Organic & Biomolecular Chemistry

Dendritic Architectures by Orthogonal Thiol-Maleimide “Click” and Furan-Maleimide Dynamic Covalent Chemistries.

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SUPPORTING INFORMATION

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I. Materials and Methods.

Unless otherwise stated chemicals were purchased from commercial suppliers and used as received. The syntheses of compounds S1, S2, S3, S4, S5, S6, S7, S8, S10, S17, S18, and tris-M11 were carried out according to modified literature procedures. Solvents were dried using an Innovative Technologies SPS-400-5 solvent purification system. All reactions were carried out under an anhydrous N2 atmosphere unless otherwise noted. Thin layer chromatography (TLC) was performed on alumina-backed sheets coated with silica gel 60 F254. TLC plates were visualized using a UV/Vis lamp and/or by staining with iodine or p-anisaldehyde solution. Column chromatography was performed using glass columns over 60 Å, 32–63 μm silica gel. Melting points were determined on a Mettler Toledo Mel-Temp II melting point apparatus and are uncorrected. Melting points for compounds containing a furan-protected maleimide are not reported due to complications arising from the thermally promoted loss of furan upon heating. All 1H and 13C NMR spectra were recorded on with a Varian Mercury (300 and 75 MHz, respectively) or Varian Unity Inova (500 and 125 MHz, respectively) spectrometer using residual solvent as the internal standard. All chemical shifts are quoted using the δ scale and all coupling constants are expressed in Hertz (Hz). Gel permeation chromatography (GPC) of THF-soluble dendrons and dendrimers was performed on a Viscotek TDA 305 eluting with THF at 35 °C at 1.0 mL min⁻¹. The Viscotek TDA 305 was arranged with one guard column (particle size 8 micron, dimensions 10x4.6 mm) and a series of two identical SEC columns (particle size 10 micron, max pore size 5,000 Å, dimensions 300x7.8 mm). The number average molecular weight (Mn), molecular weight (Mw), and polydispersity index (PDI) were determined using the Viscotek RI detector and OmniSEC software, and calculated relative to linear poly(methyl methacrylate) (PMMA) standards in the range of Mp 1,960-903,000 purchased from Polymer Standards Service. Dendrons above generation 3 were not soluble enough in THF to allow for GPC analysis using the instrument at Wesleyan University, therefore samples were analyzed at the University of Massachusetts, Amherst, using an Agilent GPC eluting with DMF. Samples were analyzed using Agilent GPC/SEC Software Version 1.2.3182.29519 and calibrated against polystyrene standards. ESI, APCI, and MALDI high-resolution mass spectrometric analysis was performed at the University of Illinois, Urbana-Champaign, the University of California, Riverside, or the University of Massachusetts, Amherst, Mass Spec facilities.
II. Synthetic Schemes.

Scheme S1: Synthesis of furan-protected maleimide linkers S3 and S5.

Scheme S2: Synthesis of propyl-linked branched monomer 1.
Scheme S3: Synthesis of tetra(ethylene glycol)-linked branched monomer 2.

Scheme S4: Synthesis of maleimide-functionalized core tris-M.
III. Experimental Procedures.

**Compound S1:** Tetraethylene glycol (100.9 g, 520.0 mmol) was added to a round-bottom flask, dissolved in 100 mL of tetrahydrofuran, and cooled to 0 °C. Separately, sodium hydroxide (3.32 g, 83.0 mmol) was dissolved in 30 mL of water. The sodium hydroxide/water solution was added to the tetraethylene glycol solution at 0 °C, and the resulting mixture was stirred for 30 minutes at 0 °C. A solution of p-toluenesulfonyl chloride (9.90 g, 52.0 mmol) in tetrahydrofuran (30 mL) was added dropwise to the solution of tetraethylene glycol solution at 0 °C over the course of 1 hour. The resulting mixture was warmed slowly to room temperature and stirred overnight at room temperature. The mixture was concentrated under reduced pressure, diluted with dichloromethane, and extracted three times with dichloromethane. The combined organic layers were washed three times with water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford 18.0 g (99%) of compound S1 as a viscous oil. Characterization matched literature values.¹

**Compound S2:** Maleimide (20.0 g, 0.21 mol) was added to a round-bottom heavy wall pressure vessel, and suspended in diethyl ether (100 mL, 2.1 M). Furan (28.1 g, 0.41 mol) was added and the pressure vessel was immediately sealed with the threaded Teflon cap. The reaction was heated at 100 °C overnight, and then allowed to cool down to room temperature. After cooling down to room temperature the reaction mixture was filtered through a fritted glass funnel and washed with excess diethyl ether. The solid was collected and dried under high vacuum to afford 33.7 g (99%) of compound S2 as a white solid. The product was used without further purification. Characterization matched literature values.²

**Compound S3:** A three-neck round-bottom flask was charged with 1,3-dibromopropane (61.1 g, 0.30 mol), potassium carbonate (41.0 g, 0.29 mol), potassium iodide (0.51 g, 31.0 mmol), and acetone (305 mL) under an atmosphere of dry N₂(g). Compound S2 (10.0 g, 0.061 mol) was added and the solution was stirred at 50 °C for 8 hours. The solution was filtered through a fritted glass funnel and the filtrate was concentrated under reduced pressure. The resulting residue was purified on a short pad of silica using a mixture of EtOAc:Hex (1:1) to yield 15.4 g (89%) of compound 2 as a white solid. Characterization matched literature values.³

