Rational design of molecularly engineered biomimetic threshold scale inhibitors

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This Supporting Information includes Materials and methods and 2 figures.

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Materials and methods

Materials

All chemicals were used as purchased without further purification except for TsCl which was recrystallized from $CHCl_3$ prior use. Nuclear magnetic resonance (NMR) spectral acquisitions were carried out on Mercury instruments (Varian, Palo Alto, CA, USA), operated through VNMRJ 2.2D (Chempack 5) and VNMRJ 2.3A (Chempack 5) software using a 5 mm Smart Probe. The chemical shifts in ppm are reported related to tetramethylsilane (TMS) as an internal standard, and solvents as references (^1H, ^{13}C); $CDCl_3$ (7.26, 77.16), $(CD_3)_2SO$ (2.50, 39.52), D_2O (4.79, -), CD_3OD (3.31, 49.00). Phosphoric acid was used for ^{31}P-NMR as a reference and recorded in other solvents.

Methods

***Chronoamperometry for electrochemical deposition of $CaCO_3$*:** Accelerated scaling was simulated by depositing calcium carbonate on a hydrochloric acid-cleaned gold electrode (fixed-disk rotating ring disk electrode, diameter ~ 5 mm, with polyether ether ketone shroud OD ~ 15 mm, Pine Research Instrumentation, U.S.A.), rotating at a constant speed (700 rpm) in a saturated solution containing calcium chloride (~ 6 mM) and sodium bicarbonate (~ 10.7 mM) by applying a constant voltage (-1 V/standard calomel electrode SCE) using a WaveDriver 10 potentiostat, controlled by AfterMath Data Organizer Software (Pine Research Instrumentation, U.S.A.). Zero current ($I \sim 0$) represented a complete coating.

***Mineralization experiments*:** Calcium chloride solution (20 mM, 15 mL) was mixed with sodium bicarbonate (20 mM, 15 mL) including a desired amount of the dendrimer, which vigorously

vortexed for 1 min, followed by incubation under the ambient conditions without agitation on acid-cleaned cover glasses. After a desired time, to quench the mineralization, the precipitate was separated from the supernatant by decantation, thoroughly washed with milli-Q water three times, and dried at 50°C for at least 24 h in an oven.

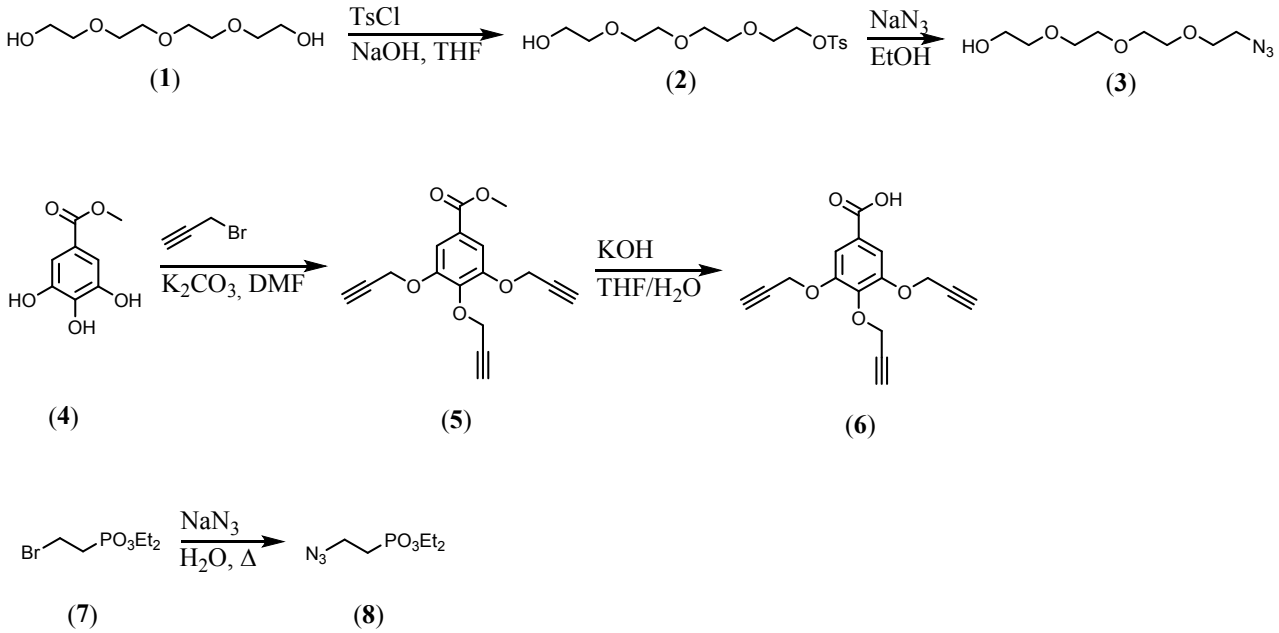
***Scanning electron microscopy (SEM)*:** Dried mineralized specimens were transferred from the vials to adhesive carbon pads and coated with Pt (4 nm-thick layer) using a vacuum sputtering instrument (Leica Microsystems EM ACE600 High Resolution Coater). SEM imaging and elemental analysis were conducted using a SEM instrument (FEI Inspect F-50 FE-SEM) equipped with the energy dispersive spectroscopic equipment EDAX Octane Super 60 mm^2 SDD and the TEAM EDS Analysis System.

***ζ-potential and hydrodynamic size*:** the ζ-potential of dendrimers/dendrons was measured using their electrophoretic mobility acquired based on the electrophoretic light scattering ELS in the universal dip cell kit using Zetasizer NanoZS equipped with a 4mW-633 nm He-Ne solid-state laser, Malvern Instruments, UK. This was used to investigate the complex formation between the dendrimers/dendrons and Ca^{2+}. Using the same instrument, dynamic light scattering (DLS) experiments were conducted in disposable cuvettes to obtain the macromolecular hydrodynamic size.

