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Multifunctionalization of Dendrimers through Orthogonal Transformations

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Abstract: A straightforward methodology for the synthesis of multifunctionalized dendrimers that is based on an orthogonal functionalization strategy has been developed. Polyamide-based dendrimers that possess both a single aldehyde and a single azide moiety on their periphery have been synthesized by using a convergent synthetic strategy. These dendrimers can be functionalized quantitatively with small organic and biological molecules that contain hydrazide and/or alkyne groups in which each functional moiety is completely specific for its complementary motif. This orthogonal functionalization strategy has the potential to be used to synthesize multifunctional dendrimers for a variety of applications, which range from targeted biological delivery vehicles to optical materials.

Keywords: chemical biology · click chemistry · dendrimers · functionalization

Introduction

The ability to directly import therapeutic agents into target cells and tissues, and to direct them to specific organelles, would greatly enhance their functional efficacy and remains a major goal in drug delivery. The spectrum of cell-penetrating peptide-based import signals[1–4] and intracellular routing signals that are available might provide practical solutions towards achieving a guided or vectorial delivery of molecules. Nonviral chemical delivery techniques, which involve cationic lipids[5] and liposomes,[6,7] peptides,[8] dendrimers,[9–11] and controlled release polymers,[12] have mainly focused on the transport of therapeutic agents or plasmids across the eukaryotic cellular membrane and into the cytoplasm. For further advances in tissue targeting, work on surface modification of such nonviral vehicles with antibodies,[13,14] proteins,[15] or ligands[16–18] that are recognized by a specific cell type or organelle is ongoing. Although significant progress has been made towards targeted delivery, the development of alternate template molecules that favor the optimal presentation of functional groups and have a capacity for encapsulation is desirable. The ideal vehicle should have highly controlled surface functionalization and a globular macromolecular architecture that can act as a host for guests and be less susceptible to uptake by the phagocytic system. One class of materials that fulfills these requirements and has also been investigated extensively for biological delivery applications over the past decade is dendrimers.[19–22]

The three-dimensional, highly branched, monodisperse structures of dendrimers, which contain sequestered cores or internal cavities, are ideal host materials for a variety of guest molecules. Examples of guests that have been encapsulated in dendrimers include molecules for drug delivery[23,24] and Au–Ag nanodots for biological imaging[25–27] or as biological probes.[28,29] The nanoscopic particle size of dendrimers, which range from 1 to 100 nm, makes them less susceptible to uptake by the reticuloendothelial system with an enhanced permeability and retention effect.[30–32] Advances towards the use of dendrimers in drug delivery are numerous, of which dendrimer subclasses, such as polyesters,[33] poly(amidoamine)s,[11] poly(propyleneimine)s,[34] polyamides,[35] and triazines that are linked by diamines,[36] have received extensive attention.

We are interested in polyamide- and polyamidoamine (PAMAM)-based dendrimers, which have low levels of transfection and can be viewed as peptide mimics owing to their amide-based backbone.[37] Although there has been significant focus on improving the pharmokinetic profile of drugs that are delivered by dendrimers,[21,38,39] research into the development of dendrimers that have unique sites for surface manipulation[40–43] or orthogonal surface functional groups[36,44–46] for multifunctionalization has been scarce. Nevertheless, there have been some examples described in the literature recently of dendrimers that have different

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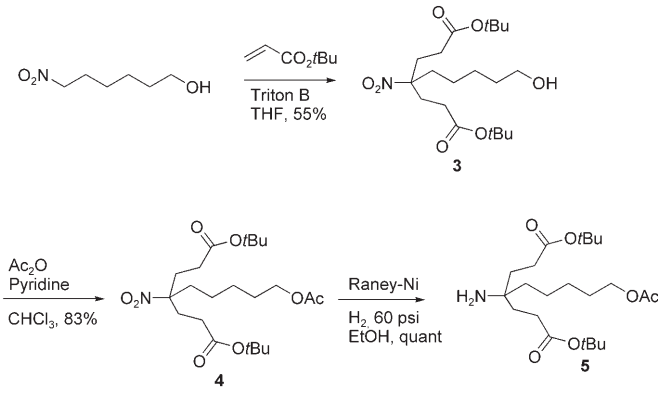
functional groups on or in close proximity to the periphery.[47–56] However, existing orthogonal dendritic architectures that are amenable to postsynthetic manipulations often suffer from nonquantitative deprotection steps or lack robust orthogonal groups, that is, chemical handles that can be functionalized in the presence of a wide variety of other functional groups without the use of protection steps. Clearly, the development of a dendrimer-based delivery vehicle that contains two robust, reactive, and distinct orthogonal functional groups with perfect specificity and selectivity for its complementary group is still an unfulfilled goal. Such a probe or vehicle could be chemoselectively ligated with desirable ligands, antibodies, or target receptor proteins.

One requirement for the realization of such a strategy is to design a biocompatible and flexible scaffold that allows for the proper presentation of multiple orthogonal functional groups or domains. Herein, we present such an approach by using polyamide-based dendrons developed by Newkome and coworkers,[57–59] to build scaffolds that contain distinct, robust, and highly selective orthogonal functional-group motifs along the surface of the dendrimer. The two functionalities that have been utilized in this study are an aldehyde group, which allows the biocompatible addition of a hydrazide or a semicarbazide,[60] and an azide group, which can be employed in 1,3-dipolar cycloaddition reactions with alkynes and is often referred to as "click" chemistry.[61] Both of these functionalities are distinctly orthogonal to each other and are individually accessable. The resulting dendrimers are biocompatible and allow either a one-step postsynthetic chemospecific multifunctionalization or a one-step single dendrimer functionalization to be performed in high yields, which allows the construction of tunable materials that have unprecedented complexity.

Results and Discussion

Synthesis of mono- and bifunctional dendrimers: Dendrimers **1** and **2** have one and two orthogonal surface groups for manipulation, respectively. The dendrimers contain an aldehyde group that can be treated with hydrazines to functionalize the surface. Dendrimer **2** also contains an azide group that can be treated with alkynes to perform 1,3-dipolar cycloadditions. Our synthetic strategy towards synthesizing these dendrimers is based on the convergent synthetic approach and the 1→(2+1) *C*-branching monomers reported by Newkome and co-workers,[57] who have reported a variety of applications of these materials in recent years.[62–64] Dendron **A** is a key building block in our design and introduces single and dual functionalities onto the dendrimer surface. Dendron **A** is obtained by a series of convergent steps from dendrons **5**, **C**, and **D**.

Dendron **5** was obtained by using the synthetic strategy shown in Scheme 1. The synthetic strategy begins with the Michael-type addition of 6-nitrohexanol[65] to *tert*-butyl acrylate in the presence of Triton B to provide monomer **3** in a yield of 55%. Subsequent acylation of the alcohol by using