**Compound S4:** Compound S2 (8.5 g, 51.0 mmol) and potassium carbonate (9.4 g, 68.0 mmol) were added to a three-neck round-bottom flask, placed under an inert N₂ atmosphere, and dissolved in acetone (34 mL, 1.0 M). In a separate round-bottom flask, compound S1 (11.9 g, 34.0 mmol) was dissolved in acetone (34 mL, 1.0 M) under an N₂ atmosphere. The solution containing compound S1 was added to the three-neck round-bottom, and the resulting mixture was heated at 50 °C for 60 hours. Solids were removed by filtration through a fritted glass funnel, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by column chromatography DCM:MeOH (98:2) to afford 11.1 g (95%) compound S4 as a viscous oil. TOF MS ESI (m/z) [M+H]+ Calculated for C₁₆H₂₄NO₇, 342.1541, found 342.1553. ¹¹H and ¹³C NMR spectroscopic characterization matched literature values.⁴
Compound S5: Triethylamine (13.2 g, 130.0 mmol) was added to a solution of compound S4 (11.1 g, 33.0 mmol) and p-toluenesulfonyl chloride (7.7 g, 41.0 mmol) in dichloromethane (66 mL, 0.5 M), and the resulting solution was stirred overnight at room temperature. The solution was diluted with water and extracted three times with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography using a mixture of DCM:Hex (80:20) to afford 10.7 g (66%) compound S5 as a viscous oil. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.82 (d, 2H, \(J = 8.0\) Hz), 7.37 (d, 2H, \(J = 8.5\) Hz), 6.53 (s, 2H), 5.28 (s, 2H), 4.18 (t, 2H, \(J = 4.5\) Hz), 3.70 (t, 4H, \(J = 5.0\) Hz), 3.64 (t, 2H, \(J = 5.0\) Hz), 3.62-3.57 (m, 8H), 2.88 (s, 2H), 2.47 (s, 3H). \(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 176.1, 144.8, 136.5, 132.9, 129.8, 128.0, 80.9, 80.8, 70.7, 70.6, 70.5, 69.3, 68.6, 67.1, 47.5, 38.2, 21.6 ppm.

Compound S6: A catalytic amount of concentrated sulfuric acid (95-98%, 1 mL) was added to a solution of 3,5-dihydroxybenzoic acid (65.0 mmol, 10.0 g) in methanol (80 mL, 0.81 M). The solution was refluxed for 5 hours, concentrated under reduced pressure and diluted with ethyl acetate. The resulting solution was washed once each with saturated sodium bicarbonate, water, and brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield 9.9 g (91%) of compound S6 as a white solid. Characterization matched literature values.\(^5\)

Compound S7: Compound S6 (9.9 g, 59.0 mmol) and potassium carbonate (37.0 g, 267.6 mmol) were added to a two-neck flask and placed under an inert N\(_2\) atmosphere. Acetone (100 mL, 0.89 M) and benzyl bromide (45.8 g, 267.6 mmol) were added and the resulting solution was stirred overnight at room temperature. The solution was diluted with ethyl acetate and water, and extracted four time with ethyl acetate. The combined organic layer were washed once with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was recrystallized three times from ether to afford 10.7 g (66%) of compound S7 as a white solid. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.46-7.35 (m, 10H), 7.32 (d, 2H, \(J = 2.0\) Hz), 6.83 (t, 1H, \(J = 2.5\) Hz), 5.10 (s, 4H), 3.93 (s, 3H). \(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 166.8, 159.9, 136.6, 132.2, 128.7, 128.2, 127.6, 108.5, 107.3, 70.3, 52.3 ppm.

Compound S8: A mixture of compound S7 (21.0 g, 60.0 mmol), powdered potassium hydroxide (8.5 g, 151.0 mmol), and ethanol (200 mL, 0.3 M) were refluxed for two hours. The resulting mixture was diluted with ethyl acetate and acidified to pH 1 with 1N HCl. The organic layer was washed twice with water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield 18.7 g (93%) of compound S8 as a white solid. \(^1\)H NMR (DMSO-d\(_6\), 500 MHz): \(\delta\) 7.46-7.33 (m, 10H), 7.15 (d, 2H, \(J = 2.5\) Hz), 6.92 (t, 1H, \(J = 2.5\) Hz), 5.15 (s, 4H). \(^13\)C NMR (75 MHz, DMSO-d\(_6\)): \(\delta\) 167.5, 159.9, 137.2, 133.7, 128.9, 128.3, 128.1, 108.6, 106.9, 70.0 ppm.

Compound S9: Compound S8 (18.0 g, 54.0 mmol), ethanolamine (4.0 g, 65.0 mmol), and triethylamine (13.6 g, 135.0 mmol) were added to a three-neck flask and placed under an inert N\(_2\) atmosphere. Anhydrous dimethylformamide (54.0 mL, 0.5 M) and anhydrous dichloromethane
(54.0 mL, 0.5 M) were added and the solution was cooled down to 0 °C. N-(3-dimethylaminopropyl)-N’-ethylecarbodiimide hydrochloride (12.4 g, 65.0 mmol) was added portion-wise to the solution at 0 °C and the cooled solution was then slowly warmed to room temperature and stirred further at room temperature for 24 hours. The resulting mixture was filtered, diluted with water, and extracted five times with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified over a short pad of silica eluting with a mixture of DCM:MeOH (97:3) and the residue was purified further by recrystallization from dichloromethane to yield 11.5 g (57%) of compound S9 as a white solid. Mp 148-150 °C. \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.45-7.29 (m, 10H), 7.03 (d, 2H, \(J = 2.5\) Hz), 6.76 (t, 1H, \(J = 2.5\) Hz), 6.57 (s, 1H), 5.08 (s, 4H), 3.85 (q, 2H, \(J = 5.0\) Hz), 3.64 (q, 2H, \(J = 5.0\) Hz), 2.48 (t, 1H, 5.0 Hz). \(^13\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 168.3, 160.0, 136.4, 128.6, 128.2, 127.6, 106.2, 105.3, 70.3, 62.0, 42.9 ppm. TOF MS ESI (m/z) [M+H]^+ Calculated for C\(_{23}\)H\(_{24}\)NO\(_4\), 378.1697, found 378.1705.

