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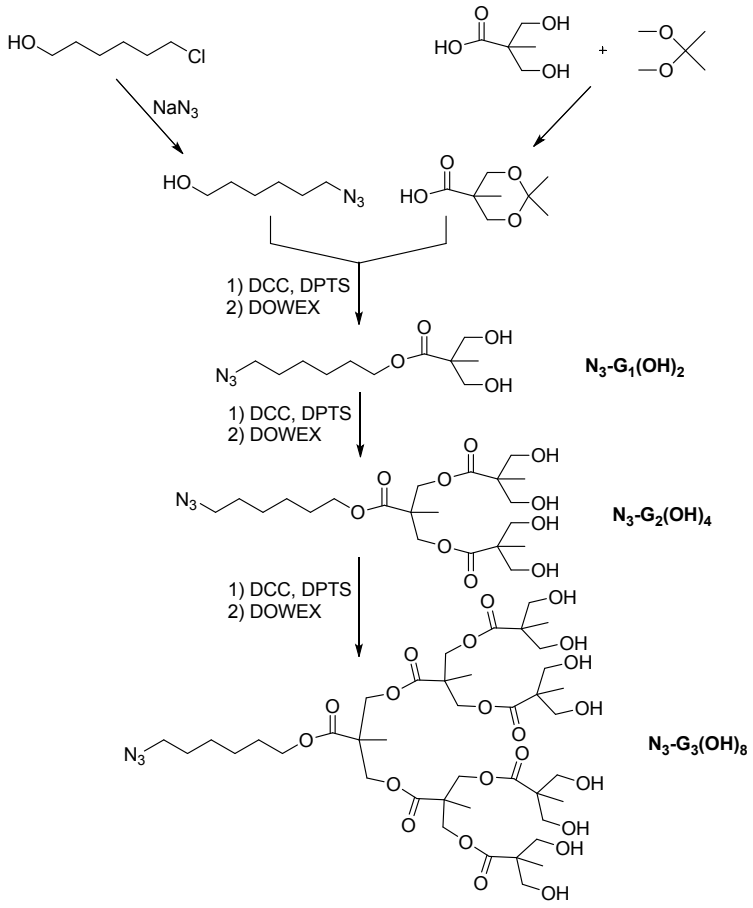
Self-assembling amphiphilic Janus dendrimers: mesomorphic properties and aggregation in water

Elisabetta Fedeli,[a,b] Alexandre Lancelot,[a,b] José Luis Serrano,[a] Pilar Calvo,[b] Teresa Sierra*[c]

ELECTRONIC SUPPLEMENTARY INFORMATION

S1 Synthesis and characterization of the hydrophilic dendrons



Scheme S1-1. Synthetic procedure employed to synthesize the hydrophilic dendrons.

Synthesis of isopropylidene-2,2-bis(methoxy)propionic Acid

Bis-MPA (10.00 g, 74.55 mmol) and (13.8 mL, 111.83 mmol) of 2,2-dimethoxypropane and (0.71 g, 3.73 mmol) of p-toluenesulfonic acid monohydrate were dissolved in acetone (50 mL). The reaction mixture was stirred for 2h at room temperature then, the catalyst was neutralized by adding approximately 1 mL of a NH_3/EtOH (50:50) solution; the solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (250 mL) and extracted with two portions of 20 mL of water each. The organic phase was dried with $MgSO_4$ and was evaporated to give compound **1** as white crystals. Yield 92%.

^{1}H-NMR ($CDCl_3$, 400MHz), δ (ppm): 4.18 (d, 2H, -CH'H''); 3.67 (d, 2H, -CH'H''); 1.44 (s, 3H, -OC-CH$_3$); 1.41 (s, 3H, -OC-CH$_3$); 1.21 (s, 3H, HOOC-C-CH$_3$), ^{13}C-NMR ($CDCl_3$, 400MHz), δ (ppm): 180.38; 98.45; 65.98; 41.87; 25.32; 22.09; 18.56. FTIR (cm^{-1}, Nujol): 3200 (ν COO-H), 2939-2846 (ν C-H), 1716 (ν C=O), 1452 (δ –CH_2-; δ_{as} -CH_3). MS (MALDI-TOF) m/z: expected: 174.09; found: 196.9

synthesis of 6-azido-hexanol

6-cloroexanol (19.53 mL, 146 mmol) was dissolved in DMF (60 mL), then sodium azide (19.99 g, 307 mmol) was added. The mixture was stirred at 140ºC for 24 hours and then at room temperature for 24 hours. After this time, the mixture was diluted with ethyl acetate and was washed with water. The organic layer was dried with magnesium sulfate and the solvent was removed under reduced pressure. The crude product was separated by liquid chromatography on silica gel, eluted with a mixture of hexane and ethy acetate, 7:3 dichloromethane. The separated product was obtained as yellow oil Yield: 83%.

^{1}H-NMR ($CDCl_3$, 400MHz), δ (ppm): 3.61 (t, 2H; -C$\underline{H_2}$OH), 3.24 (t, 2H; -C$\underline{H_2}$$N_3$), 1.56 (m, 4H; N_3-$CH_2C\underline{H_2}(CH_2)_2C\underline{H_2}$ CH_2OH), 1.36 (m, 4H; N_3CH_2 CH_2 ($C\underline{H_2}$)$_2CH_2$ CH_2OH). ^{13}C-NMR ($CDCl_3$, 400MHz), δ (ppm): 62.76; 51.44; 32.61; 28.88; 26.60; 25,41. FTIR (cm^{-1}, Nujol): 3339 (ν O-H), 2950-2850 (ν C-H), 2092 (ν N_3).

Synthesis of compound N_3-$G_1(OH)_2$

6 azidohexanol (2.4 g, 17.2 mmol), isopropylidene-2,2-bis(methoxy)propionic acid (1 g, 5.7 mmol) and DPTS (0,67 g, 2.3 mmol) were dissolved in fresh distilled dichloromethane (15 mL) under argon conditions. The solution was cooled in an ice-water bath and DCC (1.1 g, 5.7 mmol) was added drop wise. The mixture was kept in the ice-water bath for 10 min and was stirred overnight under argon atmosphere at room temperature. The white precipitate (N-N'-dicyclohexylurea) was filtered off and was washed with dichloromethane (10 mL). The crude product was separated by liquid chromatography on silica gel, eluted with dichloromethane. The compound was separated as yellow oil. The protected dendron (1 g, 3.33 mmol) was dissolved in a solution of CH_2Cl_2:MeOH 1:1 (30 mL); 10% in weight of DOWEX® resin was added and the mixture was stirred for 4 hours at room temperature. The resin was filtered off and the filtrate was concentrated and dried under reduced pressure to give the pure product as yellow viscous oil. Yield: 73%.

^{1}H-NMR ($CDCl_3$, 300MHz), δ (ppm): 4.13 (t, 2H; -C$\underline{H_2}$OCO-), 3.86 (d, 2H; C-C$\underline{H}$H'OH, J= 11 Hz), 3.67 (d, 2H; C-CH$\underline{H}$'OH, J= 11 Hz), 3.25 (t, 2H; $N_3C\underline{H_2}$-), 1.66 (m, 2H; -C$\underline{H_2}$$CH_2$-OCO), 1.59 (m, 2H; 1.43 -C$\underline{H_2}$$CH_2$-$N_3$), 1.37 (m, 4H; $N_3CH_2CH_2(C\underline{H_2})_2$), 1.04 (s, 3H; -C$\underline{H_3}$). ^{13}C-NMR ($CDCl_3$, 400MHz), δ (ppm): 176.06; 68.01; 64.98; 51.39; 49.24; 28.80; 28.51; 26.24; 25.52; 17.19. FTIR (cm^{-1}, Nujol): 3365 (ν, O-H), 2945-2852 (ν, C-H), 2092 (ν, N_3), 1724 (ν, C=O), 1458 (δ –CH_2-; δ_{as} -CH_3). MS (ESI$^+$) m/z: 282.0 EA ($C_{11}H_{21}N_3O_4$): expected: C 50.95 H 8.16 N 16.21; obtained: C 50.37 H 8.21 N 16.37.

Synthesis of compound N_3-$G_2(OH)_4$

Compound **N_3-$G_1(OH)_2$** (1 g, 2.0 mmol), isopropylidene-2,2-bis(methoxy)propionic acid (1.41 g, 8.1 mmol) and DPTS (0.29 g, 1.0 mmol) were dissolved in fresh distilled dichloromethane (15 mL) under argon condition. The solution was cooled in an ice-water bath and DCC (0.49 g, 2.8 mmol) was added drop wise. The mixture was kept in the ice-water bath for 10 min and was stirred overnight under argon atmosphere at room temperature. The white precipitate (N-N'-dicyclohexylurea) was filtered off and was washed with dichloromethane (10 mL). The organic solvent was reduced with the rotary evaporator and the solution was poured into a mixture hexane and ethyl acetate (7:·3) provoking the precipitation of a white solid as impurity. The solvent was evaporated under reduced pressure. The crude product was separated by liquid chromatography on silica gel, eluted with a mixture of hexane and ethyl acetate (7:3). The compound was separated as yellow oil. To deprotect the dendron, the oil was diluted with methanol and 10% $_{w/w}$ of DOWEX® was added. The deprotection procedure was carried on for 8 hours. The resin was filtered off and the solvent was evaporated under reduced pressure. The pure product was obtained as pale yellow oil. Yield 79%.

^{1}H-NMR ($CDCl_3$, 400MHz), δ (ppm): 4.44 (d, 2H; -CC<u>H</u>H'O-, J= 11 Hz), 4.26 (d, 2H; -CCH<u>H'</u>O-, J= 11 Hz), 4.14 (t, 2H; -CH_2-C<u>H_2</u>-OCO), 3.83-3.61 (ABq, 8H; -CC<u>H_2</u>-OH, J= 11 Hz, $\Delta\nu_{AB}$= 44 Hz), 3.27 (t, 2H; N3-C<u>H_2</u>-), 1.66 (m, 2H; -C<u>H_2</u>CH_2OCO), 1.60 (m, 2H; N_3-CH_2-C<u>H_2</u>-), 1.39 (m, 4H; N_3-CH_2-CH_2-(C<u>H_2</u>)$_2$-), 1.30 (s. 3H; C-C<u>H_3</u> interior), 1.05 (s, 6H; C-C<u>H_3</u> exterior). <u>^{13}C-NMR ($CDCl_3$, 400MHz), δ (ppm)</u>: 175.28; 173.17; 68.12; 65.55; 64.99; 51.43; 49.82; 46.50; 28.83; 28.50; 26.46; 25.60;18.29; 17.26. <u>FTIR (cm^{-1}, Nujol):</u> 3271 (ν, O-H), 2941-2850 (ν, C-H), 2094 (ν, N_3), 1732 (ν, C=O), 1460 (δ–CH_2-; δ_{as} -CH_3). MS (MALDI$^+$, ditranol) m/z: 514.3 EA ($C_{21}H_{37}N_3O_{10}$): expected: C 51.31; H 7.59; N 8.55;obtained: C 51.47; H 7.62; N 8.66.

Synthesis of compound N_3-$G_3(OH)_8$

N_3-$G_2(OH)_4$ (1 g, 7.7 mmol), acetonide protected bis-MPA (2.68 g, 15.4 mmol) and DPTS (4.53 g, 15.4 mmol) were dissolved in fresh distilled dichloromethane (30 mL) under argon conditions. The solution was cooled in an ice-water bath and then DCC (4.48 g, 21.56 mmol) was added drop wise. The mixture was stirred overnight under argon atmosphere at room temperature. The white precipitate was filtered off and was washed with dichloromethane (10 mL). The organic solvent was reduced with the rotary evaporator and the solution was poured into a mixture of hexane and ethyl acetate (7:·3) provoking the precipitation of a white solid as impurity. The crude product was purified by column chromatography using a mixture of hexane and ethyl acetate (7:3), increasing progressively the polarity to (6:4). The pure product was obtained as transparent oil. The third generation acetonide protected compound was dissolved in methanol and 10% $_{w/w}$ of DOWEX® was added. The deprotection procedure was carried on for 18 hours. The resin was filtered off and the solvent was evaporated under reduced pressure. The pure product was obtained as pale yellow oil. Yield 55%.

^{1}H-NMR (CD_3OD, 400MHz), δ (ppm): 4.37-4.25(m, 12H-CC$\underline{H_2}$O-, first and second generation), 4.19 (t, 2H; -CH_2-C$\underline{H_2}$-OCO), 3.69-3.61 (ABq, 16H; -CC$\underline{H_2}$-OH, J= 11 Hz, $\Delta\nu_{AB}$= 20.7 Hz), 1.73 (m, 2H; -C$\underline{H_2}CH_2$OCO), 1.65 (m, 2H; N_3-CH_2-C$\underline{H_2}$-), 1.47 (m, 4H; N_3-CH_2-CH_2-(C$\underline{H_2}$)$_2$-), 1.32 (s. 9H; C-C$\underline{H_3}$ interior), 1.18 (s, 12H; C-C$\underline{H_3}$ exterior). ^{13}C-NMR (CD_3OD, 400MHz), δ (ppm): 175.94; 174.05; 173.78; 67.35; 66.63; 66.20; 65.86; 52.39; 51.80; 47.96; 29.80; 29.55; 27.43; 26.62; 18.24; 18.12; 17.31. FTIR (cm^{-1}, Nujol): 3284 (ν, O-H), 2943-2850 (ν, C-H), 2092 (ν, N_3), 1730 (ν, C=O), 1458 (δ –CH_2-; δ_{as} -CH_3). MS (MALDI$^+$, ditranol) m/z: [M+Na$^+$] 978.5. EA ($C_{41}H_{69}N_3O_{22}$): expected: C 51.51; H 7.27; N 4.40; obtained: C 51.77; H 7.32; N 4.61.

