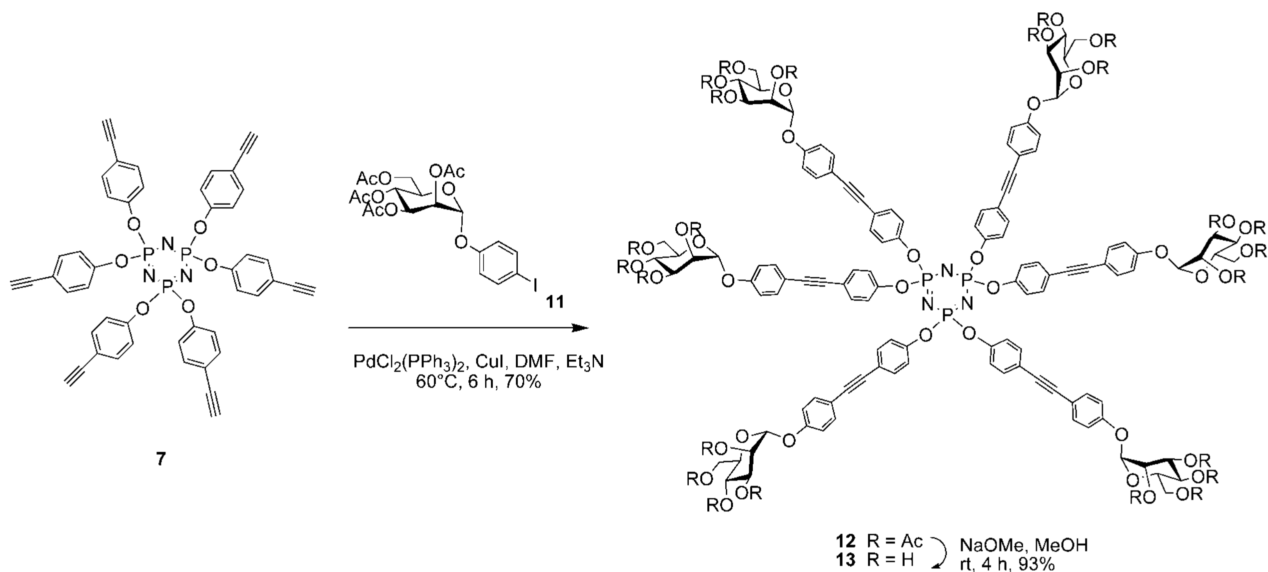
SCHEME 2



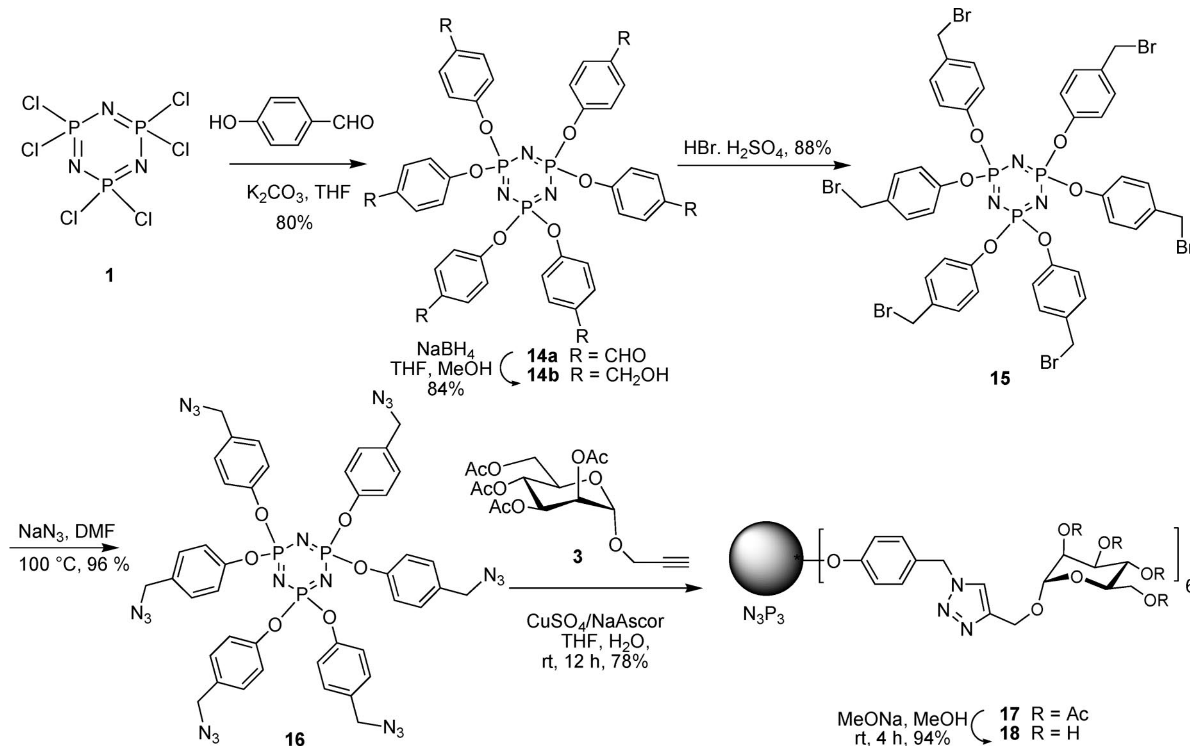
SCHEME 3



azidocyclophosphazenes. However, using a different approach, the multiple-substitution reaction involving the replacement of chlorine atoms on **1** by the nucleophilic 4-formylphenoxy groups has been successfully employed to provide the known hexaformylphenoxy core **14a**, which was next converted into the known bromomethyl bearing core **15** (Scheme 4).[56] The novel hexameric azide **16** was thus obtained by conversion of hexabrominated derivative **15**, which under the above cycloaddition conditions with propargyl mannoside **3** afforded the desired hexamannosylated dendrimer **18** after deacetylation (73% over two steps).

The syntheses of new kinds of glycoside clusters that will open the route to novel glycodendrimer libraries exhibiting varied sugars and densities should offer new opportunities for

SCHEME 4



a better understanding of multivalent carbohydrate−protein recognition processes. In line with this idea, we report herein the synthesis of the following decamannoside cluster **27** assembled using **1** as a propagating element and commercially available bisphenol A (**19**) as the central core (Scheme 5). The required bis-monosubstituted $N_3P_3Cl_5$ fragment was introduced onto the two hydroxyl groups of **19** by the monosubstitution of $N_3P_3Cl_6$ (**1**) to afford the decachloride **20**[57] in 74% yield using BuLi as the base and excess **1**. The ^{31}P NMR of **20** showed two resonances at δ 12.70 and 22.69. These signals corresponded to the two phosphine types within this cluster.

The terminal decachloride groups in **20** were converted into iodoaryl groups by the same reaction described above for the synthesis of **2**. Introduction of the 10 α-D-mannopyranoside groups was achieved by a multiple Sonogashira coupling, as described above for the synthesis of **3**, with **21** and propargyl α-D-mannopyranoside (**3**) providing compound **22** in 78% yield. The subsequent deacetylation under Zemplén conditions gave decamannoside dendrimer **23** in 94% yield.

Following our ongoing interest in the use of click chemistry for the synthesis of mannosylated dendrimers,[25,30] Scheme 6 describes the preparation of the dodecamannoside derivative **27**. The synthesis was initiated with dodecaazide **25**, which was prepared with multiple nucleophilic substitutions on each of the bromines of **15** with the known diazide **24**.[58] Multiple $CuSO_4$-catalyzed click reactions with prop-2-ynyl α-D-mannopyranoside **3**[53,54] provided dodecamer **27** in good yield after deacetylation (Scheme 6).

For the next higher member of the family, the same synthetic strategy was used as for dodecamer **27**. Starting with the hexabromomethyl scaffold **15** and the known tris-azido pentaerythritol **28**,[59] the octadecaazide **29** was obtained under a multiple nucleophilic substitution in 68% yield (NaH, DMF, 100 °C, 10 h). The azido groups of cluster **29** were then treated with propargylmannoside **3** using the above Cu(I)-catalyzed click reaction (83% yield), followed by deacetylation to give the corresponding octadecamannoside dendrimer **31** in 96% yield (Scheme 7). Thus, the syntheses of both dodeca- and octadecavalent-mannosylated dendrimers were efficiently realized.

