J. Am. Chem. Soc. **2000,** *122,* 10335−10344

Synthesis and Surface Functionalization of Aliphatic Polyether Dendrons

Scott M. Grayson and Jean M. J. Fréchet*

Contribution from the Department of Chemistry, University of California, Berkeley, California 94720-1460

Received May 30, 2000

Abstract: The convergent synthesis and surface modification of a novel family of aliphatic polyether dendrons is described. The synthesis utilizes methallyl dichloride as the monomeric building block along with peripheral benzyl ether and ketal protected hydroxy functionalities. The allylic nature of the electrophilic moieties of methallyl dichloride facilitates their nucleophilic displacement by 2 equiv of the appropriate terminal alcohol group. Having served its activating function during the coupling step, the alkene focal point can then be efficiently transformed into a primary alcohol via hydroboration−oxidation leading to a nucleophile that may then be coupled again to additional monomer. Repetition of these coupling and activation steps affords higher generation dendrons. Taking advantage of the versatility of the convergent approach and the rugged nature of the aliphatic ether building blocks, dendrimers with tailored solubility properties and well-defined unsymmetrical surfaces can be obtained.

Introduction

Dendrimers exhibit a number of unique physical properties owing to their well-defined, highly branched architecture, their globular shape, and their multiple peripheral functionalities.[1] Within the past decade, dendritic structures have been utilized for a range of technological applications,[2] including multivalent, bioactive macromolecules.[3] Recently, we have reported a novel convergent approach[4] to aliphatic polyether dendrons[5] with benzyl ether[6] or ketal[7] protecting groups. As expected, the aliphatic polyether backbone of these dendrons exhibits stability toward oxidative, reductive, strongly basic, and weakly acidic reaction conditions, thereby enabling a variety of chemical modifications[8] both at the periphery and at the focal point. In particular, both the benzyl and ketal protecting groups can be removed quantitatively to reveal the polyol periphery. As a result of their hydrophilic peripheral functionalities, many of these polyol dendrons are water-soluble, and all can easily be modified through alkylation or acylation with the appropriate electrophile. Because of their chemical robustness and increased solubility over linear analogues, these dendrons have proven to be versatile solubilizing scaffolds for the synthesis of otherwise insoluble oligothiophenes.[9]

Herein we detail the synthesis and modification of these benzyl-protected and ketal-protected dendrons. In addition, we discuss the synthesis of hybrid dendrons utilizing both benzyl and ketal protecting groups. Because these protecting groups are orthogonal to each other, they may be selectively removed thus providing excellent control over the modification of the periphery. Dendrimers with differentiated chain-end functionalities are attractive as vectors or carriers in applications such as targeted delivery.[3d]

Results and Discussion

Synthetic Design. Our synthetic design takes advantage of the convergent route[4] because this approach allows more precise control over the dendritic architecture, providing direct access to structurally uniform macromolecules as well as compounds with differentiated peripheral functionalities. Given the repetitive nature of dendrimer preparations, a successful convergent synthesis of high-generation aliphatic dendrons requires an aptly chosen monomer that will undergo high-yielding activation and growth steps. In our synthesis, the monomer selected is 3-chloro-2-chloromethyl-1-propene (methallyl dichloride or MDC). The

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10.1021/ja001903v CCC: $19.00

monomer's alkene functionality serves a dual purpose in the synthesis: first to enhance the electrophilic reactivity in the coupling step, and then to act as the masked precursor for the nucelophilic moiety. The monomer's dual allylic chloride functionalities enable two facile Williamson type nucleophilic substitutions with an appropriate alkoxide, while its symmetry ensures the formation of the same alkene product regardless of displacement mechanism (S_N1, S_N2, or S_N2'). In addition, the lack of hydrogens α to the leaving group prevents the possibility of elimination. The alkene in the product is then activated toward coupling by a regioselective hydroboration−oxidation, thereby producing a primary alcohol nucleophile. Iterative repetition of these coupling and activation steps produces higher generation dendrons.

During each step of the coupling and activation procedure, the products were purified by flash chromatography on silica gel. Because each growth step in the convergent synthesis involves only two couplings per monomer, the byproducts exhibit significantly different affinities for silica, allowing the dendrons to be isolated as monodisperse compounds, as assessed by size exclusion chromatography (SEC) and matrix-assisted laser desorption ionization mass spectrometry (MALDI-TOF MS).

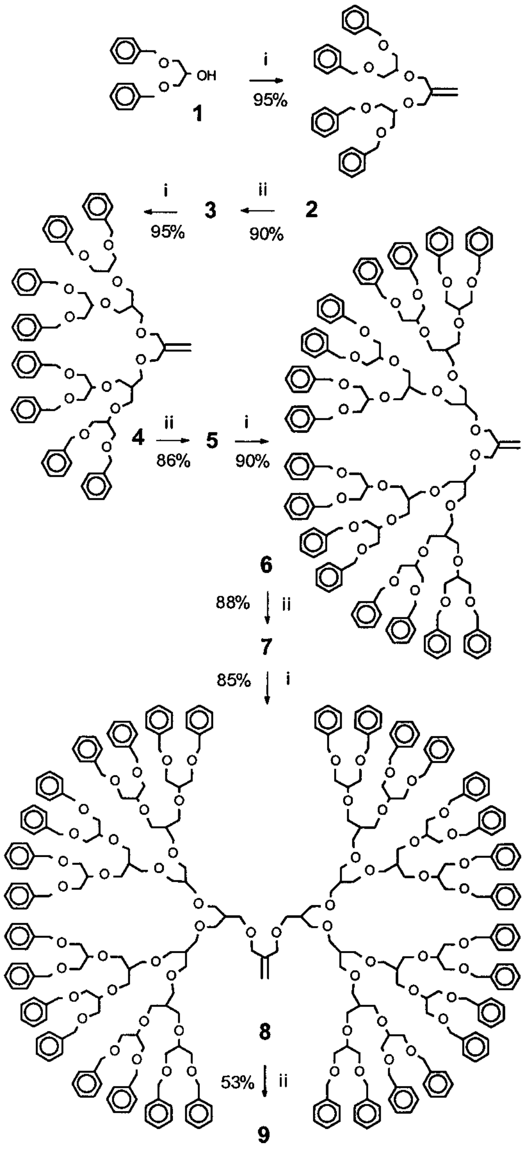
Protecting groups were necessary to mask the peripheral hydroxy functionalities during the synthesis. Dendrons uniformly protected with either benzyl or ketal groups were chosen as targets because these protecting groups are stable to the alkaline conditions used during the synthesis, and they could be easily removed by palladium-catalyzed hydrogenolysis or acid-catalyzed hydrolysis, respectively. In addition, when both protecting groups are placed on the periphery of the same dendron, their orthogonality enabled a selective modification of the surface.

In the following discussion, dendrons will be identified according to their peripheral functionality, their generation (the number of layers of branching units), and their focal functionality. Thus, compound **6** (Scheme 1), with its 16 peripheral benzyl ethers, 4 layers of branching units, and alkene focal point, would be referred to as (BnO-)$_{16}$[G-4]-ene.

Benzyl-Protected Dendrons. The first-generation benzyl-protected alcohol was prepared by reaction of an excess of benzyl alcohol with epichlorohydrin under phase-transfer conditions to afford the alcohol, **1**, that was purified by distillation. The subsequent growth step consisted of double nucleophilic displacements on the MDC monomer by the alkoxide of **1** to give (BnO-)$_4$[G-2]-ene, **2**, in 95% yield. (Scheme 1). Activation of the dendritic alkenes was carried out using standard hydroboration−oxidation conditions,[10] producing the corresponding dendritic alcohol. When the borane:THF complex was used to boronate the alkene, **2**, 5% of the undesired Markovnikov product was formed in addition to the intended primary alcohol. Use of 9-BBN was found to be more regioselective and effectively eliminated this side product, producing the primary [G-2]-ol, **3**, in 90% isolated yield.

If a very pure product is desired, intermediate purifications are required as all of the activation steps led to the formation of a trace amount of the lower generation alcohol. Because the lower generation alcohol is less hindered, it is more reactive during the coupling step and complicates the synthesis of larger dendrons if it is not removed. Milder sodium hydroxide (1 M) or sodium perborate[11] workups were investigated but did not improve the yield or purity of the desired product. Although the trace amount of lower generation byproduct can be removed successfully by flash chromatography, this becomes increasingly difficult at higher generations.

Scheme 1[a]



[a] i NaH, MDC, THF. ii. (1) 9-BBN, THF; (2) H_2O_2, NaOH.

Subsequent activation and coupling steps could be repeated with high yields throughout the third ((BnO-)$_8$[G-3]-ene, **4**, and (BnO-)$_8$[G-3]-ol**, 5**) and fourth ((BnO-)$_{16}$[G-4]-ene, **6**, and (BnO-)$_{16}$[G-4]-ol**, 7**) generations (Scheme 1). Only at the fifth generation ((BnO-)$_{32}$[G-5]-ene, **8**, and (BnO-)$_{32}$[G-5]-ol**, 9**) does it appear that the steric bulk of these compounds begins to inhibit reactions at the focal point, resulting in significantly longer reaction times and lower yields.

All of these benzyl-protected dendrons were isolated as viscous oils. The chromatography for both the coupling and the activation steps was simplified because of the vastly different polarities between the unreacted starting material and the product. At higher generations, the purification and handling of these compounds became more difficult, as the viscosity of the materials increased, and the retention factors of the alkene and alcohol converged. Because of these complications, and the decreased reactivity of the focal point at higher generations, the synthesis of dendrons above the fifth generation was not

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(10) Brown, H. C. *Hydroboration;* Benjamin: New York, 1962.

