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# Synthesis of a Nonavalent Mannoside Glycodendrimer Based on Pentaerythritol

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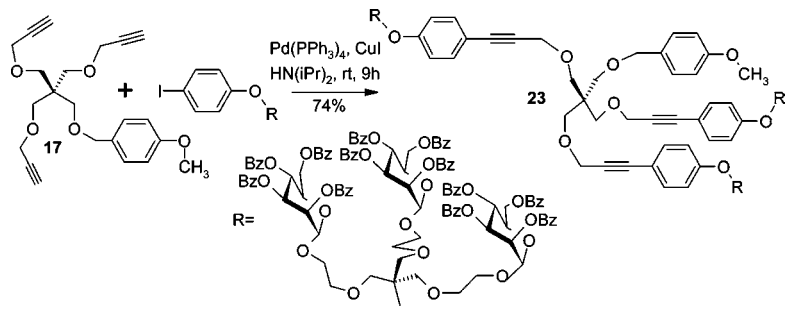


A nonavalent glycodendrimer bearing terminal α-D-mannopyranoside units has been synthesized with a convergent approach. Terminal trivalent mannoside dendrons bearing *p*-halophenyl ethers were prepared by glycosylation of pentaerythritol derivatives having three 2-hydroxyethyl ether substituents. Two efficient routes were developed for the synthesis of the pentaerythritol-based core (**17**), which has three terminal propargyl ethers. Conditions were found under which the triple Sonogashira coupling reaction of the dendron and the tri-*O*-propargyl ether (**17**) proceeded efficiently. The product was deprotected and it and precursors were fully characterized by NMR spectroscopy and FT-ICR mass spectrometry.

## Introduction

Terminal α-D-mannopyranoside residues on cell surfaces are recognized by a number of protein receptors of different types. In general, the strengths of the interactions of single monosaccharides or oligosaccharides with their protein receptors are weak; usually the dissociation constants are in the millimolar to micromolar range.[1] Multivalent presentation of the carbohydrate allows the binding strength to become sufficiently stronger[2−5] that synthetic ligands can compete with the natural polyvalent ligands.

One of the medically most significant carbohydrate−protein interactions involves the initial attachment of pathogenic bacteria to target tissues. Bacteria express lectins termed adhesins on their surfaces to attach themselves to cell surface carbohydrates from a variety of tissues. In Gram negative bacteria, these adhesins often are on pili or fimbriae protruding from the cell surface.[6] Strains of the Gram negative bacteria *Escherichia coli* are commensal inhabitants of the human intestinal tract and extraintestinal sites, particularly the urinary tract, but also cause a variety of infectious diseases. The vast majority of *E. coli* express Type 1 fimbriae that recognize terminal α-D-mannopyranoside residues present on cell surfaces via the lectin FimH.[7,8] The binding of *E. coli* to α-D-mannopyranoside residues has been recognized for some time,[9,10] and a number of dendrimers have been designed to evaluate the utility of antibacterial strategies involving this type of compound.[11−16] There is considerable variation in the binding strengths observed for *E.*

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*coli* strains,[17,18] although the actual binding site is thought to be strongly conserved. The binding of α-D-mannopyranoside residues to the FimH lectin from both an *E.coli* uropathogenic strain J96 and a K-12 laboratory strain MG1655 were shown recently to be very strong, in the micromolar to nanomolar range depending on the structure of the aglycon.[19]

A second type of important receptor is the C-lectin DC-SIGN (dendritic cell-specific ICAM-grabbing nonintegrin), present on dendritic cells which sample the microenvironment of every tissue for foreign antigens.[20−23] A number of different pathogens utilize this lectin to gain access to specific cell types: HIV-1, HIV-2, Ebola virus, hepatitis C virus, Dengue virus, cyctomagalovirus; bacteria such as *Mycobacterium* tuberculosis, *Heliobacter pylori*, and *Klebsiella pneumoniae*; yeasts such as *Candida albicans*; and parasites such as *Leishmania* and *Schistosoma*.[21] DC-SIGN is a calcium-dependent lectin, present as a tetramer,[24−26] that binds the blood group determinants containing terminal fucose, Lewis$^x$ and Lewis$^a$, as well as structures containing both internal and terminal mannose.[27−29] The closely related C-lectin DC-SIGNR only binds mannose-containing structures.[29] It has been suggested that pathogens use closely spaced glycans for multivalent binding with the multiple carbohydrate recognition domains (CRDs) in the DC-SIGN tetramer, because clusters of either mannose-type or fucose-type ligands are uncommon on endogenous cell surfaces and glycoproteins.[29] Rojo and co-workers have found that mannose-terminal glycodendrimers based on the Boltorn dendrimers were able to inhibit DC-SIGN mediated cell entry by Ebola virus at nanomolar concentration.[30,31] Other dendrimers have also been found to be active against HIV.[32]

These observations encouraged us to design a glycodendrimer with clustered terminal α-D-mannopyranoside units. In this design, the α-D-mannopyranoside units were linked via their anomeric centers to expose the maximal number of hydroxyl groups so as to aid water solubility. Aromatic groups were incorporated to aid binding to the two tyrosine units located outside the mannose binding site in the FimH lectin.[19,33] The synthetic route to the glycodendrimer allows extension to higher order dendrimers later via the hydroxyl group that can be unveiled by selective removal of the single *p*-methoxybenzyl group. The design also allows the incorporation of variable length spacer arms in later syntheses if this feature is considered desirable. This paper reports the synthesis of the glycodendrimer resulting from these considerations.

## Results and Discussion

The synthetic plan followed a convergent route where dendritic trimannoside clusters were designed to be coupled to a central propargylated pentaerythritol core via Sonagashira coupling as outlined in Scheme 1.

**Synthesis of the Dendritic Clusters.** The synthetic route to the dendritic clusters is shown in Schemes 2 and 3. Pentaerythritol tri-*O*-allyl ether (**1**), chromatographically purified from commercial technical product, was converted to the corresponding tosylate **2** by using tosyl chloride and pyridine in 84% yield. Treatment of tosylate **2** with *p*-bromophenol and *p*-iodophenol according to the method reported by Laliberté et al.,[34] used during the synthesis of pentaerythritol tetra-*O*-phenyl ether, provided precursors **3** and **4** in yields of 70% and 68%, respectively. Ozonolysis of tri-*O*-allyl ethers **3** and **4** in methanol and dichloromethane at −78 °C followed by reductive workup with sodium borohydride in ethanol afforded triols **5** and **6** in yields of 81% and 71%, respectively.

As depicted in Scheme 3, the benzoylated imidate **9** was obtained in three steps from mannose, starting with 1,2,3,4,6-penta-*O*-benzoyl-α,*β*-D-mannopyranoside (**7**) prepared according to the standard procedure reported by Fletcher et al.,[35] followed by anomeric de-*O*-benzoylation. Anomeric de-*O*-benzoylation of perbenzoylated mannose suffers from low yields and/or long reaction times of up to several days.[36] Dubber and Lindhorst[37] have examined several alternative conditions for anomeric de-*O*-benzoylation and found that the commercially available solution of $Et_2NH$ in EtOH (5.6 M) with THF as a solvent was effective for both anomeric de-*O*-benzoylations and de-*O*-acetylations. However, in the case of perbenzoylated mannose, pyridine was reported to be superior to THF; the reaction was completed within 1.5 h in yields up to 78%. Here, it was found that the commercially available solution of $MeNH_2$ in ethanol (33%) in THF effected the anomeric de-*O*-benzoylation of **7** faster, in less than 30 min, and afforded an α/*β*-mixture of **8** in

