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A New Approach to Heterofunctionalized Dendrimers: A Versatile Triallyl Chloride Core

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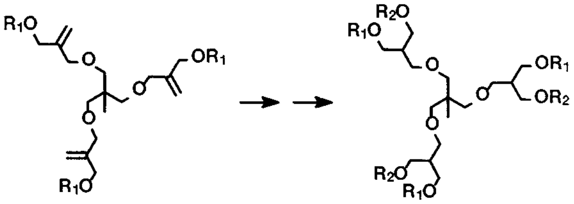
ABSTRACT



A reactive triallyl chloride moiety was prepared as a suitable core for aliphatic polyether dendrons. In addition to allowing access to fourth generation dendrimers, this core contains three alkene functionalities that can be modified after dendrimer formation and used for further dendritic growth.

Although the iterative nature of dendrimer[1] preparation involves a significantly more effort-intensive synthesis than linear or hyperbranched polymers, it also enables unparalleled control over the placement of specific functional moieties within a well-defined macromolecular structure.[2] Aliphatic dendrimers with uncharged functionalities are especially attractive for use as polyvalent drug delivery vehicles to which drug, targeting, or solubilizing moieties can be attached. Recently, our research group has reported the synthesis and functionalization of a chemically rugged aliphatic polyether dendron.[3] Because of the strong aliphatic ether linkages, these dendrons can withstand a wide range of chemical conditions, including acidic, basic, reducing, and oxidizing environments. The versatility of this scaffold was previously demonstrated through a wide range of chemical modifications of the periphery of aliphatic polyether dendrons, including the synthesis and orthogonal functionalization of hybrid dendrons.[3] We now describe a new synthetic method for accessing heterogeneous dendrimers utilizing both the convergent and divergent growth approaches.

Because the previously reported aliphatic polyether dendrons[3] possess a focal hydroxyl functionality when activated, a core was desired with highly activated sites for efficient nucleophilic displacement. The tris-allylic chloride core molecule, **1**, was synthesized by reaction of 1,1,1-tris(hydroxymethyl)ethane with an excess of 3-chloro-2-chloromethyl-1-propene in dimethyl-formamide. Although a number of byproducts are obtained in this reaction between two polyfunctional compounds, the intended tris-chloride product could be readily isolated in 20% yield by flash chromatography. The three double bonds of **1** serve the dual purpose of activating the chlorides toward nucleophilic substitution while also preventing elimination. After suc-

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[1] (a) Tomalia, D. A.; Baker, H.; Dewald, J.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. *Polym. J.* **1985**, *17*, 117. (b) Newkome, G. R.; Yao, Z.; Baker, G. R.; Gupta, V. K. *J. Org. Chem.* **1985**, *50*, 2003. (c) Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638.

[2] (a) Hecht, S.; Fréchet, J. M. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 74. (b) Grayson, S. M.; Fréchet, J. M. J. *Chem. Rev.* **2001**, *101*, 3819. (c) Matthews, O. A.; Shipway, A. N.; Stoddart, J. F. *Prog. Polym. Sci.* **1998**, *23*, 1. (d) Chow, H. F.; Mong, T. K.; Nongrum, M. F.; Wan, C. W. *Tetrahedron* **1998**, *54*, 8543 and references therein.

[3] Grayson, S. M.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2000**, *122*, 10335

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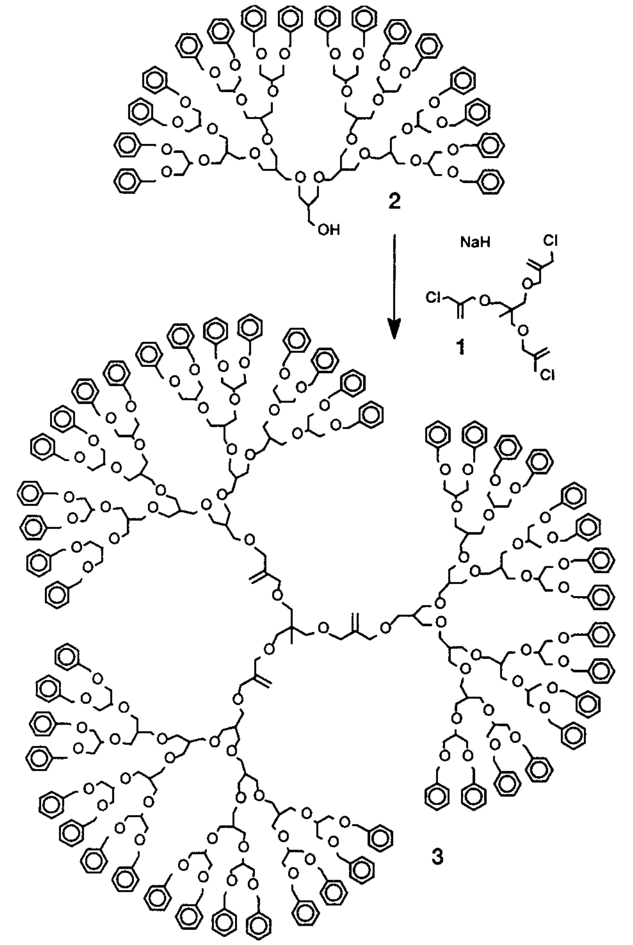
Scheme 1



cessful coupling with three dendrons, the resultant dendrimercontains three double bonds near the core that can either be reduced to yield a fully aliphatic compound or modified to incorporate multiple functionalities at the core of the dendrimer. A few of these chemical transformations have been investigated to probe the accessibility of these core functionalities.