The unprecedented glycoclusters prepared in this study displayed some structural differences that are governed by the cyclophosphazene and bisphenol A scaffolds as well as by the number of mannosyl units and their relative orientation together along with the ligation technique used for the mannoside incorporation. These disparities offer a nice opportunity to estimate their relative binding abilities while role modeling multivalent carbohydrate−protein recognition in solution. Hence, the whole ligand set including α-D-mannopyranoside dendrimers with valencies ranging from 6 to 18 units was evaluated using the well-established tetrameric phytohemeagglutinin Concanavalin A (Con A) from *C. ensiformis*.[60] The relative ability of these mannosylated dendrimers to act as cross-linking reagents was investigated using a kinetic turbidimetric assay (nephelometry) as previously used in similar circumstances.[60] Each of the

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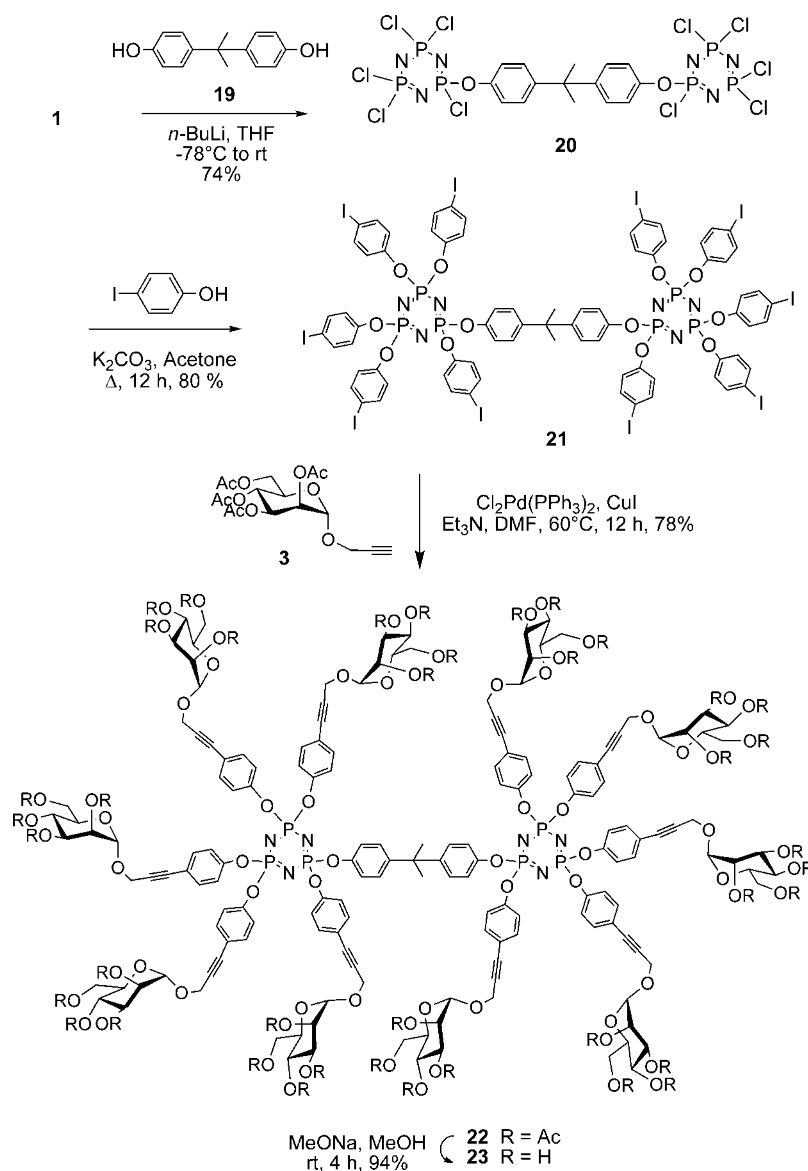
SCHEME 5



compounds and the lectin were tested at a concentration of 1 mg/mL using the polysaccharide yeast mannan as the positive control. Rapidly and within a few minutes, insoluble cross-linked complexes were formed as judged by the formation of precipitated lattices within the wells following a turbid state (Figure 1). The time course of Con A precipitation by the corresponding mannosylated dendrimers is illustrated in Figure 1.

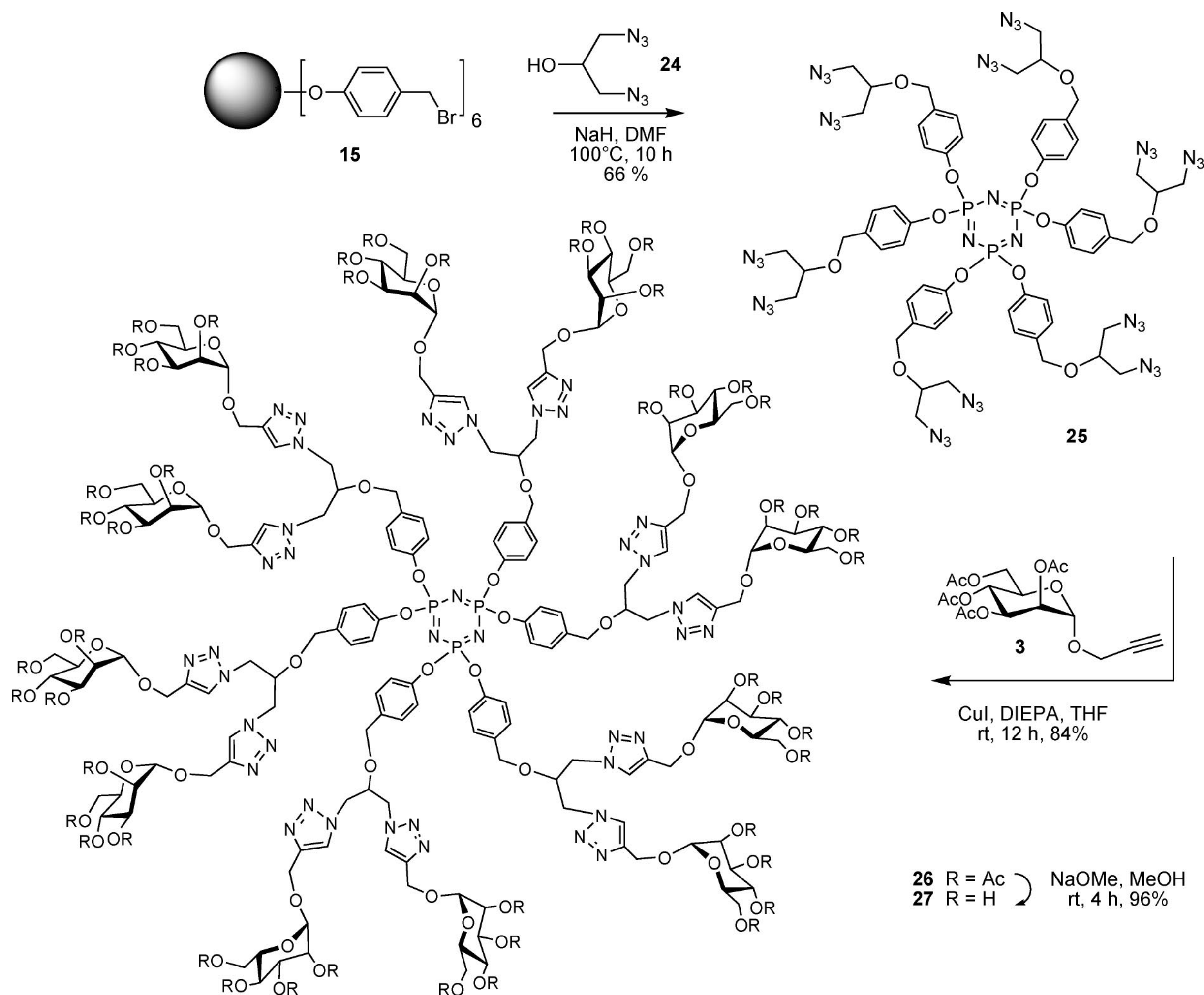
Using Con A, dendrimers exhibiting the same hexameric valency such as **5**, **10**, **13**, and **18**, differing by the mannoside spacer arm (aryl or triazole), showed highly equivalent protein binding properties compared to those of the positive control yeast mannan. Hexamers **10** and **18**, which were obtained under click conditions, showed slightly faster cross-linking behavior in comparison to that of the mannan control. The incorporation of additional mannosyl units in dodecamer **27** and octadecamer **31** led, therefore, to merely statistical binding affinity enhancements. This result supports the occurrence of a sliding process that is optimal for the hexameric compound and suffers from enthalpy−entropy compensation for more valent compounds.

The decamer-containing alkyne spacer **23** was shown to be the fastest and more complete in forming the insoluble cross-linked lattice. Interestingly, dodecamer **27** and octadecamer **31**, having a slightly longer spacer arm and more flexibility than **23**, showed lower cross-linking potencies. The noticeable cross-linking enhancement observed for **23** must be ascribed to the existence of more favorable extended intersugar distances, thus facilitating entry into the carbohydrate's active site and permitting a higher protein cross-linking ability. The special geometry arrangement also can accommodate the clustering of a few tetrameric lectins. Note, as previously described, these geometries are designed purposely to prevent the simultaneous binding of two mannosides from a single dendrimer to reach the two mannoside binding sites of a single Con A tetramer situated ~65 Å apart.

Conclusion

The above set of assays are relevant in demonstrating the relative protein binding properties of the persubstituted dendrimers synthesized herein and further substantiate the usefulness of glycodendrimers in bioassays. The above mannosylated dendrimers together with the analogous series are being evalu-

SCHEME 6



ated for their relative binding abilities with a panel of mannoside binding proteins such as DC-SIGN, the FimH of *E. coli*, and the Bcla lectin from *Burkholderia cepacia*.

