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Synthesis of difunctionalized dendrimers: an approach to main-chain poly(dendrimers)

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Abstract—Synthesis of benzyl ether dendrimers that are difunctionalized at their peripheries are described. These dendrimers should form the basis for a new class of main-chain dendritic polymers. The steric protection afforded at higher generation during the synthesis allows for facile access to these selectively functionalized dendrimers. © 2002 Elsevier Science Ltd. All rights reserved.

Dendrimers have attracted a lot of attention among chemists over the past decade due to the potential applications in several areas of chemistry.[1] For example, dendritic architectures have found use in areas such as catalysis,[2] biomimetics,[3] supramolecular chemistry,[4] surface chemistry,[5] light harvesting materials,[6] and medicine.[7] The need for synthesizing new dendrimers has increased dramatically with such application-oriented interests in this class of macromolecules. We have been interested in synthesizing dendrimers that have only two reactive functional groups in their periphery. Such dendrimers are useful as monomer units in new polymeric architectures, as schematically illustrated in Fig. 1.

The supramolecular architecture arising from such polymers should be interesting. For example, Schlüter and co-workers have incorporated dendrons as side chains of polymers such as polystyrene and poly(p-phenylene) and have observed the formation of nanocylinders.[8–10] This observation sparked our interest in probing dendritic architectures in which the dendrimer is part of the main chain. In particular, we are interested in synthesizing amphiphilic block co-polymers such as the types shown in Fig. 1. To achieve these main-chain polymeric dendrimers, it is necessary that we specifically functionalize the dendrimers, such that only two of the peripheral monomers have polymerizable functional groups. For this purpose, between the two limiting synthetic approaches, convergent synthesis is preferred due to the control it provides.[11] Fréchet and co-workers have developed protocols where they synthesized dendrimers with limited number of cyano groups in the dendritic periphery.[12,13] More recently, Schlüter and co-workers have developed a similar strategy in which bromo functionalities were incorporated in specific locations of a benzyl ether dendrimer.[14] Also notable is a particularly elegant approach developed by Simanek and co-workers, where the synthetic viability of incorporating functionalities in specific locations of a dendrimer is high.[15] However, we embarked on developing the synthetic protocols outlined here, because of the following: (a) We are interested in developing synthetic methodology for benzyl ether dendrimers, a backbone that we have used for our new amphiphilic dendrimer design.[16] Our long-term goal is to synthesize polymers of the type shown in Fig.

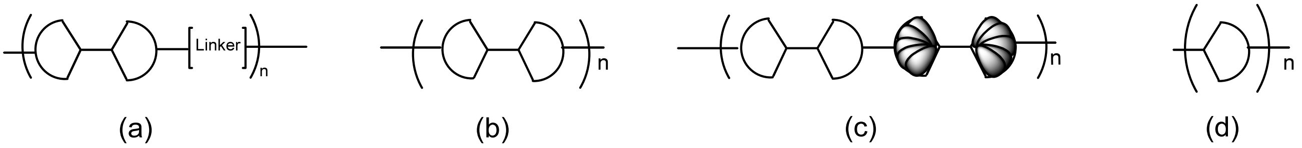

Figure 1. Polymer architectures achievable with difunctionalized dendrimers: (a) alternating main-chain copolymer of a dendrimer and a linear chain; (b) polymer with dendrimer repeat units; (c) polymers containing two different dendrimers as alternating comonomers; (d) polymerized dendrons.

