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# Orthogonally "Clickable" Biodegradable Dendrons

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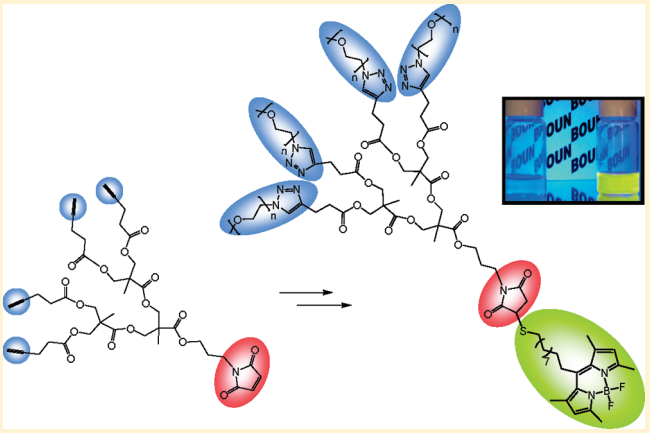
Supporting Information

**ABSTRACT:** A new class of biodegradable polyester dendrons which are orthogonally functionalizable have been synthesized and their multifunctionality has been demonstrated. The surface of these dendrons were appended with alkyne groups that can undergo efficient Huisgen type "click" cycloaddition reaction, while their focal point consists of a reactive maleimide group that can undergo facile conjugation with thiol containing molecules. Multiarm poly(ethylene glycol) polymer with a maleimide-based reactive focal point was synthesized using such a dendron. Solubilization of a hydrophobic dye, BODIPY-SH, in aqueous solution via conjugation to these reactive multiarm PEGs demonstrate possible applications of such dendrons to design water-soluble scaffolds for drug delivery.



## INTRODUCTION

Dendrimers are a unique class of globular macromolecules that are synthesized by stepwise organic reactions.[1−6] Their method of synthesis makes dendrimers monodisperse, which is a desirable but still hard to achieve property for macromolecules. The fact that they are monodisperse makes them promising scaffolds for drug delivery.[7−10] Another advantage that stems from the dendrimers architecture is the multivalency provided by the large number of functional groups at the periphery of the dendritic structure. It is possible to supplement the multivalent nature of dendritic structures with multifunctionality by incorporation of orthogonally functionalizable reactive groups.[11−17]

Dendrons serve as the building blocks or components that are stitched together during a "convergent" approach toward dendrimer synthesis. These building blocks once primarily used for the aforementioned purpose are increasingly becoming common building blocks for synthesis of novel macromolecular architectures such as dendronized polymers, and dendron-linear polymer conjugates. In recent years, dendrons have been widely used to obtain multivalent initiators bearing cores for synthesis of star polymers.[18,19] As an alternative, near monodisperse polymers such as poly(ethylene glycol)s have been conjugated to dendrons to provide dendron-polymer hybrids that possess the well-defined structure and monodisperse attributes of dendrimers.[20] Devising these kinds of systems on macromolecular scaffolds is very desirable, especially in areas of polymer conjugated drug delivery. Attachment of PEG chains to drug molecules has been studied extensively both as dendritic structures and as linear scaffolds to increase bioavailability. Interestingly, the branched structure of polymeric scaffolds was found to increase the circulation time of drug molecules compared to the linear polymers of the same molecular weight.[21,22]

Recent years have focused on extending the multivalent nature of polymeric structures to simultaneously allow incorporation of multifunctionality. Successful strategies have been demonstrated by Hawker and co-workers for functionalization of polymers using the copper catalyzed Huisgen type 1,3-dipolar cycloaddition with other chemistries such as esterification and amidation.[23] An elegant study of simultaneous orthogonal functionalization of polymers with thiol and amine group containing molecules was reported by Thayumanavan and co-workers.[24] Recently Weck et al. demonstrated orthogonal multifunctionalization of polymers by using copper catalyzed 1,3-dipolar cycloaddition, hydrazone formation and thiol conjugation.[25,26] Furthermore, such orthogonal transformations have recently been utilized for efficient synthesis of macromolecules such as dendrimers, star polymers and heterograft copolymer synthesis.[27−31]

Alternative "click" reactions that have emerged as valuable tools in macromolecular engineering have been the Diels−Alder cycloaddition and thiol-maleimide conjugation reaction. The incorporation of maleimide unit into macromolecular constructs allow facile attachment of a variety of molecules since the maleimide moiety participates efficiently in Michael addition reactions with thiols and Diels−Alder cycloaddition reactions with electron rich diene containing molecules.[32−38]

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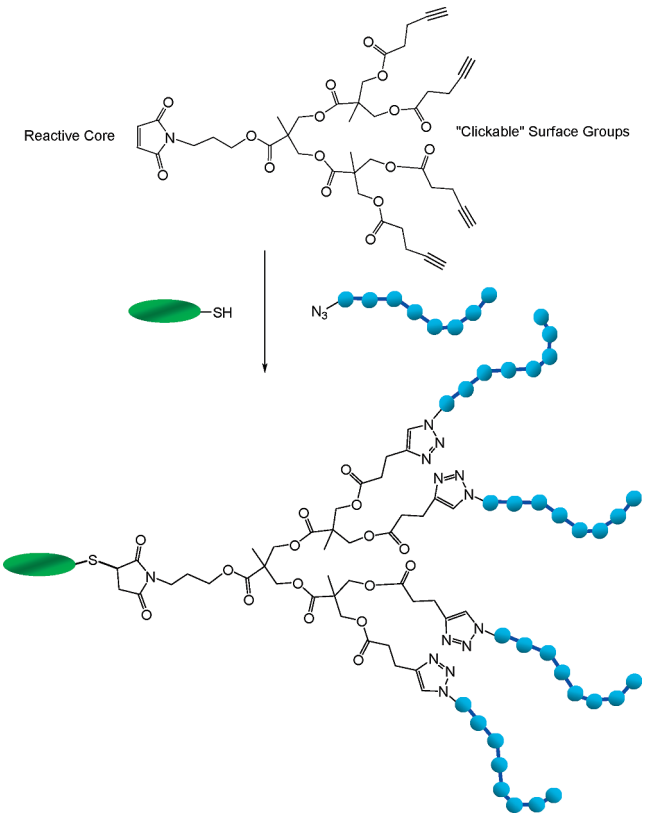
**Scheme 1. Orthogonally Functionalizable Dendron as a Scaffold for Core Reactive Multiarm Polymers**