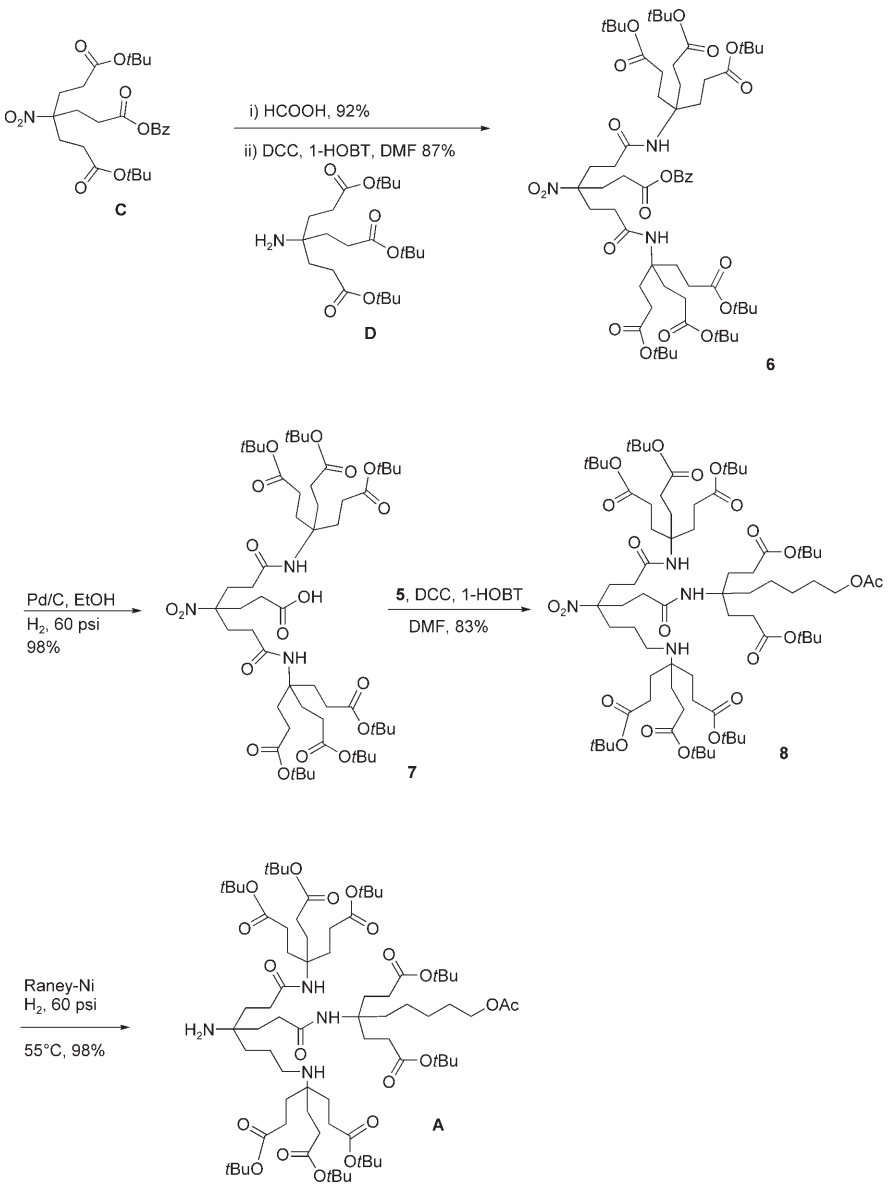


Scheme 1. Synthesis of building block dendron **5**.

Ac_2O in pyridine, followed by the catalytic reduction of the nitro group of **4** by using H_2 (60 psi) in ethanol afforded **5**. The quantitative reduction of the nitro group to form an amine was supported by a change in the chemical shift of the ^{13}C NMR spectrum of the nitro carbon from $\delta = 92.8$ to 52.6 ppm for the amine carbon. Other building blocks (**B**, **C**, and **D**) were synthesized by using procedures reported by Newkome and co-workers.[57,66]

With these basic monomers in hand, the following series of chemical transformations were used to prepare dendron **A** (Scheme 2): Deprotection of the *tert*-butyl groups on monomer **C** was followed by a coupling reaction promoted by dicyclohexyl carbodiimide (DCC) and 1-hydroxybenzotriazole (1-HOBT) promoted coupling, which involved two equivalents of **D** to afford compound **6** in a yield of 87%. Removal of the benzyl ester protecting group on **6** by using Pd/C and H_2 (60 psi) gave **7** in a yield of 98%. Dendron **7** was then coupled to **5** by using DCC and 1-HOBT to afford **8** in an isolated yield of 83%. Reduction of the nitro group of **8** by using Raney-Ni and H_2 (60 psi) at 55°C provided dendron **B** in a yield of 98%. Dendron **B** was identified by a change in the chemical shift of the ^{13}C NMR spectrum of the C^{4° moiety in the NMR spectra from $\delta = 92.5$ to 52.6 ppm and also by the molecular ion peak in the mass spectrum (ESI-MS) at m/z 1439.945 $[M+H]^+$. The overall yield of dendron **6** from its building blocks was 68%.

Monofunctional dendrimer **1** was then obtained by the stepwise incorporation of **B** and **A** onto the core molecule (Scheme 3). Dendron **B** was treated with succinic anhydride in the presence of pyridine to give **9** in a yield of 85%. Dendron **9** was then coupled to **A** by using DCC and 1-HOBT to give dendrimer **10** in a yield of 80%. Dendrimer **10** was subsequently deprotected by using K_2CO_3 to provide dendrimer **11** in a yield of 90%. The formation of the product was confirmed by the disappearance of the proton signal of the acetyl group in the ^1H NMR spectrum and a change in the chemical shift for the $-CH_2OH$ moiety from $\delta = 4.01$ to 3.60 ppm. Alcohol **11** was oxidized to form an aldehyde by using pyridinium chlorochromate (PCC) to afford dendrimer **1** in a yield of 85%. The formation of dendrimer **1** was confirmed by the appearance of a new aldehyde proton



Scheme 2. Synthesis of acetyl protected monofunctional dendron **A**.

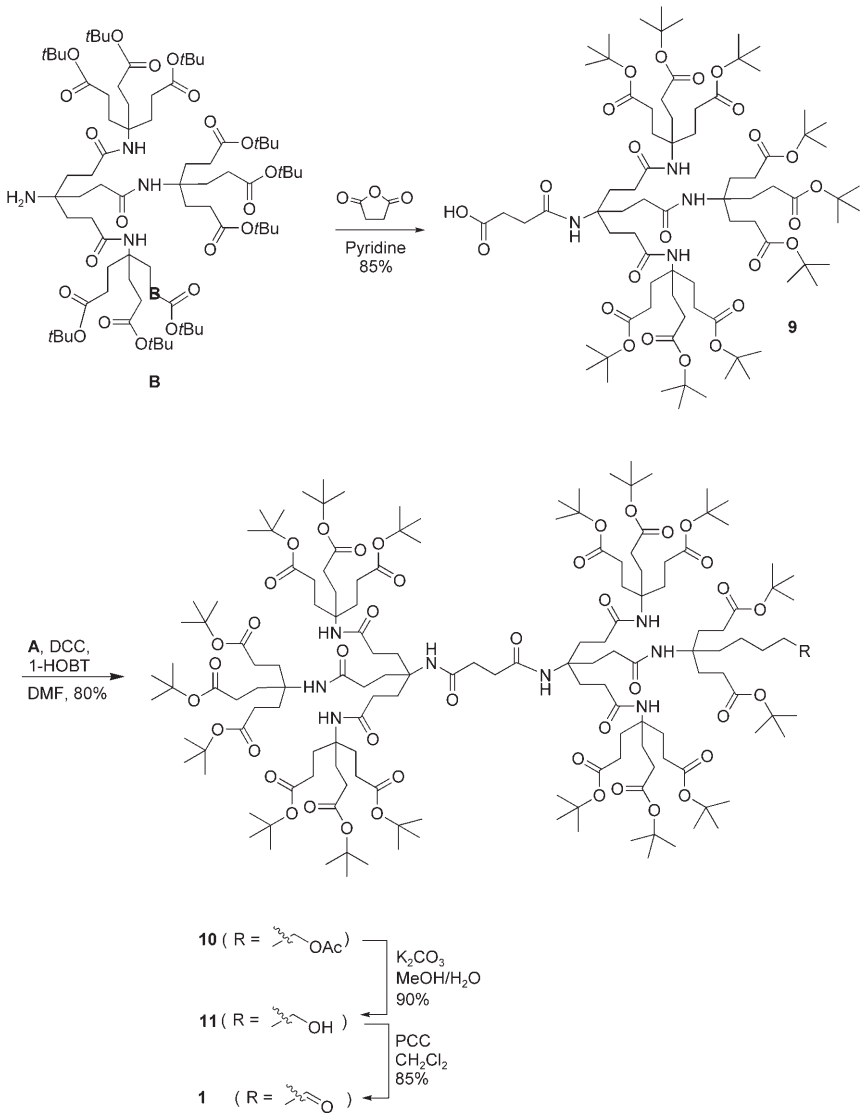
signal in the ^{1}H NMR spectrum at $\delta = 9.61$ ppm and a new signal in the ^{13}C NMR spectrum at $\delta = 201.4$ ppm for the newly formed carbonyl carbon.

The bifunctional dendrimer was obtained in a manner that was analogous to the stepwise procedure described above for the formation of the monofunctionalized dendrimer. The procedure involved the stepwise incorporation of dendron **A** to the core molecule, deprotection of the acetyl group, and conversion of the alcohol moiety into the desired aldehyde functionality. Subsequently, another molecule of **A** was coupled to the core, the acetyl group was deprotected and transformed into a terminal alcohol group, then into a tosylate group and finally into an azide moiety (Scheme 4). By using this synthetic protocol, in which all transformations were carried out in good to excellent isolated yields, dendrimer **2** was synthesized in an overall yield of 35%.