Experimental Section

Organic azides are potentially explosive substances that can decompose with the slightest input of energy from external sources such as heat, light, and pressure; therefore, precautions must taken.

General Procedure for the Azide/Alkyne Cycloaddition Catalyzed by CuI, Method A. To a 5 mL THF solution of azide (0.1 mmol) and alkyne's derivative (0.12 mmol per azide) were added *N*,*N*-diisopropylethylamine (DIPEA) (0.2 mmol per azide) and CuI (0.01 mmol per azide). The reaction mixture was then stirred at room temperature for 12 h. TLC indicated the complete consumption of the azide. After solvent evaporation, the crude product was dissolved with ethyl acetate, washed with NH_4Cl solution (3 × 10 mL) and brine (3 × 10 mL), dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was purified by column chromatography eluting with dichloromethane to gradually increase the polarity of MeOH:CH_2Cl_2 (10:90).

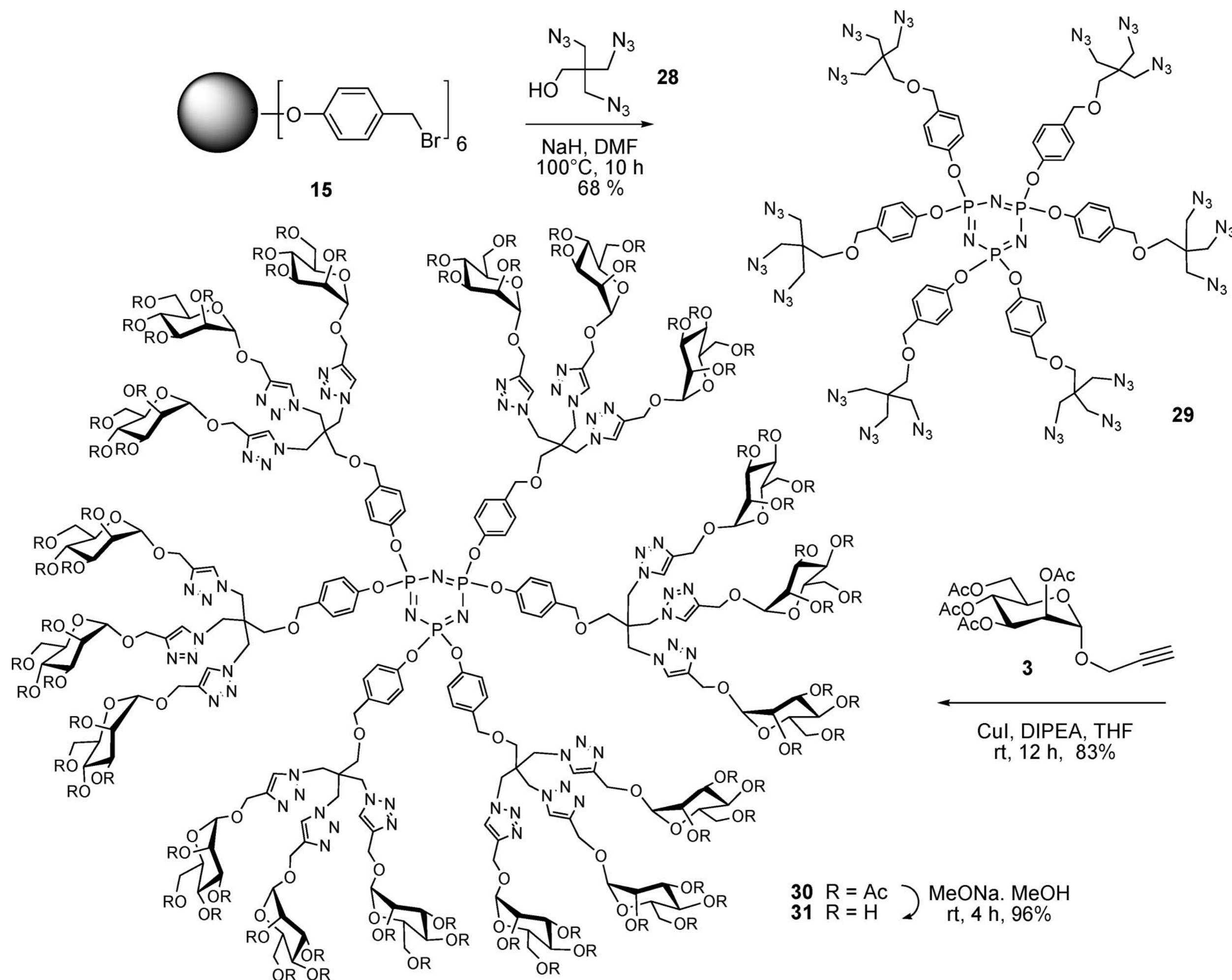
General Procedure for the Click Reaction Catalyzed by $CuSO_4$ in Water, Method B. A solution of an azide cluster (0.1 mmol), mannose propargyl (0.12 mmol per azide), $CuSO_4$ (1% per azide), and sodium ascorbate (5% per azide) was dissolved in a 1:1 mixture of water and THF (3 mL). After 12 h of reaction time, following the general workup described above, the residue was purified by column chromatography eluting with dichloromethane to gradually increase the polarity of MeOH:CH_2Cl_2 (3:97).

General Procedure for the Sonogashira Coupling Reaction. To a solution of 4-iodophenyl derivative (0.068 mmol) in 3 mL of DMF were added $Pd(PPh_3)_2Cl_2$ (0.014 mmol, 3.5 mol%), CuI (0.021 mmol, 5 mol%), alkyne's derivative (0.61 mmol), and triethylamine (1 mL). The solution was stirred under nitrogen at 60 °C for 6 h. The solvent and TEA were evaporated under reduced pressure. Water (10 mL) and dichloromethane (30 mL) were added to the reaction mixture, and the phases were separated. The aqueous phase was extracted with dichloromethane (2 × 30 mL), and the combined organic phases were washed with saturated aqueous NH_4Cl (2 × 25 mL) and brine (2 × 25 mL). The organic layers were dried over Na_2SO_4 and evaporated under reduced pressure, leaving yellow oil. The residue was purified by column chromatography eluting with dichloromethane to gradually increase the polarity of MeOH:CH_2Cl_2 (10:90).

General Procedure for De-*O*-acetylation. An acetylated glycocluster (0.1 mmol) was dissolved in dry MeOH (3 mL), and a solution of sodium methoxide (1 M in MeOH, 0.5 equiv) was added. The reaction mixture was stirred at room temperature until the starting material disappeared. The solution was neutralized by the addition of a cationic ion-exchange resin (H^+), filtered, and washed with MeOH, and then the solvent was removed in vacuo. The residue was lyophilized to yield the fully deprotected glycocluster.

Hexaiodide 2. A mixture of **1** (1 g, 2.87 mmol), 4-iodophenol (3.92 g, 17.81 mmol), and K_2CO_3 (5.16 g, 37.33 mmol) was refluxed in dry acetone (20 mL) for 12 h. The solvent was removed in vacuo. The residue was extracted with CH_2Cl_2 (3 × 25 mL). The organic phase was washed with 15 mL of H_2O and brine before being dried (Na_2SO_4) and concentrated in vacuo. The obtained solid was recrystallized in dichloromethane to afford **2** as a white solid in a 97% (4.03 g) yield

SCHEME 7



(known but never characterized).[61] Mp: 95−97 °C. R_f: 0.18 (ethyl acetate:hexanes, 10:90). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.52 (d, J (H,H) = 8.6 Hz, 12H; H_{ar}), 6.62 (d, J (H,H) = 8.6 Hz, 12H; H_{ar}). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 149.9 (C_{ar}), 138.6 (CH_{ar}), 123.01 (CH_{ar}), 89.3 (C_{ar}). ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C): δ 9.03 (s). ESI-MS *m/z*: calcd for $C_{36}H_{24}I_6O_6N_3P_3$ + (H^+), 1449.51. Found *m/z*: 1449.52.