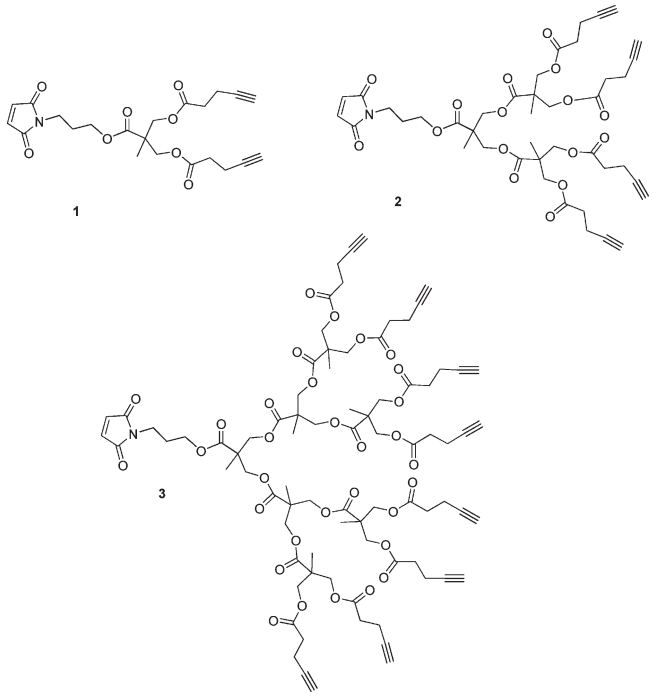




**Figure 1.** Chemical structures of the orthogonally functionalizable dendrons.

Herein we report synthesis of orthogonally functionalizable and biodegradable bis-MPA based dendrons that are furnished with alkyne moieties at the periphery and a maleimide group at the focal point. In order to provide examples demonstrating one-pot orthogonal functionalization property of these novel dendrons, a series of reactions with benzyl azide and undecene thiol was made. Furthermore, to demonstrate the utility of their multifunctionality, the periphery of these dendrons were modified with PEG chains via copper catalyzed Huisgen click reaction and the focal point was employed to attach BODIPY thiol, a hydrophobic dye via efficient Michael addition (Scheme 1).

## EXPERIMENTAL SECTION

**Materials and Characterization.** Chemicals were purchased from commercial resources and were used as received unless otherwise stated. Characterization of compounds were carried out with $^1$H and $^{13}$C solution NMR spectroscopy (Varian 400 MHz), Fourier transform infrared (FTIR) spectra were recorded on a Nicolet 360 spectrometer. Gel Permeation Chromatography (GPC) data was acquired with Viscotek GPCmax VE-2001 analysis system. PLgel (length/ID 300 mm × 7.5 mm, 5 $\mu$m particle size) Mixed-C column was calibrated with polystyrene standards, using refractive index detector. THF was used as eluent at a flow rate of 1 mL/min at 30 °C.

**Synthesis of 1b.** Compounds **A** and **B** were prepared according to previously reported literature procedures.[39,40] To a solution of **A** (2.37 g, 10.50 mmol) in dry $CH_2Cl_2$ (9 mL), **B** (5.20 g, 15.7 mmol), DMAP (0.52 g, 4.20 mmol) and pyridine (3.2 mL) was added. The mixture was stirred at ambient temperature for 12 h followed by quenching of excess anhydride with (1:1) mixture of pyridine and water (4.0 mL) for 12 h. Reaction mixture was extracted with 1 M $NaHSO_4$ (3 × 20 mL), 10% $Na_2CO_3$ (3 × 20 mL) and then with brine (1 × 20 mL) combined organic layers were dried over anhydrous $Na_2SO_4$. The residue was concentrated *in vacuo*. Crude product was purified by column chromatography and then the isolated product was dissolved in MeOH (30 mL) and to this solution Dowex H+ resin was added with a tip of spatula. The resulting mixture was stirred at ambient temperature until the consumption of the starting material was observed via TLC. The resin was then filtered off and washed with MeOH. The filtrate was concentrated *in vacuo* to give a white solid, **1a** (1.78 g, 99% yield). **1a** (0.4 g, 1.1 mmol) was then added to a solution of DMAP (0.07 g, 0.6 mmol), pyridine (0.8 mL) and compound **C** (0.60 g, 3.3 mmol) in dry $CH_2Cl_2$ (5 mL). The mixture was then stirred at room temperature for 12 h. Excess anhydride was quenched with water (2.0 mL) for 3 h. Reaction mixture was diluted with 50 mL $CH_2Cl_2$ and extracted with 1 M $NaHSO_4$ (3 × 20 mL), 10% $Na_2CO_3$ (3 × 20 mL) and then with brine (1 × 20 mL) combined organic layers were dried over anhydrous $Na_2SO_4$. The residue was concentrated *in vacuo*. Crude product was purified by column chromatography to give 0.52 g of **1b** as a colorless viscous liquid (95% yield).

$^1$H NMR ($CDCl_3$, $\delta$, ppm): 6.49 (s, 2H, C*H*═C*H*), 5.24 (s, 2H, C*H* bridgehead protons), 4.28 (dd, 4H, $J$ = 18.8, 11.1 Hz, $CH_2$ ester protons), 4.07 (t, 2H, $J$ = 6.2 Hz, $OCH_2$), 3.55 (t, 2H, $J$ = 6.8 Hz, $NCH_2$), 2.82 (s, 2H, bridge protons), 2.57(m, 4H, $CH_2CH_2C \equiv CH$), 2.45 (m, 4H, $CH_2CH_2C{\equiv}CH$), 1.96 (t, 2H, $J$ = 2.54 Hz, $C \equiv CH$), 1.91 (tt, 2H, $J$ = 6.8, 6.4 Hz, $NCH_2CH_2CH_2O$), 1.27 (s, 3H, $CCH_3$). $^{13}$C NMR ($CDCl_3$, $\delta$, ppm): 176.0, 172.4, 171.1, 136.4, 82.3, 80.9, 69.2, 65.4, 61.9, 47.3, 46.2, 35.2, 33.1, 26.6, 17.8, 14.2. FTIR ($cm^{-1}$): 1732.0, 1695.1.