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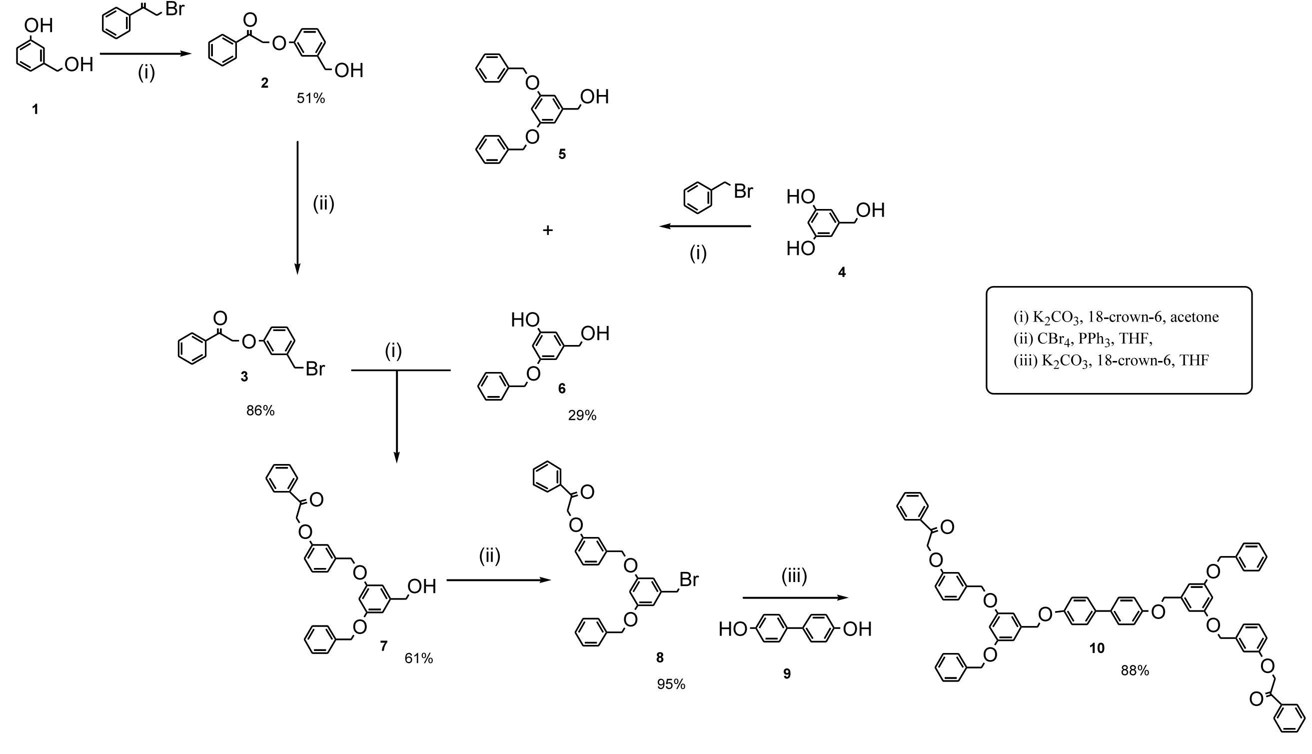
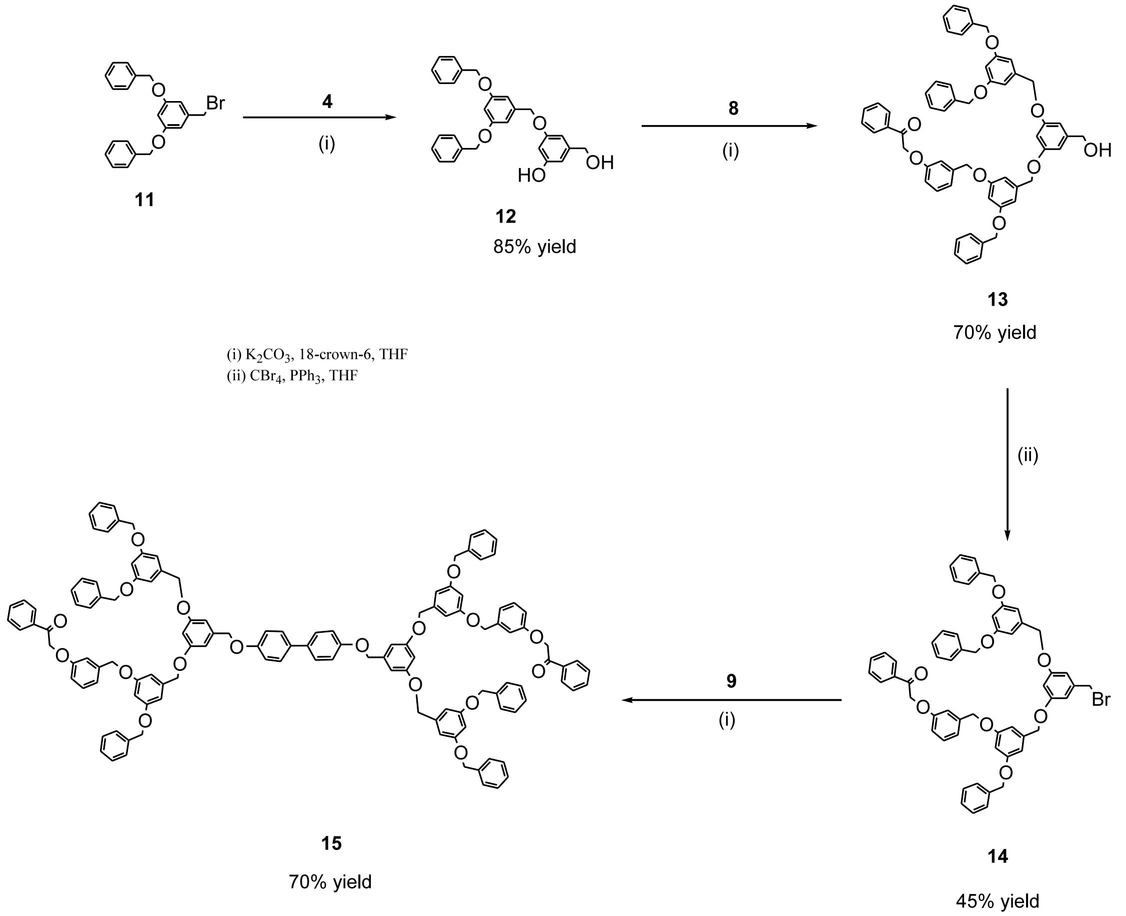
1 with these amphiphilic dendrimers. (b) We are interested in incorporating phenolic functional groups at specific locations in the periphery, since these are versatile polymerizable functionalities; for example, they can react with diisocyanates. Some of the poly(dendrimer) architectures that could be synthesized with our current approach are represented in Fig. 1. The difunctionalized dendrimers can be polymerized by reacting with a diisocyanate comonomer. This comonomer could be a hydrophilic oligomer, which can generate an alternating copolymer containing a hydrophobic dendrimer and a hydrophilic linear oligomer as the repeat units (structure a, Fig. 1). Alternately, the comonomer could be a short hydrophobic linker such as phenyldiisocyanate, which should afford essentially a homopolymer (structure b, Fig. 1). It is also possible to incorporate complementary reactive functionalities in two different difunctionalized dendrimers and copolymerize them to obtain alternating copolymers, as shown by the structure c in Fig. 1. Since we are synthesizing benzylether based dendrimers, it is also possible to envision using a dendron that has a hydroxymethyl group at the core and a single phenolic group at the periphery to synthesize poly(dendrons) as illustrated by the structure d in Fig. 1.

