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Click Chemistry Inspired Synthesis of Glycoporphyrin Dendrimers

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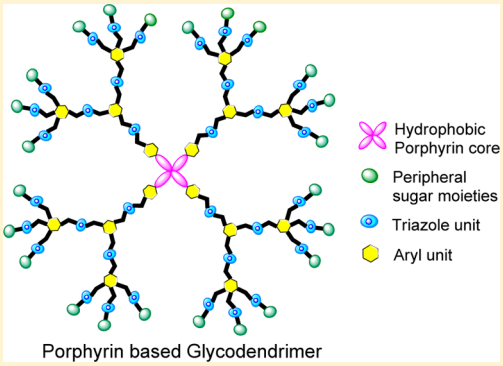
Supporting Information

ABSTRACT: A series of porphyrin-cored glycodendrimers containing 8, 12, 16, and 24 β-D-glucopyranose units at the periphery, have been synthesized by convergent methodology using click chemistry. The structure of developed dendrimers is established by ^{1}H and ^{13}C NMR, IR, MALDI-TOF MS, and SEC analysis. Absorption−emission behavior of dendrimers and its modulation under the influence of the dendritic environment is also investigated.



Porphyrins are essential components of various biological representatives, such as hemoglobin, cytochromes, and vitamin B_{12}, that play crucial roles in several biologically relevant processes on account of their distinct physical and chemical properties, including gas binding and releasing ability.[1] Several porphyrin derivatives possessing interesting photochemical, photophysical, and electrochemical properties have been obtained by suitable substitution of this macrocycle.[2] In this context, large dendrimeric architectures containing a porphyrin moiety surrounded by a variety of peripheral functional units have been developed and explored for various applications.[3] Photodynamic therapy (PDT) is one such interesting application of the porphyrin variants, which is of paramount importance in cancer treatment and has been particularly exploited in porphyrin glycoconjugates.[2b,4] Porphyrin, upon exposure to a particular wavelength of light, generates lethal singlet oxygen that kills tumor cell, whereas sugars installed over this hydrophobic core provide water solubility and increased tumor cell specificity. Therefore, the whole glycoconjugated porphyrin system acts as a promising PDT sensitizer.[5] Apart from this, multiple copies of saccharide with a specific spatial arrangement in glycodendrimers allow their potential application in the study of carbohydrate−protein and carbohydrate−lectin interactions, which enriches the field of nanomedicine.[6] Consequently, with these perspectives, synthesis of glycoporphyrin dendrimers is valuable, which can be brought about either by condensation of carbohydrate-containing benzaldehydes with pyrrole[7] or by the insertion of sugars onto the porphyrin framework.[8] The former method suffers the limitation of lower yields, however, success of the latter depends on the efficacy of the coupling methodology.[7,8]

The Cu(I)-catalyzed click reaction of terminal alkyne and azide presents an attractive strategy in this regard, as it gives a highly regioselective 1,4-disubstituted triazole product in excellent yield under mild reaction conditions.[9] This highly expeditious protocol has been widely applied in carbohydrate chemistry for generating glycoconjugates, such as glycopeptides, glyco-macrocycles, glyco-arrays, glyco-dendrimers, glyco-clusters, and glycopolymers, etc.[10] In the past few years, with the aid of a click reaction, a number of glycodendrimers comprising different peripheral sugars, such as mannose,[11a−d] lactose,[11b−d] fucose,[11c,d] xylose,[11e] and glucose,[11f] adorned over various core units have been developed. Numerous porphyrin dendrimers possessing different peripheral functionalizations have also been successfully constructed using click chemistry.[12] However, reports on porphyrin glycodendrimers is scarce and yet to be explored. Herein, we report the synthesis of glycodendrimers built on a porphyrin core by a convergent synthetic strategy using a click reaction.

A variety of first- and second-generation azide-functionalized glycosylated dendrimeric wedges were prepared and coupled with alkyne-functionalized *meso*-positions of the porphyrin core using a click reaction to obtain glycodendrimers. Glycosylated azides **13**, **14**, **16**, and **18** were obtained in a multistep synthetic strategy starting from methyl 3,5-dihydroxy benzoate **5** and methyl 3,4,5-trihydroxy benzoate **6** (Scheme 1).[11f,13] Free hydroxyl groups of each of the compounds **5** and **6** were propargylated with propargyl bromide to obtain **7** and **8**, which, on further reduction with LAH, followed by chlorination with thionyl chloride, furnished 3,5-bis(propargyloxy)benzyl chloride **9** and 3,4,5-tris(propargyloxy)benzyl chloride **10**, respectively. The reaction of **9** and **10** with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide in the presence of $CuSO_4$/sodium L-ascorbate (NaAsc) in THF/water afforded first-generation dendritic chlorides **11** and **12**, respectively, in good yields. Their formation was examined by the ^{1}H NMR spectrum, which showed the characteristic triazole proton singlet at δ 7.92

