Isophthalate Ester-Terminated Dendrimers: Versatile Nanoscopic Building Blocks with Readily Modifiable Surface Functionalities

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Abstract: The preparation and modification of highly functionalized polyether dendrimers containing a versatile diethyl isophthalate terminal group is presented. The convergent synthesis consists of the construction of diester-terminated dendrons containing benzylic bromide functions at the focal point and their subsequent attachment to 4,4′-biphenol cores. Dendrons up to the third generation can be prepared using recrystallization alone as the primary means of purification, allowing the synthesis to be performed on the scale of tens to hundreds of grams. The third and fourth generation bidendron dendrimers (with 32 and 64 terminal ester functionalities, respectively) have been subjected to a variety of surface modification reactions including hydrolysis, ester interchange, and amide−ester interchange, many of which proceed with complete conversion of the functional groups and in high isolated yield. The addition of alcohols such as benzyl alcohol or a first generation 3,5-di(benzyloxy)benzyl alcohol dendron to the dendrimer surface serves to increase the generation number of the dendrimers by one or two in what amounts to a "double convergent growth" approach. The analysis of these structurally precise dendrimers by matrix-assisted laser desorption ionization time of flight is described.

Introduction

Since Tomalia et al.[1ab] first reported the preparation of dendrimers in 1984 followed by Newkome et al.[1c] in 1985, there has been much interest in the synthesis of dendrimers containing specific surface groups[2] and these macromolecules have found use in a number of applications including, for example, solubilization,[3,4] catalysis,[5] biological recognition,[6] redox assemblies,[7] and irreversible molecular encapsulation.[8] From the studies of these existing dendritic systems, a clear objective[9] for future development is the efficient construction of dendrons and dendrimers possessing a controlled and reactive surface functionality that may be efficiently modified to accommodate specific chemical applications or to allow for further modular growth.[10]

It is envisaged that such a common and versatile dendritic precursor would find use as a general purpose nanoscopic building block or "molecular scaffold" to which specialized chemical units (such as optical chromophores, catalytic units, etc.) can be attached as needed to suit specific experimental requirements. In addition, the synthesis of a dendrimer with a high degree of surface functionalization (two or more chemical functions per chain end) would allow for the possibility of increasing the size of the dendrimer by performing subsequent branching reactions on its periphery without affecting the original dendritic pattern. In such a "double-stage" convergent growth approach,[10a,b] a dendrimer is first prepared by the convergent approach and then grown divergently by attaching additional groups or preformed dendrons to the dendrimer periphery. Finally, the presence of reactive groups on the dendrimer periphery would allow for the tailoring of select chemical properties, such as solubility characteristics or chirality, by performing chemical transformations on the surface groups.

The synthetic plan for a versatile, "general purpose" surface-functionalized dendrimer ought to allow for the production of a convenient building block which can be synthesized on a large enough scale so that multiple 100-gram quantities can be made and then taken in any applicable synthetic direction as needed. Several multiple-step syntheses have been successfully developed employing both convergent[10b,11] and divergent[10b,12] strategies. However, both synthetic strategies require rigorous

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(1) (a) Tomalia, D. A.; Dewald, J.; Hall, M.; Martin, S.; Smith, P. B. *Prepr. SPSJ Int. Polym. Conf., 1st* **1984**, 65. (b) Tomalia, D. A.; Baker, H.; Dewald, J.; Hall, M.; Kallos, F.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. *Polym. J.* **1985**, *17*, 117. (c) Newkome, G. R.; Yao, Z.-Q.; Baker, G. R.; Gupta, V. K. *J. Org. Chem.* **1985**, *50*, 2003.

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

(3) Hawker, C. J.; Wooley, K. L.; Fréchet, J. M. J. *J. Chem. Soc. Perkin. Trans. I* **1993**, 1287.

(4) (a)Newkome, G. R.; Moorefield, C. N.; Baker, G. R.; Johnson, A. L.; Behera, R. K. *Angew. Chem. Int. Ed. Eng.*, **1991**, *30*, 1176. (b) Mattei, S.; Seiler, P.; Diederich, F.; Gramlich, V. *Helv. Chim. Acta* **1995**, *78*, 1904.

(5) (a) Knapen, J. W. J.; van der Made, A. W.; de Wilde, J. C.; van Leeuwen, A. W.; Wijkens, P.; Grove, D. M.; van Koten, G. *Nature* **1994**, *372*, 659. (b) Lee, J.; Ford, W. T.; Moore, J. A.; Li, Y. *Macromolecules*, **1994**, *27*, 4632.

(6) (a) Newkome, G. R.; Lin, X.; Weic, C. D. *Tetrahedron: Asymmetry* **1991**, *2*, 957. (b) Roy, R.; Zanini, D.; Meunier, S. J.; Romanowska, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1869. (c) Aoi, K.; Itoh, K.; Okada, M. *Macromolecules* **1995**, *28*, 5391.

(7) (a) Miller, L. L.; Hashimoto, T.; Tabakovic, I.; Swanson, D. R.; Tomalia, D. A. *Chem. Mater.* **1995**, *7*, 9. (b) Bryce, M. R.; Davenport, W.; Moore, A. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1761.

(8) (a) Jansen, J. F. G. A.; Meijer, E. W.; de Brabander-van de Berg, E. M. M. *J. Am. Chem. Soc.* **1995**, *117*, 4417. (b) Jansen, J. F.; de Brabander-van den Berg, E. M. M.; Meijer, E. W. *Science* **1994**, *266*, 1226.

(9) Fréchet, J. M. J. *Science* **1994**, *263*, 1710.

(10) (a) Wooley, K. L.; Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1991**, *113*, 4252. (b) Xu, Z.; Kahr, M.; Walker, K. L.; Wilkins, C. L.; Moore, J. S. *J. Am. Chem. Soc.* **1994**, *116*, 4537. (c) Kawaguchi, T.; Walker, K. L.; Wilkins, C. L.; Moore, J. S. *J. Am. Chem. Soc.* **1995**, *117*, 2159. (d) Pesak, D. J., Moore, J. S. *Polym. Mater. Sci. Eng.* **1995**, *73*, 354.

(11) Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638. Hawker, C. J.; Fréchet, J. M. J. *J. Chem. Soc., Chem. Commun.* **1990**, 1010.

(12) (a) Tomalia, D. A.; Naylor, A. M.; Goddard, W. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 138. (b) Newkome, G. R.; Moorefield, C. N.; Baker, G. R. *Aldrichimica Acta* **1992**, *25*, 31. (c) Voit, B. I. *Acta Polym.* **1995**, *46*, 87. (d) de Brabander-van den Berg, E. M. M.; Nijenhuis, A.; Mure, M.; Keulen, J.; Reintjens, R.; Vandenbooren, B.; Bosman, B.; de Raat, R.; Frijns, T.; Wal, S. v. d.; Castelijns, M.; Put, J.; Meijer, E. W. *Macromol. Symp.* **1994**, *77*, 51. (e) Tomalia, D. A. *Adv. Mater.* **1994**, *7/8*, 529.

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purification of the intermediates to remove partially unreacted or imperfect species which may otherwise propagate to form dendrimers with greater levels of defects after subsequent synthetic steps. To this end, column chromatography has been predominantly employed. Chromatographic techniques, while efficient methods of purification, generally restrict the scale upon which dendrimer synthesis can be attempted. Typically, for the chromatographic columns used in research laboratories, only small amounts of dendrimer (ca. 20 g) may be purified at any one time. Since higher generation dendrimers can involve over ten synthetic steps before they achieve a globular shape,[9,13] it is usually necessary to begin the synthetic process with significant quantities of starting materials in order to attain suitable amounts of higher generation dendrimers. Thus, new routes to chain end functionalized dendritic structures that avoid chromatographic separations are among our primary targets.