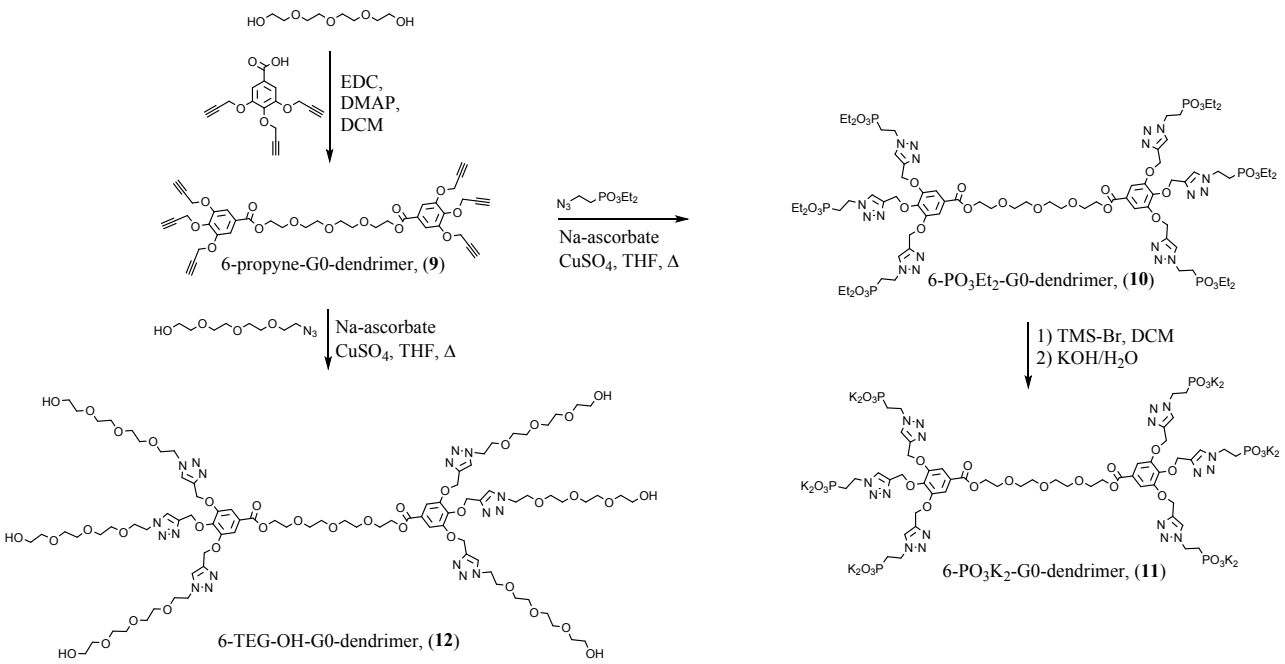
Dendrimer and dendron syntheses

We have selected tetraethylene glycol (TEG) as the core and branching entity,[1] which is very inexpensive, and is used as the starting material for the two-step synthesis of monomer **2**

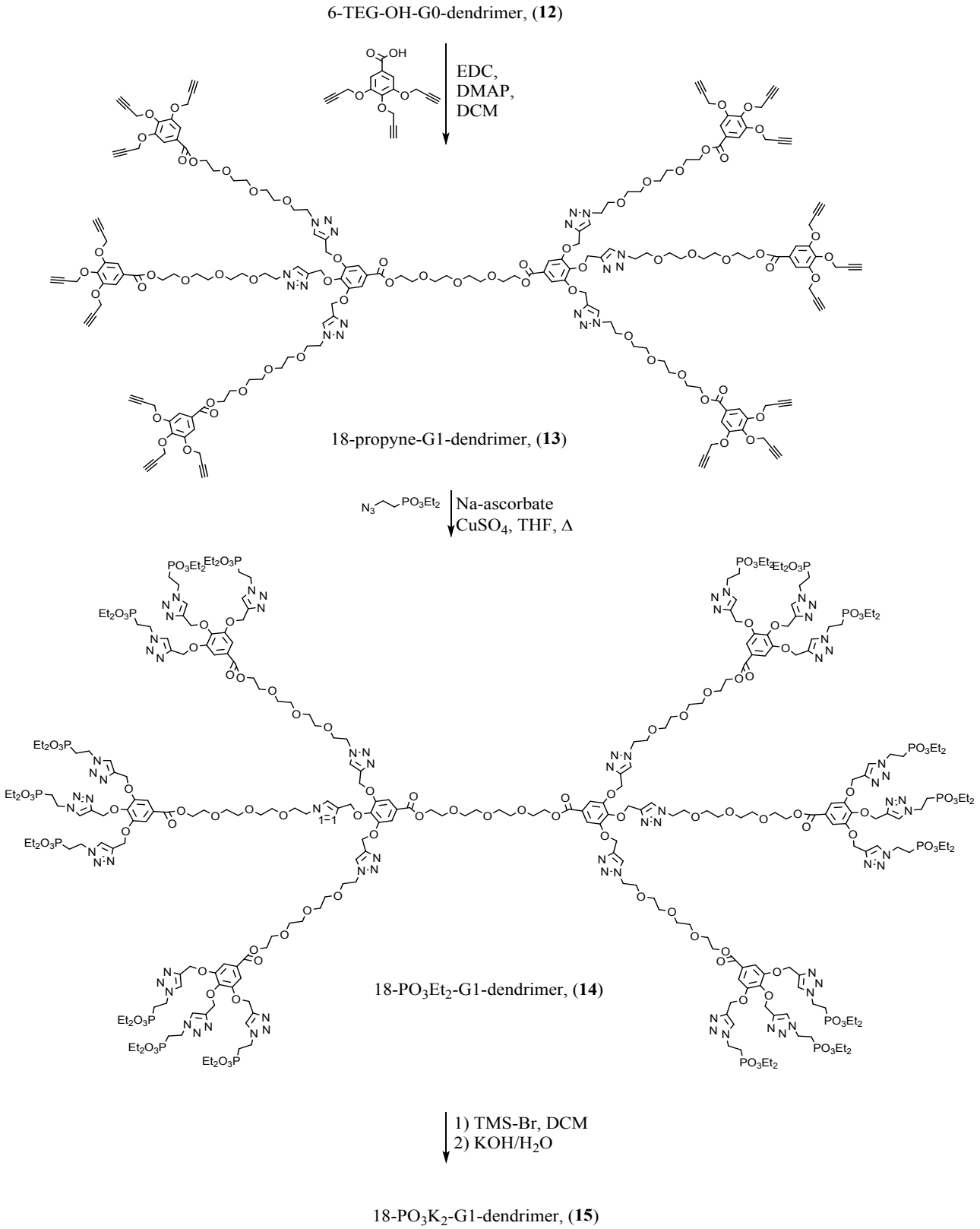
(Scheme **1**). **6** is synthesized from easily available starting materials in a two-step synthesis, both high yielding and without the need for column chromatography. This is used as the branching entity. We synthesized generations 0-2 of TEG based dendrimers containing 6, 18 and 54 phosphonates groups respectively at their periphery. The TEG unit was chosen to improve water-solublity, and the branching AB_3 system facilitates rapid increase of the number of surface groups at the periphery (multiply by 3 with each generation). Such dendrimers provide an open and flexible structure. The synthesis is adapted from details reported in reference 1, and Schemes below are reproduced here for clarity.[1]