(11) Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *J. Org. Chem.* **1989**, *54*, 5930.

attempted. It should be emphasized, however, that the dendrons we prepared are of a size sufficient for their intended uses.[3c−e,9]

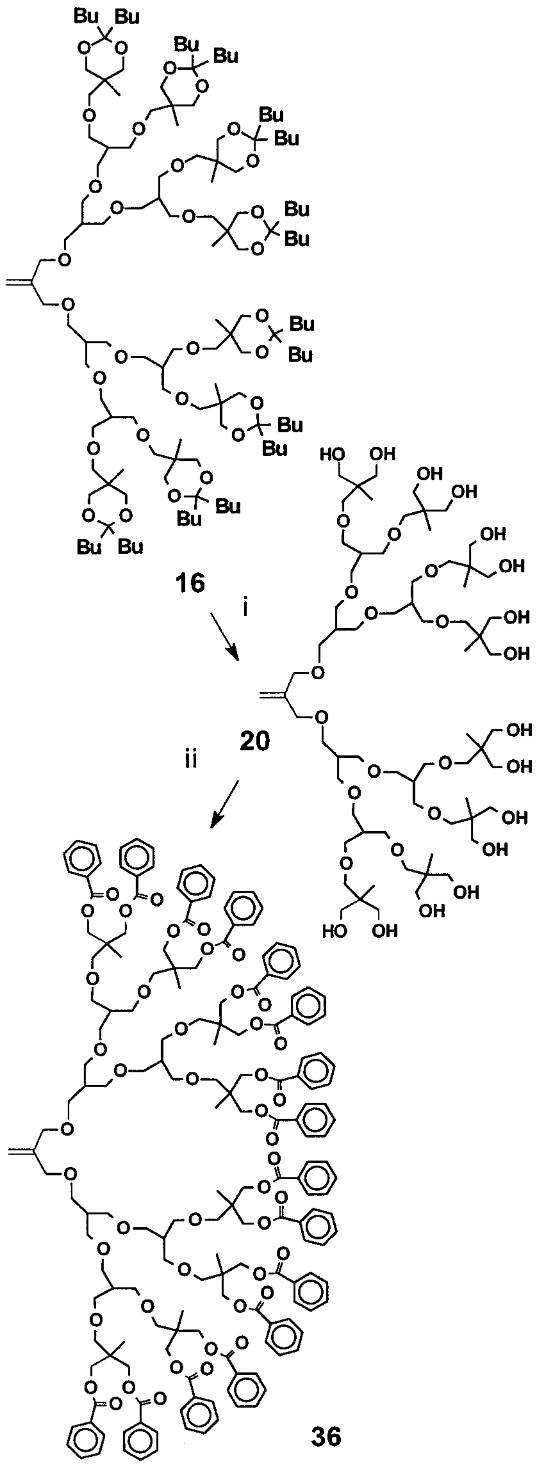
Ketal-Protected Dendrons. A second family of aliphatic polyether dendrons, utilizing the ketal protecting group, was also synthesized. Symmetrical ketones were selected as the peripheral protecting groups in order to prevent any undesirable stereochemical complications during purification and characterization. Dendritic compounds utilizing the ketals of acetone, pentanone, and nonanone were initially investigated; however, the nonanone ketal was selected for further study because the resulting dendrons are quite soluble in hexanes, thus simplifying flash chromatography.

An efficient bulk synthesis of the bis-protected triol, 11, involves the reaction of 1,1,1-tris(hydroxymethyl)ethane with an excess of nonanone and a catalytic amount of BF_3 etherate. This first-generation nonanone ketal (Nk) protected alcohol, Nk-[G-1]-ol,[12] could be isolated from the crude reaction mixture by distillation. Reaction of the alcohol, **11** (2.2 equiv), NaH, and the MDC monomer afforded the (Nk-)$_2$[G-2]-ene, **12,** in 84% yield. Activation of dendritic alkene, **12**, with 9-BBN and alkaline peroxide gave the primary (Nk-)$_2$[G-2]-ol, **13**, in 93% yield. As was the case with the benzyl ether dendrons, a minor side reaction was observed during the activation step that led to the production of the lower generation alcohol. After chromatographic purification, the subsequent activation and coupling steps continued affording high yields for the third ((Nk-)$_4$[G-3]-ene, **14**, and (Nk-)$_4$[G-3]-ol, **15**) and fourth ((Nk-)$_8$[G-4]-ene, **16**, and (Nk-)$_8$[G-4]-ol, **17**) generation dendrons. The use of *N*,*N*-dimethylacetamide (DMAc) to accelerate the coupling reaction enabled access to the fifth generation ((Nk-)$_{16}$[G-5]-ene, **18**, and (Nk-)$_{16}$[G-5]-ol, **19**).

The dendrons with ketal protecting groups were also isolated as viscous oils. Because of their peripheral lipophilic chains, these compounds exhibited high solubility in hexane and a significantly lower polarity during flash chromatography than the benzyl-protected analogues. The reduced chromatographic resolution between the alcohol and the alkene at higher generations, combined with slower reaction rates in both the coupling and activation steps, made the preparation of dendrons above the fifth generation unpractical.

Surface Modification. The benzyl ether protecting groups can be quantitatively removed through catalytic hydrogenolysis to expose a polyol periphery. Cleavage of the benzyl ethers was achieved by reaction with 10% Pd/C in 50:50 THF/EtOH under 5−10 atm of hydrogen gas. The deprotection reactions took between 24 and 48 h, depending upon generation, and could be easily monitored by MALDI-TOF MS via the analysis of a micromolar aliquot taken from the reaction mixture. Because the catalyst was heterogeneous, purification was achieved by simple filtration, affording a quantitative yield of the polyol. The use of higher pressures increased the reaction rate but also led to the reduction of a small percentage of the peripheral benzyl ethers to the cyclohexylmethyl ethers, a moiety that cannot be removed from the dendron.[13] It should be noted that cleavage of the benzyl ethers via hydrogenolysis leads to the concurrent reduction of the focal alkene functionality; therefore, any required modification at the focal point must be initiated before the hydrogenolysis.

Scheme 2[a]



[a] i. 0.2 M HCl, THF/MeOH. ii. BzCl, pyridine.

Similarly, the ketal protecting groups could be quantitatively removed by an acid-catalyzed hydrolysis.[14] The hydrolysis was achieved by reaction with either Dowex acid cation-exchange resin or dilute HCl in 50:50 THF/MeOH. Removal of the acid by either filtration of the Dowex or evaporation of the HCl solution yielded the desired polyol[15] (Scheme 2). Monitoring

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(12) Nk- is an abbreviation for the bidentate 5-nonanone ketal protecting group.

(13) Evidence for this side reaction include additional *aliphatic* resonances in the H and C NMR and well-resolved signals in the MALDI-TOF MS corresponding to an additional 96 and 192 amu above the expected molecular weight. Although this is a minor side reaction, the multiplicity of benzyl groups on high-generation dendrons causes a moderate statistical probability of defect per dendron; therefore, lower pressures were use to avoid this complication. Trace amounts of this aromatic reduction have been noted before with Pd/C catalyst. Glänzer, B. I.; Györgydeák, Z.; Benet, B.; Vasella, A. *Helv. Chim. Acta* **1991**, *74*, 343.

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Table 1. Miscibility of Surface-Functionalized Fourth-Generation Dendrons

	miscibility of (R-)$_{16}$[G-4]-ene where R^a =					
solvent	Nk	BnO	HO	TEG	BzO	Myr
water	imm	imm	misc	misc	imm	imm
MeOH	imm	imm	misc	misc	imm	imm.
DMAc	misc	misc	misc	misc	misc	misc
$CHCl_3$	misc	misc	imm	misc	misc	misc
CH_2Cl_2	misc	misc	imm	misc	misc	misc
EtOAc	misc	misc	imm	misc	misc	misc
THF	misc	misc	imm	misc	misc	misc
hexane	misc	imm	imm	imm	imm	misc

[a] Nk = nonanone ketal; TEG = tri(ethylene glycol) monomethyl ether, $CH_3(OCH_2CH_2)_3O-$; Myr = tetradecanoate (myristate) ester.

by MALDI-TOF MS showed that the reaction took between 4 and 48 h, with longer reaction times required for larger dendrons. For the fourth-generation dendron, the deprotection could be expedited by removing the released nonanone byproduct by distillation after 6 h and then refreshing the acid catalyst. The ketal-protected dendrons have a distinct advantage over the benzyl-protected dendrons since the orthogonal alkene focal functionality is preserved during removal of the protecting groups, allowing both the focal point and the periphery to be independently modified.

The polyol dendrons are highly polar molecules that are water-soluble above the third generation. At the second and third generations, the peripheral deprotected dendrons with focal alcohol functionality are water-soluble, but those with the alkene moiety at the focal point are not. At the fourth generation the hydrophilic nature of the 16 hydroxy end groups of the deprotected dendrons is sufficient to make both the (HO-)$_{16}$-[G-4]-ane, **10**, and (HO-)$_{16}$[G-4]-ene, **20**, water-miscible ($>$100 mg/mL) despite the nonpolar focal functionality.

A number of reactions were investigated to verify the ease with which the peripheral hydroxyl groups could be modified. Acylation of the peripheral groups was achieved by reaction in pyridine with benzoyl chloride (Scheme 2) or with tetradecanoic acid, DCC, and DPTS, leading to a rapid, quantitative formation to the corresponding polyesters (**36** and **38**) of (HO-)$_{16}$[G-4]-ene as judged by the MALDI-TOF MS spectrum of the crude product. Model alkylations were performed by nucleophilic substitution using NaH, and an excess of allyl bromide or the mesylate of tri(ethylene glycol) monomethyl ether. Although much slower than the acylations, full conversion could be achieved using THF as solvent for low-generation dendrons while DMAc was required at higher generations to solvate the polar dendritic polyols. MALDI-TOF MS was especially useful in monitoring the extent of reaction and characterizing the final products.

