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Novel Synthesis of Amphiphilic Dendrons by the Double-Stage Convergent Method

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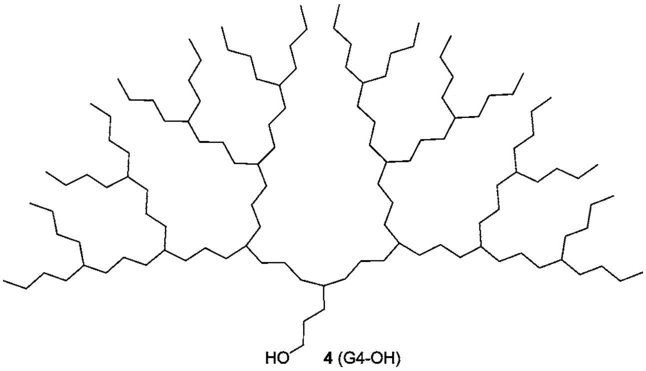
ABSTRACT



4 (G4-OH)

A series of amphiphilic dendrons (G1−G4) have been designed and synthesized, which have a highly branched aliphatic hydrocarbon skeleton and a hydrophilic hydroxyl functionality to enable conjugation with other substrates. The higher generation dendrons (G3 and G4) were synthesized by a double-stage convergent method, which shortened the synthetic route significantly and provided the products in an efficient manner. The key branching step involved a double alkyl-metal addition to an ester functionality followed by deoxygenation of a resulting tertiary alcohol by triethylsilane.

Amphiphilic dendrimers, due to their unusual structural architecture, possess many interesting and unique properties. These compounds have been used as novel agents in self-assembling,[1] gene transfection,[2] catalyst,[3] and other applications.[4] They were generally synthesized either by grafting hydrophilic chains to the surface sector of a hydrophobic dendrimer[5] or by linking linear aliphatic hydrocarbon chains to the surface sector of a hydrophilic core.[6] However, few papers reported the synthesis of hydrophobic dendrimers based on a highly branched aliphatic hydrocarbon skeleton.[7] The earliest report was by Newkome, in which a G3 aliphatic dendrimer with multiple hydrophilic hydroxyl surface was prepared by a divergent method.[7a] Later, Chow disclosed a

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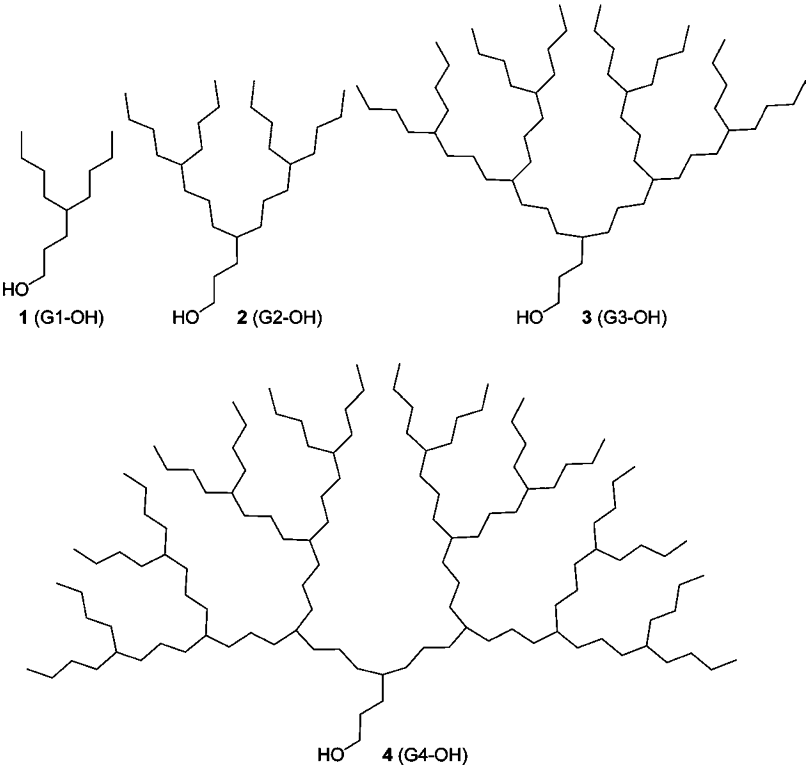

Figure 1. Structure of amphiphilic dendrons.