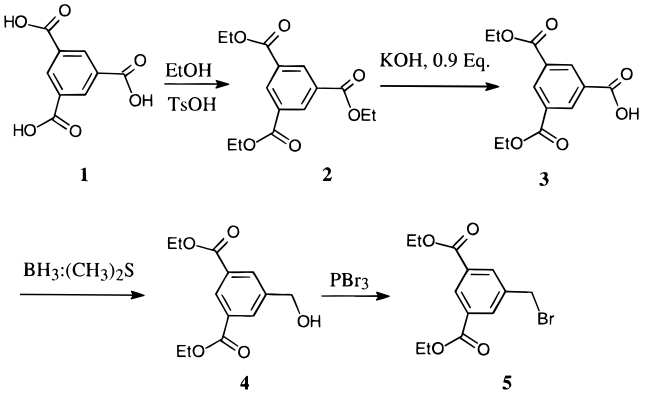
Here we present a facile, convergent synthesis of highly reactive, isophthalate ester-terminated[10d] dendrimers based upon the 3,5-dihydroxybenzyl alcohol repeating unit. Dendrons up to the third generation can be made which may be brought to high purity by recrystallization alone. When the need for column chromatography is alleviated, these dendrons may be synthesized and purified on a scale of hundreds of grams using readily available apparatus. These third and fourth generation diester-terminated dendrons may then be attached to a biphenol core to afford high yields of dendrimers containing 32 or 64 terminal ester functions, respectively. Hydrolysis of the ester groups to the carboxylic acids results in the drastic modification of the solubility properties of the dendrimer. In addition, the reaction of the peripheral ester groups with phenyl-containing nucleophiles, for example, via transesterification or amide−ester interchange, leads to the addition of one or more layers of aromatic rings which effectively increases the generation number of the dendrimer. Therefore, the reaction of a third generation bidendron dendrimer with our classical first generation benzyl ether-terminated dendron[11] would afford in a single step a final product containing two additional layers of aromatic rings.

Results and Discussion

Design and Synthesis of Isophthalate-Terminated Dendrons. Isophthalate diesters were chosen as suitable surface groups for the dendron precursors from which to further construct a general purpose molecular scaffold for several reasons. Our previous experience[3] with ester units on dendrimer peripheral surfaces has revealed that these functionalities are suitably stable to the reaction conditions of both the Williamson ether synthesis and the PPh_3/CBr_4 bromination reactions. Furthermore, the peripheral ester functionalities are capable of being converted to a wide range of other functional groups by a variety of high yielding and dependable reactions. Although we have previously synthesized monoester-terminated dendrimers,[3] we sought to develop a terminating group which would allow for a higher degree of chain end functionality while also preserving symmetry and providing access to additional reactions involving the dendrimer surface.

Dimethyl 5-(bromomethyl)isophthalate was first investigated as a suitable chain end unit for the construction of dendrons using 3,5-dihydroxybenzyl alcohol as the monomer in a convergent synthesis. This unit, because of its "meta" substitution pattern, allows for a symmetrical array of attached surface groups. It was found, however, that the first generation dendrons constructed with this terminal unit were remarkably insoluble in a wide range of organic solvents, and this reason alone prevented suitable purification and further reaction. It was expected that increasing the steric bulk of the terminal ester groups from methyl to ethyl would result in dendrons which would possess somewhat enhanced solubility characteristics and thus provide a route amenable to purification by recrystallization alone.

Scheme 1. Preparation of the Diethyl 5-(Bromomethyl)isophthalate Terminal Group



The desired diethyl 5-(bromomethyl)isophthalate terminal unit **5** was synthesized using a four-step procedure (see Scheme 1). 1,3,5-Benzenetricarboxylic acid was first converted to the ethyl triester **2** by acid catalyzed Fischer esterification employing *p*-toluenesulfonic acid as the catalyst.[14] This triester was subsequently hydrolyzed to the diester/monoacid **3** by addition of 0.9 equiv of KOH, and the carboxylic acid group was then reduced selectively[15] to the benzyl alcohol by reaction with borane−dimethyl sulfide complex. Upon treatment with PBr_3, the benzylic alcohol **4** was converted to the corresponding bromide **5** in excellent yield.

The convergent synthesis of the diester-terminated dendron fragments is shown in Scheme 2. The shorthand notation "-(*m*-$EtO_2C)_{32}$-[G-4]-OH" describes the dendrimer chain functionality (32 ethyl ester groups with "*meta*" (3,5) substitution attached to the 16 terminal aromatic rings) followed by the generation number (fourth) followed by the focal point group functionality (alcohol). Coupling of 2 equiv of the diethyl 5-(bromomethyl)isophthalate end group **5** with the 3,5-dihydroxybenzyl alcohol monomer **6** was performed in refluxing acetone in the presence of K_2CO_3 and 18-crown-6 to afford (*m*-$EtO_2C)_4$-[G-1]-OH (**7**) in 90% yield. Conversion to the corresponding benzylic bromide **8** was then undertaken by reaction[11] with PPh_3 and CBr_4 in THF. As a result of the limited solubility of the dendron **7** in THF at room temperature, this reaction was carried out at a slightly elevated temperature of 50 °C. In contrast, our previously reported benzyl ether-terminated dendrimers[11] were very soluble in THF at room temperature up to the sixth generation.

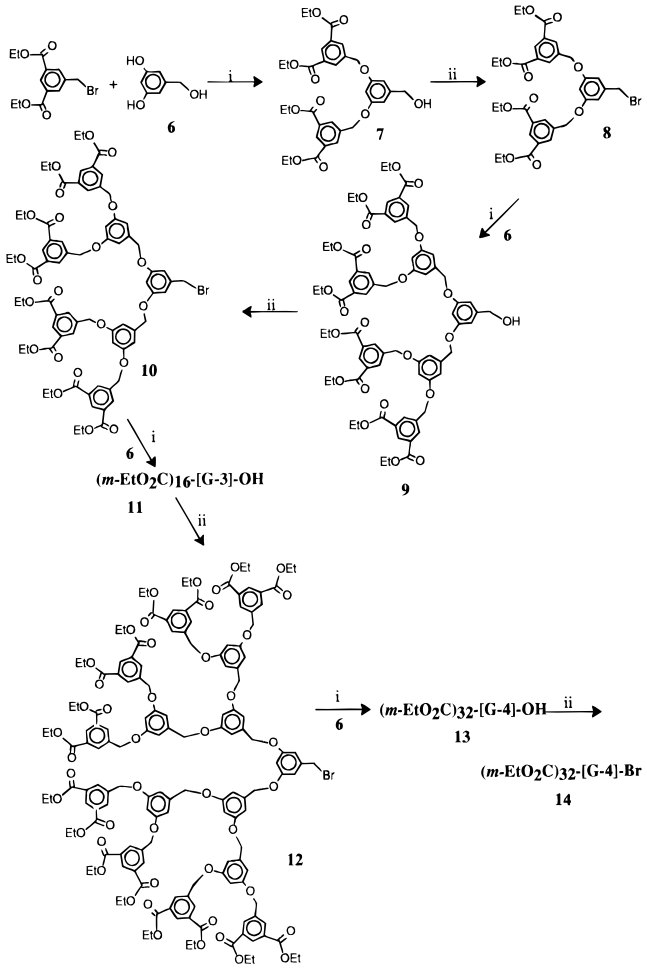
Surprisingly, the coupling reaction of the second generation alcohol **8** with monomer **6** under standard alkylation conditions (4 equiv of K_2CO_3, 0.1 equiv of 18-crown-6 in refluxing acetone or THF) afforded a complex mixture of at least six different compounds. Analysis of the reaction mixture by matrix-assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF MS) showed molecular weights corresponding to transesterification products formed by the reaction of the

(13) (a) Mourey, T. H.; Turner, S. R.; Rubinstein, M.; Fréchet, J. M. J. *Macromolecules* **1992**, *25*, 2401. (b) Hawker, C. J.; Wooley, K. L.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1993**, *115*, 4375. (c) Saville, P. M.; Reynolds, P. A.; White, J. W.; Hawker, C. J.; Fréchet, J. M. J; Wooley, K. L.; Penfeld, J.; Webster, J. R. P. *J. Phys. Chem.* **1995**, *99*, 8283. (d) Naylor, A. M.; Goddard, W. A., Kiefer, G. E., Tomalia, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 2339.

(14) (a) Mp 133−134 °C, lit.[14b] 133−134 °C. (b) Linde, D. R., Ed.; *CRC Handbook of Chemistry and Physics*, 74th ed.; CRC Press: Boca Raton, FL, 1993; p 3−94.

(15) Hutchins, R. O.; Cistone, F. *Org. Prep. Proced. Int.* **1981**, *13*, 225.