The modification of the surface moieties on fourth-generation dendrons with focal alkene functionalities demonstrates the importance of the peripheral functionality in determining the solubility of the resultant dendrons (Table 1). Initially the benzyl ether (**6**) and ketal protected (**16**) dendrons appear to be miscible in most organic solvents except those that were polar protic solvents (e.g., water and methanol.) The nonanone ketal has the additional advantage of being miscible in extremely nonpolar solvents such as hexane. However, after the removal of the protecting groups to expose a polyhydroxylated surface, we observed a reversal in the solubility trends, in which the polyols, **10** and **20**, are only miscible in water, methanol, DMAc, and pyridine. The solubility of the polyol dendrons can be reversed again, by acylation of the hydroxy groups. The lipophilic nature of the tetradecanoate esters of **38** made that compound miscible in all but the polar protic solvents, whereas the poly(benzoyl ester) dendron, **36**, like the poly(benzyl ether), **6**, was miscible in all solvents but the extremely nonpolar (hexane) and polar protic (methanol and water.) The addition of the methoxy-terminated tetraethylene glycol chain ends led to a compound (**37**) with more versatile solubility, being miscible in water, methanol, ethyl acetate, chloroform, and most other solvents, except hexane. These solubility trends reinforce the now widely accepted notion that as a dendron's generation increases, the peripheral functional groups dominate its solubility properties.[16]

Hybrid Peripheral Copolymer Dendrons. Making use of the versatility of the convergent synthesis,[17] orthogonally protected hybrid dendrons utilizing both the ketal and benzyl protecting groups were synthesized. The use of these orthogonal protecting groups enables the selective modification of the peripheral hydroxy groups with complementary functionalities for applications such as drug delivery.[3c−e] Two architectures were investigated: the first, an alternating hybrid, incorporated alternating pairs of benzyl- and ketal-protected hydroxy units on the periphery; the second, a block hybrid, was comprised of two structurally separated blocks with benzyl and ketal protecting groups, respectively. To distinguish between these constitutional isomers the alternating hybrids will be given the prefix *alt*- whereas the block hybrids will be given the prefix *block*-.

Alternating Hybrids. For the synthesis of the alternating hybrids, a single chloride group of the MDC monomer was functionalized with the alkoxide of the first-generation benzyl-protected alcohol, **1** (Scheme 3). This was achieved by using a 2-fold excess of MDC, ensuring high yields of the monosubstituted monomer, **21**. The remaining allylic chloride of **21** was reacted with the alkoxide of the first-generation ketal-protected alcohol, **11**, to yield *alt*-(BnO-)$_2$Nk-[G-2]-ene, **22**. Repetition of the activation and growth steps led to the production of *alt*-(BnO-)$_8$(Nk-)$_4$[G-4]-ene, **26**.

Block Hybrids. The block hybrids were prepared by reaction of the third-generation ketal-protected alcohol, **15**, with an excess of the MDC, yielding the monocoupled product, **29**. The resulting allylic chloride, **29** was then treated with the third-generation benzyl-protected alcohol, **5**, to yield *block*-(BnO-)$_8$-(Nk-)$_4$[G-4]-ene, **30**.

Selective Deprotection of Hybrids. As a result of the orthogonality of the chosen protecting groups, ketal deprotection of the fourth-generation hybrid alkenes (**26** and **30)** could be achieved by acid-catalyzed hydrolysis, producing hybrid dendrons with eight hydroxy groups and eight benzyl ethers (**27** and **31**) in quantitative yields (Scheme 4). Similarly, the hydrogenolysis of the benzyl groups from **26** and **30** followed the procedure established for the wholly benzyl protected dendrons, except basic alumina was added to the reaction mixture to preserve the acid-sensitive ketal groups. This reaction afforded the debenzylated polyols, **28** and **32**, in quantitative yields.

The utility of the orthogonally protected surface was demonstrated by a selective functionalization of the dendritic periphery (Scheme 5). The fourth-generation block hybrid alkene, **30**, was first partially deprotected by an acid-catalyzed hydrolysis of the ketals. The eight exposed hydroxyl groups of

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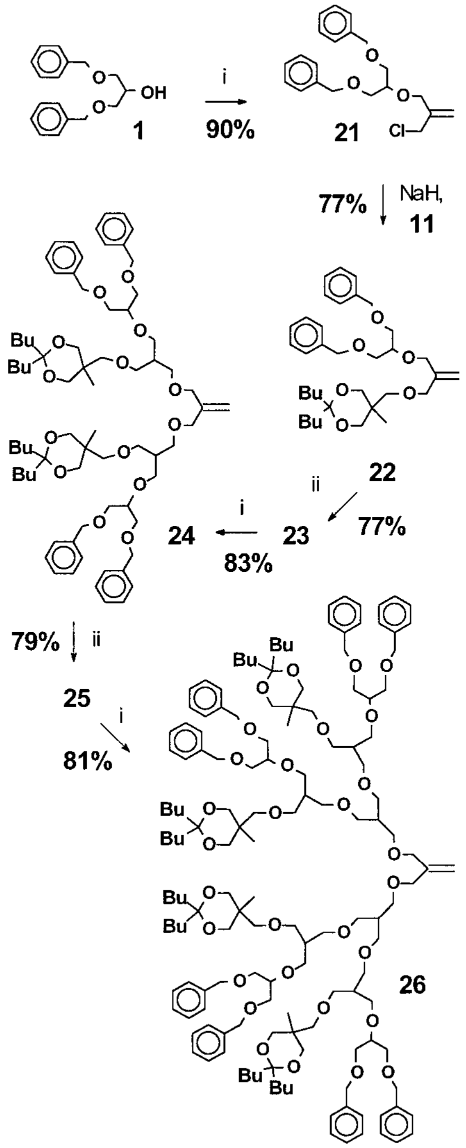
(15) It was observed that if the reaction conditions were too acidic (greater than 1 M HCl), cleavage of the allyl ether bonds could occur.

(16) Wooley, K. L.; Fréchet, J. M. J.; Hawker, C. J. *Polymer* **1994**, *35*, 4489.

(17) Hawker, C. J.; Fréchet, J. M. J. *Macromolecules* **1990**, *23*, 4726. Wooley, K. L.; Hawker, C. J.; Fréchet, J. M. J. *J. Chem Soc., Perkin Trans. 1* **1991**, 1059. Hawker, C. J.; Wooley, K. L.; Fréchet, J. M. J. *J. Chem Soc., Perkin Trans. 1* **1993**, 1287.

Scheme 3[a]



[a] i. NaH, MDC, THF. ii. (1)9-BBN, THF; (2)H_2O_2, NaOH.

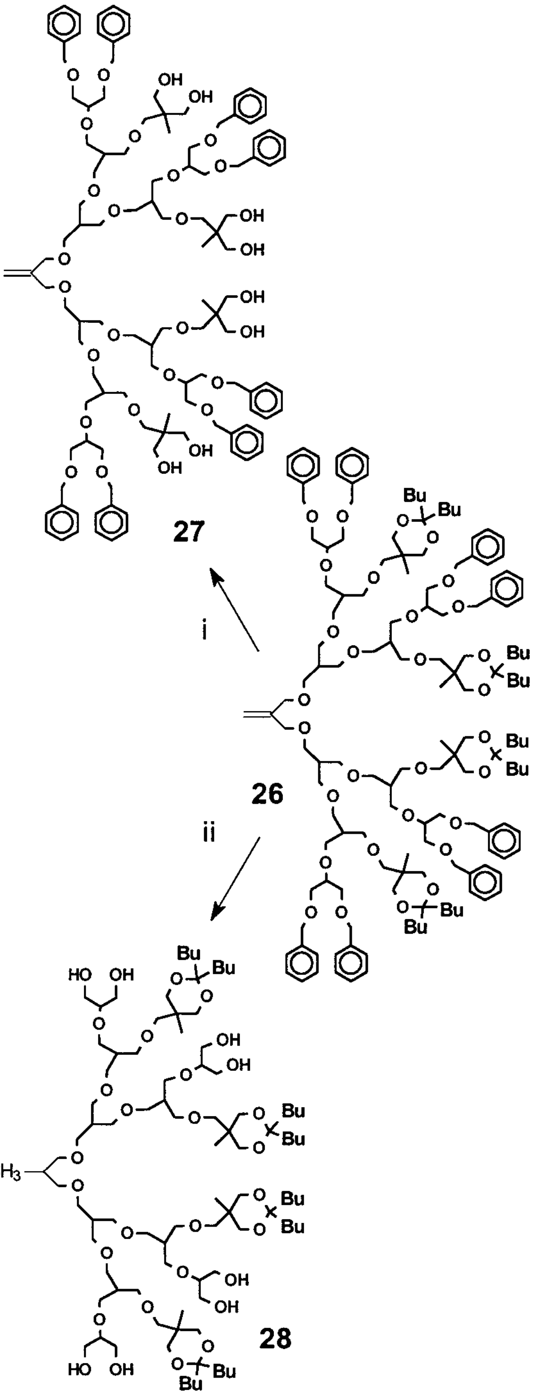
31 were then alkylated with short oligo(ethylene glycol) chains by nucleophilic substitution using NaH and an excess of the mesylate of tri(ethylene glycol) monomethyl ether. The desired fully alkylated product, **33**, was isolated in 89% yield over the two steps from *block*-(BnO-)$_8$(Nk-)$_4$[G-4]-ene, **30**. Next, the benzyl ethers were removed by palladium-catalyzed hydrogenolysis, and the peripheral alcohols were then acylated with benzoyl chloride in pyridine affording the product, **35**, in a 78% yield. MALDI-TOF MS was used to verify that each of these surface modifications was driven to completion (Figure 1).

Characterization

For all of the compounds synthesized, the data obtained from ^{1}H NMR, ^{13}C NMR, SEC, and MALDI-TOF MS were sufficient to unambiguously identify these compounds and verify their structural integrity.