The second through fourth (**3**) generation benzyl-protected dendrimers were prepared (Scheme 1) by coupling the corresponding alkoxide dendron, created in situ by reaction of dendron **2** with NaH, to the tris-allylic chloride core, **1**. Although these reactions could be carried out in THF, reaction rates and yields were improved, especially for the higher generations, when dimethyl-acetamide was used as the solvent. The dendrimers were isolated by column chromatography on silica gel, providing a pure macromolecule, as verified by both MALDI-TOF MS and SEC. As a result of increasing steric congestion, as well as more difficult chromatographic separation on silica gel, the yield obtained during the dendrimer coupling reaction decreased with increasing generation. Attempts to form the dendrimers from the ketal-protected dendrons were also successful (Scheme 2), but their chromatographic purification proved to be more demanding at higher generations because of the modest differences in polarity between the desired product and starting materials.

After isolating the dendrimers, a variety of core modification reactions were attempted to demonstrate the reactivity of the focal functionalities. Catalytic hydrogenolysis of the benzyl-protected dendrimers (e.g. compound 3) successfully removed the peripheral protecting groups and also led to the reduction of the core alkene functionalities, as ^{1}H NMR of the reaction mixture showed no proton resonances downfield of 4 ppm. Attempts to convert the double bond to a hydroxyl functionality resulted in low yields of the triol for the second generation dendrimer and no observed reaction for the fourth generation.

The ketal-protected dendrimers proved to be more amenable to core functionalization (Scheme 2). Treatment of the second generation dendrimer, **5**, with 9-BBN, followed by oxidation with hydrogen peroxide afforded triol, **6**, in a 73% isolated yield. The three hydroxyl groups at the core of the dendrimer provided a unique functional handle to probe further modification of the core of these dendrimers.

The three primary alcohols near the core of **6** provide an ideal substrate for the divergent grafting of polyester dendrons, while the functional groups contained within the ketal-protected dendrons[4] were compatible with the conditions required for growth and deprotection. The resultant hybrid dendrimer exhibits a radially segmented architecture,[5] with alternating ether and ester wedges (Scheme 2). Though Caminade, Majoral, and co-workers originally reported the concept of grafting dendrons from within a dendrimer,[6] this synthesis represents the first time both convergent and divergent dendrimer growth strategies have been combined to assemble hybrid dendrimers.

The divergent grafting[4] was initiated by esterification of **6** with 1.2 equiv of acid anhydride **4** per hydroxyl group and a catalytic amount of DMAP in dichloromethane to yield **7**. The excess anhydride was quenched for 6 h with a water/pyridine solution, and the resultant carboxylic acid byproduct and DMAP catalyst were removed by successive washes with aqueous sodium bicarbonate and sodium sulfate. The product was isolated from trace amounts of dendritic byproducts by chromatography on silica gel. The benzylidene protecting groups of the ester wedges of **7** could then be quantitatively removed by hydrogenolysis with 10% Pd/C catalyst and 10 atm of hydrogen gas. Basic alumina was added to the reaction mixture to prevent the removal of the ketal protecting groups on the ether wedges.[3] The product, **8**, could be isolated from the catalyst by simple filtration over Celite. The hybrid second generation poly-