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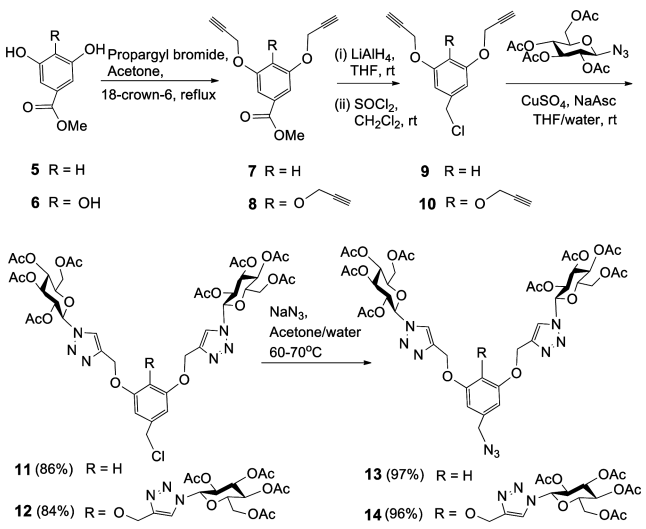
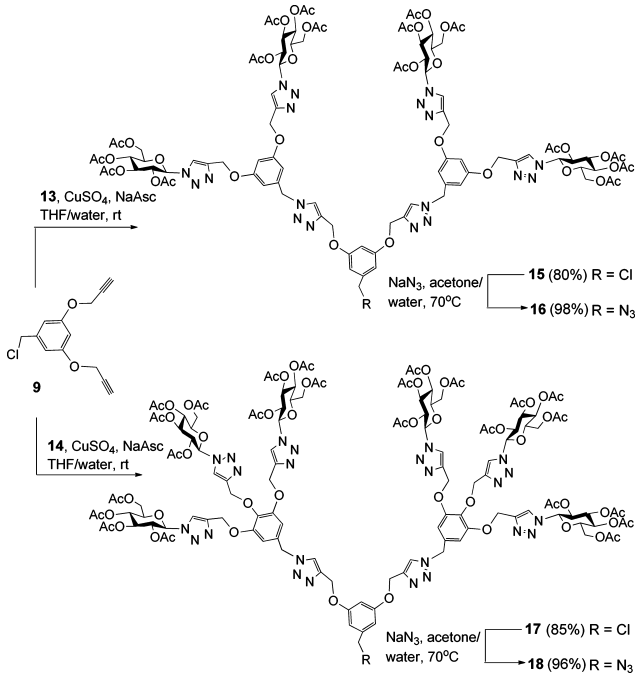
Scheme 1. Synthesis of First-Generation Azide-Functionalized Dendrons



Scheme 2. Synthesis of Second-Generation Dendritic Azide



for **11**, whereas, for **12**, more downfield signals were observed at δ 8.45 and 8.33 in a 2:1 ratio. Two distinct triazolyl singlets and anomeric doublets identified in **12** corresponded to two chemically nonequivalent triazolyl glycosides in a 2:1 ratio. In ^{13}C NMR, the peaks appeared at δ 121.3 and 144.6 for **11** and δ 122.0, 122.6, and 144.8 for **12**, which confirmed the presence of triazolyl carbons. In the next step, azidation of **11** and **12** was brought about by their reaction (at 70 °C) with NaN_3 in acetone/water to generate dendritic azides **13** and **14** in quantitative yields. This transformation was established by IR spectra of **13** and **14**, where an intense peak characteristic to the azide functionality appeared at around 2105 cm^{-1}. In ^{1}H NMR, this is further followed by the upfield shifting of the $-CH_2Cl$ singlet upon $-CH_2N_3$ conversion.

After synthesizing first-generation azides, utilizing them, we next attempted the synthesis of second-generation dendritic azides. The azide-functionalized dendrons **13** and **14** (2 equiv) were clicked with 3,5-bis(propargyloxy)benzyl chloride **9** to afford the respective dendritic chloride **15** and **17** (Scheme 2). The appearance of a new triazolyl peak at δ 7.63 for **15** and δ 7.67 for **17** with integrals corresponding to two protons confirmed this click transformation. Subsequently, these two chlorides were quantitatively converted into their respective azides **16** and **18**, and characterized on the basis IR and NMR spectroscopy.

We next prepared the click counterpart of dendritic azides, that is, compound **19**, for which the porphyrin core obtained by *Lindsey*-type condensation[14] was primarily functionalized with the propargyl group to obtain a tetra-alkyne armed porphyrin macrocycle and then metalated with Zn via refluxing in the presence of zinc acetate in chloroform/methanol. Protection of the porphyrin by Zn(II) complexation is essential prior to the Cu(I)-catalyzed click reaction, since Zn insertion sufficiently stabilizes the system against any replacement by Cu(II) ions.[15]

Finally, the tetrasubstituted porphyrin **19** was utilized as the starting material for the coupling of azidic wedges **13**, **14**, **16**, and **18** each, using $CuSO_4$/NaAsc in THF/water to derive their respective glycoporphyrin dendrimers **1a**, **2a**, **3a**, and **4a** (Scheme 3). The column chromatographic purification afforded a good to satisfactory yield of **1a**–**4a** (40–64%) without any significant involvement of steric congestion imposed by large azidic wedges.

The symmetrical structures of **1a**–**4a** and their extensive spectral studies (NMR, IR, MALDI-TOF MS, and size exclusion chromatography (SEC) techniques) led to an unambiguous structural determination. Synthesis of **1a**–**4a** was evidenced by the appearance of newly formed triazolyl protons at δ 7.43, 7.69, 7.58, and 7.89, respectively, in their ^{1}H NMR spectrum. IR spectral analysis confirmed the completion of reaction since characteristic peaks corresponding to alkynyl and azide functionalities were no longer seen in the spectrum. SEC analysis of the dendrimers ascertained a well-defined molecular structure for all the four glycodendrimers with a low polydispersity ranging between 1.01 and 1.03 and an implicated dendrimer size growth from **1a**–**4a** having a retention time of 29.88, 29.63, 28.78, and 28.57 min for **1a**–**4a**, respectively (Figure 1).

The structure of developed glycodendrimers and their purity was also elucidated by MALDI-TOF MS. In all the cases, most intense peak was observed for $[M + H - Zn]^+$ species along with $[M + H]^+$ peak that suggested the loss of Zn metal under ionization conditions. Also, with increasing generations of dendrimers, a poor quality of the baseline, broadened peaks, and fragmentation in compounds was noticed due to the requirement of higher laser power in MALDI analysis.[11c] In this way, after complete characterization of **1a**–**4a**, the acetyl protection of sugar moieties residing over dendrimers was quantitatively removed under slightly modified Zemplen's transesterification conditions[16] to obtain water-soluble final products (**1b**–**4b**). The structure of these compounds was determined by MALDI-TOF MS analysis only.