Functionalizations: Amino acids and peptides are the simplest protein mimics, and polymer surfaces that have been functionalized with them have been investigated to generate materials for drug delivery, protein–surface recognition, asymmetric catalysis, and biocompatible materials.[67–69] Another important biological moiety is biotin because of its high-binding affinity for the protein streptavidin. This ligand–receptor interaction is widely used in biosensing, purification, and drug delivery.[70–72] Applications that involve protein recognition of biotinylated species, such as polymers, small molecules, and nanoparticles, have been utilized as model systems to study and mimic the multivalent interactions that occur in protein–cell recognition.[70–72] Given the high application potential and fundamental significance of biotinylated and amino acid functionalized species, functionalization of the dendrimer with these molecules was undertaken. Therefore, we investigated the functionalization of **1** and **2** with these biologically significant molecules as a proof of principle for our orthogonal multifunctionalization strategy.

Two factors are essential for the success of our multifunctionalizable dendritic scaffolds that bear one and two orthogonal groups on their surface: 1) the chemical transformations must take place in high yields, and 2) the functional groups must retain their orthogonality, that is, during the chemical transformations they should not show any interference with each other or with the rest of dendrimer backbone. Therefore, we investigated the orthogonality by coupling small organic and biologically relevant molecules onto **1** and **2**.

Initially, we investigated chemical transformations on the single aldehyde group present in dendrimer **1** (we have recently reported the functionalization of polyamide-based dendrimers by using click chemistry).[74] The aldehyde group can be used for Schiff base coupling reactions with molecules that bear hydrazides, semicarbazides, and aminoxy moieties.[60] As an example of these possible transformations, we investigated the hydrazide-based coupling reac-



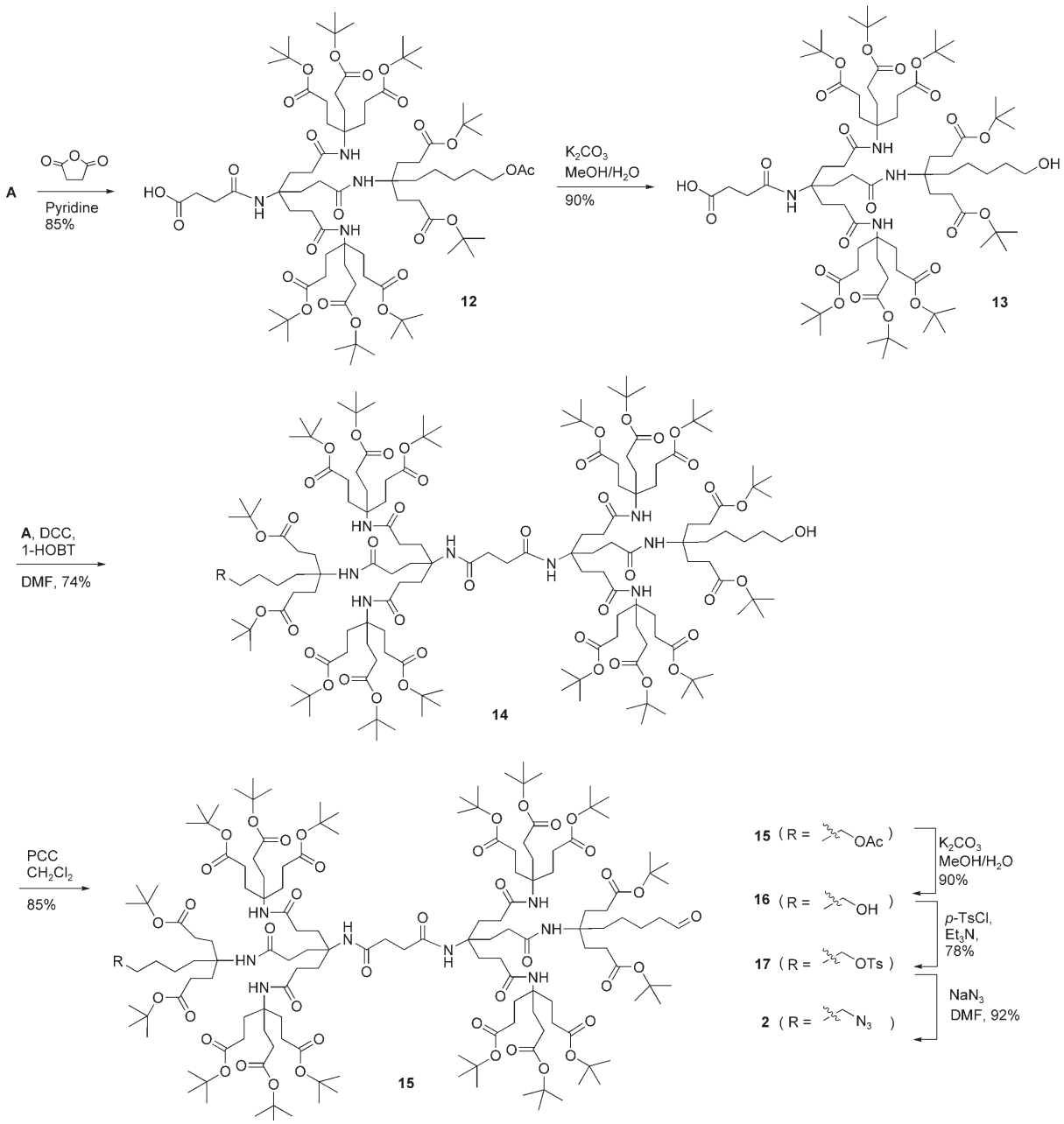
Scheme 3. Synthesis of monofunctional dendrimer **1**.

tions of **1** to phenyl hydrazine, anisic hydrazine, and biotin hydrazide. All coupling reactions were carried out in ethanol or DMSO for 16 h and the results are presented in Table 1. In all cases, we observed quantitative conversions of the aldehyde to the corresponding Schiff base products, which were characterized by the disappearance of the singlet at $\delta = 9.61$ ppm in the ^{1}H NMR spectrum that corresponds to the aldehyde proton and the appearance of a new triplet for the methine proton (−C*H*=N−NH−R) at $\delta = 7.48$ to 7.50 ppm, which varied depending upon the R group present. The final products were obtained in isolated yields of 97 to 98% and were identified by ^{1}H and ^{13}C NMR spectroscopies and MALDI-TOF mass spectrometry.

Dendrimer **2** is the foundation for our main goal, which is the one-step bifunctionalization of polyamide-based dendrimers through 1,3 dipolar cycloadditions and Schiff base coupling reactions. Dendrimer **2** contains two single orthogonal functionalities on the surface, an aldehyde group for Schiff base coupling reactions and an azide for click and Staudinger ligations (Table 2). To demonstrate the possibility of using this multifunctionalization concept for biomaterials applications, we used **2** for coupling reactions with two representative biological molecules, propargyl glycine and biotin hydrazide, which both bear complementary functional groups to those on the dendritic scaffold. Dendrimer **2** was treated with biotin hydrazide in ethanol overnight to obtain **20** in an isolated yield of 96%. Dendrimer **20** was characterized by the disappearance of the singlet at $\delta = 9.61$ ppm in the ^{1}H NMR spectrum that corresponds to the aldehyde proton and the appearance of a new triplet that corresponds to the methine proton (−C*H*=N−) at $\delta = 7.48$ ppm in the and also by a diagnostic shift in the ^{13}C NMR spectrum from $\delta = 200.2$ to 154.3 ppm (−*C*H=N−). After successful introduction of the aldehyde functionality, dendrimer **20** was treated with propargyl glycine under standard click conditions by using sodium ascorbate and $CuSO_4 \cdot 5H_2O$ in a 1:1 mixture of *t*BuOH/H_2O in a sealed glass vial in a microwave reactor. The reaction was completed in ten minutes to afford triazole product **21** in an isolated yield of 97%. The conversion was confirmed by the presence of a newly formed signal at $\delta = 7.57$ ppm in the ^{1}H NMR spectrum for the proton on the triazole moiety. Both of these functional-group conversions, 1,3 dipolar cycloaddition and Schiff base coupling reactions, are fully tolerant of each other and any other functional groups that are present in dendrimers **1** and **2**. No changes in the chemical nature of the dendrimer scaffold were observed after each reaction. These studies clearly demonstrate that the orthogonality of the functional groups on the surface of mono- and bifunctional dendrimers is preserved.