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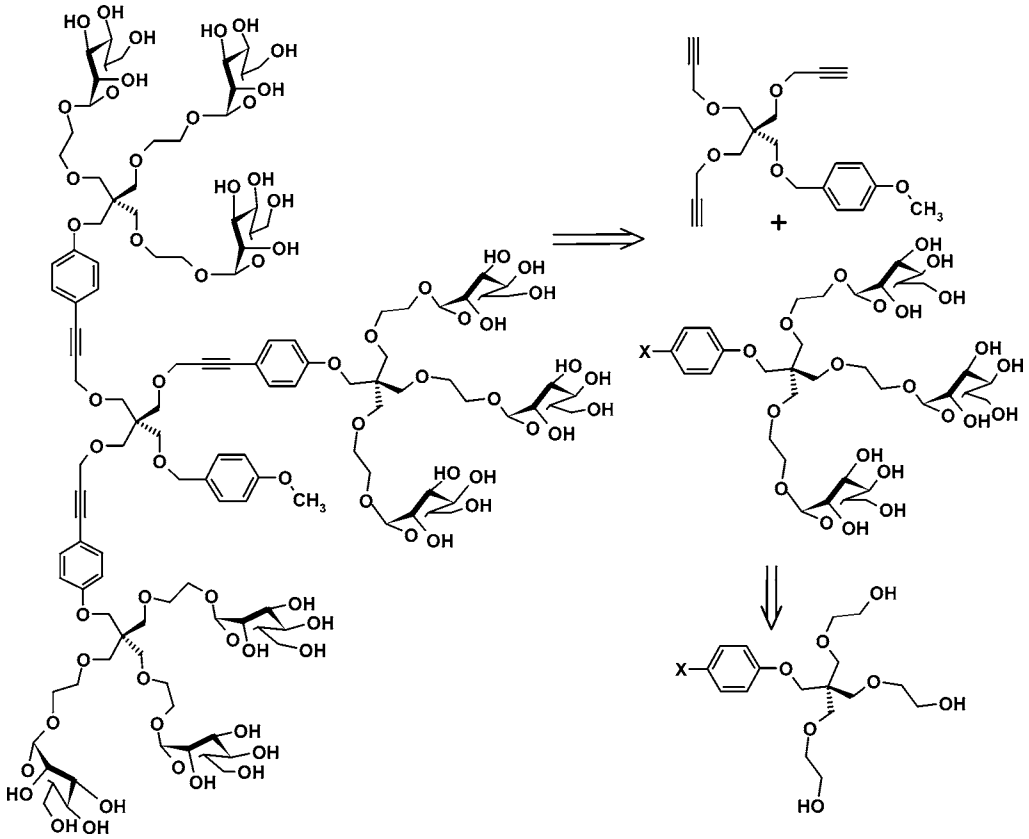
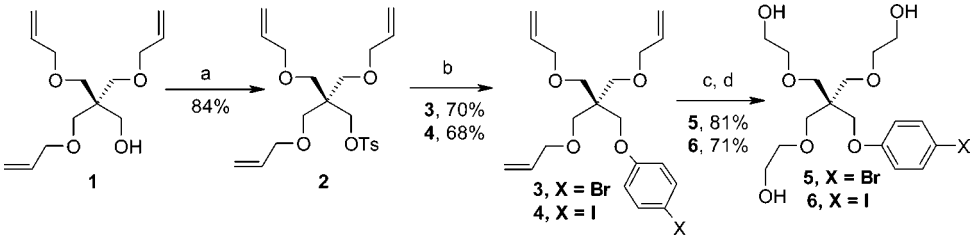
**SCHEME 1. Retrosynthetic Analysis**

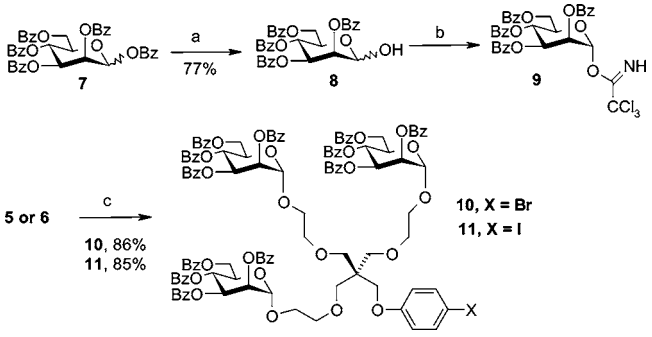


**SCHEME 2. Synthesis of the Cluster Core**[a]




[a] Reagents and conditions: (a) TsCl (2 equiv), Py, 0 °C to room temperature, 12 h; (b) *p*-halophenol (1.25 equiv), DMF, NaOH (1.25 equiv), reflux, 12 h; (c) $O_3$ (g), $CH_2Cl_2$, MeOH (1:1), −78 °C; $Me_2S$, -78 °C; (d) $NaBH_4$, EtOH, 0 °C to room temperature, 24 h.

**SCHEME 3. Synthesis of Trivalent Cluster Mannosides 10 and 11**[a]




[a] Reagents and conditions: (a) $MeNH_2$ (33%) in EtOH, THF, 30 min; (b) $Cl_3CCN$, DBU; (c) 9 (3.75 equiv), $CH_2Cl_2$, TMSOTf, 10 h.

77% yield. Base-catalyzed addition of **8** to trichloroacetonitrile according to the procedure reported by Ziegler and Bien[38] yielded **9**. The benzoylated glycosyl imidate **9** was quite stable; no decomposition was detected after it was stored at room temperature for more than one month.

Coupling of the glycosyl donor **9** with triol **5** or **6** in the presence of TMSOTf as catalyst in dichloromethane as solvent at room temperature furnished the desired tris-α-D-mannopyranoside dendrons **10** and **11**, in yields of 86% and 85%, respectively, after column chromatography. No benzoyl group transfer products, ortho esters, or mono- and divalent clusters were observed. The expected α-stereochemistries of the D-mannosides **10** and **11** were established from their $^1H$ and $^{13}C$ NMR spectra. The signals of the anomeric protons appeared in the $^1H$ NMR spectra at 5.15 and 5.17 ppm, respectively, as doublets with identical $^3J_{1,2}$ values of 1.6 Hz. This value is consistent with an equatorial−equatorial relationship between H-1 and H-2.[39,40] The α-configurations were confirmed from

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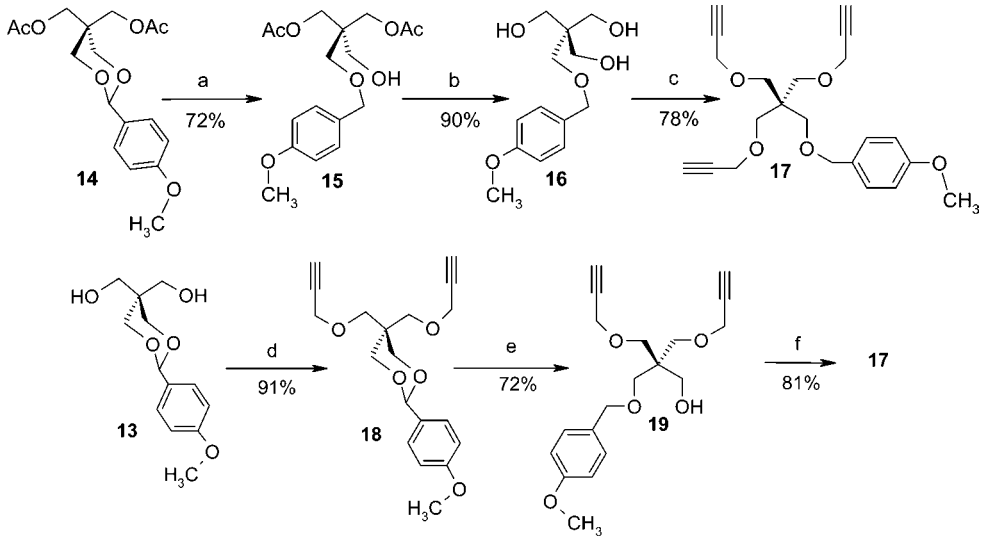
**SCHEME 4. Syntheses of the Tri-*O*-propargyl Ether 17**[a]




[a] Reagents and conditions: (a) $Et_3SiH$ (1.2 equiv), $EtAlCl_2$ (3.3 equiv), $CH_2Cl_2$, −78 °C, 35 min; (b) NaOMe, MeOH, 1 h; (c) NaH (4.6 equiv), DMF, propargyl bromide (4.0 equiv), 0 °C to room temperature, 5 h; (d) NaH (3.3 equiv), DMF, propargyl bromide (2.8 equiv), 0 °C to room temperature, 4 h; (e) $Et_3SiH$ (1.2 equiv), $EtAlCl_2$ (1.7 equiv), $CH_2Cl_2$, −78 °C, 40 min; (f) NaH (1.2 equiv), DMF, propargyl bromide (1.2 equiv), −10 °C to room temperature, 8 h.

the magnitudes of the one bond $^{13}C-^{1}H$ coupling constants. The $J_{C1-H1}$ coupling of **10** and **11** was found to be 173.7 and 173.4 Hz, respectively, from the $^{13}C$ undecoupled HSQC experiment. Values of 160 Hz are typical of $\beta$-anomers while those of ∼170 Hz are typical of α-anomers.[39,40] The molecular masses of clusters **10** and **11** were established from their mass spectra. The ESI mass spectrum of cluster **10**, a bromo derivative with the formula $C_{119}H_{105}BrO_{34}$, was recorded on an ion trap mass spectrometer. The resolution at *m*/*z* 2180, where $M + Na^+$ occurs, was >1 Da and the peak at this mass extended from *m*/*z* 2179.6 to 2186.6 with a maximum at *m*/*z* 2181.6. The relative intensities of the various unit mass peaks were calculated with the program ISOMABS,[41] and it was found that the most intense peak in this cluster should occur at *m*/*z* 2181.6, exactly matching the observed position, and the general shape of the molecular ion peak matched that calculated. In contrast, the mass spectrum of cluster **11** was recorded with a MALDI FT-ICR mass spectrometer, which had a resolution of <0.01 Da at this mass. The individual peaks in this cluster were very well resolved, separated by about 30 line widths. The mass-to-charge ratio for the $[M + Na]^+$ peak was calculated to be *m*/*z* 2227.542, and was observed at 2227.546, in excellent agreement, and the intensities of the M + 1 + Na, M + 2 + Na, M + 3 + Na, and M + 4 + Na peaks also fit the intensities calculated with ISOMABS[41] well.