Absorption and emission studies of protected dendrimers were performed in order to investigate the effect of dendritic environments over the photophysical properties of the porphyrin core. UV–visible spectra of **1a**–**4a** recorded in dichloromethane showed typical metalloporphyrin behavior.[17] All the dendrimers displayed the characteristic soret band in the

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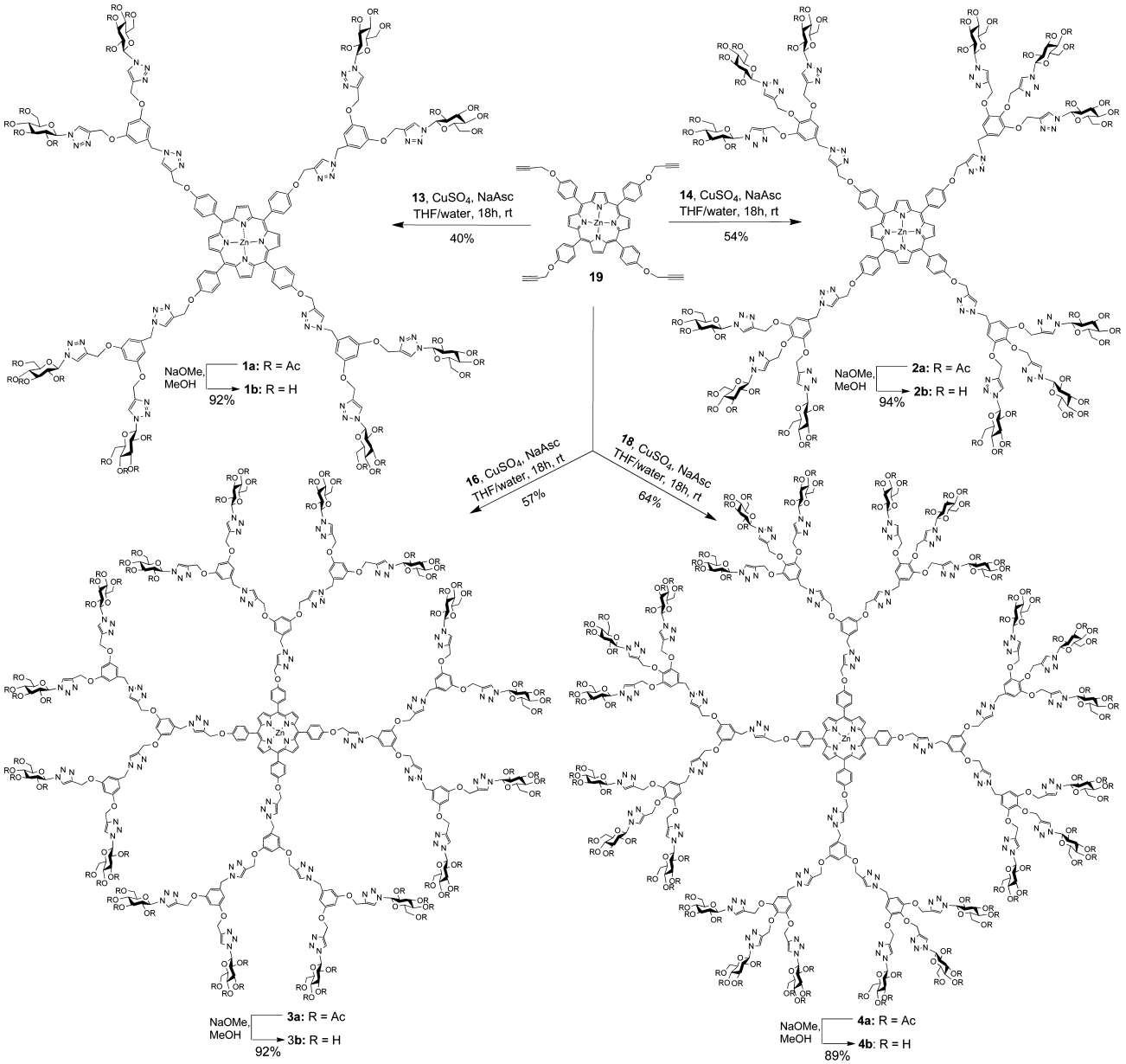
Scheme 3. Synthesis of First- and Second-Generation Glycoporphyrin Dendrimers



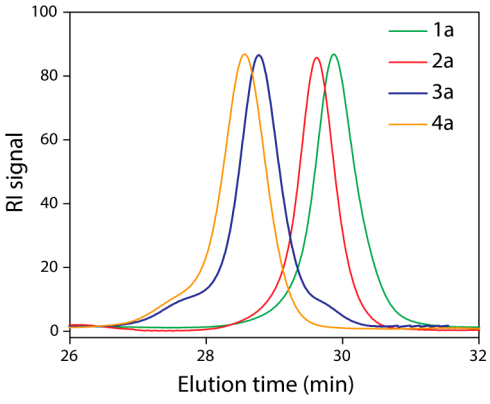


Figure 1. SEC diagrams of glycoporphyrin dendrimers.

426−428 nm range along with two Q bands in 557−561 and 599−603 nm ranges (Figure 2). On going from first-generation to second-generation, a small red shift (2−3 nm) along with an insignificant decrease in extinction coefficient was noticed in absorption maxima. However, in comparison to reference compound **19**, a remarkable red shift of almost 10 nm in Q absorption bands was observed. An absorption study of deprotected dendrimers (**1b**−**4b**) was done in DMSO, water, and DMSO/water mixed systems of various compositions. All of them showed an intense soret band in DMSO, and no significant change in spectra was observed upon successively increasing the percentage of water in DMSO. This result implicated a single molecular dispersion of dendrimers in solvents. However, a gradual decrease in peak intensity and peak broadening was found when the water content goes beyond 50%. UV−vis spectra studied in water still exhibited the original soret band, which suggested a good water solubility of **1b**−**4b** arising due to effective shielding of the hydrophobic porphyrin and aromatic systems by hydrophilic peripheral sugars. Also, a little red shift along with a strict peak broadening