Concluding Remarks

The synthesis of dendrimers that contain orthogonal functional groups on their surfaces that can be derivatized with biological moieties will be crucial for further developments

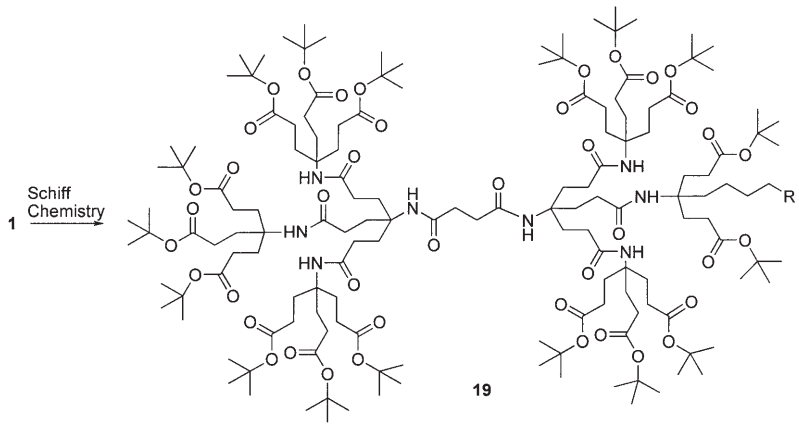


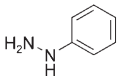
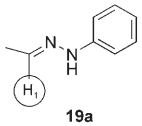
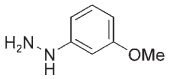
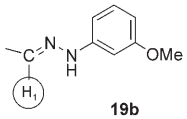
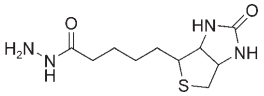
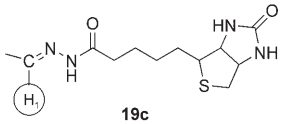
Scheme 4. Synthesis of bifunctional dendrimer **2**.

in targeted delivery, molecular imaging, and materials applications. The goal of the research reported herein was to fabricate such a dendrimer, which could act as a delivery vehicle that contained two distinct orthogonal functional groups on its surface. These functional groups allowed quantitative and orthogonal functionalization of the dendrimer with biologically important moieties. Towards this end, we have demonstrated the first successful synthesis of a bifunctional second-generation polyamide-based dendrimer that bears two orthogonal functional handles on its surface. In particular, a dendrimer that contains both azide and aldehyde moieties, which allows Schiff base and 1,3 dipolar cycloaddition transformations to be performed, was synthesized by using a convergent synthetic strategy. Most importantly, we have demonstrated the targeted and quantitative functionalization of both chemical handles with biologically relevant molecules.

Our approach allows the chemoselective conjugation of desired molecules, which are tolerant to click and/or Schiff base coupling reaction conditions, to our polyamide-based dendritic scaffolds. This strategy has the potential to be of particular importance in delivery chemistry because nuclei receptors, trans-membrane proteins, and other important targeting moieties can be attached quickly, selectively, and quantitatively to the dendrimer scaffold in an orthogonal fashion. Therefore, as a result of their ready tunability, the

Table 1. Schiff base coupling reactions of molecules onto dendrimer **1**.[a]



Reactants	Product **19** (R =)	δ[b] [ppm]	Yield [%]
	 **19a**	7.50	98
	 **19b**	7.50	98
	 **19c**	7.48	97

[a] Reaction conditions: Ethanol (**19a** and **19b**) or DMSO (**19c**), RT, 16 h. [b] Chemical shift for the newly formed Schiff base product proton H_1.

mono- and bifunctionalized dendrimers described herein should provide guidelines for the development of synthetic multivalent frameworks for many applications in chemical biology.

Experimental Section

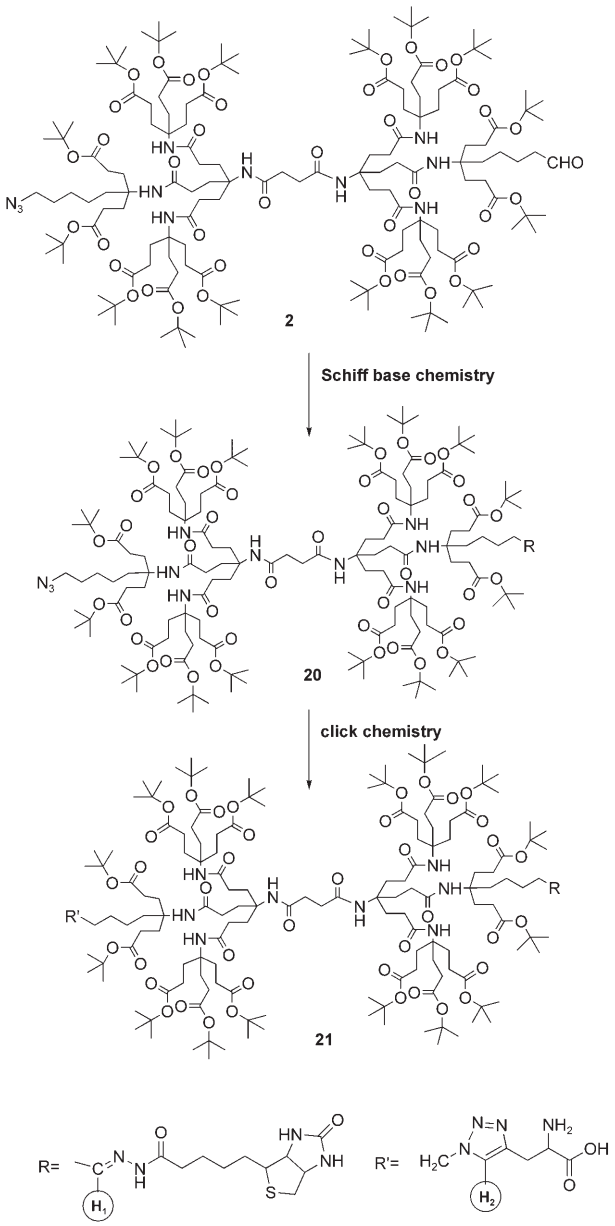
General methods: All reagents were purchased from Acros Organics, Aldrich, or Alfa Aesar, and were used without further purification unless otherwise noted. Propargyl glycine was purchased from ChemImpex. THF was distilled from sodium benzophenone ketyl, dichloromethane and pyridine were distilled from calcium hydride. Dry DMF that had been stored over 4 Å molecular sieves was used. NMR spectra were acquired by using a Varian Mercury 400 (^{1}H, 400.0 Hz; ^{13}C, 100.6 MHz) or a Varian Mercury 300 (^{1}H, 300.0 MHz; ^{13}C, 75.5 MHz) spectrometer. Chemical shifts are reported in ppm and are referenced to the residual nuclei in the corresponding deuterated solvents. Abbreviations used in the NMR data include broad (br), singlet (s), doublet (d), triplet (t), quartet (q), and unresolved multiplet (m). Mass spectral analyses were provided by the Georgia Tech Mass Spectrometry Facility by using a VG-70 se spectrometer for ESI or FAB, and by using a ABI 4700 Proteomics Analyzer for MALDI-TOF. Elemental analyses were performed by using a Perkin–Elmer Series II CHNS/O Analyzer 2400. All microwave irradiation experiments were carried out by using a CEM Discover microwave synthesizer.

Di-*tert*-butyl 4-(5-hydroxypentyl)-4-nitroheptanedioate (3): Triton-B (5.50 mL, 40 wt% solution in MeOH) was added at room temperature over 2 h to a solution of 6-nitrohexanol (16.3 g, 110 mmol) and *tert*-butyl acrylate (35.3 mL, 244 mmol) in THF (220 mL). After stirring for 15 h at room temperature, all the volatile materials were removed in vacuo to give a dark yellowish residue. The residue was dissolved in diethyl ether, washed with 5% aqueous HCl, 10% aqueous $NaHCO_3$, and saturated NaCl solutions, before the organic layer was dried over $MgSO_4$. After filtration, the organic mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography by using EtOAc/hexane (1:1) as the eluent to give **3** as a white solid (24.4 g, 55%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.25 (m, 2H), 1.38 (m, 2H), 1.44 (s, 18H), 1.56 (m, 3H), 1.88 (t, ^3J(H,H) = 7.8 Hz, 2H), 2.19 (m, 8H), 3.63 ppm (t, ^3J(H,H) = 6.3 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS): δ = 23.3, 25.7, 27.9, 29.8, 30.3, 32.1, 35.3, 62.3, 81.0, 92.9, 171.2 ppm; HRMS (MALDI-TOF): *m*/*z*: calcd for $C_{20}H_{38}NO_7$: 404.2648; found, 404.2661 $[M+H]^+$; elemental analysis calcd (%) for $C_{20}H_{37}NO_7$: C 59.53, H 9.24, N 3.47; found: C 59.40, H 9.32, N 3.48.

