Supplementary Material (ESI) for Chemical Communications

Supplementary Material

for

A Chemoselective Approach for the Accelerated Synthesis of Well-Defined Dendritic Architectures

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Materials

All chemicals were used as received from Sigma-Aldrich. Flash chromatography was performed using 32-64 D 60 Å silica gel from ICN SiliTech (ICN Biomedicals GmbH, Eschwege, Germany). Matrix preparation for MALDI: 9-Nitroanthracene (20 mg) was dissolved in THF (1 ml) and trifluoro acetic acid (TFA) sodium salt (one tip of a knife) was added. Sample preparation: 5 mg of sample was dissolved in THF. 5 µl of the solution was added to 20 µl of the matrix solution.0.5 µl of the sample-matrix solution was added to the MALDI target plate.

Nomenclature

F = Fréchet-type dendrimer

Bis-MPA = 2,2-bis(methylol)propionic acid

G# = Generation number

Acet = Acetylene

OH = Hydroxyl

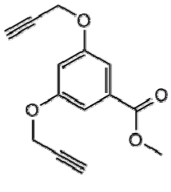
Ac = Acetonide

N_3 = Azide

Instrumental

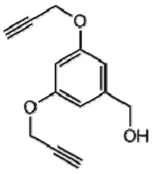
NMR experiments were performed on a Bruker Avance 400 MHz NMR instrument. Proton NMR spectra were acquired with a spectral window of 20 ppm, an acquisition time of 4 seconds, a relaxation delay of 1 second. ^{13}C NMR spectra were acquired with a spectral window of 240 ppm, an acquisition time of 0.7 seconds, a relaxation delay of 2 seconds. The MALDI-TOF MS spectrum acquisitions were conducted on a Bruker UltraFlex MALDI-TOF MS with SCOUT-MTP Ion Source (Bruker Daltonics, Bremen) equipped with a N_2-laser (337nm), a gridless ion source and reflector design. All spectra were acquired using a reflector-positive method with an acceleration voltage of 25kV and a reflector voltage of 26,3kV. The detector mass range was set to 500-10000Da in order to exclude high intensity peaks from the lower mass range. The laser intensity was set to the lowest value possible to acquire high resolution spectra. The obtained spectra were analyzed with FlexAnalysis Bruker Daltonics, Bremen, version 2.2.

Fréchet-type dendrimers



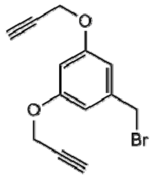
[1]

Synthesis of Methylester-benzene-(Acet)$_2$ (1). Propargyl bromide (10.18 g, 71 mmol) was added to a solution of methyl 3,5-dihydroxybenzoate (5.00 g, 0.029 mol), K_2CO_3 (9.84 g, 71 mmol) and 18-crown-6 (0.78 g, 2.97 mmol) dissolved in 100 ml of acetone. The reaction was refluxed over night and then filtered. The filtrate was concentrated and purified by flash chromatography eluting the product in 10:90 EtOAc:Hep. Yield: 90% (6.4 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.54 (t, 2H, -OCCC**H**), 3.91 (s, 3H, -OC**H$_3$**), 4.72 (d, 4H, J = 2.4 Hz, -OC**H$_2$**CCH), 6.82 (s, 1H, Ar**H**) and 7.30 (d, 2H, J = 2.5 Hz, Ar**H**) ppm; ^{13}C NMR ($CDCl_3$) δ 52.4, 56.1, 75.9, 78.0, 107.5, 108.9, 132.2, 158.5 and 166.6 ppm.



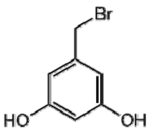
[2]

Synthesis of Hydroxymethyl-benzene-(Acet)$_2$ (2). A three necked round bottomed flask was put in an oven set to 100°C and left over night. The flask was then equipped with a cooler and a stirrer while the system constantly was rinsed with N_2. $LiAlH_4$ (1.27 g, 0.033 mol) was dissolved in anhydrous THF (50 ml) and added to the flask Compound **1** (4.08 g, 0.017 mol) was dissolved in 25 ml of anhydrous THF and dropwise slowly added to the solution. The reaction was left to reflux for 18 hours in N_2 atmosphere before it was cooled to room temperature. Bäckströms regent was added to the solution until no H_2-bubbles was formed. The solid was filtered off and the filtrate concentrated followed by purification by flash chromatography eluting the product in 30:70 EtOAc:Hep. Product obtained as a white powder after evaporation of solvent. Yield: 98% (3.6 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.53 (t, 2H, -OCCC**H**), 4.64 (d, 2H, J = 2.4 Hz, -C**H$_2$**OH), 4.68 (d, 4H, J = 2.1 Hz, -OC**H$_2$**CCH), 6.55 (t, 1H, Ar**H**) and 6.64 (d, 2H, Ar**H**) ppm; ^{13}C NMR ($CDCl_3$) δ 55.9, 65.1, 75.6, 78.3, 101.5, 106.2, 143.5 and 158.8 ppm.