**Compound S10:** 10 wt % Palladium on carbon (1.15 g) was added to a solution of compound S9 (11.5 g, 30.0 mmol) in ethanol (60 mL) and ethyl acetate (40 mL) under a hydrogen atmosphere (1.0 atm). The suspension was stirred at room temperature for 16 hours and then filtered through celite while washing with excess ethyl acetate. The filtrate was concentrated under reduced pressure and recrystallized from warm methanol to afford 5.3 g (88%) of compound S10\(^9\) as a brown solid. \(^1\)H NMR (CD\(_3\)OD, 500 MHz): \(\delta\) 6.73 (d, 2H, \(J = 1.5\) Hz), 6.42 (t, 1H, \(J = 2.0\) Hz), 3.70 (t, 2H, \(J = 6.0\) Hz), 3.48 (t, 2H, \(J = 6.0\) Hz). \(^12\)C NMR (125 MHz, CD\(_3\)OD): \(\delta\) 169.5, 158.4, 136.4, 105.4, 105.3, 60.3, 42.1 ppm. TOF MS ESI (m/z) [M+H]^+ Calculated for C\(_9\)H\(_{10}\)NO\(_4\), 196.0604, found 196.0610.

**Compound S11:** A three-neck round-bottom flask was charged with compound S3 (7.02 g, 0.025 mol), potassium carbonate (3.4 g, 0.025 mol), potassium iodide (91 mg, 0.55 mmol), and acetone (22 mL) under an inert N\(_2\) atmosphere. After stirring for 10 minutes at room temperature, compound S10 (2.2 g, 0.011 mol) was added and the resulting mixture was heated overnight at 50 °C. The mixture was filtered through a fritted funnel and the filtrate was concentrated under reduced pressure. The resulting residue was purified by column chromatography using a mixture of EtOAc:MeOH (96:4) to yield 4.2 g (62%) of S11 as a white solid. \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 6.88 (d, 2H, \(J = 2.4\) Hz), 6.72 (s, 1H), 6.54 (t, 1H, \(J = 2.4\) Hz), 6.51 (s, 4H), 5.25 (s, 4H), 3.96 (t, 4H, \(J = 6.8\) Hz), 3.81 (q, 2H, \(J = 5.4\) Hz), 3.69 (t, 4H, \(J = 6.8\) Hz), 3.58 (q, 2H, \(J = 5.4\) Hz), 2.85 (s, 4H), 2.75 (t, 1H, \(J = 5.7\) Hz), 2.05 (p, 4H, \(J = 6.6\) Hz). \(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 176.2, 168.3, 159.9, 136.5, 136.2, 105.9, 105.4, 80.9, 65.6, 62.6, 47.4, 43.0, 36.1, 27.1 ppm. TOF MS ESI (m/z) [M+H]^+ Calculated for C\(_{31}\)H\(_{34}\)N\(_3\)O\(_{10}\), 608.2244, found 608.2250.

**Compound S12:** A three-neck round-bottom flask was charged with compound S11 (3.2 g, 0.0053 mol) and dry dichloromethane (27 mL) under an inert N\(_2\) atmosphere. The three-neck round-bottom flask was charged with carbon tetrabromide (2.1 g, 0.0063 mol) and triphenylphosphine (1.7 g, 0.0063 mol) and stirred at room temperature overnight. The solution
was concentrated under reduced pressure and purified by column chromatography using a mixture of EtOAc:Hex (3:1) to yield 3.0 g (86%) of S12 as a white solid. ^1^H NMR (CDCl$_3$, 300 MHz): δ 6.87 (d, 2H, J = 1.8 Hz), 6.63 (s, 1H), 6.54 (s, 1H), 6.51 (s, 4H), 5.25 (s, 4H), 3.96 (t, 4H, J = 6.0 Hz), 3.81 (q, 2H, J = 6.0 Hz), 3.69 (t, 4H, J = 6.0 Hz), 3.57 (t, 2H, J = 6.0 Hz), 2.85 (s, 4H), 2.06 (p, 4H, J = 6.6 Hz). ^13^C NMR (CDCl$_3$): δ 176.2, 167.3, 159.8, 136.5, 105.8, 105.0, 80.9, 80.8, 47.4, 43.0, 36.1, 32.2, 27.1 ppm. TOF MS ESI (m/z) [M+H]^+ Calculated for C$_{31}$H$_{33}$N$_{3}$O$_{9}$, 670.1400, found 670.1410.

**Compound S13:** A three-neck round-bottom flask was charged with compound S12 (2.0 g, 0.003 mol), potassium thioacetate (0.68 g, 0.006 mol), potassium iodide (25 mg, 0.15 mmol), acetic acid (0.27 g, 0.0045 mol), and tetrahydrofuran under inert atmosphere. The solution was concentrated under reduced pressure, and the residue was purified by column chromatography using a mixture EtOAc:Hex (2:1) to yield 0.7 g (78%) of S13 as a white solid. ^1^H NMR (CDCl$_3$, 300 MHz): δ 6.84 (d, 2H, J = 1.8 Hz), 6.61 (s, 1H), 6.53 (s, 1H), 6.51 (s, 4H), 5.26 (s, 4H), 3.96 (t, 4H, J = 5.9 Hz), 3.69 (t, 4H, J = 6.8 Hz), 3.59 (q, 2H, J = 6.5 Hz), 3.11 (t, 2H, J = 6.5 Hz), 2.85 (s, 4H), 2.37 (s, 3H), 2.06 (p, 4H, J = 6.2 Hz). ^13^C NMR (CDCl$_3$): δ 196.4, 176.1, 167.2, 159.8, 136.5, 136.2, 105.7, 105.1, 80.9, 65.5, 47.4, 43.0, 36.1, 30.7, 28.7, 27.2 ppm. TOF MS ESI (m/z) [M+H]^+ Calculated for C$_{33}$H$_{36}$N$_{3}$O$_{9}$S, 666.2121, found 666.2124.