Di-*tert*-butyl 4-(5-acetoxypentyl)-4-nitroheptanedioate (4): Ac_2O (6.09 mL, 64.9 mmol) was added at 0 °C to a solution of **3** (21.8 g, 54.1 mmol) and pyridine (5.25 mL, 64.9 mmol) in $CHCl_3$ (180 mL). The mixture was warmed to room temperature slowly and stirred for 15 h. The mixture was washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by silica gel column chromatography by using EtOAc/hexane (1:3) as the eluent to give compound **4** as a white solid (19.9 g, 83%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.25 (m, 2H), 1.37 (m, 2H), 1.43 (s, 18H), 1.63 (m, 2H), 1.88 (t, ^3J(H,H) = 8.1 Hz, 2H), 2.19 (m, 8H), 2.04 (s, 3H), 4.04 ppm (t, ^3J(H,H) = 6.6 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS): δ = 20.9, 23.3, 26.0, 28.0, 28.3, 29.8, 30.3, 35.3, 64.2, 81.1, 92.8, 171.1, 171.2 ppm; HRMS (MALDI-TOF): *m*/*z*: calcd for $C_{22}H_{40}NO_8$: 446.2754; found: 446.2776 $[M+H]^+$; elemental analysis calcd (%) for $C_{22}H_{39}NO_8$: C 59.31, H 8.82, N 3.14; found: C 59.20, H 8.80, N 3.36.

Di-*tert*-butyl 4-(5-acetoxypentyl)-4-aminoheptanedioate (5): Raney-Ni (6.28 g) was added to a solution of **4** (7.00 g, 15.7 mmol) in absolute EtOH (160 mL). The reaction mixture was stirred under H_2 (60 psi) for 12 h at room temperature. The solution was filtered through Celite to remove the catalyst and the filtrate was concentrated in vacuo to afford amine **5** as a colorless oil (6.39 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.24 (m, 6H), 1.38 (s, 18H), 1.57 (m, 6H), 1.99 (s, 3H), 2.17 (t, ^3J(H,H) = 8.2 Hz, 4H), 3.99 ppm (t, ^3J(H,H) = 6.6 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS): δ = 20.9, 23.0, 26.5, 28.0, 28.5, 29.9, 34.5, 39.4, 52.5, 64.4, 80.1, 171.0, 173.1 ppm; HRMS (MALDI-TOF): *m*/*z*: calcd for $C_{22}H_{42}NO_6$: 416.3012; found: 416.3017 $[M+H]^+$.

Nitro dendron 6: The mixture of di-*tert*-butyl 4-(2-*tert*-benzyloxycarbonylethyl)-4-nitroheptanedioate or **C** (33.8 g, 70.6 mmol) dissolved in HCO_2H (266 mL) was stirred for 6 h at room temperature. The mixture was concentrated in vacuo to afford the diacid as a white solid (23.8 g,



Scheme 5. Schiff base and click coupling reactions on dendrimer **2**.

Table 2. Schiff base and click coupling reactions on dendrimer **2** give the products shown in Scheme 5.[a]

Dendrimer	Reactants	Products	δ[b] [ppm]	Yield [%]
2	biotin hydrazide	**20**	7.48	96
20	propargyl glycine	**21**	7.57	97

[a] Reaction conditions: 1) Schiff base coupling: DMSO, RT, 16 h; 2) Click coupling: *t*BuOH/H_2O (1:1), 10 mol% sodium ascorbate, 5 mol% $CuSO_4 \cdot 5H_2O$. [b] Chemical shift for the newly formed Schiff base product proton H_1 and triazole proton H_2.

92%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 2.26$ (m, 6H), 2.36 (m, 6H), 5.11 (s, 2H), 7.34 ppm (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS): $\delta = 28.4$, 28.5, 29.3, 30.6, 67.0, 91.8, 128.3, 128.5, 128.6, 135.2, 171.8, 178.0 ppm; HRMS (MALDI-TOF): *m/z*: calcd for $C_{17}H_{22}NO_8$: 368.1345; found: 368.1367 $[M+H]^+$; elemental analysis calcd (%) for $C_{17}H_{21}NO_8$: C 55.58, H 5.76, N 3.81; found: C 55.36, H 5.62, N 3.81.

DCC (4.96 g, 24.1 mmol) and 1-HOBT (3.25 g, 24.1 mmol) were added at room temperature to a solution of the diacid monomer described above (3.93 g, 10.7 mmol) in DMF (120 mL). After the mixture was stirred for 2 h, dendron **D**[73] (10.00 g, 24.1 mmol) was added and then the resulting mixture was stirred for 3 d at room temperature. After filtration, the filtrate was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and washed with saturated aqueous solutions of $NaHCO_3$ (2×) and NaCl. The organic phase was dried over $MgSO_4$, filtered, concentrated in vacuo, and purified by silica gel column chromatography by using EtOAc/hexane (2:3) as the eluent to afford **6** as a white solid (10.9 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 1.39$ (s, 54H), 1.91 (m, 12H), 2.06 (m, 4H), 2.17 (m, 18H), 2.35 (m, 2H), 5.08 (s, 2H), 6.16 (s, 2H), 7.31 ppm (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS): $\delta = 28.0$, 28.6, 29.8, 29.9, 31.2, 31.3, 57.6, 66.7, 80.7, 92.3, 128.3, 128.3, 128.5, 135.5, 170.1, 171.8, 172.8 ppm; HRMS (MALDI-TOF): *m/z*: calcd for $C_{61}H_{99}N_3O_{18}Na$: 1184.6821; found: 1184.6507 $[M+Na]^+$; elemental analysis calcd (%) for $C_{61}H_{99}N_3O_{18}$: C 63.03, H 8.58, N 3.61; found: C 63.08, H 9.02, N 3.73.

Nitro dendron 7: In the presence of 10% Pd/C (1.20 g), a solution of dendron **6** in absolute EtOH (110 mL) was hydrogenated with of H_2 (60 psi) at room temperature for 12 h. The solution was filtered through Celite and the solvent was removed in vacuo to afford monoacid dendron **7** as a white solid (6.11 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 1.42$ (s, 54H), 1.92 (m, 12H), 2.10 (m, 4H), 2.20 (m, 16H), 2.31 (m, 4H), 6.14 ppm (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS): $\delta = 28.0$, 28.3, 28.9, 29.8, 30.0, 31.1, 31.3, 57.5, 80.9, 92.5, 170.7, 173.1, 174.7 ppm; HRMS (MALDI-TOF): *m/z*: calcd for $C_{54}H_{93}N_3O_{18}Na$: 1094.6351; found: 1094.6018 $[M+Na]^+$; elemental analysis calcd (%) for $C_{54}H_{93}N_3O_{18}$: C 60.48, H 8.74, N 3.92; found: C 60.45, H 8.97, N 4.04.

Nitro dendron 8: DCC (1.41 g, 6.84 mmol) and 1-HOBT (0.924 g, 6.84 mmol) were added at room temperature to a solution of **7** (6.11 g, 5.70 mmol) in DMF (60 mL). After the mixture was stirred for 2 h, a solution of **5** (2.84 g, 6.84 mmol) in DMF (20 mL) was added and then the resulting mixture was stirred for 3 d at room temperature. After filtration, the filtrate was concentrated in vacuo to give a white residue. The residue was dissolved in CH_2Cl_2 (30 mL) and washed with saturated aqueous solutions of $NaHCO_3$ (2×) and NaCl. The organic phase was dried over $MgSO_4$, filtered, concentrated in vacuo, and purified by silica gel column chromatography by using EtOAc/hexane (1:1) as the eluent to afford dendron **8** as a white solid (6.94 g, 83%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 1.27$ (m, 4H), 1.43 (s, 72H), 1.65 (m, 4H), 1.94 (m, 16H), 2.04 (s, 3H), 2.10 (m, 4H), 2.20 (m, 24H), 4.03 (t, $^3J(H,H) = 6.6$ Hz, 2H), 5.77 (s, 1H), 6.08 ppm (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS): $\delta = 21.0$, 22.7, 26.0, 28.0, 28.3, 29.7, 29.8, 30.0, 31.2, 34.8, 57.5, 58.0, 64.3, 80.6, 92.5, 170.3, 170.4, 171.3, 172.7, 172.9 ppm; HRMS (MALDI-TOF): *m/z*: calcd for $C_{76}H_{132}N_4O_{23}Na$: 1491.9180; found: 1491.8817 $[M+Na]^+$; elemental analysis calcd (%) for $C_{76}H_{132}N_4O_{23}$: C 62.10, H 9.05, N 3.81; found C 62.09, H 9.07, N 4.05.