Scheme 1. Structure and synthesis of the building blocks used for the synthesis of TEG-based dendrimers.[1]

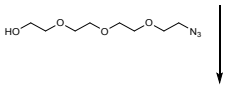


Scheme 2. Synthesis of TEG-based dendrimers of generation 0, and the synthesis of 6-TEG-OH-G0-dendrimer (**12**).[1]



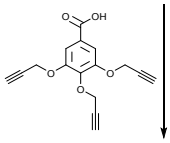
Scheme 3. Synthesis of TEG dendrimers: 6-TEG-OH-G1 and 18-PO_3K_2-G1.[1]

18-propyne-G1-dendrimer, (**13**)



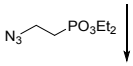
Na-ascorbate
$CuSO_4$, THF, D

18-TEG-OH-G1-dendrimer, (**16**)



EDC,
DMAP,
DCM

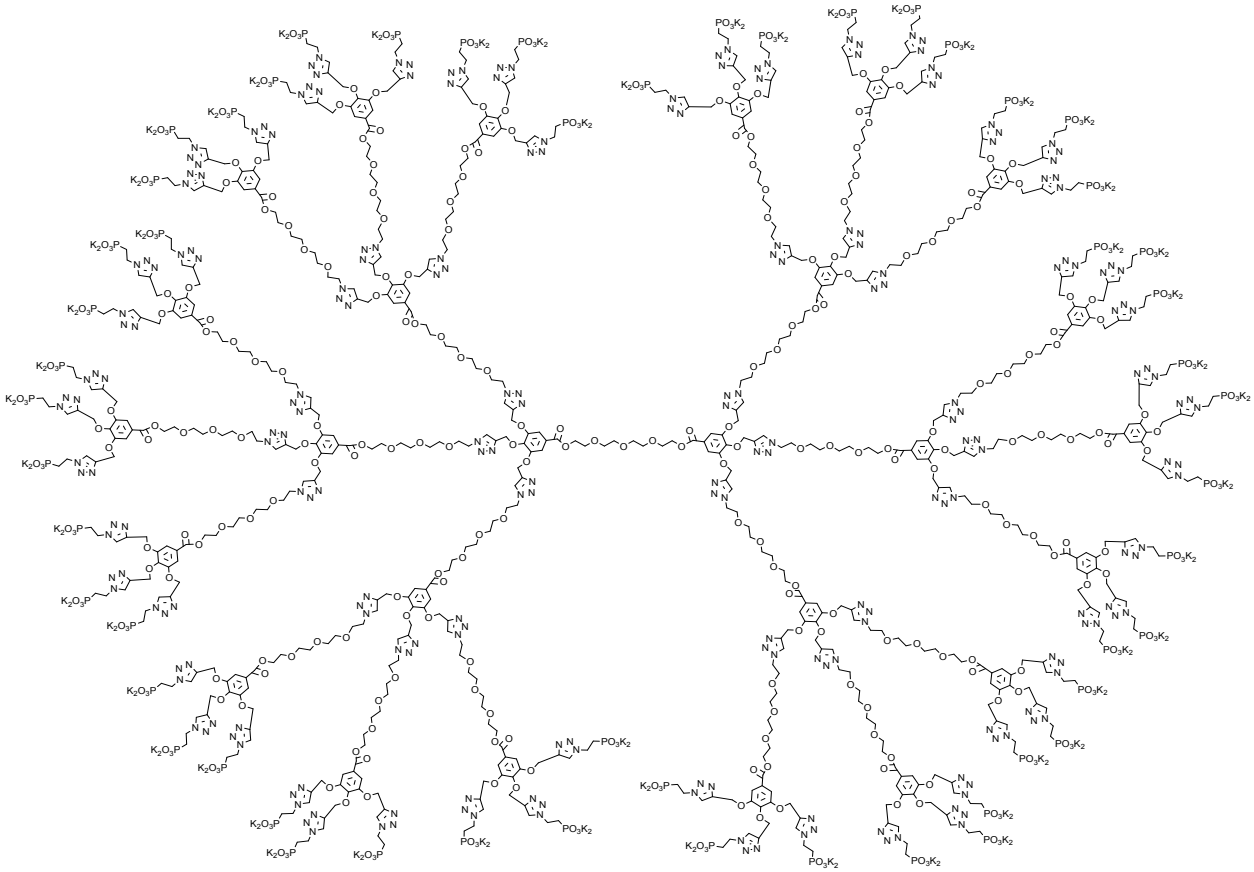
54-propyne-G2-dendrimer, (**17**)



Na-ascorbate
$CuSO_4$, THF, Δ

54-PO_3Et_2-G2-dendrimer, (**18**)

1) TMS-Br, DCM
2) KOH/H_2O



54-PO_3K_2-G2-dendrimer, (**19**)

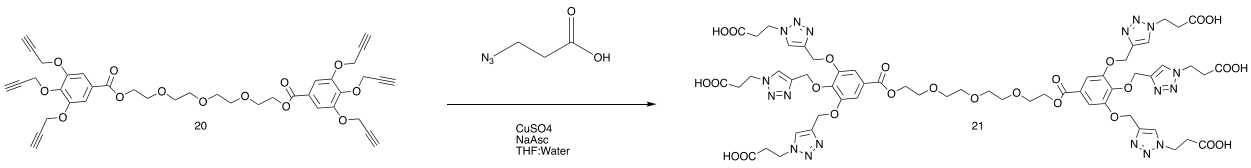
Scheme 4. Synthesis of dendrimers with 18 terminal alkynes (**13**), and 54-PO_3K_2-G3-dendrimer (**19**).[1]

3-Azidopropanoic acid (20)

Sodium azide (0.955 g, 6.25 mmol) was added to a solution of 3-bromopropionic acid (0.813 g, 12.5 mmol) in acetonitrile (10 mL) and the reaction mixture was stirred under reflux for 4 hours. An extraction was performed with dichloromethane, the organic phase was dried with $MgSO_4$, filtered and the residue obtained was a yellow oil (0.35 g, 2.17 mol, 35%). ^{1}H NMR (300MHz, $CDCl_3$): δ = 3.59 (t, *J* = 6.4, 2H), 2.64 (t, *J* = 6.4, 2H). NMR data consistent with literature.[2]