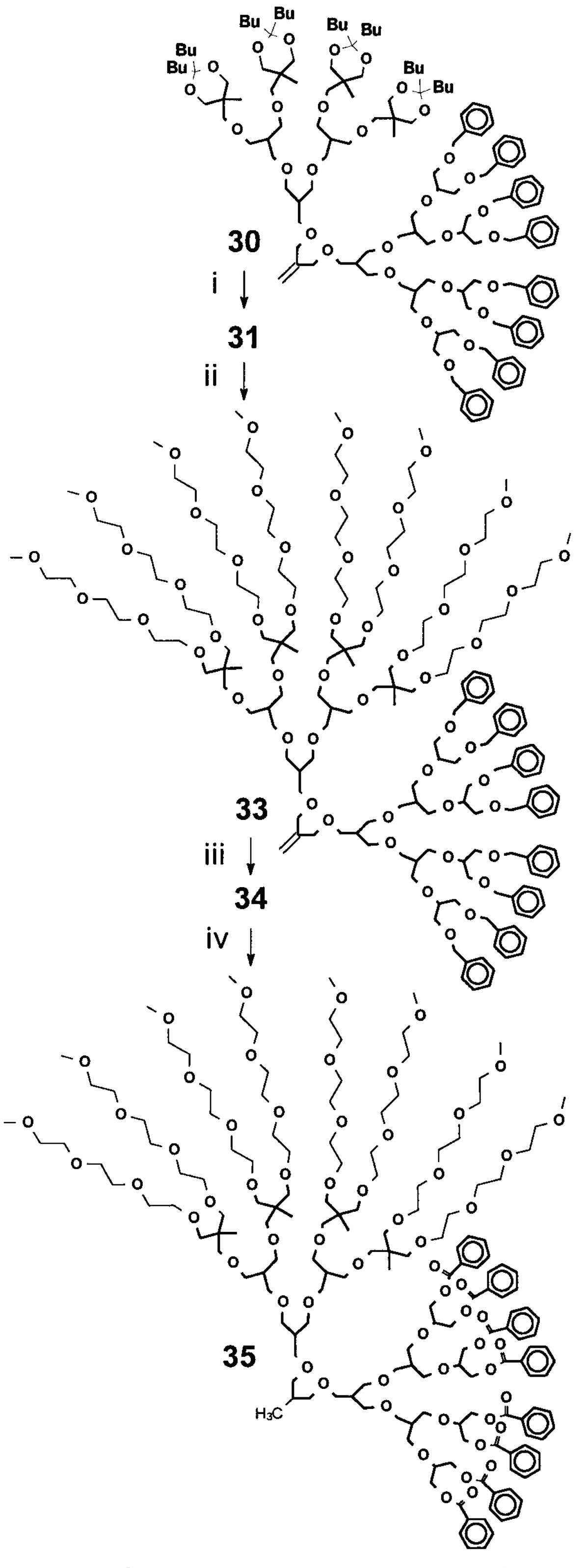
Although IR spectroscopy and elemental analysis were used to characterize all of the polyether dendrons, these techniques have limitations when distinguishing between dendritic compounds with similar peripheral functionalities.[4] At higher generations, the infrared signals of the focal functionalities are overwhelmed by those of the repeat units, making it difficult to observe the alkene double-bond stretch above the third generation. In addition, the elemental ratios converge with increasing generation, making it difficult to distinguish between dendrons or verify their purity solely by elemental analysis. However, these techniques were useful for characterizing the dendrons after peripheral modifications, since these surface alterations correspond to significant changes in functionality as well as elemental composition. For example, after the hydrolysis of (Nk-)$_8$[G-4]-ene, **16**, to produce the polyol, **20**, the FTIR spectrum shows the appearance of a broad hydroxyl band centered around 3390 cm^{-1}. Acylation to form the polybenzoate, **36**, leads to the complete disappearance of the hydroxyl band and the appearance of a sharp carbonyl band at 1724 cm^{-1}.

Scheme 4[a]



[a] i. 0.2 M HCl, THF/MeOH. ii. 7 atm H_2, Pd/C, basic alumina, THF/EtOH.

Scheme 5[a]



[a] i. 0.2 M HCl, THF/MeOH. ii. NaH, $CH_3O(CH_2CH_2O)_3Ts$, THF. iii. 7 atm H_2, Pd/C, THF/EtOH. iv. BzCl, pyridine, THF.

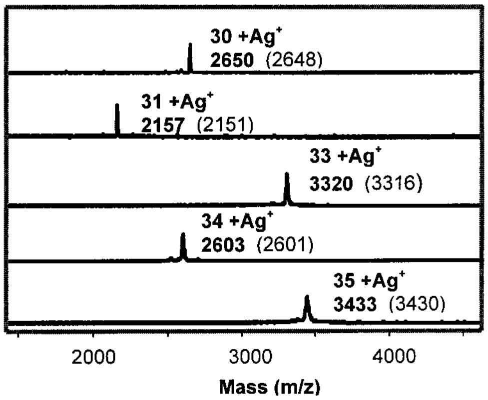


Figure 1. MALDI-TOF mass spectral data for the selective peripheral modification of the hybrid dendrons.

^{1}H and ^{13}C NMR. a. Benzyl-Protected Dendrons. The high degree of symmetry in these dendrons enabled facile confirmation of both structure and purity by ^{1}H and ^{13}C NMR. Figure 2 shows the ^{1}H NMR of the $(BnO\text{-})_8$[G-4]-ene and the $(BnO\text{-})_8$-[G-4]-ol. The focal alkene or alcohol functionalities can easily be identified because their resonances are isolated from those of the polyether framework and the peripheral benzyl ethers. The dendritic alkenes exhibit an allylic singlet at 3.8 ppm and a vinylic singlet at 5.1 ppm in the ^{1}H NMR (Figure 2) as well as alkene resonances at 113 and 143 ppm in the ^{13}C NMR (Figure 3). The dendritic alcohols display an alcohol triplet between 2.8 and 3.1 ppm in the ^{1}H NMR (Figure 2), while the adjacent methylene has a resonance at 64 ppm in the ^{13}C NMR (Figure 3).

b. Ketal-Protected Dendrons. The ketal-protected dendrons also exhibited well-isolated resonances for the focal functionalities in both the ^{1}H and ^{13}C NMR. The dendritic alkenes exhibit an allylic singlet at 3.9 ppm and a vinylic singlet at 5.1 ppm in the ^{1}H NMR as well as alkene resonances near 113 and 143 ppm in the ^{13}C NMR. The dendritic alcohols display an alcohol triplet between 2.4 and 2.5 ppm in ^{1}H NMR, while the adjacent methylene shows a triplet at 3.7 ppm in the ^{1}H NMR and a resonance at 64 ppm in the ^{13}C NMR.

In addition to being able to determine the focal functionality, comparison of the ^{1}H NMR integration values between the focal functionality and the peripheral benzyl or ketal protecting groups accurately verifies the generation of the dendrons.

c. Functionalization. Both the hydrogenolysis and the hydrolysis deprotection reactions were quantitative, and ^{1}H NMR confirmed the full removal of the aromatic and the ketal groups, respectively. Modification of the peripheral alcohol groups through acylation or etherification could be verified by the loss of the alcohol resonances and the appearance of new resonances corresponding to the benzoate ester (^{1}H NMR $\delta = 4.30, 7.38, 7.51, 7.98$), the myristate ester (^{1}H NMR $\delta = 1.60, 2.30, 3.98$), the allyl ether (^{1}H NMR $\delta = 5.16, 5.21, 5.89$), or the oligo(ethylene glycol) ether (^{1}H NMR $\delta = 3.36, 3.52, 3.59$).

d. Hybrid Dendrons. The hybrid dendrons could easily be characterized as a result of the significant differences between the resonances of the two protecting groups. The focal alcohol and alkene functionalities show similar resonances to those seen in the fully benzyl or fully ketal protected dendrons. The fourth-generation alternating hybrid could be distinguished from the same generation block hybrid by examining the ^{1}H NMR shifts of the allylic methylene protons adjacent to the focal alkene ($\delta = 3.87$ ppm). In the alternating hybrid, these groups are chemically identical as a result of molecular symmetry and therefore appear as a singlet; however, in the block hybrid, each allylic methylene is attached to a dendritic block with different surface protecting groups, resulting in two overlapping but distinct resonances.

MALDI-TOF MS. MALDI-TOF MS was especially useful in characterizing these dendritic compounds (Figure 4) and monitoring their reactions. Samples were prepared by dissolving