convergent way to obtain a series of G1−G3 aliphatic dendrons with a polar hydrophilic carboxylic acid core[7c] and used them in polymer chemistry and catalytic reaction.[8] The advantages of the divergent approach are the rapid growth of the dendrimer series, the rapid increase of the size of the dendritic species, and the better overall yield of the dendrimer products. However, the limiting features of this method are the possibility of generating molecular imperfection at higher generations and the difficulty in selectively modifying the peripheral functionality. On the other hand, the convergent approach offers attractive features such as greater control of the dendrimer growth and easy placement of specific peripheral functionality. Nonetheless, the inherent limitations of this approach are: the dendritic growth is slow, the branching reaction is highly susceptible to steric inhibition at the focal point, and there is a generally lower overall yield of the target products due to the increasing number of synthetic operations.[9] In this paper, we report the synthesis of aliphatic hydrocarbon dendrons **1**−**4** (Figure 1) with a hydroxyl focal point using a double-stage convergent approach to overcome the problem of steric inhibition in preparation of the higher generation G3 and G4 dendrons. The growth cycle in this present method involves only four operations, and the G4 dendron could be prepared in an overall yield of 12% from readily available starting materials in 13 steps.

In our synthetic scheme, we chose the addition reaction of ester with alkyl-metal reagent as the pivotal step in the branching growth of such dendrons. First, two key branching intermediates, ester **6**[10] and diester **11**, used separated on the convergent growth and the double-stage convergent growth, respectively, were prepared (Scheme 1). Ester **6** was prepared from commerically available alcohol **5** by Jones oxidation followed by esterification with ethanol (cat. H_2SO_4) in 75% yield in 50 g scale. On the other hand, brancher **11** was prepared in six steps in 31% overall yield from the known dibromide **7**. Hence, the monobromide **8**[11] was obtained in 80% yield by reaction of 4-methoxybenzyl alcohol (PMBOH) with 1,4-dibromobutane in the presence of NaOH. The bromide was converted into the correspondng Grignard reagent and reacted with the ester **6** to afford a tertiary alcohol **9** in 87% yield. Then, removal of two PMB protecting groups in **9** with ammonium ceric nitrate (CAN) furnished the synthesis of triol **10** in 79% yield. Subsequently, oxidation of the two primary hydroxyl groups in **10** to the corresponding diacid with Jones reagent followed by esterification with ethanol (cat. H_2SO_4) gave a mixture of isomeric unsaturated diesters due to the elimination of the tertiary hydroxyl group. The isomeric mixture of unsaturated diesters was then hydrogenated in the presence of 10%

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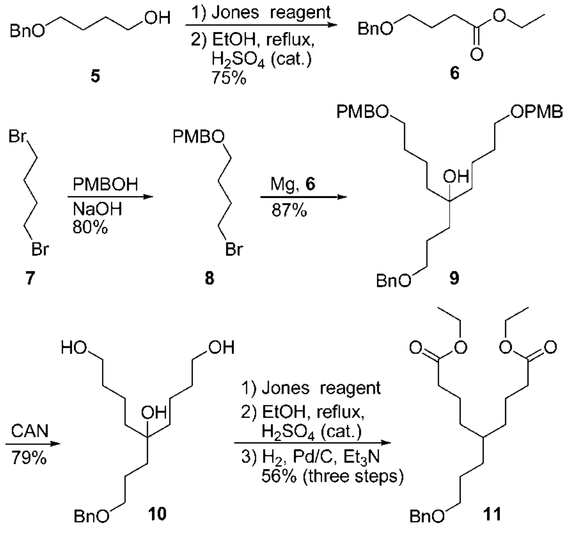
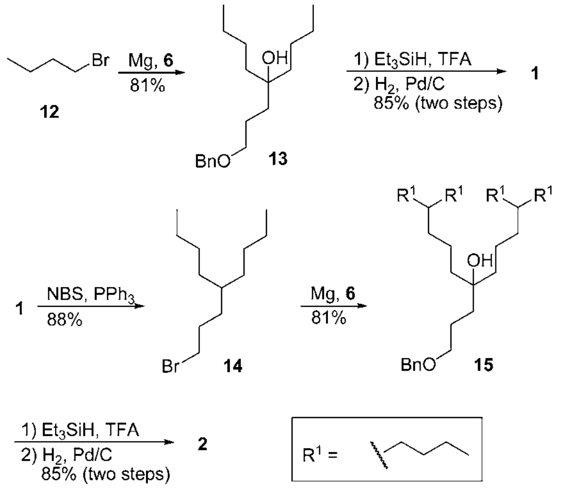
Scheme 1. Synthesis of **6** and **11**



Pd−C and Et_3N under H_2 atmosphere (1 atm)[12] to give diester **11** in 56% overall yield in three steps.