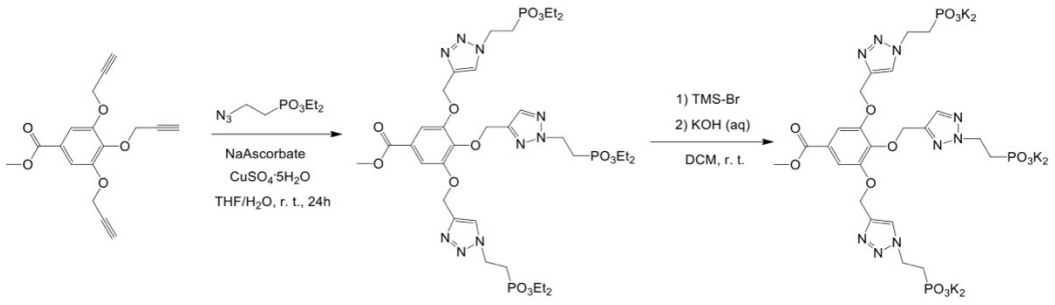
TEG-G0-COOH (21)

A solution of **9** (81 mg; 0.112 mmol), Na-ascorbate (27 mg; 0.134 mmol) and **8** (93 mg; 0.81 mmol) in THF (3 mL) was added to a solution of $CuSO_4$•$5H_2O$ (17 mg; 0.067 mmol) in water (1 mL) and stirred for two days at 40°C. NaEDTA (100 mg) was added to the reaction and stirred for 1h. The mixture was then triturate with water, DCM and ether to give a brown solid. Yield above 100% due to residual water in product. ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 8.19 (s,s, 6H), 7.41 (s, 4H), 5.17 (s,s, 12H), 4.70 – 4.25 (m, 16H), 3.88 – 3.19 (m, 12H), 2.97 – 2.70 (m, 12H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 172.27, 165.62, 152.20, 141.57, 125.48, 125.23, 114.56, 109.11, 74.12, 70.27, 68.73, 64.64, 62.75, 45.89, 34.44. MS: ESI-ve mode $[M-H]^{2-}$: calcd. for $C_{58}H_{66}N_{18}O_{25}$: 707.2229 *m/z*; found: 707.2223 *m/z*.



The dendrons were synthesized according to the following steps:

B-dendron-G0 (23)

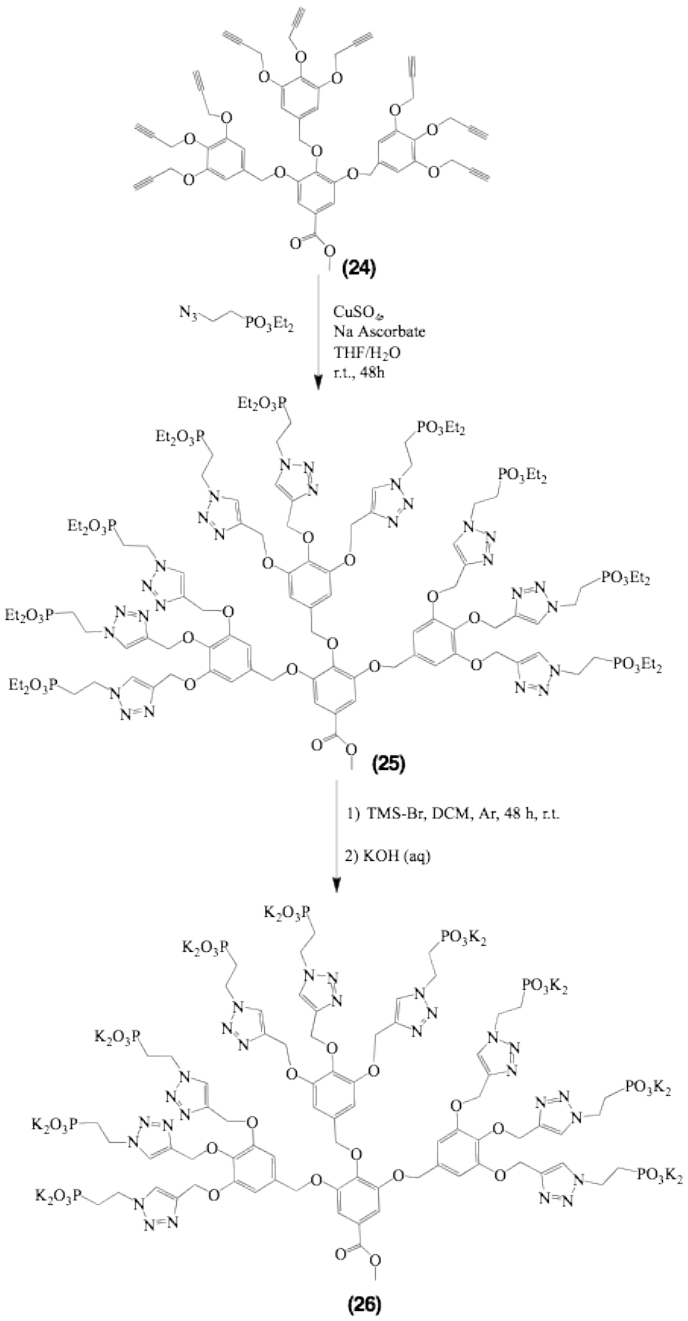


(5) **(22)** **(23)**

Synthesis of dendron 22. Compound **5** (0.34 mmol, 100 mg) and diethyl-azidoethylene phosphonate (1.02 mmol, 212 mg) were dissolved in THF (3 mL), after being degassed and refilled with N_2, $CuSO_4 \cdot 5H_2O$ (0.34 mmol, 85 mg) aqueous solution was added, followed by dropwise addition of sodium ascorbate (0.68 mmol, 134 mg) aqueous solution. The reaction mixture was stirred at r.t. for 24 h under N_2. After removal of the organic solution *in vacuo*, the mixture was dissolved in DCM (2 mL) and treated with saturated $EDTA_{(aq)}$ (2 mL) for 30 min. The organic solution was isolated and washed with water (3 × 10 mL). Compound **22** (**G0-PO_3Et_2)** was obtained as a brown gel-like material. ^1H NMR ($CDCl_3$, 400 MHz): δ_{ppm} 7.91 (3H, C*H*$_{trz}$), 7.44 (2H, C*H*$_{Ar}$), 5.26 (6H, -OCH_2-trz), 4.68-4.64 (6H, -CH_2C*H*$_2$-trz), 4.15-4.08 (12H, CH_3C*H*$_2$O-), 3.93(3H, C*H*$_3$O-), 2.51-2.45 (6H, -C*H*$_2$P-), 1.34-1.30 (18H, C*H*$_3$$CH_2$-). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_{ppm} 166.2, 151.9, 125.8, 123.6, 109.2, 63.1, 62.2, 62.1, 53.4, 52.3, 44.7, 27.7, 26.6, 25.6, 16.4, 16.3. ^{31}P ($CDCl_3$, 81 MHz): δ_{ppm} 25.6, 25.4.

