Versatile Synthesis of Amphiphilic Oligo(Aliphatic-Glycerol) Layer-Block Dendrons with Different Hydrophilic-Lipophilic Balance Values

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Abstract: A series of amphiphilic oligo(glycerol-aliphatic) layer-blocked dendrons with different hydrophilic-lipophilic balance values (3.5–15.0) was prepared for use in controlled drug delivery and self-assembly studies. The synthetic strategies involved first a convergent growth of the inner hydrophobic sector followed by a divergent growth of the outer hydrophilic sector.

Key words: dendrimers, dihydroxylation, Mitsunobu reaction

Amphiphilic dendrimers are an interesting class of molecules with novel self-assembling properties.[1] They are often prepared either by attaching linear hydrophilic groups such as oligoethyleneglycol,[2] anionic carboxylate[3] or cationic ammonium[4] groups to the periphery of a hydrophobic dendrimer, or by anchoring linear fatty acid chains to the surface of a hydrophilic dendrimer.[5] They are useful compounds for gene transfection and for biomedical and controlled drug delivery applications.[6] Hence, the synthesis of amphiphilic dendrimers with new internal hydrophilic or hydrophobic repeating architecture and interesting guest-encapsulating properties is still in demand. To date, only a limited number of hydrophilic dendritic/hyperbranched compounds based on pentaerythritol,[7] tris(hydroxymethyl)methane,[8] or glycerol[9] repeating units are known, as are hydrophobic dendrimers based on tetrakis(butylene)methane[10] or isoprene[11] repeating units. For controlled release applications, molecules with an optimal hydrophilic-lipophilic balance (HLB) are needed.[12] Therefore, the availability of a series of amphiphilic dendrimers with different HLB values is highly desirable. Herein, we wish to report the synthesis of a new series of amphiphilic dendrons G[m+n]-$(X)_k$(Y) (e.g., **1**; Figure 1) bearing *m* outer layers of polyglycerol and *n* inner layers of isoprene hydrophobic units with *k* X surface groups and a focal point functionality Y. This set of amphiphilic dendrons possesses a range of HLB (3.5–15.0) values to cater for different controlled delivery applications. The present synthetic protocol also makes use of the advantages of both convergent (fewer defective products) and divergent (rapid growth of dendrimer) synthetic strategies. Hence, the di-C-allylation of Meldrum's acid[13] was used for the inward construction of the hydrophobic aliphatic inner core to ensure good structural homogeneity, while the allylation–dihydroxylation sequence reported by Haag[9b] was employed for the rapid outward growth of the hydrophilic polyglycerol outer sector. This synthesis allows a library of amphiphilic dendrons of different HLB values to be rapidly assembled in good yields for various applications.

The starting material was 5-hydroxylmethyl-2,2,5-trimethyl-1,3-dioxane (**2**; Scheme 1).[14] The acetonide moiety served as the protective group of the 1,3-diol that could be elaborated into the hydrophilic polyglycerol layer later in the synthesis. Alcohol **2** was subjected to Swern oxidation and the resulting aldehyde was immediately reacted with $Ph_3P{=}CHCO_2Me$ to give the *trans*-α,β-unsaturated ester **3** in 85% overall yield.[15,16] Ester **3** was then reduced to the corresponding *trans*-allylic alcohol **4** by diisobutylaluminum hydride (DIBAL-H) in 93% yield. Reaction of two equivalents of **4** with Meldrum's acid in the presence of diisopropyl azodicarboxylate (DIAD) in toluene at –10 °C gave the C-diallylation product **5** in 73% yield. The acetonide group at the focal point was then cleaved by NaOMe to produce the monoacid-monoester **6** in 79% yield. Decarboxylation of **6** in pyridine at 110 °C proceeded smoothly to give diene-ester **7** in 78% yield. The double bonds were then hydrogenated in the presence of 10% Pd/C to afford saturated ester **8** in 89% yield. A small amount of powdered K_2CO_3 was required to prevent cleavage of the acetonide groups under the reaction conditions. Finally, the ester was reduced to the corresponding alcohol **9** in 99% yield by lithium aluminum hydride (LAH). This series of reactions then completed the convergent iterative reaction cycle. The overall yield from dendron G[0+0]-$(dioxane)_1$(OH) **2** to compound G[0+1]-$(dioxane)_2$(OH) **9** was 31%.