**Synthesis of the Core Molecule.** Pentaerythritol mono-*p*-methoxybenzyl ether (**16**) was selected as a core to allow future extension by selective deprotection and further reaction of the exposed alcohol. Burns et al.[42] described a procedure of the synthesis of triol **16**, involving the reductive opening of the pentaerythritol mono-*p*-methoxybenzylidene acetal (**13**) with DIBAL in toluene at room temperature in good yield, but we were unable to repeat this procedure. Two alternatives were developed. As outlined in Scheme 4 (top), the diacetate **14**, prepared (87% yield) in two straightforward steps from pentaerythritol,[43] was reductively cleaved by addition of $EtAlCl_2-Et_3SiH$[44] in $CH_2Cl_2$ to produce the corresponding alcohol **15** in 72% yield. Removal of the acetyl groups with sodium methoxide in MeOH gave triol **16** in 90% yield that yielded the tri-*O*-propargyl ether **17** in 78% yield on treatment with propargyl bromide and NaH in DMF.

Initial difficulties with the reduction of *p*-methoxybenzylidene acetal (**13**), ultimately overcome through the use of the diacetate **14** as outlined above, led to the development of a second approach (Scheme 4, bottom) to tri-*O*-propargyl ether **17**. Diol **13** was treated with propargyl bromide in the presence of sodium hydride in DMF to give di-*O*-propargyl ether **18** in 91% yield. Reductive opening of the *p*-methoxybenzylidene acetal as for **14** gave the desired alcohol **19** in 72% yield. Alkylation of alcohol **19** was then achieved with propargyl bromide in the presence of sodium hydride in DMF to give the tri-*O*-propargyl ether **17** in 81% yield. This synthesis is shorter (3 steps from **13**) and higher yielding than the previous route (53% vs 44%).

With the key intermediates **11** and **17** in hand, we were able to focus on combining them via triple Sonogashira coupling reactions. In a series of papers, Roy et al.[45−49] demonstrated the usefulness of the Sonogashira reaction in the construction of divalent glycoclusters and high-order glycoclusters having different geometries and shapes. It was found that the reaction of propargyl glycosides and phenyl halides could be performed at high temperature in DMF as a solvent and $Et_3N$ as a base, using either $Pd(PPh_3)_2Cl_2$ or $Pd(PPh_3)_4$ as catalyst in the absence

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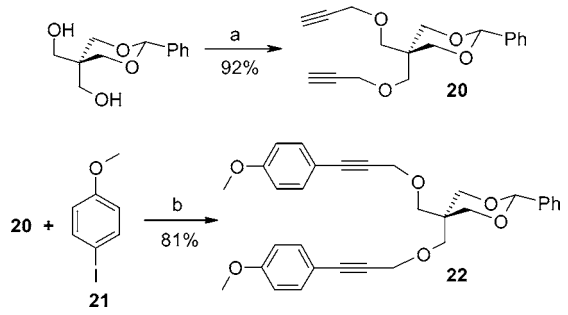
**SCHEME 5. Preparation of the Model Di-*O*-propargyl Ether 20 and Its Coupling Reaction[a]**




[a] Reagents and conditions: (a) NaH (3.3 equiv), DMF, propargyl bromide (2.5 equiv), 0 °C to room temperature; (b) $Pd(PPh_3)_4$ (5 mol %), CuI (20 mol %), DMF−$Et_3N$ (1:1), room temperature, 6 h.

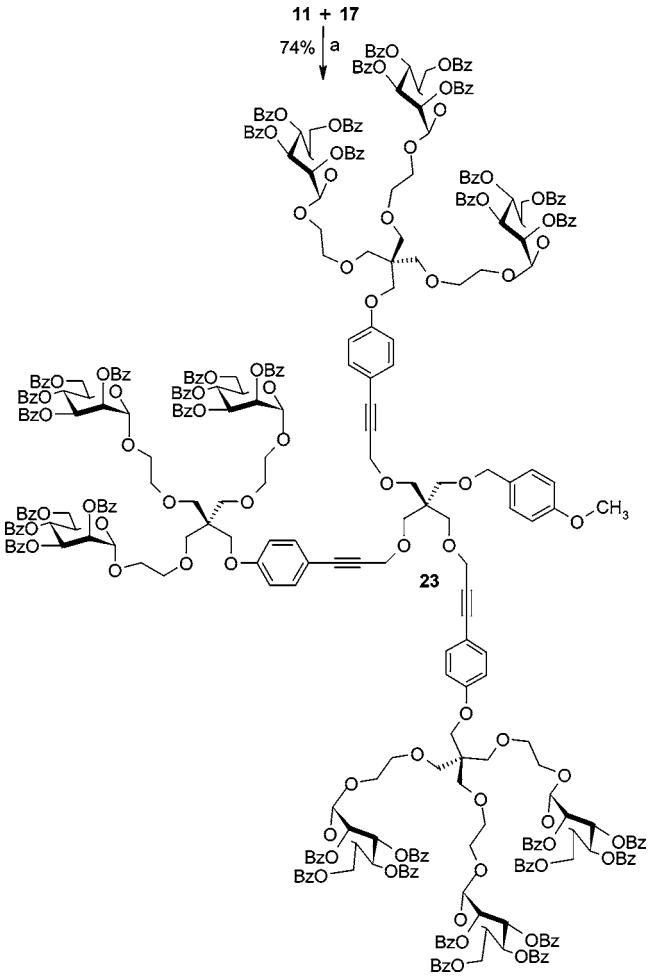
of CuI.[48−50] This latter point was significant because in the absence of CuI, the oxidative homodimerization of the alkynyl moiety was not observed.

Initially, Sonogashira coupling between the dendron **11** and the tri-*O*-propargyl ether **17** was attempted at high temperature and in the absence of CuI, following Roy's observations. No cross product was formed. The dendron **11** was recovered and the tri-*O*-propargyl ether was consumed during the course of the reaction. It is noteworthy to mention that the tri-*O*-propargyl ether **17** is not stable, decomposing after being stored for 2 days at 5 °C in the dark. Therefore, a model reaction was employed to develop conditions under which Sonogashira coupling of this type of propargyl ethers was viable. As a starting point of investigation, the di-*O*-propargyl ether **20** was prepared in 92% yield by reacting monobenzylidene pentaerythritol with propargyl bromide and NaH in DMF. 4-Iodoanisole **(21)** was chosen as the coupling partner.

To find optimal reaction conditions for coupling, the reaction between the di-*O*-propargyl ether **20** and *p*-iodoanisole **21** was performed under a variety of reaction conditions. Unfortunately, all attempts to accomplish the coupling under copper-free condition were unsuccessful. On the other hand, the reaction was found to be successful on the addition of CuI. In the presence of 5 mol % of $Pd(PPh_3)_4$ and 20 mol % of CuI the reaction proceeded at room temperature in a mixture of DMF and $Et_3N$ (1:1) to give the cross coupling product **22** in 81% yield after column chromatography (Scheme 5).

Surprisingly, when the same conditions were applied to couple compounds **11** and **17**, no cross product formed. Krause and Thorand[51] observed that the rate of the palladium-catalyzed coupling of terminal alkynes with aryl bromides increased markedly when the coupling was performed in THF, rather than DMF. Using THF as a solvent led to the isolation of the glycodendrimer **23** in good yield. Indeed, the dendron **11** reacted smoothly with **17** in the presence of $Pd(PPh_3)_4$, CuI, and HN(*i*-Pr)$_2$ in THF at room temperature to afford the desired coupling product, the 9-mer **23** in 74% yield after column chromatography (Scheme 6). No mono- and disubstituted products were observed. The side reaction, the homocoupling of the tri-*O*-propargyl ether **17**, was prevented almost completely by adding **17** in THF slowly to keep its concentration in the reaction mixture very low. The optimized conditions were found to be 10 mol % of $Pd(PPh_3)_4$, 30 mol % of CuI, and HN(*i*-pr)$_2$ (4.5 equiv). $Pd(PPh_3)_4$) was the best catalyst for this reaction while $PdCl_2(PPh_3)_2$ was less effective. Both bases ($Et_3N$ and HN(*i*-pr)$_2$) can be used in this reaction.

**SCHEME 6. Synthesis of Mannoside Glycodendrimer 23[a]**




[a] Reagents and conditions: (a) $Pd(PPh_3)_4$ (10 mol %), CuI (30 mol %), HN(*i*-Pr)$_2$, THF, room temperature, 9 h.

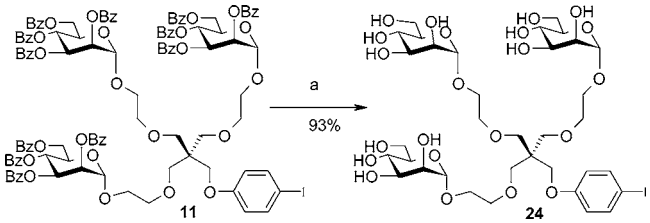
The $^1H$ and $^{13}C$ NMR spectra were consistent with the proposed structure depicted in Scheme 6. The mass spectrum, recorded on an FT-ICR mass spectrometer, with MALDI ionization, contained well resolved M + Na, M + 1 + Na, M + 2 + Na, M + 3 + Na, etc. peaks of appropriate intensities as calculated by the ISOMABS program.[41] The *m*/*z* value calculated for the M + Na peak, 6623.1, agreed with the observed value within 0.3.