B-dendron-G0 (23)

A solution of compound **22** (**G0-PO$_3$Et$_2$)** (312 mg; 0.62 mmol) and TMS-Br (1.226 g; 7.44 mmol) in DCM (10 mL) was stirred for 48 h. The volatile components were removed *in vacuo* and the residue was taken up in DCM. $KOH_{(aq)}$ (1M) was added to adjust the pH to 8-9. The DCM was removed gradually under reduced pressure (a needle through a septum works well) and the aqueous solution was stirred for 2 h. The volatile components were removed under reduced pressure to give compound (**3**) **G0-P3** dendron as a solid (yield: 100%). ^{1}H NMR (D_2O, 400 MHz): δ_{ppm} 8.40 (2H, C*H*$_{trz}$), 8.07 (1H, C*H*$_{trz}$) 7.62 (2H, C*H*$_{Ar}$), 5.44-5.38 (6H, -OC*H*$_2$-trz), 4.84 (6H, -CH$_2$C*H*$_2$-trz), 4.16 (3H, C*H*$_3$O-), 2.33-18 (6H, -C*H*$_2$P-).^{13}C NMR (D_2O, 100 MHz): δ_{ppm} 168.2, 151.6, 151.3, 143.0, 139.8, 126.2, 125.6, 125.4, 109.3, 65.6, 62.9, 48.3, 48.1, 31.9, 30.9. ^{31}P (D_2O, 81 MHz): δ_{ppm} 15.82, 15.67.



G1-9PO_3Et_2 (25)

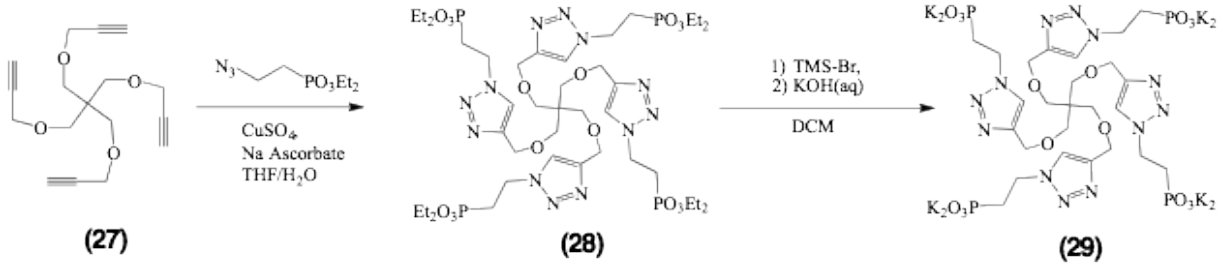
Compound 24 (316 mg; 0.33 mmol)[3] and diethyl-azidoethylene phosphonate (218 mg; 1.04 mmol) was dissolved in THF (3 mL), after degassed and refilled with N2, $CuSO_4 \cdot 5H_2O$ (123 mg; 0.49 mmol) aqueous solution was added, followed by dropwise addition of sodium ascorbate (196 mg; 0.98 mmol) aqueous solution. The reaction mixture was stirred at r.t. for 24 h under N_2.

After removal of the organic solution in vacuo, the mixture was dissolved in DCM and treated with EDTA aqueous solution for 30 min. The organic solution was isolated and washed with water (3 × 10 mL). The crude product was collected and purified by precipitation in ether. Compound 25 (G1-9PO_3Et_2) was obtained as a brown solid (yield: 90%). ^{1}H NMR (Acetone-d_6, 400 MHz): δppm 8.20- 8.09 (9H, C*H*trz), 7.51 (2H, C*H*Ar) 7.09-7.52 (6H, CH_{Ar}), 5.24-5.21 (6H, -OCH_2-trz), 5.09-4.89 (18H, -OCH_2-trz), 4.64-4.60 (18H, -CH_2CH_2-trz), 4.08-4.06 (36H, CH_3CH_2-), 3.91 (3H, CH_3O-), 2.50-2.45 (18H, -CH_2P-), 1.27 (54H, C$H_3$$CH_2$-). ^{13}C NMR (Acetone-$d_6$, 100 MHz): δ_{ppm} 165.9, 152.7, 152.5, 152.2, 144.4, 143.2, 137.3, 134.1, 132.9, 124.2, 109.1, 107.0, 106.7, 74.7, 71.0, 66.4, 62.6, 62.5, 62.4, 61.5, 61.4, 44.3, 44.2, 27.0, 25.9, 15.9, 15.8. ^{31}P (Acetone-d_6, 81 MHz): δ_{ppm} 25.8-25.7.

B-dendron-G1 (26)

A solution of **G1-9PO_3Et_2 (25)** (730 mg; 0.25 mmol) and TMS-Br (1.53 g; 20 mmol) in DCM (10 mL) was stirred for 48 h. The volatile components were removed *in vacuo* and the residue was taken up in DCM. $KOH_{(aq)}$ (1M) was added to adjust the pH to 8-9. The DCM was removed gradually under reduced pressure (a needle through a septum works well) and the aqueous solution was stirred for 2 h. The volatile components were removed under reduced pressure to give compound **6** (**G1-P9**) dendron as a brown solid material. Yield: 100%. ^{31}P (D_2O, 81 MHz): δ_{ppm} 15.8-15.6.MS: ESI-ve mode $[M-H]^{5-}$: calcd. for $C_{74}H_{92}N_{27}O_{41}KP_9$: 466.86 *m/z*; found: 466.46 *m/z*.