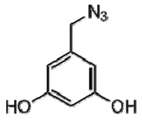
[3]

Synthesis of Bromomethyl-benzene-(Acet)$_2$ (3). Carbon tetra bromide (6.00 g, 0.018 mol) and compound 2 (3.0 g, 0.014 mol) was dissolved in 80 ml of THF. The solution was put on ice bath followed by addition on TPP (8.65 g, 0.033 mol) portion wise. The reaction was quenched with water after 30 minutes followed by removal of THF. The water phase was extracted with 2x150 ml of DCM and dried with $MgSO_4$. The product was eluted in 20:80 DCM:Hep and collected as a powder after removal of the solvent. Yield: 52% (2.0 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.54 (t, 2H, -OCCC**H**), 4.42 (s, 2H, -C**H**$_2$Br), 4.68 (d, 4H, J = 2.3 Hz, -OC**H**$_2$CCH), 6.56 (t, 1H, Ar**H**) and 6.65 (d, 2H, J = 1.9 Hz, Ar**H**) ppm; ^{13}C NMR ($CDCl_3$) δ 33.2, 56.0, 75.8, 78.1, 102.4, 108.7, 139.8 and 158.7 ppm.



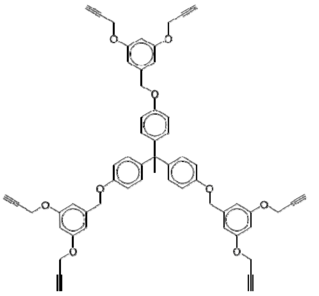
[4]

Synthesis of 5-(bromomethyl)benzene-1,3-diol (4). 5-(hydroxymethyl)benzene-1,3-diol (10.27 g, 0.073 mol) was added to 200 ml anhydrous THF together with carbon tetra bromide (31.5 g, 0.095 mol). The solution was put on ice where after TPP (25 g, 0.095 mol) was added in small portions. The flask was taken out of the ice bath and left to react for 30 minutes at RT and was then quenched with water. The THF was evaporated and the resulting water phase was extracted with 2x150 ml DCM. The combined organic phases were extracted with 20 ml of brine and dried with $MgSO_4$. The solvent was removed and the crude product was purified by flash chromatography eluting the product in 30/70 EtOAc:Hep. The product was obtained as brown powder after removal of solvent. Yield: 40% (6.0 g). ^{1}H NMR (400 MHz, DMSO): δ 4.45 (s, 2H, -C**H**$_2$Br), 6.13 (t, 1H, Ar**H**) and 6.26 (d, 2H, J = 1.8 Hz, Ar**H**) ppm; ^{13}C NMR (DMSO) δ 35.1, 102.7, 107.4, 139.6 and 158.5 ppm.



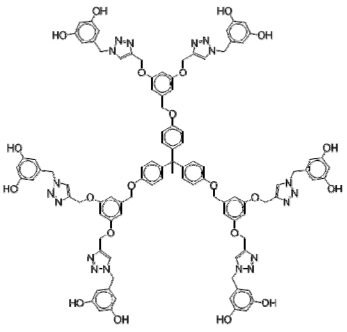
[5]

Synthesis of 5-(azidomethyl)benzene-1,3-diol (5). Compound **4** (5.00 g, 0,025 mol) was dissolved in 30 ml DMSO. NaN_3 was added to the solution and left to react 80°C over night. The solution was extracted with 2x500 ml of ether and the combined organic phases were extracted with 5x100 ml of water. The organic phase was dried with $MgSO_4$ and followed by removal of ether. The product was obtained as lightly brown colored oil. Yield: 79% (3.1 g). ^{1}H NMR (400 MHz, DMSO): δ 4.2 (s, 2H, -C**H**$_2$N$_3$) and 6.18 (m, 3H, Ar**H**) ppm; ^{13}C NMR (DMSO) δ 53.7, 102.1, 106.2, 137.3 and 158.6 ppm.



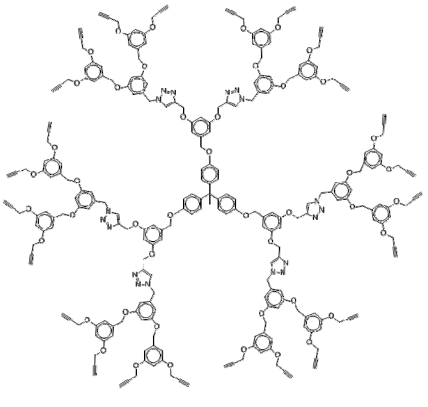
[6]