Scheme 2. Synthesis of Diester-Terminated Dendrons[a]



[a] Reagents: *i*, K_2CO_3, 18-crown-6; *ii*, CBr_4, PPh_3.

benzylic hydroxyl group of the product **9** with a terminal ester function of another molecule (either product **9** or precursor **8)**. Another dominant byproduct evident in the MALDI-TOF spectrum had a molecular weight corresponding to the addition of three molecules of the bromide **8** to a single unit of monomer **6**. Such a compound might also have been formed by reaction of the desired dendron product **9** with an additional equivalent of the benzylic bromide **8** either by carbon (ring) or oxygen (benzyl alcohol) alkylation mechanisms. Extensive investigation revealed that the formation of these byproducts was temperature dependent and could be suppressed by decreasing the reaction temperature to 40 °C and employing a higher concentration of 18-crown-6 (0.8 equiv). Repeated recrystallization of the product in 3:1 acetone/THF afforded the desired dendron **9** in high purity and reasonable yield (69%). The benzylic alcohol **9** was subsequently converted to the benzylic bromide **10** in 89% yield by employing PPh_3 and CBr_4 in THF at 60 °C and purified by recrystallization from THF/acetone.

The coupling reaction of the second generation bromide **10** with monomer **6** to give the third generation alcohol **11** proved to be less susceptible to the formation of byproducts than the formation of **9**. The alkylation was carried out at a slightly higher temperature (45−50 °C) in THF due to the low solubility of **10** in acetone. Again, a high concentration of 18-crown-6 (0.65 equiv) was used to drive the reaction to completion in 72 h. The product was recrystallized twice from THF/CH_2Cl_2 to give a 77% yield of the pure product. Conversion to the bromide **12** proceeded with a yield of 82% after purification by recrystallization (once from THF and once from THF/MeOH).

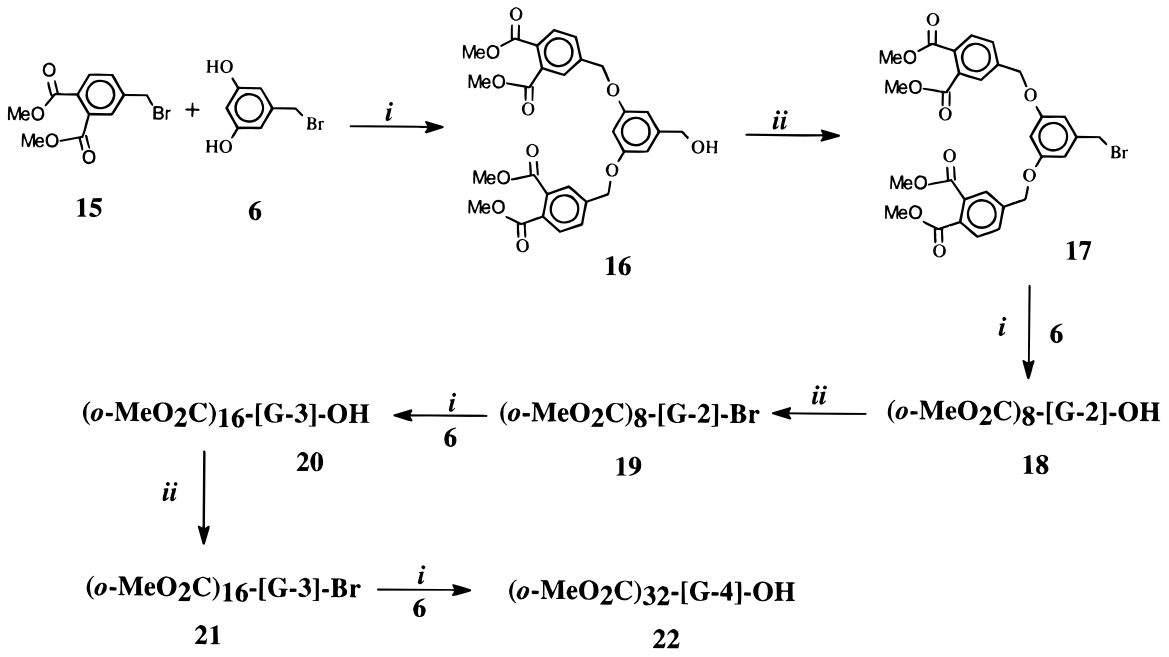
The G-3 bromide **12** is the largest diester-terminated dendrimer that can be purified by recrystallization alone, and hence, the largest that can be synthesized in quantity without resorting to chromatographic purification. The reaction of **12** with monomer **6** to yield the fourth generation dendron **13** was quite slow and a reaction time of 1 week was required for completion. The product, a clear, amorphous material, proved difficult to purify using silica gel column chromatography, since the bands tended to elute out as a single fraction with little separation. Nonetheless, use of a slowly increasing solvent gradient (1−15% of Et_2O in CH_2Cl_2 as eluent) allowed isolation of a product of acceptable purity in 63% yield. The fourth generation alcohol **13** was brominated in 77% yield using 3 equiv of CBr_4 and PPh_3. Again, column chromatography with a slow gradient (1−10% Et_2O/CH_2Cl_2) was employed for purification.

Due to the availability of large quantities of the 4-methylphthalic anhydride starting material, we also tested asymmetric dimethyl 4-(bromomethyl)phthalate (**15**) as a candidate for a potential diester terminating group. The synthesis, which consisted of esterification of the anhydride with MeOH followed by benzylic bromination with *N*-bromosuccinimide, proved to be difficult, since the bromination step afforded a mixture of starting material and mono- and dibrominated products from which the desired bromide could only be isolated in 95% purity by repeated vacuum distillations. Dendrimers up to the fourth generation (see Scheme 3) synthesized with this end group existed either as oils or as amorphous solids and could only be purified by column chromatography. The isophthalate ester unit, thus, was chosen as our peripheral group of choice due to the ability to recrystallize (and hence purify) the dendrons terminated with this unit.

Coupling of Dendrons to Core Units. Although we have previously synthesized "tridendron" dendrimers through the attachment of three dendritic bromide fragments to a 1,1,1-tris-(4-hydroxyphenylethane) "tricore",[11] the isophthalate ester-terminated dendrons proved relatively unreactive to this trifunctional core under conditions identical to those used previously for our benzyl ether-terminated dendrimers.[11,2] Similar observations were also made in our previous work with methyl benzoate(monoester)-terminated dendrimers.[16] MALDI-TOF MS monitoring of the progress of the coupling reaction typically showed a very slow disappearance of the dendritic bromide, with concurrent appearance of the desired tridendron. Long reaction times (∼1 week in refluxing THF) were required to drive the reaction to ca. 40% completion, after which further heating only resulted in the gradual hydrolysis of the bromide. Even for dendrons as small as the second generation, the reaction proved surprisingly sluggish. Although MALDI-TOF MS monitoring of the reaction sometimes showed very small, transitory peaks corresponding to the intermediate mono- and dialkylated components, the only peaks of significant magnitude observed were those corresponding to the unreacted bromide, the fully alkylated core, and the hydrolyzed bromide. Such observations suggest a coupling process in which rapid secondary and tertiary alkylations follow a slow, initial alkylation. Qualitatively similar results were observed in previous work[10a] in which dendritic bromide units were attached to macromolecular "hypercores" containing large numbers of phenolic surface functionalities. For example, GPC monitoring of the attachment of six polyether dendrons[11] to a hexafunctional phenolic core showed that the hexadendron dendrimer was the major product observed throughout the alkylation reaction. It appears that the attachment of one dendron to a mutifunctional core enhances its reactivity toward further alkylation. This