Due to the poor solubility of the benzoylated glycoclusters in methanol, Lindhorst et al. reported that elongated reaction times of up to two weeks were necessary to make the de-*O*-benzoylation reaction go to completion.[13] Here, it was found that a mixture of THF and methanol (2:1, v/v) is an excellent solvent system for the de-*O*-benzoylation of benzoylated glycoclusters. Before attempting the de-*O*-benzoylation of the 9-mer, cluster **11**, dissolved in a 2:1 mixture of THF and methanol, was treated with 0.5 M NaOMe/methanol solution for 4 h. The corresponding de-*O*-benzoylated cluster **24** was obtained in 93% yield (Scheme 7).

In the case of the 9-mer, it was dissolved in a mixture of THF and methanol (1:2, v:v) and treated as for cluster **11**. The

(50) Liu, B.; Roy, R. *Tetrahedron* **2001**, *57*, 6909−6913.
(51) Thorand, S.; Krause, N. *J. Org. Chem.* **1998**, *63*, 8551−8553.

**SCHEME 7. De-*O*-benzoylation of Mannoside Cluster 11**[a]




[a] Reagents and conditions: (a) 0.5 M NaOMe, THF−MeOH (2:1), room temperature, 4 h.

corresponding de-*O*-benzoylated 9-mer was obtained in 91% yield in 8 h at room temperature (Scheme 8).

Water-insoluble clusters will be biologically inactive and solubility has been a problem for some clusters prepared previously.[14] The compounds synthesized here, trivalent cluster **24** and the 9-mer **25**, were found to exhibit good solubilities in water.

## Conclusions

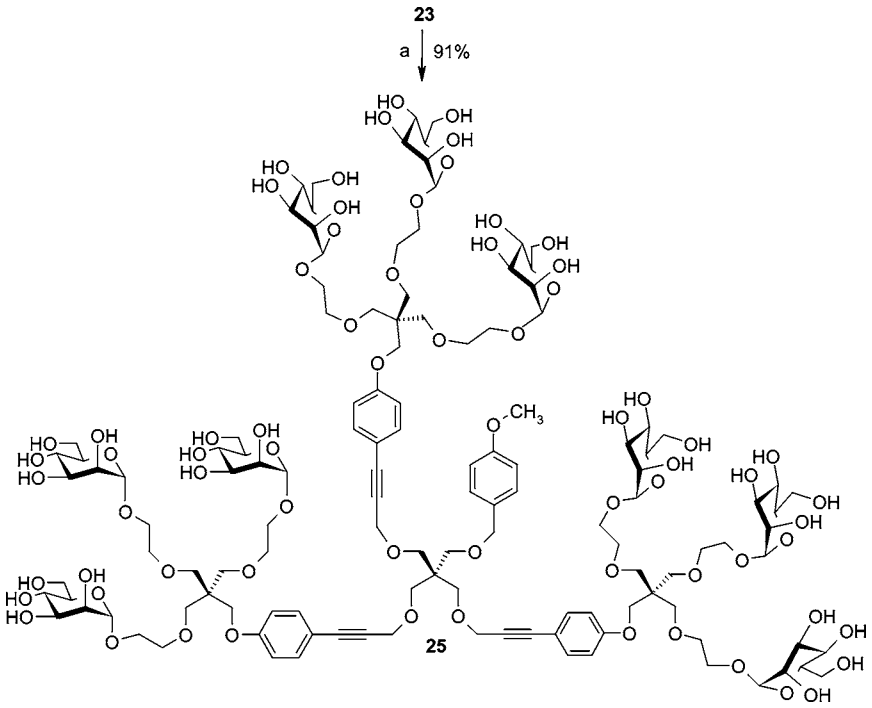
A nonavalent glycodendrimer bearing terminal α-D-mannopyranoside units has been synthesized by using a convergent approach. The terminal trivalent mannoside dendron bearing a *p*-halophenyl ether was prepared by glycosylation of a pentaerythritol derivative having three 2-hydroxyethyl ether substituents. Two efficient routes were developed for the synthesis of the pentaerythritol-based core (**17**), which has three terminal propargyl ethers. Conditions were found under which the triple Sonogashira coupling reaction of the dendron and the tri-*O*-propargyl ether (**17**) proceeded efficiently. The product was deprotected and it and precursors were fully characterized by NMR spectroscopy and FT-ICR mass spectrometry.

## Experimental Section

**1,3-Bis(allyloxy)-2-allyloxymethyl-2-[(*p*-toluenesulfonyloxy)-methyl]propane (2).** To a cold (0 °C, ice−water bath) solution of tri-*O*-allyl pentaerythritol (**1**, 0.73 g, 2.85 mmol) in dry pyridine (13 mL) was added *p*-toluenesulfonyl chloride (1.1 g, 5.7 mmol) and the resulting reaction mixture was stirred at room temperature for 12 h and concentrated. The residue was dissolved in dichloromethane (50 mL) and the resulting solution was washed with saturated $NaHCO_3$ (50 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to a residue that was purified by flash column chromatography (hexanes−EtOAc (7:1), $R_f$ 0.32) to give the title compound as a colorless oil (0.98 g, 84%). $^1$H NMR $\delta$ 7.79−7.30 (m, 4H, PhH), 5.79 (m, 3H, 3 × C*H*═), 5.20 (dq, 3H, $^3J_{trans}$ = 17.4 Hz, $^2J_{H,H}$ = $^4J_{trans}$ = 1.7 Hz, ═CH*H*$_{trans}$), 5.13 (dq, 3H, $^3J_{cis}$ = 10.4 Hz, ═CH*H*$_{cis}$), 4.07 (s, 2H, $CH_2$OTs), 3.86 (dt, 6H, $^3J_{H,H}$ = 5.5 Hz, $^4J_{cis}$ = $^4J_{trans}$ = 1.4 Hz, 3 × allylic $CH_2$), 3.38 (s, 6H, 3 × $CH_2$-OAll), 2.43 ($CH_3$); $^{13}$C NMR $\delta$ 144.6, 132.8, 129.8, 128.0 (PhC), 134.7 (3 × *C*H═$CH_2$), 116.4 (3 × CH═*C*$H_2$), 72.2 (3 × allylic $CH_2$), 69.7 ($CH_2$OTs), 68.1 (3 × $CH_2$OAll), 44.8 (qC), 21.6 ($CH_3$). LR ESI MS: *m*/*z* calcd for $C_{21}H_{30}O_6S$ + Na 433.17, found 433.1.

**1,3-Bis(allyloxy)-2-allyloxymethyl-2-[(*p*-bromophenoxy)methyl]propane (3).** To a stirred solution of compound **2** (1.3 g, 3.2 mmol) and *p*-bromophenol (0.69 g, 4 mmol, 1.25 equiv) in dry DMF (50 mL) was added powdered NaOH (0.16 g, 4 mmol, 1.25 equiv) and the resulting reaction mixture was heated at reflux for 12 h, then concentrated. Water (40 mL) was added and the reaction mixture was extracted with dichloromethane (3 × 35 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (hexanes:EtOAc, 6:1, $R_f$ 0.72) to give the title compound as a syrup (0.91 g, 70%). $^1$H NMR $\delta$ 7.36−6.78 (m, 4H, PhH), 5.86 (m, 3H, 3 × C*H*), 5.20 (dq, 3H, $^3J_{trans}$ = 17.1 Hz, $^2J_{H,H}$ = $^4J_{trans}$ = 1.7 Hz, ═CH*H*$_{trans}$), 5.11 (dq, 3H, $^3J_{cis}$ = 10.4 Hz, ═CH*H*$_{cis}$), 3.97 (s, 2H, $CH_2$OPh), 3.96 (dt, 6H, $^3J_{H,H}$ = 5.2 Hz, $^4J_{cis}$ = $^4J_{trans}$ =1.4 Hz, 3 × allylic $CH_2$), 3.54 (s, 6H, 3 × $CH_2$-OAll); $^{13}$C NMR $\delta$ 158.6, 132.3, 116.7, 112.8 (PhC), 135.2 (3 × *C*H═$CH_2$), 116.6 (3 × CH═*C*$H_2$), 72.5 (3 mtmex allylic $CH_2$),

**SCHEME 8. De-*O*-benzoylation of 9-Mer 23**[a]




[a] Reagents and conditions: (a) 0.5 M NaOMe, THF−MeOH (1:2), room temperature, 8 h.

69.0 (3 × $CH_2OAll$), 67.5 ($CH_2OPh$), 45.4 (qC). LR ESI MS: *m*/*z* calcd for $C_{20}H_{27}BrO_4$ + Na 433.10, found 433.1.