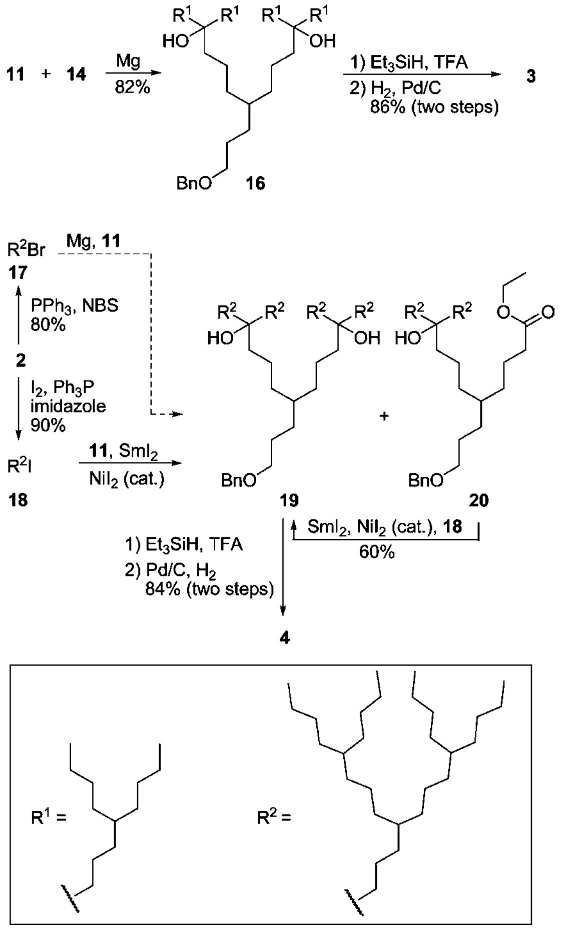
Scheme 2. Synthesis of G1 and G2 Dendrons



With the requisite **6** in hand, we began to accomplish the synthesis of G1 and G2 dendrons **1**[13] and **2** (Scheme 2). First, 1-bromobutane **12** was converted into the corresponding Grignard reagent and then reacted with ester **6** to form tertiary alcohol **13** in 81% yield. The hydroxyl group in **13** was then treated with Et_3SiH and trifluoroacetic acid (TFA) in CH_2Cl_2 at room temperature to give a mixture of deoxygenation as well as elimination products,[14] which could not be separated by column chromatography. The mixture was then hydrogenated in the presence of 10% Pd−C under H_2 atmosphere (1 atm) to produce **1** in 85% yield from **13**. During this transformation, the hydrogenation of the double bond and the removal of the benzyl group were carried out simultaneously. Thus, the first iterative synthetic cycle was completed by three steps, and the G1 dendron was obtained in 69% yield from **12**.

For the synthesis of the G2 dendron, compound **1** was brominated with NBS and PPh_3 in CH_2Cl_2 at −78 °C to produce bromide **14**[13] in 88% yield. The bromide **14** was found to react smoothly with Mg in ether to produce the corresponding Grignard reagent, followed by addition with ester **6** to produce tertiary alcohol **15** in 81% yield. It was noteworthy to comment that Grignard formation could only be initiated when the concentration of the bromide **14** was higher than 1 M. The tertiary hydroxyl group in **15** was then subjected to the same deoxygenation protocol (Et_3SiH/TFA followed by hydrogenation) to produce the G2 dendron **2** in 85% yield from **15**. Again, dendritic growth could be completed in four synthetic steps from **1**. Each of them was efficient, and all of the products formed could be purified by column chromatography.