**Synthesis of 2b.** Compound **1a** (1.1 g, 3.2 mmol) was added to a solution of DMAP (0.30 g, 2.4 mmol), pyridine (2.0 mL) and **B** (3.20 g, 9.7 mmol) in dry $CH_2Cl_2$ (5 mL). The mixture was then stirred at room temperature for 12 h. Excess anhydride was quenched with (1:1) mixture of pyridine and water (4.5 mL) for 12 h. Reaction mixture was

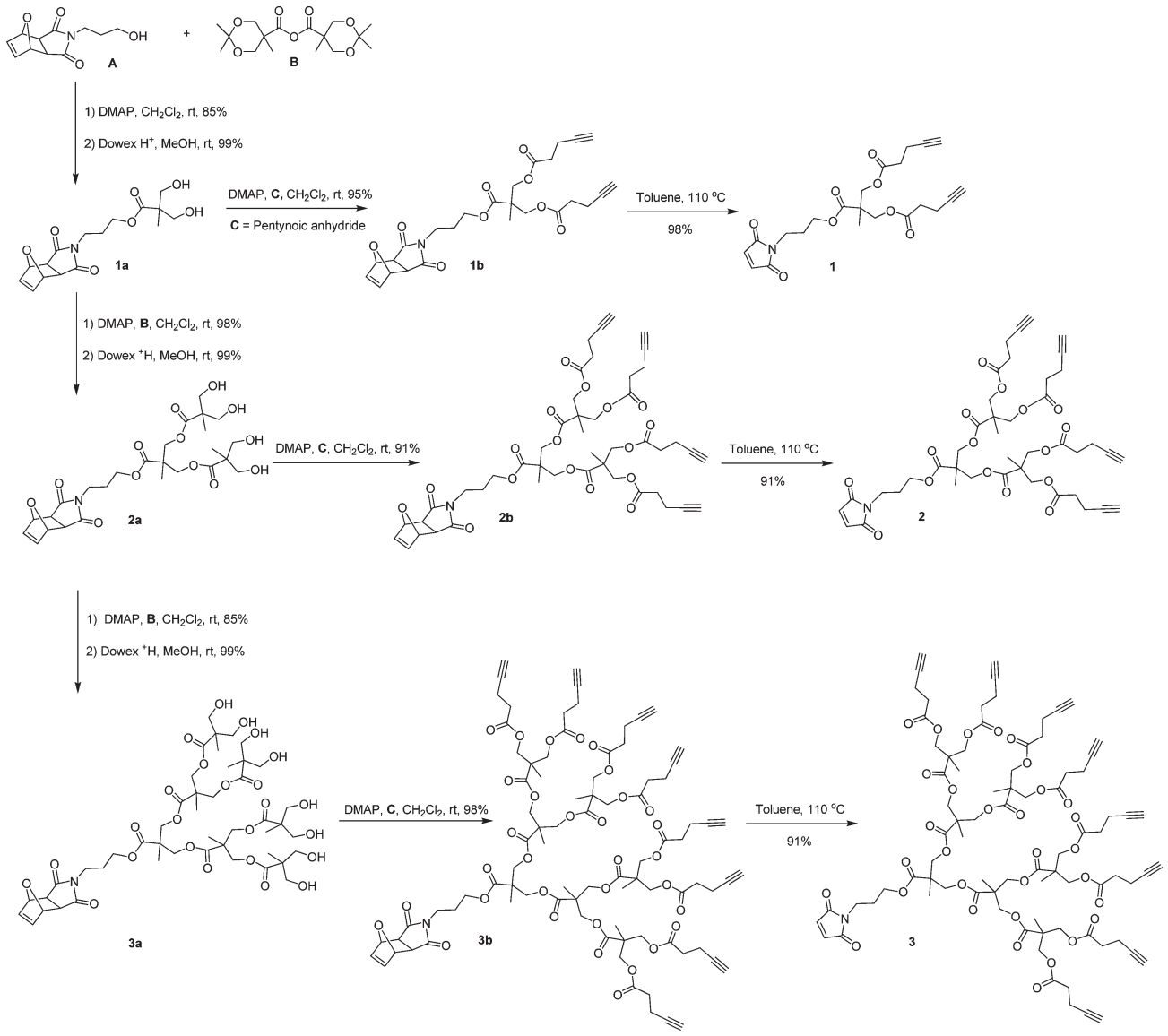



**Figure 2.** Synthesis of bifunctional dendrons.

diluted with 50 mL $CH_2Cl_2$ and extracted with 1 M $NaHSO_4$ (3 × 20 mL), 10% $Na_2CO_3$ (3 × 20 mL) and then with brine (1 × 20 mL) combined organic layers were dried over anhydrous $Na_2SO_4$. The residue was concentrated *in vacuo*. Crude product was purified by column chromatography. The isolated product was then dissolved in MeOH (10 mL) and to this solution Dowex $H^+$ resin was added with the tip of a spatula. The resulting mixture was stirred at ambient temperature until the consumption of was observed via TLC. The resin was then filtered off and washed with MeOH. The filtrate was concentrated *in vacuo* to give a white solid, **2a**, (0.86 g, 98% yield). **2a** (0.14 g, 0.20 mmol) was then added to a solution of DMAP (0.03 g, 0.20 mmol), pyridine (0.4 mL) and **C** (0.26 g, 1.20 mmol) in dry $CH_2Cl_2$ (3 mL). The mixture was then stirred at room temperature for 12 h. Excess anhydride was quenched with water (2.0 mL) for 3 h. Reaction mixture was diluted with 20 mL $CH_2Cl_2$ and extracted with 1 M $NaHSO_4$ (3 × 20 mL), 10% $Na_2CO_3$ (3 × 20 mL) and then with brine (1 × 20 mL) combined organic layers were dried over anhydrous $Na_2SO_4$. The residue was concentrated in *vacuo*. Crude product was purified by column chromatography to give 0.20 g of **2b** as a colorless viscous liquid (91% yield).