Synthesis of generation 1 Fréchet-type dendrimer, F-G#1-(Acet)$_6$ (6). Trisphenol (0.33 g, 1.08 mmol) was dissolved in 25 ml of acetone together with 18-crown-6 (point of a knife). K_2CO_3 (0.30 g, 5.6 mmol) was added to the solution under vigorously stirring followed by addition of compound **3** (1.00 g, 3.58 mmol). The reaction was kept over night at reflux under N_2 atmosphere and then cooled to RT. The solid was filtered of followed by removal of acetone. The crude product was purified by flash chromatography eluting the product in 40/60 EtOAc:Hep and obtained as a viscous oil. Yield: 91% (0.89 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.10 (s, 3H, -C**H**$_3$, core), 2.56 (t, 6H, -OCCC**H**), 4.67 (d, 12H, J = 2.3 Hz, -OC**H**$_2$CCH) 5.00 (s, 6H, -OC**H**$_2$Ar, generation 1), 6.57 (s, 3H, Ar**H**, generation 1), 6.68 (d, 6H, J = 2.3 Hz, Ar**H**, generation 2), 6.85 (d, 6H, J = 8.9 Hz, Ar**H**, core) and 6.97 (d, 6H, J = 8.9 Hz, Ar**H**, core) ppm; ^{13}C NMR ($CDCl_3$) δ 30.7, 50.6, 55.9, 69.7, 75.7, 78.2, 101.7, 106.8, 114.0, 129.6, 139.8, 142.1, 156.6 and 158.8 ppm. MALDI: Theoretical M_W^+= 901.10 g/mol, Found M_W^+= 899.75 g/mol.



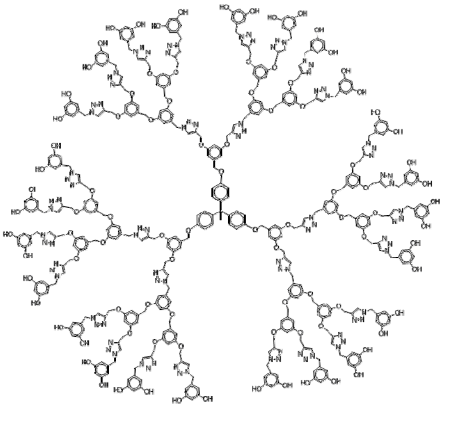
[7]

Synthesis of generation 2 Fréchet-type dendrimer, F-G#2-(OH)$_{12}$ (7). Compound **6** (0.50 g, 0.55 mmol) and **5** (0.66 g, 4.00 mmol) was dissolved in 6 ml of THF followed by addition of sodium ascorbate (0.13 g, 0.66 mmol). $CuSO_4$ (0.53 g, 0.33 mmol) was dissolved in 1 ml of water and added to the solution. The reaction vessel was filled with N_2 and sealed and left to react over night at 40°C. THF/H_2O was evaporated and the crude product was purified by flash chromatography eluting the product in 3/97 MeOH:THF. The product was obtained as a brown powder after removal of solvent. Yield: 93% (0.97 g). ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 2.03 (s, 3H, -C**H**$_3$, core), 4.98 (s, 6H, -OC**H**$_2$-Ar, generation 1), 5.12 (s, 12H, -OC**H**$_2$-triazole, generation 1), 5.40 (s, 12H, -triazole-C**H**$_2$-Ar, generation 2), 6.12 – 6.14 (m, 21H, Ar**H**, generation 1, Ar**H**, generation 2, Ar**H**, generation 2), 6.71 (s, 6H, Ar**H**, generation 1) 6.91 (q, 12H, Ar**H**, core) and 8.22 (s, 6H, triazole**H**) ppm; ^{13}C NMR (DMSO-d$_6$) δ 30.2, 50.2, 52.7, 61.0, 68.9, 100.6, 102.1, 105.6, 106.2, 113.8, 124.8, 129.1, 137.7, 139.1, 141.5, 142.7, 156.2, 158.6, and 159.2 ppm. MALDI: Theoretical M_W^+= 1891.90 g/mol, Found M_W^+= 1892.62 g/mol.



[8]