**1,3-Bis(allyloxy)-2-allyloxymethyl-2-[(*p*-iodophenoxy)methyl]-propane (4).** To a stirred solution of compound **2** (13.0 g, 32 mmol) and *p*-iodophenol (8.80 g, 40 mmol, 1.25 equiv) in dry DMF (120 mL) was added powdered NaOH (1.60 g, 40 mmol, 1.25 equiv) and the resulting reaction mixture was heated at reflux for 12 h, then concentrated. Water (100 mL) was added and the reaction mixture was extracted with dichloromethane (3 × 50 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (hexanes−EtOAc (7:1), $R_f$ 0.58) to give the title compound as a pale yellow oil (9.97 g, 68%). $^1$H NMR $\delta$ 7.51−6.66 (m, 4H, PhH), 5.79 (m, 3H, 3 × C*H*═), 5.20 (dq, 3H, $^3J_{trans}$ = 17.8 Hz, $^2J_{H,H}$ = $^4J_{trans}$ = 1.8 Hz, ═CH*H*$_{trans}$), 5.10 (dq, 3H, $^3J_{cis}$ = 11.8 Hz, ═CH*H*$_{cis}$), 3.98 (s, 2H, $CH_2OPh$), 3.90 (dt, 6H, $^3J_{H,H}$ = 5.2 Hz, $^4J_{cis}$ = $^4J_{trans}$ =1.4 Hz, 3 × allylic $CH_2$), 3.54 (s, 6H, 3 × $CH_2OAll$,); $^{13}$C NMR $\delta$ 159.2, 138.1, 117.1, 82.7 (PhC), 135.1 (3 × *C*H═$CH_2$), 116.4 (3 × CH═*C*H$_2$), 72.3 (3 × allylic $CH_2$), 68.8 (3 × $CH_2OAll$), 67.2 ($CH_2OPh$), 45.2 (qC). LR ESI MS: *m*/*z* calcd for $C_{20}H_{27}IO_4$ + Na 481.18, found 481.0.

**5-[(*p*-Bromophenoxy)methyl]-5-[(2-hydroxyethoxy)methyl]-3,7-dioxa-1,9-nonanediol (5).** Ozone was bubbled through a solution of compound **3** (2.82 g, 6.88 mmol) in dichloromethane−methanol (150 mL, 1:1) at −78 °C until the reaction mixture turned blue, and the complete consumption of the olefin was then verified by TLC. After the removal of residual ozone by bubbling nitrogen through the solution for 25 min, excess dimethyl sulfide was added at −78 °C and the resulting solution was then allowed to warm to room temperature and then concentrated. The oily residue was dissolved in ethanol (100 mL) and cooled to 0 °C (ice−water bath). Sodium borohydride (3.90 g, 100 mmol) was added in portions. After the reaction mixture was allowed to reach room temperature, it was stirred for a further 24 h. Water (50 mL) was added and the reaction mixture was acidified with 20% HCl to pH 6 (pH paper), then filtered. The filtrate was concentrated and the residue was extracted with dichloromethane (3 × 30 mL). The combined extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by flash column chromatography (pure EtOAc, $R_f$ 0.28) afforded the title compound as a viscous colorless oil (2.35 g, 81%). $^1$H NMR $\delta$ 7.36−6.78 (m, 4H, PhH), 3.93 (s, 2H, $CH_2OPh$), 3.67 (t, 6H, $J$ = 4.2 Hz, 3 × C*H*$_2$OH), 3.58 (s, 6H, 3 × $CCH_2O$), 3.53 (t, 6H, $J$ = 4.2 Hz, 3 × $CH_2OCH_2$); $^{13}$C NMR $\delta$ 158.2−113.0 (PhC), 72.7 (3 × $CH_2OCH_2$), 69.9 (3 × C*C*H$_2$O), 67.4 ($CH_2OPh$), 61.4 (3 × $CH_2OH$), 45.3 (qC). EI HRMS: *m*/*z* calcd for $C_{17}H_{27}BrO_7$ 422.0940, found 422.0941.

**5-[(*p*-Iodophenoxy)methyl]-5-[(2-hydroxyethoxy)methyl]-3,7-dioxa-1,9-nonanediol (6).** Ozone was bubbled through a solution of compound **4** (4.23 g, 9.2 mmol) in dichloromethane−methanol (120 mL, 1:1) at −78 °C until the reaction mixture turned blue, and complete consumption of the olefin was then verified by TLC. After nitrogen was bubbled through the solution for 30 min, excess dimethyl sulfide was added at −78 °C and the resulting solution was allowed to warm to room temperature and then concentrated. The oily residue was dissolved in ethanol (100 mL) and cooled to 0 °C (ice−water bath). Sodium borohydride (3.14 g, 83 mmol) was added in portions. After the reaction mixture had been allowed to reach room temperature, it was stirred for a further 18 h. Water (50 mL) was added and the reaction mixture was acidified with 20% HCl to pH 6 (pH paper) then filtered. The filtrate was concentrated and the residue was extracted with dichloromethane (3 × 50 mL). The combined extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by flash column chromatography (EtOAc−MeOH (95:5), $R_f$ 0.30) afforded the title compound as a viscous yellow oil (3 g, 71%). $^1$H NMR $\delta$ 7.54−6.67 (m, 4H, PhH), 3.93 (s, 2H, $CH_2OPh$), 3.66 (t, 6H, $J$ = 3.7 Hz, 3 × C*H*$_2$OH), 3.57 (s, 6H, 3 × $CCH_2O$), 3.52 (t, 6H, $J$ = 3.9 Hz, 3 × $CH_2OCH_2$); $^{13}$C NMR $\delta$ 158.9−82.9 (PhC), 72.7 (3 × $CH_2OCH_2$), 69.8 (3 × C*C*H$_2$O), 67.2 ($CH_2OPh$), 61.3 (3 × $CH_2$-OH), 45.2 (qC). EI HRMS: *m*/*z* calcd for $C_{17}H_{27}IO_7$ 470.0801, found 470.0812.

**2,3,4,6-Penta-*O*-benzoyl-α,*β*-D-mannopyranoside (8).** A solution of methylamine in ethanol (33%, 30 mL) was added to a solution of 1,2,3,4,6-penta-*O*-benzoyl-α,*β*-D-mannopyranoside (**7**)[35] (25 g, 36 mmol) in THF (250 mL) at room temperature and the reaction mixture was stirred for 30 min. The reaction mixture was concentrated and the resulting residue was purified by column chromatography (hexane:EtOAc, 2:1 → 1:1) to give the title compound as a white solid (16.5 g, 77%). $R_f$ 0.70 (hexane:EtOAc, 1:1); mp 191−193 °C (lit.[52] mp 181−182 °C); $^1$H and $^{13}$C NMR data were consistent with those reported previously.[53]

**1,9-Bis(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyloxy)-5-(4-[2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyloxy]-2-oxabutyl)-5-(*p*-bromophenoxymethyl)-3,7-dioxanonane (10).** A two-necked round-bottomed flask (flame-dried), equipped with a magnetic stirrer bar, was charged with triol **5** (0.22 g, 0.52 mmol) and 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl trichloroacetimidate **9**[38] (1.45 g, 1.95 mmol). The flask was evacuated and backfilled with argon. Dry dichloromethane (15 mL) was added via a syringe and the reaction mixture was stirred at room temperature for 25 min. TMSOTf (0.1 mL) was added to the reaction mixture dropwise via a syringe. The reaction mixture was stirred at room temperature for 10 h, neutralized with $NaHCO_3$ (1 g), and filtered and the filtrate was concentrated. The resulting residue was purified by flash column chromatography (hexanes:EtOAc, 3:1 → 2:1 → 1:1, $R_f$ 0.49 (hexanes:EtOAc, 1:1)) to give the title compound as a white crystalline powder (0.96 g, 86%). $[\alpha]_D$ −44.7 (*c* 1.0, $CHCl_3$); $^1$H NMR $\delta$ 7.91−6.79 (complex m, 64H, PhH), 6.12 (t, 3H, $J_{3,4}$ = $J_{4,5}$ = 10 Hz, 3 × H-4$_{man}$), 5.94 (dd, 3H, $J_{2,3}$ = 3.3 Hz, $J_{3,4}$ = 10.1 Hz, 3 × H-3$_{man}$), 5.71 (dd, 3H, $J_{1,2}$ = 1.8 Hz, $J_{2,3}$ = 3.2 Hz, 3 × H-2$_{man}$), 5.15 (d, 3H, $J_{1,2}$ = 1.6 Hz, 3 × H-1$_{man}$), 4.67 (m, 3H, 3 × H-6a$_{man}$), 4.50−4.45 (m, 6H, 3 × H-6b$_{man}$, 3 × H-5$_{man}$), 4.07, 4.03 (AB q, 2H, $J$ = 9.2 Hz, $CH_2OPh$), 3.90, 3.77 (m, 6H, $OCH_2CH_2O$), 3.75−3.71 (m, 6H, $OCH_2CH_2O$), 3.72 (s, 6H 3 × C*C*H$_2$O); $^{13}$C NMR $\delta$ 166.3, 165.7, 165.6, 165.5 (12 × CO), 158.5−112.8 (PhC), 97.9 (3 × C-1$_{man}$), 70.8 (3 × $OCH_2CH_2O$), 70.7 (3 × C-2$_{man}$), 70.3 (3 × C-3$_{man}$), 70.0 (3 × C*C*H$_2$O), 69.0 (3 × C-5$_{man}$), 67.5 ($CH_2OPh$), 67.4 (3 × $OCH_2CH_2O$), 67.2 (3 × C-4$_{man}$), 63.0 (3 × C-6$_{man}$), 45.8 (qC). ESI MS on Agilent ion trap *m*/*z* calcd for $C_{119}H_{105}BrO_{34}$ + Na 2179.56, found 2179.6. Calcd for the tallest mass peak of the M + Na cluster (M + 2 + Na) 2181.6, found 2181.6.