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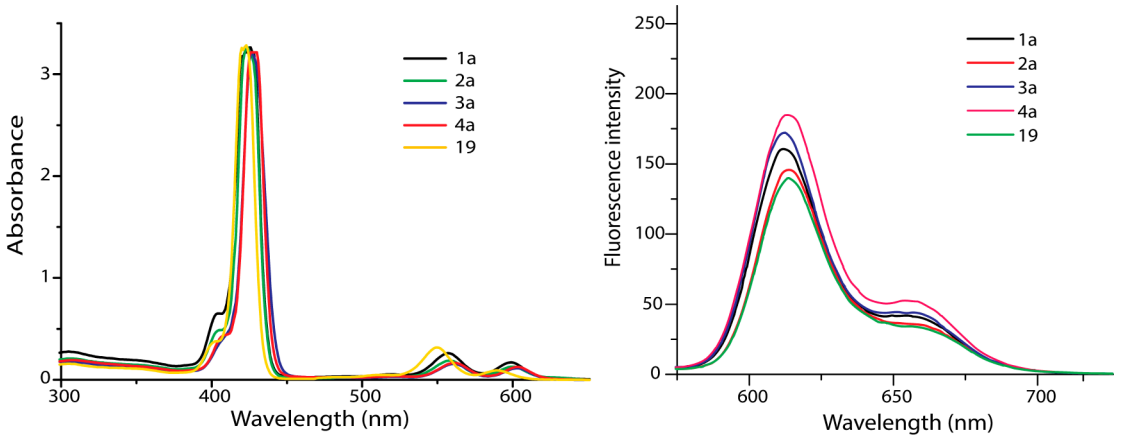

Figure 2. Absorption and emission spectra of dendrimers **1a**−**4a** in dichloromethane.

attributable to strong aggregations via hydrophobic interactions was observed in water. A fluorescence study of the dendrimers **1a**−**4a** was also carried out, which showed a slightly higher fluorescence intensity in comparison to reference **19**, but in all, a negligible difference in emission behavior of dendrimers was observed under dendritic influences (Figure 2) (see the Supporting Information, Table 1, p 55).

In conclusion, the click reaction coupling of tetrafurcated propargylated porphyrin with azide-functionalized glycosylated wedges allowed the efficient synthesis of G(1) and G(2) glycodendrimers. Synthesized dendrimers were characterized by ^{1}H and ^{13}C NMR, MALDI-TOF MS, and SEC analysis. The specific topology attained by sugar moieties over the porphyrin core and good water solubility of **1b**−**4b** make them promising for a lectin binding study. In the absorption study of dendrimers **1a**−**4a**, a significant red shifting in Q bands was observed, which is encouraging toward evaluation of their behavior as a photosensitizer in PDT.

EXPERIMENTAL SECTION

General Methods. All reagents and solvents used were of pure analytical grade. Thin-layer chromatography (TLC) was performed on 60 F254 silica gel, precoated on aluminum plates and visualized either by a UV lamp or by spraying with methanolic H_2SO_4 solution and subsequent charring by heating at 100 °C. Flash column chromatography was performed using silica gel 60 (230−400 mesh). ^{1}H and ^{13}C spectra were recorded at 300 and 75 MHz spectrometers, respectively, using the internal standard tetramethylsilane (TMS). Chemical shifts are given in parts per million, and J values are in hertz. Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) was performed with a 2,5-dihydroxy benzoic acid (DHB) matrix. The number-average molecular weight (M_n) and polydispersity index (M_w/M_n) were determined in DMF at 40 °C with a flow rate of 0.5 mL/min on two polystyrene gel columns. The columns were calibrated against seven poly(methyl methacrylate) (PMMA) standard samples. Electronic absorption and emission spectra were obtained in air-equilibrated solvents at room temperature.

Experimental Procedure for Cu(I)-Catalyzed Azide−Alkyne Cycloaddition (A). Polypropargylated moieties (1.0 equiv) and azide-functionalized compounds (1.2 equiv per azide functionalization), $CuSO_4{\cdot}5H_2O$ (0.3 equiv per propargyl group), and sodium L-ascorbate (0.3 equiv per propargyl group) were stirred at room temperature for 18 h in THF/water. After confirming the completion of reaction on TLC, ethyl acetate was added to the reaction mixture and washed with saturated aqueous NH_4Cl (2 × 10 mL), water (10 mL), and brine (10 mL). The separated organic layer was dried over Na_2SO_4 and evaporated to obtain the crude product. Purification was done by flash chromatography.

Experimental Procedure for Azidation of Dendritic Chlorides (B). Dendritic chloride (1.0 equiv) and NaN_3 (1.5 equiv) were heated at 70 °C in acetone/water (10 mL/10 mL) for 4 h. After completion of reaction, acetone was evaporated and dichloromethane was added in the reaction mixture. The organic layer was washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, and evaporated to obtain the azide-functionalized product with good purity.

Glycoconjugate Dendron ***11***. Compound **9** (0.4 g, 1.70 mmol, 1.0 equiv) was reacted with 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl azide (1.53 g, 4.1 mmol, 2.4 equiv), $CuSO_4{\cdot}5H_2O$ (0.26 g, 1.0 mmol, 0.6 equiv), and sodium L-ascorbate (0.20 g, 1.0 mmol, 0.6 equiv) in THF/water (10 mL/10 mL) using procedure **A**. Pure compound **11** was obtained by silica gel column chromatography (hexane/ethyl acetate) as a white solid; Yield 1.44 g, 86%; R_f = 0.52 hexane/EtOAc (1:1); IR (υ, cm^{-1}) 3483, 3094, 2925, 1753; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.92 (s, 2 H), 6.64 (s, 3 H), 5.91 (d, 2 H, J = 8.7 Hz), 5.46−5.42 (m, 4 H), 5.30−5.20 (m, 6 H), 4.51 (s, 2 H), 4.31 (dd, 2 H, J = 12.6, 4.8 Hz), 4.17−4.13 (m, 2 H), 4.04−4.01 (m, 2 H), 2.08, 2.04 (each s, 18 H), 1.86 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5, 169.9, 169.4, 168.9, 159.4, 144.6, 139.8, 121.3, 108.2, 101.7, 85.8, 75.1, 72.6, 70.3, 67.7, 61.9, 61.5, 46.0, 20.7, 20.5, and 20.1 ppm.