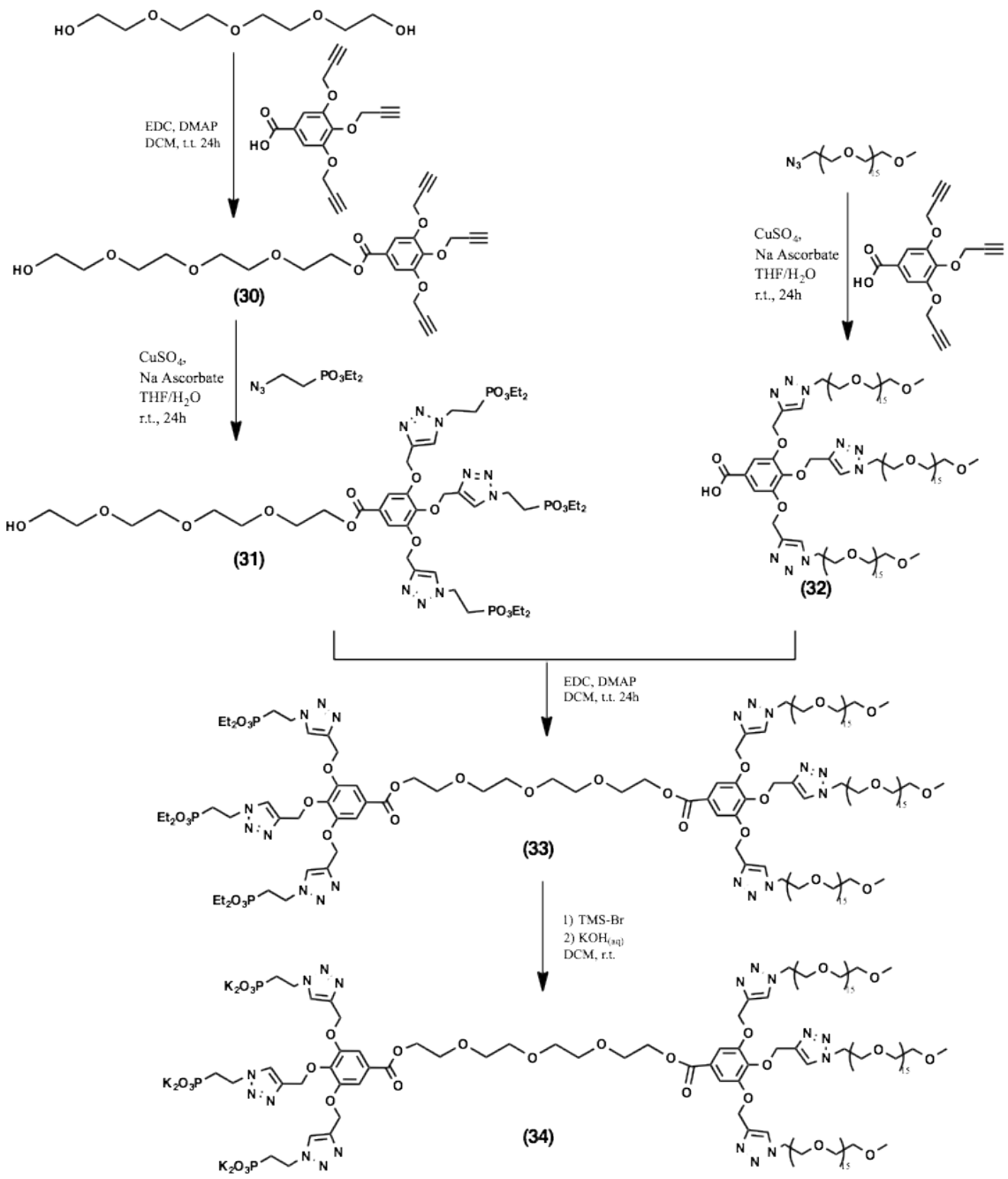
P-dendron-G0 (29):



G0-alkyne (**27**) (72 mg; 0.25 mmol)[4] and diethyl azidoethylenephosphonate (207 mg; 1.0 mmol) were dissolved in THF (5 mL). $CuSO_4.5H_2O$ (125 mg; 0.5 mmol) in aqueous solution was added, followed by dropwise addition of a freshly prepared aqueous solution of sodium ascorbate (198 mg; 1 mmol) to obtain a 1:1 THF/water ratio. The obtained solution was stirred overnight at r.t. under N_2. After removal of THF in *vacuo*, DCM (5 mL) and EDTA(aq) (5 mL; sat.) were added. The mixture was stirred during 30 min to remove the Cu ions trapped inside the dendrimer. Then the organic layer was collected and washed with water (3 × 10 mL). After drying with anhydrous $MgSO_4$, solvent was removed *in vacuo*. Compound **28** was obtained as brown gel (yield >95%).

To a solution of **28** (248 mg, 0.5 mmol) in DCM (7 mL) was added TMS-Br (3.3 g, 22 mmol) and the mixture was stirred for 48 h. $KOH_{(aq)}$ (1M) was added to adjust the solution to pH 8, and the mixture was stirred for 3 h. The DCM was removed tenderly under reduced pressure (a needle through a septum works well). All the volatile components were removed *in vacuo* to give (0.6 g, yield: 100%) of the product (**29**) as a light brown solid. ^{1}H NMR (400 MHz, D_2O): δ_{ppm} 8.27 (1H, -C*H*$_{trz}$), 4.78-4.74 (4H, -C*H*$_2$-trz-C*H*$_2$), 3.62 (2H, -CC*H*$_2$O), 2.27 (2H, -C*H*$_2$P). ^{13}C NMR (125 MHz, D_2O): δ_{ppm} 144.3, 125.1, 124.9, 68.6, 47.9, 45.0, 31.8, 30.8.

^{31}P NMR (81 MHz, D_2O): δ_{ppm} 16.1. MS: ESI-ve mode $[M\text{-}H]^{3-}$: calcd. for $C_{25}H_{43}N_{12}O_{16}P_4$, 297.1 *m/z*; found at 296.3 *m/z* (with all the K atoms were replaced by H).



Compound (30):

Compound **6** (852 mg; 3 mmol) and TEG (5.8 g; 30 mmol) was dissolved in dry DCM, EDC (1.7 g; 9 mmol) and DMAP (732 mg; 6 mmol) were added successively. The reaction mixture was stirred at r.t. for 24 h under N_2. The reaction mixture was washed with water (3 × 20 mL) and then treated with 2N $HCl_{(aq)}$ (2 × 20 mL), and further washed with water (3 × 20 mL). Compound **30** was obtained as colorless gel (yield: 90%).^{1}H NMR ($CDCl_3$, 400 MHz): δ_{ppm} 7.52 (2H, CH_{Ar}), 4.85-4.83 (6H, ArOCH_2-), 4.50 (2H, -COOCH_2-), 3.86 (2H, -COOCH$_2$CH_2-), 3.74-3.68 (10H, CH_2CH_2O-), 3.61 (2H, -CH_2OH), 2.57 (2H, -C≡C*H*), 2.48 (1H, -C≡C*H*).^{13}C NMR ($CDCl_3$, 100 MHz): δ_{ppm} 165.7, 151.3, 141.2, 125.7, 110.16, 78.7, 78.0, 76.3, 75.6, 72.5, 70.7, 70.6, 70.6, 70.6, 70.3, 69.2, 64.4, 61.7, 60.3, 57.1. MS: Calcd. for $C_{24}H_{29}O_9$: 461.18 *m/z*, found at 461.18 *m/z*.