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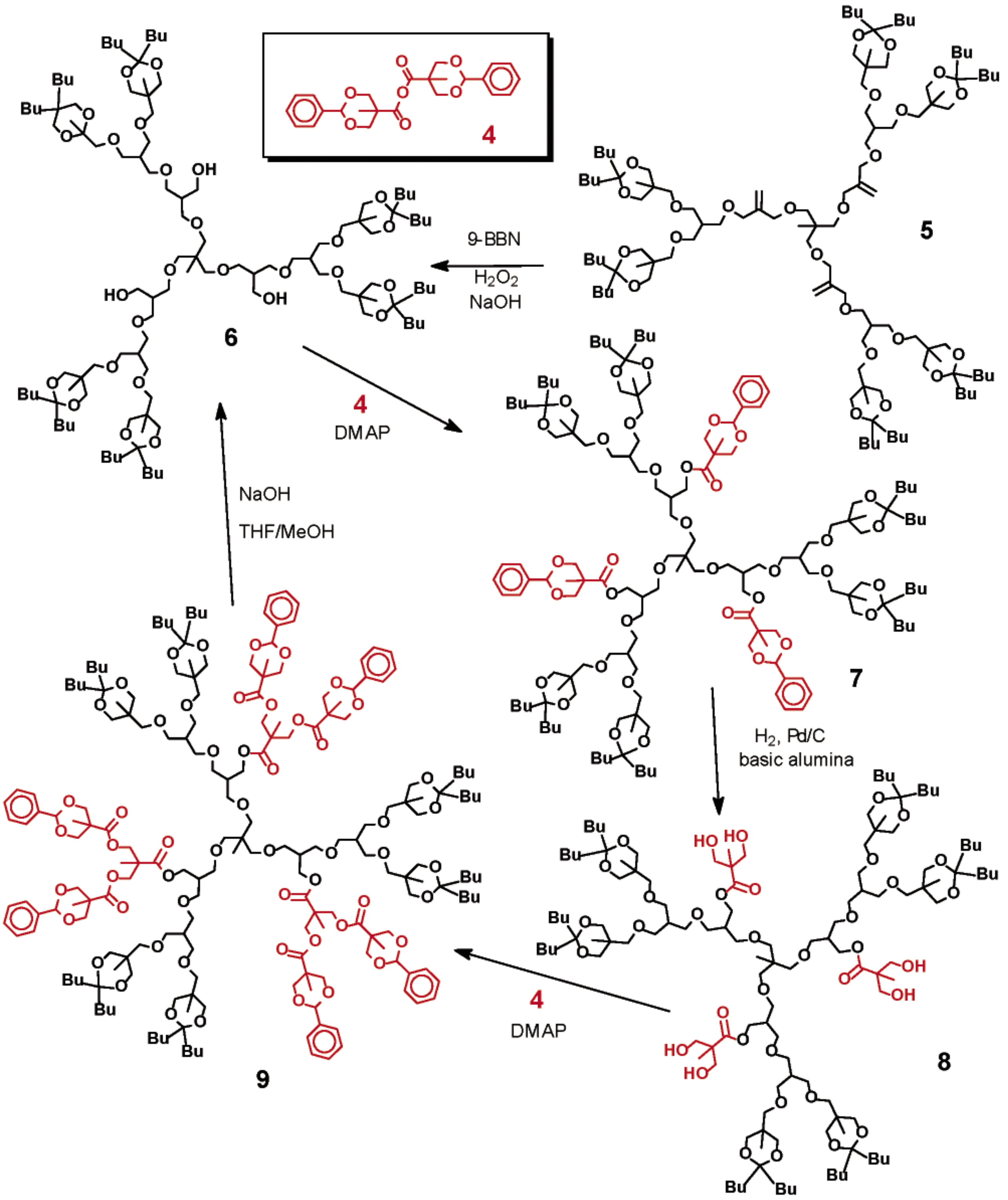
(4) Ihre, H.; Padilla de Jesús, O. L.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2001**, *123*, 5908. Ihre, H. R.; Padilla de Jesús, O. L.; Szoka, F. C., Jr.; Fréchet, J. M. J. *Bioconj. Chem.* **2002**, *13*, 443. Padilla de Jesús, O. L.; Ihre, H. R.; Gagne, L.; Fréchet, J. M. J.; Szoka, F. C., Jr. *Bioconj. Chem* **2002**, *13*, 453.

(5) Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1992**, *114*, 8405.

(6) Maraval, V.; Laurent, R.; Donnadieu, B.; Mauzac, M.; Caminade, A.-M.; Majoral, J.-P. *J. Am. Chem. Soc.* **2000**, *122*, 2499. Galliot, C.; Larre, C.; Caminade, A.-M.; Majoral, J.-P. *Science* **1997**, *277*, 1981.

Scheme 2



ether−second generation polyester dendrimer **9** could be obtained by repetition of the esterification conditions mentioned above.

As expected, the ester portions of the dendrimer, **9**, were significantly more labile than the ether portions and could be selectively degraded by hydrolysis in 0.5 M sodium hydroxide in a solution of 50/50 methanol/tetrahydrofuranto yield the parent dendrimer, **6**. The reaction was rapid, taking only a few hours to complete, and could be easily monitored by MALDI-TOF MS (Figure 1). Examination of the mass spectra revealed that the ester dendrons preferentially cleaved at the inner generation rather than the outer layer. This

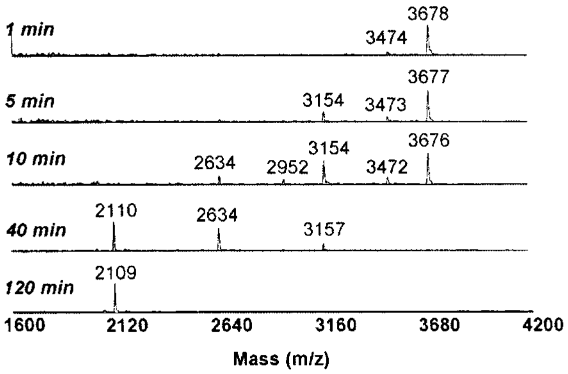


Figure 1. MALDI-TOF mass spectra of the hydrolytic degradation of compound **9** over time.

behavior is presumably due to the hindered nature of the outer generation resulting from quaternary carbons β on either side of the ester C−O bond. The dendritic triol, **6**, could be isolated after the degradation by an organic extraction from aqueous base.

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Supporting Information Available: Complete details for the synthesis and characterization of compounds **1**, **3**, and **5**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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