$^1$H NMR ($CDCl_3$, $\delta$, ppm): 6.50 (s, 2H, C*H*═C*H*), 5.24 (s, 2H, C*H* bridgehead protons), 4.27 (s, 4H), 4.24 (d, 4H, *J* = 11.3 Hz, $CH_2$ ester protons), 4.21 (d, 4H, *J* = 11.2 Hz, $CH_2$ ester protons), 4.04 (t, 2H, *J* = 6.2 Hz, $OCH_2$), 3.56 (t, 2H, *J* = 6.8 Hz, $NCH_2$), 2.84 (s, 2H, bridge protons), 2.56−2.53 (m, 8H, $CH_2CH_2C{\equiv}CH$), 2.49−2.44 (m, 8H, $CH_2CH_2C{\equiv}CH$), 1.96 (t, 4H, *J* = 2.6 Hz, C≡C*H*), 1.92 (tt, 2H, *J* = 6.8, 6.2 Hz, $NCH_2CH_2CH_2O$), 1.27 (s, 3H, $CCH_3$), 1.23 (s, 6H, $CCH_3$). $^{13}$C NMR ($CDCl_3$, $\delta$, ppm): 176.1, 171.9, 171.8, 171.1, 136.4, 82.3, 80.9, 69.2, 65.6, 65.3, 61.9, 47.4, 46.6, 46.3, 35.2, 33.1, 26.5, 17.8, 17.5, 14.2. FTIR ($cm^{-1}$): 1732.0, 1697.8.

**Synthesis of 3b.** Compound **2b** (1.1 g, 3.2 mmol) was added to a solution of DMAP (0.30 g, 2.4 mmol), pyridine (2.0 mL) and **B** (3.20 g, 9.7 mmol) in dry $CH_2Cl_2$ (5 mL). The mixture was then stirred at room temperature for 12 h. Excess anhydride was quenched with (1:1) mixture of pyridine and water (4.5 mL) for 12 h. Reaction mixture was diluted with 50 mL $CH_2Cl_2$ and extracted with 1 M $NaHSO_4$ (3 × 20 mL), 10% $Na_2CO_3$ (3 × 20 mL) and then with brine (1 × 20 mL) combined organic layers were dried over anhydrous $Na_2SO_4$. The residue was concentrated *in vacuo*. Crude product was purified by column chromatography and then the isolated product was dissolved in MeOH (8 mL) and to this solution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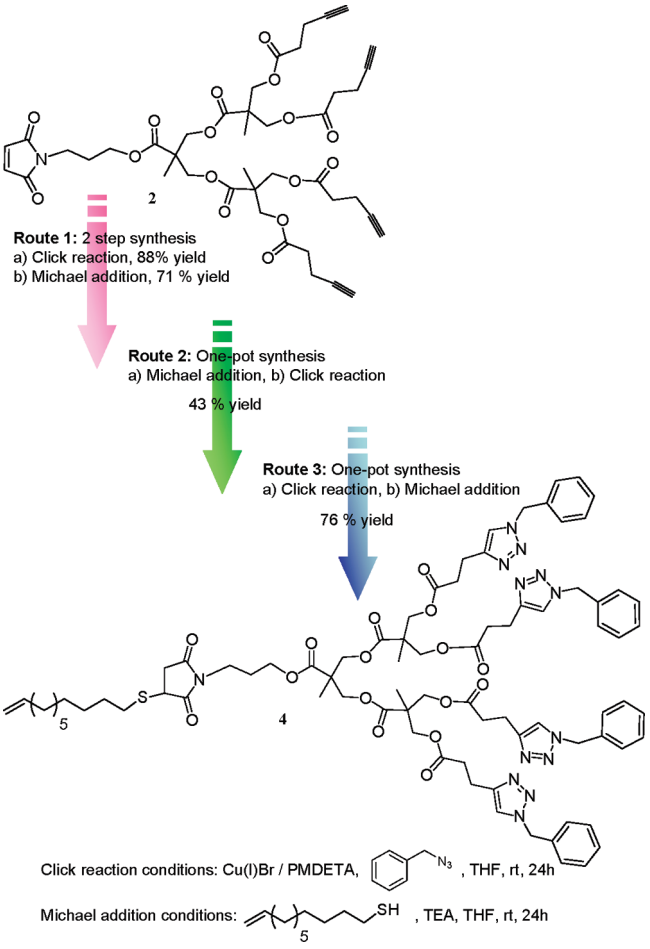


**Figure 3.** Model reactions to demonstrate the orthogonal reactivity of the dendrons.

Dowex $H^+$ resin was added with a tip of spatula. The resulting mixture was stirred at ambient temperature until the consumption of the starting material was observed via TLC. The resin was then filtered off and washed with MeOH. The filtrate was concentrated in *vacuo* to give **3a** as a white solid (0.17 g, 98% yield). **3a** (0.09 g, 0.1 mmol) was then added to a solution of DMAP (0.02 g, 0.2 mmol), pyridine (0.3 mL) and compound **C** (0.24 g, 1.4 mmol) in dry $CH_2Cl_2$ (5 mL). The mixture was then stirred at room temperature for 12 h. Excess anhydride was quenched with water (3.0 mL) for 12 h. Reaction mixture was diluted with 30 mL $CH_2Cl_2$ and extracted with 1 M $NaHSO_4$ (3 × 20 mL), 10% $Na_2CO_3$ (3 × 20 mL) and then with brine (1 × 20 mL) combined organic layers were dried over anhydrous $Na_2SO_4$. The residue was concentrated in *vacuo*. Crude product was purified by column chromatography to give 0.15 g of **3b** as a colorless viscous liquid (98% yield).