Example of ^{1}H-NMR of the hydrophilic dendron: N_3-$G_3(OH)_8$

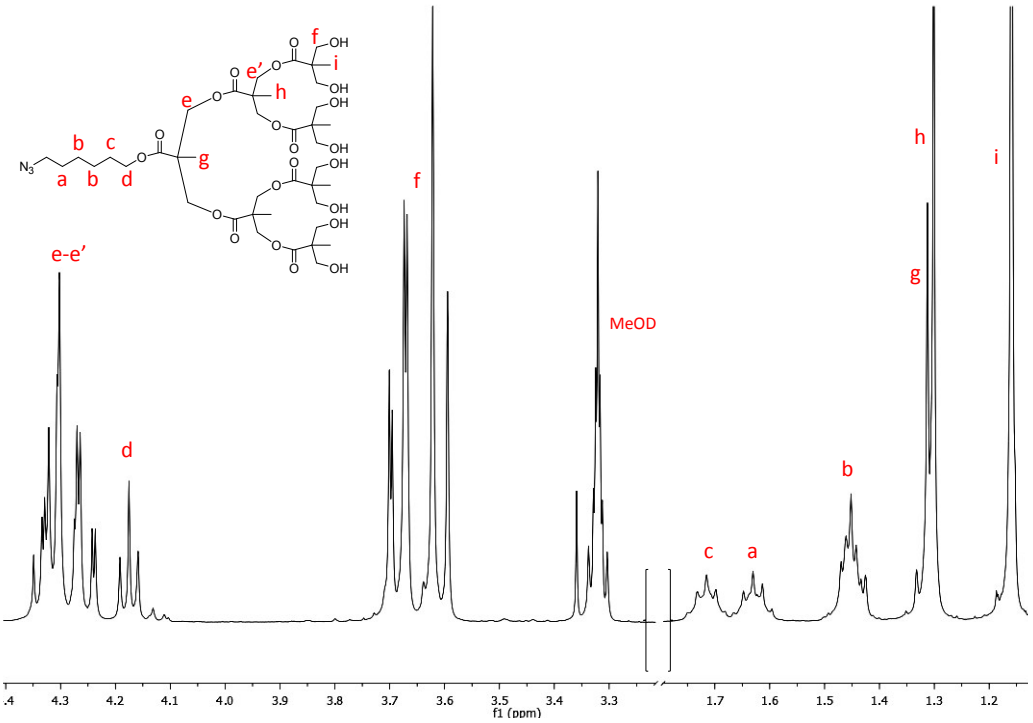


Figure S1-1. ^{1}H-NMR spectra (CD_3OD, 300MHz) of third generation hydrophilic dendron, chemical structure and peaks assignation. The spectrum was cut in order to better visualize the signals; no signals were recorded in omitted zone (brackets).

The presence of the n-C_6H_{12} spacer bearing the azide group is confirmed by: the signal at δ_H=4.18 ppm (t, 2H), relative to the two protons of "d" hydrogens; the multiplet at δ_H=1.72 ppm (m, 2H) relative to the "c" hydrogens; the multiplet at δ_H=1.63 ppm (m, 2H) relative to the "a" hydrogens; the multiplet at δ_H=1.45 ppm (m, 4H) relative to the "b" hydrogens. The signal related to the -CH_2- directly linked to the azide group is covered by the solvent signal at 3.3 (not shown in Figure S1-2). The complete deprotection of the terminal –OH groups is

confirmed by the absence of the signals relative to the eight methyl groups of the acetal groups (δ_H=1.41 ppm, s, 12H; δ_H=1.34 ppm, s, 12H on the ^{1}H-NMR spectra of the protected compound) and by the presence of the ABq produced by the diastereotopic protons of the methylene groups in α to the terminal –OH groups).

^{1}H-NMR signal control over the correct deprotection of the hydroxyl groups

In the acetal-protected third generation dendron, the "**f**" protons of the methylene groups, in □ to the terminal protected –OH groups, are diastereotopic and form a second order AB system that produces a characteristic quadruplet. Upon comparison of the spectra represented in figure S1-3, which correspond to the third generation hydrophilic dendron (**$\underline{N_3\text{-}G_3(OH)_8}$**) before (up in the figure) and after the deprotection of the terminal –OH groups (down in the figure), it is possible to note the modification of the AB quadruplet. When the terminal –OH groups are acetal-protected, the doublets of the quartet (J_{AB}=11 Hz) are so separated and present such a high value of $\Delta\nu_{AB}$=210 Hz) that the system has to be treated as a first order signal composed by two doublets (δ_H= 4.15 ppm. 8H, J_{AB}= 11.8 Hz; δ_H= 3.62 ppm, 8H, J_{AB}= 11.9 Hz) as usual for systems with $\Delta\nu_{AB}/J_{AB}$> 4. The deprotection of the terminal –OH groups provokes the decrease of the ν between the two doublets; the AB quartet becomes perfectly visible and is treated as a second order system ($\Delta\nu_{AB}/J_{AB}$ <4). The new signal is recorded at lower ppm; the integration of the quadruplets is coherent with the sum of the integrals of the two doublets in the protected compound (δ_H= 3.65 ppm, 16H, ABq, J_{AB}=10.8, $\Delta\nu_{AB}$ 20.9 Hz).

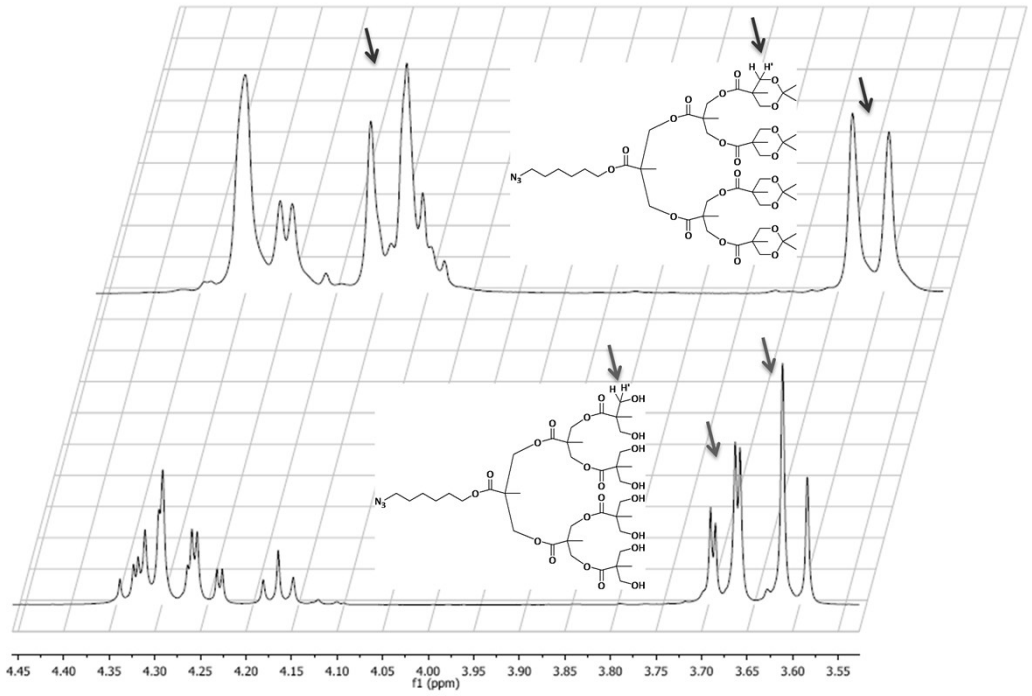


Figure S1-2. Comparison between the ^{1}H-NMR spectra of **$N_3\text{-}G_3(OH)_8$**, before and after the deprotection of the terminal –OH groups by Dowex.

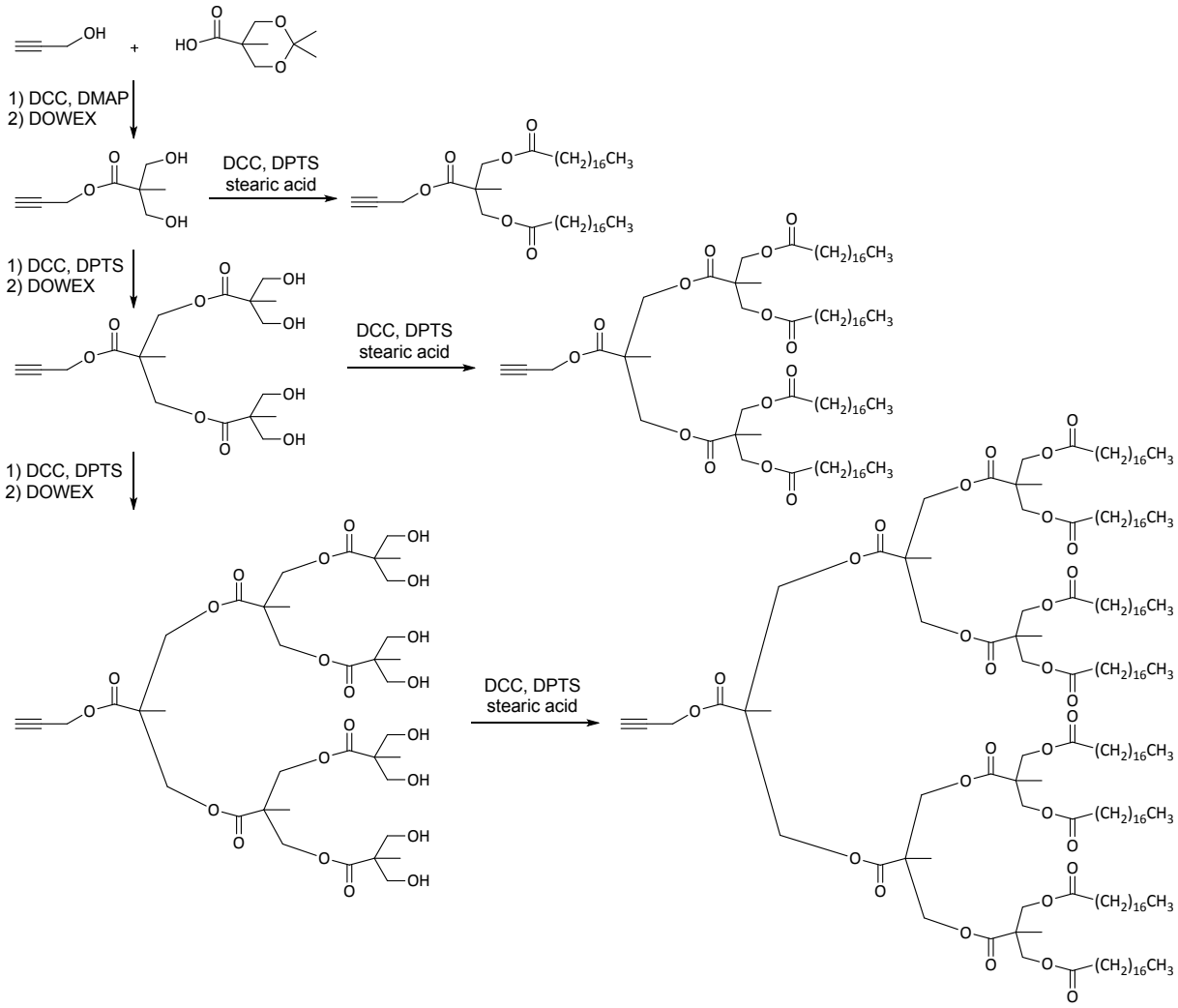
MALDI-TOF results for the hydrophilic dendrons

Table S1-1. Results of MALDI-TOF analysis.

		MALDI-TOF (m/z)[b]
Dendron	**M_w[a]**	**$[M+Na]^+$**
N_3-$G_1(OH)_2$	259.3	282.0
N_3-$G_2(OH)_4$	491.5	514.3
N_3-$G_3(OH)_8$	955.9	978.5

[a] calculated molecular mass.

S2 Synthesis and characterization of the lipophilic dendrons



Scheme S2-1. synthetic procedure employed to synthesize the hydrophilic dendrons.

Synthesis of HC≡C-G_1(C 17)$_2$

Propargyl alcohol (5 g, 89.2 mmol), isopropylidene-2,2-bis(methoxy)propionic acid (5.2g, 29.8 mmol) and DPTS (10.5g, 35.7 mmol) were dissolved in fresh distilled dichloromethane (29 mL) under argon conditions. The solution was cooled in an ice-water bath and then DCC (6.1 g, 29.7 mmol) was added drop wise. The mixture was kept in the ice-water bath for 10 min and was stirred overnight under argon atmosphere at room temperature. The white precipitate (N-N'-dicyclohexylurea) was filtered off and washed with dichloromethane (10 mL). The organic solvent was reduced with the rotary evaporator and the solution was poured into a mixture of hexane and ethyl acetate (7:·3) provoking the precipitation of a white solid as impurity. The crude product was purified by liquid

chromatography on silica gel, eluted with a mixture of hexane and ethyl acetate (7:3). The yellow viscous oil obtained was diluted in methanol and 10% $_{w/w}$ of DOWEX® was added. The deprotection procedure was carried on for 4 hours. The resin was filtered off and the solvent was evaporated under reducer pressure. The pure product (HC≡C-$G_2(OH)_2$, yield 80%) was obtained as uncolored oil. ^{1}H-NMR ($CDCl_3$, 400MHz), δ (ppm): 4.74 (d, 2H, HC≡C-CH_2-); 3.90 (d, 2H, -C-CHH'-O, J=11 Hz); 3.71 (d, 2H, -C-CHH'-O, J=11 Hz); 2.49 (t, 1H, HC≡C-); 1.09 (s, 1H, C-CH_3). ^{13}C-NMR ($CDCl_3$, 400MHz), δ (ppm): 175.18; 77.45; 75.38; 67.76; 52.59; 49.46; 17.11.