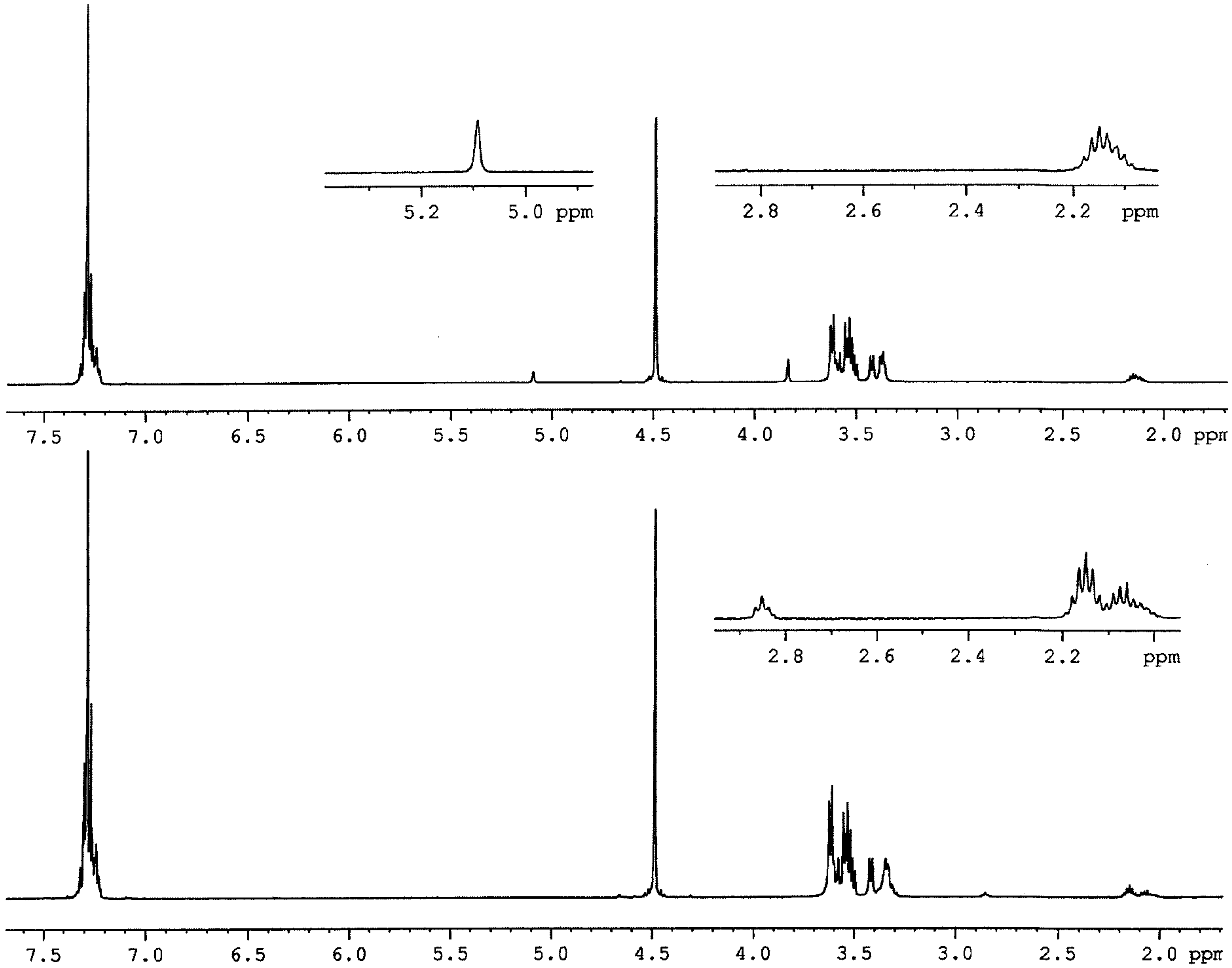


Figure 2. ^{1}H NMR spectra of the benzyl-protected fourth-generation dendrons with alkene (above) and alcohol (below) focal functionalities.

micromolar quantities of the dendritic material in THF with α-cyano-4-hydroxycinnamic acid as a matrix and silver trifluoroacetate to produce a detectable silver cationic complex. For the dendritic compounds bearing ketals, this acidic matrix appeared to slowly catalyze the removal of the ketal groups; therefore, 9-nitroanthracene with silver trifluoroacetate was used as the matrix. All of the spectra displayed a very prominent $[M + Ag]^+$ peak corresponding to the dendritic polyether compound complexed with a silver cation, as well as faint $[M + Na]^+$ and $[M + K]^+$ peaks from residual cations. The observed molecular masses were calibrated against bovine insulin and gave molecular weight calculations consistently within 0.2% of the theoretical values (Tables 2−4).

Size Exclusion Chromatography. The dendritic polyethers were also characterized by size exclusion chromatography in THF and calibrated against polystyrene standards (Tables 2−4). A UV detector was used to evaluate all of the dendrons with benzyl protecting groups, whereas those dendrons without aromatic rings required the use of a refractometer. Although MALDI-TOF offers much more accurate molecular weight and more meaningful polydispersity data for such monodisperse molecules, SEC provides valuable data confirming the purity of these dendrons, and their globular conformation in solution. All compounds exhibited a SEC polydispersity index (PDI) of less than 1.01, confirming the absence of lower molecular weight byproducts that may occur from incorporation of alcohol impurities during the coupling step or premature cleavage of the protecting groups. As reported for other highly branched, globular materials,[4,18] the ratio between log M_w and the retention time shows a distinctly different trend than linear polymers. This observed effect is a result of the increasingly compact nature of high-generation dendrons, with respect to linear polymers of comparable molecular weights. Their compact conformation corresponds to a smaller hydrodynamic volume, longer retention times, and therefore an underestimation of the molecular weight.

Conclusion

We have demonstrated that the convergent approach can be applied toward an efficient synthesis of aliphatic polyether dendrons with differentiated surface functionalities. These dendrons are chemically robust and easily functionalized at both the focal point and periphery, making them versatile scaffolds for a host of applications. This family of dendrons complements the widely used poly(benzyl ether) dendrons[4] that had been developed previously in our laboratory.

The convergent synthesis does have a distinct limitation as steric hindrance around the focal functionality prevents access to dendrons above the fifth generation. However, we have demonstrated that this technique can be used to synthesize pure aliphatic ether dendritic compounds of molecular weights up

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(18) Aharoni, S. M.; Crosby, C. R.; Walsh, E. K.; *Macromolecules* **1982**, *15*, 1093. Morena-Bondi, M. C.; Orellana, G. Turro, N. J., Tomalia, D. A. *Macromolecules* **1990**, *23*, 910.

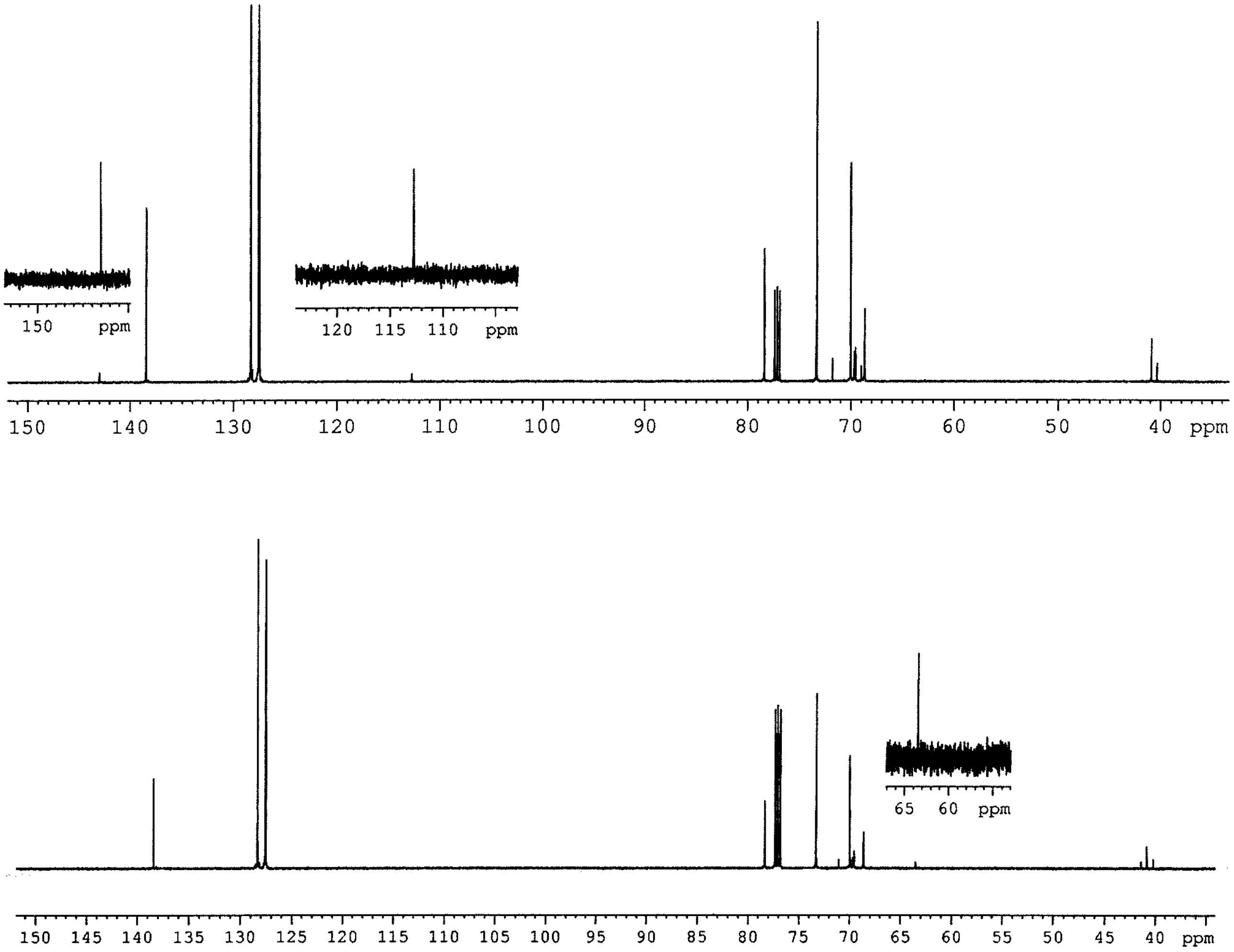

Figure 3. ^{13}C NMR spectra of the benzyl-protected fourth-generation dendrons with alkene (above) and alcohol (below) focal functionalities.

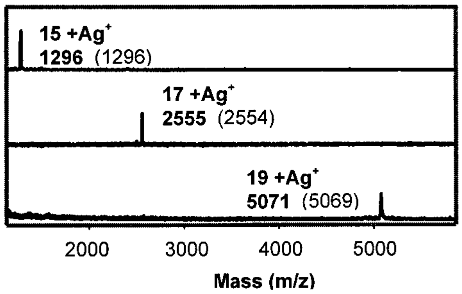

Figure 4. MALDI-TOF mass spectra of the third-, fourth-, and fifth-generation ketal-protected alcohols.

Table 2. Mass Spectral and Size Exclusion Chromatographic Data for the Benzyl-Protected Polyether Dendrons

compound	calculated MW	MALDI-TOF MS MW	SEC M_n
[G-2]-ene	596.7	597[a]	580
[G-2]-ol	614.7	615[a]	590
[G-3]-ene	1281.6	1280	1220
[G-3]-ol	1299.6	1299	1190
[G-4]-ene	2651.4	2651	1980
[G-4]-ol	2669.4	2670	1990
[G-5]-ene	5390.8	5394	3560
[G-5]-ol	5408.9	5408	3520

[a] The mass spectra for the second-generation dendrons were acquired using FAB MS.