**Compound 1:** A three-neck round-bottom flask was charged with compound S9 (1.0 g, 0.0015 mol) and tetrahydrofuran under an inert N$_2$ atmosphere. Hydrazine monohydrate (0.14 g, 0.0045 mol) was added and the reaction was stirred at room temperature for 4 hours and quenched with acetic acid (0.27 g, 0.0045 mol). The solution was concentrated under reduced pressure, and extracted three times from water using dichloromethane. The organic layers were collected and concentrated under reduced pressure, and the residue was purified by column chromatography using a mixture of DCM/MeOH (99:1) to yield 0.7 g (78%) of 1 as a white solid. ^1^H NMR (CDCl$_3$, 300 MHz): δ 6.87 (d, 2H, J = 2.4 Hz), 6.63 (s, 1H), 6.54 (s, 1H), 6.51 (s, 4H), 5.25 (s, 4H), 3.96 (t, 4H, J = 6.2 Hz), 3.69 (t, 4H, J = 7.1 Hz), 3.59 (q, 2H, J = 6.3 Hz), 2.84 (s, 4H), 2.76 (q, 2H, J = 6.3 Hz), 2.06 (p, 4H, J = 6.3 Hz), 1.41 (t, 1H, J = 8.4 Hz). ^13^C NMR (75 MHz, CDCl$_3$): δ 176.2, 167.3, 159.8, 136.5, 135.8, 105.8, 104.8, 80.9, 65.5, 47.4, 43.0, 36.0, 27.1, 24.4 ppm. TOF MS ESI (m/z) [M+H]^+ Calculated for C$_{33}$H$_{36}$N$_{3}$O$_{9}$S, 624.1212, found 624.2016.

**Compound S14:** A three-neck round-bottom flask was charged with compound S5 (9.9 g, 0.02 mol), potassium carbonate (2.8 g, 0.02 mol), and acetone (45 mL) under an inert N$_2$ atmosphere. After stirring for 10 minutes at room temperature, compound S10 (1.8 g, 0.009 mol) was added and heated overnight at 50 °C. The mixture was filtered through a fritted glass funnel and the filtrate was concentrated under reduced pressure. The resulting residue was purified by column chromatography using a mixture of EtOAc:MeOH (96:4) to yield 1.2 g (16%) of S14 as a white solid. ^1^H NMR (CDCl$_3$, 500 MHz): δ 7.02 (t, 1H, J = 5.5 Hz), 6.99 (d, 2H, J = 2.5 Hz), 6.63 (t, 1H, J = 2.5 Hz), 6.50 (s, 4H), 5.25 (s, 4H), 4.15 (t, 4H, J = 4.5 Hz), 3.85 (t, 4H, J = 4.5 Hz), 3.82 (t, 2H, J = 5.0 Hz), 3.72-3.60 (m, 26H), 3.09 (t, 1H, J = 5.5 Hz), 2.86 (s, 4H). ^13^C NMR (125 MHz, CDCl$_3$): δ 176.2, 168.0, 159.8, 136.5, 106.0, 104.6, 80.9, 80.8, 70.6, 70.5, 70.4, 70.0, 69.5,
67.6, 67.0, 61.8, 47.4, 43.0, 38.1 ppm. TOF MS ESI (m/z) [M+H]^+ Calculated for C_{41}H_{54}N_{12}O_{14}, 844.3499, found 844.3504.

**Compound S15:** A three-neck round-bottom flask was charged with compound S14 (1.2 g, 0.0014 mol) and dry dichloromethane (14 mL) under an inert N₂ atmosphere. The three-neck round-bottom flask was charged with carbon tetrabromide (0.57 g, 0.0017 mol) and triphenylphosphine (0.45 g, 0.0017 mol) and stirred at room temperature overnight. The solution was concentrated under reduced pressure and purified by column chromatography using a mixture of EtOAc:Hex (3:1) to yield 0.9 g (70%, crude yield) of S15 as a white solid.¹H NMR (CDCl₃, 500 MHz): δ 7.12 (d, 2H, J = 2.0 Hz), 6.64 (s, 1H), 6.51 (s, 4H), 5.27 (s, 4H), 4.44 (t, 2H, J = 9.5 Hz), 4.15 (t, 4H, J = 5.0 Hz), 4.07 (t, 2H, J = 9.5 Hz), 3.86 (t, 4H, J = 5.0 Hz), 3.73-3.63 (m, 26H), 2.87 (s, 4H).¹³C NMR (125 MHz, CDCl₃): δ 176.0, 164.2, 159.6, 136.5, 106.5, 105.3, 80.8, 80.7, 70.6, 70.5, 70.4, 70.0, 69.4, 67.6, 67.0, 54.7, 47.3, 38.1 ppm. TOF MS ESI (m/z) [M+H]^+ Calculated for C_{41}H_{52}N_{12}O_{15}, 826.3392, found 826.3398.