Compound HC≡C-$G_2(OH)_2$ (0.5g, 2.9 mmol), stearic acid (1.65g, 5.8 mmol) and DPTS (1.7g, 5.8 mmol) were dissolved in fresh distilled dichloromethane (30 mL) under argon conditions. The solution was cooled in an ice-water bath and then DCC (1.67g, 8.12 mmol) was added drop wise. The mixture was kept in the ice-water bath for 10 min and was stirred overnight under argon atmosphere at room temperature. The white precipitate (N-N'-dicyclohexylurea) was filtered off and was washed dichloromethane (10 mL). The solution was concentrated under reduce pressure. The pure product was obtained by precipitating into cold aceton. Yield 84%.

^{1}H-NMR ($CDCl_3$, 400MHz), δ (ppm): 4.71 (d, 2H, HC≡C-CH_2-); 4.23 (ABq, 4H, -C-CHH'-O, J= 11 Hz, $\Delta\nu_{AB}$= 6.2 Hz), 2.45 (t, 1H, HCC-); 2.29 (t, 4H, -O-CO-CH_2-); 1.59 (m, 4H, -O-CO-CH_2-CH_2-); 1.25 (m, ≅56H, -(CH_2)$_{14}$-; 0.88 (t, 6H, -CH_2CH_3). ^{13}C-NMR ($CDCl_3$, 400MHz), δ (ppm): 173.40; 173.25; 75.25; 75.22; 65.31; 52.70; 46.57; 34.28; 32.08; 29.85; 29.81; 29.77; 29.63; 29.51; 29.41; 29.29; 25.04; 22.84; 17.84; 14.25. FTIR (cm^{-1}, Nujol): 3290 (ν, C-H alkyne); 2939-2848 (ν, C-H); 2131 (ν, C≡C); 1731 (ν, C=O); 1459 (δ –CH_2-; δ_{as} -CH_3). EA ($C_{44}H_{80}O_6$): expected: C 74.95; H 11.44; obtained: C 75.48; H 11.65.

Synthesis of HC≡C-G_2(C 17)$_4$

Compound HC≡C-$G_1(OH)_2$ (3 g, 17.4 mmol), isopropylidene-2,2-bis(methoxy)propionic acid (6.1 g, 34.6 mmol) and DPTS (10.2 g, 34.6 mmol) were dissolved in fresh distilled dichloromethane (60 mL) under argon conditions. The solution was cooled in an ice-water bath and then DCC (16 .9g, 82.1 mmol) was added drop wise. The mixture was kept in the ice-water bath for 10 min and was stirred overnight under argon atmosphere at room temperature. The white precipitate (N-N'-dicyclohexylurea) was filtered off and was washed with dichloromethane (30 mL). The white precipitate (N-N'-dicyclohexylurea) was filtered off and washed with dichloromethane (10 mL). The organic solvent was reduced with the rotary evaporator and the solution was poured into a mixture of hexane and ethyl acetate (7:·3) provoking the precipitation of a white solid as impurity. The crude product was purified by liquid chromatography on silica gel, eluted with a mixture of hexane and ethyl acetate (7:3). The filtrated solution was evaporated over vacuum. The compound was separated as yellow oil. Protected dendron was diluted with methanol and 10%$_{w/w}$ of DOWEX® was added. The deprotection procedure was carried on for 8 hours. The resin was filtered off and

the solvent was evaporated under reduced pressure. HC≡C-$G_2(OH)_4$ was obtained as pale yellow oil. Yield 60%.

^{1}H-NMR ($CDCl_3$, 400MHz), δ (ppm): 4.76 (d, 2H, HC≡C-CH_2-); 4.29 (ABq, 4H, -C-CHH'-O, J= 11 Hz, $\Delta\nu_{AB}$= 8.3 Hz; first generation), 3.68-3.60 (ABq, 8H, -C-CHH'-OH, J= 11 Hz, $\Delta\nu_{AB}$= 27.1 Hz), 2.96 (t, 1H, HC≡C-), 1.31 (s, 3H, -C-CH_3, first generation), 1.15 (s, 6H, -C-CH_3, second generation). ^{13}C-NMR ($CDCl_3$, 400MHz), δ (ppm): 175.88; 173.63; 78.51; 76.67; 66.29; 65.77; 53.54; 47.87; 40.41; 18.05; 17.25.

Compound HC≡C-$G_2(OH)_4$ (1 g, 2.47 mmol), stearic acid (2.81 g, 9.89 mmol) and DPTS (2.98 g, 9.89 mmol) were dissolved in fresh distilled dichloromethane (40 mL) under argon conditions. The solution was cooled in an ice-water bath and then DCC (2.85 g, 13.84 mmol) was added drop wise. The mixture was kept in the ice-water bath for 10 min and was stirred overnight under argon atmosphere at room temperature. The white precipitate (N-N'-dicyclohexylurea) was filtered off and was washed with dichloromethane (10 mL). The pure product was obtained by precipitating into cold acetone. Yield: 83%.

^{1}H-NMR ($CDCl_3$, 400MHz), δ (ppm): 4.72 (d, 2H, HC≡C-C<u>H_2</u>-); 4.27 (ABq, 4H, -C-C<u>HH'</u>-O, J= 11 Hz, $\Delta\nu_{AB}$= 12.2 Hz; first generation), 4.19 (m, 8H, -C-C<u>HH'</u>-O, second generation), 2.50 (t, 1H, <u>H</u>C≡C-), 2.29 (t, 8H, -OCO-C<u>H_2</u>-), 1.57 (m, 8H, -OCO-CH_2-C<u>H_2</u>-), 1.25 (m, ≈ 112H, OCO-CH_2-CH_2-(C<u>H_2</u>)14-CH_3), 0.88 (t, 12H, -$(CH_2)_{14}$-CH_3). ^{13}C-NMR ($CDCl_3$, 400MHz), δ (ppm):173.33; 172.24; 171.59; 77.36; 75.63; 65.70; 65.21; 52.90; 46.88; 46.65; 34.22; 32.09; 29.87; 29.67; 29.52; 29.46; 29.32; 25.04; 22.84; 17.94; 17.61; 17.55; 14.24. FTIR (cm^{-1}, Nujol): 3307 (ν, C-H alkyne); 2942-2850 (ν, C-H); 1735 (ν, C=O); 1456 (δ – CH_2-; δ_{as} -CH_3). MS (MALDI$^+$, ditranol) m/z: 1492.4 EA ($C_{90}H_{164}O_{14}$): expected: C 73.52; H 11.24; obtained: C 74.02; H 11.60.

Synthesis of HC≡C-G_3(C17)$_8$

Compound **HC≡C-$G_2(OH)_4$** (1 g, 2.47 mmol), isopropylidene-2,2-bis(methoxy)propionic acid (1.72 g, 9.89 mmol) and DPTS (2.91g, 9.89 mmol) were dissolved in fresh distilled dichloromethane (20 mL) under argon conditions. The solution was cooled in an ice-water bath and then DCC (2.85 g, 13.8 mmol) was added drop wise. The mixture was kept in the ice-water bath for 10 min and was stirred overnight under argon atmosphere at room temperature. The white precipitate (N-N'-dicyclohexylurea) was filtered off and washed with dichloromethane (10 mL). The organic solvent was reduced with the rotary evaporator and the solution was poured into a mixture of hexane and ethyl acetate (7:·3) provoking the precipitation of a white solid as impurity. The crude product was purified by column chromatography using a mixture of hexane and ethyl acetate (7:3), increasing progressively the polarity to (5:5). Yield: 66%. Protected dendron was diluted with methanol and 10% w/w of DOWEX® was added. The deprotection procedure was carried on for 18 hours. The resin was filtered off and the solvent was evaporated under reduced pressure.

^{1}H-NMR (CD_3OD, 400MHz), δ (ppm): 4.78 (d, 2H, HC≡C-CH_2-); 4.35-4.23 (m, 12H, -C-CHH'-O, formed by the two ABq systems of first generation and second generation), 3.67-3.59 (ABq, 16H, -C-CHH'-OH, J= 11 Hz, $\Delta\nu_{AB}$= 28.5 Hz), 2.99 (t, 1H, HC≡C-), 1.32 (s, 3H, -C-CH_3, first generation), 1.30 (s, 6H, -C-CH_3, second generation), 1.15 (s, 12H, -C-CH_3, third generation). ^{13}C-NMR (CD_3OD, 400MHz), δ (ppm): 175.90; 173.73; 173.16; 78.53; 77.00; 67.21; 66.17; 65.82; 53.76; 51.78; 47.95; 47.93; 18.23; 17.98; 17.29.

HC≡C-$G_3(OH)_8$ (1 g, 1.2 mmol), stearic acid (2.6 g, 9.20 mmol) and DPTS (1.13g, 3.8 mmol) were dissolved in fresh distilled dichloromethane (40 mL) under argon conditions. The solution was cooled in an ice-water bath and then DCC (1.9 g, 9.20 mmol) was added drop wise. The mixture was kept in the ice-water bath for 10 min and was stirred overnight under argon atmosphere at room temperature. The white precipitate (N-N'-dicyclohexylurea) was filtered off and was washed with dichloromethane (20 mL). The pure product was obtained by precipitation into cold acetone. Yield: 46.8%.

^{1}H-NMR ($CDCl_3$, 400MHz), δ (ppm): 4.74 (d, 2H, HC≡C-CH_2-); 4.32-4.14 (m, 28H, -C-CHH'-O, first generation, second generation and third generation), 2.52 (t, 1H, HC≡C-), 2.29 (t, 16H, -OCO-CH_2-$(CH_2)_{15}$-CH_3),1.64-1.51 (m, 16H, -OCO-CH_2-CH_2-(CH_2)14-CH3), 1.36-1.12 (m, ≈245H, formed by -OCO-CH_2-CH_2-$(CH_2)_{14}$-CH_3; C-CH_3, first, second and third generation), 0.88 (t, 24H, -OCO-CH_2-CH_2-$(CH_2)_{14}$-CH_3). ^{13}C-NMR ($CDCl_3$, 400MHz), δ (ppm): 173.29; 172.18; 171.60; 171.44; 77.37; 75.76; 66.40; 65.42; 65.07; 52.97; 46.90; 46.83; 46.56; 34.19; 32.09; 29.88; 29.83; 29.69; 29.52; 29.49; 29.33; 25.03; 22.84; 17.94; 17.67; 17.59; 14.25. FTIR (cm-1, Nujol): 3250 (ν, C-H alkyne); 2940-2850 (ν, C-H); 1730 (ν, C=O); 1460 (δ –CH2-; δ as-CH3). MS (MALDI^{+}, ditranol) m/z: [M+Na^{+}] 3022.9; EA ($C_{182}H_{332}O_{30}$): expected: C 72.85; H 11.15; obtained: C 73.08; H 9.4

^{1}H-NMR of compound HC≡C-G$_3$(OH)$_8$ used as example to explain the characterization of the lipophilic dendrons

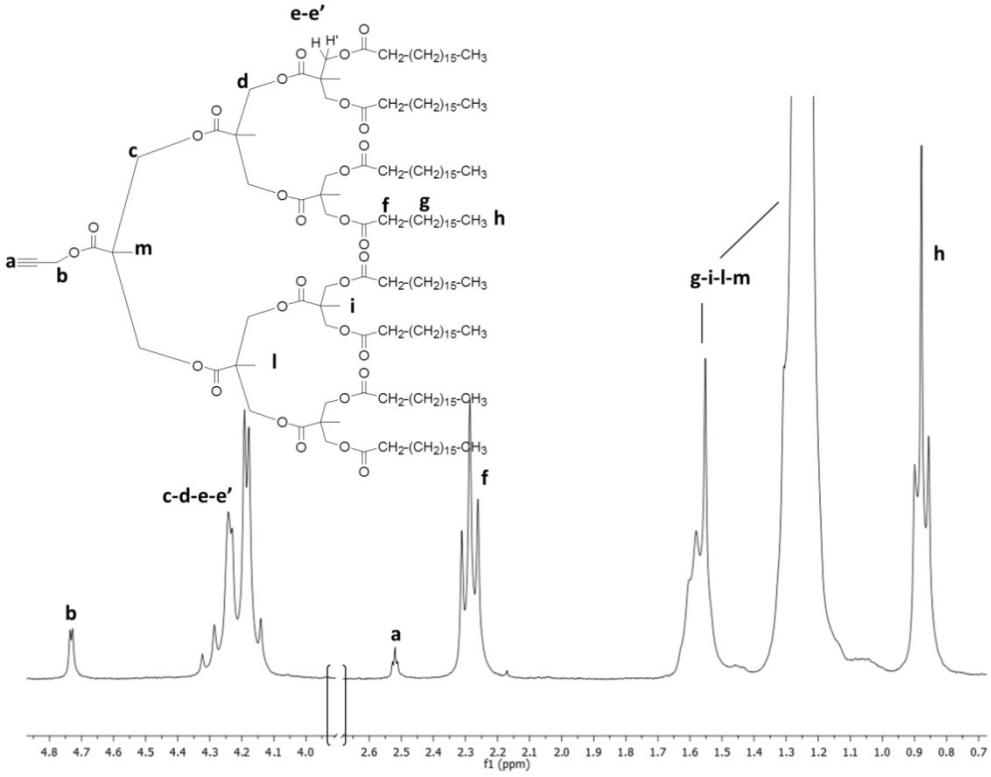


Figure S2-1. ^{1}H-NMR spectra ($CDCl_3$, 300MHz) of the third generation lipophilic dendron **HC≡C-G$_3$(OH)$_8$**, chemical structure and peak assignation.