Table 3. Mass Spectral and Size Exclusion Chromatographic Data for the Ketal-Protected Polyether Dendrons

compound	calculated MW	MALDI-TOF MS MW	SEC M_n
[G-2]-ene	540.8	541[a]	600
[G-2]-ol	558.8	559[a]	710
[G-3]-ene	1169.8	1170	1400
[G-3]-ol	1187.8	1189	1410
[G-4]-ene	2427.6	2429	2390
[G-4]-ol	2445.6	2446	2420
[G-5]-ene	4943.3	4941	4370
[G-5]-ol	4961.3	4963	4210

[a] The mass spectra for the second-generation dendrons were acquired using FAB MS.

Table 4. Mass Spectral and Size Exclusion Chromatographic Data for the Hybrid Polyether Dendrons

compound	calculated MW	EI-TOF MS MW	SEC M_n
[G-2]-ene	568.4	568.4	640
[G-2]-ol	586.4	586.4	650
[G-3]-ene	1224.8	1224.7	1270
[G-3]-ol	1242.8	1242.7	1250
[G-4]-ene	2539.5	2547.1[a]	2180

[a] The mass spectra for the fourth-generation dendron was acquired using MALDI-TOF MS.

to 5000 Da in high yield. The enormous advantage of the convergent approach is its precise control of functionality at both the focal point and the periphery of the molecule, thus permitting the synthesis of a variety of hybrid structures. Placement of orthogonal protecting groups on the surface of these materials enables their regioselective modification with excellent control over the placement and ratio of peripheral moieties. We are currently evaluating these hybrid dendrons for applications such as drug delivery devices that require water-soluble macromolecules with a multivalent, diversely functionalized periphery. Presently, in vivo and in vitro studies are in progress to determine the biocompatibility of these new branched analogues of poly(ethylene glycol).

Experimental Section

Materials. All reagents were purchased from Aldrich and used without further purification, unless otherwise noted. Tetrahydrofuran (THF) was distilled over sodium/benzophenone. All other solvents (Fischer) were reagent grade (99.9%).

General. All reactions were performed under a dry nitrogen atmosphere. Thin-layer chromatography was performed on Merck Kieselgel 60 F_{254} plates. Silica used for flash chromatographic separation was Merck Kieselgel 60 (230−400 mesh). Isolated materials were dried under vacuum for 12 h.

Characterization. All ^{1}H NMR spectra were acquired at room temperature with a Bruker AM spectrometer at 400 MHz. All ^{13}C NMR and distortionless enhancement by polarization transfer (DEPT) spectra were obtained with a Bruker DRX spectrometer at 125 MHz. All NMR data are reported in parts per million and calibrated (^{1}H against TMS = 0.00 ppm, ^{13}C against $CDCl_3$ = 77.00 ppm). Infrared spectra were collected on a Mattson Genesis II FT-IR using a reflective mirror surface. For compounds with a molecular mass of 1200 or less, mass spectral data was collected by EI-TOF MS on either a Micromass LCT instrument or a Hewlett-Packard 6890 GC attached to a HP 5973 mass selective detector. For compounds with a greater molecular mass, MALDI-TOF MS data was collected on a PerSeptive Biosystems Voyager-DE instrument in positive ion mode. MALDI-TOF MS samples were prepared in either an α-cyano-4-hydroxycinnamic acid or 9-nitroanthracene matrix with silver trifluoroacetate, and the instrument was calibrated against bovine insulin standards. M-H-W Laboratories (Pheonix, AZ) performed elemental analysis. Size exclusion chromatography was carried out on a Waters GPC 150-CV plus system (Milford, MA) with an attached M486 tunable absorbance detector (λ = 254 nm). Eighteen polystyrene standards from Polymer Laboratories (Amherst, MA) were used for calibration, and the mobile phase was tetrahydrofuran (1 mL/minute, 45 °C). A bank of 4 PL Gel columns (5 μm) from Polymer Laboratories (Amherst, MA) was used: 100 Å, 100 Å, 500 Å, and a Mixed C.

Representative Procedure for the Synthesis of Dendrons with Focal Alkene Functionality via Coupling with Monomer: (BnO-)$_{16}$[G-4]-ene (6). Dry NaH (2.2 equiv) and methallyl dichloride (3-chloro-2-chloromethyl-1-propene) (1.0 equiv) were placed in a dry round-bottom flask under N_2 atmosphere. To the reaction mixture was added (BnO-)$_8$[G-(3)]-ol (2.2 equiv), **5**, diluted to 1 M concentration in freshly distilled THF. The mixture was stirred at room temperature for ∼15 min and overnight at ∼65 °C. After cooling to room temperature, the reaction mixture was quenched with water and extracted twice with ether. The organic layers were dried over anhydrous $MgSO_4$, and the solvent was removed in vacuo. The product was purified by flash column chromatography on silica gel with hexanes−ethyl acetate gradient from 5% ethyl acetate to 35% ethyl acetate: yield 90%; ^{1}H NMR ($CDCl_3$) δ = 2.14 (m, 6), 3.5−3.8 (m, 76), 3.83 (s, 4), 4.48 (s, 32), 5.08 (s, 2), 7.2−7.4 (m, 80); ^{13}C NMR ($CDCl_3$) δ = 40.2 (CH), 41.0 (CH), 68.6 (CH_2), 68.9 (CH_2), 69.6 (CH_2), 69.7 (CH_2), 70.0 (CH_2), 71.8 (CH_2), 73.2 (CH_2), 78.3 (CH), 116.4(CH_2), 127.4 (CH), 127.5 (CH), 128.3 (CH), 138.4 (C), 143.0 (C); FTIR ν = 3030 cm^{-1} (H−Ar), 1104 cm^{-1} (C−O−C); MS (MALDI-TOF) $[M + Ag]^+$ (calcd 2759.2) found 2759.4; elemental analysis calcd (%) for $C_{164}H_{200}O_{30}$ (2651.4) C, 74.29; H, 7.60; found C, 74.13; H, 7.43.

Representative Procedure for the Synthesis of Dendrons with Focal Alcohol Functionality via Hydroboration−Oxidation of Alkene: (BnO-)$_{16}$[G-4]-ol (7). Freshly distilled dry THF and (BnO-)$_{16}$[G-4]-ene, **6**, (1 equiv) were placed in a dry round-bottom flask under N_2 and cooled to 0 °C in a ice bath. To this flask, 0.5 M 9-BBN solution in THF (1.1 equiv) was added slowly and allowed to stir at 0 °C for 2 h. The reaction mixture was then quenched with 3 M NaOH solution in water (4.5 equiv) followed by addition of 30% H_2O_2 aqueous solution (3.0 equiv) and stirred at room temperature for 1 h. The reaction mixture was saturated with K_2CO_3 and extracted twice with ether. The organic layers were dried over anhydrous $MgSO_4$, and the solvent was removed in vacuo. The residue was purified by flash column chromatography on silica gel with hexanes−ethyl acetate gradient from 5% ethyl acetate to 35% ethyl acetate: yield 88%; ^{1}H NMR ($CDCl_3$) δ = 2.08 (m, 3), 2.15 (m, 4), 2.86 (t, 1), 3.5−3.8 (m, 82), 4.49 (s, 32), 7.2−7.4 (m, 80); ^{13}C NMR ($CDCl_3$) δ = 40.2 (CH), 40.9 (CH), 41.4 (CH), 63.5 (CH_2), 68.6 (CH_2), 69.5 (CH_2), 69.6 (CH_2), 69.9 (CH_2), 70.0 (CH_2), 71.0 (CH_2), 73.3 (CH_2), 78.3 (CH), 127.5 (CH), 127.5 (CH), 128.3 (CH), 138.4 (C); FTIR ν = 3493 cm^{-1} (OH), 3030 cm^{-1} (H−Ar), 1106 cm^{-1} (C−O−C); MS (MALDI-TOF) $[M + Ag]^+$ (calcd 2777.5) found 2777.7; elemental analysis calcd (%) for $C_{164}H_{202}O_{31}$ (2669.4) C, 73.79; H, 7.63; found C, 73.60; H, 7.64.

Representative Procedure for the Deprotection of Dendrons with Peripheral Benzyl Ethers: (HO-)$_{16}$[G-4]-ane (10). To a 20 mL scintillation vial containing 0.43 g (0.16 mmol) of the (Bn-)$_{16}$[G-4]-ene, **6**, were added 0.04 g of 10% Pd/C and 5 mL of 50:50 THF/EtOH. The vial was placed inside a steel bomb and stirred under 7 atm of hydrogen gas. After the first 24 h, an additional 0.02 g of catalyst was added to the vial, and the bomb was pressurized again to 7 atm of hydrogen gas. After an additional 24 h the reaction appeared complete by MALDI-TOF MS. The catalyst was removed from the reaction mixture via vacuum filtration through Celite, and the solvent was removed from the filtrate in vacuo. The viscous polyol was characterized without further purification: 99% yield; ^{1}H NMR ($(CD_3)_2SO$) δ = 0.87 (d, 3), 1.9−2.1 (m, 7), 3.19 (m, 8), 3.3−3.6 (m, 72), 4.46 (s, 16); ^{13}C NMR ($(CD_3)_2SO$) δ = 14.8 (CH_3), 34.8 (CH), 40.2 (CH), 41.0 (CH), 68.2 (CH_2), 69.2 (CH_2), 69.3 (CH_2), 69.5 (CH_2), 73.4 (CH_2), 82.1 (CH); FTIR ν = 3380 cm^{-1} (OH), 1118 cm^{-1} (C−O−C); MS (MALDI-TOF) $[M + Ag]^+$ (calcd 1319.3) found 1324.3; elemental analysis calcd (%) for $C_{52}H_{106}O_{30}$ (1211.4) C, 51.56; H, 8.82; found C, 51.38; H, 8.75.