Glycoconjugate Dendron ***12***. Compound **10** (0.4 g, 1.39 mmol, 1.0 equiv) was reacted with 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl azide (1.86 g, 4.98 mmol, 3.6 equiv), $CuSO_4{\cdot}5H_2O$ (0.31 g, 1.25 mmol, 0.9 equiv), and sodium L-ascorbate (0.24 g, 1.25 mmol, 0.9 equiv) in THF/water (10 mL/10 mL) using procedure **A**. The compound **12** was purified by silica gel column chromatography (hexane/ethyl acetate) as a white solid; Yield 1.64 g, 84%; R_f = 0.42 hexane/EtOAc (3:7); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.45 (s, 2 H), 8.33 (s, 1 H), 6.71 (s, 2 H), 6.23 (d, 1 H, J = 9.6 Hz), 5.97 (d, 2 H, J = 9.3 Hz), 5.65−5.38 (m, 9 H), 5.28−5.20 (m, 6 H), 4.53 (s, 2 H), 4.31 (dd, 3 H, J = 12.3, 4.5 Hz), 4.18−4.15 (m, 4 H), 4.05 (m, 2 H), 2.09, 2.05, 2.04, 2.01 (each s, 27 H), 1.86, 1.80 (each s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5 170.0, 169.5, 169.0, 168.9, 152.1, 144.8, 137.4, 133.6, 122.6, 122.0, 107.8, 85.7, 85.4, 75.0, 74.7, 73.0, 72.7, 70.4, 70.1, 67.8, 66.0, 63.1, 61.6, 60.4, 46.3, 21.0, 20.6, 20.5, 20.2, and 20.1 ppm.

Glycoconjugate Dendron ***13***. Compound **11** (1.44 g, 1.47 mmol, 1.0 equiv) and NaN_3 (0.14 g, 2.2 mmol, 1.5 equiv) was reacted in acetone/water (10 mL/10 mL) according to method **B** to afford compound **13** as a white solid; Yield 1.41 g, 97%; R_f = 0.52 hexane/EtOAc (1:1); IR (υ, cm^{-1}) 3482, 3153, 2925, 2104, 1756; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.93 (s, 2 H), 6.65−6.57 (m, 3 H), 5.92 (d, 2 H, J = 8.4 Hz), 5.50−5.40 (m, 4 H), 5.29−5.21 (m, 6 H), 4.34−4.28 (m, 4 H), 4.17−4.13 (m, 2 H), 4.05−4.02 (m, 2 H), 2.08, 2.04 (each s, 18 H), 1.86 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5, 169.9, 169.3, 168.9, 159.5, 144.6, 138.0, 121.3, 107.7, 101.5, 85.8, 75.1, 72.6, 70.3, 67.7, 61.9, 61.5, 54.6, 20.6, 20.5, and 20.1 ppm.

Glycoconjugate Dendron ***14***. Compound **12** (1.64 g, 1.16 mmol, 1.0 equiv) was heated with NaN_3 (0.11 g, 1.75 mmol, 1.5 equiv) in acetone/water (10 mL/10 mL) according to method **B** to afford

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compound **14** as a white solid; Yield 1.58 g, 96%; R_f = 0.42 hexane/EtOAc (3:7); IR (υ, cm^{-1}) 3478, 3082, 2960, 2106, 1749; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.46 (s, 2 H), 8.32 (s, 1 H), 6.64 (s, 2 H), 6.23 (d, 1 H, J = 9.6 Hz), 5.97 (d, 2 H, J = 9.3 Hz), 5.67−5.38 (m, 9 H), 5.28−5.20 (m, 6 H), 4.29 (m, 5 H), 4.18−4.05 (m, 6 H), 2.09, 2.05, 2.04, 2.00 (each s, 27 H), 1.86, 1.81 (each s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5, 170.0, 169.5, 168.9, 152.4, 144.9, 137.3, 131.7, 122.0, 107.4, 85.8, 85.4, 75.1, 74.8, 72.8, 70.5, 70.1, 67.8, 66.0, 63.1, 61.6, 54.7, 20.6, 20.5, and 20.1 ppm.

Glycoconjugate Dendron ***15***. Compound **9** (0.1 g, 0.43 mmol, 1.0 equiv) was stirred at room temperature with **13** (1.0 g, 1.02 mmol, 2.4 equiv), $CuSO_4{\cdot}5H_2O$ (0.06 g, 0.26 mmol, 0.6 equiv), and sodium L-ascorbate (0.05 g, 0.26 mmol, 0.6 equiv) in THF/water (10 mL/10 mL) using procedure **A**. The compound was purified by silica gel column chromatography ($CHCl_3$/MeOH) as a white solid; Yield 0.75 g, 80%; R_f = 0.56 $CHCl_3$/MeOH (97:3); IR (υ, cm^{-1}) 3488, 3145, 2942, 1755; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.94 (s, 4 H), 7.63 (s, 2 H), 6.63−6.51 (m, 9 H), 5.91 (d, 4 H, J = 8.7 Hz), 5.49−5.39 (m, 12 H), 5.30−5.15 (m, 16 H), 4.47 (s, 2 H), 4.30 (dd, 4 H, J = 12.6, 4.8 Hz), 4.16−4.13 (m, 4 H), 4.04−4.00 (m, 4 H), 2.07, 2.05, 2.02 (each s, 36 H), 1.82 (s, 12 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5, 169.9, 169.4, 168.9, 159.7, 159.5, 150.4, 144.3, 136.9, 123.0, 121.5, 108.1, 107.8, 101.8, 100.3, 85.8, 75.1, 72.6, 70.3, 67.7, 61.8, 61.5, 44.6, 20.7, 20.6, and 20.1 ppm.