Compound (31)

Compound **30** (322 mg; 0.7 mmol) and diethyl-azidoethylene phosphonate (466 mg; 2.2 mmol) were dissolved in THF (3 mL), after being degassed and refilled with N_2, a $CuSO_4 \cdot 5H_2O$ (175 mg; 0.7 mmol) aqueous solution was added, followed by dropwise addition of sodium ascorbate$_{(aq)}$ (277 mg; 1.4 mmol). The reaction mixture was stirred at r.t. for 24 h under N_2. After removal of the organic solution *in vacuo*, the mixture was dissolved in DCM and treated with $EDTA_{(aq)}$ for 30 min. The organic solution was isolated and washed with water. The crude product was purified by flash column chromatography (DCM/MeOH 50:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_{ppm} 8.07 (1H, CH_{trz}), 7.98 (2H, CH_{trz}), 7.47 (2H, CH_{Ar}), 5.28-5.27 (6H, -ArOCH$_2$-), 4.67 (6H, trz-CH_2-), 4.50 (2H, COOCH_2-), 4.12 (12H, CH$_3$CH_2PO-), 4.18 (2H, -COOCH$_2$CH_2-),

3.73 (10H, -CH_2CH_2O-), 3.60 (t, 2H, -CH_2OH), 2.50 (6H, -CH$_2$CH_2PO), 1.33 (18H, -CH_3).^{13}C NMR ($CDCl_3$, 100 MHz): δ_{ppm} 165.7, 151.9, 144.2, 143.4, 141.6, 125.79, 124.2, 123.7, 109.3, 72.5, 70.7, 70.65, 70.60, 70.3, 69.2, 66.2, 64.4, 63.1, 62.2, 62.17, 62.12, 61.6, 44.6, 44.5, 27.7, 26.5, 16.4, 16.3.^{31}P ($CDCl_3$, 81 MHz): δ_{ppm} 25.6, 25.5.MS: Calcd. for $C_{42}H_{70}N_9O_{18}P_3Na$, 1104.97 *m/z*; Found at 1104.39 *m/z*.

Compound (32)

Compound **6** (284 mg; 1.0 mmol) and PEG750-azide (2.28 g; 3 mmol) were dissolved in THF (5 mL), after being degassed and refilled with N_2, $CuSO_4 \cdot 5H_2O_{(aq)}$ (175 mg; 0.7 mmol) was added, followed by dropwise addition of sodium ascorbate$_{(aq)}$ (277 mg; 1.4 mmol). The reaction mixture was stirred at r.t. for 24 h under N_2. After removal of the organic solution *in vacuo*, the reaction mixture was dissolved in DCM and treated with EDTA$_{(aq)}$ for 30 min. The organic solution was isolated and washed with water. After removal of the solvent, compound **32** was obtained as colorless gel (yield: 93%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_{ppm} 8.02 (3H, CH_{trz}), 7.46 (2H, CH_{Ar}), 5.32, 5.27 (6H, ArOCH_2-), 4.59 (6H, -CH$_2$CH_2-trz), 3.92 (6H, CH_2CH$_2$N-), 3.67-3.55 (180H, -CH_2CH_2O-), 3.39 (9H, CH_3-).^{13}C NMR ($CDCl_3$, 100 MHz): δ_{ppm} 166.7, 151.9, 143.1, 124.5, 109.4, 71.9, 70.5,9, 70.53, 70.4, 69.3, 63.0, 59.0, 50.3.MS: Calcd. for $C_{115}H_{213}N_9O_{53}Na$: 2592.9 *m/z*; found at 2591.5 *m/z*.

Compound (33)

To a DCM (4 mL) solution of **31** (108 mg; 0.1 mmol) and **32** (256 mg; 0.1 mmol), DMAP (12 mg; 0.1 mmol) and EDC (29 mg; 0.15 mmol) were added successively. The reaction mixture was

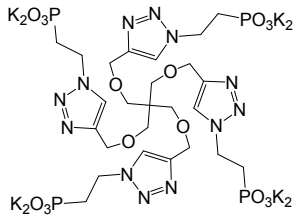
stirred at r.t. for 2 days under N_2. After quenching with H_2O, the obtained solution was treated with $HCl_{(aq)}$ (3 × 10 mL, 2N) and then washed with H_2O (3 × 10 mL). The organic phase was dried over $MgSO_4$ and then the solution was removed under vacuum. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_{ppm} 7.91(6H, C*H*$_{trz}$), 7.40 (4H, C*H*$_{Ar}$), 5.19 (12H, -OC*H*$_2$-trz), 4.61-4.40 (16H, -CH$_2$C*H*$_2$-trz, -COOC*H*$_2$-), 4.06 (12H, -C*H*$_2$CH$_3$), 3.86-3.78 (10H, -OC*H*$_2$CH$_2$-trz, COOCH$_2$C*H*$_2$), 3.66-3.57 (200H, -OC*H*$_2$C*H*$_2$O-), 3.33 (9H, C*H*$_3$O-), 2.46-2.40 (6H, -C*H*$_2$P-), 1.29-1.25 (-C*H*$_2$C*H*$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_{ppm} 165.7, 152.0, 151.9, 143.4, 141.8, 109.4, 71.9, 70.5, 69.3, 66.3, 66.2, 64.3, 64.2, 63.2, 63.1, 62.1, 62.0, 58.9, 50.2, 50.0, 44.6, 44.5, 29.6, 27.6, 26.5, 16.4, 16.3.

^{31}P ($CDCl_3$, 81 MHz): δ_{ppm} 25.5, 25.4.

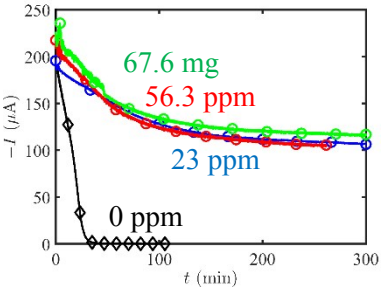
TEG-G0-PEG (34)

A solution of **33** (300 mg; 0.08 mmol) and TMS-Br (220 mg; 1.44 mmol) in DCM (10 mL) was stirred for 48 h. The volatile components were removed *in vacuo* and the residue was taken up in DCM. $KOH_{(aq)}$ (1M; 2 mL) was added, the DCM was removed gradually under reduced pressure (a needle through a septum works well) and the aqueous solution was stirred for 2 h. The pH was adjusted to 8-9. The volatile components were removed under reduced pressure to give compound **34** as a brown solid (yield: 100%). ^{1}H NMR (D_2O, 400 MHz): δ_{ppm} 8.23- 7.92(6H, C*H*$_{trz}$), 7.52 (4H, C*H*$_{Ar}$), 5.32-5.24 (12H, -OC*H*$_2$-trz), 4.54 (6H, -C*H*$_2$CH$_2$P-), 4.03-3.93 (16H, , -CH$_2$C*H*$_2$-trz, -COOC*H*$_2$-), 3.77-3.61 (200H, -OC*H*$_2$C*H*$_2$O-), 3.45 (9H, C*H*$_3$O), 2.16-2.01 (6H, -C*H*$_2$P-). ^{13}C NMR (D_2O, 100 MHz): δ_{ppm} 167.1, 167.0, 151.7, 143.1, 125.9, 125.8, 125.0, 109.3, 71.7, 71.2, 70.1, 69.8, 68.8, 67.6, 65.4, 62.4, 62.3, 58.4, 50.3, 50.2, 47.9, 47.7, 31.7, 30.7. ^{31}P