$^1$H NMR ($CDCl_3$, $\delta$, ppm) 6.50 (s, 2H, C*H*═C*H*), 5.23 (s, 2H, C*H* bridgehead protons), 4.30−4.19 (m, 28H, $CH_2$ ester protons), 4.05 (t, 2H, $J$ = 6.0 Hz, $OCH_2$), 3.56 (t, 2H, $J$ = 6.6 Hz, $NCH_2$), 2.84 (s, 2H, bridge protons), 2.56−2.53 (m, 16H, $CH_2CH_2C{\equiv}CH$), 2.48−2.44 (m, 16H, $CH_2CH_2C{\equiv}CH$), 1.97 (t, 8H, $J$ = 2.4 Hz, C ≡ C*H*), 1.93 (tt, 2H, $J$ = 6.6, 6.0 Hz, $NCH_2CH_2CH_2O$), 1.30 (s, 3H, $CCH_3$), 1.24 (s, 6H, $CCH_3$), 1.23 (s, 12H, $CCH_3$). $^{13}$C NMR ($CDCl_3$, $\delta$, ppm): 176.1, 171.8, 171.7, 171.4, 171.0, 136.5, 82.3, 80.9, 69.3, 66.1, 65.3, 65.2, 62.1, 47.4, 46.7, 46.6, 46.3, 35.2, 33.1, 26.6, 17.7, 17.5, 17.4, 14.2. FTIR ($cm^{-1}$): 1731.6, 1699.0

**Synthesis of 1.** Compound **1b** (0.14 g, 0.28 mmol) was dissolved in dry toluene (15 mL) and the mixture was heated to reflux. Progress of the reaction was monitored by TLC until consumption of compound **1b** is observed. The mixture was then concentrated *in vacuo* to give **1** (0.12 g, 98%) as a pale yellow viscous liquid.

$^1$H NMR ($CDCl_3$, $\delta$, ppm): 6.68 (s, 2H, C*H*═C*H*), 4.29 (d, 2H, $J$ = 11.2 Hz, $CH_2$ ester protons), 4.24 (d, 2H, $J$ = 11.2 Hz, $CH_2$ ester protons), 4.08 (t, 2H, $J$ = 6.2 Hz, $OCH_2$), 3.59 (t, 2H, $J$ = 6.8 Hz, $NCH_2$), 2.56−2.53 (m, 4H, $CH_2CH_2C{\equiv}CH$), 2.48−2.44 (m, 4H, $CH_2CH_2C{\equiv}CH$), 1.99−1.90 (m, 4H, C≡C*H* and $NCH_2CH_2CH_2O$), 1.26 (s, 3H, $CCH_3$). $^{13}$C NMR ($CDCl_3$, $\delta$, ppm): 172.5, 171.2, 170.5, 134.2, 82.3, 69.2, 65.5, 62.2,46.4, 34.6, 33.2, 27.6, 17.8, 14.3. FTIR ($cm^{-1}$): 1732.5, 1701.8. Anal. Found: C, 61.2; H, 5.9; N, 3.7. Calcd for $C_{22}H_{25}NO_8$: C, 61.25; H, 5.8; N, 3.25.

**Synthesis of 2.** Compound **2b** (0.25 g, 0.28 mmol) was dissolved in dry toluene (15 mL) and the mixture was heated to reflux. Progress of the reaction was monitored by TLC until consumption of compound **2b** is observed. The mixture was then concentrated *in vacuo* to give **2** (0.20 g, 91%) as a pale yellow viscous liquid.

$^1$H NMR ($CDCl_3$, $\delta$, ppm): 6.70 (s, 2H, C*H*═C*H*), 4.26 (s, 4H, $CH_2$ ester protons), 4.25 (d, 4H, $J$ = 11.2 Hz, $CH_2$ ester protons), 4.21 (d, 4H, $J$ = 11.2 Hz, $CH_2$ ester protons), 4.07 (t, 2H, $J$ = 6.4 Hz, $OCH_2$), 3.61 (t, 2H, $J$ = 6.4 Hz, $NCH_2$), 2.56−2.53 (m, 8H, $CH_2CH_2C{\equiv}CH$), 2.48−2.44 (m, 8H, $CH_2CH_2C{\equiv}CH$), 1.98−1.92 (m, 6H, C≡C*H* and $NCH_2CH_2CH_2O$), 1.27 (s, 3H, $CCH_3$), 1.24 (s, 6H, $CCH_3$). $^{13}$C NMR ($CDCl_3$, $\delta$, ppm): 171.6, 170.8, 170.3, 133.9, 82.1, 69.1, 65.3, 65.0, 61.9, 46.3, 46.0, 34.0, 32.8, 27.2, 17.5, 17.3, 13.9. FTIR ($cm^{-1}$): 1732.2, 1704.7. Anal. Found: C, 61.15; H, 6.0; N, 2.0. Calcd for $C_{42}H_{49}NO_{16}$: C, 60.8; H, 5.85; N, 1.7.

**Synthesis of 3.** Compound **3b** (0.07 g, 0.042 mmol) was dissolved in dry toluene (10 mL) and the mixture was heated to reflux. Progress of the reaction was monitored by TLC until consumption of compound **3b** is observed. The mixture was then concentrated *in vacuo* to give **3** (0.06 g, 91%) as a pale yellow viscous liquid.

$^1$H NMR ($CDCl_3$, $\delta$, ppm) 6.71 (s, 2H, C*H*═C*H*), 4.30−4.19 (m, 28H, $CH_2$ ester protons), 4.09 (t, 2H, $J$ = 5.6 Hz, $OCH_2$), 3.61 (t, 2H, $J$ = 6.0 Hz, $NCH_2$), 2.56−2.52 (m, 16H, $CH_2CH_2C{\equiv}CH$), 2.50−2.44 (m, 16H, $CH_2CH_2C{\equiv}CH$), 1.97 (bs, 8H, C≡C*H*), 1.84 (bm, 2H, $NCH_2CH_2CH_2O$), 1.30 (s, 3H, $CCH_3$), 1.23 (s, 18H, $CCH_3$). $^{13}$C NMR ($CDCl_3$, $\delta$, ppm): 171.9, 171.8, 171.4, 171.1, 170.6, 134.2, 82.3, 69.3, 66.2, 65.3, 65.2, 62.4, 46.7, 46.6, 46.3, 34.4, 33.1, 27.5, 17.8, 17.52, 17.48, 14.3, FTIR ($cm^{-1}$): 1731.1, 1707.4. Anal. Found: C, 61.2; H, 5.9; N, 1.0. Calcd for $C_{82}H_{97}NO_{32}$: C, 61.2; H, 6.1; N, 0.9.

