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

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ABSTRACT

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 dendrimer⁵ 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

-stage convergent apof steric inhibition in furnished the synthe

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. H₂SO₄) 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. H₂SO₄) 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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Pd-C and Et₃N under H_2 atmosphere (1 atm)¹² to give diester **11** in 56% overall yield in three steps.

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 Et₃SiH and trifluoroacetic acid (TFA) in CH₂Cl₂ 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 H₂ 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 PPh₃ in CH₂Cl₂ at -78 °C to produce bromide 14¹³ 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 (Et₃SiH/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.

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 Et₃SiH/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 PPh₃. 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 I₂, Ph₃P, 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 Namy¹⁵ 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 SmI₂ (6.0 equiv) and NiI₂ (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 ¹³C NMR, DPET spectroscopy, mass spectrometry, and exact mass measurement (Table 1). ¹H NMR spectra were proved

Table 1. Mass Spectral Data of Synthesized Compounds

compound	found	calculated
1^{a}	$168 \ [{ m M}-{ m H_2O}]^+$	186.1984
2	$449.4122^{b} \ [\mathrm{M+K}]^{+}$	449.4119
3	$881.9407^{b} \ [\mathrm{M+Na}]^{+}$	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	$275.2368^{b} [M - H_{2}O + H]^{+}$	275.2369
15	$499.4884^{b} [M - H_2O + H]^+$	499.4873
16	$1003.9760^{b} \ [{ m M+Na}]^+$	1003.9756
19	$1900.9 \ [M + Na]^+$	1900.9772
^a Known compound. ^b High-resolution mass spectral result.		

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



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

3 (G3-OH), and 24.2:1 (theoretical 24:1) in **4** (G4-OH), respectively.

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 Et₃SiH-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, ¹³C 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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