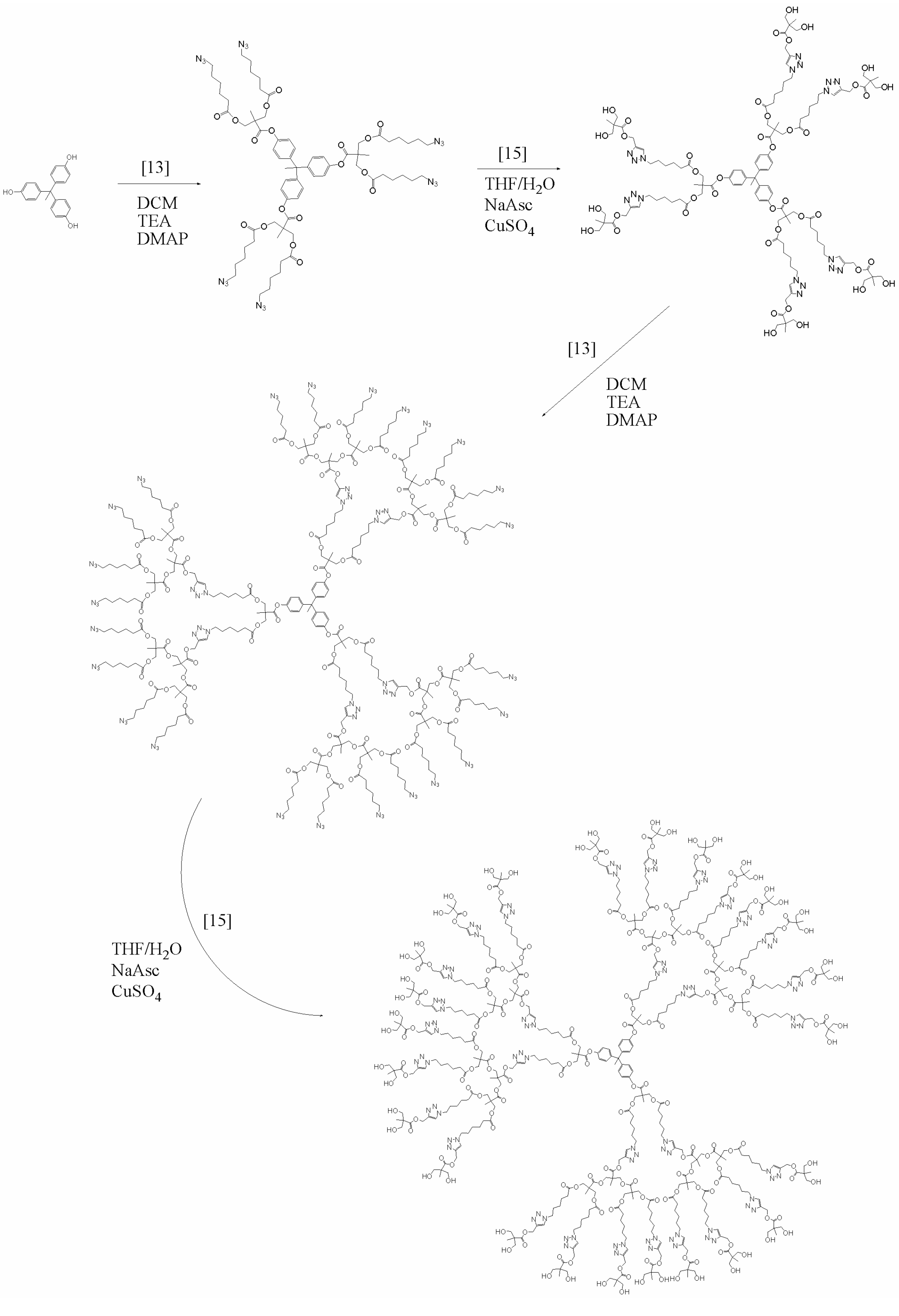
Synthesis of generation 3 Fréchet-type dendrimer, F-G#3-(Acet)$_{24}$ (8). Compound **7** (0.60 g, 0.31 mmol) was dissolved in 10 ml of acetone together with 18-crown-6 (catalytic amount) and K_2CO_3 (514 mg, 3.72 mmol) followed by addition of compound **3** (1.35 g, 4.83 mmol) The reaction was refluxed over night in N_2-atmosphere and then cooled down to RT. The solid was filtered off and the filtrate was concentrated. The crude product was purified by flash chromatography, eluting the monomer in DCM and the product in 1/99 MeOH:DCM. The product was obtained as a beige powder after removal of solvent. Yield: 90% (1.19 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.06 (s, 3H, -C**H**$_3$, core) 2.49 (t, 24H, -OCCC**H**), 4.62 (d, 48H, J = 2.4 Hz, -OC**H**$_2$CCH), 4.90 (s, 30H, -OC**H**$_2$-Ar, generation 1 and -OC**H**$_2$-Ar, generation 3), 5.11 (s, 12H, -OC**H**$_2$-triazole), 5.38 (s, 12H, triazole-C**H**$_2$-Ar), 6.42 (s, 12H, Ar**H**, generation 3), 6.43 – 6.64 (m, Ar**H**, generation 1, Ar**H**, generation 1, Ar**H**, generation 2, Ar**H**, generation 2 and Ar**H**, generation 3), 6.80 (d, 6H, J = 9.0 Hz, Ar**H**, core), 6.94 (d, 6H, J = 9.0 Hz, Ar**H**, core) and 7.51 (s, 6H, triazole**H**) ppm; ^{13}C NMR ($CDCl_3$) δ 30.7, 50.6, 54.1, 55.9, 62.0, 69.8, 75.9, 78.3, 101.2, 101.8, 102.3, 106.6, 106.7, 107.2, 114.0, 122.8, 129.6, 136.7, 139.0, 139.8, 142.0, 144.3, 156.6, 158.8, 159,8 and 160.1 ppm. MALDI: Theoretical M_W+Na$^+$= 4293.51 g/mol, Found M_W+Na$^+$= 4295.06 g/mol.