We report here the synthesis of two difunctionalized dendrimers. The functionalities that we have incorporated in these benzyl ether dendrimers are phenolic functionalities. Since the assembly of the benzyl ether dendrimers themselves heavily uses phenolic groups,[17] we protected this functionality. First, we attempted the use of *tert*-butyldimethylsilyl moiety as the protecting group. However, we noted that these functional groups are unstable to the alkylation conditions of potassium carbonate in acetone, THF or DMF. Therefore, we used phenacyl group as the protecting group. The phenacyl group has been previously demonstrated by Hawker to be stable under benzyl ether dendrimer assembly conditions.[18] The synthesis of the first generation dendrimer is shown in Scheme 1. Treatment of phenacyl bromide with 3-hydroxybenzyl alcohol (**1**) afforded the phenacyl protected product **2** in 51% yield. The hydroxymethyl group of **2** was converted to bromomethyl group to afford **3** in 86% yield. Treatment of 3,5-dihydroxybenzyl alcohol (**4**) with just 1 equiv. of benzyl bromide afforded the monosubstituted product **6** in 29% yield. The rest of the product mixture contained the disubstituted product **5**. Compound **5** was carried over to assemble the second-generation dendrimer (see below). The reaction between **3** and **6** in the presence of potassium carbonate in acetone afforded the product **7** in 61% yield. The hydroxymethyl moiety of **7** was converted to bromomethyl moiety using triphenylphosphine and carbon tetrabromide to afford **8** in 95% yield. Treatment of the compound **8** with 0.5 equiv. of 4,4′-dihydroxybiphenyl (**9**) in THF afforded the difunctionalized first generation dendrimer **10**[20] in 88% yield. When this reaction was carried out in acetone, the yield of the product **10** was not optimal. Improved yields were realized when the reaction was carried out in THF. Deprotection of the phenacyl group was facilitated by treating compound **10** with zinc and acetic acid to afford the corresponding diphenolic dendrimer.