Representative Procedure for the Deprotection of Dendrons with Peripheral Ketal Groups: (HO-)$_{16}$[G-4]-ene (20). To a round-bottom flask containing 0.93 g (0.38 mmol) of the (Nk-)$_8$[G-4]-ene (**16**) were added 4 cm^3 of Dowex-50W (50X1-100) acidic resin beads and 10 mL of 50:50 THF/MeOH. A stirbar was added to facilitate the reaction, and after 36 h the reaction appeared complete by MALDI-TOF MS. The resin was removed via vacuum filtration, and the solvent was removed from the filtrate in vacuo producing 0.262 g (97% yield) of the viscous, oily polyol. ^{1}H NMR ($(CD_3)_2SO$) δ = 0.76 (s, 24), 2.01 (m, 6 J = 6.0 Hz), 3.16 (s, 16), 3.24 (m, 32), 3.32 (m, 36), 3.87 (s, 4), 4.25 (s,16), 5.10 (s, 2); ^{13}C NMR (CD_3OD) δ = 15.9 (CH_3), 40.1 (CH), 40.2 (CH), 41.2 (C), 65.1 (CH_2), 68.4 (CH_2), 69.2 (CH_2), 69.4 (CH_2), 69.6 (CH_2), 71.3 (CH_2), 73.8 (CH_2), 112.9 (CH_2), 143.1 (C); FTIR ν = 3390 cm^{-1} (OH), 1128 cm^{-1} (C−O−C); MS (MALDI-TOF) (m/z), $[M + Ag]^+$ (calcd 1541.7) found 1546.7; elemental analysis calcd (%) for $C_{68}H_{136}O_{30}$ (1433.8) C, 56.96; H, 9.56; found C, 56.79; H, 9.35.

Representative Procedure for the Acylation of Dendrons with Peripheral Alcohol Functionalities: (BzO-)$_{16}$[G-4]-ene (36). To a round-bottom flask containing 0.16 g (0.11 mmol) of the (HO-)$_{16}$-[G-4]-ene (**20**) were added 4 mL of pyridine and 0.48 g (3.5 mmol) of benzoyl chloride. The reaction mixture was stirred at 60 °C for 4 h, at which time the reaction appeared complete by MALDI-TOF MS. After cooling to room temperature, the reaction mixture was poured into water and extracted twice with ether. The organic layers were dried over anhydrous $MgSO_4$, and the solvent was removed in vacuo. The product was purified by flash column chromatography on silica with hexanes−ethyl acetate gradient from 10% ethyl acetate to 40% ethyl acetate: yield 59%; ^{1}H NMR ($CDCl_3$) δ = 1.10 (s, 24), 2.01 (m, 2, J = 5.9 Hz), 2.08 (m, 4, J = 5.8 Hz), 3.30 (m, 20), 3.38 (m, 32), 3.82 (s, 4), 4.28 (d, 16, J = 11.1 Hz), 4.32 (d, 16, J = 11.1 Hz), 5.08 (s, 2), 7.38 (m, 32), 7.51 (m, 16), 7.98 (m, 32); ^{13}C NMR ($CDCl_3$) δ = 15.9 (CH_3), 40.1 (CH), 40.2 (CH), 41.2 (C), 65.1 (CH_2), 68.4 (CH_2), 69.2 (CH_2), 69.4 (CH_2), 69.6 (CH_2), 71.3 (CH_2), 73.8 (CH_2), 112.9 (CH_2), 143.1 (C); FTIR ν = 1724 cm^{-1} (C=O), 1109 cm^{-1} (C−O−C); MS (MALDI-TOF) (m/z), $[M + Ag]^+$ (calcd 3207.3) found 3214.0; elemental analysis calcd (%) for $C_{180}H_{200}O_{46}$ (3199.4) C, 69.75; H, 6.50; found C, 69.57; H, 6.63.

Representative Procedure for the Alkylation of Dendrons with Peripheral Alcohol Functionalities: ($CH_3(OCH_2CH_2)_3O$-)$_{16}$[G-4]-

ene (37). To a round-bottom flask containing 0.09 g (0.06 mmol) of the (HO-)$_{16}$[G-4]-ene (**20**) were added 3 mL of DMAc and 0.50 g (1.51 mmol) of the tosylate of tri(ethylene glycol), monomethyl ether. The reaction mixture was stirred at 60 °C, while 0.02 g of NaH powder was added every 6 h. After 36 h, the reaction appeared complete by MALDI-TOF MS and was cooled to room temperature. The reaction mixture was poured into water and extracted twice with ether. The organic layers were dried over anhydrous $MgSO_4$, and the solvent was removed in vacuo. The product was purified by flash column chromatography on silica with dichloromethane−methanol gradient from 3% methanol to 8% methanol: yield 52%; ^{1}H NMR ($CDCl_3$) $\delta = 0.76$ (s, 24), 2.01 (m, 6, $J = 6.0$ Hz), 3.1−3.7 (m, 324), 3.87 (s, 4), 5.10 (s, 2); ^{13}C NMR ($CDCl_3$) $\delta = 17.3$ (CH_3), 40.3 (CH), 40.4 (CH), 41.0 (C), 59.0 (CH_3), 69.6 (CH_2), 69.7 (CH_2), 69.8 (CH_2), 70.4 (CH_2), 70.5 (CH_2), 70.6 (CH_2), 70.6 (CH_2), 71.0 (CH_2), 71.3 (CH_2), 71.9 (CH_2), 73.9 (CH_2), 73.9 (CH_2), 112.6 (CH_2), 142.8 (C); FTIR $\nu = 1650$ cm^{-1} (C═C), 1140 cm^{-1} (C−O−C); MS (MALDI-TOF) (*m/z*), [M + Ag]$^+$ (calcd 3881) found 3884; elemental analysis calcd (%) for $C_{180}H_{360}O_{78}$ (3772.8) C, 57.30; H, 9.62; found C, 57.13; H, 9.43.

Block Hybrid Copolymer. a. (Nk-)$_4$[G-4]-methylallyl Chloride (29). This was prepared from (Nk-)$_4$[G-3]-ol (**15**) and purified by flash column chromatography on silica gel with hexanes−ethyl acetate gradient from 5% ethyl acetate to 10% ethyl acetate: yield 97%; ^{1}H NMR ($CDCl_3$) $\delta = 0.86$ (s, 12), 0.91 (t, 12, $J = 7.0$ Hz), 0.92 (t, 12, $J = 7.0$ Hz), 1.2−1.4 (m, 32), 1.63 (m, 8), 1.72 (m, 8), 2.15 (m, 3, $J = 5.9$ Hz), 3.35 (s, 8), 3.4−3.5 (m, 16), 3.50 (d, 8, $J = 11.7$ Hz), 3.66 (d, 8, $J = 11.7$ Hz), 4.04 (s, 1), 4.08 (s, 1), 5.21 (s, 1), 5.27 (s, 1); ^{13}C NMR ($CDCl_3$) $\delta = 14.1$ (CH_3), 14.1 (CH_3), 18.5 (CH_3), 23.0 (CH_2), 23.1 (CH_2), 25.2 (CH_2), 25.6 (CH_2), 31.3 (CH_2), 34.3 (C), 35.4 (CH_2), 40.3 (CH), 45.1 (CH), 65.9 (CH_2), 69.5 (CH_2), 69.7 (CH_2), 69.8 (CH_2), 71.1 (CH_2), 74.1 (CH_2), 100.5 (C), 116.3 (CH_2), 142.3 (C); FTIR $\nu = 1657$ cm^{-1} (C═C), 1108 cm^{-1} (C−O−C); LC-MS (M + Na$^+$ = 1297.94); observed [M + Na]$^+$ = 1297.92; elemental analysis calcd (%) for $C_{74}H_{144}O_{15}$ (1274.96) C, 67.76; H, 10.66; found C, 67.71; H, 10.54.

b. *Block*-(BnO-)$_8$(Nk-)$_4$[G-4]-ene (30). This was prepared from (Nk-)$_4$[G-4]-methylallyl chloride (**29**) and purified by flash column chromatography on silica gel with hexanes−ethyl acetate gradient from 5% ethyl acetate to 10% ethyl acetate: yield 55%; ^{1}H NMR ($CDCl_3$) $\delta = 0.86$ (s, 12), 0.91 (t, 12, $J = 7.0$ Hz), 0.92 (t, 12, $J = 7.0$ Hz), 1.2−1.4 (m, 32), 1.62 (m, 8), 1.72 (m, 8), 2.15 (m, 6, $J = 5.8$ Hz), 3.3−3.7 (m, 80), 3.86 (s, 2), 3.87 (s, 2) 4.49 (s, 16), 5.11 (s, 2), 7.2−7.4 (m, 40); ^{13}C NMR ($CDCl_3$) $\delta = 14.1$ (CH_3), 14.1 (CH_3), 18.5 (CH_3), 23.0 (CH_2), 23.0 (CH_2), 25.2 (CH_2), 25.6 (CH_2), 31.3 (CH_2), 34.2 (C), 35.3 (CH_2), 40.3 (CH), 40.9 (CH), 65.9 (CH_2), 68.6 (CH_2), 68.9 (CH_2), 69.5 (CH_2), 69.6 (CH_2), 69.7 (CH_2), 69.8 (CH_2), 70.0 (CH_2), 71.3 (CH_2), 71.7 (CH_2), 73.3 (CH_2), 73.4 (CH_2), 74.1 (CH_2), 78.3 (CH), 100.5 (C), 112.7 (CH_2), 127.5 (CH), 127.5 (CH), 128.3 (CH), 138.4 (C), 142.9 (C); FTIR $\nu = 3030$ cm^{-1} (H−Ar), 1123 cm^{-1} (C−O−C); MS (MALDI-TOF) (*m/z*), [M + Ag]$^+$ (calcd 2648.4) found 2649.6; elemental analysis calcd (%) for $C_{152}H_{232}O_{30}$ (2539.5) C, 71.89; H, 9.21; found C, 71.68; H, 9.03.