[9]

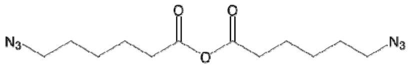
Synthesis of generation 4 Fréchet-type dendrimer, F-G#4-(OH)$_{48}$ (9). Compound **8** (0.20 g, 0.047 mmol) was dissolved in 3 ml of DMF together with compound **5** (1.95 g, 1.18 mmol) and sodium ascorbate (0.09 g, 0.45 mmol). $CuSO_4$ (0.035 g, 0.22 mmol) was dissolved in 0.5 ml of water and added to the solution. The reaction was kept over night at 40°C and in N_2 atmosphere. DMF was distilled off and the crude product was purified by precipitation in ether 3 times. Yield: 91% (0.35 g). ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 1.99 (s, 3H, -C**H**$_3$, core), 4.96 (s, 30H, -OC**H**$_2$-aromat, generation 1 and 3), 5.09 (s, 60H, -OC**H**$_2$-triazole, generation 2 and 4), 5.37 (s, 48H, -triazole-C**H**$_2$-aromat, generation 4), 5.50 (s, 12H, -triazole-C**H**$_2$-Ar, generation 2) 6.11 – 6.14 (m, 93H, Ar**H** (3H), generation 1, Ar**H** (6H), generation 2, Ar**H** (12H), generation 3, Ar**H** (24H), generation 4, Ar**H** (48), generation 4), 6.59 – 6.68 (m, 42H, Ar**H** (6H), generation 1, Ar**H** (12H), generation 1, Ar**H** (24H), generation 1), 6.90 6.92 (d, 6H, J = 9.0 Hz, Ar**H**, core), 6.92 (d, 6H, J = 9.0 Hz, Ar**H**, core), 8.19 (s, 24H, triazole**H**, generation 4) and 8.28 (s, 6H, triazole**H**, generation 2) ppm; ^{13}C NMR (DMSO-d$_6$) δ 30.2, 50.2, 52.7, 52.8, 61.0, 61.1, 68.9, 100.1, 102.0, 102.1, 104.5, 105.6, 106.5, 100.7, 113.8, 124.7, 124.8, 129.1, 136.8, 137.7, 139.1, 141.5, 142.5, 142.6, 142.7, 156.2, 158.6, 159.1, 159.2 and 162.2 ppm. MALDI: Theoretical M_W+Na$^+$= 8257.10 g/mol, Found M_W+Na$^+$= 8260.24 g/mol.

Bis-MPA-type dendrimers



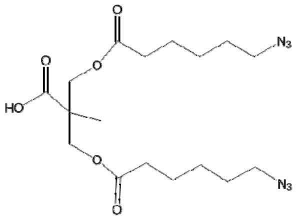
[10]

Synthesis of 6-azidohexanoic acid (10). 6-chlorohexanoic acid (5.0 g, 33.2 mmol) was dissolved in 50 ml of H_2O followed by addition of NaN_3 (10.8 g, 166 mmol). The reaction was refluxed over night. The reaction solution was cooled to RT followed by drop wise addition of 50% HCl solution until pH~2 was reached. The solution was extracted with 2x200 ml of ether and dried with $MgSO_4$. Yield: 92% (4.8 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (m, 2H, C=OCCC**H**$_2$CCN$_3$), 1.56 – 1.69 (m, 4H, C=OCC**H**$_2$CC**H**$_2$CN$_3$), 2.35 (t, 2H, C=OC**H**$_2$CCCCN$_3$) and 3.26 (t, 2H, C=OCCCCC**H**$_2$N$_3$) ppm; ^{13}C NMR ($CDCl_3$) δ 24.0, 26.0, 28.4, 33.8, 51.1 and 180.0 ppm.



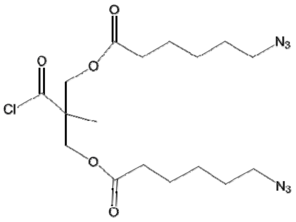
[11]

Synthesis of 6-azidohexanoic anhydride (11). Compound 21 (4.0 g, 25.4) was dissolved in a 10 ml DCM followed by addition of DCC (5.23 g, 25.4 mmol). The reaction was kept over night at RT and then filtered. Yield: 82% (6.2 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (q, 4H, -C=OCCC**H**$_2$CCN$_3$), 1.56 – 1.76 (m, 8H, -C=OCC**H**$_2$CC**H**$_2$CN$_3$), 2.49 (t, 4H, -C=OC**H**$_2$CCCCN$_3$) and 3.30 (t, 4H, -C=OCCCCC**H**$_2$N$_3$) ppm; ^{13}C NMR ($CDCl_3$) δ 24.6, 25.4, 27.9, 34.5, 50.9 and 168.8 ppm.