For the synthesis of the G[0+2] dendrons, alcohol **9** was subjected to Swern oxidation followed by reaction with $Ph_3P{=}CHCO_2Me$ to give the *trans*-α,β-unsaturated ester **10** in 96% overall yield (Scheme 2). The ester was then converted into the corresponding allylic alcohol **11** in 96% yield through DIBAL-H mediated reduction. Mitsunobu C-diallylation of Meldrum's acid with **11** gave an inseparable 9:1 mixture of C-diallylation product **12** and O-monoallylation product **13** in a combined yield of 81%. Upon treatment of the mixture with NaOMe in MeOH followed by chromatographic purification, monoacid-monoester **14** was obtained in pure form in 85% yield.

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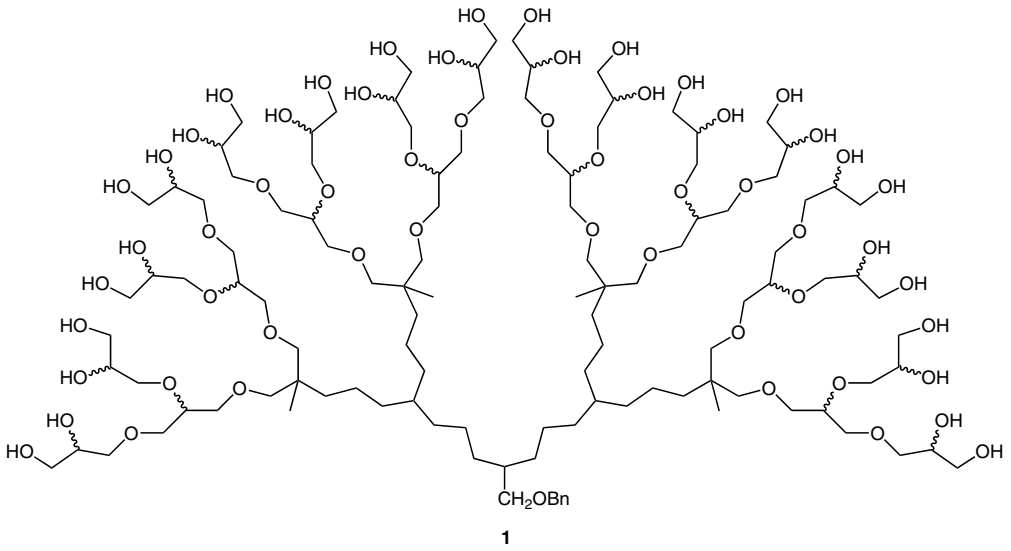

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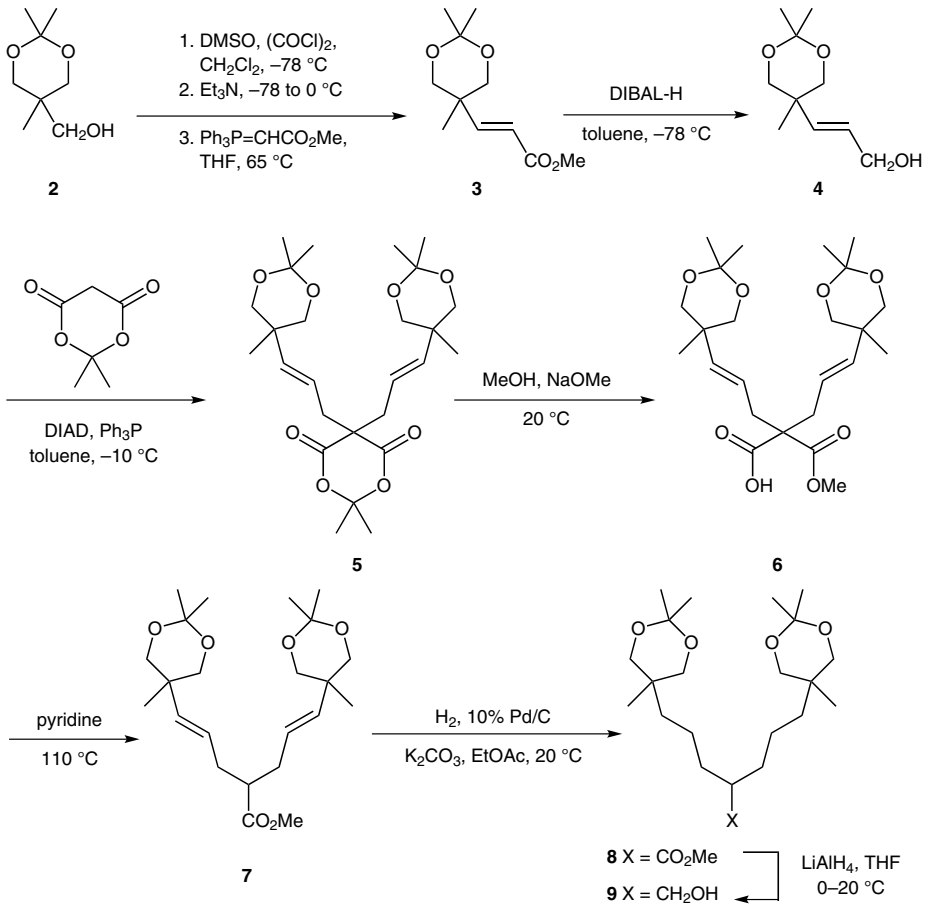
Figure 1 Structure of amphiphilic dendron **1**