**1,9-Bis(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyloxy)-5-(4-[2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyloxy]-2-oxabutyl)-5-(*p*-iodophenoxymethyl)-3,7-dioxanonane (11).** A two-necked round-bottomed flask (flame-dried), equipped with a magnetic stirrer bar, was charged with triol **6** (0.4 g, 0.85 mmol) and compound **9**[38] (2.36 g, 3.2 mmol). The flask was evacuated and backfilled with argon. Dry dichloromethane (20 mL) was added with a syringe and the reaction mixture was stirred at room temperature for 30 min. TMSOTf (0.2 mL) was added to the reaction mixture dropwise via a syringe. The reaction mixture was stirred at room temperature for 10 h, neutralized with $NaHCO_3$ (2 g), and filtered and the filtrate was concentrated. The resulting residue was purified by flash column chromatography (hexanes:EtOAc, 3:1 → 2:1 → 1:1, $R_f$ 0.65 (hexanes:EtOAc, 1:1)) to give the title compound as a white foamy solid (1.59 g, 85%). $[\alpha]_D$ −41 (*c* 1.0, $CHCl_3$); $^1$H NMR $\delta$ 8.01−6.6.13 (complex m, 64H, PhH), 6.13 (t, 3H, $J_{3,4}$ = $J_{4,5}$ = 10.0 Hz, 3 × H-4$_{man}$), 5.91 (dd, 3H, $J_{2,3}$ = 3.3 Hz, $J_{3,4}$ = 10.1 Hz, 3 × H-3$_{man}$), 5.73 (dd, 3H, $J_{1,2}$ = 1.7 Hz, $J_{2,3}$ = 3.2 Hz, 3 × H-2$_{man}$), 5.17 (d, 3H, $J_{1,2}$ = 1.6 Hz, 3 × H-1$_{man}$), 4.69 (m, 3H, 3 × H-6a$_{man}$), 4.52−4.46 (m, 6H, 3 × H-6b$_{man}$, 3 × H-5$_{man}$), 4.09, 4.06 (AB q, 2H, $J$ = 9.1 Hz, $CH_2OPh$), 3.92, 3.76 (m, 6H, 3 × $OCH_2CH_2O$), 3.82−3.72 (m, 6H, 3 × $OCH_2CH_2O$), 3.72 (s, 6H, 3 × C*C*H$_2$O);

(52) Nikolaev, A. V.; Ivanova, I. A.; Shibaev, V. N.; Kochetkov, N. K. *Carbohydr. Res.* **1990**, *204*, 65−78.

(53) Mbadugha, B. N. A.; Menger, F. M. *Org. Lett.* **2003**, *5*, 4041−4044.

$^{13}$C NMR $\delta$ 166.3, 165.7, 165.6, 165.5 (12 × CO), 138.3−117.3 (PhC), 97.9 (3 × C-$1_{man}$), 70.8 (3 × $OCH_2CH_2O$), 70.7 (3 × C-$2_{man}$), 70.3 (3 × C-$3_{man}$), 70.0 (3 × C*C*$H_2O$), 69.0 (3 × C-$5_{man}$), 67.4 ($CH_2OPh$), 67.4 (3 × $OCH_2CH_2O$), 67.2 (3 × C-$4_{man}$), 63.0 (3 × C-$6_{man}$), 45.8 (qC). MALDI FTICR MS: *m*/*z* calcd for $C_{119}H_{105}IO_{34}$ + Na 2227.542, found 2227.546.

**2,2-Bis(acetoxymethyl)-3-(*p*-methoxybenzyloxy)propanol (15).** To a stirred solution 5,5-bis(acetoxymethyl)-2-(*p*-methoxyphenyl)-1,3-dioxane (**14**)[43] (2.5 g, 7.4 mmol, dried by coevaporation with dry toluene) in dry dichloromethane (60 mL) under nitrogen was added $Et_3SiH$ (8.9 mmol, 1.2 equiv, 1.4 mL) and the reaction mixture was cooled to −78 °C. $EtAlCl_2$ (1.8 M in toluene, 24.4 mmol, 3.3 equiv, 13.3 mL) was added dropwise and the reaction mixture was stirred at −78 °C for 35 min and quenched with saturated $NaHCO_3$ (100 mL), extracted with dichloromethane (5 × 50 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (EtOAc−hexane (1:1), $R_f$ 0.48) to afford the title compound as a colorless oil (1.82 g, 72%). $^1$H NMR $\delta$ 7.23−6.85 (m, 4H, PhH), 4.42 (s, 2H, $OCH_2$-Ph), 4.10 (s, 4H, 2 × $CH_2OAc$), 3.79 (s, 3H, $OCH_3$), 3.58 (d, 2H, $J$ = 6.4 Hz, C*H*$_2$OH), 3.44 (s, 2H, $CCH_2O$), 2.85 (t, 1H, $J$ = 5.5 Hz, OH), 2.01 (s, 6H, 2 × $CH_3$); $^{13}$C NMR $\delta$ 171.1 (2 × CO), 159.3−113.8 (PhC), 73.2 ($OCH_2Ph$), 69.1 (C*C*$H_2O$), 62.9 (2 × $CH_2$-OAc), 62.4 ($CH_2OH$), 55.2 ($OCH_3$), 43.8 (qC), 20.8 (2 × $CH_3$). EI HRMS: *m*/*z* calcd for $C_{17}H_{24}O_7$ 340.1522, found 340.1517.

**2-Hydroxymethyl-2-[3-*p*-methoxyphenyl-2-oxapropyl]-1,3-propanediol (16).**[42] 2,2-Bis(acetoxymethyl)-3-(*p*-methoxybenzyloxy)propanol (**15**, 2.88 g, 8.5 mmol) was dissolved in dry methanol (50 mL). A catalytic amount of sodium metal (15 mg) was added and the reaction mixture was stirred for 1 h. The reaction mixture was neutralized with Amberlite IR-120 ($H^+$), then filtered. The ion-exchange resin was washed with methanol (2 × 15 mL) and the combined filtrate and washings were concentrated. The crude product was purified by flash column chromatography (pure EtOAc), $R_f$ 0.47) to afford the title compound **16** (1.96 g, 90%) as a white solid. Mp 57−58 °C; $^1$H NMR $\delta$ 7.23−6.86 (m, 4H, PhH), 4.42 (s, 2H, $OCH_2Ph$), 3.80 (s, 6H, 3 × C*H*$_2$OH), 3.66 (s, 3H, $OCH_3$), 3.44 (s, 2H, $CCH_2O$); $^{13}$C NMR $\delta$ 159.6−114.1 (PhC), 73.7 ($OCH_2Ph$), 72.2 (C*C*$H_2O$), 64.4 (3 × $CH_2OH$), 55.5 ($OCH_3$), 45.2 (qC). EI HRMS: *m*/*z* calcd for $C_{13}H_{20}O_5$ 256.1311, found 256.1317.

**2-(*p*-Methoxyphenyl)-5,5-bis[(prop-2-ynyloxy)methyl]-1,3-dioxane (18).** To a stirred solution of 5,5-bis(hydroxymethyl)-2-(*p*-methoxyphenyl)-1,3-dioxane (**13**)[54] (2.5 g, 8.9 mmol) in dry DMF (70 mL) was added NaH (1.17 g, 29.4 mmol, 60% in mineral oil) in portions at 0 °C. After 30 min propargyl bromide (3.46 g, 24.5 mmol, 80% in toluene) was added and the reaction mixture was allowed to stir for 4 h at room temperature. Water (35 mL) was added and the product was extracted with $Et_2O$ (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The crude product was purified by flash column chromatography (EtOAc−hexane (1:4), $R_f$ 0.53) to yield the title compound as a pale yellow oil (2.9 g, 91%). $^1$H NMR $\delta$ 6.85−7.40 (m, 4H, PhH), 5.35 (s, 1H, acetal H), 4.18, 4.08 (2d, 4H, $J$ = 2.4 Hz, 2 × propargylic $CH_2$), 4.08, 3.33 (2s, 4H, 2 × exocyclic $CH_2$), 4.07, 3.84 (AB q, 4H, $J$ = 12.1 Hz, dioxane $CH_2$), 3.75 (s, 3H, $OCH_3$), 2.45, 2.44 (2 overlapping triplets, 2H, 2 × acetylenic H); $^{13}$C NMR $\delta$ 160.1−113.7 (PhC), 101.7 (acetal C), 80.1, 79.7, 74.8, 74.5 (acetylenic carbons), 69.9 (C-4 and C-6, dioxane), 69.8, 68.7 (2 × exocyclic $CH_2$), 58.8 (2 × propargylic $CH_2$), 55.3 ($OCH_3$), 38.5 (qC). EI HRMS: *m*/*z* calcd for $C_{19}H_{22}O_5$ 330.1467, found 330.1460.