Amine dendron A: Raney-Ni (2.00 g) was added to a solution of **8** (7.03 g, 4.95 mmol) in absolute EtOH (50 mL). The reaction mixture was stirred under H_2 (60 psi) for 24 h at 55°C. The solution was filtered through Celite to remove the catalyst and the filtrate was concentrated in vacuo to afford amine dendron **A** as a white solid (6.98 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 1.26$ (m, 4H), 1.42 (s, 72H), 1.61 (m, 10H), 1.92 (m, 16H), 2.03 (s, 3H), 2.16 (m, 22H), 4.01 (t, $^3J(H,H) = 6.6$ Hz, 2H), 5.86 (s, 1H), 6.14 ppm (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS): $\delta = 21.0$, 22.7, 26.1, 28.0, 28.3, 29.8, 30.0, 31.5, 31.6, 34.7, 35.2, 52.6, 57.3, 57.7, 64.4, 80.6, 171.3, 172.5, 172.6, 172.7, 172.9 ppm; MS (ESI): *m/z*: calcd for $C_{76}H_{135}N_4O_{21}$: 1439.9; found: 1439.9 $[M+H]^+$; elemental analysis calcd (%) for $C_{76}H_{134}N_4O_{21}$: C 63.39, H 9.38, N 3.89; found: C 62.93, H 9.35, N 4.06.

Dendron 9: A solution of **B** (1.56 g, 1.08 mmol) and succinic anhydride (0.164 g, 1.63 mmol) in pyridine (22 mL) was stirred at room temperature for 48 h. The solution was concentrated under reduced pressure, the residue was dissolved in $CHCl_3$, and washed with an aqueous solution that contained 10% HCl (2×). The organic layer was dried over $MgSO_4$, filtered, and concentrated to dryness. The crude material was purified by silica gel column chromatography by using EtOAc/hexane (2:1) as the

eluent to afford **9** as a white solid (1.39 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ=1.43 (s, 81H), 1.92 (m, 24H), 2.15 (m, 24H), 2.37 (m, 2H), 2.64 (m, 2H), 6.05 (s, 3H), 7.24 ppm (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS): δ=28.0, 29.8, 30.0, 31.6, 31.7, 57.2, 57.3, 80.7, 171.3, 173.1, 175.3 ppm; MS (ESI): *m/z*: 1539.8 $[M+H]^+$; elemental analysis calcd (%) for $C_{80}H_{138}N_4O_{24}$: C 62.39, H 9.03, N 3.64; found: C 62.34, H 9.11, N 3.91.

Dendrimer 10: DCC (0.197 g, 0.957 mmol) and 1-HOBT (0.129 g, 0.957 mmol) were added at room temperature to a solution of **9** (1.34 g, 0.870 mmol) in DMF (9 mL). After the mixture was stirred for 2 h, dendron **A** (2.84 g, 0.957 mmol) was added and then the resulting mixture was stirred for 3 d at room temperature. After filtration, the filtrate was concentrated in vacuo to give a white residue. The residue was dissolved in CH_2Cl_2 (20 mL) and washed with saturated aqueous solutions of $NaHCO_3$ (2×) and NaCl. The organic layer was dried over $MgSO_4$, filtered, concentrated in vacuo, and purified by silica gel column chromatography by using EtOAc/hexane (3:2) as the eluent to afford dendrimer **10** as a white solid (2.17 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ= 1.25 (m, 4H), 1.44 (s, 153H), 1.60 (m, 4H), 1.92 (m, 46H), 2.01 (s, 3H), 2.03 (m, 46H), 2.40 (s, 4H), 4.01 (t, ^3J(H,H)=6.8 Hz, 2H), 6.23 (s, 1H), 6.38 (s, 5H), 7.24 (s, 1H), 7.30 ppm (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS): δ=21.0, 26.1, 28.0, 28.1, 29.7, 31.4, 32.8, 52.2, 57.6, 57.7, 64.5, 80.3, 171.8, 172.7, 172.8, 172.9 ppm; MS (MALDI-TOF): 2983.2 $[M+Na]^+$; elemental analysis calcd (%) for $C_{156}H_{270}N_8O_{44}$: C 63.26, H 9.19, N 3.78; found C 63.04, H 9.35, N 4.13.

Dendrimer 11: A solution of K_2CO_3 (0.150 g, 1.09 mmol) in H_2O (2 mL) was added at room temperature to a solution of **10** (1.61 g, 0.544 mmol) in MeOH (20 mL). After stirring for 2 h, the mixture was diluted with CH_2Cl_2 (80 mL) and then quenched with H_2O (20 mL). The resulting solution was extracted with CH_2Cl_2 (3×40 mL). The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, concentrated in vacuo, and purified by silica gel column chromatography by using EtOAc/hexane (2:1) as the eluent to afford dendrimer **11** as a white solid (1.46 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ= 1.26 (m, 4H), 1.43 (s, 153H), 1.63 (m, 4H), 1.94 (m, 46H), 2.03 (m, 46H), 2.40 (s, 4H), 3.60 (t, ^3J(H,H)=6.2 Hz, 2H), 6.34 (s, 2H), 6.41 (s, 1H), 6.44 (s, 3H), 7.44 ppm (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS): δ=28.1, 29.8, 31.5, 32.2, 32.8, 52.2, 57.3, 57.3, 57.7, 57.8, 62.3, 80.4, 172.7, 172.8, 172.9, 173.0 ppm; MS (MALDI-TOF): *m/z*: 2942.4 $[M+Na]^+$; elemental analysis calcd (%) for $C_{154}H_{268}N_8O_{43}$: C 63.35, H 9.25, N 3.84; found: C 62.82, H 9.19, N 4.30.

Dendrimer 1: Dendrimer **11** (0.165 g, 0.0565 mmol) was added to a suspension of PCC (14.6 mg, 0.0678 mmol) in CH_2Cl_2 (6 mL). After stirring for 3 h at room temperature the mixture was diluted with CH_2Cl_2 and filtered through Celite. The filtrate was concentrated in vacuo and purified by silica gel column chromatography by using EtOAc/hexane (7:3) as the eluent to afford **1** as a yellow solid (12.4 mg, 85%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ=1.26 (m, 2H), 1.43 (s, 153H), 1.63 (m, 4H), 1.94 (m, 46H), 2.03 (m, 46H), 2.40 (m, 6H), 6.41 (s, 2H), 6.44 (s, 3H), 7.32 (s, 1H), 7.41 (s, 2H), 9.61 ppm (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS): δ=28.1, 29.8, 31.5, 32.2, 32.8, 52.2, 57.3, 57.3, 57.7, 57.8, 80.4, 172.1, 172.7, 172.8, 173.2, 201.4 ppm; MS (MALDI-TOF): *m/z*: 2939.3 $[M+Na]^+$; elemental analysis calcd (%) for $C_{154}H_{266}N_8O_{43}$: C 63.39, H 9.19, N 3.84; found: C 62.88, H 9.11, N 3.54.

Dendron 12: A solution of **A** (0.654 g, 0.454 mmol) and succinic anhydride (0.0953 g, 0.953 mmol) in pyridine (15 mL) was stirred at room temperature for 48 h. The solution was concentrated under reduced pressure and the residue was dissolved in $CHCl_3$ and washed with an aqueous solution that contained 10% HCl (2×). The organic layer was dried over $MgSO_4$, filtered, and concentrated to dryness. The crude material was purified by silica gel column chromatography by using EtOAc/hexane (2:1) as the eluent to afford **12** as a white solid (0.60 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ=1.26 (m, 4H), 1.43 (s, 72H), 1.61 (m, 10H), 1.92 (m, 16H), 2.03 (s, 3H), 2.15 (m, 22H), 2.40 (m, 2H), 2.62 (m, 2H), 4.01 (t, ^3J(H,H)=6.6 Hz, 2H), 5.82 (s, 1H), 6.08 (s, 2H), 7.31 ppm (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS): δ=21.0, 24.2, 26.1, 28.5, 29.8, 30.1, 39.0, 40.1, 41.7, 64.6, 80.4, 170.3, 172.8, 173.2 ppm; MS (ESI): *m/z*: 1541.6 $[M+H]^+$; elemental analysis calcd (%) for $C_{80}H_{138}N_4O_{24}$: C 62.39, H 9.03, N 3.64; found: C 62.34, H 8.99, N 3.41.