Compound **14** was then similarly converted into the corresponding G[0+2]-(dioxane)$_4$(OH) **17** in overall 82% yield through a decarboxylation, hydrogenation and LAH-mediated reduction sequence.

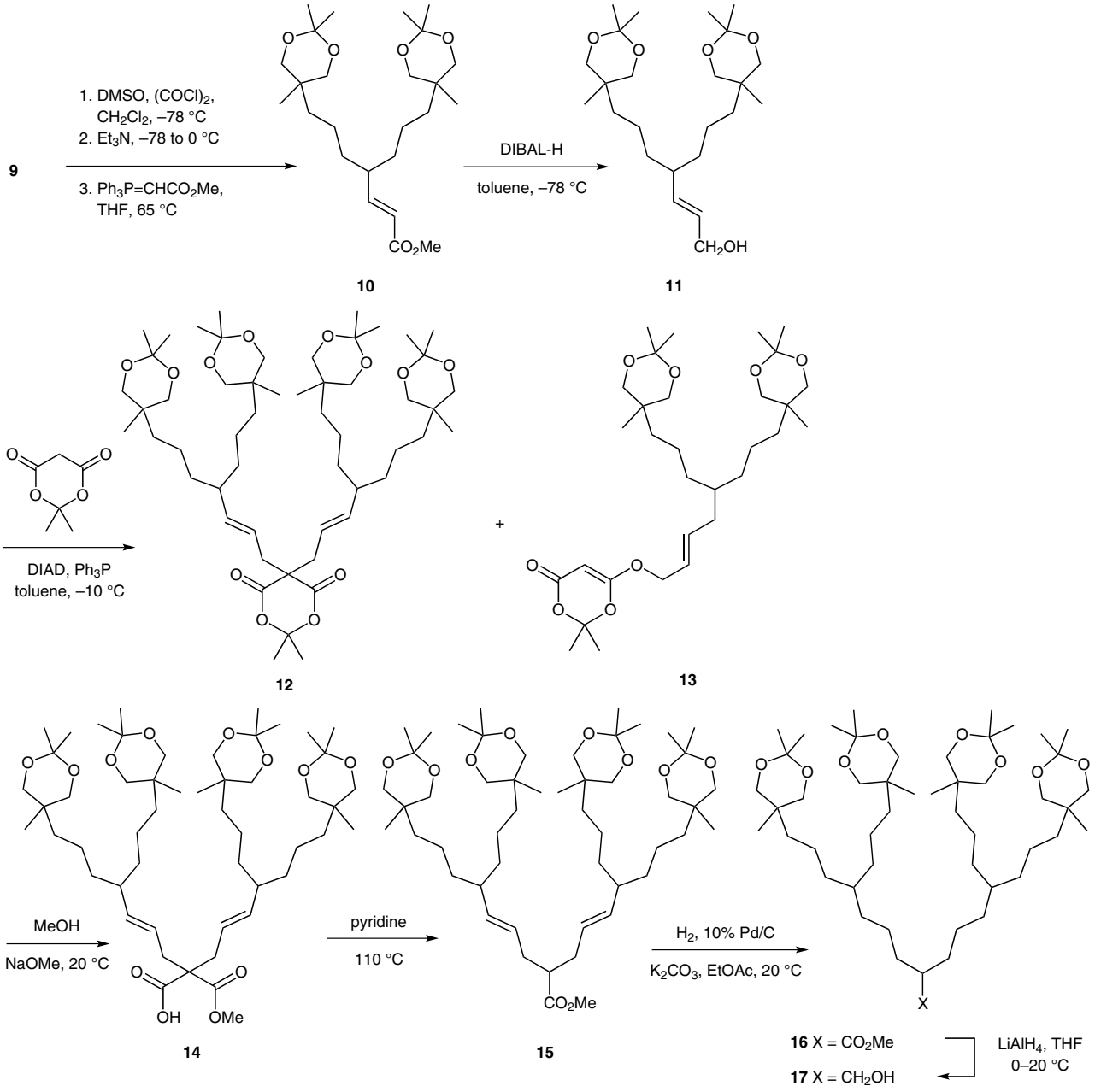
The same reaction sequence was then applied to the synthesis of the G[0+3]-dendrons (Scheme 3), however, two issues were identified. First, for the Mitsunobu reaction between the G[0+2]-(dioxane)$_4$(allylic-OH) **18** with Meldrum's acid, the C-diallylation product **19**[17] could only be obtained in 40% yield. The yield could not be improved by changing the reaction solvent or by adding [Pd(PPh$_3$)$_4$].[13a] Second, the C=C double bonds of product