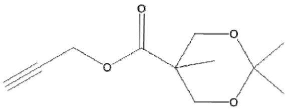
[12]

Synthesis of Bis-MPA-(C_5-N_3)$_2$ (12). Compound **11** (5 g, 16.1 mmol) was added to a solution of bis-MPA (720 mg, 5.37 mmol), DMAP (catalytic amount), 10 ml DCM and 3 ml pyridine. The reaction was kept over night at RT before the solvent was evaporated. The crude product was purified by flash chromatography eluting 6-azidohexanoic acid in 5/95 EtOAc:Hep 1% acetic acid and the product in 10/90 EtOAc:Hep 1% acetic acid. Yield: 89% (2.0 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (s, 3H, -CC**H**$_3$), 1.38 (q, 4H, -C=OCCC**H**$_2$CCN$_3$), 1.60 (m, 8H, -C=OCC**H**$_2$CC**H**$_2$CN$_3$), 2.33 (t, 4H, -C=OC**H**$_2$CCCCN$_3$), 3.26 (t, 4H, -C=OCCCCC**H**$_2$N$_3$), 4.24 (q, 4H, -CC**H**$_2$O) ppm; ^{13}C NMR ($CDCl_3$) δ 17.7, 24.1, 26.1, 28.5, 33.8, 46.1, 51.2, 65.1, 172.9 and 179.8 ppm.



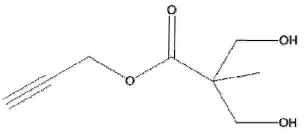
[13]

Synthesis of Cl-Bis-MPA-(C_5-N_3)$_2$ (13). Oxaloyl chloride (0.92 g, 7.26 mmol) was added to compound **12** (1.5 g, 3.63 mmol) dissolved in 15 ml of $CHCl_3$. 1 drop of DMF was added to catalyze the reaction. The reaction was then kept at RT for 2h followed stripping of oxaloyl chloride using 5x15 ml of $CHCl_3$. The pure product was obtained as oil. Yield: 99% (1.55 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (s, 3H, -CC**H**$_3$), 1.40 (q, 4H, -C=OCCC**H**$_2$CCN$_3$), 1.63 (m, 8H, -C=OCC**H**$_2$CC**H**$_2$CN$_3$), 2.35 (t, 4H, -C=OC**H**$_2$CCCCN$_3$), 3.28 (t, 4H, -C=OCCCCC**H**$_2$N$_3$) and (q, 4H, -CCH$_2$O-) ppm; ^{13}C NMR ($CDCl_3$) δ 17.9, 24.3, 26.2, 28.5, 33.7, 51.2, 56.1, 64.9, 172.5 and 175.1 ppm.



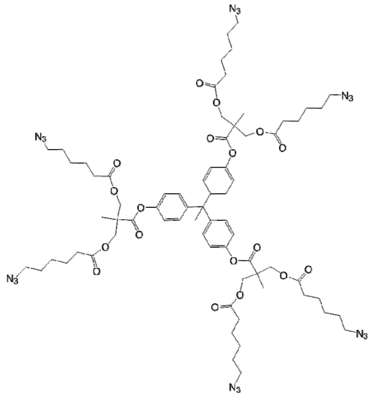
[14]

Synthesis of Acet-Bis-MPA-Ac (14). Synthesized according to reference 9.



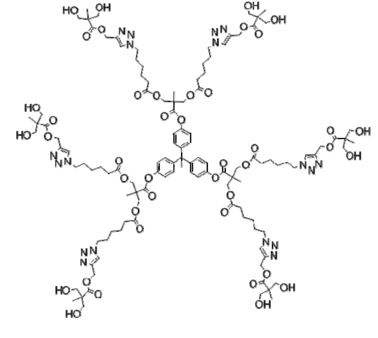
[15]

Synthesis of Acet-Bis-MPA-(OH)$_2$ (15). Synthesized according to reference 9.



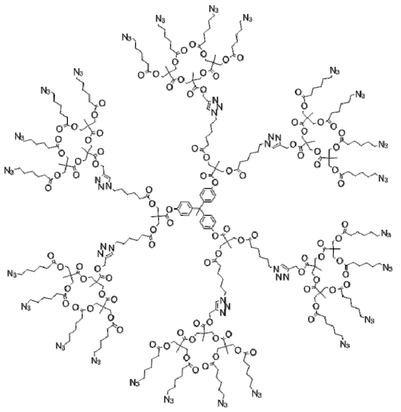
[16]