**Compound S16:** A three-neck round-bottom flask was charged with compound S15 (3.0 g, 0.0033 mol), potassium thioacetate (0.76 g, 0.0066 mol), potassium iodide (55 mg, 0.33 mmol), and acetonitrile (16.5 mL) under an inert N₂ atmosphere. The solution was stirred at room temperature for 5 hours before it was filtered through a fritted glass funnel. The filtrate was concentrated under reduced pressure and purified by column chromatography using a mixture EtOAc:Hex (2:1) to yield 0.8 g (27%) of S16 as a white solid.¹H NMR (CDCl₃, 500 MHz): δ 6.98 (d, 2H, J = 2.0 Hz), 6.80 (s, 1H), 6.65 (t, 1H, J = 2.0 Hz), 6.50 (s, 4H), 5.26 (s, 4H), 4.16 (t, 4H, J = 5.0 Hz), 3.86 (t, 4H, J = 5.0 Hz), 3.73-3.61 (m, 28H), 2.87 (s, 4H), 1.45 (t, 1H, J = 8.5 Hz).¹³C NMR (125 MHz, CDCl₃): δ 176.2, 167.2, 160.0, 136.5, 136.4, 106.0, 104.7, 80.6, 70.7, 70.6, 70.5, 70.1, 69.6, 67.7, 67.1, 47.4, 43.0, 38.2, 25.4 ppm. TOF MS ESI (m/z) [M+H]^+ Calculated for C_{34}H_{56}N_{12}O_{16}S, 902.3373, found 902.3381.

**Compound 2:** A three-neck round-bottom flask was charged with compound S16 (0.8 g, 0.88 mmol) and tetrahydrofuran under an inert N₂ atmosphere. Hydrazine monohydrate (138.8 mg, 1.77 mmol) was added, and the reaction was stirred at room temperature for 4 hours and quenched with acetic acid (106.3 mg, 1.77 mmol). The solution was concentrated under reduced pressure, and extracted three times from water using dichloromethane. The organic layers were collected and concentrated under reduced pressure, and the residue was purified by column chromatography eluting with a mixture of DCM/MeOH (99:1) to yield 0.6 g (65%) of 2 as a white solid.¹H NMR (CDCl₃, 500 MHz): δ 6.95 (d, 2H, J = 2.5 Hz), 6.79 (t, 1H, J = 5.5 Hz), 6.64 (t, 1H, J = 2.5 Hz), 6.50 (s, 4H), 5.26 (s, 4H), 4.16 (t, 2H, J = 5.0 Hz), 3.86 (t, 4H, J = 4.5 Hz), 3.73-3.62 (m, 28H), 3.15 (t, 2H, J = 6.0 Hz), 2.87 (s, 4H), 2.38 (s, 3H).¹³C NMR (125 MHz, CDCl₃): δ 196.6, 176.2, 167.2, 160.0, 136.7, 136.3, 105.8, 105.0, 80.9, 80.8, 70.6, 70.1, 69.6, 67.7, 67.1, 47.5, 40.1, 38.2, 30.7, 28.8 ppm. TOF MS ESI (m/z) [M+H]^+ Calculated for C_{41}H_{54}N_{12}O_{15}S, 860.3256, found 860.3276.

**Compound S17:** N-bromosuccinimide (NBS) was dissolved in near-boiling (~90 °C) water, gravity filtered into a round-bottom flask that was preemptively cooled down to 0 °C, and
allowed to recrystallize at 0 °C for 2 hours. The crystals were filtered through a Buchner funnel and washed with ca 100 mL of ice water before drying under high vacuum. The freshly recrystallized NBS (6.7 g, 0.038 mol), mesitylene (1.3 g, 0.011 mol), and benzoyle peroxide (0.78 g, 0.003 mol) were dissolved in chloroform (16 mL, 0.7 M) and refluxed at 70 °C for 6 hours. The crude reaction mixture was filtered, washed with water, and extracted 3 times with DCM. The combined organic layers were washed once with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography using mixture of Hexanes:EtOAc (98:2) to afford 2.8 g (72%) of S₁₇ as a light yellow solid. Characterization matched literature values.

**Compound S₁₈**: S₂ (4.3 g, 0.026 mol) and potassium carbonate (4.3 g, 0.031 mol) were added to a 3-arm flask and placed under an inert N₂ atmosphere and dissolved in anhydrous acetonitrile (9 mL, 0.87 M). Compound S₁₇ (2.8 g, 0.0078 mol) was dissolved in anhydrous acetonitrile (9 mL, 0.87 M) under N₂, and added to the 3-arm flask. The reaction mixture was heated at 50 °C for 48 hours, and the completion of the reaction was monitored by TLC. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by column chromatography eluting with a mixture of EtOAc:MeOH (98:2) to afford 0.9 g (19%) of S₁₈ as a white solid. 

**Compound tris–M**: S₁₈ (0.9 g, 0.0015 mol) was added to a round-bottom flask and suspended in anisole (5 mL). The reaction mixture was heated at 140 °C for 1 hour, and then allowed to cool down to room temperature. The crude reaction was added directly to a silica gel column. Excess anisole was removed by eluting with hexanes. The remaining residue was purified in an elution mixture to DCM:MeOH (99:1) to afford 0.5 g (83%) of tris–M as a white solid. 