Ketal Deprotection. *Block*-(BnO-)$_8$(HO-)$_8$[G-4]-ene (31). This was prepared from the hydrolysis of *block*-(BnO-)$_8$(Nk-)$_4$[G-4]-ene (**30**) with 0.2 M HCl in MeOH and characterized without further purification: yield 99%; ^{1}H NMR ($CDCl_3$) $\delta = 0.79$ (s, 12), 2.14 (m, 6, $J = 6.0$ Hz), 3.3−3.7 (m, 80), 3.87 (s, 2), 3.89 (s, 2), 4.49 (s, 16), 5.11 (s, 2), 7.2−7.4 (m, 40); ^{13}C NMR ($CDCl_3$) $\delta = 17.1$ (CH_3), 39.9 (CH), 40.0 (CH), 40.3 (CH), 40.9 (C), 67.8 (CH_2), 68.6 (CH_2), 68.8 (CH_2), 69.4 (CH_2), 69.5 (CH_2), 69.6 (CH_2), 69.8 (CH_2), 69.9 (CH_2), 70.2 (CH_2), 71.7 (CH_2), 71.7 (CH_2), 73.3 (CH_2), 75.9 (CH_2), 78.4 (CH), 113.2 (CH_2), 127.5 (CH), 127.6 (CH), 128.3 (CH), 138.0 (C), 142.8 (C); FTIR $\nu = 3420$ cm^{-1} (O−H), 3029 cm^{-1} (H−Ar), 1111 cm^{-1} (C−O−C); MS (MALDI-TOF) (*m/z*), [M + Ag]$^+$ (calcd 2150.5) found 2157.3; elemental analysis calcd (%) for $C_{152}H_{232}O_{30}$ (2042.6) C, 68.21; H, 8.29; found C, 68.10; H, 8.15.

Benzyl Ether Deprotection. *Block*-(HO-)$_8$(Nk-)$_4$[G-4]-ane (32). This was prepared from the hydrogenolysis of *block*-(BnO-)$_8$(Nk-)$_4$-[G-4]-ene (**30**) with 10% Pd/C in THF with basic alumina and characterized without further purification: yield 99%; ^{1}H NMR ($CDCl_3$) $\delta = 0.83$ (s, 12), 0.90 (t, 12, $J = 7.0$ Hz), 0.92 (t, 12, $J = 7.0$ Hz), 1.23 (d, 3), 1.2−1.4 (m, 32), 1.62 (m, 8), 1.71 (m, 8), 1.97 (m, 1, $J = 6.0$ Hz), 2.0−2.3 (m, 6), 3.3−3.7 (m, 84); ^{13}C NMR ($CDCl_3$) $\delta = 14.1$ (CH_3), 14.1 (CH_3), 18.5 (CH_3), 23.0 (CH_2), 23.1 (CH_2), 25.1 (CH_2), 25.6 (CH_2), 25.8 (CH_2), 31.2 (CH_2), 34.3 (C), 35.4 (CH_2), 40.0 (CH), 40.1 (CH), 40.2 (CH), 62.1 (CH_2), 62.1 (CH_2), 62.2 (CH_2), 62.3 (CH_2), 65.9 (CH_2), 69.2 (CH_2), 69.5 (CH_2), 69.7 (CH_2), 69.8 (CH_2), 74.1 (CH_2), 80.9 (CH), 100.5 (C); FTIR $\nu = 3434$ cm^{-1} (O−H), 1096 cm^{-1} (C−O−C); MS (MALDI-TOF) (*m/z*), [M + Ag]$^+$ (calcd 1928.4) found 1925.2; elemental analysis calcd (%) for $C_{96}H_{186}O_{30}$ (1820.5) C, 63.34; H, 10.30; found C, 63.23; H, 10.14.

Selective Functionalization. a. *Block*-(BnO-)$_8$($CH_3(OCH_2CH_2)_3$-O-)$_8$[G-4]-ene (33). This was prepared by alkylation of *block*-(BnO)$_8$-(HO)$_8$-[G-4]-ene (**31**) with the tosylate of triethylene glycol monomethyl ether and purified by flash column chromatography on silica gel with CH_2Cl_2/MeOH gradient from 3% methanol to 5% methanol: yield 89%; ^{1}H NMR ($CDCl_3$) $\delta = 0.91$ (s, 12), 2.07−2.17 (m, 6), 3.1−3.7 (m, 200), 3.86 (s, 2), 3.87 (s, 2), 4.48 (s, 16), 5.11 (s, 2), 7.2−7.4 (m, 40); ^{13}C NMR ($CDCl_3$) $\delta = 17.3$ (CH_3), 40.2 (CH), 40.3 (CH), 40.8 (CH), 40.9 (C), 58.9 (CH_3), 68.5 (CH_2), 68.8 (CH_2), 69.3 (CH_2), 69.5 (CH_2), 69.6 (CH_2), 69.7 (CH_2), 69.7 (CH_2), 69.8 (CH_2), 70.3 (CH_2), 70.4 (CH_2), 70.5 (CH_2), 70.5 (CH_2), 70.9 (CH_2), 71.6 (CH_2), 71.8 (CH_2), 73.1 (CH_2), 73.8 (CH_2), 78.2 (CH), 112.5 (CH_2), 127.3 (CH), 127.4 (CH), 128.2 (CH), 138.3 (C), 142.8 (C); FTIR $\nu = 3030$ cm^{-1} (H−Ar), 1125 cm^{-1} (C−O−C); MS (MALDI-TOF) (*m/z*), [M + Ag]$^+$ (calcd 3320.0) found 3315.6; elemental analysis calcd (%) for $C_{172}H_{280}O_{54}$ (3212.0) C, 64.32; H, 8.79; found C, 64.54; H, 8.96.

b. *Block*-(HO-)$_8$($CH_3(OCH_2CH_2)_3$O-)$_8$[G-4]-ane (34). This was prepared from the hydrogenolysis of *block*-(BnO)$_8$($CH_3(OCH_2CH_2)_3$O)$_8$-[G-4]-ene (**33**) with 10% Pd/C in THF and characterized without further purification: yield 99%; ^{1}H NMR ($CDCl_3$) $\delta = 0.91$ (s, 12), 0.93 (s, 3), 1.95−2.15 (m, 7), 3.0−3.7 (m, 212); ^{13}C NMR ($CDCl_3$) $\delta = 17.3$ (CH_3), 40.1 (CH), 40.2 (CH), 40.3 (CH), 41.0 (C), 58.9 (CH_3), 62.0 (CH_2), 69.4 (CH_2), 69.8 (CH_2), 70.4 (CH_2), 70.5 (CH_2), 70.6 (CH_2), 70.6 (CH_2), 70.9 (CH_2), 71.9 (CH_2), 73.9 (CH_2), 80.7 (CH); FTIR $\nu = 3430$ cm^{-1} (O−H), 1116 cm^{-1} (C−O−C); MS (MALDI-TOF) (*m/z*), [M + Ag]$^+$ (calcd 2601.0) found 2603.0; elemental analysis calcd (%) for $C_{116}H_{234}O_{54}$ (2493.1) C, 55.89; H, 9.46; found C, 55.72; H, 9.29.

c. *Block*-(BzO-)$_8$($CH_3(OCH_2CH_2)_3$O-)$_8$[G-4]-ane (35). This was prepared by esterification of *block*-(HO)$_8$($CH_3(OCH_2CH_2)_3$O)$_8$-[G-4]-ane (**34**) with BzCl in THF and purified by flash column chromatography on silica gel with dichloromethane−methanol gradient from 2% methanol to 4% methanol: yield 78%; ^{1}H NMR ($CDCl_3$) $\delta = 0.87$ (d, 3, $J = 6.7$ Hz) 0.91 (s, 12), 1.95−2.17 (m, 7), 3.1−3.7 (m, 188), 4.42 (m, 16), 7.39 (t, 16, $J = 7.6$ Hz), 7.52 (t, 8, $J = 7.4$ Hz), 8.00 (d, 16, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$) $\delta = 14.6$ (CH_3), 17.3 (CH_3), 34.2 (CH), 40.1 (CH), 40.2 (CH), 40.3 (CH), 40.7 (CH), 41.0 (C), 58.9 (CH_3), 63.5 (CH_2), 68.5 (CH_2), 69.0 (CH_2), 69.3 (CH_2), 69.5 (CH_2), 69.6 (CH_2), 69.7 (CH_2), 69.8 (CH_2), 70.3 (CH_2), 70.4 (CH_2), 70.5 (CH_2), 70.6 (CH_2), 70.9 (CH_2), 71.8 (CH_2), 73.8 (CH_2), 73.8 (CH_2), 75.7 (CH), 128.3 (CH), 129.5 (CH), 129.7 (C), 133.0 (CH), 166.0 (C); FTIR $\nu = 3030$ cm^{-1} (H−Ar), 1724 cm^{-1} (C═O), 1125 cm^{-1} (C−O−C); MS (MALDI-TOF) (*m/z*), [M + Ag]$^+$ (calcd 3432.8) found 3430.1; elemental analysis calcd (%) for $C_{172}H_{266}O_{62}$ (3326.0) C, 62.11; H, 8.06; found C, 62.28; H, 8.07.

Acknowledgment. Thanks are due to NSF-DMR 9816166 and the Molecular Design Institute (MDI-2) of the Lawrence Berkeley National Laboratory funded by DOE and ONR for financial support of this research. The authors also acknowledge Dr. M. Jayaraman.

Supporting Information Available: Experimental procedures and full characterization (^{1}H NMR, ^{13}C NMR, FTIR, MS, and elemental analysis), as well as the ^{1}H NMR spectra of compounds **14**, **15**, **26**, and **30**; the ^{13}C NMR spectra of compounds **14**, and **15**; and the MALDI-TOF mass spectra of compounds **4**, **6**, **8**, **16**, **20**, and **36**. This material is available free of charge via the Internet at http://pubs.acs.org. See any current masthead page for ordering information and Web access instructions.

JA001903V