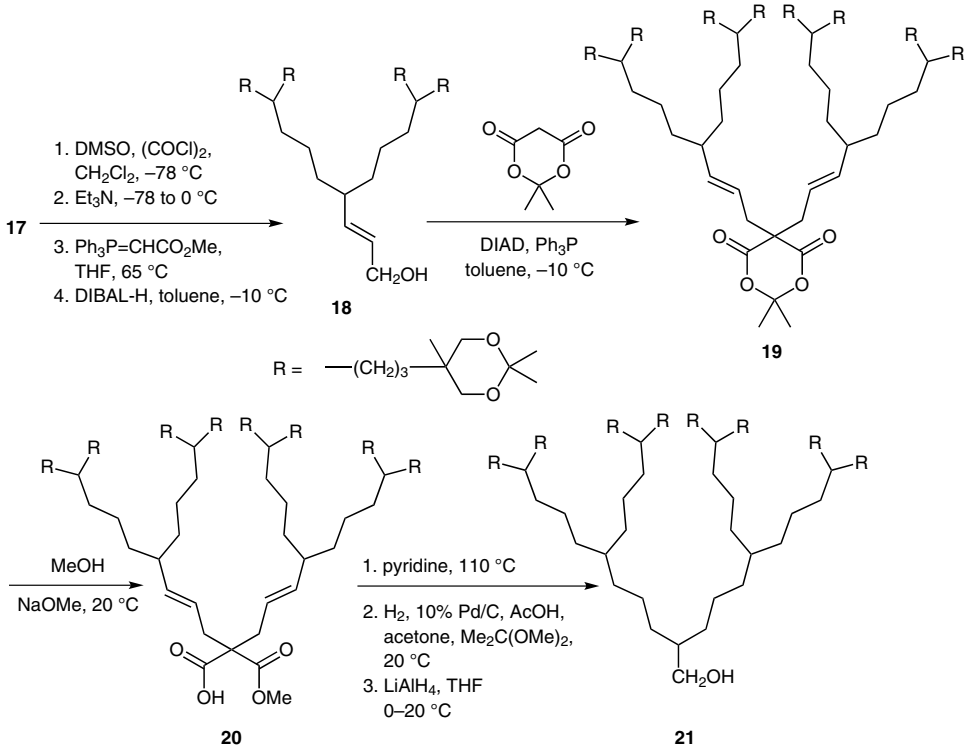
Scheme 1 Synthesis of G[0+1]-dendrons

20 could not be saturated when the reduction was conducted in EtOAc, and the reaction was carried out in acetic acid/acetone/2,2-dimethoxypropane. Finally, G[0+3]-(dioxane)$_8$(OH) **21** was obtained in an overall yield of 17% from compound **17**.