**General Procedure for Dendron Synthesis**: Growth step: N-methylmaleimide (1.0 equiv) and either 1 or 2 (1.05 equivs) were added to a 3 dram vial and dissolved in 1.0 M deuterated chloroform. A catalytic amount of Et₃N was added and the reaction mixture was stirred under ambient atmosphere for 2-16 hours as monitored by TLC. The crude reaction mixture was added directly to a short pad of silica and eluted using a mixture of CH₂Cl₂/MeOH. Activation step: The dendron sample (1 equiv) was added to a 10 mL round-bottom flask and suspended in 3 mL of anisole or toluene. The reaction mixture was heated at 140 °C for 1-8 hours. After cooling down to room temperature the crude reaction mixture was added directly to a short pad of silica. Anisole or toluene was removed by eluting with hexanes and the activated dendron was obtained by eluting with a mixture of CH₂Cl₂/MeOH. The above growth and activation steps were repeated sequentially, doubling the molar equivalents of 1 or 2 at each growth step, up to the synthesis of a G₄ₓ dendron.
General Procedure for Dendrimer Synthesis: Dendrimer synthesis followed the same steps as dendron synthesis with the key difference being that tris-maleimide tris-M is used as a core molecule in place of N-methylmaleimide. Growth step: Compound S19 (1.0 equiv) and either 1 or 2 (3.15 equivs) was added to a 3 dram vial and dissolved in 1.0 M deuterated chloroform. A catalytic amount of Et3N was added and the reaction mixture was stirred under ambient atmosphere for 2-16 hours as monitored by TLC. The crude reaction mixture was added directly to a short pad of silica and purified with a mixture of CH2Cl2/MeOH. Activation step: The dendrimer sample (1 equiv) was added to 10 mL round-bottom flask and suspended in toluene (3 mL). The reaction mixture was heated at 100 °C for 1-8 hours. After cooling down to room temperature the crude reaction mixture was added directly to a short pad of silica. Anisole was removed by eluting with hexanes and the activated dendrimer was obtained by eluting with a mixture of CH2Cl2/MeOH. The above growth and activation steps were repeated sequentially using a 1.05:1 molar equivalent of 1 or 2 to maleimide at each growth step, up to the synthesis of a G3F dendrimer.

G1F Dendron: N-methylmaleimide (28.9 mg, 0.26 mmol) and 1 (170.0 mg, 0.27 mmol) were added to a 3 dram vial and dissolved in CDCl3 (0.5 mL). Et3N (12.5 mg, 0.124 mmol) was added, the vial was capped, and the reaction was allowed to stir at room temperature for 2 hours. The solution was concentrated under reduced pressure and purified by column chromatography using a mixture of CH2Cl2:MeOH (99:1) to afford 160.0 mg (80%) of G1F dendron as a white solid. ESI-TOF MS (m/z) [M+H]+ calculated for C36H39N4O11S, 735.2331, found, 735.2359.

G1M Dendron: G1F dendron (140.0 mg, 0.19 mmol) was added to a 100 mL round-bottom flask and suspended in toluene (30 mL). The reaction mixture was heated at 100 °C for 8 hours, and it should be noted that G1F dendron is only soluble in toluene at higher temperatures. The reaction mixture was concentrated under reduced pressure and purified by column chromatography using a mixture of CH2Cl2:MeOH (99:1) to afford 160.0 mg (96%) of G1M dendron as a white solid. ESI-TOF MS (m/z) [M+H]+ calculated for C28H31N4O9S, 599.1812, found, 599.1813.

G2F Dendron: G1M dendron (84.0 mg, 0.140 mmol) and 1 (184.0 mg, 0.295 mmol) were added to a 3 dram vial and dissolved in CDCl3 (0.5 mL). Et3N (29.8 mg, 0.295 mmol) was added, the vial was capped, and the reaction was allowed to stir overnight at room temperature. The solution was concentrated under reduced pressure and purified by column chromatography using a mixture of CH2Cl2:MeOH (97:3) to afford 189.0 mg (73%) of G2F dendron as a white solid. ESI-TOF MS (m/z) [M+H]+ calculated for C90H97N10O27S3, 1845.5681, found, 1845.5676.

G2M Dendron: G2F dendron (170.0 mg, 0.092 mmol) was added to a 100 mL round-bottom flask and suspended in toluene (30 mL). The reaction mixture was heated at 100 °C for 8 hours, and it should be noted that G2F dendron is only soluble in toluene at higher temperatures. The reaction mixture was concentrated under reduced pressure and purified by column chromatography using a mixture of CH2Cl2:MeOH (97:3) to afford 50.0 mg (34%) of G2M dendron as a white solid. ESI-TOF MS (m/z) [M+H]+ calculated for C78H81N10O23S3, 1573.4638, found, 1573.4619.
**G3_F Dendron:** G2_M dendron (40.0 mg, 0.023 mmol) and 1 (61.3 mg, 0.098 mmol) were added to a 3 dram vial and dissolved in CDCl₃ (0.5 mL). Et₃N (1.2 mg, 0.012 mmol) was added, the vial was capped, and the reaction was allowed to stir overnight at room temperature. The solution was concentrated under reduced pressure and purified by column chromatography using a mixture of CH₂Cl₂:MeOH (95:5) to afford 40.0 mg (39%) of G3_F dendron as a white solid. The parent ion of the G3_F dendron could not be observed under MALDI ionization conditions, however the parent ion of the fully deprotected G3_M dendron was found. As discussed in the text, it is believed that all eight peripheral furan protecting groups are removed by a thermal retro-Diels-Alder reaction during ionization under vacuum. MALDI-TOF MS (m/z) [M+Na]⁺ calculated for the deprotected G3_M dendron C₁₆₆H₁₈₀N₂₂NaO₅₁S₇ (observed during measurement of the G3_F dendron), 3544.01, found, 3543.9.

**G3_M Dendron:** G3_F dendron (80.0 mg, 0.019 mmol) was added to a 50 mL round-bottom flask and suspended in toluene (20 mL). The reaction mixture was heated at 100 °C for 8 hours, and it should be noted that G3_F dendron is only soluble in toluene at higher temperatures. The reaction mixture was concentrated under reduced pressure and purified by column chromatography using a mixture of CH₂Cl₂:MeOH (97:3) to afford 33.0 mg (48%) of G3_M dendron as a white solid. MALDI-TOF MS (m/z) [M+Na]⁺ calculated for C₁₆₆H₁₈₀N₂₂NaO₅₁S₇, 3544.01, found, 3546.0.