Synthesis of generation 1 Bis-MPA-type dendrimer, Bis-MPA-G#1-(N$_3$)$_6$ (16). Trisphenol (0.31 g, 1.00 mmol) was dissolved in 10 ml of DCM together with TEA (0.46 g, 4.5 mmol) and DMAP (catalytic amount). Compound **13** (1.55 g, 3.60 mmol) was added to the solution and was the left to react at RT over night. The reaction was quenched with water followed by extraction with 3x5 ml brine. The organic phase was dried with $MgSO_4$, concentrated and purified by flash chromatography eluting the product in 40/60 EtOAc:Hep. Yield: 95% (1.42 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (q, 12H, -OC=OCCC**H**$_2$CCN$_3$), 1.40 (s, 9H, -CC**H**$_3$), 1.59 (q, 12H, -C=OCC**H**$_2$CCCN$_3$), 1.65 (q, 12H, -C=OCCCC**H**$_2$CN$_3$), 2.53 (s, 3H, -CC**H**$_3$, core), 2.36 (t, 12H, -C=OC**H**$_2$CCCCN$_3$), 3.24 (t, 12H, -C=OCCCCC**H**$_2$N$_3$), 4.35 (q, 12H, -CC**H**$_2$O-), 6.94 (d, 6H, J = 9.1 Hz, Ar**H**, core) and 7.08 (d, 6H, J = 9.1 Hz, Ar**H**, core) ppm; ^{13}C NMR ($CDCl_3$) δ 17.7, 24.3, 26.2, 28.5, 30.5, 33.8, 46.8, 51.1, 65.3, 120.7, 129.7, 146.3, 148.6, 171.4 and 172.8 ppm. MALDI: Theoretical $M_W+Na^+= 1512.63$ g/mol, Found $M_W+Na^+= 1512.50$ g/mol.



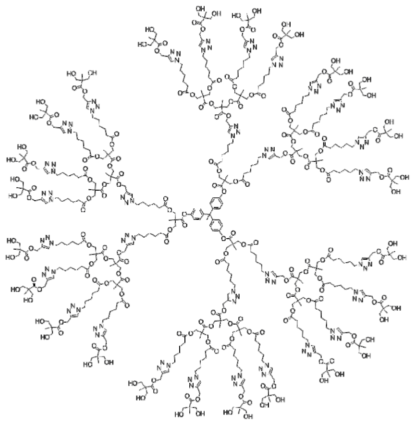
[17]

Synthesis of generation 2 Bis-MPA-type dendrimer, Bis-MPA-G#2-(OH)$_{12}$ (17). Compound **16** (220 mg, 0.15 mmol) was dissolved in 5 ml of THF together with compound **15** (167 mg, 0.97 mmol) NaAsc (88 mg, 0.44 mmol). CuSO$_4$ (14 mg, 0.088 mmol) was dissolved in 1 ml of water and added to the solution. The reaction was kept over night followed by removal of solvents. The crude product was purified by flash chromatography eluting the product in 30/70 MeOH/EtOAc. Yield: 91% (0.34 g). ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 1.02 (s, 18H, -CC**H**$_3$, generation 2), 1.22 (q, 12H, -C=OCCC**H**$_2$CC-Triazole, generation 1), 1.51 (s, 9H, -CC**H**$_3$, generation 1), 1.53 (q, 12H, -C=OCC**H**$_2$CCC-Triazole, generation 1), 1.75 (q, 12H, -C=OCCCC**H**$_2$C-Triazole, generation 1), 2.11 (s, 3H, -CC**H**$_3$, core), 2.33 (t, 12H, -C=OC**H**$_2$CCCC-Triazole, generation 1), 3.42 (q, 24H, -CC**H**$_2$O-, generation 2), 4.24 – 4.30 (m, 24H, -C=OCCCCC**H**$_2$-Triazole and CC**H**$_2$O), 5.09 (s, 12H, Triazole-C**H**$_2$OC=O), 7.02 (d, 6H, J = 9.1 Hz, Ar**H**, core), 7.08 (d, 6H, J = 9.1 Hz, Ar**H**, core) and 8.04 (s, 6H, Triazole**H**) ppm; ^{13}C NMR (DMSO-d$_6$) δ 16.8, 17.0, 20.4, 23.7, 25.2, 29.2, 30.5, 33.0, 46.0, 46.4, 50.2, 60.4, 63.9, 65.0, 121.0, 122.0, 129.3, 145.1, 146.1, 148.2, 171.1, 171.6 and 174.5 ppm. MALDI: Theoretical M_W+Na^+= 2545.70 g/mol, Found M_W+Na^+= 2546.50 g/mol.



[18]