^{1}H-NMR signal control over the correct deprotection of the hydroxyl groups

One of the evidence that the dendron is fully functionalized is the presence of a unique multiplet relative to the methylenic protons "**c**, **d**, **e**, **e'**" of the repeating units of bis-MPA (figure S2-2). In the ^{1}H-NMR spectrum of **HC≡C-G$_3$(OH)$_8$**, the AB systems formed by the diasterotopic hydrogens of the methylene groups "**e-e'**", in α to the free terminal OH, is represented as a quadruplet as described for the hydrophilic dendron (δ_H= 3.63 ppm, J_{AB}= 10.8 Hz, $\Delta\nu_{AB}$= 29.1 Hz). After the complete functionalization of all the eight OH groups with aliphatic chains, the quadruplet downfield shifts and forms a multiplet characteristic of all the methylene groups present on the interior part of the dendron.

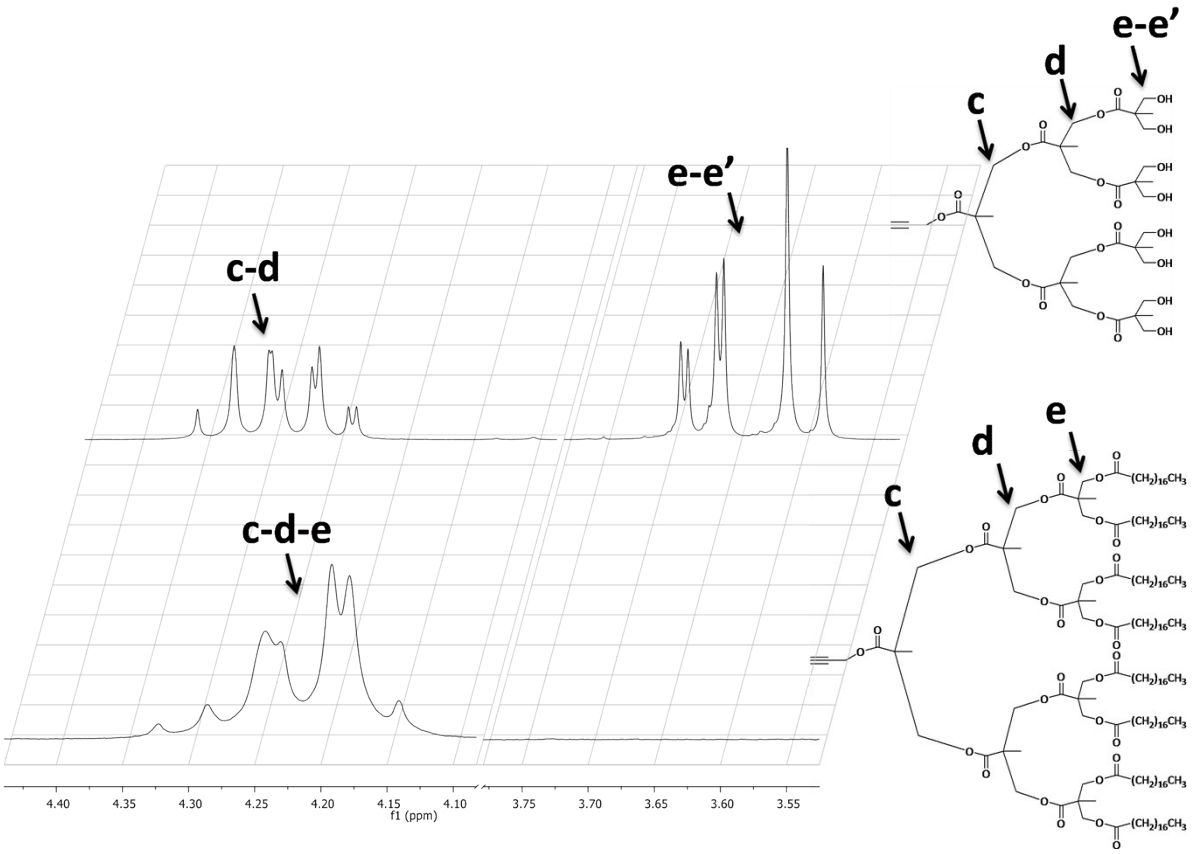


Figure S2-2. Comparison between ^{1}H-NMR spectra ($CDCl_3$, 300MHz) of **HC≡C-G$_3$(C17)$_8$** and **HC≡C-G$_3$(OH)$_8$**; difference between the signals relative to methylene groups of the repeating units of bis-MPA.

MALDI-TOF results for the lipophilic dendrons

The results of MS analysis are gathered in table S2-1.

Table S2-1. Results of MALDI-TOF analysis.

Dendron	M_w[a]	MALDI-TOF (m/z)[b] $[M+Na]^+$
HC≡C-$G_1(C17)_2$	705.1	727.5
HC≡C-$G_2(C17)_4$	1470.2	1492.4
HC≡C-$G_3(C17)_8$	3000.5	3022.9

[a] molecular mass calculated summing up the atomic masses of all the atoms that composed the molecule; [b] the MS analysis was run using ditranol as matrix;

S3 Synthesis and characterization of the Janus dendrimers

Synthesis of $G_1(C17)_2$-$G_1(OH)_2$

$CuSO_4.5H_20$, (72.21 mg, 0.289 mmol) and sodium ascorbate (114.50 mg, 0.578 mmol) of were stirred with 2 ml of CH_2Cl_2:DMF:H_2O (8:1:1) for 1 hour at room temperature. The mixture of the catalysts was added to 5 ml of a solution in dry dichloromethane of compound **HC≡C-$G_1(C17)_2$** (407.5 mg 0.578 mmol) and compound **N_3-$G_1(OH)_2$** (150 mg 0.578 mmol). The reaction was stirred for 48 hours at room temperature. The mixture was diluted in dichloromethane and was washed with a solution of KCN in water to remove copper traces and DMF. The organic fraction was dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude product was dissolved in a small amount of dichloromethane and was precipitated in cold methanol, the solid precipitate was filtered. This operation was repeated twice. Finally, the solid was washed with cold hexane to remove traces of compound **HC≡C-$G_1(C17)_2$**. The pure product was obtained as pale yellow solid. Yield: 80%.

^{1}H-NMR ($CDCl_3$, 400MHz), δ (ppm): 7.58 (s, 1H, -N-C<u>H</u>-C), 5.25 (s, 2H, -N-C-C<u>H_2</u>-OCO), 4.35 (t, 2H; N-N-C<u>H_2</u>-), 4.21 (ABq, 4H, -C<u>HH'</u>-OCO-, J= 11 Hz, $\Delta\nu_{AB}$= 16.3 Hz non-polar block),4. 16 (t, N-$(CH_2)_5$-C<u>H_2</u>-OCO), 3.90 (d, 2H; C-C<u>H</u>H'OH, J= 11 Hz), 3.72 (d, 2H; C-CH<u>H'</u>OH, J= 11 Hz), 2.24 (t, 4H, -O-CO-C<u>H_2</u>-$(CH_2)_{15}$-), 1.93 (m, 2H, N-CH_2-C<u>H_2</u>-), 1.67 (m, 2H, O-CH_2-C<u>H_2</u>-), 1.56 (m, 4H, -O-CO-CH_2-C<u>H_2</u>-$(CH_2)_{14}$-), 1.45-1.33 (m, 4H, O-CH2-CH_2-(C<u>H_2</u>)$_2$-CH_2-CH_2-N), 1.31-1.20 (m, ≈59H, formed by: -O-CO-CH_2-CH_2-(C<u>H_2</u>)$_{14}$-CH_3; 3H, -C-C<u>H_3</u>), 1.06 (s, 3H, -C-C<u>H_3</u>), 0.88 (t, 6H. -$(CH_2)_{14}$-C<u>H_3</u>). ^{13}C-NMR ($CDCl_3$, 400MHz), δ (ppm): 173.42; 172.96; 142.59; 123.78; 68.81; 65.22; 64.80; 58.61; 50.25; 49.24; 46.50; 32.08; 29.85; 29.81; 29.78; 29.51; 25.01; 22.84; 17.88; 17.30; 14.27. FTIR (cm^{-1}, Nujol): 3419 (ν, O-H); 2945-2850 (ν, C-H); 1740 (ν, C=O); 1464 (δ –CH_2-; δ_{as} -CH_3). MS (MALDI$^+$, ditranol) m/z: [M+Na^+] 986.7. EA ($C_{55}H_{101}N_3O_{10}$): expected: expected: C 68.50 H 10.56 N 4.36; obtained: C 67.76 H 11.18 N 3.58.

Synthesis of $G_1(C17)_2$-$G_2(OH)_4$

$CuSO_4.5H_2O$ (104.48 mg, 0.354 mmol) and sodium ascorbate (140.45 mg, 0.709 mmol) were stirred with 2ml of CH_2Cl_2:DMF:H_2O (8:1:1) for 1 hour at room temperature. To 5 ml of a dry dichloromethane solution of compound **HC≡C-$G_1(C17)_2$** (500 mg 0.709mmol) and compound **N_3-$G_2(OH)_4$** (348.49 mg 0.709 mmol), was added the mixture of the catalyst. The reaction was stirred for 48 hours at 70°C. Then, the volatile solvent was removed under reduced pressure and the solution was diluted with a mixture of hexane and ethyl acetate (1:1) and washed with an aqueous solution of KCN. The organic fraction was dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude product was recrystalized twice in hot hexane leading to a white solid. Yield: 60%.

^{1}H-NMR ($CDCl_3$, 400MHz), δ (ppm): 7.58 (s, 1H, -N-C<u>H</u>-C), 5.25 (s, 2H, -N-C-C<u>H$_2$</u>-OCO), 4.43 (d, 2H, -C<u>H</u>H'-O, J= 11 Hz, first generation polar block), 4.35 (t, 2H; N-N-C<u>H$_2$</u>-), 4.29 (d, 2H, -CH<u>H</u>'-O, J= 11 Hz, first generation polar block), 4.21 (ABq, 4H, -C<u>HH</u>'-OCO-, J= 11 Hz, $\Delta\nu_{AB}$= 8.3 Hz, non-polar block), 4. 13 (t, N-$(CH_2)_5$-C<u>H$_2$</u>-OCO), 3.84-3.72 (ABq, 8H; C-C<u>H</u>H'OH, J= 11 Hz, $\Delta\nu_{AB}$= 44 Hz, second generation polar block), 2.24 (t, 4H, -O-CO-C<u>H$_2$</u>-$(CH_2)_{15}$-), 1.97-1.89 (m, 2H, N-CH_2-C<u>H$_2$</u>-), 1.69-1. 61 (m, 2H, O-CH_2-C<u>H$_2$</u>-), 1.60-1.50 (m, 4H, -O-CO-CH_2-C<u>H$_2$</u>-$(CH_2)_{14}$-), 1.45-1.32 (m, 4H, O-CH2-CH_2-(C<u>H$_2$</u>)$_2$-CH_2-CH_2-N), 1.32-1.18 (m, ≈62H, formed by: -O-CO-CH_2-CH_2-(C<u>H$_2$</u>)$_{14}$-CH_3; 3H, -C-C<u>H$_3$</u> first generation polar and non-polar blocks), 1.06 (s, 6H, C-C<u>H$_3$</u> second generation polar block), 0.88 (t, 6H. -$(CH_2)_{14}$-C<u>H$_3$</u>). ^{13}C-NMR ($CDCl_3$, 400MHz), δ (ppm): 175.26; 173.42; 173.13; 172.95; 142.20; 124.39; 68.18; 68.12; 65.66; 65.42; 65.20; 65.06; 50.29 49.89; 46.58; 46.50; 34.23; 32.07; 29.85; 29.81; 29.78; 29.64; 29.51; 29.42; 29.28; 25.00; 22.84; 18.27; 17.87; 17.28; 14.27. FTIR (cm^{-1}, Nujol): 3384 (ν, O-H); 2964-2848 (ν, C-H); 1727 (ν, C=O); 1463 (δ –CH_2-; δ_{as} -CH_3). MS (MALDI$^+$, ditranol) m/z: [M+Na$^+$] 1218.8. EA ($C_{65}H_{117}N_3O_{16}$): expected: C 65.24; H 9.86; N 3.51; obtained: C 65.31; H 10.37; N 3.80.

$G_1(C17)_2$-$G_3(OH)_8$

$CuSO_4.5H_2O$ (77.06 mg, 0.261 mmol) and sodium ascorbate (103.61 mg, 0.523 mmol) e were stirred with 2ml of CH_2Cl_2:DMF:H2O (8:1:1) for 1 hour at room temperature. Compound **HC≡C-$G_1(C17)_2$** (368.75mg 0.523mmol) and compound **N_3-$G_3(OH)_8$** (500mg 0.523mmol) were dissolved in 5 ml of dry dichloromethane; to this solution was added the catalysts mixture. The reaction was stirred for 48 hours at 70°C. Once removed the dichloromethane by reduced pressure, the solution was diluted with hexane and ethyl acetate (1:1) and washed twice with and aqueous solution of KCN. The organic fraction was dried over magnesium sulfate and the solvent was removed under reduced pressure. The solid was recristallized from hot hexane. The precipitate was filtered off and washed several times with methanol. Yield 30%.