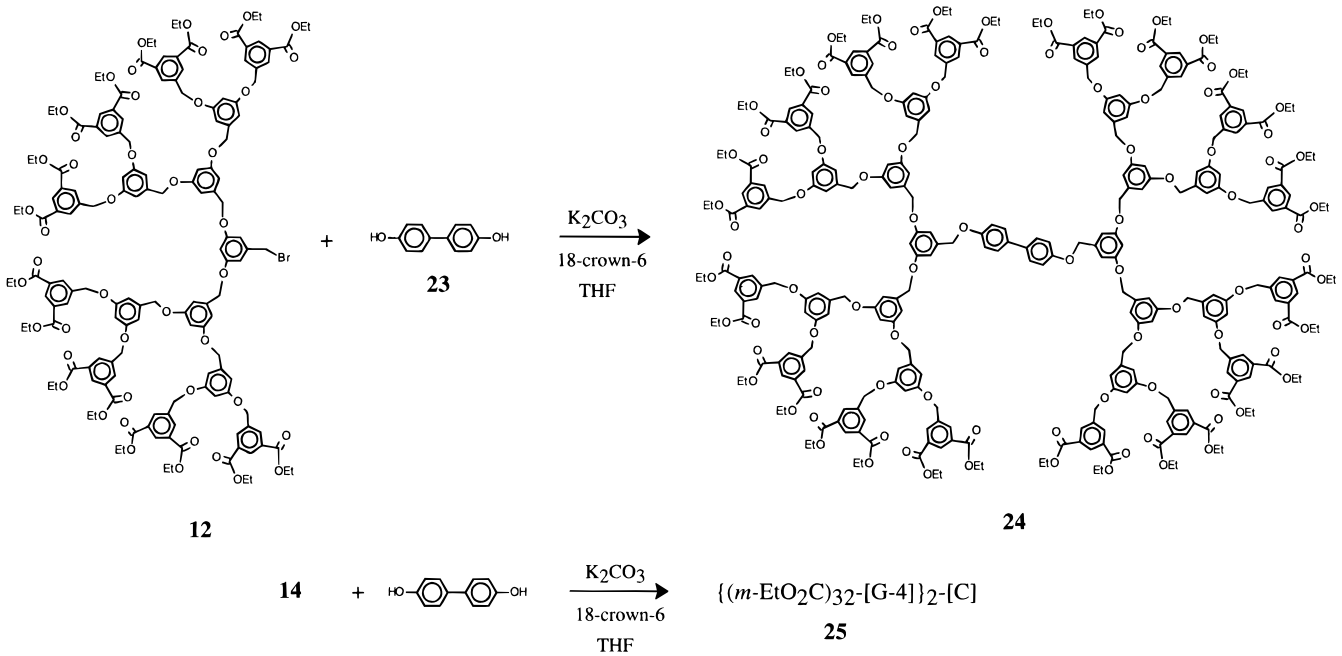
(16) Hawker, C. J.; Fréchet, J. M. J. Unpublished results.

Scheme 3. Synthesis of Dendrons Terminated with Asymmetric Dimethyl 5-(Bromomethyl)phthalate End Group[a]



[a] Reagents: *i*, K_2CO_3, 18-crown-6; *ii*, CBr_4, PPh_3.

Scheme 4. Coupling Reactions of Third and Fourth Generation Dendritic Bromides with 4,4′-Biphenol

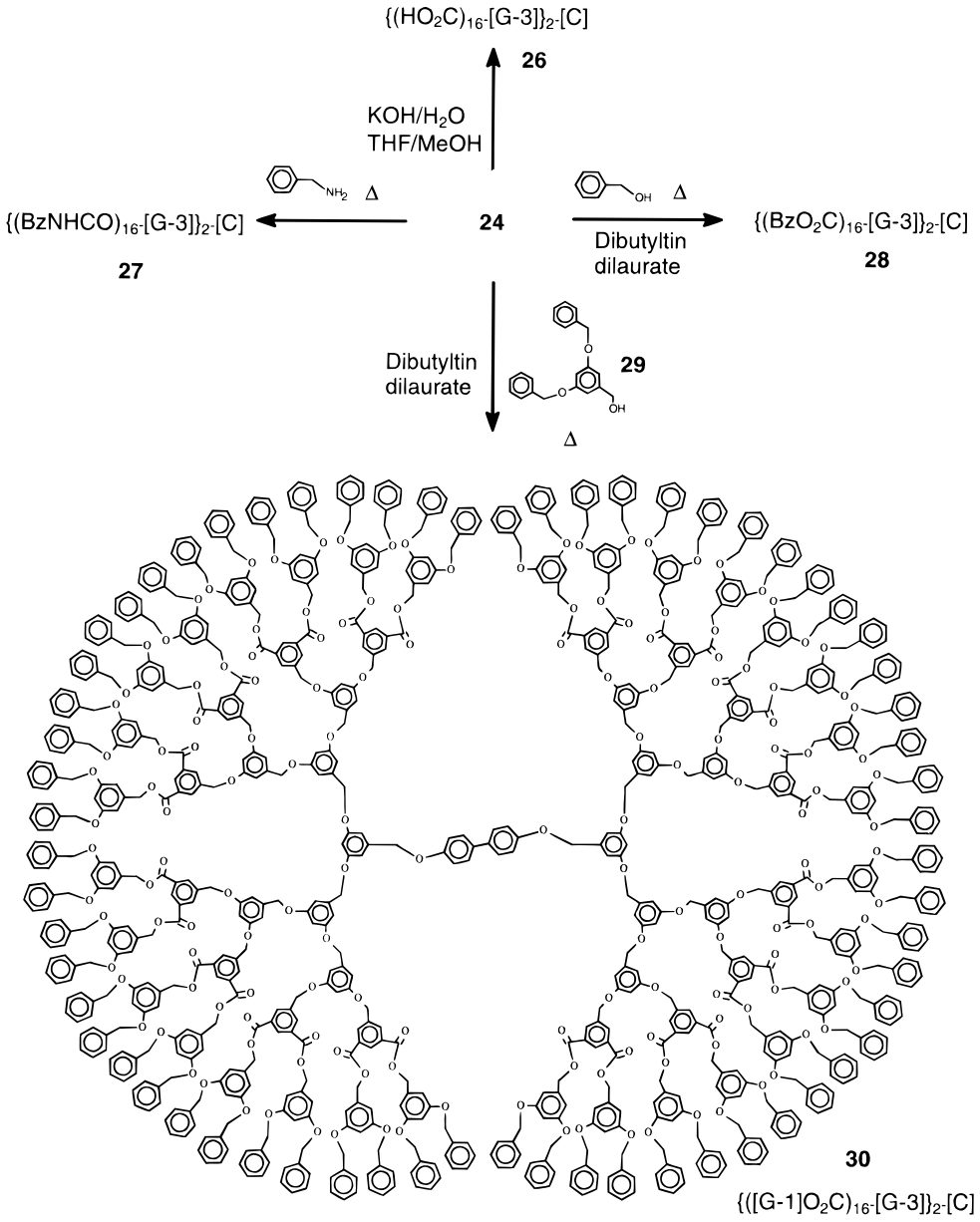


finding may be related to a simple phenomenon of enhanced solubility or to a local polarity or nanoenvironment effect. It is interesting to note that the unsubstituted benzylether-terminated dendrons[10a,11] readily couple to a trifunctional-, hexafunctional-, or even larger polyfunctional core to afford high yields of the fully alkylated dendrimers, while the analogous ester-terminated dendrons are sluggish in their reaction with a simple trifunctional core.

In contrast to the results with the trifunctional core, the alkylation reactions of difunctional core biphenol (**23**) with either (m-$EtO_2C)_{16}$-[G-3]-Br (**12**) or (m-$EtO_2C)_{32}$-[G-4]-Br (**14**) proceed cleanly to completion in 24 h with typical yields of 90−95%. The resultant third and fourth generation bidendron dendrimers **24** and **25** (see Scheme 4) have nominal molecular weights of 5646 and 11346 amu respectively. Again, monitoring of the alkylation of the bifunctional core by chromatography or MALDI only reveals the fully alkylated product and starting material, with little or no monoalkylated core visible throughout the reaction.