**3-(*p*-Methoxybenzyloxy)-2,2-bis[(prop-2-ynyloxy)methyl]propanol (19).** To a stirred solution of 2-(*p*-methoxyphenyl)-5,5-bis-[(prop-2-ynyloxy)methyl]-1,3-dioxane (**18**, 2.5 g, 7.6 mmol, dried by coevaporation with dry toluene) in dry dichloromethane (50 mL) under nitrogen was added $Et_3SiH$ (9.1 mmol, 1.45 mL) and the reaction mixture was cooled to −78 °C. $EtAlCl_2$ (1.8 M in toluene, 13 mmol, 7 mL) was added dropwise and the reaction mixture was stirred at −78 °C for 40 min and quenched with saturated $NaHCO_3$ (100 mL). The resulting mixture was extracted with dichloromethane (5 × 50 mL) and the combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (EtOAc−hexane (1:3), $R_f$ 0.32) to afford the title compound as a pale yellow oil (1.12 g, 72%). $^1$H NMR $\delta$ 7.23−6.85 (m, 4H, PhH), 4.42 (s, 2H, $OCH_2Ph$), 4.10 (d, 4H, $J$ = 2.4 Hz, 2 × propargylic $CH_2$), 3.78 (s, 3H, $OCH_3$), 3.69 (d, 2H, $J$ = 6.2 Hz, C*H*$_2$OH), 3.55 (s, 4H, 2 × $CCH_2O$), 3.49 (s, 2H, $CH_2$-OBn), 2.67 (t, 1H, $J$ = 6.3 Hz, OH), 2.43 (t, 2H, $J$ = 2.4 Hz, 2 × acetylenic H); $^{13}$C NMR $\delta$ 159.3−113.9 (PhC), 79.9, 74.6 (acetylenic carbons), 73.3 ($OCH_2Ph$), 70.5 ($CH_2OBn$), 70.2 (2 × C*C*$H_2O$), 65.2 ($CH_2OH$), 58.8 (2 × propargylic $CH_2$), 55.3 ($OCH_3$), 44.9 (qC). EI HRMS: *m*/*z* calcd for $C_{19}H_{24}O_5$ 332.1624, found 332.1616.

**1-(*p*-Methoxybenzyloxy)-3-(prop-2-ynyloxy)-2,2-bis(prop-2-ynyloxy)methyl]propane (17). Method A:** To a stirred solution of 2-hydroxymethyl-2-[3-*p*-methoxyphenyl-2-oxapropyl)]-1,3-propanediol (**16**, 0.29 g, 1.1 mmol) in dry DMF (50 mL) was added NaH (0.20 g, 5.1 mmol, 60% in mineral oil) in portions at 0 °C. After 30 min, propargyl bromide (0.65 g, 4.5 mmol, 80% in toluene) was added and the reaction mixture was allowed to stir for 5 h at room temperature. Water (25 mL) was added and the product was extracted with $Et_2O$ (4 × 40 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The crude product was purified by flash column chromatography on silica gel (EtOAc−hexane (1:3), $R_f$ 0.74) to yield the title compound as a yellow oil (0.32 g, 78%). $^1$H NMR $\delta$ 7.28−6.87 (m, 4H, PhH), 4.43 (s, 2H, $OCH_2Ph$), 4.10 (d, 6H, $J$ = 2.4 Hz, 3 × propargylic $CH_2$), 3.80 (s, 6H, 3 × $CCH_2O$), 3.54 (s, 3H, $OCH_3$), 3.46 (s, 2H, $CH_2OBn$), 2.40 (t, 3H, $J$ = 2.1 Hz, 3 × acetylenic H); $^{13}$C NMR $\delta$ 159.1−113.7 (PhC), 80.2, 74.3 (acetylenic carbons), 73.0 ($OCH_2Ph$), 69.2 (C*C*$H_2O$), 68.9 ($CH_2OBn$), 58.8 (3 × propargylic $CH_2$), 55.3 ($OCH_3$), 45.1 (qC). EI HRMS: *m*/*z* calcd for $C_{22}H_{26}O_5$ 370.1780, found 370.1775.

**Method B:** To a stirred solution of 3-(*p*-methoxybenzyloxy)-2,2-bis[(prop-2-ynyloxy)methyl]propanol (**19**, 0.76 g, 2.3 mmol) in dry DMF (20 mL) was added NaH (0.11 g, 2.8 mmol, 60% in mineral oil) in portions at −10 °C. After the reaction mixture had been stirred for 20 min, propargyl bromide (0.43 g, 2.9 mmol, 80% in toluene) was added and the reaction mixture was allowed to warm and then was stirred for 8 h. Water (10 mL) was added and the product was extracted with $Et_2O$ (3 × 35 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The crude product was purified as in method A, yield 0.69 g, 81%.

**2-Phenyl-5,5-bis(prop-2-ynyloxymethyl)-1,3-dioxane (20).** To a stirred solution of 5,5-bis(hydroxymethyl)-2-phenyl-1,3-dioxane[55] (2.5 g, 11.2 mmol) in dry DMF (150 mL) was added NaH (1.34 g, 33.6 mmol, 60% in mineral oil) in portions at 0 °C. After 30 min, propargyl bromide (4.17 g, 28 mmol, 80% in toluene) was added and the reaction mixture was allowed to stir for 4 h at room temperature. Water (15 mL) was added and the product was extracted with $Et_2O$ (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The crude product was purified by flash column chromatography (EtOAc−hexane (1:4), $R_f$ 0.53) to yield the title compound as a pale yellow oil (3.1 g, 92%). $^1$H NMR $\delta$ 7.49−7.32 (m, 5H, PhH), 5.39 (s, 1H, acetal H), 4.16, 4.06 (2d, 4H, $J$ = 2.4 Hz, 2 × propargylic $CH_2$), 4.08, 3.84 (AB q, 4H, $J$ = 11.6 Hz, dioxane $CH_2$), 4.07, 3.83 (2s, 4H, 2 × exocyclic $CH_2$), 2.44, 2.43 (2 overlapping triplets, 2H, 2 × acetylenic H); $^{13}$C NMR $\delta$ 138.3−126.2 (PhC), 101.7 (acetal C), 79.9, 79.6, 74.9, 74.5 (4 × acetylenic carbons), 69.8 (C-4 and C-6, dioxane), 69.8, 68.6 (2 × exocyclic $CH_2$), 58.7 (2 × propargylic

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$CH_2$), 38.5 (qC). EI HRMS: *m*/*z* calcd for $C_{18}H_{20}O_4$ 300.1361, found 300.1360.

**5,5-Bis[5-(*p*-methoxyphenyl)-2-oxapent-4-ynyl]-2-phenyl-1,3-dioxane (22).** A two-necked round-bottomed flask (flame-dried), equipped with a magnetic stirrer bar, was charged with *p*-iodoanisole (21, 0.19 g, 0.81 mmol, 2.2 equiv), CuI (31 mg, 0.16 mmol, 20 mol %), and $Pd(PPh_3)_4$ (93.5 mg, 0.081 mmol, 10 mol %). The flask was evacuated and argon was bubbled through the reaction mixture for 30 min. This process was repeated two times. Anhydrous DMF (1 mL) was added via a syringe followed by anhydrous triethylamine (0.5 mL) and the reaction mixture was stirred at room temperature for 5 min under argon. To the reaction mixture was added di-*O*-propargyl ether **20** (111 mg, 0.37 mmol) in DMF (1 mL) drop by drop over a 20 min period. The reaction mixture was stirred at room temperature for 6 h under argon. The solvent and triethylamine were removed under reduced pressure and the resulting residue was purified by flash column chromatography (hexanes:EtOAc, 4:1, $R_f$ 0.28) to give the title compound as a viscous orange oil (153 mg, 81%). $^1$H NMR $\delta$ 6.76−7.46 (m, 13H, PhH), 5.44 (s, 1H acetal H), 4.41, 4.32 (2s, 4H, 2 × propargylic $CH_2$), 4.16, 3.92 (AB q, 4H, $J$ = 11.9 Hz, dioxane $CH_2$), 3.96, 3.45 (2s, 4H, 2 × exocyclic $CH_2$), 3.78, 3.77 (2s, 6H, 2 × $OCH_3$); $^{13}$C NMR $\delta$ 160.0−114.1 (PhC), 102.0 (acetal C), 86.5, 86.3, 84.2, 83.8 (4 × acetylenic carbons), 70.2 (C-4 and C-6, dioxane), 70.0, 68.8 (2 × exocyclic $CH_2$), 59.9, 59.8 (2 × propargylic $CH_2$), 55.5 ($OCH_3$), 38.9 (qC). LS ESI MS: *m*/*z* calcd for $C_{32}H_{32}O_6$ + Na 535.21, found 535.2.