Glycoconjugate Dendron ***16***. Compound **15** (0.75 g, 0.34 mmol, 1.0 equiv) was heated with NaN_3 (0.03 g, 0.58 mmol, 1.5 equiv) in acetone/water (6 mL/6 mL) according to method **B** to afford compound **16** as a white solid; Yield 0.73 g, 98%; R_f = 0.56 $CHCl_3$/MeOH (97:3); IR (υ, cm^{-1}) 3476, 3143, 2926, 2104, 1754; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.94 (s, 4 H), 7.62 (s, 2 H), 6.64−6.51 (m, 9 H), 5.91 (d, 4 H, J = 8.4 Hz), 5.50−5.39 (m, 12 H), 5.30−5.15 (m, 16 H), 4.33−4.13 (m, 10 H) 4.04−4.01 (m, 4 H), 2.07, 2.05, 2.02 (each s, 36 H), 1.83 (s, 12 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5, 169.9, 169.4, 168.9, 159.7, 159.6, 152.2, 144.2, 137.8, 136.9, 123.0, 121.5, 107.7, 107.6, 101.8, 85.7, 75.1, 72.6, 70.3, 67.6, 62.1, 61.7, 61.5, 54.6, 54.0, 20.5, and 20.1 ppm.

Glycoconjugate Dendron ***17***. Compound **9** (0.1 g, 0.43 mmol, 1.0 equiv) was reacted with compound **14** (1.45 g, 1.02 mmol, 2.4 equiv), $CuSO_4{\cdot}5H_2O$ (0.06 g, 0.26 mmol, 0.6 equiv), and sodium L-ascorbate (0.05 g, 0.26 mmol, 0.6 equiv) in THF/water (10 mL/10 mL) using procedure **A**. Pure compound **17** was obtained by silica gel column chromatography ($CHCl_3$/MeOH) as a white solid; Yield 1.11 g, 85%; R_f = 0.64 $CHCl_3$/MeOH (95:5); IR (υ, cm^{-1}) 3478, 3139, 2937, 1755; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.47 (s, 4 H), 8.36 (s, 2 H), 7.67 (s, 2 H), 6.64−6.61 (m, 7 H), 6.23 (d, 2 H, J = 9.6 Hz), 5.97 (d, 4 H, J = 9.3 Hz), 5.67−5.40 (m, 18 H), 5.46−5.17 (m, 20 H), 4.49 (s, 2 H), 4.34−4.28 (m, 6 H), 4.18−4.04 (m, 12 H), 2.09, 2.04, 2.02, 1.99 (each s, 54 H), 1.81, 1.79 (each s, 18 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5, 170.0, 169.5, 169.0, 168.9, 159.4, 152.4, 144.8, 144.5, 144.1, 139.7, 137.6, 130.7, 123.1, 122.7, 122.2, 108.1, 107.4, 101.8, 85.7, 85.4, 75.0, 74.7, 72.9, 72.7, 70.4, 70.1, 67.7, 66.0, 62.9, 62.0, 61.6, 54.1, 46.1, 20.6, 20.5, and 20.1 ppm.

Glycoconjugate Dendron ***18***. Compound **15** (1.11 g, 0.36 mmol, 1.0 equiv) was heated with NaN_3 (0.04 g, 0.54 mmol, 1.5 equiv) in acetone/water (6 mL/6 mL) according to method **B** to afford **18** as a white solid; Yield 1.07 g, 96%; R_f = 0.64 $CHCl_3$/MeOH (95:5); IR (υ, cm^{-1}) 3484, 3144, 2941, 2105, 1755; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.47 (s, 4 H), 8.35 (s, 2 H), 7.67 (s, 2 H), 6.62, 6.58 (each s, 7 H), 6.23 (d, 2 H, J = 9.6 Hz), 5.97 (d, 4 H, J = 9.0 Hz), 5.67−5.36 (m, 18 H), 5.30−5.17 (m, 20 H), 4.34−4.26 (m, 8 H), 4.18−4.05 (m, 12 H), 2.13, 2.09, 2.04, 2.02, 1.99, 1.96 (each s, 54 H) 1.82, 1.79 (each s, 18 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5, 170.0, 169.5, 169.0, 168.9, 159.6, 152.4, 144.8, 144.5, 144.1, 137.8, 137.6, 130.6, 123.0, 122.7, 122.2, 107.6, 107.4, 101.6, 85.7, 85.3, 75.0, 74.7, 72.9, 72.7, 70.4, 70.0, 67.7, 66.0, 62.9, 62.0, 61.6, 54.6, 54.1, 20.6, and 20.1 ppm.