**Synthesis of 4 According to Route 1.** Compound **2** (0.05 g, 0.061 mmol) was dissolved in 3 mL of THF and benzyl azide (0.04 g, 0.27 mmol), $Cu^IBr$ (0.003 g, 0.02 mmol), and PMDETA (5.01 $\mu$L, 0.02 mmol) were then added to the solution and the mixture was stirred at ambient temperature for 24 h. The mixture was then diluted with $CH_2Cl_2$ (10 mL) and extracted with water (3 × 10 mL) combined organic layers were dried over anhydrous $Na_2SO_4$. The residue was concentrated in *vacuo*. Crude product was purified by column chromatography to give 0.07 g of **4a** (88% yield). 0.04 g of the isolated compound (0.03 mmol) was dissolved in 1 mL THF along with undecene thiol (0.007 g, 0.04 mmol) and triethylamine (0.3 mL) and was stirred at room temperature for 24 h. The mixture was then diluted with $CH_2Cl_2$ (10 mL) and extracted with water (2 × 10 mL), combined organic layers were dried over anhydrous $Na_2SO_4$ and the residue was concentrated in *vacuo*. The crude product was purified by column chromatography to give 0.03 g of **4** (71% yield).

$^1$H NMR ($CDCl_3$, $\delta$, ppm) 7.31−7.18 (m, 24H, aromatic and triazole C*H*═C*H*), 5.75 (tt, 1H, $J$ = 17.0, 6.6 Hz, $CH_2$ = C*H*), 5.41 (s, 8H, benzylic protons), 4.98−4.84 (m, 2H, $CH_2$═CH), 4.16 (s, 4H, $CH_2$ ester protons), 4.08−3.98 (m, 10H, $CH_2$ ester protons and $OCH_2$), 3.51 (t, 2H, $J$ = 6.9 Hz, $NCH_2$), 3.08 (dd, 1H, $J$ = 18.6, 9.0 Hz, $CH_2$−CH−S), 2.90 (t, 8H, $J$ = 7.3 Hz, $CH_2CH_2C_2H_3N_3$), 2.83−2.76 (m, 1H, CH−S−$CH_2$), 2.64 (m, 10H, $CH_2CH_2C_2H_3N_3$ and $CH_2$−S), 2.42

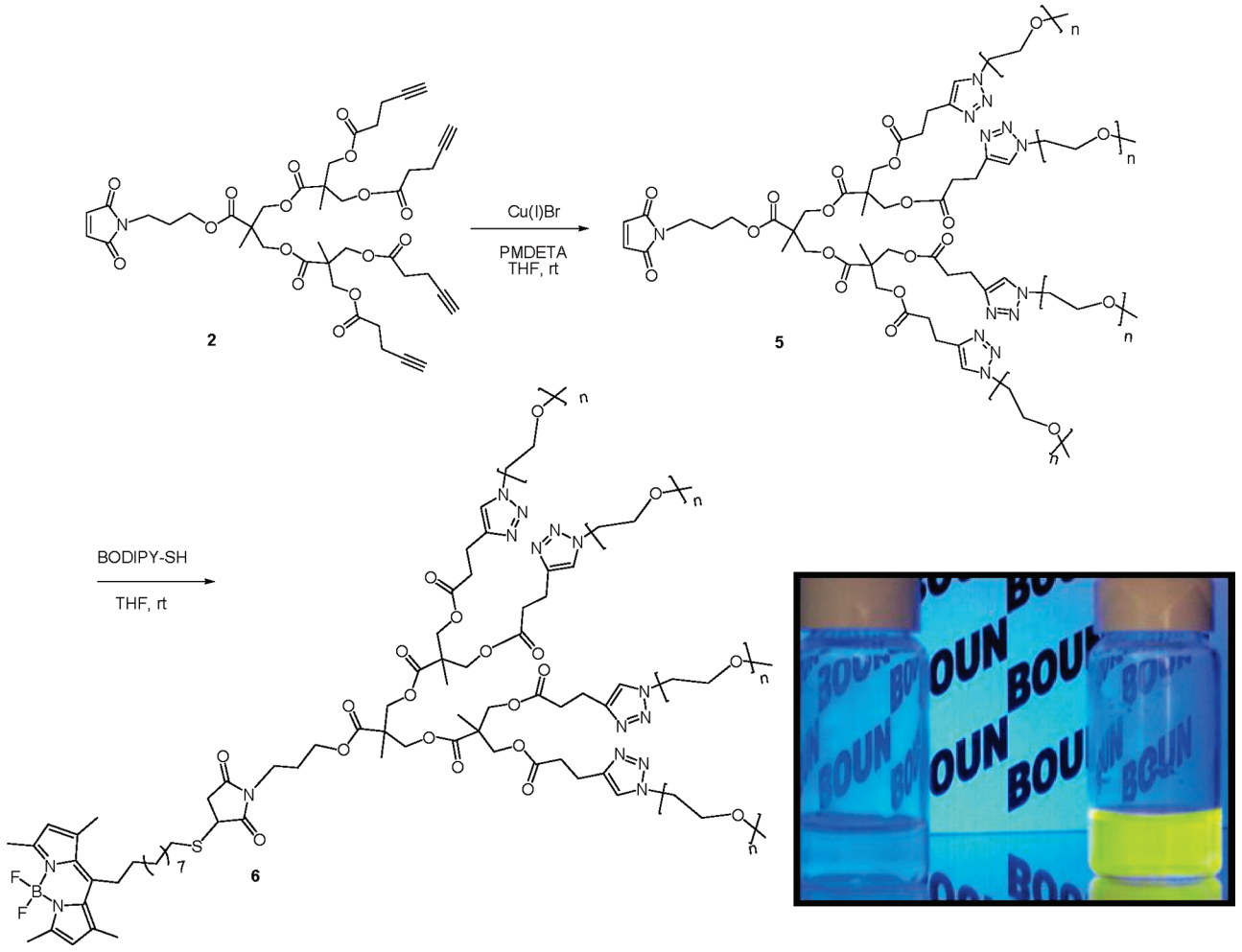


**Figure 4.** Orthogonal functionalization of dendron **2**. Inset: Aqueous solution of BODIPY-SH (on the left) and aqueous solution of polymer conjugated BODIPY-SH **6** (on the right).

