A Convergent Route to Novel Aliphatic Polyether Dendrimers

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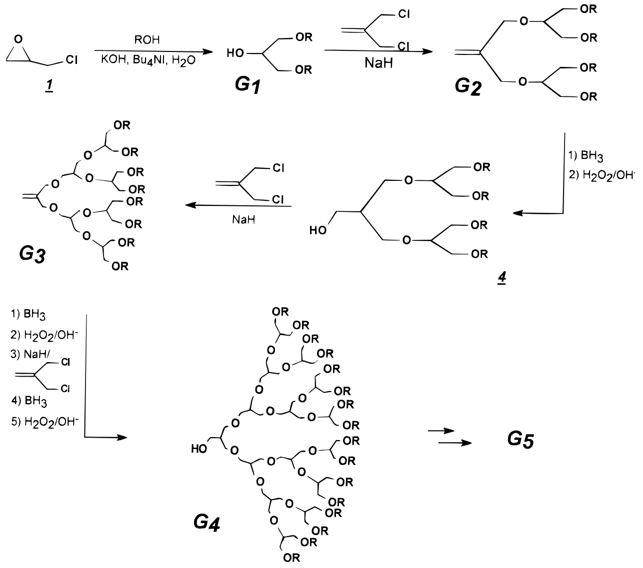
Interest in dendrimers has increased almost exponentially in the past few years as the unique features of these globular molecules are better understood and their potential applications are explored.[1] Dendrimers that are currently available include aliphatic amides, aliphatic amines, aliphatic esters, aromatic hydrocarbons, aromatic ethers, and aromatic esters.[2] The convergent method of synthesis[3] we first introduced in 1989 has proven to be very versatile and the aromatic polyether dendrons[3] with their distinct functionalities at their focal point and chain ends have been widely used[4] in the preparation of a broad array of functional dendritic structures.

This communication describes the convergent synthesis of a new family of dendrimers with an aliphatic polyether backbone. This new class of well-defined dendrimers has great potential as a result of the combination of its inert, low absorbance building blocks, multiple reactive chain ends, and uniquely functionalized focal point. In addition, these dendrimers with their polar 2-hydroxymethyl-1,3-propanediol building blocks might show improved biocompatibility and be rendered water-soluble or water-dispersible by varying their surface functionality

Methallyl dichloride,[5] readily obtained from Pentaerythritol, was chosen as the monomer because its allylic functionality provides for the facile nucleophilic substitution of its two electrophilic sites, while the double bond itself acts as a masked functionality for the subsequent activation-growth steps. Therefore, in this approach the nucleophilic displacement of the allylic chlorides in a Williamson ether synthesis is the growth step, while the derivatization of the olefinic double bond is the activation step. This activation may be accomplished either via hydroboration−oxidation to afford a primary alcohol or by ozonolysis followed by reduction to give a secondary alcohol. Dendrons up to generation 5 have been prepared in high yields through a sequential growth and activation protocol. A divergent route to analogous polyethers proposed earlier[6] suffered from incomplete coupling reactions due to excessive crowding.

Scheme 1. Synthesis of Dendrons [G-2] through [G-5]



Scheme 1 shows the synthesis of dendrons [G-2]-ene to [G-5]-ol. Compound **1** was prepared by reaction of 2 equiv of benzyl alcohol with epichlorohydrin.[7] This secondary alcohol with its single branch point serves as the activated [G-1]-ol dendron. Benzyl ether was chosen as the chain-end moiety both for its ability to serve as an NMR "tag" for the characterization of the growing molecule and for its ease of removal by hydrogenolysis. Etherification of methallyl dichloride by the [G-1]-ol was achieved by using NaH in THF. The stoichiometry of the reagents determines the product that is obtained. Using 1.1 equiv of the alcohol results in quantitative conversion of the methallyl dichloride to the [G-2]-ene, whereas using 2 equiv of methallyl dichloride leads to the formation of the monosubstituted product in high yield. This mono-etherification reaction constitutes a useful approach to unsymmetrical dendrons[8] for the construction of complex dendritic architectures with different end groups or building blocks.

The [G-2]-ene was easily separated from the excess alcohol starting material by flash chromatography as the two compounds have vastly different polarities, thus providing the desired product in high yield (90−95%). Table 1 lists the yields obtained in the synthesis of dendrons [G-2]-ene through [G-5]-ol.