**G4_F Dendron** (compound designated as 3 in the main text): G3_M dendron (25.0 mg, 0.007 mmol) and 1 (37.2 mg, 0.060 mmol) were added to a 3 dram vial and dissolved in CDCl₃ (0.5 mL). Et₃N (0.9 mg, 0.009 mmol) was added, the vial was capped, and the reaction was allowed to stir overnight at room temperature. The solution was concentrated under reduced pressure and purified by column chromatography using a mixture of CH₂Cl₂:MeOH (95:5) to afford 33.8 mg (56%) of G4_F dendron as a white solid. As with the G3_F dendron, the parent ion of the G4_F dendron could not be observed under MALDI ionization conditions. The parent ion of the fully deprotected G4_M dendron, however, was found during MALDI analysis of the intended G4_F dendron. MALDI-TOF MS (m/z) [M+Na]⁺ calculated for the deprotected G4_M dendron C₃₅₀H₃₈₀N₄₆NaO₁₀₇S₁₅ (observed during measurement of the G4_F dendron), 7441.14, found, 7443.5.

**G1_F Dendrimer: Tris-M** (50.0 mg, 0.124 mmol) and 2 (243.0 mg, 0.389 mmol) were added to a 3 dram vial and dissolved in CDCl₃ (0.5 mL). Et₃N (12.5 mg, 0.124 mmol) was added, the vial was capped, and the reaction was allowed to stir at room temperature overnight. The solution was concentrated under reduced pressure and purified by column chromatography using a mixture of CH₂Cl₂:MeOH (97:3) to afford 238.0 mg (85%) of G1_F as a white solid. Analysis by MALDI-TOF MS resulted in thermal deprotection of the three peripheral furan groups of dendrimer G1_F, revealing the parent ion corresponding to its deprotected analogue G1_M. MALDI-TOF MS (m/z) [M+Na]⁺ calculated for C₉₀H₉₀N₁₂NaO₂₇S₃, 1889.51, found, 1889.7.

**G1_M Dendrimer:** G1_F (93.0 mg, 0.041 mmol) was added to a 10 mL round-bottom flask and suspended in anisole (3 mL). The reaction mixture was heated at 145 °C for 1 hour, and it should be noted that G1_F is only soluble in anisole at higher temperatures. The reaction mixture was
cooled to room temperature and purified by column chromatography using a mixture of CH$_2$Cl$_2$:MeOH (97:3) to afford 69.0 mg (91%) of G$_1$M as a white solid. MALDI-TOF MS ($m/z$) [M+Na]$^+$ calculated for C$_{90}$H$_{90}$N$_{12}$NaO$_{27}$S$_3$, 1889.51, found, 1890.9.

**G$_2$F Dendrimer: G$_1$M** (100.0 mg, 0.054 mmol) and 1 (210.0 mg, 0.337 mmol) were added to a 3 dram vial and dissolved in CDCl$_3$ (0.5 mL). Et$_3$N (5.4 mg, 0.054 mmol) was added, the vial was capped, and the reaction was allowed to stir at room temperature overnight. The solution was concentrated under reduced pressure and purified by column chromatography using a mixture of CH$_2$Cl$_2$:MeOH (95:5) to afford 180.0 mg (60%) of G$_2$F as a white solid.

**G$_2$M Dendrimer: G$_2$F** (150.0 mg, 0.027 mmol) was added to a 10 mL round-bottom flask and suspended in anisole (3 mL). The reaction mixture was heated at 145 °C for 1 hour, and it should be noted that G$_2$F is only soluble in anisole at higher temperatures. The reaction mixture was cooled to room temperature and purified by column chromatography using a mixture of CH$_2$Cl$_2$:MeOH (95:5) to afford 58.0 mg (45%) of G$_2$M as a white solid.

**G$_3$F Dendrimer** (compound designated as 4 in the main text): G$_2$M (44.0 mg, 0.009 mmol) and 1 (72.1 mg, 0.116 mmol) were added to a 3 dram vial and dissolved in CDCl$_3$ (0.5 mL). Et$_3$N (0.93 mg, 0.009 mmol) was added, the vial was capped, and the reaction was allowed to stir at room temperature overnight. The solution was concentrated under reduced pressure and purified by column chromatography using a mixture of CH$_2$Cl$_2$:MeOH (93:7) to afford 86.0 mg (76%) of G$_3$F as a white solid. MALDI-TOF MS positively identified the parent [M+Na]$^+$ ion of the G$_3$M ion arising from thermal deprotection of peripheral furan groups under ionization conditions. [M+Na]$^+$ ($m/z$) calculated for C$_{504}$H$_{540}$N$_{66}$NaO$_{153}$S$_{21}$, 10658.05, found, 10662.4.

**G$_3$F Dendrimer** (compound designated as 5 in the main text): G$_2$M (37.0 mg, 0.008 mmol) and 2 (83.6 mg, 0.097 mmol) were added to a 3 dram vial and dissolved in CDCl$_3$ (0.5 mL). Et$_3$N (0.78 mg, 0.008 mmol) was added, the vial was capped, and the reaction was allowed to stir at room temperature overnight. The solution was concentrated under reduced pressure and purified by column chromatography using a mixture of CH$_2$Cl$_2$:MeOH (93:7) to afford 72.0 mg (62%) of G$_3$F as a white solid.
IV. NMR and Mass Spectra.

Figure S1. $^1$H NMR spectrum (500 MHz) of compound S9.

Figure S2. $^{13}$C NMR spectrum (125MHz) of compound S9.
Figure S3. TOF ESI MS of compound S9.
**Figure S4.** $^1$H NMR spectrum (500 MHz) of compound S10.

**Figure S5.** $^{13}$C NMR spectrum (125 MHz) of compound S10.
Figure S6. TOF ESI MS of compound S10.
Figure S7. $^1$H NMR spectrum (300 MHz) of compound S11.