Peracetylated Hexamannoside 4. From **2** (100 mg, 0.069 mmol), prop-2-ynyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (**3**) (192 mg, 0.49 mmol), $PdCl_2(PPh_3)_2$ (17 mg, 0.024 mmol, 5 mol%), and CuI (10 mg, 0.052 mmol, 10 mol %) dissolved in DMF (4 mL) and Et_3N (1 mL), and after 6 h of reaction time following the general procedure described above, glycocluster **3** (169 mg, 82%) was obtained as a white foam. R_f: 0.21 (ethyl acetate:hexanes, 80:20). $[\alpha]_D^{20}$ = +39.1 (c = 1.0 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.31 (d, J (H,H) = 8.6 Hz, 12H; H_{ar}), 6.91 (d, J (H,H) = 8.6 Hz, 12H; H_{ar}), 5.37−5.29 (m, 18H; H-2, H-3, H-4), 5.12 (d, J (H,H) = 1.4 Hz, 6H; H-1), 4.52−4.51 (m, 12H; $OC\underline{H}_2CC$), 4.31 (dd, J (H,H) = 12.2, 4.8 Hz, 6H; H-6a), 4.15−4.06 (m, 12H; H-6b, H-5), 2.16−1.99 (4*s*, 72H; $COC\underline{H}_3$). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 170.6, 169.9, 169.8, 169.6 ($\underline{C}OCH_3$), 150.5 ($O\underline{C}_{ar}$), 133.2 ($\underline{C}H_{ar}$), 120.8 ($\underline{C}H_{ar}$), 119.2 ($C\underline{C}_{ar}$), 96.1 (C-1), 86.2 ($C_{ar}C\underline{C}$), 83.5 ($C_{ar}\underline{C}C$), 69.4 (C-2), 68.9 (C-6, C-4), 65.9 (C-3), 62.3 (C-5), 55.75 ($\underline{C}H_2CC$), 20.8 ($CO\underline{C}H_3$), 20.7 ($CO\underline{C}H_3$), 20.6 ($CO\underline{C}H_3$), 20.6 ($CO\underline{C}H_3$). ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C): δ 8.1 (s). HRMS *m/z*: calcd for $C_{138}H_{150}N_3O_{66}P_3$ + ($2Na^+$), 1521.8735. Found *m/z*: 1521.8752.

Hexamannoside 5. From **4** (100 mg, 0.033 mmol) and sodium methoxide (25 μL from 1 M solution in MeOH) in 3 mL of methanol, and after 4 h of reaction time following the general procedure described above, deprotected glycocluster **5** (66 mg, 99%) was obtained as white foam. R_f: 0.22 (CH_3CN:H_2O, 7:3). $[\alpha]_D^{20}$ = +29.3 (c = 1.0 in CH_3OH). ^{1}H NMR (300 MHz, DMSO-D_6, 25 °C): δ 7.40 (d, J (H,H) = 8.2 Hz, 12H; H_{ar}), 6.93 (d, J (H,H) = 8.2 Hz, 12H; H_{ar}), 4.85 (s, br, 18H; H-1, $OC\underline{H}_2CC$), 4.55−4.52 (m, 6H; H-2), 4.47−4.43 (m, 12H; H3, H-4), 3.69−3.63 (m, 6H; H-6a), 3.47−3.35 (m, 12H; H-6b, H-5). ^{13}C NMR (75 MHz, DMSO-D_6, 25 °C): δ 149.7 ($O\underline{C}_{ar}$), 133.3 ($\underline{C}H_{ar}$), 120.7 ($\underline{C}H_{ar}$), 119.3 ($C\underline{C}_{ar}$), 98.4 (C-1), 86 ($C_{ar}C\underline{C}$), 84.4 ($C_{ar}\underline{C}C$), 74.4 (C-2), 70.9 (C-5), 70.1 (C-3), 66.8 (C-4), 61.1 (C-6), 53.7 ($\underline{C}H_2CC$). ^{31}P NMR (121 MHz, DMSO-D_6, 25 °C): δ 11.75 (s). HRMS *m/z*: calcd for $C_{90}H_{102}N_3O_{42}P_3$ + (H^+), 1990.5223. Found *m/z*: 1990.5183.

Compound 6. From **2** (100 mg, 0.069 mmol), trimethylsilylacetylene (49 mg, 0.49 mmol), $PdCl_2(PPh_3)_2$ (17.5 mg, 0.025 mmol, 5 mol %), and CuI (10 mg, 0.052 mmol, 10 mol %) dissolved in DMF (3 mL) and Et_3N (1 mL), and after 6 h of reaction time at 40 °C following the general procedure described above, glycocluster **6** (84 mg, 96%) was obtained as a yellow solid. R_f: 0.21 (ethyl acetate:hexanes, 10:90). Mp: 72−74 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.33 (d, J (H,H) = 8.6 Hz, 12H; H_{ar}), 6.76 (d, J (H,H) = 8.6 Hz, 12H; H_{ar}), 0.27 (s, 54H; $Si(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 150.2 ($O\underline{C}_{ar}$), 133.3 ($\underline{C}H_{ar}$), 120.9 ($\underline{C}H_{ar}$), 120.3 ($C\underline{C}_{ar}$), 103.9 ($C_{ar}C\underline{C}$), 94.5 ($C_{ar}\underline{C}C$), −0.2 ($SiCH_3$). ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C): δ 7.36 (s). HRMS *m/z*: calcd for $C_{66}H_{78}N_3O_6P_3Si_6$ + (H^+), 1270.3797. Found *m/z*: 1270.3839.

(61) Allcock, H. R.; Ngo, D. C.; Parvez, M.; Visscher, K. B. *Inorg. Chem.* **1994**, *33*, 2090–2102.

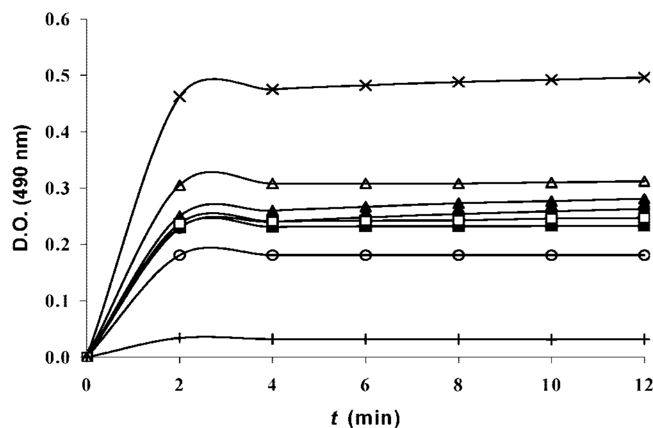


FIGURE 1. Turbidimetric analysis (microprecipitation) of Con A with hexamers **5** (■), **10** (▲), **13** (○), and **18** (●), decamer **23** (×), dodecamer **27** (□), octadecamer **31** (△), and yeast mannan (l) used as the positive control. Measurements were done in phosphate-buffered saline (PBS) at 1 mg mL^{-1} using a microplate reader at 25 °C and are the average of triplicate values.

Compound 7. To a solution of **6** (50 mg, 0.039 mmol) in 2.5 mL of diethyl ether were added 2.5 mL of methanol and 1 mL of an aqueous 10% sodium hydroxide solution. After 10 min of stirring at room temperature, the reaction mixture was neutralized with 1 M HCl solution. The organic layer was separated, and the aqueous layer was back-extracted with diethyl ether. The combined organic layers were washed with brine and water, dried over Na_2SO_4, and concentrated to afford, after column chromatography (acetate:hexanes, 6:94) purification, 29.7 mg (90%) of **7** as a white solid. Mp: 128−130 °C. R_f: 0.23 (ethyl acetate:hexanes, 10:90). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.35 (d, J (H,H) = 8.5 Hz, 12H; H_{ar}), 6.84 (d, J (H,H) = 8.5 Hz, 12H; H_{ar}), 3.1 (s, 6H; CCH). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 150.4 (OC_{ar}), 133.5 (CH_{ar}), 120.9 (CH_{ar}), 119.3 (CC_{ar}), 82.5 ($C_{ar}CC$), 77.6 ($C_{ar}CC$). ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C): δ 7.32 (s). HRMS *m/z*: calcd for $C_{48}H_{30}N_3O_6P_3$ + (H^+), 838.1420. Found *m/z*: 838.1415.

Peracetylated Hexamannoside 9. Compound **7** (50 mg, 0.059 mmol), 2′-azidoethyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (**8**) (187 mg, 0.45 mmol), $CuSO_4 \cdot 5H_2O$ (12 mg, 0.05 mmol), and sodium ascorbate (2.73 mg, 0.045 mmol) were dissolved in THF:H_2O (1:1) (5 mL). After 12 h of reaction time, the mixture was treated following the general procedure described above, and glycocluster **9** (167 mg, 84%) was obtained as a white solid. Mp: 118−120 °C R_f: 0.19 (MeOH: CH_2Cl_2 5:95). $[\alpha]_D^{20}$ = +49.6 (c = 1.0 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.95 (s, 6H; CH=C), 7.61 (d, J (H,H) = 8.4 Hz, 12H; H_{ar}), 7.02 (d, J (H,H) = 8.4 Hz, 12H; H_{ar}), 5.24−5.16 (m, 18H; H-2, H-3, H-4), 4.88 (d, J (H,H) = 1.4 Hz, 6H; H-1), 4.68 (s br, 12H; CH_2-N), 4.21−4.09 (m, 18H; H-6a, OCH_2CH_2), 4.0−3.95 (m, 12H; H-6b, H-5), 2.12, 2.06, 2.02, 1.97 (s, 72H; $COCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 170.5, 169.9, 169.8, 169.6 ($COCH_3$), 150.1 (C=CH), 146.9 (OC_{ar}), 127.5 (CH_{ar}), 126.9 (C=CH), 121.3 (CH_{ar}), 121.2 (C_{ar}), 97.2 (C-1), 69.2 (C-2), 68.4 (C-5), 66 (C-3, C-4), 65.5 (OCH_2), 62.1 (C-6), 49.7 (CH_2N), 20.8, 20.7, 20.6, 20.4 ($COCH_3$). ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C): δ 9.39 (s). HRMS *m/z*: calcd for $C_{144}H_{168}N_{21}O_{66}P_3$ + ($2H^+$), 1670.9897. Found *m/z*: 1670.9903.