Surface Modification Reactions. The diester-terminated bidendron dendrimers were subjected to a variety of chemical transformations of the ester functionality including hydrolysis, ester interchange, and ester−amide interchange. Both **24** and **25** could be easily hydrolyzed to the corresponding carboxylic acid-terminated dendrimers **26** and **31** (see Schemes 5 and 6) in very high yield (98% for each). Both hydrolyses were carried out using a large excess of KOH in a three-component solution of THF/H_2O/MeOH. While **26** could be isolated by precipitation with acid followed by filtration on a membrane filter, acidification of the crude fourth generation carboxylate-terminated dendrimer **31** afforded a milky suspension which could not be successfully filtered. The product was isolated

Scheme 5. Surface Group Transformations of Third Generation Diester-Terminated Bidendron Dendrimer **24**



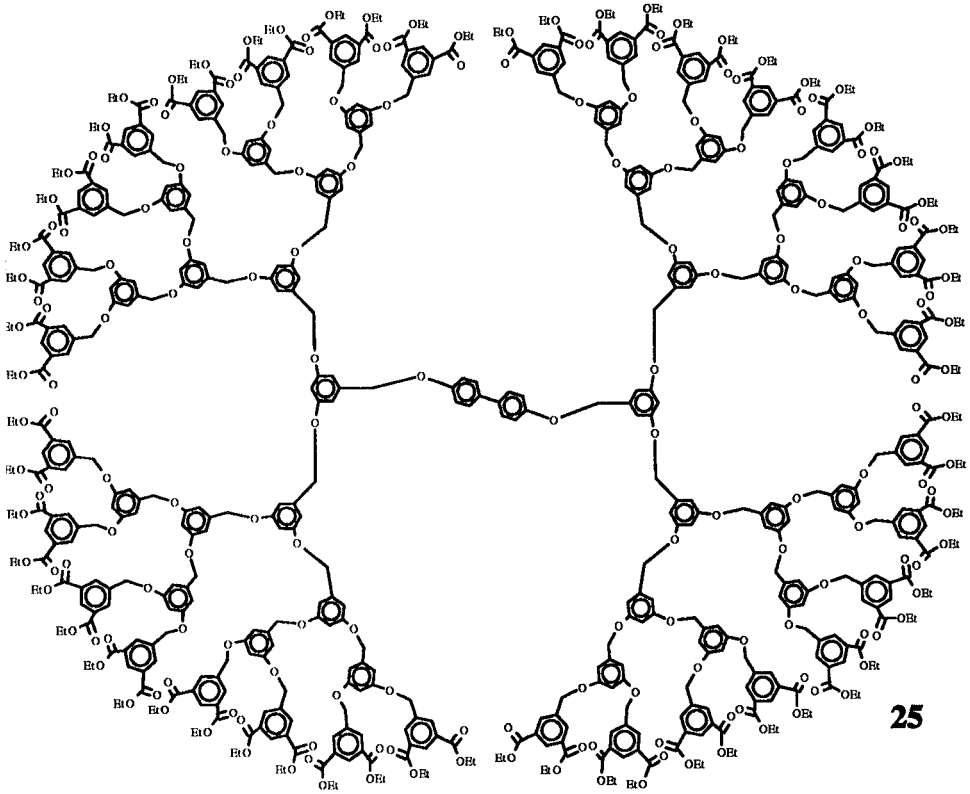
by concentrating the suspension, adding brine, and extracting with THF. Both isophthalic acid-terminated dendrimers have a high solubility in aqueous base, are slightly soluble in DMF, DMSO, pyridine, and THF, and are completely insoluble in solvents of low to medium polarity.

Attempted amide−ester interchange reactions of the diester-terminated bidendron dendrimer **24** gave different results depending on the specific amine nucleophile used. In a typical reaction, **24** was heated at 130−160 °C for 72 h in one of four different neat amines, at which time the excess amine was removed *in vacuo* and the products were analyzed. The reaction with the secondary amines *N*-methyl benzylamine and *N*-methyl aniline gave complete recovery of starting material. The reaction with nonylamine gave a polydisperse, partially reacted product (∼70% mean conversion) after 48 h and could not be driven appreciably further by longer reaction times, possibly due to steric crowding by the bulky, long-chain amines. Raising the temperature of the reaction to 190 °C led to the gradual decomposition of the dendrimer. The product (**27**) of the reaction with benzylamine was only soluble in DMSO and DMF and could not be fully purified. Nonetheless, ^{1}H NMR analysis showed a spectrum consistent with the expected product, with complete disappearance of the ethyl ester resonances. Despite the low solubility of the product in THF, a MALDI-TOF spectrum could be obtained which showed a weak, broad signal at 7398 amu (7600 calculated). Similarly, IR analysis gave a spectrum consistent with the proposed structure, where the ester carbonyl band at 1725 cm^{-1} is replaced by an amide carbonyl band at 1655 cm^{-1}.

The third and fourth generation diester-terminated bidendron dendrimers (**24** and **25**) yielded the benzyl ester-terminated dendrimers **28** and **32** respectively when heated for 24 h in neat benzyl alcohol in the presence of dibutytin dilaurate catalyst. The products, obtained in respective yields of 90 and 88%, were easily soluble in THF and CH_2Cl_2, and no residual ethyl ester groups could be detected by ^{1}H (see Figure 1) or ^{13}C NMR analysis.

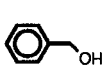
The ester interchange reaction with benzyl alcohol leads to a molecular weight increase from 5644 to 7630 amu (calculated values) for the third generation dendrimer **24** and from 11346 to 15318 amu (calculated values) for the fourth generation dendrimer **25**. The addition of another layer of aromatic rings, in effect, increases the generation number of the dendrimers by one, leading to structures **28** and **32** that are equivalent to fourth and fifth generation bidendrons, respectively.

Scheme 6. Surface Group Transformations of Fourth Generation Diester-Terminated Bidendron Dendrimer **25**