^{1}H-NMR ($CDCl_3$, 400MHz), δ (ppm): 7.58 (s, 1H, -N-C<u>H</u>-C), 5.25 (s, 2H, -N-C-C<u>H$_2$</u>-OCO), 4.37-4.26 (m, 14H, formed by: N-N-C<u>H$_2$</u>-; -C<u>H</u>H'-O, first and second generation polar block), 4.21 (ABq, 4H, J= 11Hz, ΔνAB= 19.6 Hz, -C<u>HH</u>'-OCO- non-polar block), 4.11 (t, 2H, N-$(CH_2)_5$-C<u>H$_2$</u>-OCO), 3.75-3.67 (m, 16H; C-C<u>H</u>H'OH), 2.25 (t, 4H, -O-CO-C<u>H$_2$</u>-$(CH_2)_{15}$-), 1.97-1.89 (m, 2H, N-CH_2-C<u>H$_2$</u>-), 1.70-1. 61 (m, 2H, O-CH_2-C<u>H$_2$</u>-), 1.60-1.51 (m, 4H, -O-CO-CH_2-C<u>H$_2$</u>-$(CH_2)_{14}$-), 1.44-1.34 (m, 4H, O-CH2-CH_2-(C<u>H$_2$</u>)$_2$-CH_2-CH_2-N), 1.33-1.15 (m, ≈68H, formed by: -O-CO-CH_2-CH_2-(C<u>H$_2$</u>)$_{14}$-CH_3; -C-C<u>H$_3$</u> first and second generation polar and first generation non-polar blocks), 1.07 (s, 12H, C-C<u>H$_3$</u> third generation polar block), 0.88 (t, 6H. -$(CH_2)_{14}$-C<u>H$_3$</u>). ^{13}C-NMR ($CDCl_3$, 400MHz), δ (ppm): 173.41; 172.94; 172.61; 66.56; 66.04; 65.51; 65.17; 46.70; 46.49; 34.02; 32.07; 30.26; 29.85; 29.81; 29.78; 29.65; 29.51; 29.42; 29.28; 28.43; 27.84; 27.03; 25.51; 25.01; 22.84; 17.43; 14.27. FTIR (cm^{-1}, Nujol): 3363 (ν, O-H); 2939-2846 (ν, C-H); 1722 (ν, C=O); 1461 (δ –CH_2-; δ_{as} -CH_3). EA ($C_{85}H_{149}N_3O_{28}$): expected: C 61.46; H 9.04; N 2.53; obtained: C 54.81; H 8.95; N 2.36.

Synthesis of $G_2(C17)_4$-$G_2(OH)_4$

$CuSO_4.5H_2O$ (8.46 mg, 0.170 mmol) and sodium ascorbate (67.65 mg, 0.341mmol) were stirred with 2ml of CH_2Cl_2:DMF:H2O (8:1:1) for 1 hour at room temperature. Compound **HC≡C-$G_2(C17)_4$** (500 mg, 0.341 mmol) and compound **N_3-$G_2(OH)_4$** (167.6 mg 0.341 mmol) were dissolved in 5 ml of dry dichloromethane; to this solution was added the mixture of the catalyst. The reaction was stirred for 48 hours at 70°C. The mixture was then diluted in dichloromethane and was washed with an aqueous solution of KCN. The organic layer was dried over magnesium sulfate and the solvent was removed under reduced pressure. The solid was washed with cold methanol first and then with cold hexane. In order to remove the traces of compound **HC≡C-$G_2(C17)_4$** still present, the solid was dissolved in MeOH:CH_2Cl_2 (7:3) and dialyzed against the same mixture of solvent with milli-pore membrane of 1000MW cut-off. The solvent was removed under reduced pressure to lead the pure product as white solid Yield 40%. ^{1}H-NMR ($CDCl_3$, 400MHz), δ (ppm): 7.70 (s, 1H, -N-C<u>H</u>-C), 5.24 (s, 2H, -N-C-C<u>H$_2$</u>-OCO), 4.43 (d, 2H, -C<u>H</u>H'-O, J= 11 Hz, first generation polar block), 4.37 (t, 2H; N-N-C<u>H$_2$</u>-), 4.29 (d, 2H, -CH<u>H'</u>-O, J= 11 Hz, first generation polar block), 4.24 (ABq, 4H, -C<u>HH'</u>-OCO-, J= 11 Hz, $\Delta\nu_{AB}$= 12.1, first generation non-polar block), 4. 17-4.10 (m, 11H formed by: N-$(CH_2)_5$-C<u>H$_2$</u>-OCO; C-C<u>H</u>H'O, ABq system of second generation non-polar block), 3.84-3.72 (ABq, 8H; C-CH<u>H'</u>OH, J= 11 Hz, $\Delta\nu_{AB}$= 47 Hz), 2.28 (t, 8H, -O-CO-C<u>H$_2$</u>-$(CH_2)_{15}$-), 1.94 (m, 2H, N-CH_2-C<u>H$_2$</u>-$(CH_2)_2$-CH_2-CH_2-O), 1.65 (m, 2H, N-CH_2-CH_2-$(CH_2)_2$-C<u>H$_2$</u>-CH_2-O), 1.58 (m, 8H, COO-CH_2-C<u>H$_2$</u>-), 1.43-1.33 (m, 4H, O-CH_2-CH_2-(C<u>H$_2$</u>)$_2$-CH_2-CH_2-N), 1.30-1.22 (m, ≈124H, formed by –C-C<u>H$_3$</u>; -O-CO-CH_2-CH_2-(C<u>H$_2$</u>)$_{14}$-), 1.18 (s, 6H, C-C<u>H$_3$</u>), 1.06 (s, 6H, C-C<u>H$_3$</u>), 0.88 (t, 6H. -$(CH_2)_{14}$-C<u>H$_3$</u>). ^{13}C-NMR ($CDCl_3$, 400MHz), δ (ppm): 175.27; 173.43; 173.13; 172.32; 172.17; 142.20; 124.39; 68.27; 68.22; 65.66; 65.42; 65.10; 65.05; 58.56; 50.29; 49.88; 46.81; 46.58; 46.49; 34.20; 32.08; 29.86; 29.84; 29.81; 29.67; 29.51; 29.46; 29.30; 25.02; 22.84; 18.27; 17.90; 17.64; 17.27; 14.27. FTIR (cm^{-1}, Nujol): 3394 (ν, O-H); 2942-2848 (ν, C-H); 1731 (ν, C=O); 1463 (δ –CH_2-; δ_{as} -CH_3). MS (MALDI$^+$, ditranol) m/z: [M+Na^+] 1984.3. EA ($C_{111}H_{201}N_3O_{24}$): expected: C 67.69 H 10.33 N 2.14; obtained: C 66.06 H 9.95 N 2.49.

Synthesis of $G_2(C17)_4$-$G_3(OH)_8$

$CuSO_4.5H_2O$ (50.11 mg, 0.170mmol) and sodium ascorbate (67.35 mg, 0.340 mmol) were stirred with 2ml of CH_2Cl_2:DMF:H_2O (8:1:1) for 1 hour at room temperature. To 5 ml of a solution in dry dichloromethane of compound **HC≡C-$G_2(C17)_4$** (500 mg, 0.340mmol) and compound **N_3-$G_3(OH)_8$** (325.0 mg 0.340 mmol) were added to the mixture of the catalyst. The reaction was stirred for 48 hours at 70°C. The organic solvent was removed under reduced pressure, the solution was diluted with hexane and ethyl acetate (1:1) and was washed twice with an aqueous solution of KCN. The organic phase was dried with $MgSO_4$, was filtered and the solvent was removed under reduced pressure. The solid was dissolved in dichloromethane and the product was precipitated in cold ether. The solid was filtered and washed with cold ether, cold methanol and hexane. The pure product was obtained as white solid. Yield: 55%.

^{1}H-NMR ($CDCl_3$, 400MHz), δ (ppm): 7.72 (s, 1H, -N-C<u>H</u>-C), 5.24 (s, 2H, -N-C-C<u>H$_2$</u>-OCO), 4.40-4.20 (m, 18H, -C<u>HH'</u>-O, first and second generation polar block; -C<u>HH'</u>-O first generation non-polar block; N-N-C<u>H$_2$</u>-), 4.17-4.10 (m, 10H, -C<u>HH'</u>-OCO- second generation non-polar block; N-$(CH_2)_5$-C<u>H$_2$</u>-OCO), 3.81-3.71 (ABq, 16H; C-CH<u>H'</u>OH, J= 11 Hz, $\Delta\nu_{AB}$= 20.7 Hz), 2.28 (t, 8H, -O-CO-C<u>H$_2$</u>-$(CH_2)_{15}$-), 1.94 (m, 2H, N-CH_2-C<u>H$_2$</u>-$(CH_2)_2$-CH_2-CH_2-O), 1.66 (m, 2H, N-CH_2-CH_2-$(CH_2)_2$-C<u>H$_2$</u>-CH_2-O), 1.57 (m, 8H, COO-CH_2-C<u>H$_2$</u>-), 1.43-1.33 (m, 4H, O-CH_2-CH_2-(C<u>H$_2$</u>)$_2$-CH_2-CH_2-N), 1.29-1.22 (m, ≈124H, formed by –C-C<u>H$_3$</u>; -O-CO-CH_2-CH_2-(C<u>H$_2$</u>)$_{14}$-), 1.18 (s, 6H, C-C<u>H$_3$</u>), 1.07 (s, 12H, -C-C<u>H$_3$</u>), 0.88 (t, 6H. -$(CH_2)_{14}$-C<u>H$_3$</u>). ^{13}C-NMR ($CDCl_3$, 400MHz), δ (ppm):175.20. 173.43; 172.31; 172.15; 171.93; 67.76; 67.62; 65.09; 64.93; 50.00; 46.74; 46.48; 34.19; 32.08; 29.87; 29.82; 29.67; 29.54; 29.47; 29.30; 25.02; 22.84; 18.19; 17.91; 17.31; 14.27. FTIR (cm^{-1}, Nujol): 3357 (ν, O-H); 2942-2848 (ν, C-H); 1733 (ν, C=O); 1465 (δ –CH_2-; δ_{as} -CH_3). MS (MALDI$^+$, ditranol) m/z: [M+Na^+] 2448.8. EA ($C_{131}H_{233}N_3O_{36}$): expected: C 65.23; H 9.82; N 1.74; obtained: C 64.49; H 10.14; N 1.87.

Synthesis of $G_3(C17)_8$-$G_3(OH)_8$)

$CuSO_4.5H_2O$ (34.21 mg, 0.137mmol) and sodium ascorbate (54.28 mg, 0.274 mmol) were stirred with 2 mL of CH_2Cl_2:DMF:H_2O (8:1:1) for 1 hour at room temperature. Compound **HC≡C-$G_3(C17)_8$** (822.34 mg, 0.274 mmol) and compound **N_3-$G_3(OH)_8$** (262.00 mg 0.274 mmol) were added to the mixture of the reaction. It was stirred for 48 hours at 70°C. The organic solvent was evaporated than the solution was diluted with dichloromethane and washed twice with an aqueous solution of KCN. The organic phase was dialyzed overnight against dichloromethane:methanol (4:6) employing milli-pore membrane of 3500MW cut-off. The solvent was reduced by evaporation and the product was precipitate in cold hexane. The solid precipitated was filtered and let dry under reduced pressure. The residual DMF was eliminated by washing the solid with cold distilled water to lead to the pure product as white solid. Yield: 53%.

^{1}H-NMR ($CDCl_3$, 400MHz), δ (ppm): 7.74 (s, 1H, -N-C<u>H</u>-C), 5.24 (s, 2H, -N-C-C<u>H$_2$</u>-OCO), 4.41-4.09 (m, 44H, -C<u>HH'</u>-O, first and second generation of both polar and non-polar blocks plus third generation non-polar block; N-N-C<u>H$_2$</u>-$(CH_2)_4$-C<u>H$_2$</u>-O), 3.81-3.71(ABq, 16H; C-CH<u>H'</u>OH, J= 11 Hz, $\Delta\nu_{AB}$ = 20.7 Hz), 2.28 (t, 16H, -O-CO-C<u>H$_2$</u>-$(CH_2)_{15}$-), 1.94 (m, 2H, N-CH_2-C<u>H$_2$</u>-$(CH_2)_2$-CH_2-CH_2-O), 1.67 (m, 2H, N-CH_2-CH_2-$(CH_2)_2$-C<u>H$_2$</u>-CH_2-O), 1.57 (m, 16H, COO-CH_2-C<u>H$_2$</u>-), 1.44-1.35 (m, 4H, O-CH_2-CH_2-(C<u>H$_2$</u>)$_2$-CH_2-CH_2-N), 1.29-1.22 (m, ≈124H, formed by –C-C<u>H$_3$</u>; -O-CO-CH_2-CH_2-(C<u>H$_2$</u>)$_{14}$-), 1.18 (s, 6H, C-C<u>H$_3$</u>), 1.07 (s, 12H, -C-C<u>H$_3$</u>), 0.88 (t, 24H. -$(CH_2)_{14}$-C<u>H$_3$</u>). ^{13}C-NMR ($CDCl_3$, 400MHz), δ (ppm): 175.18; 173.33; 172.57; 172.44; 172.21; 172.18; 171.56; 142.11; 124.40; 67.69; 67.55; 66.18; 65.63; 65.31; 65.00; 64.92; 50.00; 46.79; 46.75; 46.49; 34.17; 32.07; 29.87; 29.82; 29.69; 29.52; 29.49; 29.32; 25.02; 22.84; 18.18; 17.94; 17.59; 17.30; 14.26. FTIR (cm^{-1}, Nujol): 3374 (ν, O-H); 2942-2848 (ν, C-H); 1729 (ν, C=O); 1464 (δ –CH_2-; δ_{as} -CH_3). MS (MALDI$^+$, ditranol) m/z: [M+Na^+] 3978.7. EA ($C_{224}H_{405}N_3O_{52}$): expected: C 67.69; H 10.22; N 1.06; obtained: C 67.38; H 10.60; N 1.38.