Hexamannoside 10. Compound **9** (109 mg, 0.031 mmol) and sodium methoxide (16 μL from 1 M solution in MeOH) in 3 mL of methanol were stirred for 4 h, and the mixture was treated following the general procedure described above. Deprotected glycocluster **10** (70 mg, 95%) was obtained as a white foam. R_f: 0.18 (H_2O:CH_3CN, 3:7). $[\alpha]_D^{20}$ = +37.2 (c = 1.0 in CH_3OH). ^{1}H NMR (300 MHz, DMSO-D_6, 25 °C): δ 8.41 (s, 6H; CH=C), 7.49 (d, J (H,H) = 8.6 Hz, 12H; H_{ar}), 7.03 (d, J (H,H) = 8.6 Hz, 12H; H_{ar}), 4.72−4.70 (m, 12H; OCH_2CH_2N), 4.64 (s br, 6H; H-1), 4.49−4.45 (m, 12H; OCH_2CH_2N), 4.03−3.99 (m, 6H; H-2), 3.78−3.83 (m, 6H; H-3), 3.63−3.54 (m, 12H; H-4, H-6a), 3.39−3.16 (m, 12H; H-6b, H-5). ^{13}C NMR (75 MHz, DMSO-D_6, 25 °C): δ 149.3 (CH=C), 145.3 (OC_{ar}), 128.2 (CH_{ar}), 126.6 (C=CH), 121.6 (CH_{ar}), 120.9 (C_{ar}), 99.9 (C-1), 74.2 (C-2), 70.8 (C-3), 70 (C-5), 66.7 (C-4), 64.8 (OCH_2CH_2N), 61.1 (C-6), 49.5 (OCH_2CH_2N). ^{31}P NMR (121 MHz, DMSO-D_6, 25 °C): δ 13.91 (s). HRMS *m/z*: calcd for $C_{96}H_{122}N_{21}O_{42}P_3$ + ($2H^+$), 1166.8629. Found *m/z*: 1166.8661.

Peracetylated Haxamannoside 12. From **7** (50 mg, 0.059 mmol), 4-iodophenyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (**11**) (227 mg, 0.41 mmol), $PdCl_2(PPh_3)_2$ (13 mg, 0.018 mmol, 5 mol%), and CuI (7 mg, 0.036 mmol, 10 mol%) dissolved in DMF (4 mL) and Et_3N (1 mL), and after 6 h of reaction time following the general procedure described above, glycocluster **12** (140 mg, 70%) was obtained as a white foam. R_f: 0.21 (ethyl acetate:hexanes, 80:20). $[\alpha]_D^{20}$ = +38.1 (c = 1.0 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.45 (d, J (H,H) = 8.5 Hz, 12H; H_{ar}), 7.41 (d, J (H,H) = 8.5 Hz, 12H; H_{ar}), 7.06 (d, J (H,H) = 8.5 Hz, 12H; H_{ar}), 6.96 (d, J (H,H) = 8.5 Hz, 12H; H_{ar}), 5.57−5.53 (m, 18H; H-2, H-3, H-4), 5.45 (d, J (H,H) = 1.4 Hz, 6H; H-1), 4.28 (dd, J (H,H) = 12.6, 5.7 Hz, 6H; H-6a), 4.08−4.04 (m, 12H; H-6b, H-5), 2.21, 2.06, 2.04, 1.96 (s, 72H; $COCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 170.4, 169.9, 169.8, 169.7 ($COCH_3$), 155.4 (OC_{ar}), 145.2 (OC_{ar}), 133 (CH_{ar}), 132.8 (CH_{ar}), 120.9 (CH_{ar}), 120.4 (C_{ar}), 117.6 (C_{ar}), 116.4 (CH_{ar}), 95.5 (C-1), 89 (CC), 87.8 (CC), 69.2 (C-2), 69.2 (C-5), 68.7 (C-4), 65.8 (C-3), 62 (C-6), 20.8, 20.7, 20.6, 20.4 ($COCH_3$). ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C): δ 7.54 (s). HRMS *m/z*: calcd for $C_{168}H_{162}N_3O_{66}P_3$ + (Na^+ + H^+), 1696.9295. Found *m/z*: 1696.9297.

Hexamannoside 13. Compound **12** (40 mg, 0.012 mmol) and sodium methoxide (5 μL from 1 M solution in MeOH) in 3 mL of methanol were stirred for 4 h, and the mixture was treated following the general procedure described above. Deprotected glycocluster **13** (26 mg, 93%) was obtained as a white foam. R_f: 0.18 (H_2O:CH_3CN, 3:7). $[\alpha]_D^{20}$ = +32.7 (c = 1.0 in CH_3OH). ^{1}H NMR (300 MHz, DMSO-D_6, 25 °C): δ 7.48 (d, J (H,H) = 7.8 Hz, 12H; H_{ar}), 7.41 (d, J (H,H) = 7.8 Hz, 12H; H_{ar}), 7.04 (d, J (H,H) = 7.8 Hz, 12H; H_{ar}), 6.96 (d, J (H,H) = 7.8 Hz, 12H; H_{ar}), 4.47 (s br, 6H; H-1), 3.83 (s br, 6H; H-2), 3.69−3.65 (m, 6H; H-3), 3.58−3.42 (m, 12H; H-4, H-6a), 3.33−3.22 (m, 12H; H-6b, H-5). ^{13}C NMR (75 MHz, DMSO-D_6, 25 °C): δ 156.6 (OC_{ar}), 149.3 (OC_{ar}), 132.9 (CH_{ar}), 132.8 (CH_{ar}), 120.9 (CH_{ar}), 120 (C_{ar}), 116.9 (C_{ar}), 115.3 (CH_{ar}), 98.6 (C-1), 89.6 (CC), 87.1 (CC), 75.1 (C-2), 70.5 (C-5), 69.9 (C-4), 66.5 (C-3), 60.9 (C-6). ^{31}P NMR (121 MHz, DMSO-D_6, 25 °C): δ 12.96 (s). HRMS *m/z*: calcd for $C_{120}H_{114}N_3O_{42}P_3$ + (H^+), 2362.6162. Found *m/z*: 2362.6161.

Compound 14a. Compound **1** (500 mg, 1.44 mmol), 4-hydroxybenzaldehyde (1.1 g, 9 mmol), and K_2CO_3 (2.5 g, 18.08 mmol) were stirred in dry acetone (15 mL) for 12 h, and the mixture was treated following the general procedure described for **2** synthesis. Silica gel chromatography (EtOAc:hexanes, 1:1) provided **14a** (984 mg, 80%) as a white solid. Mp: 92−94 °C. R_f: 0.30 (EtOAc:hexanes, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 9.94 (6H, COH), 7.72 (d, J (H,H) = 8.5 Hz, 12H; H_{ar}), 7.13 (d, J (H,H) = 8.5 Hz, 12H; H_{ar}). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 190.31 (CO), 154.32 (C_{ar}), 133.59 (CH_{ar}), 131.24 (CH_{ar}), 121.07 (C_{ar}). ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C): δ 6.02 (s). HRMS *m/z*: calcd for $C_{42}H_{30}N_3O_{12}P_3$ + (H^+), 862.1115. Found *m/z*: 862.1105.

Compound 14b. To a solution of compound **14a** (500 mg, 0.58 mmol) in a mixture of THF and methanol (50 mL, 1:l) was added sodium borohydride (140 mg, 3.75 mmol) at room temperature. The reaction mixture was stirred for 12 h at the same temperature. After evaporation of the solvents, the resulting solids were recrystallized from 90% ethanol to give **14b** (440 mg, 87%) as a white solid. Mp: 215−217 °C. R_f: 0.28 (MeOH:CH_2Cl_2, 1:1). ^{1}H NMR (300 MHz, DMSO, 25 °C): δ 7.18 (d, J (H,H) = 7.7 Hz, 12H; H_{ar}), 6.79 (d, J (H,H) = 7.7 Hz, 12H; H_{ar}), 5.23 (br s, 6H, CH_2OH), 4.45 (d, 12H, J (H,H) = 4.9 Hz, CH_2OH). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 148.61 (C_{ar}), 139.43 (CH_{ar}), 127.66 (CH_{ar}), 120.11 (C_{ar}), 62.24 (CH2). ^{31}P NMR (121 MHz, DMSO, 25 °C): δ 12.9 (s). HRMS *m/z*: calcd for $C_{42}H_{42}N_3O_{12}P_3$ + (H^+), 874.2054. Found *m/z*: 874.2043.