**9-Mer (23).** A two-necked round-bottomed flask (flame-dried), equipped with a magnetic stirrer bar, was charged with mannoside cluster **11** (364 mg, 0.165 mmol), CuI (9.5 mg, 30 mol %), and $Pd(PPh_3)_4$ (19 mg, 10 mol %). The flask was evacuated and argon was bubbled through the reaction mixture for 30 min. THF (3 mL) was added via a syringe followed by *N*,*N*-diisopropylamine (0.1 mL) and the reaction mixture was stirred at room temperature for 10 min. To the reaction mixture was added tri-*O*-propargyl ether (17) (18 mg, 0.05 mmol) in THF (1 mL) drop by drop over a 20 min period. The reaction mixture was stirred at room temperature for 9 h under argon. The solvent and *N*,*N*-diisopropylamine were removed under reduced pressure and the resulting residue was purified by flash column chromatography (hexanes:EtOAc, 3:1 → 2:1 → 1:1 → 1:2, $R_f$ 0.65 (hexanes:EtOAc, 1:2)) to give the title compound as a pale yellow powder (244 mg, 74%). $[\alpha]_D$ −39.7 (*c* 1.0, $CHCl_3$); $^1$H NMR $\delta$ 8.09−6.70 (complex m, 196H, PhH), 6.12 (t, 9H, $J_{3,4} = J_{4,5}$ = 10.0 Hz, 9 × H-$4_{man}$), 5.95 (dd, 9H, $J_{2,3}$ = 3.3 Hz, 9 × H-$3_{man}$), 5.80 (br s, 9H, 9 × H-$2_{man}$), 5.17 (br s, 9H, 9 × H-$1_{man}$), 4.69 (br d, 9H, $J_{6a,6b}$ = 11.7 Hz, 3.3 Hz, 9 × H-$6b_{man}$), 4.48−4.38 (m, 18H, 9 × H-$6b_{man}$, 9 × H-$5_{man}$), 4.38 (s, 2H, $OCH_2$-Ph), 4.31 (s, 6H, 3 × propargylic $CH_2$), 4.17, 3.76 (m, 18H, $OCH_2$-$CH_2O$), 4.01 (br s, 6H, $CH_2OPh$), 3.90−3.72 (m, 18H, $OCH_2CH_2O$), 3.72 (s, 24H, 12 × C$CH_2O$), 3.66 (s, 3H, $OCH_3$), 3.60 (s, 2H, $CH_2$-OBn); $^{13}$C NMR $\delta$ 166.3, 165.7, 165.6, 165.5 (36 × CO), 159.5−113.8 (PhC), 97.9 (9 × C-$1_{man}$), 86.0, 84.2 (6 × acetylenic carbons), 73.2 ($OCH_2Ph$), 70.8 (9 × $OCH_2CH_2O$), 70.7 (9 × C-$2_{man}$), 70.4 (9 × C-$3_{man}$), 70.0 (12 × C$CH_2O$), 69.6 ($CH_2OBn$), 69.0 (9 × C-$5_{man}$), 67.4 (9 × $OCH_2CH_2O$), 67.4 (3 × $CH_2OPh$), 67.2 (9 × C-$4_{man}$), 63.1 (9 × C-$6_{man}$), 59.9 (3 × propargylic $CH_2$), 55.3 ($OCH_3$), 45.8, 45.5 (4 × qC). MALDI FTICR MS: *m*/*z* calcd for $^{12}C_{378}{}^{13}C_1H_{338}O_{107}$ + Na 6624.093, found 6624.13.

**1,9-Bis(α-D-mannopyranosyloxy)-5-(4-[α-D-mannopyranosyloxy]-2-oxabutyl)-5-(*p*-iodophenoxymethyl)-3,7-dioxanonane (24).** To a stirred solution of cluster **11** (100 mg, 0.045 mmol) in THF (50 mL) and MeOH (25 mL) was added sodium methoxide (0.5 M in MeOH, 5 mL). After the solution was stirred for 4 h, TLC (EtOAc−MeOH−$H_2O$, 10:5:1) showed complete conversion to a product ($R_f$ 0.43), and the reaction mixture was neutralized with Amberlite IR-120 ($H^+$), filtered, and concentrated. The resulting residue was dissolved in $H_2O$ (2 mL) and extracted with $CH_2Cl_2$ (3 × 4 mL), and the aqueous portion was evaporated. The resulting residue was purified by size exclusion chromatography on a Sephadex G-25 column (elution $H_2O$) to afford the completely de-*O*-benzoylated dendron (**24**) as a glassy solid (40 mg, 93%). $[\alpha]_D$ +37.1 (*c* 1.0, $CH_3OH$); $^1$H NMR (methanol-$d_4$, 500.13 MHz) $\delta$ 7.56−6.76 (m, 4H, PhH), 4.85 (d, 3H, $J_{1,2}$ = 1.7 Hz, 3 × H-$1_{man}$), 3.95 (s, 2H, $CH_2OPh$), 3.84−3.72 (m, 12H, 3 × H-$3_{man}$, 3 × H-$6a_{man}$, 3 × H-$6b_{man}$, 3 × H-$2_{man}$), 3.79−3.62 (m, 6H, $OCH_2$-$CH_2O$), 3.64−3.59 (m, 12H, 3 × H-$5_{man}$, 3 × H-$4_{man}$, 3 × $OCH_2$-$CH_2O$), 3.61 (s, 6H, C$CH_2O$); $^{13}$C NMR (methanol-$d_4$,125.77 MHz) $\delta$ 160.7−118.4 (PhC), 101.6 (3 × C-$1_{man}$), 74.5 (3 × C-$5_{man}$), 72.7 (3 × C-$3_{man}$), 72.2 (3 × C-$2_{man}$), 72.0 (3 × $OCH_2CH_2O$), 70.7 (3 × C$CH_2O$), 68.3 ($CH_2OPh$), 67.7 (3 × $OCH_2CH_2O$), 67.2 (3 × C-$4_{man}$), 62.9 (3 × C-$6_{man}$), 46.6 (qC). MALDI FTICR MS: *m*/*z* calcd for $C_{35}H_{57}IO_{22}$ + Na 979.2, found 979.3.

**De-*O*-benzoylated 9-Mer (25).** To a stirred solution of the 9-mer **23** (25 mg, 0.0038 mmol) in THF (25 mL) and MeOH (50 mL) was added sodium methoxide (0.5 M in MeOH, 5 mL). The reaction mixture was stirred for 8 h and neutralized with Amberlite IR-120 ($H^+$), filtered, and concentrated. The resulting residue was dissolved in $H_2O$ (1 mL) and extracted with $CH_2Cl_2$ (3 × 2 mL), and the aqueous portion was evaporated. The resulting residue was purified by size exclusion chromatography on a Sephadex G-25 column (elution $H_2O$) to afford the completely de-*O*-benzoylated dendron (**25**) as a film (10 mg, 91%). $[\alpha]_D$ +23.8 (*c* 1.0, $CH_3OH$); $^1$H NMR (methanol-$d_4$, 500.13 MHz) $\delta$ 8.01−6.88 (m, 16H, PhH), 4.82 (d, 9H, $J_{1,2}$ = 1.7 Hz, 9 × H-$1_{man}$), 4.42 (s, 2H, $OCH_2Ph$), 4.31 (s, 6H, 3 × propargylic $CH_2$), 3.98, (s, 6H, 3 × $CH_2OPh$), 3.84−3.70 (m, 36H, 9 × H-$3_{man}$, 9 × H-$6a_{man}$, 9 × H-$6b_{man}$, 9 × H-$2_{man}$), 3.79−3.56 (m, 54H, 9 × $OCH_2CH_2O$, 9 × H-$5_{man}$, 9 × H-$4_{man}$), 3.62 (s, 24H, 12 × C**C**$H_2O$), 3.58 (s, 3H, $OCH_3$), 3.50 (s, 2H, $CH_2$-OBn); $^{13}$C NMR (methanol-$d_4$,125.77 MHz) $\delta$ 134.5−116.0 (PhC), 101.8 (9 × C-$1_{man}$), 86.5, 84.6 (6 × acetylenic carbons), 74.7 (9 × C-$5_{man}$), 72.8 (9 × C-$3_{man}$), 72.3 (9 × C-$2_{man}$), 72.1 (9 × $OCH_2$-$CH_2O$), 70.8 (12 × C$CH_2O$), 68.8 ($CH_2OBn$), 68.1 (3 × $CH_2OPh$), 67.8 (9 × $OCH_2CH_2O$), 68.8 (9 × C-$4_{man}$), 63.1 (9 × C-$6_{man}$), 58.6 (3 × propargylic $CH_2$), 55.3 ($OCH_3$), 46.3 (4 × qC). MALDI FTICR MS: *m*/*z* calcd for $C_{127}H_{194}O_{71}$ + Na 2878.1, found 2877.8.

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**Supporting Information Available:** $^1$H and $^{13}$C NMR spectra of all products and partial FT-ICR mass spectra of the **23** and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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