Activation of the focal point of the [G-2]-ene was achieved by regioselective hydroboration−oxidation[9] to afford the [G-2]-ol. When the borane:THF complex was used as the hydroboration reagent, some unwanted tertiary alcohol side-product was formed along with the desired primary alcohol. Using the more sterically hindered 9-BBN as the borane reagent essentially eliminates this side product. The desired primary alcohol was then purified by flash chromatography on silica gel with use of a mixture of hexanes and ethyl acetate as the eluent affording isolated yields of 80 to 90%. The two-step nucleophilic substitution−hydroboration−oxidation sequence was repeated to prepare dendrons up to the 5th generation in multigram quantities. As the generation increases, the increased steric crowding of the focal point only marginally affects the yield of the desired product in the growth step (Table 1). This small decrease may in part be attributable to chromatographic losses as the resolution between [G-*n*]-ol and

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Table 1. Yields for the Preparation and Activation of Dendrons [G-2] through [G-5]

generation	growth step	activation step
[G-2]	95	90
[G-3]	95	86
[G-4]	90	88
[G-5]	85	85

[G-n+1]-ene decreases with increasing “n”. The yields obtained in the activation step did not vary appreciably with increasing generation.

The characteristic signals in the ^{1}H NMR spectra of the functional group at the focal point of the dendrons facilitate identification of both the alkene and the alcohol. The spectrum of the alkene shows a singlet at δ 5.1 ppm corresponding to the terminal olefin and another singlet at δ 4.1 ppm corresponding to the two allylic ether methylene groups. Integration of these two singlets versus the singlet corresponding to the benzylic chain end protons at δ 4.45 ppm serves as a reliable handle to assist in characterizing all of the alkene dendrons.

The monosubstituted product also has characteristic peaks corresponding to the alkene and allylic protons. The olefinic protons appear as two sharp singlets at δ 5.2 and δ 5.15 ppm and the allylic protons appear as singlets at δ 4.05 and δ 4.15 ppm.

Formation of the alcohols was accompanied by the disappearance of the olefinic and allylic protons and the appearance of a triplet at 2.8 ppm corresponding to the alcoholic proton and a multiplet at 2.1 ppm corresponding to the methine proton. Once again, integration of the methine protons versus the benzylic protons was used to characterize the primary alcohols.

Molecular weight determinations were carried out with FAB MS, MALDI-TOF MS, and SEC. Dendrons up to the 3rd generation were analyzed by both FAB MS and MALDI-TOF MS while 4th and 5th generation dendrons could only be analyzed by MALDI-TOF MS. The MALDI-TOF MS were recorded in α-cyano-4-hydroxycinnamic acid matrix along with silver trifluoroacetate without further purification of the material. Both techniques confirmed the molecular weights of the dendrons (Figure 1).

As expected, the molecular weights measured by size exclusion chromatography (SEC vs polystyrene standards) were lower than the calculated values and the differences between measured and calculated values increased with generation number. This has been well documented in the dendrimer literature and is attributed to the compact nature of the dendrimers.[3,10] Given the greater size accuracy of the dendrons when compared to the polymer standards used for SEC, it is not surprising that the polydispersities measured were all below 1.01. Table 2 compares the calculated and experimental molecular weights of [G-3]-ene to [G-5]-ol.

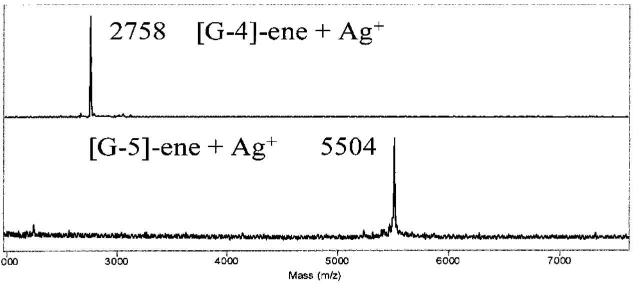

Figure 1. MALDI-TOF spectra of [G-4]-ene and [G-5]-ene.

Table 2. MALDI-TOF MS and SEC Data for Dendrons [G-3]-ene to [G-5]-ol

compd	expected MW	MALDI MW	SEC MW[a]
[G-3]-ene	1281	1279	1229
[G-3]-ol	1299	1299	1200
[G-4]-ene	2651	2650	2252
[G-4]-ol	2669	2669	1820
[G-5]-ene	5391	5396	3695
[G-5]-ol	5409	5414	3500

[a] Relative molecular weights by size exclusion chromatography with polystyrene standards.

To confirm the ready accessibility of the focal point of the higher generation dendrons toward other low molecular weight reagents, a hydrosilylation with trimethoxysilane was carried out. This reaction proceeds quantitatively under typical hydrosilylation conditions.

In conclusion, we have presented the convergent synthesis of a new class of aliphatic polyether dendrons using Williamson etherification chemistry. Work is currently in progress to attach these dendrons to an aliphatic multifunctional core molecule to make wholly aliphatic polyether dendrimers. The ability to make the focal point of the core active toward both electrophilic and nucleophilic substitutions as well as hydrosilylation and Heck type coupling reactions adds versatility to the choice of the core molecule and the chemistry that may be employed to incorporate these dendrons into larger structures.

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Supporting Information Available: Experimental procedures for the synthesis of [G-2]-ene and [G-2]-ol and analytical data (^{1}H NMR and FAB MS) (6 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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