Compound 15. 14b (170 mg, 0.19 mmol) was dissolved in a mixture of 48% HBr (3 mL) and concentrated H_2SO_4 (0.5 mL), and the solution was refluxed for 8 h. Precipitates were collected by

filtration and washed with a copious amount of water (300 mL) until neutral. The product was isolated by column chromatography on silica gel (20% ethyl acetate in hexane) to give **15** (190 mg, 78%) as a white solid. Mp: 147−149 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.25 (d, *J* (H,H) = 8.2 Hz, 12H; H_{ar}), 6.90 (d, *J* (H,H) = 8.2 Hz. 12H; H_{ar}), 4.49 (s, 6H, CH_2Br). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 150.13 (C_{ar}), 133.54 (CH_{ar}), 130.34 (CH_{ar}), 121.17 (C_{ar}), 32.82 (CH2). ^{31}P NMR (121 MHz, DMSO, 25 °C): δ 7.82 (s). HRMS *m/z*: calcd for $C_{42}H_{36}Br_6N_3O_6P_3$ + (H^+), 1245.6989. Found *m/z*: 1245.6927.

Hexaazide 16. NaN_3 (116 mg, 1.78 mol) was added to a solution of **15** (1 g, 0.84 mol) in DMF (3 mL) under N_2, and the resulting mixture was heated to 100 °C. After 10 h, the solution was cooled, poured into water (250 mL), and extracted with Et_2O (50 mL and then 4 × 20 mL). Because of the potential explosiveness of the azides, the organic fractions were combined, dried (Na_2SO_4), and concentrated in vacuo at <40 °C. Purification by column chromatography (eluent, CH_2Cl_2:hexanes, 2:8) gave **12** (73 mg, 96%) as a white solid. Mp: 125−126 °C. R_f: 0.28 (EtOAc:hexanes, 3:7). IR (NaCl): γ 2097 cm^{-1} (N_3). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.16 (d, *J* (H,H) = 8.5 Hz, 12H; H_{ar}), 6.97 (d, *J* (H,H) = 8.5 Hz, 12H; H_{ar}), 4.32 (s, 12H; CH_2N_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 150.3 (OC_{ar}), 132.2 ($\underline{C}H_{ar}$), 129.3 ($\underline{C}H_{ar}$), 121.2 ($\underline{C}_{ar}$). ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C): δ 8.04 (s). HRMS *m/z*: calcd for $C_{42}H_{36}N_{21}O_6P_3$ + (H^+), 1024.2443. Found *m/z*: 1024.2458.

Peracetylated Hexamannoside 17. Hexaazide **16** (50 mg, 0.05 mmol), prop-2-ynyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (**3**) (142 mg, 0.36 mmol), *N,N*-diisopropylethylamine (65 μL, 0.37 mmol), and CuI (7 mg, 0.036 mmol) were dissolved in THF (5 mL), and after 12 h of reaction time following the general procedure described above, compound **17** (127 mg, 78%) was obtained as a white foam. R_f: 0.17 (MeOH:CH_2Cl_2, 4:96). $[\alpha]_D^{20}$ = +38.1 (*c* = 1.0 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.69 (s, 6H; $\underline{CH}$=C), 7.07 (d, *J* (H,H) = 8.1 Hz, 12H; H_{ar}), 6.87 (d, *J* (H,H) = 8.1 Hz, 12H; H_{ar}), 5.51 (s, 12H; CCH_2N), 5.33−5.20 (m, 18H; H-4, H-3, H-2), 4.95 (d, *J* (H,H) = 1.4 Hz, 6H; H-1), 4.83 (d, *J* (H,H) = 12.5 Hz, 6H; OCH), 4.65 (d, *J* (H,H) = 12.5 Hz, 6H; OCH), 4.29 (dd, *J* (H,H) = 4.8, 12.5 Hz, 6H; H-6a), 4.11−4.07 (m, 12H; H-6b, H-5), 2.13, 2.10, 2.02, 1.96 (s, 72H; $COCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 170.6, 169.9, 169.9, 169.6 ($\underline{C}OCH_3$), 150.3 (OC_{ar}), 143.7 (CH=$\underline{C}$), 131.7 ($\underline{C}H_{ar}$), 129.1 ($\underline{C}H_{ar}$), 123.4 ($\underline{CH}$=C), 121.3 ($\underline{C}_{ar}$), 96.8 (C-1), 69.3 (C-2), 69 (C-3), 68.6 (C-5), 65.9 (C-4), 62.2 ($\underline{CH_2}OCH$), 60.8 (C-6), 53.2 ($C\underline{CH_2}N$), 20.8, 20.7, 20.6, 20.6 ($CO\underline{CH_3}$). ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C): δ 7.89 (s). HRMS *m/z:* calcd for $C_{144}H_{168}N_{21}O_{66}P_3$ + ($2H^+$), 1670.9896. Found *m/z*: 1670.9880.

Hexamannoside 18. Compound **17** (105 mg, 0.03 mmol) and sodium methoxide (16 μL from 1 M solution in MeOH) in 3 mL of methanol were stirred for 4 h, and the mixture was treated following the general procedure described above. Deprotected glycocluster **18** (68.8 mg, 94%) was obtained as a white foam. R_f: 0.28 (H_2O:CH_3CN, 3:7). $[\alpha]_D^{20}$ = +39.7 (*c* = 1.0 in CH_3OH). ^{1}H NMR (300 MHz, DMSO-D_6, 25 °C): δ 8.18 (s, 6H; $\underline{CH}$=C), 7.17 (d, *J* (H,H) = 8.4 Hz, 12H; H_{ar}), 6.81 (d, *J* (H,H) = 8.4 Hz, 12H; H_{ar}), 5.57 (s, 12H; $C\underline{CH_2}N$), 4.78 (s br, 6H; H-1), 4.70−4.47 (m, 30H; H-4, H-3, H-2, $\underline{CH_2}OCH$), 3.67−3.54 (m, 6H; H-6a), 3.46−3.34 (m, 12H; H-6b, H-5). ^{13}C NMR (75 MHz, DMSO-D_6, 25 °C): δ 149.4 (OC_{ar}), 143.8 (CH=$\underline{C}$), 133.1 ($\underline{C}H_{ar}$), 129.5 ($\underline{C}H_{ar}$), 124.3 ($\underline{CH}$=C), 120.7 ($\underline{C}_{ar}$), 99 (C-1), 74.1 (C-2), 70.8 (C-5), 70.1 (C-3), 66.9 (C-4), 61.2 ($\underline{CH_2}OCH$), 59 (C-6), 52 ($C\underline{CH_2}N$). ^{31}P NMR (121 MHz, DMSO-D_6, 25 °C): δ 12.81 (s). HRMS *m/z:* calcd for $C_{96}H_{122}N_{21}O_{42}P_3$ + ($2H^+$), 1166.8629. Found *m/z*: 1166.8622.

Decachloride 20. *n*-BuLi solution in hexanes (2.3 M, 0.7 mL, 1.63 mmol) was added dropwise to a solution of 2,2-bis(4-hydroxyphenyl)-propane (bisphenol A, **19**) (164 mg, 0.71 mmol) in THF (15 mL) at −78 °C. The white mixture was added to a solution of **1** (1.25 g, 3.6 mmol) in THF (3 mL) at 0 °C. The resulting pale yellow solution was allowed to reach room temperature and stirred for 2 h. The solution was then dried in vacuo, and the addition of hexane led to the precipitation of the residual **1**. After filtration, $CHCl_3$ (25 mL) was added, and the solution was washed with brine (2 × 20 mL) and H_2O (2 × 20 mL) and dried over Na_2SO_4. The residue was purified by silica gel chromatography (dissolved in a minimal amount of CH_2Cl_2 and eluted with 2% EtOAc in hexanes) to provide **20** (452 mg, 74%) as a white solid. Mp: 98−100 °C. R_f: 0.28 (EtOAc:hexanes, 5:95). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.24−7.14 (m, 10H; H_{ar}), 1.67 (s, 6H; $C(\underline{CH_3})_2$). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 148.7 (OC_{ar}), 147.3 ($C(CH_3)_2\underline{C}_{ar}$), 128.2 ($\underline{C}H_{ar}$), 120.8 ($CH_{ar}$), 42.5 ($\underline{C}(CH_3)_2C_{ar}$), 30.7 ($C(\underline{CH_3})_2C_{ar}$). ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C): δ 22.69 (d, *J* (P,P) = 59.8 Hz), 12.7 (t, *J* (P,P) = 59.8 Hz). HRMS *m/z*: calcd for $C_{15}H_{14}Cl_{10}N_6O_2P_6$ + (H^+), 846.6562. Found *m/z*: 846.6555.