FTIR spectrum of the Janus dendrimer $G_1(C17)_2$-$G_1(OH)_2$

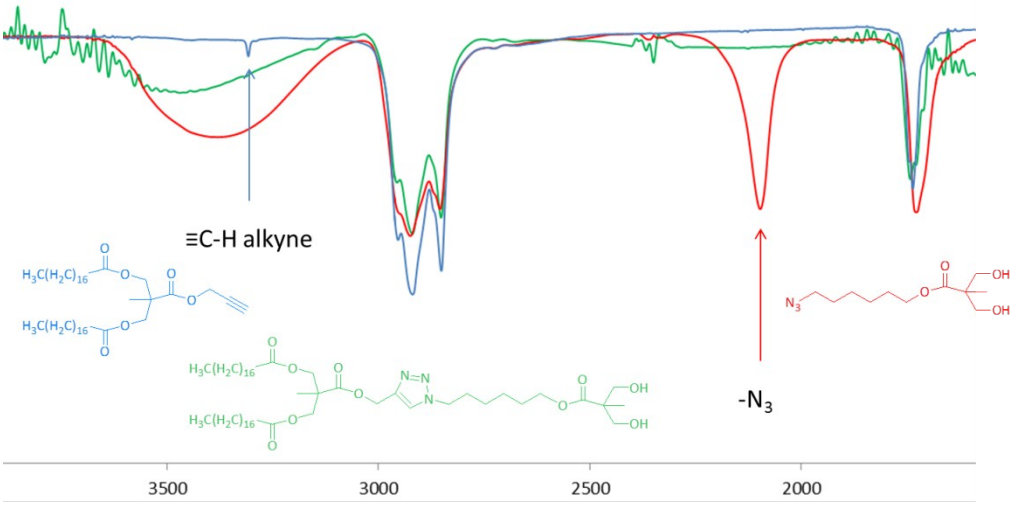


Figure S3-1. Comparison between the FTIR spectra of the starting dendrons (green and blue lines, respectively compounds **N_3-G_1(OH)** and **HC≡C-$G_1(C17)_2$**) and the final product (yellow line, **$\underline{G_1(C17)_2 - G_1(OH)_2}$**). In the same colors, are reported also the structures of the molecules.

GPC and MALDI-TOF results for the Janus dendrimers

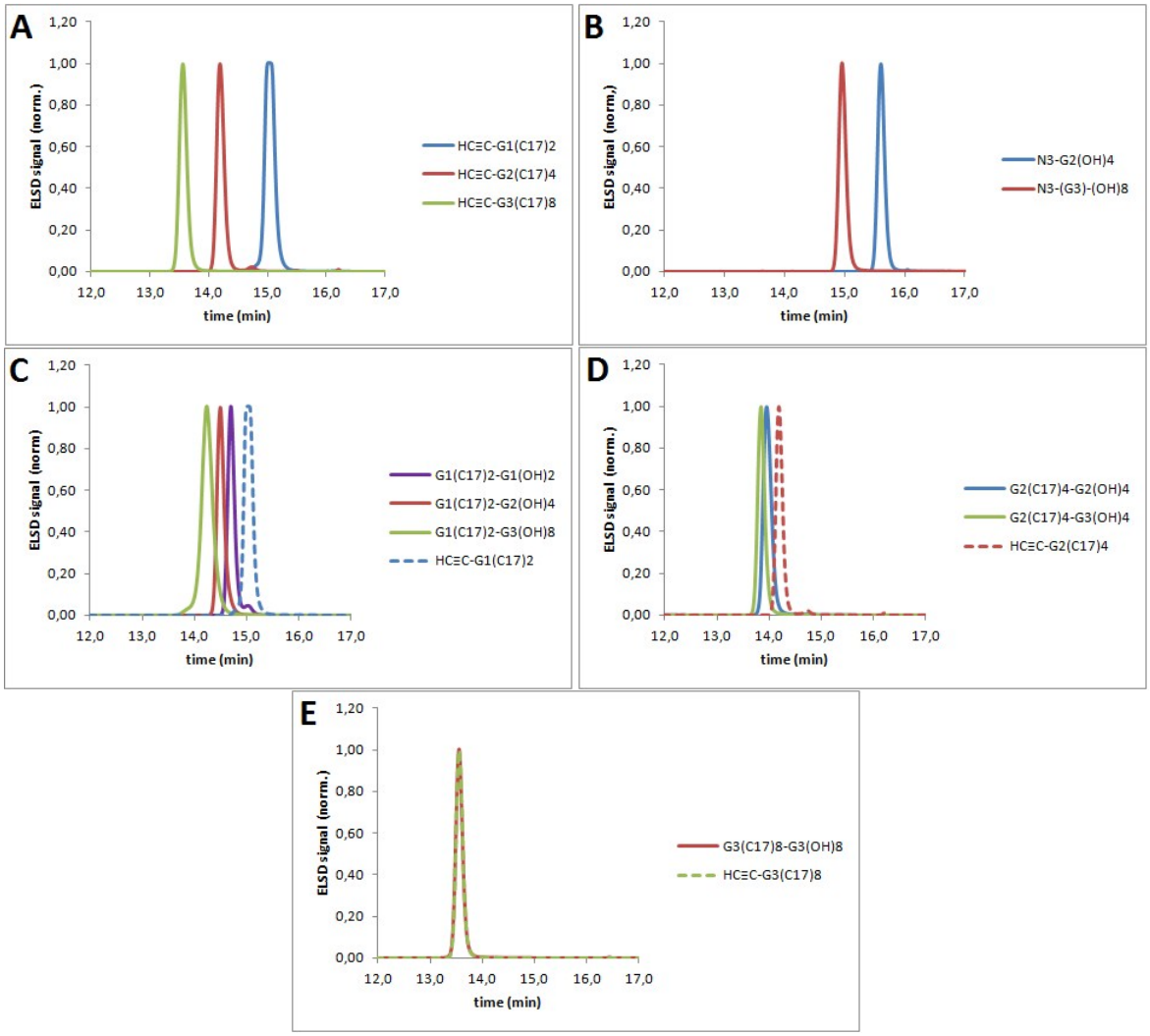


Figure S3-2. GPC chromatograms for the three apolar dendrons (HC≡C-$G_1(C_{17})_2$, HC≡C-$G_2(C_{17})_4$, HC≡C-$G_3(C_{17})_8$) (**A**), two polar dendrons (N_3-$G_2(OH)_4$ and N_3-G_2 $(OH)_8$)* (**B**), the three Janus dendrimers synthesized with the HC≡C-$G_1(C_{17})_2$ dendron (**C**), the two Janus dendrimers synthesized with the HC≡C-$G_2(C_{17})_4$ dendron (**D**) and the Janus dendrimers synthesized with the HC≡C-$G_3(C_{17})_8$ dendron (**E**).

* Polar dendron N_3-$G_2(OH)_2$ has a molecular weight too low to be detected by the GPC equipment.

All the chromatograms were recorded with a Walter 2695 employing two in series Ultrastyragel columns of 500 and 10^4 Å of pore size and a light scattering detector. Solvent was THF and a flow rate of 1mL/min; PMMA or PS were used as standars for calibration.

Table S3-1. Results of MALDI-TOF analysis.

Dendrimer	M_w[a]	MALDI-TOF (m/z)[b] $[M+Na]^+$
$G_1(C17)_2$-$G_1(OH)_2$	963.75	986.7
$G_1(C17)_2$-$G_2(OH)_4$	1195.84	1218.8
$G_1(C17)_2$-$G_3(OH)_8$	1660.03	-[c]
$G_2(C17)_4$-$G_2(OH)_4$	1960.46	1984.3
$G_2(C17)_4$-$G_3(OH)_8$	2424.65	2448.8
$G_3(C17)_8$-$G_3(OH)_8$	3953.88	3978.7

[a] molecular mass calculated by summing up the atomic masses of all the atoms of the molecule; [b] the MS analysis was run using ditranol as matrix; [c] $G_1(C17)_2$-$G_3(OH)_8$presents a distribution of molecular masses.

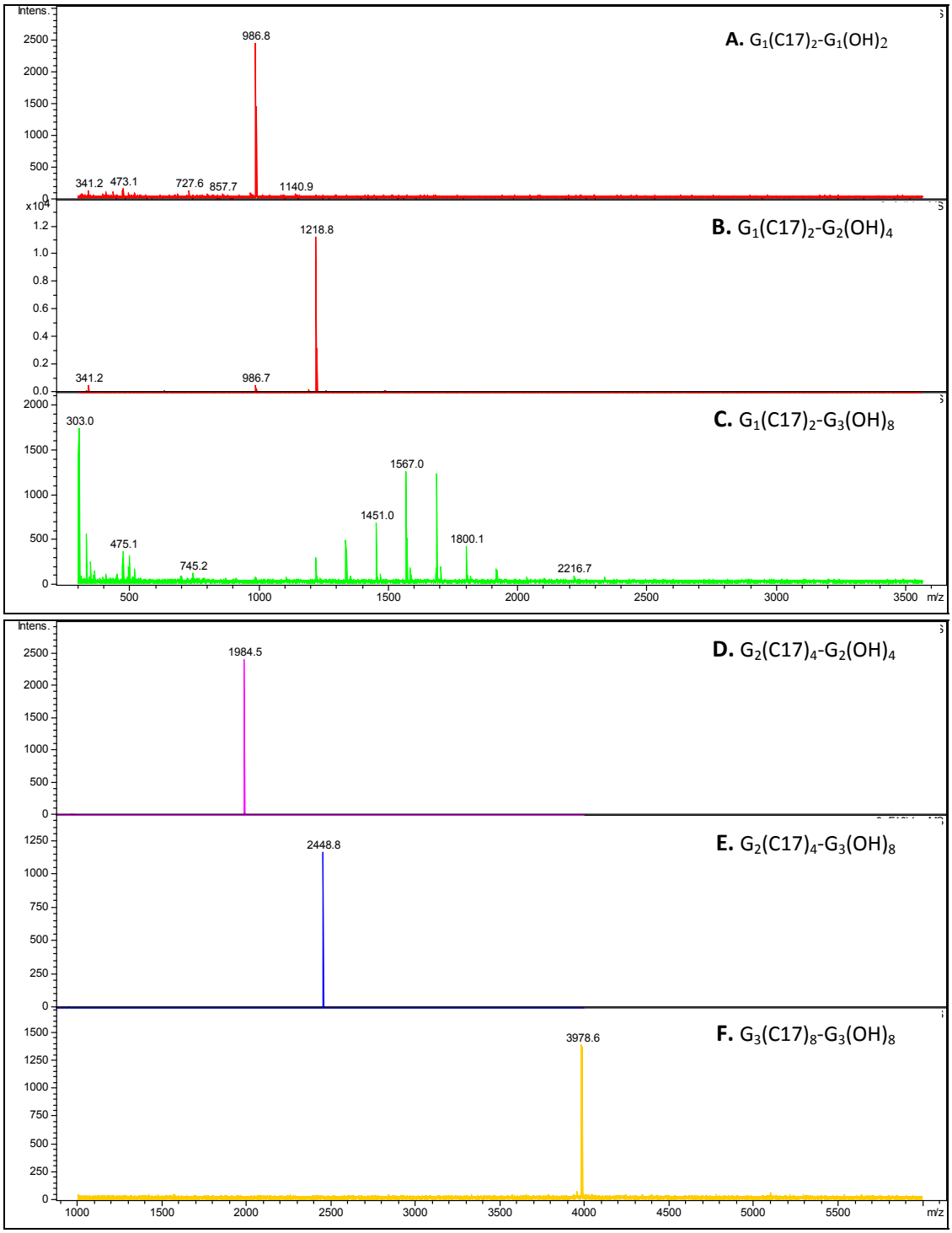


Figure S3-3. MS MALDI-TOF spectra of the six Janus dendrimers using ditranol as matrix: $G_1(C17)_2$-$G_1(OH)_2$ (**A**), $G_1(C17)_2$-$G_2(OH)_4$ (**B**), $G_1(C17)_2$-$G_3(OH)_8$ (**C**), $G_2(C17)_4$-$G_2(OH)_4$ (**D**), $G_2(C17)_4$-$G_3(OH)_8$ (**E**) and $G_3(C17)_8$-$G_3(OH)_8$ (**F**).

Observing the mass spectra of the compounds, it can be deduced that they all present a single peak corresponding to the molecular peak of the derivative except for compound **$G_1(C17)_2$-$G_3(OH)_8$**. The mass spectrum of this compound presents a distribution of molecular masses around the molecular peak (figure S3-3, A). The difference between two contiguous peaks is of almost 116, which corresponds to the molecular mass of a unit of the bis-MPA monomer.