Dendron 13: A solution of K_2CO_3 (0.127 g, 0.925 mmol) in H_2O (1 mL) was added at room temperature to a solution of dendron **12** (0.713 g, 0.463 mmol) in MeOH (8 mL). After stirring for 2 h, the mixture was diluted with CH_2Cl_2 (30 mL) and then quenched with H_2O (8 mL). The resulting solution was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with a saturated aqueous solution of NaCl, dried over $MgSO_4$, filtered, concentrated in vacuo, and purified by silica gel column chromatography by using EtOAc/hexane (2:1) as the eluent to afford dendron **13** as a white solid (0.626 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ=1.26 (m, 4H), 1.44 (s, 72H), 1.62 (m, 10H), 1.92 (m, 16H), 2.15 (m, 22H), 2.40 (m, 2H), 2.62 (m, 2H), 3.60 (t, ^3J(H,H)= 6.2 Hz, 2H), 6.08 (s, 2H), 6.12 (s, 1H), 7.31 ppm (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS): δ=21.0, 24.7, 25.9, 27.2, 28.3, 29.8, 30.0, 32.1, 40.1, 41.7, 62.5, 81.4, 172.1, 172.8, 173.2 ppm; MS (ESI): *m/z*: 1497.8 $[M+H]^+$; elemental analysis calcd (%) for $C_{78}H_{136}N_4O_{23}$: C 62.54, H 9.15, N 3.74; found C 62.52, H 9.02, N 3.65.

Dendrimer 14: DCC (0.039 g, 0.189 mmol) and 1-HOBT (0.026 g, 0.189 mmol) were added at room temperature to a solution of dendron **13** (0.236 g, 0.157 mmol) in DMF (9 mL). After the mixture was stirred for 2 h, dendron **A** (0.272 g, 0.189 mmol) was added and the resulting mixture was stirred for 3 d at room temperature. After filtration, the filtrate was concentrated in vacuo to give a yellow residue. The residue was dissolved in CH_2Cl_2 and washed with saturated aqueous solutions of $NaHCO_3$ (2×) and NaCl. The organic layer was dried over $MgSO_4$, filtered, concentrated in vacuo, and purified by silica gel column chromatography by using EtOAc/hexane (1:1) as the eluent to afford **14** as a white solid (0.338 g, 74%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ=1.24 (m, 4H), 1.44 (s, 144H), 1.53 (m, 2H), 1.60 (m, 2H), 1.92 (m, 48H), 2.03 (s, 3H), 2.10 (m, 48H), 2.40 (s, 4H), 3.60 (m, 2H), 4.00 (t, ^3J(H,H)= 6.8 Hz, 2H), 6.23 (s, 1H), 6.32 (s, 5H), 6.41 (s, 1H), 7.30 ppm (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS): δ=20.1, 21.0, 24.3, 26.1, 28.0, 28.6, 29.7, 32.4, 38.8, 40.3, 42.1, 62.6, 64.7, 80.9, 170.8, 171.8, 172.0, 173.0 ppm; MS (MALDI-TOF): *m/z*: 2942.4 $[M+Na]^+$; elemental analysis calcd (%) for $C_{154}H_{268}N_8O_{43}$: C 63.35, H 9.25, N 3.84; found: C 63.18, H 9.23, N 3.62.

Dendrimer 15: Dendrimer **14** (0.145 g, 0.0496 mmol) was added to the solution of PCC (0.0128 g, 0.0595 mmol) suspended in CH_2Cl_2 (5 mL). After stirring for 3 h at room temperature the mixture was diluted with CH_2Cl_2 (15 mL) and filtered through Celite. The filtrate was concentrated in vacuo and purified by preparatory TLC by using EtOAc/hexane (2:1) as the eluent to afford **15** as a yellow solid (0.122 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ=1.24 (m, 4H), 1.44 (s, 144H), 1.60 (m, 2H), 1.92 (m, 48H), 2.03 (s, 3H), 2.10 (m, 48H), 2.40 (m, 6H), 4.00 (t, ^3J-(H,H)=6.8 Hz, 2H), 6.23 (s, 1H), 6.32 (s, 5H), 6.41 (s, 1H), 7.30 (s, 1H), 9.61 ppm (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS): δ=20.1, 21.0, 24.3, 28.0, 28.1, 28.6, 29.7, 38.8, 40.3, 42.1, 43.3, 64.7, 80.9, 170.8, 171.8, 172.0, 173.0, 200.2 ppm; MS (MALDI-TOF): *m/z*: 2941.6$[M+Na]^+$; elemental analysis calcd (%) for $C_{154}H_{266}N_8O_{43}$: C 63.39, H 9.19, N 3.84; found C 63.34, H 9.11, N 3.68.

Dendrimer 16: A solution of K_2CO_3 (12.1 mg, 0.0877 mmol) in H_2O (1 mL) was added at room temperature to a solution of **15** (0.128 g, 0.0438 mmol) in MeOH (8 mL). After stirring for 2 h, the mixture was diluted with CH_2Cl_2 (40 mL) and then quenched with H_2O (8 mL). The resulting solution was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with a saturated aqueous solution of NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford **16** as a yellow solid (0.114 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ=1.24 (m, 4H), 1.44 (s, 144H), 1.60 (m, 2H), 1.92 (m, 48H), 2.10 (m, 48H), 2.40 (m, 6H), 3.62 (t, ^3J(H,H)=6.4 Hz, 2H), 6.23 (s, 1H), 6.32 (s, 5H), 6.41 (s, 1H), 7.30 (s, 1H), 9.61 ppm (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS): δ=20.1, 24.3, 25.6, 28.0, 28.1, 28.6, 29.7, 32.0, 38.8, 40.3, 42.1, 43.3, 63.1, 80.9, 171.8, 172.0, 173.0, 200.2 ppm; MS (MALDI-TOF): *m/z*: 2897.5 $[M+Na]^+$; elemental analysis calcd (%) for $C_{152}H_{264}N_8O_{42}$: C 63.48, H 9.25, N 3.90; found C 63.02, H 9.21, N 3.82.

Dendrimer 17: NEt_3 (0.016 mL, 0.131 mmol) and *p*-TsCl (0.025 g, 0.131 mmol) were added at 0°C to a solution of **16** (0.126 g, 0.0438 mmol) in CH_2Cl_2 (2 mL). After stirring for 1 h at 0°C, the mixture was warmed to room temperature and stirred for 20 h. The mixture was

quenched with H_2O and then extracted with CH_2Cl_2 (2×15 mL). The combined organic layers were washed with a saturated aqueous solution of NaCl, dried over $MgSO_4$, concentrated in vacuo, and purified by preparatory TLC by using EtOAc as the eluent to afford **17** as a yellow solid (0.103 g, 78%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.24 (m, 4H), 1.44 (s, 144H), 1.60 (m, 2H), 1.92 (m, 48H), 2.10 (m, 48H), 2.40 (m, 9H), 3.97 (t, ^3J(H,H) = 6.0 Hz, 2H), 6.23 (s, 1H), 6.32 (s, 5H), 6.41 (s, 1H), 7.30 (s, 1H), 7.44 (d, ^3J(H,H) = 5.8 Hz, 2H), 7.62 (d, ^3J(H,H) = 6.1 Hz, 2H), 9.61 ppm (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS): δ = 20.1, 21.2, 24.3, 25.6, 28.0, 28.1, 28.6, 28.7, 29.7, 38.8, 40.3, 42.1, 43.3, 69.7, 80.9, 128.0, 130.6, 140.3, 144.3, 171.8, 172.0, 173.0, 200.2 ppm; MS (MALDI-TOF): *m*/*z*: 3051.2 [*M*+Na]$^+$; elemental analysis calcd (%) for $C_{159}H_{270}N_8O_{44}S$: C 63.03, H 8.98, N 3.70; found: C 62.91, H 8.82, N 3.70.

Dendrimer 2: NaN_3 (0.0021 g, 0.0323 mmol) was added to a solution of **17** (0.065 g, 0.0215 mmol) in DMF. The reaction mixture was stirred at 80°C for 2 d. After the mixture was cooled down to room temperature, H_2O was added and the resulting solution was extracted with CH_2Cl_2 (3× 15 mL). The combined organic layers were washed with H_2O and then saturated NaCl solution, dried over $MgSO_4$, concentrated in vacuo and purified by preparatory TLC by using EtOAc as the eluent to afford **2** as a yellow solid (0.057 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.24 (m, 2H), 1.31 (m, 2H), 1.44 (s, 144H), 1.60 (m, 2H), 1.92 (m, 48H), 2.10 (m, 48H), 2.40 (m, 6H), 3.26 (m, 2H), 6.23 (s, 1H), 6.32 (s, 5H), 6.98 (s, 1H), 7.20 (s, 1H), 9.61 ppm (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS): δ = 20.1, 24.3, 25.6, 28.0, 28.1, 28.6, 29.7, 30.0, 38.8, 40.3, 42.1, 43.3, 49.7, 80.9, 171.8, 172.0, 173.0, 200.2 ppm; MS (MALDI-TOF): *m*/*z*: 2921.7 [*M*+Na]$^+$; elemental analysis calcd (%) for $C_{152}H_{263}N_{11}O_{41}$: C 62.94, H 9.14, N 5.31; found: C 62.81, H 9.10, N 5.34.