Decaiodide 21. Compound **20** (89 mg, 0.1 mmol), 4-iodophenol (276 mg, 17.81 mmol), and K_2CO_3 (347 g, 37.33 mmol) were refluxed in dry acetone (10 mL) for 12 h, and the mixture was treated following the general procedure described for **2** synthesis. Silica gel chromatography (EtOAc:hexanes, 4:6) provided **21** (225 mg, 80%) as a white solid. Mp: 78−80 °C. R_f: 0.30 (EtOAc:hexanes, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.52−7.46 (m, 20H; H_{ar}), 7.08 (d, *J* (H,H) = 8.7 Hz, 4H; H_{ar}), 6.78 (d, *J* (H,H) = 8.7 Hz, 4H; H_{ar}), 6.67 (d, *J* (H,H) = 8.7 Hz, 8H; H_{ar}), 6.59 (d, *J* (H,H) = 8.7 Hz, 12H; H_{ar}), 1.69 (s, 6H; $C(\underline{CH_3})_2$). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 150.1, 148.7 (OC_{ar}), 147.2 ($C(CH_3)_2\underline{C}_{ar}$), 138.6, 127.8, 123.2, 123, 120.1 (CH_{ar}), 89.2 (IC_{ar}), 42.3 ($\underline{C}(CH_3)_2C_{ar}$), 31 ($C(\underline{CH_3})_2C_{ar}$). ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C): δ 9.04−8.96 (s br). HRMS *m/z:* calcd for $C_{75}H_{54}I_{10}N_6O_{12}P_6$ + (H^+), 2686.2746. Found *m/z*: 2686.2695.

Peracetylated Decamannoside 22. From **21** (100 mg, 0.04 mmol), prop-2-ynyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (**3**) (172.6 mg, 0.44 mmol), $PdCl_2(PPh_3)_2$ (16 mg, 0.023 mmol, 5 mol%), and CuI (9 mg, 0.05 mmol, 10 mol%) dissolved in DMF (4 mL) and Et_3N (1 mL), and after 6 h of reaction time following the general procedure described above, glycocluster **22** (153 mg, 78%) was obtained as a white foam. R_f: 0.18 (ethyl acetate:hexanes, 8:2). $[\alpha]_D^{20}$ = +31.6 (*c* = 1.0 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.31−7.28 (m, 20H; H_{ar}), 7.07 (d, *J* (H,H) = 8.8 Hz, 8H; H_{ar}), 6.93−6.84 (m, 20H; H_{ar}), 5.38−5.27 (m, 30H; H-4, H-3, H-2), 5.12 (d, *J* (H,H) = 1.4 Hz, 10H; H-1), 4.52−4.46 (m, 20H, $O\underline{CH_2}CC$), 4.34−4.27 (m, 10H; H-6a), 4.15−4.06 (m, 20H; H-6b, H-5), 2.15, 2.09, 2.03, 1.98 (s, 120H; $COCH_3$), 1.63 (s, 6H; $C(\underline{CH_3})_2$). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 170.5, 169.8, 169.8, 169.6 ($COCH_3$), 150.5, 147.2 (OC_{ar}), 133.2, 127.8, 120.9, 120.8 (CH_{ar}), 120.2, 119 (CC_{ar}), 96 (C-1), 86.2 ($C_{ar}CC$), 83.4 ($C_{ar}CC$), 69.4 (C-2), 68.9 (C3, C-4), 65.9 (C-5), 55.5 ($\underline{CH_2}CC$), 42.2 ($\underline{C}(CH_3)_2C_{ar}$), 30.8 ($C(\underline{CH_3})_2C_{ar}$), 20.8, 20.6, 20.7, 20.6 ($CO\underline{CH_3}$). ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C): δ 8.33 (s). HRMS *m/z*: calcd for $C_{245}H_{264}N_6O_{112}P_6$ + ($2H^+$), 2634.6859. Found *m/z*: 2634.6775.

Decamannoside 23. Compound **22** (100 mg, 0.02 mmol) and sodium methoxide (10 μL from 1 M solution in MeOH) in 3 mL of methanol were stirred for 4 h, and the mixture was treated following the general procedure described above. Deprotected glycocluster **23** (64 mg, 94%) was obtained as a white foam. R_f: 0.12 (H_2O:CH_3CN, 3:7). $[\alpha]_D^{20}$ = +30.6 (*c* = 1.0 in CH_3OH). ^{1}H NMR (300 MHz, DMSO-D_6, 25 °C): δ 7.41−7.34 (m, 20H; H_{ar}), 7.09−7.06 (m, 8H; H_{ar}), 6.92−6.79 (m, 20H; H_{ar}), 4.85 (s br, 10H; H-1), 4.66−4.47 (m, 50H; H-4, H-3, H-2, $\underline{CH_2}CC$), 3.63−3.34 (m, 30H; H-6, H-5), 1.65 (s, 6H; $C(\underline{CH_3})_2$). ^{13}C NMR (75 MHz, DMSO-D_6, 25 °C): δ 149.7, 147.2 (OC_{ar}), 133.2, 127.8, 120.7 (CH_{ar}), 119.9, 119.1 (CC_{ar}), 98.4 (C-1), 85.9 ($C_{ar}CC$), 84.4 ($C_{ar}CC$), 69.3 (C-2), 70.9 (C-4), 70.1 (C-3), 66.8 (C-5), 61.1 (C-6), 53.7 ($\underline{CH_2}CC$), 41.8 ($\underline{C}(CH_3)_2C_{ar}$), 30.2 ($C(\underline{CH_3})_2C_{ar}$). ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C): δ 8.24 (s). HRMS *m/z*: calcd for $C_{165}H_{184}N_6O_{44}P_6$ + ($2H^+$), 1794.4746. Found *m/z*: 1794.4705.

Dodecaazide 25. To a stirred suspension of NaH (60% in mineral oil, 17.5 mg, 0.73 mmol) in DMF (4 mL) at room temperature was added dropwise diazide **15** (52 mg, 0.36 mmol). The mixture was stirred for 30 min prior to the dropwise addition of **15** (50 mg, 0.04 mmol) in DMF (1 mL). The solution was stirred at room temperature for 12 h followed by quenching with H_2O (5 mL). The layers were separated, and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic layers were washed with H_2O (3 × 10 mL) and brine (3 × 10 mL), dried over Na_2SO_4, and concentrated on

a rotary evaporator. The residue was purified by silica gel chromatography (dissolved in a minimal amount of CH_2Cl_2 and eluted with 30% EtOAc in hexanes) to provide **25** as a yellow oil (42.2 mg, 66%). R_f: 0.20 (CH_2Cl_2). IR (film): 2100 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.22 (d, J (H,H) = 8.5 Hz, 12H; H_{ar}), 6.95 (d, J (H,H) = 8.5 Hz, 12H; H_{ar}), 4.63 (s, 12H; $Ph\underline{CH_2}O$), 3.68 (q, J (H,H) = 5.2 Hz, 6H; $O\underline{CH}(CH_2)_2$), 3.39 (d, J (H,H) = 5.2 Hz, 24H; $\underline{CH_2}N_3$). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 150.3 (OC_{ar}), 133.9 ($\underline{C}H_{ar}$), 128.9 ($\underline{C}H_{ar}$), 121 ($\underline{C}_{ar}$), 77.1 ($Ph\underline{C}H_2O$), 71.8 ($\underline{C}HCH_2N$), 51.7 (CH_2N_3). ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C): δ 8.03 (s). HRMS m/z: calcd for $C_{60}H_{66}N_{39}O_{12}P_3 + (H^+)$, 1618.5038. Found m/z: 1618.5028.

Peracetylated Dodecaazide 26. From dodecaazide **25** (19.5 mg, 0.012 mmol), prop-2-ynyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (**3**) (70 mg, 0.18 mmol), *N*,*N*-diisopropylethylamine (32 μL, 0.18 mmol), and CuI (3.5 mg, 0.018 mmol) dissolved in THF (5 mL), and after 12 h of reaction time following the general procedure described above, glycocluster **26** (63 mg, 84%) was obtained as a white foam. R_f: 0.29 (MeOH:CH_2Cl_2, 5:95). $[\alpha]_D^{20} = +44.3$ (c = 1.0 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.80 (s, 12H; $\underline{CH}{=}C$), 7.08 (d, J (H,H) = 8.4 Hz, 12H; H_{ar}), 6.85 (d, J (H,H) = 8.4 Hz, 12H; H_{ar}), 5.34−5.24 (m, 24H; H-4, H-3), 5.23−5.19 (m, 12H; H-2), 4.95 (s br, 12H; H-1), 4.80 (d, J (H,H) = 12.2 Hz, 12H; OCHN), 4.65 (d, J (H,H)= 12.2 Hz, 12H; OCHN), 4.50−4.45 (m, 42H; $Ph\underline{CH_2}O$, $O\underline{CH}CH_2$, $OCH(\underline{CH_2})_2$), 4.28 (dd, J (H,H) = 4.6, 12.3 Hz, 12H; H-6), 4.11−4.08 (m, 24H; H-6b, H-5), 2.11, 2.10, 2.01, 1.95 (s, 144H; $COCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 170.6, 170, 169.9, 169.6 ($\underline{C}OCH_3$), 150.3 (OC_{ar}), 143.3 ($CH{=}\underline{C}$), 133.8 ($\underline{C}H_{ar}$), 129.3 ($\underline{C}H_{ar}$), 125 ($\underline{CH}{=}C$), 121 ($\underline{C}_{ar}$), 96.7 (C-1), 75.4 ($O\underline{CH}(CH_2N)_2$), 71.7 ($Ph\underline{CH_2}O$), 69.3 (C-2), 69 (C-3), 68.6 (C-5), 65.7 (C-4), 62.2 ($\underline{CH_2}OCH$), 60.5 (C-6), 50.4 ($O\underline{CH}(CH_2N)_2$), 20.8, 20.7, 20.6, 20.6 ($CO\underline{CH_3}$). ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C): δ 8.09 (s). HRMS m/z: calcd for $C_{264}H_{330}N_{39}O_{132}P_3 + (4H^+)$, 1563.7453. Found m/z: 1563.7375.