25

Dibutyltin dilaurate

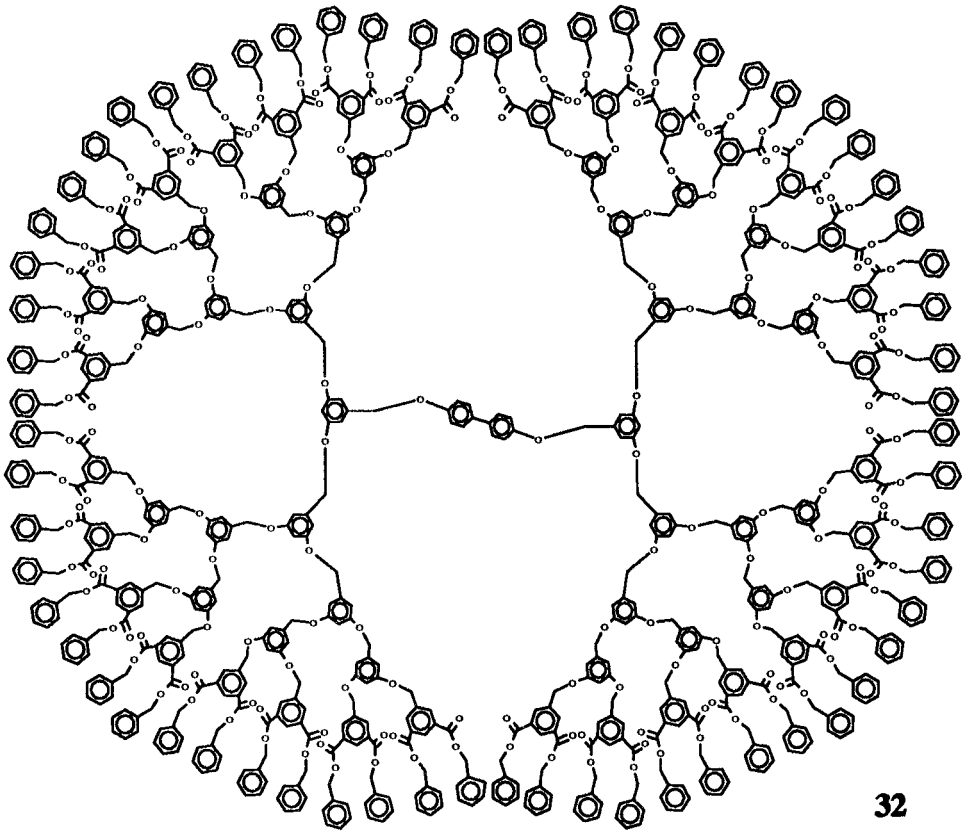


Δ

KOH/H_2O
THF/MeOH

$\{(HO_2C)_{32}[G\text{-}4]\}_2[C]$

31



32

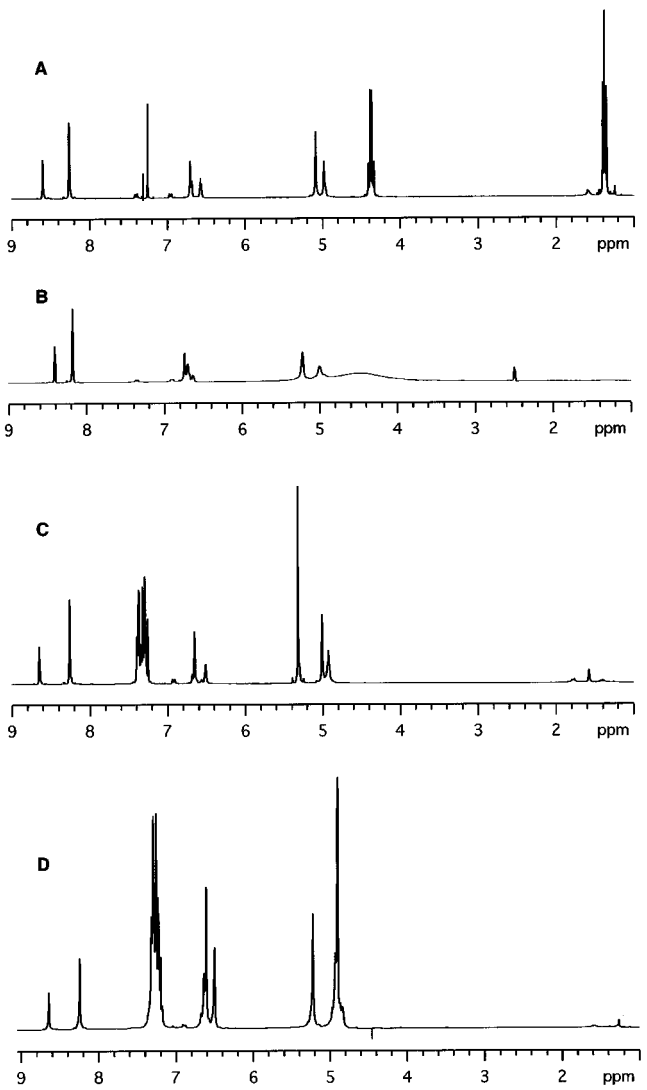


Figure 1. Comparison of ^{1}H NMR spectra of (a) {(*m*-$EtO_2C)_{16}$-[G-3]}$_2$-[C] (**24**)/$CDCl_3$, (b) {$(HO_2C)_{16}$-[G-3]}$_2$-[C] (**26**)/DMSO-d_6, (c) {-$(BzO_2C)_{16}$-[G-3]}$_2$-[C] (**28**)/$CDCl_3$, (d) {([G-1]-$O_2C)_{16}$-[G-3]}$_2$-[C] (**30**)/$CDCl_3$.

The success of the ester interchange reactions using benzyl alcohol led us to attempt the "one-pot" addition of two generations at once via the reaction with 3,5-di(benzyloxy)benzyl alcohol ([G-1]-OH) (**29**). The third generation bidendron **24** was heated in molten **29** in the presence of the dibutytin dilaurate catalyst for 36 h at 160−170 °C and then purified by column chromatography followed by precipitation into methanol. Analysis of the product by ^{1}H and ^{13}C NMR and MALDI-TOF MS again indicated that the reaction had proceeded with complete conversion to yield the expected bidendron **30**, which is essentially equivalent to a fifth generation [G-5] dendrimer. This one-pot reaction resulted in a very substantial increase in molecular weight from 5644 to 14422 amu, and the addition of two layers of aromatic rings to the periphery of the dendrimer. The high reaction yield (87%) suggests that it may be possible to carry out the addition of even larger dendritic alcohols using this very simple and efficient method.

This use of this ester interchange double-stage convergent growth approach differs from other known accelerated dendrimer syntheses[10] in several respects. In a previous paper,[10a] we reported a double-stage convergent growth approach in which a variety of dendritic hypercores containing protected terminal phenol groups was utilized. After deprotection, each of the hypercores was allowed to react with the required amount of dendritic bromides of various sizes to afford good yields of fully alkylated large dendrimers with molecular weights up to 160 000 amu. The hypercores, however, were composed of extended, flexible segments which provide for ample spacing of the attached dendritic fragments but which differ from them in chemical topology. The ester interchange double-stage convergent method, in contrast, largely preserves the chemical homogeneity, regularity of branching, and semirigid nature of the dendrimer. A notable feature of our new approach is that the diester-terminated dendrimers contain two reactive functional groups per chain end, compared to one for the hypercore, and no deprotection step is required to activate the peripheral groups.

The recently reported "double-exponential" growth approach[10c] of Moore et al. provides a particularly elegant example of a somewhat different strategy for accelerated dendrimer growth. Moore's strategy, involving the use of an AB_2 type monomer with orthogonally protected, reactive functions, offers the advantage of simultaneous growth of both the hypercore and the peripheral dendrons.

MALDI-TOF MS Characterization. The primary analytical techniques used in the analysis of the isophthalate-terminated dendrons, bidendron dendrimers, and reactive intermediates were ^{1}H NMR, FT-IR, and MALDI-TOF MS. Of these methods, MALDI-TOF MS proved the most valuable, giving a fast and accurate indication of the purity of the dendrimer analyzed and allowing for the identification of defects or impurities present. In addition, MALDI-TOF spectra could be easily taken from samples withdrawn directly from the reaction mixtures for TLC analysis, thus providing a convenient way to monitor ongoing reactions and identify all of the species present. The success of this method is known to be very dependent on the choice of both the matrix and the solvent used in sample preparation. Of the many matrices tested in this study, the previously reported[17] system of indoleacrylic acid/THF gave the best results for all of the dendritic compounds reported. 2-(4-Hydroxyphenylazo)-benzoic acid (HABA)[18] also gave good MALDI spectra in most cases, albeit with larger peak widths. In addition, 2,5-dihydroxybenzoic acid, which has found use as a matrix for polar linear polymers,[19] gave acceptable results for the acid-terminated dendrimer **26** in both positive and negative ion modes. Clear spectra with good signal to noise ratios were obtained over the entire molecular weight range studied from 609 amu for **7** 15318 amu for **32** and with typical mass error measurements of between 0.05 and 0.1%.

Figures 2 and 3 show representative MALDI-TOF spectra of several of the larger dendrimers synthesized. All of the spectra confirm that the products are of very high purity and essentially monodisperse. For the sample containing free carboxylic end groups, small peaks that may be indicative of a decarboxylation process caused by the MALDI measurement itself are seen. For example, the spectrum in Figure 2b taken for compound **26** shows the expected peak near a mass of 4781 corresponding to the K-metalated mass ion (M + K), with very small peaks near 4601, 4300, and 3700. Perhaps coincidentally, these three peaks could be attributed to the loss of 4, 11, and 25 molecules of CO_2 from the mass ion. For compound **31**, which also has a surface rich in carboxylic acid groups (it has 64), small peaks that may suggest the loss of 4, 11, 25, and 53 molecules of CO_2 are visible at 9386, 9090, 8463, and 7287 D, in addition to the expected and dominant peak for the pure product at 9566 (M + Na). The periodicity observed for the number of CO_2 molecules that may be lost as a result of the measurement may or may not be a coincidence.

(17) Leon, J. W.; Fréchet, J. M. J. *Polym. Bull.* **1995**, *35*, 449.
(18) Montaudo, G.; Montaudo, M. S.; Puglisi, C.; Samperi, F. *Rapid Commun. Mass Spectrom.* **1994**, *8*, 1011.
(19) Bahr, U.; Deppe, A.; Karas, M.; Hillenkamp, F. *Anal. Chem.* **1994**, *64*, 2866.