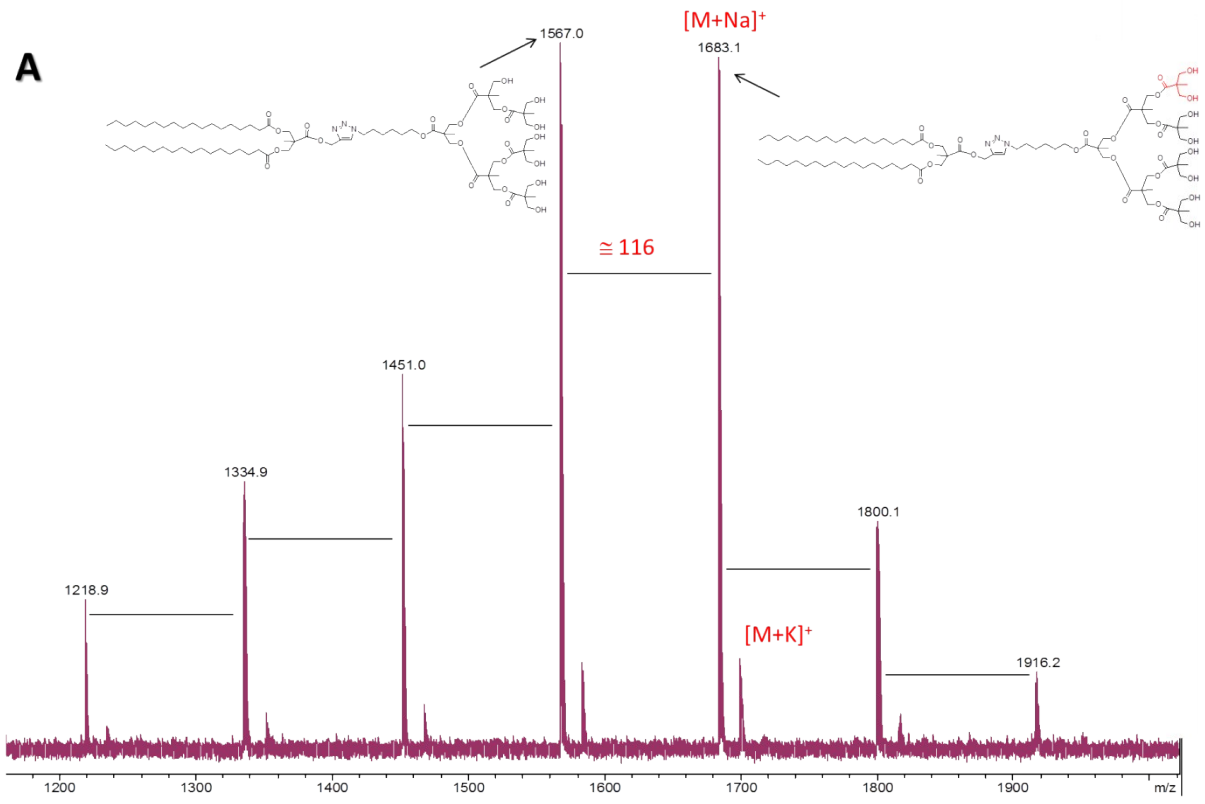


Figure S3-4. MALDI-TOF Mass spectra of compound $G_1(C17)_2$-$G_3(OH)_8$ (A), and compound **N_3-$G_3(OH)_8$** (B); (C) GPC chromatogram of $G_1(C17)_2$-$G_3(OH)_8$.

An incomplete functionalization of the starting hydrophilic dendron could have explained this anomalous MS spectrum. However, the mass spectrum of this reagent excludes this possibility as it presents a single molecular peak corresponding to the molecular mass of the product plus the molecular mass of the Na^+ ion (figure 3.1.14, B). A second hypothesis is the rupture of the final compound due to the reaction conditions or the purification processes. Also this explanation can be refuted, as the GPC analysis of the Janus dendrimer confirms its presence, showing a unique monomodal and symmetric peak (figure S3-3, C). The most probable reason of this result is that the high power required for the ionization of the compound provokes fractures on the molecule, and these results in a distribution of peaks.

S4 Thermal and mesomorphic properties

Thermal stability

TGA curves corresponding to the decomposition process of the amphiphilic Janus dendrimers

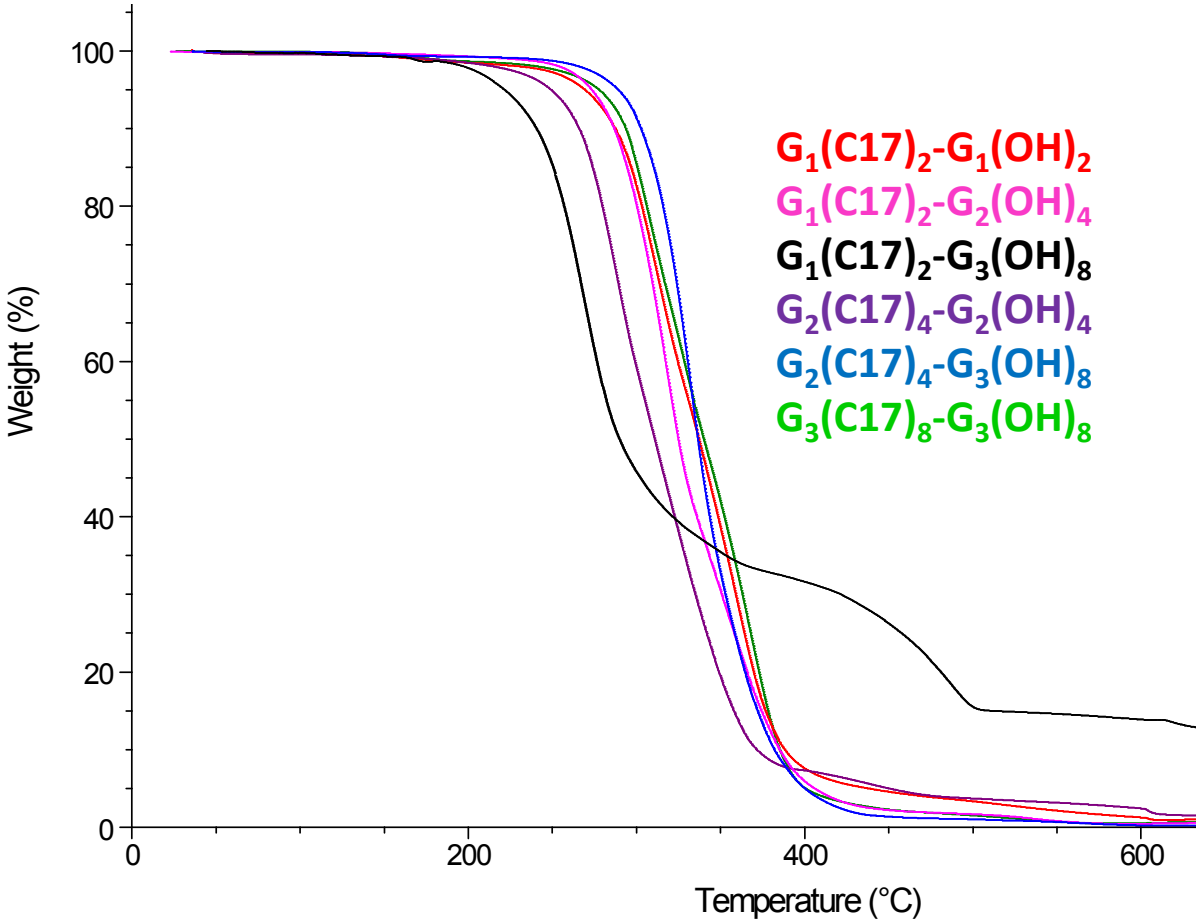


Figure S4-1. TGA curves of the Janus amphiphilic dendrimers

Table S4-1. Thermogravimetric analysis data relative to Janus dendrimers.

Dendrimer	$T_{5\%}$	T_{MAX}	T_{onset}	$Res_{600°C}$
$G_1(C17)_2$-$G_1(OH)_2$	269	313	290	1.2
$G_1(C17)_2$-$G_2(OH)_4$	273	318	288	0.4
$G_1(C17)_2$-$G_3(OH)_8$	221	268 487	243 452	14
$G_2(C17)_4$-$G_2(OH)_4$	249	289	264	2.4
$G_2(C17)_4$-$G_3(OH)_8$	289	332	308	0.2
$G_3(C17)_8$-$G_3(OH)_8$	277	368	308	0.5

The temperatures are expressed in °C and the mass loss in %. T_{MAX} is obtained by the maximum temperature of the first derivative of the slope.

Only one decomposition process was recorded for every compound and no secondary decompositions were detected except for compound **$G_1(C17)_2$-$G_3(OH)_8$** that shows two decomposition processes. The presence of volatile compounds or products with low boiling points was excluded.

Mesomorphic properties: POM and DSC

Table S4-2. DSC results for the starting dendrons

Dendrimer	Thermal transitions (°C) [kJ/mol]
N_3-$G_1(OH)_2$	-
N_3-$G_2(OH)_4$	-
N_3-$G_3(OH)_8$	g -5.7 I
HC≡C-$G_1(C17)_2$	C 32.1 [59.1] I
HC≡C-$G_2(C17)_4$	C 35.7 [108.0] I
HC≡C-$G_3(C17)_8$	C 38.8 [250.4] I

Data are relative to the second heating cycle, which was recorded at 10°C/min. C: crystalline solid; I: isotropic liquid; g: glass transition temperature. The temperature corresponds to the temperature of *onset.*

POM observations and DSC studies of the starting dendrons indicated crystalline nature for the lipophilic dendrons of the three generations. In contrast, the three generations of hydrophilic dendrons were amorphous materials that showed neither mesomorphic nor crystalline nature. The third generation hydrophilic dendrons showed semicrystalline behavior presenting a glass transition temperature at -5.7°C.

All the DSC curves (figure S4-2, S4-3), during the heating process, presented a first intense endothermic peak corresponding to the transition between the crystalline phase and the isotropic liquid (compounds **$G_1(C17)_2$-$G_1(OH)_2$**, **$G_1(C17)_2$-$G_2(OH)_4$**, **$G_3(C17)_8$-$G_3(OH)_8$**) or the mesophase (compounds **$G_1(C17)_2$-$G_3(OH)_8$**, **$G_2(C17)_4$-$G_2(OH)_4$**, **$G_2(C17)_4$-$G_3(OH)_8$**). **$G_2(C17)_4$-$G_2(OH)_4$**, **$G_2(C17)_4$-$G_3(OH)_8$**, presented several endothermic peaks before the formation of the mesophase that corresponded to the transition between different crystalline forms. Moreover, they showed small peaks with low enthalpy values (0.6 kJ/mol) that correspond to the transition between the SmA phase and the isotropic liquid. This peak was not observed for the mesogenic compound **$G_1(C17)_8$-$G_3(OH)_8$**, the clearing temperature of which was deduced from POM observations.

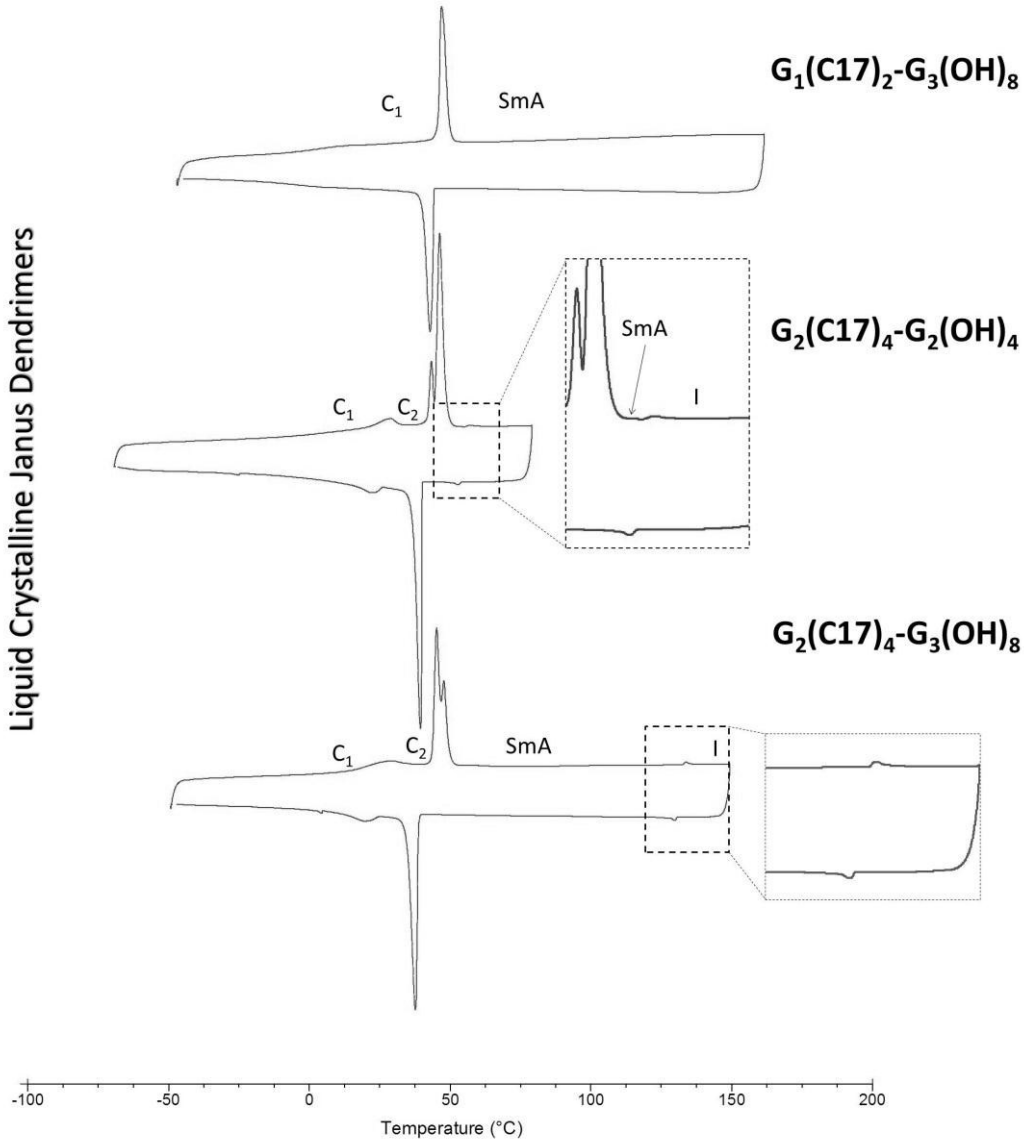


Figure S4-2. DSC curves (down exothermic) of the compounds that showed mesomorphic behavior, i.e. $G_1(C17)_2$-$G_3(OH)_8$, $G_2(C17)_4$-$G_2(OH)_4$, $G_2(C17)_4$-$G_3(OH)_8$. The thermograms are relative to the second heating/cooling.