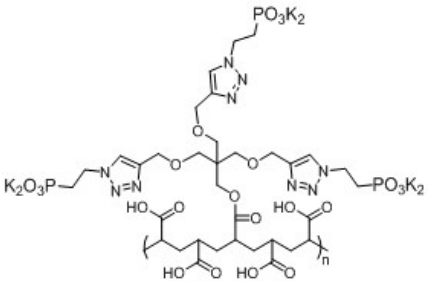
(D_2O, 81 MHz): δ_{ppm} 15.6. MS: calcd. for $C_{139}H_{239}K_3N_{18}Na_2O_{67}P_3$ (three of the K^+ cations were replaced by one H^+ and two Na^+ in MS analysis): 3490.66 *m/z*; found at 3489.8 *m/z*.



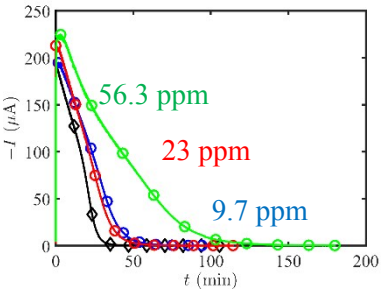
P4-G0
Mw = 1197



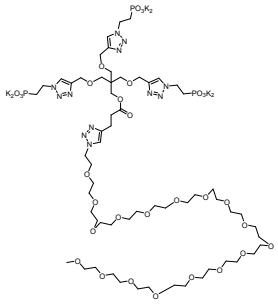
(a)



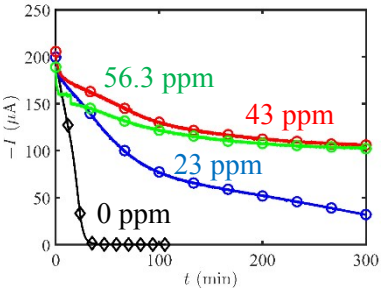
Dendronized polymer G0
Mw = 2863



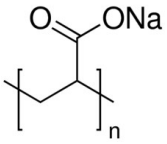
(b)



PEG-G0-P3
Mw = 1818

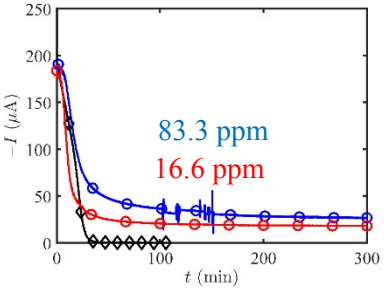


(c)

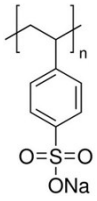


Polyacrylic acid sodium salt (PAA)

M_w = 15 kDa

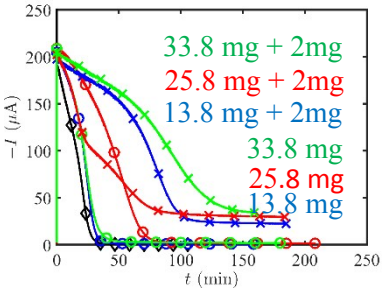


(d)



Poly(sodium 4-styrenesulfonate)

Mw = 70kDa + KG8010 (2mg)



(e)

Figure S1. Antiscaling performance of (**a**) P4-G0 dendrimer, (**b**) dendronized polymer, (**c**) PEG-G0-P3 dendrimer, and well-known antisclants, namely (**d**) polyacrylic acid and (**e**) poly(sodium 4-styrenesulfonate). While the P4-G0 dendrimer (**a**) is more flexible than the tris-G0 dendron (**Figure 3** in the manuscript), its antiscaling performance is weaker. The scale inhibition capability of P4-G0 dendrimer further decreases when it is grafted on a linear polymer backbone (dendronized polymer, **b**). Moreover, substituting one phosphonate group of P4-G0 dendrimer with PEG (Mn = 750) deteriorates its antiscaling performance (**c**), similar to the TEG-based dendrimer. In our accelerated scaling system, polyacrylic acid (**d**) and poly(sodium 4-styrenesulfonate) (**e**) are not able to prevent scaling even at high concentrations (e.g., ~ 80 ppm, **d**). Interestingly, while a synergistic performance between the poly(sodium 4-styrenesulfonate) (**e**) and the industrial scale inhibitor (KG8010) is observed, scaling was not completely inhibited.

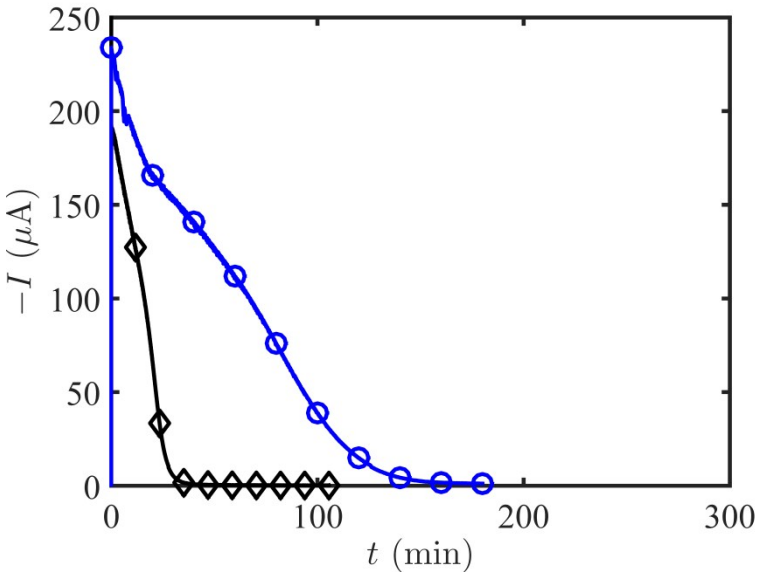


Figure S2. Evolution of current (*I*) versus time (*t*), obtained from the chronoamperometry experiments with the same operating conditions as **Figure 1** for an inhibitor-free system (black) and in the presence of 10 µL of pure azidoethyl phosphonate (blue). Despite using a large amount of pure linear phosphonated species, the scaling takes place in less than 2 h, which necessitates the development of more efficient macromolecules.

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