Scheme 3. Synthesis of G3 and G4 Dendrons



For the synthesis of G3 and G4 dendrons, diester **11** was used as a starting material by an accelerated double-stage convergent method (Scheme 3). Hence, diester **11** was reacted with 5.2 equiv of the Grignard reagent generated in situ from **14** to afford the desired diol **16** in 82% yield. The two tertiary hydroxyl groups in **16** were then deoxygenated smoothly with Et_3SiH/TFA followed by the hydrogenation and concomitant removal of the focal point benzyl group to produce the G3 dendron **3** in 86% yield from **16**. Likewise, the fourth synthetic cycle began with the same G2 alcohol **2**, which was first converted to the corresponding bromide **17** (80% yield) in the presence of NBS and PPh_3. Unfortunately, the Grignard reagent from bromide **17** could not be obtained as the reaction could not be initiated despite many attempts, and only unreacted bromide **17** was recovered. Hence, alcohol **2** was converted to corresponding iodide **18** in 90% yield by treatment with I_2, Ph_3P, and imidazole in dichloromethane. Subsequently, diester **11** was reacted with **18** (6.0 equiv) in the presence of SmI_2 (12.0 equiv) and NiI_2 (cat.) according to the method reported by Namy[15] to produce desired diol **19** (50% yield) together with an incomplete addition product **20** (10% yield). Compound **20** could be converted to **19** in 60% yield by further treatment with **18** (3.0 equiv) in the presence of SmI_2 (6.0 equiv) and NiI_2 (cat.). Finally, the tertiary hydroxyl groups in **19** were cleanly converted to the target G4 dendron **4** in 84% yield from **19**.

All synthesized compounds were characterized by ^1H and ^{13}C NMR, DPET spectroscopy, mass spectrometry, and exact mass measurement (Table 1). ^1H NMR spectra were proved to be very useful in the characterization of the various products. Thus, the chemical shift patterns and relative integration values obtained from ^1H NMR spectra were very useful to ascertain the generation as well as the focal point functional group identity of all compounds (Figure 2). Hence, the diagnostic integration ratio of the surface methyl protons (δ 0.89) to the α-methylene protons (δ 3.64) adjacent to the oxygen atom was 3.0:1 (theoretical 3:1) in **1** (G1-OH), 6.0:1 (theoretical 6:1) in **2** (G2-OH), 12.2:1 (theoretical 12:1) in **3** (G3-OH), and 24.2:1 (theoretical 24:1) in **4** (G4-OH), respectively.

Table 1. Mass Spectral Data of Synthesized Compounds

compound	found	calculated
1[a]	168 $[M - H_2O]^+$	186.1984
2	449.4122[b] $[M + K]^+$	449.4119
3	881.9407[b] $[M + Na]^+$	881.9388
4	1778.9 $[M + Na]^+$	1778.9404
9	582.3779[b] $[M + NH_4]^+$	582.3789
10	325.2371[b] $[M + H]^+$	325.2373
11	393.2633[b] $[M + H]^+$	393.2636
13	275.2368[b] $[M - H_2O + H]^+$	275.2369
15	499.4884[b] $[M - H_2O + H]^+$	499.4873
16	1003.9760[b] $[M + Na]^+$	1003.9756
19	1900.9 $[M + Na]^+$	1900.9772

[a] Known compound. [b] High-resolution mass spectral result.

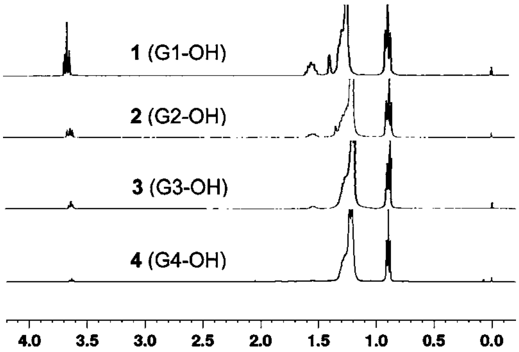


Figure 2. ^1H NMR spectra of **1** (G1-OH), **2** (G2-OH), **3** (G3-OH), and **4** (G4-OH).

In conclusion, we have synthesized a series of amphiphilic dendrons (G1−G4), which possess a highly branched hydrophobic aliphatic hydrocarbon skeleton and a hydrophilic hydroxyl focal point group. The synthesis of the G3 and G4 was highly efficient by a double-stage convergent method. Hence, the G4 dendron could be prepared only in 13 steps from alcohol **5** in 12% overall yield. The key reaction steps involved are a metal-mediated double alkylation to an ester functionality and an Et_3SiH-mediated deoxygenation reaction. This method allowed the straightforward and rapid construction of such dendritic species for their structural and properties investigations. Furthermore, the presence of the hydroxyl or halogen functional group in these dendrons enables their conjugations to other functional moieties to modify their self-assembly properties. These works are currently underway in our laboratory.

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Supporting Information Available: Experimental procedure, characterization for compounds **1**−**4**, **6**, **8**−**11**, and **13**−**20**, and ^1H, ^{13}C NMR, and DEPT 135 spectra of compounds **1**−**4**, **9**−**11**, **13**, and **15**−**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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