Convergent synthesis and 'surface' functionalization of a dendritic analog of poly(ethylene glycol)

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Aliphatic polyether dendrons exhibit easily modified surface functionality.

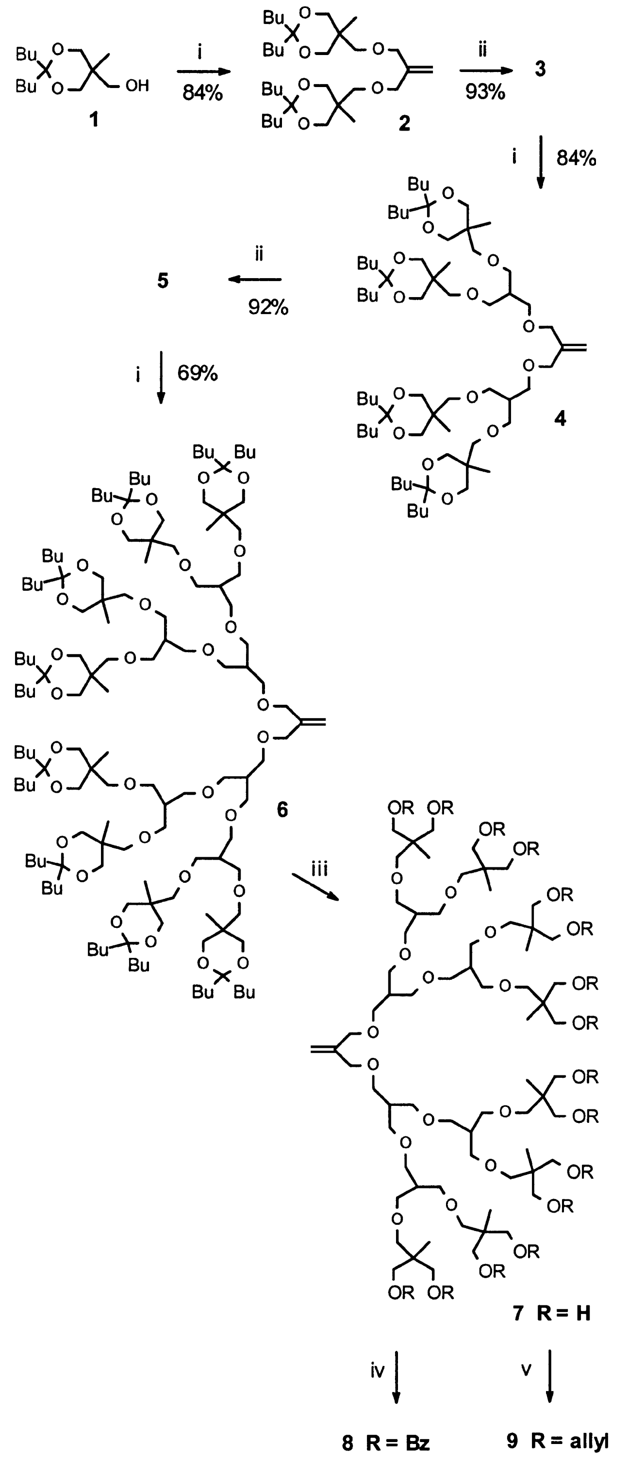
Because of its water solubility and non-ionic character, linear poly(ethylene glycol) has been utilized widely for applications ranging from surfactants to biocompatible drug solubilizers.[1] Although a variety of dendrimers have been reported to date,[2] few possess the structural features that would endow them with analogous solubility properties. An early, imaginative, divergent approach towards aliphatic polyether dendrimers reported by Hall *et al.* over a decade ago[3] has not been widely used due to synthetic complications. We have recently reported an efficient convergent route to dendrons containing an aliphatic polyether backbone and peripheral benzyl ether protecting groups.[4] Now, we report a very versatile convergent synthesis of hydroxy-terminated aliphatic polyether dendrons that may be considered dendritic analogs of poly(ethylene glycol) because of the 2 : 1 carbon : oxygen ratio in the branched repeat unit. These dendrons may prove valuable in polymer therapeutics as a result of their compact shape, high polarity, and multiple chain end functionalities.[5]

The hallmark of a successful convergent synthesis is an aptly chosen monomer that enables simple, high-yielding activation and growth steps. Our monomer, 3-chloro-2-chloromethylprop-1-ene, is well suited for high-yield Williamson coupling with two dendritic alcohols, since its symmetrical and activated allylic functionalities afford the same product regardless of displacement mechanism (S_N1, S_N2, or S_N2'). The resulting olefinic dendron can then be converted to the primary dendritic alcohol in high yield and with excellent regioselectivity *via* standard hydroboration reaction conditions. Further growth results from a repetitive cycle of coupling and activation reactions to afford larger dendrons.

Ketals were chosen as the surface protecting groups primarily because they are unaffected by the basic conditions required throughout the synthesis. While several acetals and ketals were tested, the lipophilic nature of the dibutyl ketal protecting group confers upon these dendrons excellent solubility in hexanes, thus facilitating their purification by chromatography. In addition, these protecting groups allow a facile deprotection under mildly acidic conditions, exposing terminal hydroxy functionalities that can be further modified if desired.

The synthesis of the first generation terminal moiety, [G-1]-ol, was achieved by protecting two of the hydroxy functionalities of 1,1,1-tris(hydroxymethyl)ethane with nonan-5-one in the presence of $BF_3\cdot OEt_2$.[6] Reaction of the [G-1]-ol, **1**, NaH, and 3-chloro-2-chloromethylprop-1-ene, in the presence of catalytic amounts of KI and 18-crown-6 afforded the second generation alkene, **2**, in 84% yield. This alkene was converted effectively to the activated primary [G-2]-ol, **3**, through hydroboration with 9-BBN,[7] followed by oxidation in alkaline H_2O_2 (92%). Repetition of the coupling and activation steps led to the preparation of higher generation dendrons up to [G-4]-ene, **6** (Scheme 1). All of the materials were purified by flash column chromatography on silica gel using EtOAc–hexane as eluent and were obtained as transparent, viscous oils.