After successfully synthesizing the G[0+n]-dendrons, the divergent growth of the hydrophilic oligo(glycerol) outer sector employing Haag's method[9b] was examined. Thus, G[0+2]-(dioxane)$_4$(OH) **17** was first converted into the corresponding benzyl ether G[0+2]-(dioxane)$_4$(OBn) in 98% yield through application of the Williamson synthesis (Scheme 4). The acetonide protecting groups were then removed in the presence of acetic acid in MeOH to give the octa-alcohol **22** in 87% yield. Initial O-allylation of **22** with allyl bromide, NaOH, and tetrabutylammonium iodide (TBAI) in THF/water (1:1) at 45 °C proceeded very slowly. Although the starting octa-alcohol disappeared after two days, only partially allylated intermediates were formed. After seven days, only a small amount of the octa-allylated product **23** was isolated. Alternative reaction conditions employing Williamson ether synthesis (NaH, allyl bromide, DMF) gave the octa-allylation product **23**, albeit in poor conversion (ca. 10%). The starting octa-alcohol was still present in large quantities even using excess NaH (80 equiv). Interestingly, no partially allylated compounds were found. Hence, it appeared that once one of the hydroxyl groups was allylated, subsequent allylations proceeded much faster to give the octa-allylated compound under the Williamson conditions. Because Haag's procedure could afford a mixture of partially al-

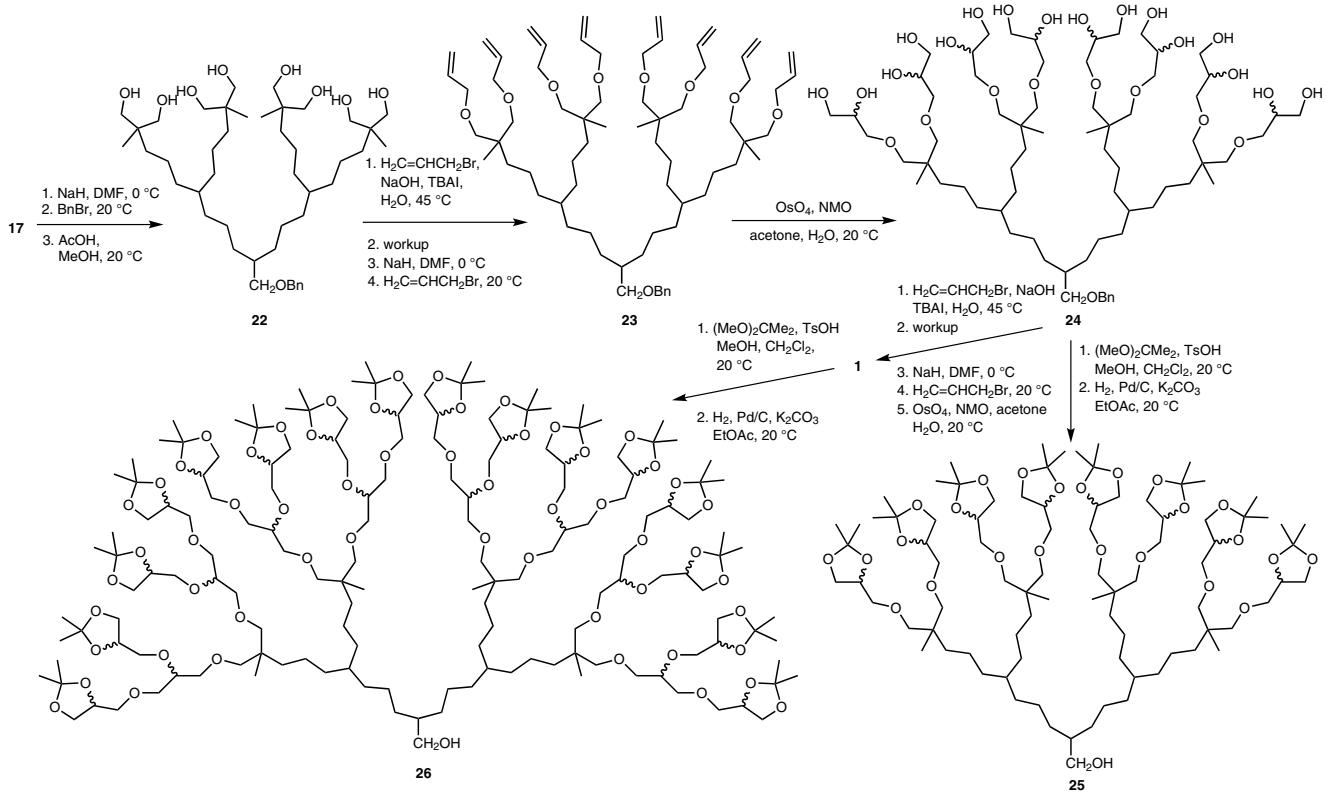


Scheme 2 Synthesis of G[0+1]-dendrons



Scheme 3 Synthesis of G[0+3]-dendrons

lylated products, the Haag and Williamson procedures were then employed sequentially to ensure complete allylation. Hence, the octa-alcohol **22** was first subjected to Haag's conditions for two days. After workup, the mixture was subjected to Williamson conditions to produce the octa-allylated compound **23** in 85% yield. Compound **23** was unstable at room temperature and was immediately dihydroxylated using a catalytic amount of OsO_4 and 4-