General procedure for Schiff base couplings: The appropriate hydrazide was added to a solution of **1** in ethanol (for **19a** and **19b**) or DMSO (for **19c**) and the reaction was stirred for 16 h at room temperature. The reaction mixture was concentrated in vacuo, redissolved in CH_2Cl_2, washed with H_2O and brine, dried over $MgSO_4$, and filtered. The solvent was removed in vacuo to give the target compound.

Compound 19a: Dendrimer **1** (50.0 mg, 0.017 mmol) was treated with phenyl hydrazine (1.85 mg, 0.017 mmol) to afford compound **19a** as a yellowish solid (50.1 mg, 98%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.26 (m, 2H), 1.31 (m, 2H), 1.43 (s, 153H), 1.63 (m, 4H), 1.94 (m, 46H), 2.17 (m, 46H), 2.40 (s, 4H), 6.41 (s, 2H), 6.44 (s, 5H), 6.91 (d, ^3J(H,H) = 8.2 Hz, 1H), 7.25 (d, ^3J(H,H) = 6.2 Hz, 2H), 7.32 (s, 1H), 7.34 (d, ^3J(H,H) = 5.6 Hz, 2H), 7.50 (t, ^3J(H,H) = 5.8 Hz, 1H), 10.73 ppm (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS): δ = 28.1, 29.8, 31.5, 32.2, 32.8, 52.2, 57.3, 57.3, 57.7, 57.8, 80.4, 115.4, 130.1, 142.8, 159.2, 172.1, 172.7, 172.8, 173.2 ppm; MS (MALDI-TOF): *m*/*z*: 3031.6 [*M*+Na]$^+$.

Compound 19b: Dendrimer **1** (12.0 mg, 0.004 mmol) was treated with anisic hydrazine (0.68 mg, 0.004 mmol) to afford compound **19b** as a yellowish solid (12.4 mg, 98%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.26 (m, 2H), 1.31 (m, 2H), 1.43 (s, 153H), 1.63 (m, 4H), 1.94 (m, 46H), 2.17 (m, 46H), 2.40 (s, 4H), 3.82 (s, 3H), 6.16 (s, 1H), 6.37 (*d*, ^3J(H,H) = 6.4 Hz, 1H), 6.41 (s, 2H), 6.44 (s, 5H), 6.91 (d, ^3J(H,H) = 8.2 Hz, 1H), 7.14 (m, 1H), 7.32 (s, 1H), 7.50 (t, ^3J(H,H) = 5.8 Hz, 1H), 10.72 ppm (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS): δ = 28.1, 29.8, 31.5, 32.2, 32.8, 52.2, 55.4, 57.2, 57.3, 57.7, 57.8, 80.4, 98.6, 106.1, 130.3, 143.6, 159.2, 161.5, 172.1, 172.7, 172.8, 173.2 ppm; MS (MALDI-TOF): *m*/*z*: 3059.5 [*M*+Na]$^+$.

Compound 19c: Dendrimer **1** (16.0 mg, 0.005 mmol) was treated with biotin hydrazide (1.41 mg, 0.005 mmol) to afford compound **19c** as a yellowish solid (16.2 mg, 97%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.24 (m, 2H), 1.26 (m, 2H), 1.31 (m, 2H), 1.43 (s, 153H), 1.52 (m, 2H), 1.63 (m, 6H), 1.94 (m, 46H), 2.17 (m, 46H), 2.32 (m, 2H), 2.40 (s, 4H), 2.83 (d, ^3J(H,H) = 5.2 Hz, 2H), 3.27 (m, 1H), 4.62 (t, ^3J(H,H) = 6.5 Hz, 1H), 4.91 (d, ^3J(H,H) = 7.0 Hz, 1H), 6.22 (s, 2H), 6.41 (s, 2H), 6.44 (s, 5H), 7.32 (s, 1H), 7.48 (t, ^3J(H,H) = 6.2 Hz, 1H), 10.52 ppm (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS): δ = 28.1, 29.8, 31.5, 32.2, 32.8, 38.8, 52.2, 55.1, 57.2, 57.3, 57.7, 57.8, 63.9, 80.4, 154.3, 166.2, 169.2, 172.1, 172.7, 172.8, 173.2 ppm; MS (MALDI-TOF): *m*/*z*: 3181.2 [*M*+Na]$^+$.

Compound 20: Dendrimer **2** (22.0 mg, 0.007 mmol) was treated with biotin hydrazide (1.9 mg, 0.007 mmol) to afford compound **20** as a yellowish solid (22.8 mg, 96%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.23 (m, 2H), 1.24 (m, 2H), 1.31 (m, 6H), 1.44 (s, 144H), 1.52 (m, 2H), 1.60 (m, 2H), 1.92 (m, 48H), 2.10 (m, 48H), 2.32 (m, 2H), 2.40 (m, 4H), 2.83 (d, ^3J(H,H) = 5.4 Hz, 2H), 3.26 (m, 2H), 3.27 (m, 1H), 4.62 (t, ^3J(H,H) = 6.1 Hz, 1H), 4.91 (d, ^3J(H,H) = 7.3 Hz, 1H), 6.23 (s, 3H), 6.32 (s, 5H), 6.98 (s, 1H), 7.20 (s, 1H), 7.48 (t, ^3J(H,H) = 7.2 Hz, 1H), 10.51 ppm (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS): δ = 20.1, 24.3, 25.6, 26.2, 28.0, 28.1, 28.6, 29.7, 30.0, 38.2, 38.8, 40.3, 42.1, 49.7, 55.2, 63.9, 80.9, 154.3, 166.3, 169.2, 171.8, 172.0, 173.0 ppm; MS (MALDI-TOF): 3164.4 [*M*+Na]$^+$.

Compound 21: Sodium ascorbate (10 mol%) and $CuSO_4$·5H_2O (5 mol%) were added to a solution of **20** (22.8 mg, 0.007 mmol) and propargyl glycine (0.82 mg, 0.007 mmol) in a 1:1 mixture of water/*t*BuOH (1 mL each) in a 10 mL glass vial equipped with a small magnetic stirrer bar. After the vial was tightly sealed with an aluminum/Teflon crimp top, the mixture was irradiated for 10 min by using the power–time control method (irradiation power: 100 W; maximum temperature: 100°C). During the reaction, the maximum temperature reached was 91°C. After completion of the reaction, the mixture was cooled down to room temperature and then diluted with CH_2Cl_2 (10 mL). The resulting solution was washed with water twice and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford **21** as a yellowish solid (22.9 mg, 97%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.23 (m, 2H), 1.24 (m, 2H), 1.31 (m, 6H), 1.44 (s, 144H), 1.52 (m, 2H), 1.60 (m, 2H), 1.92 (m, 48H), 2.10 (m, 48H), 2.32 (m, 2H), 2.40 (m, 4H), 2.83 (d, ^3J(H,H) = 5.4 Hz, 2H), 3.21 (d, ^3J(H,H) = 5.1 Hz, 2H), 3.27 (m, 1H), 4.22 (m, 1H), 4.42 (d, ^3J(H,H) = 5.7 Hz, 2H), 4.62 (t, ^3J(H,H) = 6.1 Hz, 1H), 4.91 (d, ^3J(H,H) = 7.3 Hz, 1H), 6.23 (s, 3H), 6.32 (s, 5H), 6.98 (s, 1H), 7.20 (s, 1H), 7.48 (t, ^3J(H,H) = 7.2 Hz, 1H), 7.57 (s, 1H), 10.51 (s, 1H), 12.47 ppm (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS): δ = 20.1, 24.3, 25.6, 26.2, 28.0, 28.1, 28.6, 29.7, 30.0, 38.2, 38.8, 40.3, 42.1, 49.7, 55.2, 63.9, 80.9, 154.3, 166.3, 169.2, 171.8, 172.0, 173.0 ppm; MS (MALDI-TOF): 3276.4 [*M*+Na]$^+$.

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