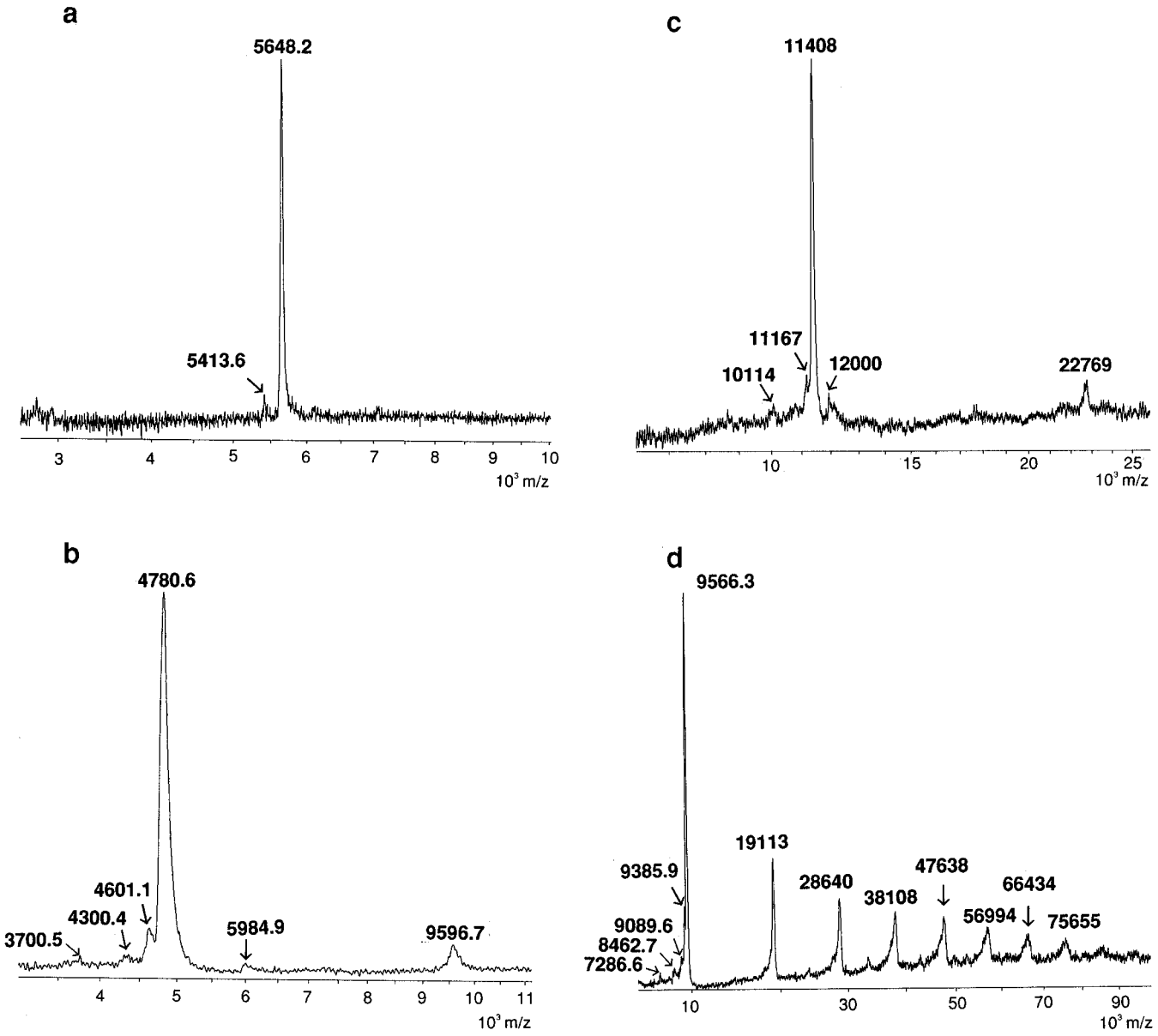


Figure 2. MALDI-TOF MS of diester- and diacid-terminated dendrimers: (a) {(*m*-$EtO_2C)_{16}$ -[G-3]}$_2$-[C] (**24**); (b) {$(HO_2C)_{16}$-[G-3]}$_2$-[C] (**26**); (c) {(*m*-$EtO_2C)_{32}$-[G-4]}$_2$-[C] (**25**); (d) {$(HO_2C)_{32}$-[G-4]}$_2$-[C] (**31**).

Another interesting feature of the MALDI spectra is the phenomenon of "clustering" manifested by the appearance of singly charged multiples of the mass ion, which is evident to some degree in most of the spectra. The spectra of **24** and **25** each contain a $2M^+$ cluster in addition to the metalated (potassium for **24** and **25**) mass ion. This clustering phenomenon is evident to a much greater degree in the spectra of dendrimers **28**, **30**, **31**, and **32**, each showing higher clusters with intensities that decrease with molecular weight. The largest cluster present is a $9M^+$ ion which appears in the spectrum of the acid-terminated dendrimer **31**. Although the clustering phenomenon is not uncommon in MALDI-TOF MS and has been documented for both linear polymers[20] and dendrimers,[21] such a large cluster is unusual, since clusters larger than a tetramer had not been previously reported. Analysis of these compounds by other methods, including gel permeation chromatography, shows no evidence for the existence of these higher molecular weight multiples as discrete species.

(20) Danis, P. O.; Karr, D. E. *Org. Mass Spectrom.* **1993**, *28*, 923.
(21) Walker, K. L.; Kahr, M. S.; Wilkins, C. L.; Xu, Z.; Moore, J. S. *J. Am. Soc. Mass Spectrom.* **1994**, *5*, 731.

^{1}H NMR. In general, ^{1}H NMR showed the same, expected trends seen in our previous studies of benzyl ether-[11] and monoester-terminated dendrimers.[3] In addition to its use for routine characterization, ^{1}H NMR proved invaluable for the monitoring of hydrolysis, ester interchange, and amidation reactions for the diester-terminated dendrimers. Figure 1 shows proton spectra of the ethyl ester- and carboxylic acid-terminated third generation bidendron dendrimers (**24** and **26**, respectively) in addition to the "pseudo" fourth and fifth generation dendrimers **28** and **30** synthesized by the ester interchange method. For both the hydrolysis and ester interchange products, note the complete disappearance of the triplet at δ 1.37 ppm and the quartet at δ 4.37 ppm pertaining to the ethyl ester protons. For the benzyl-terminated products **28** and **30**, the presence of the added peripheral benzyl groups is evidenced by appearance of its characteristic aromatic multiplet at δ 7.2−7.4 ppm. Both compounds also show the growth of additional peaks in the benzylic region (δ 4.9−5.4 ppm), corresponding to the benzyl groups introduced by the ester interchange reaction. The ^{13}C NMR spectra also showed the complete disappearance of the ethyl carbons and the appearance of the carbon resonances

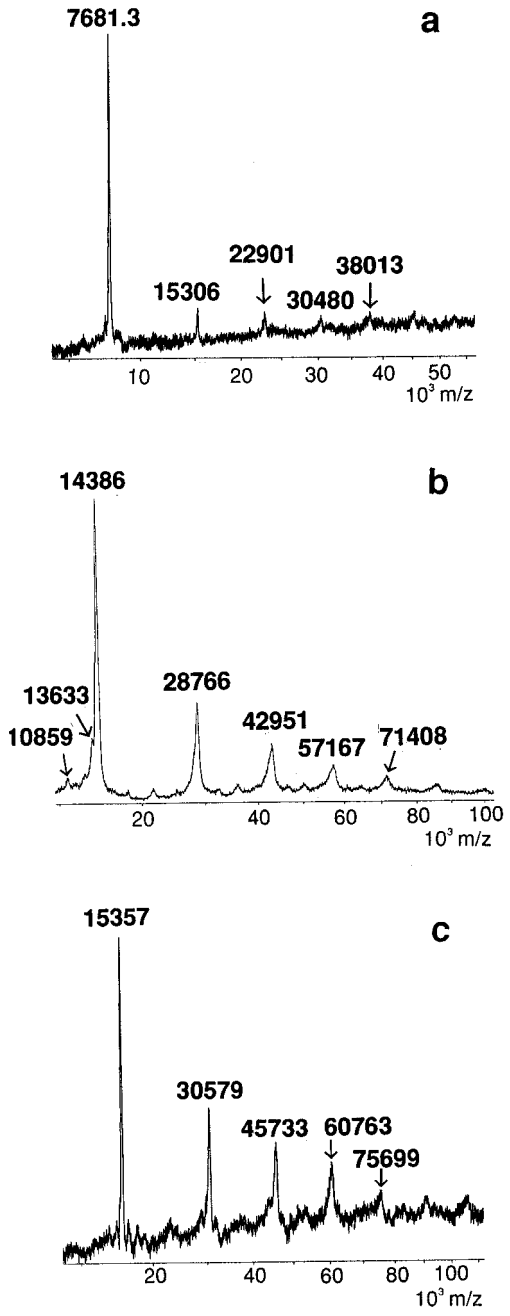


Figure 3. MALDI-TOF MS of dendrimers prepared by the ester interchange double-stage convergent method: (a) $\{(BzO_2C)_{16}$-[G-3]$\}_2$-[C] (**28**); (b) $\{([G\text{-}1]\text{-}O_2C)$ -[G-3]$\}_2$-[C] (**30**); (c) $\{(BzO_2C)_{32}$-[G-4]$\}_2$-[C] (**32**).

pertaining to the peripheral benzyl groups. The analogous fourth generation bidendron compounds show the same general trends in the NMR spectra, although a broadening of the proton peaks is observed.