Scheme 4 Synthesis of G[1+2]- and G[2+2]-dendrons

methylmorpholine *N*-oxide (NMO) in aqueous acetone to give the G[1+2]-$(OH)_{16}$(OBn) **24** as a mixture of diastereoisomers in 64% yield. The allylation–dihydroxylation sequence was once again employed on **24** to give the corresponding G[2+2]-$(OH)_{32}$(OBn) **1**,[18] after purification by dialysis in MeOH, in overall 87% yield. Compound **1** has 24 chiral centers and is a mixture of more than 10^6 stereoisomers. The peripheral 1,2-diols in compounds **24** and **1** could be protected as the dioxalanes using 2,2-dimethoxypropane and the focal point benzyl ether functionality could be removed by hydrogenolysis to produce compounds **25** (64%) and **26** (70%), respectively. The focal point alcohol functionality can serve as a handle for its attachment to other molecular entities.

The conversion efficiency of the divergent allylation–dihydroxylation reaction was assessed by mass spectroscopy using either electrospray or MALDI-TOF ionization techniques.[16] For example, the MALDI-TOF mass spectrum of G[2+2]-$(OH)_{32}$(OBn) **1** showed a major peak at *m*/*z* 2569 $[M + Na]^+$, and several structurally defective peaks of less than 10% relative intensity corresponding to peaks with one or two non-allylated, or one non-dihydroxylated species (Figure 2). Based on the relative intensities of these defective peaks, one could estimate that 80% of the sample was the defect-free dendron after two iterative growth cycles, highlighting the good efficiency of Haag's divergent synthetic protocol.

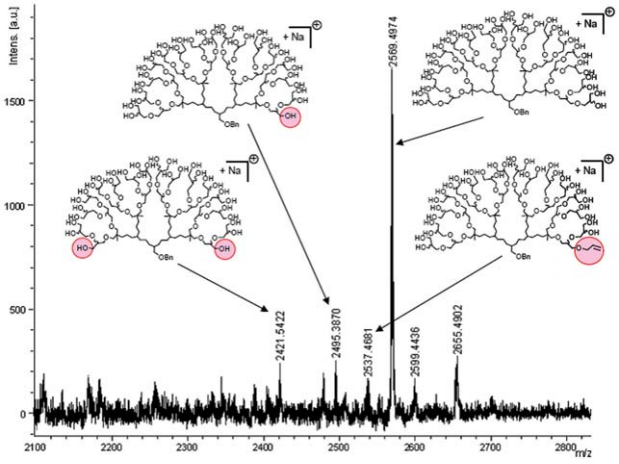


Figure 2 MALDI-TOF spectrum of G[2+2]-$(OH)_{32}$(OBn) **1**

The aqueous solubility of G[0+2]-$(OH)_8$(OBn) **22**, G[1+2]-$(OH)_{16}$(OBn) **24** and G[2+2]-$(OH)_{32}$(OBn) **1** were found be to $<10^{-3}$, 2.9 and >7.5 M, respectively, reflecting the gradual increase of HLB value [**22** (3.5), **24** (10.7) and **1** (15.0)].[16] Apparently, the highly polar nature of the larger-sized oligo(glycerol) sector overwhelmed the non-polar nature of the aliphatic core and enabled compounds **24** and **1** to become miscible with water through unimolecular micelle and aggregate formation.