5,10,15,20-Tetrakis(4-propargyloxyphenyl)-Zn(II)-porphyrin ***19***. 5,10,15,20-Tetrakis(4-hydroxyphenyl)-porphyrin (0.5 g, 0.737 mmol, 1.0 equiv) was dissolved in anhydrous DMF under an argon atmosphere, and then K_2CO_3 (1.0 g, 7.374 mmol, 10 equiv) and propargyl bromide (0.39 mL, 4.42 mmol, 6 equiv) were added. The reaction was allowed to stir at room temperature for overnight. After completion of reaction, DMF was evaporated under reduced pressure and extracted with the CH_2Cl_2/H_2O system at least three times to remove excess K_2CO_3. The organic layer was dried over Na_2SO_4, filtered, and concentrated to obtain a purple solid. The crude mixture was further purified by flash chromatography over SiO_2 (hexane/ethyl acetate) to give 5,10,15,20-tetrakis(4-propargyloxyphenyl)-porphyrin; Yield 0.58 g, 95%; UV−vis abs (CH_2Cl_2) λ_{max} (nm) = 420, 517, 554, 592, 647; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.85 (s, 8 H), 8.11 (d, 8 H, J = 8.4 Hz), 7.32 (d, 8 H, J = 8.4 Hz), 4.94 (s, 8 H), 2.67 (s, 4 H), −2.76 (s, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.4, 135.5, 119.6, 113.1, 78.7, 75.9, and 56.1 ppm. A solution of this tetrapropargyl-functionalized porphyrin (0.58 g, 0.702 mmol, 1.0 equiv) in $CHCl_3$ (7 mL) and a solution of zinc acetate (0.77 g, 3.514 mmol, 5 equiv) in methanol (7 mL) were mixed and refluxed under N_2 for 2−3 h. The reaction mixture was concentrated by vacuum evaporation, and CH_2Cl_2 was added. The organic layer was washed with water (3 × 20 mL), dried over Na_2SO_4, filtered, and concentrated. The crude mixture was further purified by flash chromatography over SiO_2 (hexane/ethyl acetate) to give pure compound **19** as a purple solid; Yield 0.61 g, 98%; UV−vis abs (CH_2Cl_2) λ_{max} (nm) = 422, 550, 590; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.86 (s, 8 H), 8.13 (d, 8 H, J = 8.4 Hz), 7.36 (d, 8 H, J = 8.4 Hz), 4.99 (m, 8 H), 2.70 (s, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.3, 150.4, 136.1, 135.4, 131.9, 120.6, 113.0, 78.7, 75.8, and 56.2 ppm.

Experimental Procedure for Deprotection of Glycodendrimers. The acetyl-protected glycodendrimer was dissolved in dry MeOH (if needed, a few drops of CH_2Cl_2 added), and a solution of sodium methoxide (1 M in MeOH, 5 μL per 30 min period) was added (till pH 9) and stirred for overnight. Further, the reaction mixture was neutralized by an ion-exchange resin (Amberlite IR 120 H^+), filtered, and evaporated. This way, completely deprotected water-soluble glycodendrimers **1b**−**4b** were obtained and characterized by MALDI-TOF MS spectra.

Glycoporphyrin Dendrimer ***1a***. Compound **19** (0.1 g, 0.11 mmol, 1.0 equiv) was reacted with **13** (0.53 g, 0.54 mmol, 4.8 equiv), $CuSO_4{\cdot}5H_2O$ (0.03 g, 0.13 mmol, 1.2 equiv), and sodium L-ascorbate (0.03 g, 0.13 mmol, 1.2 equiv) in THF/water (5 mL/5 mL) according to procedure **A**. Pure compound **1a** was isolated by silica gel column chromatography as a purple solid with hexane/ethyl acetate, followed by $CHCl_3$; Yield 0.22g, 40%; MW 4845.80 $g{\cdot}mol^{-1}$; R_f = 0.64 $CHCl_3$/MeOH (95:5); IR (υ, cm^{-1}) 3454, 3146, 2924, 1755; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.90 (s, 8 H), 8.03 (d, 8 H, J = 7.2 Hz), 7.71 (s, 8 H), 7.43 (s, 4 H), 7.18 (d, 8 H, J = 7.5 Hz), 6.61−6.36 (m, 12 H), 5.60 (d, 8 H, J = 8.7 Hz), 5.43−5.18 (m, 44 H), 5.01−4.81 (m, 12 H) 4.17−4.14 (m, 8 H), 3.96−3.92 (m, 8 H), 3.75 (m, 8 H), 2.02, 1.99 (each s, 72 H), 1.76 (s, 24 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.4, 169.8, 169.3, 168.8, 159.6, 157.5, 150.3, 144.0, 136.8, 136.1, 135.6, 131.8, 122.6, 121.7, 120.4, 112.9, 107.5, 101.7, 85.4, 74.8, 72.5, 70.1, 67.5, 61.6, 61.3, 60.3, 53.9, 53.4, 21.0, 20.6, 20.5, 20.4, and 20.0 ppm; SEC shows polydispersity 1.01; m/z MALDI-TOF MS calcd for $C_{220}H_{232}N_{40}O_{84}Zn$ 4843.447, found 4846.493 $[M + H]^+$.

Deprotected Dendrimer ***1b***. Yield 0.11 g, 92%; MW 3500.62 $g{\cdot}mol^{-1}$; m/z MALDI-TOF MS calcd for $C_{156}H_{168}N_{40}O_{52}Zn$ 3498.11, found 3490.298 $[M + H]^+$.

Glycoporphyrin Dendrimer ***2a***. Compound **19** (0.05 g, 0.056 mmol, 1.0 equiv) was reacted with **14** (0.38 g, 0.27 mmol, 4.8 equiv), $CuSO_4{\cdot}5H_2O$ (0.016 g, 0.067 mmol, 1.2 equiv), and sodium L-ascorbate (0.013 g, 0.067 mmol, 1.2 equiv) in THF/water (6 mL/6 mL) using procedure **A**. Pure compound **2a** was obtained by silica gel column chromatography using $CHCl_3$/MeOH as a purple solid; Yield 0.19 g, 54%; MW 6555.25 $g{\cdot}mol^{-1}$; R_f = 0.56 $CHCl_3$/MeOH (95:5); IR (υ, cm^{-1}) 3472, 3146, 2924, 1755; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.93 (s, 8 H), 8.25 (s, 12 H), 8.10 (d, 8 H, J = 7.8 Hz), 7.70 (s, 4 H), 7.32 (d, 8 H, J = 7.5 Hz), 6.56 (s, 8 H), 6.20 (d, 6 H, J = 9.6 Hz), 5.94 (d, 3 H, J = 9.3 Hz), 5.66−5.55 (m, 12 H), 5.45−5.31 (m, 48 H), 5.20−5.18 (m, 5 H), 5.07 (m, 4 H), 4.90 (m, 10 H), 4.28−4.09 (m, 24 H), 4.01−3.97 (m, 6 H), 3.82 (m, 6 H), 2.05, 2.01 (broad s, 126 H), 1.93 (s, 18 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 170.5, 169.9, 169.5, 169.0, 168.7, 157.7, 152.3, 150.3, 144.6, 144.4, 144.1, 137.4, 136.3,

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135.7, 131.8, 130.6, 123.0, 122.6, 122.1, 120.3, 113.3, 107.3, 85.5, 85.3, 74.8, 74.6, 72.9, 72.6, 70.3, 70.0, 67.7, 67.6, 65.6, 62.5, 61.7, 61.4, 54.2, 20.6, 20.5, 20.1, and 20.0 ppm; SEC shows polydispersity 1.01; *m*/*z* MALDI-TOF MS calcd for $C_{288}H_{316}N_{52}O_{124}Zn$ 6553.94, found 6556.78 $[M + H]^+$ and 6493.67 $[M + H - Zn]^+$.