Synthesis of generation 3 Bis-MPA-type dendrimer, Bis-MPA-G#3-(N$_3$)$_{24}$ (18). Compound **17** (0.2 g, 0.079 mmol) was dissolved in 5 ml of anhydrous THF together with TEA (144 mg, 1.4 mmol) and DMAP (17 mg, 0.14 mmol). Compound **13** (0.61 g, 14.2 mmol)was added to the solution and was the left to react at RT over night. The reaction was quenched with water followed by extraction with 2x3 ml brine. The organic phase was dried with MgSO$_4$, concentrated and purified by flash chromatography eluting the product in 60/40 EtOAc:Hep. Yield: 90% (0.52 g). ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.19 (s, 36H, -CC**H**$_3$, generation 3), 1.24 (s, 18H, -CC**H**$_3$, generation 2), 1.28 (s, 9H, -CC**H**$_3$, generation 1), 1.36 – 1.43 (m, 12H, -C=OCCC**H**$_2$CC-triazole, generation 1 and 48H, -C=OCCC**H**$_2$CCN$_3$, generation 3), 1.57 – 1.71 (m, 12H, -C=OCC**H**$_2$CCC-triazole, generation 1, 48H, -C=OCC**H**$_2$CCCN$_3$, generation 3 and 48H, -C=OCCCC**H**$_2$CN$_3$, generation 3), 1.94 (q, 12H, -C=OCCCC**H**$_2$C-triazole, generation 1), 2.30 – 2.37 (m, 12H, -C=OC**H**$_2$CCCC-triazole, generation 1 and 48H, -C=OCC**H**$_2$CCCN$_3$, generation 3), 3.28 (t, 48H, -C=OCCCCC**H**$_2$N$_3$, generation 3), 4.06 – 4.39 (m, 12H, CC**H**$_2$O-, generation 1, 24H, -CC**H**$_2$O-, generation 2, 48H, -CC**H**$_2$O-, generation 3 and 12H, -C=OCCCCC**H**$_2$-triazole, generation 1), 5.24 (s, 12H, triazole-C**H**$_2$OC=O-), 6.96 (d, 6H, J = 9.1 Hz, Ar**H**, core), 7.08 (d, 6H, J = 9.1 Hz, Ar**H**, core) and 7.67 (s, 6H, triazole**H**) ppm; ^{13}C NMR (CDCl$_3$) δ 17.4, 17.6, 17.7, 24.0, 24.2, 24.3, 25.9, 26.0, 26.1, 28.2, 28.4, 29.9, 30.8, 33.5, 33.6, 46.2, 46.5, 46.6, 50.0, 51.1, 58.3, 64.9, 65.3, 124.0, 129.6, 141.8, 146.2, 148.5, 162.6, 171.3, 171.8, 172.0, 172.5 and 172.7. MALDI: Theoretical M_W+Na^+= 7273.81 g/mol, Found M_W+Na^+= 7282.44 g/mol.



[19]

Synthesis of generation 4 Bis-MPA-type dendrimer, Bis-MPA-G#4-(OH)$_{48}$ (19). Compound **18** (0.15 g, 0.021 mmol) was dissolved in 5 ml of DMF together with compound **15** (0.093 g, 0.54 mmol) NaAsc (0.050 g, 0.25 mmol). CuSO$_4$ (0.008 g, 0.049 mmol) was dissolved in 1 ml of water and added to the solution. The reaction was kept over night followed dialysis in water for 3 days. The product was obtained as a beige powder after freeze drying over night. Yield: 89% (0.21 g). ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 1.00 – 1.30 (m, 195H, -CC**H**$_3$, generation 4, -CC**H**$_3$, generation 3, -CC**H**$_3$, generation 2, -CCH$_3$, generation 1, -C=OCCC**H**$_2$CC-triazole, generation 1, -C=OCCC**H**$_2$CC-triazole, generation 3), 1.50 (q, 6H, -C=OCC**H**$_2$CCC-triazole generation 1 and 3), 1.78 (q, 60H, -C=OCCCC**H**$_2$C-triazole, generation 1 and 3), 2.11 (s, 3H, Ar**H**, core), 2.28 (m, 60H, -C=OC**H**$_2$CCCC-triazole, generation 1 and 3), 3.45 (split d, 96H, CC**H**$_2$OH, generation 4), 4.06 – 4.31 (m, 144H, -CC**H**$_2$O-, generation 3, CC**H**$_2$O, generation 2, CC**H**$_2$O, generation 1, -C=OCCCCC**H**$_2$-triazole, generation 1 and -C=OCCCCC**H**$_2$-triazole, generation 3), 5.09 (s, 48H, triazole-C**H**$_2$O-, generation 4 and triazole-C**H**$_2$O-, generation 2), 7.02 (d, 12H, J = 9.1 Hz, Ar**H**, core), 7.08 (d, 12H, J = 9.1 Hz, Ar**H**, core), 8.05 (s, 24H, triazole**H**, generation 4) and 8.09 (s, 6H, triazole**H**, generation 2) ppm; ^{13}C NMR (DMSO-d$_6$) δ 16.7, 16.9, 17.0, 17.1, 20.3, 23.6, 23.8, 25.2, 25.4, 29.2, 29.3, 30.5, 30.6, 32.9, 45.9, 46.0, 46.1, 49.8, 50.1, 51.2, 57.2, 60.2, 63.2, 63.7, 64.7, 65.0, 120.9, 120.8, 123.9, 129.3, 142.1, 146.1, 146.3, 148.2, 171.0, 171.5, 171.7, 172.2, 174.3 and 174.4 ppm. MALDI: Theoretical M$_W$+Na$^+$= 11434.09 g/mol, Found M$_W$+Na$^+$= 11439.21 g/mol.