In summary, we have reported the versatile synthesis of a series of new amphiphilic layer-block dendrons. The synthesis made use of favorable attributes of both divergent and convergent strategies to enable their efficient synthesis and good structural homogeneity. The divergent growth strategy, in principle, can also be applied to the G[0+1]- and G[0+3]-dendrons to furnish amphiphilic dendrimers with a broader range of HLB values for future self-assembly and controlled release property studies.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(15) The structural properties of all compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and/or elemental analysis. Their good purities were also confirmed by a polydispersity index of <1.02 by size-exclusion chromatographic analysis.
(16) See the Supporting Information for details.
(17) **Synthesis of 19:** A solution of DIAD (0.53 mL, 2.67 mmol) in toluene (6 mL) was added dropwise to a stirred solution of allylic alcohol **18** (1.78 g, 2.06 mmol), Ph_3P (0.70 g, 2.67 mmol), and Meldrum's acid (0.15 g, 1.03 mmol) in toluene (6 mL) at –10 °C. The progress of the reaction was monitored by TLC. When the reaction was complete

(ca. 30 min), hexane (30 mL) was added to the mixture to precipitate Ph_3PO, which was removed by filtration. The excess solvent was removed and the yellow residue was purified by flash column chromatography on silica gel (hexane–EtOAc, 3:1→1:1, in the presence of 1% Et_3N) to afford the target compound **19** (0.76 g, 40%) as a colorless oil. R_f = 0.54 (hexane–acetone, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (s, 24 H, CH_2CCH_3), 1.00–1.50 (m, 76 H), 1.38 (s, 24 H, $OCCH_3$), 1.39 (s, 24 H, $OCCH_3$), 1.64 (s, 6 H, CO_2CCH_3), 1.78–1.95 (m, 2 H, CHC=C), 2.66 (d, *J* = 6.9 Hz, 4 H, CH_2C=C), 3.45 (AB system, *J* = 11.4 Hz, 16 H, COC*H*H), 3.55 (AB system, *J* = 11.4 Hz, 16 H, COCH*H*), 5.20 (dt, *J* = 15.3, 7.2 Hz, 2 H, CH_2CH=CH), 5.36 (dd, *J* = 15.0, 8.4 Hz, 2 H, CH_2CH=C*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.8, 20.2, 23.7, 24.1, 24.5, 30.2, 32.7, 34.0, 34.5, 34.6, 35.6, 36.0, 37.4, 42.7, 43.1, 56.1, 69.6, 97.9, 105.3, 121.8, 142.3, 168.8; MS (FAB): *m*/*z* (%) = 1823 (100) [M – CH_3^+]; HRMS (FAB): *m*/*z* calcd for ($C_{110}H_{196}O_{20}$ – CH_3)$^+$: 1822.4080; found: 1822.4113.

(18) **Synthesis of G[2+2]-(OH)$_{32}$(OBn) 1:** OsO_4 (2.5 wt% in *t*-BuOH, 0.44 mL, 0.044 mmol) was added dropwise to a solution of 16-ene **32** (873 mg, 0.44 mmol) and NMO (1.23 g, 10.46 mmol) in acetone–H_2O (20 mL, 10:1, v/v) at 0 °C. The mixture was stirred at 20 °C for 48 h and the progress of the reaction was monitored by NMR analysis until all allyl groups had reacted. The solvent was removed in vacuo and the dark-brown residue was purified by membrane dialysis in MeOH using regenerated cellulose (MWCO = 1,000) to give the target compound **1** (1.02 g, 92%) as a viscous brown liquid. R_f = 0.08 (EtOAc–MeOH, 1:3); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.78 (s, 12 H, CH_3), 0.92–1.45 (m, 38 H), 1.45–1.61 (m, 1 H, C*H*CH_2OBn), 3.00–3.23 (m, 16 H, CH_3CCHHO), 3.23–3.46 (m, 90 H, OC*H*CH_2O and CHCH_2OBn), 3.46–3.68 (m, 32 H, OC*H*CH_2O), 4.42 (t, *J* = 5.7 Hz, 10 H, OH and $PhCH_2O$), 4.47 (t, *J* = 5.7 Hz, 8 H, OH), 4.51 (t, *J* = 4.8 Hz, 8 H, OH), 4.60 (dd, *J* = 4.8, 1.2 Hz, 8 H, OH), 7.16–7.45 (m, 5 H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 19.6, 20.0, 23.4, 31.8, 33.7, 34.6, 35.1, 36.8, 37.8, 38.7, 63.4, 63.5, 70.7, 70.9, 71.0, 71.3, 71.89, 71.93, 72.4, 73.1, 75.5, 78.1, 127.6, 127.8, 128.4, 139.0; HRMS (MALDI-TOF): *m*/*z* calcd for ($C_{117}H_{228}O_{57}$ + Na)$^+$: 2569.4869; found: 2569.4974.