Dodecamannoside 27. Compound **26** (30 mg, 0.005 mmol) and sodium methoxide (3 μL from 1 M solution in MeOH) in 3 mL of methanol were stirred for 4 h, and the mixture was treated following the general procedure described above. Deprotected glycocluster **27** (17.5 mg, 96%) was obtained as a white foam. R_f: 0.17 (H_2O:CH_3CN, 3:7). $[\alpha]_D^{20} = +44.7$ (c = 1.0 in CH_3OH). ^{1}H NMR (300 MHz, DMSO-D_6, 25 °C): δ 7.77 (s, 12H; $\underline{CH}{=}C$), 6.65 (d, J (H,H) = 8.4 Hz, 12H; H_{ar}), 6.48 (d, J (H,H) = 8.4 Hz, 12H; H_{ar}), 4.70 (s br, 12H; H-1), 4.70−4.47 (m, 102H; $Ph\underline{CH_2}O$, H-4, H-3, H-2, $\underline{CH_2}OCH$, $O\underline{CH}(CH_2)_2$, $OCH(\underline{CH_2})_2$), 3.69−3.66 (m, 12H; H-6a), 3.47−3.41 (m, 24H; H-6b, H-5). ^{13}C NMR (75 MHz, DMSO-D_6, 25 °C): δ 148.7 (OC_{ar}), 143.2 ($CH{=}\underline{C}$), 133.6 ($\underline{C}H_{ar}$), 129.4 ($\underline{C}H_{ar}$), 125.4 ($\underline{CH}{=}C$), 120.2 ($\underline{C}_{ar}$), 98.9 (C-1), 75.1 ($O\underline{CH}(CH_2N)_2$), 72.5 ($Ph\underline{CH_2}O$), 70.8 (C-2), 70.1 (C-5), 69.5 (C-3), 66.9 (C-4), 60.4 ($\underline{CH_2}OCH$), 59.1 (C-6), 50.6 ($O\underline{CH}(CH_2N)_2$). ^{31}P NMR (121 MHz, DMSO-D_6, 25 °C): δ 11.15 (s). HRMS m/z: calcd for $C_{168}H_{237}N_{39}O_{84}P_3 + (3H^+)$, 1412.4889. Found m/z: 1412.4885.

Octadecaazide 29. From NaH (60% in mineral oil, 35 mg, 1.46 mmol), triazide **28** (152 mg, 0.72 mmol), and hexabromo derivative **15** (100 mg, 0.08 mmol), and following the procedure described above for **25** synthesis, compound **29** (109 mg, 68%) was obtained as a yellow oil. R_f: 0.22 (CH_2Cl_2). IR (film): 2103 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.16 (d, J (H,H) = 8.5 Hz, 12H; H_{ar}), 6.98 (d, J (H,H) = 8.5 Hz, 12H; H_{ar}), 4.45 (s, 12H; $Ph\underline{CH_2}O$), 3.36−3.31 (m, 48H; $O\underline{CH_2}C$, 3 $\underline{CH_2}N_3$). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 150.4 (OC_{ar}), 134.2 ($\underline{C}H_{ar}$), 128.8 ($\underline{C}H_{ar}$), 120.9 ($\underline{C}_{ar}$), 72.7 ($Ph\underline{CH_2}O$), 68.7 ($C\underline{CH_2}O$), 51.4 (CH_2N_3), 44.6 ($\underline{C}CH_2N_3$). ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C): δ 7.87 (s). HRMS m/z: calcd for $C_{72}H_{84}N_{57}O_{12}P_3 + (H^+)$, 2032.7000. Found m/z: 2032.9663.

Peracetylated Octadecamannoside 30. From the polyazide **29** (73 mg, 0.036 mmol), prop-2-ynyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (**3**) (313 mg, 0.81 mmol), *N*,*N*-diisopropylethylamine (142 μL, 0.81 mmol), and CuI (16 mg, 0.08 mmol) dissolved in THF (5 mL), and after 12 h of reaction time following the general procedure described above, glycocluster **30** (296 mg, 83%) was obtained as a white foam. R_f: 0.19 (MeOH:CH_2Cl_2, 5:95). $[\alpha]_D^{20} = +32.3$ (c = 1.0 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.64 (s, 18H; $\underline{CH}{=}C$), 6.85 (d, J (H,H) = 8.1 Hz, 12H; H_{ar}), 6.59 (d, J (H,H) = 8.1 Hz, 12H; H_{ar}), 4.85 (s, 12H; $Ph\underline{CH_2}O$), 4.81−4.79 (m, 54H; H-4, H-3, H-2), 4.68 (s br, 18H; H-1), 4.49 (s br, 36H; $C\underline{CH_2}N$) 4.33 (d, J (H,H) = 12.2 Hz, 18H; 2 COCH), 4.17 (d, J (H,H) = 12.2 Hz, 18H; 2 COCH), 4.03−4.98 (m, 12H; $O\underline{CH_2}C$), 3.82−3.80 (m, 18H; H-6a), 3.64−3.61 (m, 36H; H-6b, H-5), 1.95, 1.62, 1.57, 1.51 (s, 216H; $COCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 170.5, 169.91, 169.7, 169.6 ($\underline{C}OCH_3$), 150.3 (OC_{ar}), 142.8 ($CH{=}\underline{C}$), 134.2 ($\underline{C}H_{ar}$), 129.4 ($\underline{C}H_{ar}$), 126.5 ($\underline{CH}{=}C$), 120.8 ($\underline{C}_{ar}$), 96.6 (C-1), 69.3 (C-2, $Ph\underline{CH_2}O$), 68.9 (C-3), 68.6 (C-5), 65.8 (C-4), 62.2 ($\underline{CH_2}OCH$), 60.2 (C-6), 49.2 ($C\underline{CH_2}N$), 45.9 ($\underline{C}CH_2N$), 20.8, 20.7, 20.6, 20.5 ($CO\underline{CH_3}$). ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C): δ 7.45 (s). HRMS m/z: calcd for $C_{378}H_{480}N_{57}O_{192}P_3 + (3H^+)$, 2996.3033. Found m/z: 2996.3022.

18-mer 31. Compound **30** (175 mg, 0.02 mmol) and sodium methoxide (10 μL from 1 M solution in MeOH) in 3 mL of methanol were stirred for 4 h, and the mixture was treated following the general procedure described above. Deprotected glycocluster **31** (111 mg, 96%) was obtained as a white foam. R_f: 0.22 (H_2O:CH_3CN, 3:7). $[\alpha]_D^{20} = +49.7$ (c = 1.0 in CH_3OH). ^{1}H NMR (300 MHz, DMSO-D_6, 25 °C): δ 8.15 (s, 18H; $\underline{CH}{=}C$), 7.27 (d, J (H,H) = 8.2 Hz, 12H; H_{ar}), 6.94 (d, J (H,H) = 8.2 Hz, 12H; H_{ar}), 4.71 (s br, 18H; H-1), 4.66−4.47 (m, 102H; H-4, H-3, H-2, $Ph\underline{CH_2}O$, $C\underline{CH_2}N$), 3.65−3.35 (m, 102H; 3 $O\underline{CH_2}CH$, $O\underline{CH_2}C$, H-6, H-5). ^{13}C NMR (75 MHz, DMSO-D_6, 25 °C): δ 149.6 (OC_{ar}), 143.6 ($CH{=}\underline{C}$), 134.9 ($\underline{C}H_{ar}$), 129.4 ($\underline{C}H_{ar}$), 126.6 ($\underline{CH}{=}C$), 120.4 ($\underline{C}_{ar}$), 99.2 (C-1), 74.2 (C-2, $Ph\underline{CH_2}O$), 70.9 (C-3), 70.2 (C-5), 66.9 (C-4), 61.3 ($\underline{CH_2}OC$, $C\underline{CH_2}OCH$), 60.3 (C-6), 49.2 ($C\underline{CH_2}N$), 45.9 ($\underline{C}CH_2N$). ^{31}P NMR (121 MHz, DMSO-D_6, 25 °C): δ 12.36 (s). HRMS m/z: calcd for $C_{234}H_{340}N_{57}O_{120}P_3 + (4H^+)$, 1490.2861. Found m/z: 1490.2882.

Turbidimetric Analysis. Turbidimetry experiments were performed in microtitration plates where 100 mL/well of stock Con A solution, prepared from 1 mg mL^{-1} PBS, was mixed with 100 mL/well of a mannosylated cluster solution and incubated at room temperature for 12 min (Figure 1). The turbidity of the solutions was monitored by reading the optical density (O.D.) at 490 nm at regular time intervals until no noticeable changes could be observed. Each test was done in triplicate.

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Supporting Information Available: ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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