(dd, 1H, $J$ = 18.6, 15.1 Hz, $CH_2$−CH−S), 2.00−1.95 (m, 2H, $NCH_2CH_2CH_2O$), 1.86 (m, 2H, $CH_2$=CH−$CH_2$), 1.31−1.18 (m, 18H, $CH_2$ protons of undecene thiol and $CCH_3$), 1.06 (s, 6H, $CCH_3$). $^{13}$C NMR ($CDCl_3$, $\delta$, ppm): 176.6, 174.7, 172.0, 171.95, 171.91, 146.5, 139.2, 134.9, 129.0, 128.6, 128.0, 121.2, 114.1, 65.6, 65.1, 62.2, 53.9, 46.5, 46.3, 39.1, 36.1, 35.4, 33.8, 33.2, 31.8, 29.38, 29.36, 29.1, 29.05, 28.95, 28.86, 28.7, 26.6, 20.9, 17.6, 17.5. ESI-TOF: $m/z$ calcd for $[M + H]^+$, 1542.7130; found, 1542.7126.

**Synthesis of 4 According to Route 2.** Compound **2** (0.03 g, 0.036 mmol) was dissolved in 3 mL of THF, and benzyl azide (0.02 g, 0.16 mmol), triethyl amine (5.00 $\mu$L, 0.036 mmol), and undecene thiol (0.01 g, 0.06 mmol) were then added to the solution and the mixture was stirred at ambient temperature for 24 h. Without any isolation, $Cu^IBr$ (0.002 g, 0.01 mmol), and PMDETA (3.01 $\mu$L, 0.01 mmol) was added to the reaction mixture solution and the mixture was stirred at ambient temperature for another 24 h. The mixture was then diluted with $CH_2Cl_2$ (10 mL) and extracted with water (3 × 10 mL) combined organic layers were dried over anhydrous $Na_2SO_4$. The residue was concentrated *in vacuo*. Crude product was purified by column chromatography to give 0.02 g of **4** (43% yield).

**Synthesis of 4 According to Route 3.** Compound **2** (0.03 g, 0.036 mmol) was dissolved in 3 mL of THF, and benzyl azide (0.02 g, 0.16 mmol), $Cu^IBr$ (0.002 g, 0.01 mmol), and PMDETA (3.01 $\mu$L, 0.01 mmol) were then added to the solution and the mixture was stirred at ambient temperature for 24 h. Without any isolation, a solution of triethyl amine (5.00 $\mu$L, 0.036 mmol) and undecene thiol (0.03 g, 0.14 mmol) in 3 mL of THF was added to the reaction mixture and stirred at ambient temperature for 24 h. The mixture was then diluted with $CH_2Cl_2$ (10 mL) and extracted with water (3 × 10 mL) combined organic layers were dried over anhydrous $Na_2SO_4$. The residue was concentrated *in vacuo*. Crude product was purified by column chromatography to give 0.04 g of **4** (76% yield).

**Synthesis of Multiarm PEG-BODIPY Conjugate 6.** $PEG_{750}N_3$ was prepared according to previously reported literature procedure.[34] $PEG_{750}N_3$ (0.166 g, 0.218 mmol) was dissolved in THF and mixed with compound **2** (0.04 g, 0.048 mmol) in the presence of Cu(I)Br/PMDETA catalyst system under $N_2$ atmosphere. The mixture was then stirred at room temperature for 24 h. Product was purified by precipitation in ether and dialysis to give **5** (0.14 g, 69%) as a light brown viscous liquid. GPC revealed a single monomodal peak $M_n$ = 3445, PDI = 1.1. Compound **5** (0.008 g, 0.002 mmol) was dissolved in THF and mixed with Bodipy-SH (0.008 g, 0.02 mmol). The reaction mixture was then stirred at room temperature for 24 h. HNMR of the crude revealed complete consumption of the maleimide functional group. Product was purified by $SiO_2$ column chromatography using $MeOH/CH_2Cl_2$ solution as a solvent.

## RESULTS AND DISCUSSION

Three generations of biodegradable polyester dendrons that can be functionalized at the periphery and the focal point using