Deprotected Dendrimer ***2b***. Yield 0.12 g, 94%; MW 4537.48 g·mol^{-1}; *m*/*z* MALDI-TOF MS calcd for $C_{192}H_{220}N_{52}O_{76}Zn$ 4535.431, found 4470.583 $[M + H - Zn]^+$.

Glycoporphyrin Dendrimer ***3a***. Compound **19** (0.05 g, 0.056 mmol, 1.0 equiv) was reacted with **16** (0.59 g, 0.27 mmol, 4.8 equiv), $CuSO_4·5H_2O$ (0.016 g, 0.067 mmol, 1.2 equiv), and sodium L-ascorbate (0.013 g, 0.067 mmol, 1.2 equiv) in THF/water (6 mL/6 mL) using procedure **A**. Pure compound **3a** was obtained by silica gel column chromatography with $CHCl_3$/MeOH as a purple solid; Yield 0.37 g, 57%; MW 9762.29 g·mol^{-1}; R_f = 0.40 $CHCl_3$/MeOH (95:5); IR (υ, cm^{-1}) 3437, 3153, 2924, 1755; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.84 (s, 8 H), 7.99, 7.83, 7.55 (m, 36 H), 7.27 (m, 8 H), 6.56–6.34 (m, 36 H), 5.73 (10 H), 5.93–4.96 (m, 134 H), 4.16–3.87 (m, 48 H), 2.02, 1.98, 1.76 (192 H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.4, 169.9, 169.4, 168.8, 159.6, 157.5, 150.2, 144.0, 143.7, 139.2, 137.0, 136.0, 135.6, 131.8, 123.3, 121.7, 114.0, 107.5, 101.7, 85.5, 74.8, 70.2, 67.5, 61.5, 61.4, 60.4, 53.8, 20.6, 20.5, and 20.0 ppm; SEC shows polydispersity 1.03; *m*/*z* MALDI-TOF MS calcd for $C_{436}H_{472}N_{88}O_{172}Zn$ 9759.031, found 9758.225 $[M + H]^+$, 9696.891 $[M + H - Zn]^+$.

Deprotected Dendrimer ***3b***. Yield 0.25 g, 92%; MW 7071.93 g·mol^{-1}; *m*/*z* MALDI-TOF MS calcd for $C_{308}H_{342}N_{88}O_{108}Zn$ 7069.352, found 7007.376 $[M + H - Zn]^+$.

Glycoporphyrin Dendrimer ***4a***. Compound **19** (0.025 g, 0.028 mmol, 1.0 equiv) was reacted with **18** (0.41 g, 0.13 mmol, 4.8 equiv), $CuSO_4·5H_2O$ (0.008 g, 0.034 mmol, 1.2 equiv), and sodium L-ascorbate (0.007 g, 0.034 mmol, 1.2 equiv) in THF/water (6 mL/6 mL) using procedure **A**. Pure compound **4a** was obtained by silica gel column chromatography ($CHCl_3$/MeOH) as a purple solid; Yield 0.24 g, 64%; MW 13181.19 g·mol^{-1}; R_f = 0.37 $CHCl_3$/MeOH (95:5); IR (υ, cm^{-1}) 3480, 3145, 2927, 1756; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.86 (s, 8 H), 8.39, 8.28 (m, 24 H), 8.08 (d, 8 H, *J* = 7.2 Hz), 7.87 (s, 4 H), 7.64 (s, 8 H), 7.33 (d, 8 H, *J* = 7.8 Hz), 6.64, 6.53 (m, 28 H), 6.20 (d, 8 H, *J* = 9.0 Hz), 5.82 (d, 15 H, *J* = 8.4 Hz), 5.59–5.30 (m, 123 H), 5.16–4.92 (m, 46 H), 4.24–3.96 (m, 72 H), 2.05, 2.01, 1.99, 1.93 (each s, 228 H), 1.74 (m, 60 H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5, 169.9, 169.5, 169.0, 168.8, 159.7, 157.7, 152.3, 150.2, 144.6, 144.3, 143.7, 137.3, 137.0, 136.2, 135.7, 131.7, 130.8, 123.4, 122.6, 122.2, 107.6, 107.2, 102.0, 85.5, 85.2, 74.8, 74.6, 72.9, 72.6, 70.3, 70.0, 67.6, 65.8, 65.6, 62.6, 61.5, 53.9, 20.6, 20.5, and 20.0 ppm; SEC shows polydispersity 1.02; *m*/*z* MALDI-TOF MS calcd for $C_{572}H_{640}N_{112}O_{252}Zn$ 13177.01671, found 13111.248 $[M + H - Zn]^+$.

Deprotected Dendrimer ***4b***. Yield 0.15 g, 89%; MW 9145.66 g·mol^{-1}; *m*/*z* MALDI-TOF MS calcd for $C_{380}H_{448}N_{112}O_{156}Zn$ 9142.999, found 9078.450 $[M + H - Zn]^+$

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectroscopic data, ^{1}H and ^{13}C NMR, MALDI-TOF MS, SEC, and absorption–emission spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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