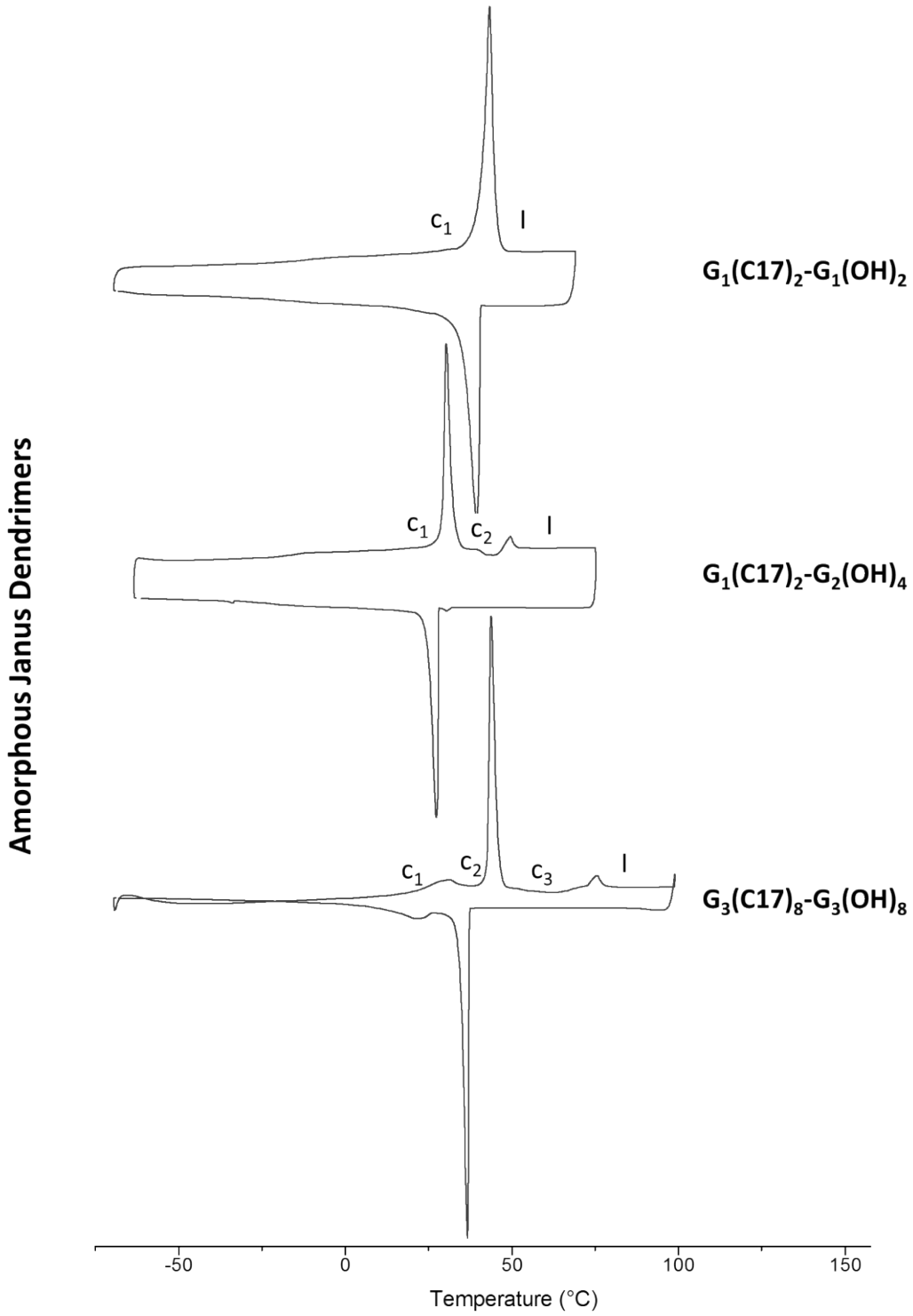


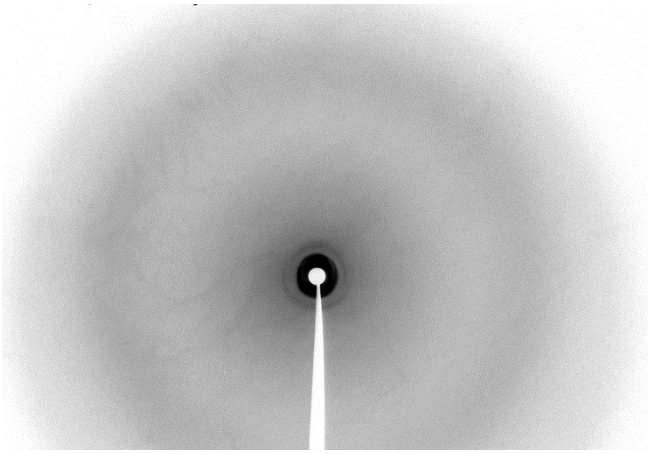
Figure S4-3. DSC curves (down exothermic) of the compounds that did not show mesomorphic behavior, i.e. **$G_1(C17)_2$-$G_1(OH)_2$**, **$G_1(C17)_2$-$G_2(OH)_4$**, **$G_3(C17)_8$-$G_3(OH)_8$**. The thermograms are relative to the second heating/cooling.

X-ray studies

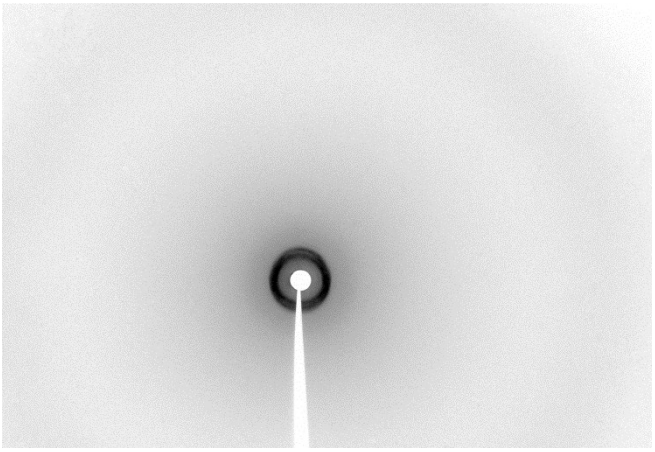
The three mesomorphic compounds were studied by X-ray diffraction to confirm the organization into the SmA mesophase and to establish their respective structural parameters. The diffraction patterns presented two maxima in the small angle region.(figure S4-4) The relation between the distances of both maxima was 1:2 confirming that the mesophase was lamellar.

The calculated molecular lengths (Chem3D Ultra 7.0 included in the ChemOffice 2002 software pack) are in accordance with the layer thicknesses measured by X-Ray diffraction, being the latter slightly smaller taking into account the disordered conformations of long alkyl chains of the hydrophobic dendrons in the mesomorphic state.

a)



b)



c)

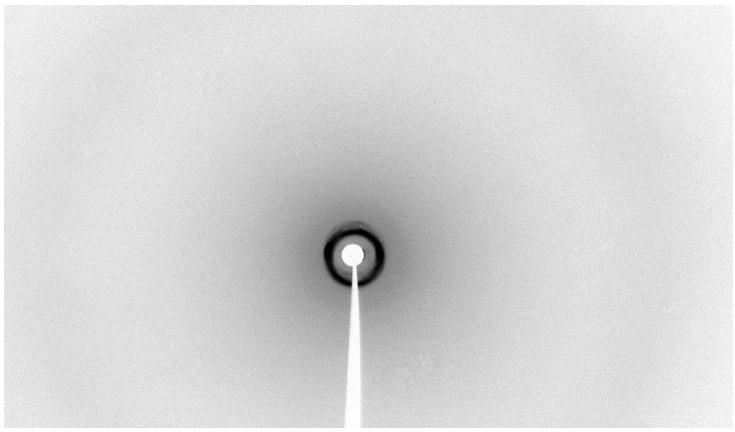


Figure S4-4. X-Ray diffractograms of compounds (a) **$G_1(C17)_2$-$G_3(OH)_8$** (70 ºC) , (b) **$G_2(C17)_4$-$G_2(OH)_4$** (50 ºC), **(c) $G_2(C17)_4$-$G_3(OH)_8$** (95 ºC).

Table S4-3. Layer parameter obtained by X-Ray diffraction and the value calculated using Chem 3D Ultra 7.0 software.

Dendrimer	$d(Å)_{RX}$	$d(Å)_{theory}$
$G_1(C17)_2$-$G_3(OH)_8$	56	59
$G_2(C17)_4$-$G_2(OH)_4$	50	53
$G_2(C17)_4$-$G_3(OH)_8$	56	57

X-ray diffraction experiments of the mesophases were performed in a pinhole camera (Anton-Paar) operating with a point focused Ni filtered Cu-Kα beam. Lindemann glass capillaries with 0.9 mm inner diameter were used to contain the sample. The capillary axis was held perpendicular to the X-ray beam and the pattern collected on flat photographic film. Bragg´s law was used to calculate the *d* spacings.

S5 Maximum solubility and aggregation methods

Maximum solubility limits

The amount of compound required to obtain 2 mL of water solution with concentration 0,5 µmol/mL was dissolved in a vial with 0.5 mL of dichloromethane. To this solution, 2 mL of milli-Q water were added slowly and the mixture was shaken in an orbital shaker for approximately 4 hours allowing the complete evaporation of the organic fraction. After this step, a solid precipitate appeared in all the cases and this indicated a lower solubility of the compounds. Then, in order to evaluate the actual concentration of the corresponding compound in solution, and hence the solubility maximum limit, the mixture was washed twice with dichloromethane, and the organic fraction was removed and put in a new vial with known weight. This vial containing the organic fraction was dried under vacuum for 3 days at 50°C until its weight remained constant. By weight difference, the quantity of precipitate was calculated and this allowed the estimation of the actual concentration in solution. It is necessary to take into account that aggregates are dynamic structures in which molecules are in dynamic equilibrium from being free in solution to be part of the supramolecular aggregate. The washing procedure with dichloromethane could have altered such equilibrium sweeping away also molecules that were actually dissolved in water, thus lowering the real value of solubility. However, in order to reduce the error in the calculation of the solubility limit due to this phenomenon the entire procedure was repeated twice and the reported values are an average of the two experiments.

Table S5-1. Lipophilic content and solubility limit of the Janus amphiphilic dendrimers

Dendrimer	Lipophilic content (%)	Solubility mg/mL	limit M (mol/L)
$G_1(C17)_2$-$G_1(OH)_2$	54	0.04	$4.1\cdot10^{-5}$
$G_1(C17)_2$-$G_2(OH)_4$	42	0.03	$2.5\cdot10^{-5}$
$G_1(C17)_2$-$G_3(OH)_8$	30	0.38	$2.5\cdot10^{-4}$
$G_2(C17)_4$-$G_2(OH)_4$	50	0.13	$6.6\cdot10^{-5}$
$G_2(C17)_4$-$G_3(OH)_8$	40	0.15	$6.1\cdot10^{-5}$
$G_3(C17)_8$-$G_3(OH)_8$	49	0.21	$5.2\cdot10^{-5}$

Aggregation method

All the compounds were dissolved in 0.5 mL of dichloromethane, and 1 mL of milli-Q water was added. The amount of each compound corresponded to a concentration of 0.5 μmol/mL in water. The mixture was shaken in an orbital shaker to open air at room temperature until the complete evaporation of the organic fraction. The insoluble fraction was filtered off and the solution was stored at -5°C and used without further treatment.

S6 Encapsulation procedure

The encapsulation procedure was performed employing the "oil-in-water method" explained in section S5 and adapted for this specific procedure. For the initial concentration of the amphiphiles, the highest used to establish the maximum solubility limit: 0.5 μmol/mL (annex 2) was maintained. In order to exploit the complete payload capacity of the aggregates, a concentration of Plitidepsin of 1 μmol/mL, which is twice the concentration of the amphiphile, was chosen to perform the encapsulation.
Procedure:

- the amphiphile and Plitidepsin were dissolved in separated vials in 0.5 mL of dichloromethane. The quantity of each component was chosen in order to obtain 1 mL of water solution with concentration 0.5 μmol/ml of the dendrimeric derivative and 1 μmol/mL of Plitidepsin (1.11 mg, M_w 1110.34).
- The two organic solutions were mixed together and stirred for few minutes in a closed vial to allow the complete stabilization of the solution.
- 1 mL of Milli-Q water was gently added and the open vial was shaken in an orbital shaker at room temperature till complete evaporation of the organic solvent.

After the complete evaporation of the organic fraction, a solid precipitate appeared. The exact concentration of Plitidepsin in solution was established by HPLC using a standard procedure developed by Pharma Mar. In order to establish the real concentration in solution of the amphiphile, the water solution of the host-guest complex was washed twice with dichloromethane in order to dissolve the solid precipitate. The organic fraction was removed and put in a new vial with known weight; this vial was dried under vacuum for 3 days at 50°C until its weight remained constant. By weight difference, the quantity of precipitate was calculated. Since the concentration of Plitidepsin in solution was established by HPLC, its amount in the solid precipitate was calculated by difference with the initial amount of Plitidepsin (1.11 mg). Knowing the global amount of the precipitate and the fraction of Plitidepsin the quantity of amphiphile in the precipitate and, consequently its concentration in water was extrapolated.