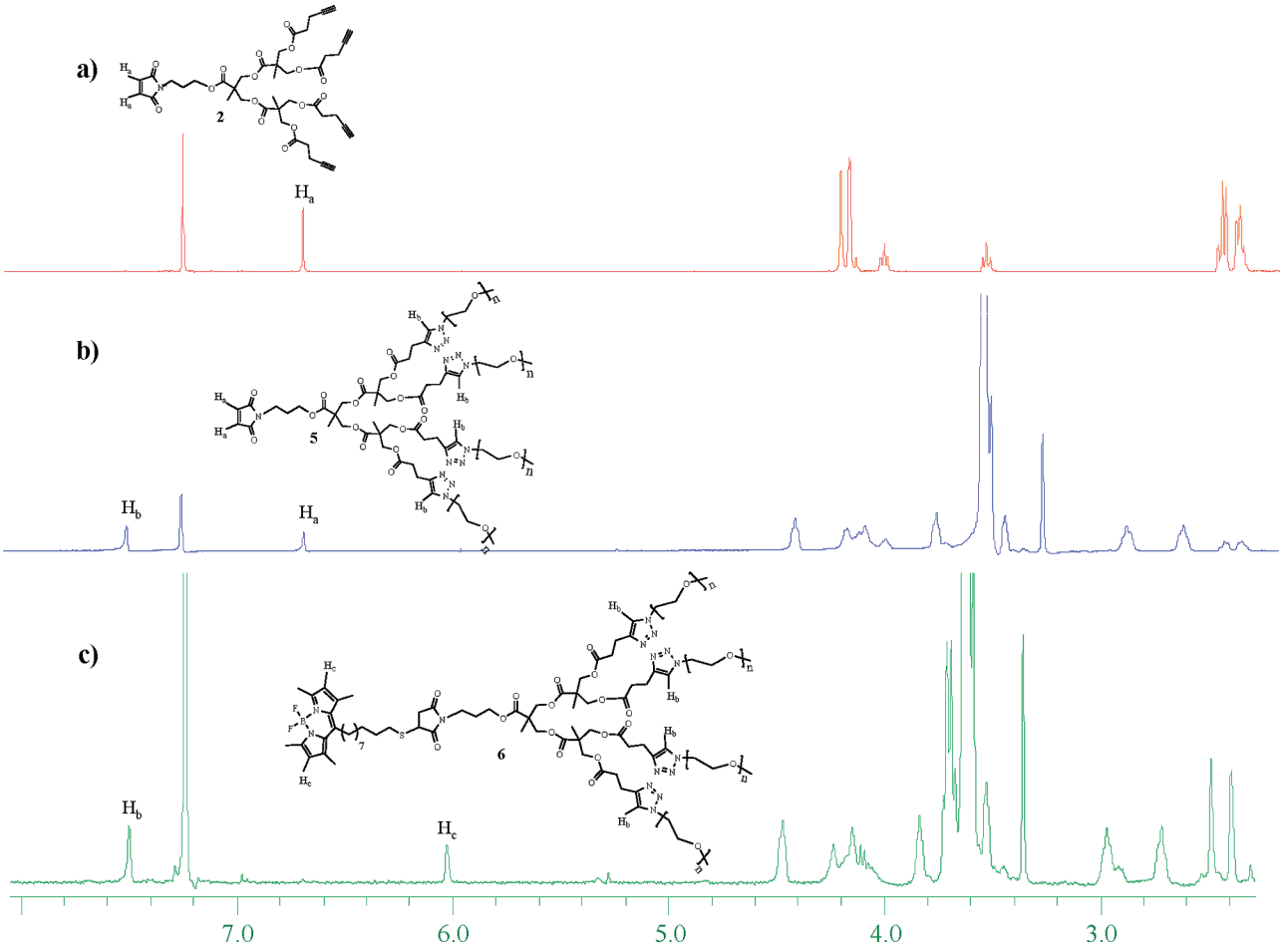


**Figure 5.** $^1$H NMR spectrum: (a) dendron **2**; (b) dendron **2** + $PEG_{750}$ after click reaction; (c) dendron **2** + $PEG_{750}$ + BODIPY dye after Michael addition to the maleimide unit.

orthogonal chemical transformations were designed (Figure 1). The periphery of dendrons was appended with alkyne functional groups capable of undergoing copper catalyzed Huisgen type [3 + 2] cycloaddition reaction with azide containing molecules. The focal point of the dendrons consists of electron deficient maleimide units that can undergo either a [4 + 2] cycloaddition reaction with diene appended molecules or a Michael type conjugate addition with molecules containing a thiol unit.

During the synthesis of the dendrons, maleimide unit was protected with a furan moiety to prevent any possible side reactions. After the alkyne moieties were attached onto the periphery of the dendrons, the focal point was activated by subjecting the dendrons to cycloreversion conditions at elevated temperatures (Figure 2). This unmasking of the protected maleimide to their reactive form results in the formation of bifunctional dendrons.

In order to evaluate the conditions for orthogonal functionalization of the bifunctional dendrons, reactions utilizing undecene thiol for use in Michael addition to the maleimide unit and benzyl azide for the click reaction were carried out (Figure 3). First a stepwise sequence was followed: Cu(I) catalyzed Huisgen type click reaction with benzyl azide was carried out, followed by conjugate addition of undecene thiol to the isolated product. As expected, both steps proceeded uneventfully in good yields. As an alternative, one-pot simultaneous addition of both the thiol nucleophile and the azide along with the Cu(I) catalyst was evaluated. The desired compound was isolated in 43% yield. Lower than expected yields could be due to deactivation of the copper catalyst by remnant thiol nucleophiles. On the basis of this hypothesis, sequential addition of click reagents along with benzyl azide, followed by the addition of undecene thiol after 24 h was attempted. As expected, a much higher isolated yield (76%) was obtained using this route.

The bifunctional nature of these dendrons was used to synthesize a multiarm PEG polymer with a maleimide based reactive focal point. A sequential stepwise route was chosen to afford an all purpose multiarm water-soluble macromolecule. The second generation dendron **2** was used for click reaction with $PEG_{750}$—$N_3$. The cycloaddition reaction was carried out at room temperature in presence of $Cu^IBr$/PMDETA catalyst system using THF as solvent to afford multiarm polymer **5** in 69% isolated yield ($M_n$ = 3445, PDI = 1.1) after precipitation and dialysis in ether (Figure 4). The reaction was very clean and no interference with the maleimide group was observed. It must be noted that loss of maleimide unit was observed at reaction temperatures around 50 °C, probably due to competing cycloaddition of the azides to the reactive alkene group of the maleimide.

$^1$H NMR of the multiarm PEG product **5**, has shown that the peak at 6.70 ppm which corresponds to the double bond of the maleimide was retained, thus proving that the system is indeed

orthogonal; furthermore, complete disappearance of the triplet at ~1.96 ppm corresponding to the proton of the terminal alkyne moieties and formation of a new peak at 7.49 ppm arising from the newly formed triazole ring were observed (Figure 5b).

The multiarm PEG polymer formed after the click reaction was subjected to conjugate addition with a hydrophobic thiol containing dye BODIPY-SH,[41] at room temperature to demonstrate efficient functionalization of the focal point. Efficient conjugation reaction was evident from $^1$H NMR spectra that showed the complete disappearance of the maleimide peak around 6.7 ppm, and appearance of peaks corresponding to BODIPY skeleton, noticeably the resonances around 6.0 ppm due to the pyrrole units (Figure 5c). Unbound BODIPY dye could be easily removed via $SiO_2$ column chromatography. It is clearly visible that while the nonconjugated dye is insoluble in aqueous solution containing 10% methanol, the polymer conjugated dye is freely soluble (inset, Figure 4). Thus, the periphery and the focal point of these dendrons can be independently manipulated to furnish functional macromolecular architectures.

## CONCLUSION

A new class of biodegradable orthogonally functionalizable dendrons has been synthesized. The periphery of these dendrons can be functionalized with azide containing small molecules and polymers using the efficient copper catalyzed Huisgen type [3 + 2] cyccloaddition reaction, while the focal of these dendrons can be functionalized with the Michael addition reaction with thiol containing molecules. Utilization of such dendrons toward the synthesis of a water-soluble multiarm PEG polymer with a reactive focal point was demonstrated. Thus, the obtained reactive polymer was utilized for solubilizing a hydrophobic dye molecule, BODIPY via thiol−ene conjugation.

## ASSOCIATED CONTENT

**Supporting Information.** Characterization of dendrons, multiarm PEG, and core functionalization including NMR spectra and GPC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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