Figure S8. $^{13}$C NMR spectrum (75 MHz) of compound S11.
**Figure S9. TOF ESI MS of compound S11.**
Figure S10. $^1$H NMR spectrum (300 MHz) of compound S12.

Figure S11. $^{13}$C NMR spectrum (75 MHz) of compound S12.
Figure S12. TOF ESI MS of compound S12.
Figure S13. $^1$H NMR spectrum (300 MHz) of compound S13.

Figure S14. $^{13}$C NMR spectrum (75 MHz) of compound S13.
Figure S15. TOF ESI MS of compound S13.
Figure S16. $^1$H NMR spectrum (300 MHz) of compound 1.

Figure S17. $^{13}$C NMR spectrum (75 MHz) of compound 1.
Figure S18. TOF ESI MS of compound 1.
Figure S19. $^1$H NMR spectrum (500 MHz) of compound S14.

Figure S20. $^{13}$C NMR spectrum (125 MHz) of compound S14.
Figure S21. TOF ESI MS of compound S14.
Figure S22. $^1$H NMR spectrum (500 MHz) of compound S15.

Figure S23. $^{13}$C NMR spectrum (125 MHz) of compound S15.
Figure S24. TOF ESI MS of compound S15.
Figure S25. $^1$H NMR spectrum (500 MHz) of compound S16.

Figure S26. $^{13}$C NMR spectrum (125 MHz) of compound S16.
Figure S27. TOF ESI MS of compound S16.
Figure S28. $^1$H NMR spectrum (500 MHz) of compound 2.

Figure S29. $^{13}$C NMR spectrum (125 MHz) of compound 2.
Figure S30. TOF ESI MS of compound 2.
Figure S31. $^1$H NMR spectrum (300 MHz) of the G1$_F$ dendron.

Figure S32. $^{13}$C NMR spectrum (75 MHz) of the G1$_F$ dendron.
Figure S33. TOF ESI MS of the G1₉ dendron.
Figure S34. $^1$H NMR spectrum (300 MHz) of the G1$_M$ dendron.

Figure S35. $^{13}$C NMR spectrum (75 MHz) of the G1$_M$ dendron.
Figure S36. TOF ESI MS of compound the G1M dendron.
Figure S37. $^1$H NMR spectrum (300 MHz) of the G2$_F$ dendron.

Figure S38. $^{13}$C NMR spectrum (75 MHz) of the G2$_F$ dendron.
Figure S39. TOF ESI MS of compound the G2_F dendron.
Figure S40. $^1$H NMR spectrum (300 MHz) of the G2$_M$ dendron.

Figure S41. $^{13}$C NMR spectrum (75 MHz) of the G2$_M$ (A-R-B$_2$/A-R-B$_2$) dendron.
Figure S42. TOF ESI MS of compound the G2M dendron.
Figure S43. $^1$H NMR spectrum (300 MHz) of the G3$_F$ dendron.

Figure S44. $^{13}$C NMR spectrum (75 MHz) of the G3$_F$ dendron.
Figure S45. MALDI MS of G3_F dendron results in the observation of the parent [M+Na]^+ ion of the fully deprotected dendron G3_M. Minor peaks can be observed below that of the parent ion, and the spacing between these peaks is approximately equal to the mass of thermally deprotected branched monomer 1 (m/z calculated for C_{23}H_{25}N_{3}O_{7}S is 487.14). Konkolewicz and co workers have observed thermally promoted retro-thiol-Michael reactions.\textsuperscript{12-13} It is possible that such retro-thiol-maleimide reactions could occur under MALDI conditions, which would explain the agreement between the regular spacing of minor peaks observed in several MALDI MS results.

Figure S46. MALDI MS of G3_M dendron. Minor peaks with approximate m/z spacing of 487 are observed.
Figure S47. MALDI MS of G4ₐ dendron results in the observation of the parent [M+Na]⁺ ion of the fully deprotected dendron G4ₘ. Minor peaks with approximate $m/z$ spacing of 487 are observed.

Figure S48. $^1$H NMR spectrum (500 MHz) of G1ₐ (A-R-B₂) dendrimer.
Figure S49. $^{13}$C NMR spectrum (125 MHz) of G1$_F$ dendrimer.

Figure S50. MALDI MS of G1$_F$ dendrimer results in the observation of the fully thermally deprotected G1$_M$ dendrimer.
**Figure S51.** $^1$H NMR spectrum (500 MHz) of G1$_M$ dendrimer.

**Figure S52.** $^{13}$C NMR spectrum (125 MHz) of G1$_M$ dendrimer.
Figure S53. MALDI MS of G1_M dendrimer.

Figure S54. †H NMR spectrum (500 MHz) of G2_F dendrimer.
Figure S55. $^{13}$C NMR spectrum (125 MHz) of G2_F dendrimer.

Figure S56. $^1$H NMR spectrum (500 MHz) of G2_M dendrimer.
Figure S57. $^{13}$C NMR spectrum (125 MHz) of G2$_m$ dendrimer.

Figure S58. $^1$H NMR spectrum (500 MHz) of G3$_F$ dendrimer 4.
Figure S59. $^{13}$C NMR spectrum (125 MHz) of G3$_F$ (A-R-B$_2$/A-R-B$_2$/A-R-B$_2$) dendrimer.

Figure S60. MALDI MS of G3$_F$ results in the observation of the thermally deprotected G3$_M$ dendrimer. Minor peaks with approximate $m/z$ spacing of 487 are observed.
Figure S61. $^1$H NMR spectrum (500 MHz) of G3$_F$ dendrimer 5.
Figure S62. $^{13}$C NMR spectrum (125 MHz) of G3$_F$ (A-R-B$_2$/A-R-B$_2$/A'-R'-B$_2$) dendrimer.

V. Supporting References