The assembly of the second generation of the difunctionalized dendrimer is shown in Scheme 2. The disub-



Scheme 1.



Scheme 2.

stituted by-product **5** was treated with triphenylphosphine and carbon tetrabromide to afford the bromomethyl functionalized compound **11**. Treatment of **11** with 1 equiv. of **4** afforded the monosubstituted product **12** in 85% yield. Note that a similar reaction with 1 equiv. of benzyl bromide in Scheme 1 afforded only 29% yield. The higher yield obtained in the synthesis of **12** is attributed to the increased steric protection of the second phenolic group. After the first dendron is substituted on to one of the phenolic groups of **4**, the second phenolic group becomes less reactive due to the steric hindrance between the incoming dendron and the one already substituted. Treatment of the compound **12** with **8** in the presence of potassium carbonate afforded **13** in 70% yield. Conversion of the hydroxymethyl group to bromomethyl group was accomplished using triphenylphosphine and carbon tetrabromide to afford **14** in 45% yield. Treatment of compound **14** with 0.5 equiv. of **9** afforded the second-generation difunctionalized dendrimer **15** in 70% yield.[20]

In summary, we have outlined the synthesis of polymerizable, difunctionalized dendrimers. For this synthesis to be facile, it is necessary to have one of the two phenolic groups in dihydroxybenzyl alcohol more reactive than the other. Although the synthesis of the first generation dendrimers afforded statistical mixture of the mono- and disubstituted products, it is clear that monosubstitution during the synthesis of higher generation dendrimers is easier due to steric protection. We observed this phenomenon with even higher generation dendrons in other systems.[19] The unique topography of the difunctionalized dendritic monomers reported herein should permit the generation of novel main-chain dendritic polymers. Progress towards achieving such polymers is currently under way in our laboratories.

Acknowledgements

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20. Characterizing data for compound **10**: ^{1}H (400 MHz, CDCl$_3$): δ 7.99–7.94 (m, 4H), 7.62–7.56 (m, 2H), 7.46–7.24 (m, 20H), 7.06–7.00 (m, 4H), 6.99 (s, 2H), 6.96 (s, 2H), 6.90–6.86 (m, 2H), 6.69–6.67 (m, 2H), 6.66–6.64 (m, 2H), 6.54–6.52 (m, 2H), 5.21 (s, 4H), 4.98–5.05 (b, 12H). ^{13}C (100 MHz, CDCl$_3$): δ 194.6, 160.4, 160.3, 158.5, 158.0, 139.8, 138.8. 137.0, 134.7, 134.2, 133.9, 130.0, 129.1, 128.8, 128.4, 128.3, 128.0, 127.8, 120.8, 115.4, 114.6, 114.1, 106.6, 106.5, 101.7, 71.0, 70.3, 70.2, 70.0. MALDI-ToF: Mass of $C_{70}H_{58}O_{10}$ was calculated to be 1058.4. Found 1081.2 (M+Na$^+$).

    Characterization data for compound **15**: ^{1}H (400 MHz, CDCl$_3$): δ 7.97 (bd, 4H), 7.58 (m, 2H), 7.49–7.25 (m, 40H), 7.01–6.94 (m, 8H), 6.87 (bd, 2H), 6.62–6.70 (m, 12H), 6.58–6.52 (m, 6H), 5.24 (s, 4H), 4.99 (s, 16H), 4.98–4.92 (m, 12H). ^{13}C (100 MHz, CDCl$_3$): δ 194.8, 160.4, 160.3, 139.5, 137.0, 134.2, 130.1, 129.1, 128.9, 130.1, 129.1, 128.9, 128.4, 128.3, 127.9, 127.8, 115.4, 114.1, 106.6, 101.8, 70.3, 70.2, 70.0. MALDI-ToF: Mass of $C_{126}H_{106}O_{19}$ was calculated to be 1906.7. Found 1929.5 (M+Na$^+$).