Identification of the focal functionality by NMR and FT-IR facilitated the characterization of these dendritic compounds. In



Scheme 1 *Reagents and conditions*: i, NaH, THF, KI, 18-crown-6, $(ClCH_2)_2C{=}CH_2$; ii, 9-BBN, THF, then H_2O_2–NaOH; iii, H^+ Resin, MeOH; iv, BzCl, pyridine; v, allyl bromide, NaH, DMA–THF.

Table 1 MS and SEC data for second, third, and fourth generation dendrons

Compound	Calculated MW	FAB/MALDI MW	SEC^a M_n	PDI
[G-2]-ene	540.8	540.7	600	1.01
[G-2]-ol	558.8	558.7	720	1.00
[G-3]-ene	1169.8	1170	1400	1.00
[G-3]-ol	1187.8	1189	1420	1.00
[G-4]-ene	2427.6	2429	2450	1.01
[G-4]-ol	2445.6	2446	2470	1.01

[a] SEC analysis was performed using THF as the eluent and was calibrated against polystyrene standards.

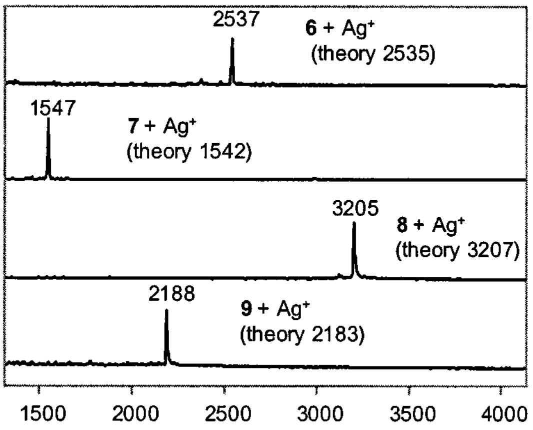


Fig. 1 MALDI-TOF MS data for the deprotection and derivatization of [G-4]-ene.

$CDCl_3$ the dendritic alkenes showed a singlet at δ 5.15 in the ^1H NMR spectrum, peaks at δ 143 and 113 in the ^{13}C NMR spectrum, and an absorbance at 1650–1660 cm^{-1} in the FT-IR spectrum, corresponding to the focal carbon–carbon double bond. The dendrons with focal hydroxy functionalities exhibited a broad absorbance at 3300–3500 cm^{-1} in the FT-IR spectrum, as well as a triplet at δ 2.7 in the ^1H NMR spectrum and a peak at δ 63 in the ^{13}C NMR spectrum corresponding to the adjacent methylene. The integration ratio between the peripheral acetals and the focal functionality verified both the generation of the dendron, and the retention of all protection groups.

Molecular weights of the dendritic molecules were monitored by mass spectrometry (MS) using fast atom bombardment (FAB) MS for those below 1000 Daltons, and matrix assisted laser desorption ionization time of flight (MALDI-TOF) MS for those above 1000 Daltons. In addition, the narrow signal obtained by size exclusion chromatography (SEC) further confirmed the monodisperse nature of the compounds, as expected in a convergent dendrimer synthesis (Table 1).

Deprotection of the chain-ends of the dendrons was achieved using an acid cation exchange resin. Because of the highly polar character of the resultant hydroxy-terminated dendron, and the insolubility of the polymeric catalyst, the product, **7**, could be isolated in near quantitative yield by a simple filtration of its methanol solution. At the fourth generation, these hydroxy-terminated compounds exhibited the desired water solubility regardless of the focal functionality. This was expected as previous studies of dendrimers' physical properties verified that the solubility of dendritic polymers is dominated at higher generation by the peripheral functionalities.[8]

The high reactivity of the 'surface' hydroxy functionalities was confirmed through simple modification reactions (Scheme 1). For example, reaction of the sixteen free hydroxy groups of $(OH)_{16}$[G-4]ene, **7**, with a two-fold excess of BzCl in pyridine afforded the fully esterified product, **8**. Similarly, a nucleophilic substitution reaction was performed with **7**, NaH, and a two-fold excess of allyl bromide to produce the fully allylated dendron, **9**. Both reactions appeared to be quantitative, as no partially functionalized dendrons were isolated by chromatography or observed in the MALDI-TOF MS of the crude reaction mixture.

Characterization of the surface modified dendrons was also achieved by monitoring changes in functionality. The end-deprotected dendrons exhibited a broad absorbance at 3300–3500 cm^{-1} in the FT-IR spectrum corresponding to the multiple hydroxy functionalities. Conversion of the surface groups to benzoate esters resulted in the appearance of a characteristic narrow carbonyl absorbance at 1724 cm^{-1} in the FT-IR spectrum, as well as aromatic resonances in the ^1H NMR, while the allyl ethers exhibited an alkene absorbance at 1646 cm^{-1} in the FT-IR spectrum as well as additional resonances for the vinyl protons (δ 5.2, 5.3, and 5.9) in the ^1H NMR. MALDI-TOF MS data of both functionalized dendrons exhibited a single peak with molecular weights corresponding closely to the expected values (Fig. 1.)

We believe that the unique and high yielding chemistry used in the preparation of these dendrons, as well as the flexibility of their functionalization at the focal point and at the chain ends, makes them suitable for broad use as building blocks in a variety of dendritic structures where they will complement the widely used aromatic polyethers we developed earlier.[9]

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