FT-IR. FT-IR analysis was especially useful in analyzing the products of the surface modification reactions, particularly in identifying the resulting carbonyl moieties and in providing an indication of the completeness of reaction by determining if more than one type of carbonyl function is present. The ethyl ester- and benzyl ester-terminated dendrimers typically showed sharp carbonyl absorbances in the region of 1722−1725 cm^{-1}. For the benzyl amide-terminated dendrimer **27**, the carbonyl absorbance is shifted to the lower frequency of 1655 cm^{-1} and a broad N−H stretch is evident at ca. 2000−3750 cm^{-1}. Similarly, both carboxylic acid-terminated dendrimers (**26** and **31**) showed strong carbonyl absorbances at frequencies slightly lower than those of the esters (1710−1711 cm^{-1}) and broad O−H stretch bands at 2000−3750 cm^{-1}.

Conclusions. We have demonstrated that the use of diethyl isophthalate-terminating groups with the 3,5-dihydroxybenzyl alcohol monomer allows for the efficient convergent synthesis of dendritic macromolecules with readily modifiable surface functionalities. Dendrons as large as the third generation bromide (containing 16 terminal ester groups) may be synthesized in high purity using recrystallization as the sole method of purification. This enables the synthesis to be run on the scale of hundreds of grams thus allowing large amounts of this convenient building block to be accumulated. The third and fourth generation dendritic bromides have been reacted with a biphenol core to yield bidendron dendrimers with a high degree of surface functionality: 32 and 64 terminal ester functions, respectively. These dendrimers were subjected to a variety of surface modification reactions, many of which proceeded with complete conversion of the functional groups and in high isolated yield.

By reacting the peripheral ester groups with phenyl-containing nucleophiles, it is possible to add additional layers of aromatic rings to the dendrimer, resulting in a net effective increase of the generation number by one or two for a benzyl alcohol nucleophile or a dendritic [G-1]-OH nucleophile, respectively. The high reaction yields of the latter reaction suggest that we have not yet reached the limits of steric exclusion[22] and that even more rapid dendrimer growth through the use of larger dendritic alcohols may be possible. Efforts are currently underway to test the limits of this technique.

The success of our use of a tin-catalyzed ester interchange reaction as the basis for double-stage convergent growth suggests that this may be good general method for the attachment of more complex units. These results are encouraging since the functional group transformations used in this paper represent only a small fraction of the known high-yield chemical conversions of the ester functionality. Efforts are currently underway to utilize other types of basic reactions with these dendrimers, such as reductions and the reaction with carbon nucleophiles. The possibility of extending the ester interchange reaction to include the use of larger dendritic alcohols, optical chromophores, and linear polymers is also being explored.

Experimental Section

General Methods. All starting materials were obtained from Aldrich and used without further purification unless otherwise stated. Diethyl 5-(hydroxymethyl)isophthalate was either prepared by the procedure listed or purchased from Aldrich Custom Synthesis. THF was distilled from sodium/benzophenone. All ^1H NMR spectra were recorded on a Bruker WM-300 300 MHz NMR with the solvent proton signal as the standard. ^{13}C NMR spectra were recorded on a Bruker WM-300 spectrometer at 75 MHz with the solvent carbon signal as standard. FT-IR spectra were recorded on a Nicolet IR44 spectrometer using either a KBr pellet preparation or NaCl plates where noted. Melting points were measured using a Gallenkamp melting point apparatus and are uncorrected. MALDI-TOF spectra were recorded on a Finnigan Mat LASERMAT instrument used in positive ion mode using *trans*-3-indoleacrylic acid as the matrix. The sample preparation for MALDI-TOF analysis was used as described in a previous publication.[17]

Synthesis of Diethyl Isophthalate-Terminated Dendritic Compounds. (A) Diethyl 1,3,5-Benzenetricarboxylate (3).[23] Triethyl 1,3,5-benzene tricarboxylate (282.95 g, 0.96 mol) was combined with absolute EtOH (750 mL) and THF (500 mL) in a 2 L three-necked round-bottomed flask equipped with a mechanical stirrer, reflux condenser, and heating mantle. The mixture was heated to reflux thus ensuring the dissolution of all of the solids. Powdered KOH (assay:

(22) Tomalia, D. A.; Durst, Dupont *Top. Curr. Chem.* **1993**, *165*, 193.
(23) Whitmore, K. E.; Made, P. M. U.S. Patent 3,227,550, 1966.

87.6%, 53.97 g, 0.84 mol) was then added portionwise over 30 min to avoid an exotherm. The solution was heated at reflux for 12 h after which a small amount of solid precipitate was produced. The reaction mixture was concentrated *in vacuo* to afford a thick slurry which was partitioned between water and CH_2Cl_2. The aqueous phase was washed with CH_2Cl_2, and then concentrated HCl (85 mL) was added to precipitate the product. The product was collected by vacuum filtration and then redissolved in EtOAc, dried over $MgSO_4$, and evaporated to dryness. The product was recrystallized from absolute EtOH to afford **3** as white crystals (182.94 g , 71.5%): mp 153−154 °C; ^{1}H NMR ($CDCl_3$) δ 1.11(t, 6 H, J = 7.12 Hz, CH_3), 4.11 (q, 4 H, J = 7.11 Hz, OCH_2), 8.50 (d, 1 H, J = 1.66 Hz, aromatic), 8.53 (d, 2 H, J = 1.56 Hz, aromatic). Anal. Calcd for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30. Found: C, 58.52; H, 5.46.

(B) Diethyl 5-(Hydroxymethyl)isophthalate (4). Diethyl 1,3,5-benzenetricarboxylate (3) (301.12 g, 1.11 mol) was dissolved in THF (800 mL) in a 2 L three-necked round-bottomed flask equipped with a mechanical stirrer, reflux condenser, and addition funnel fitted with a rubber septum. BH_3·$(CH_3)_2S$ (2.0 M in THF, 613 mL, 1.23 mol) was carefully transferred to the addition funnel via a cannula. The flask was placed on a large ice bath, and the borane solution was added dropwise over 3 h. Caution: special care must be taken to avoid a vigorous exotherm! Use of a larger flask is advised. After two-thirds of the borane solution was added, the reaction solution solidified. The ice bath was replaced by a heating mantle, and the mixture was gently warmed until a homogeneous solution was again attained. The addition of the BH_3·$(CH_3)_2S$ was then continued to completion, and the reaction mixture was heated at 60 °C overnight. The reaction was neutralized by the addition of 1:2 H_2O/glacial acetic acid (150 mL). The reaction mixture was then concentrated to a thick slurry which was dissolved in hot absolute EtOH (800 mL) and precipitated into water to retrieve a white powder. Following filtration, the product was purified by recrystallization from absolute EtOH and dried in a vacuum oven at 60 °C overnight to afford **4** as white crystals (222 g, 78%): mp 82−84 °C; ^{1}H NMR ($CDCl_3$) δ 1.33 (t, 6 H, J = 7.13 Hz, CH_3), 4.33 (q, 4 H, J = 7.11 Hz, OCH_2), 8.15 (s, 1 H, aromatic), 8.51 (d, 2 H, aromatic). Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 62.07; H, 6.59.

(C) Diethyl 5-(Bromomethyl)isophthalate (5).[24] Diethyl 5-(hydroxymethyl) isophthalate (4) (524.3 g, 2.1 mol) was dissolved in THF (2 L) in an open 4 L beaker equipped with a large magnetic stir bar. The reaction apparatus was placed in an ice bath, and a steady stream of N_2 was blown over the surface of the stirred solution to prevent moisture from settling. PBr_3 (145.0 mL, 1.5 mol) was added dropwise via addition funnel over 40 min. When the addition was ∼two-thirds complete, a white precipitate began to form and CH_2Cl_2 (500 mL) was added to restore homogeneity. The reaction was allowed to stir on the ice bath for an additional 2 h, after which the reaction was complete by TLC analysis. The beaker was removed from the ice bath and placed on a hot plate, and the solvent was evaporated under a stream of nitrogen until a final volume of 1.5 L was reached. Absolute EtOH (500 mL) was added, and the reaction vessel was placed in a freezer overnight. A white crystalline product was collected by suction filtration, washed with MeOH (2 × 500 mL), and dried overnight in a vacuum oven at 50 °C to afford **5** as brilliant plate crystals (583.3 g, 90%): mp 112−113 °C); ^{1}H NMR ($CDCl_3$) δ 1.41(t, 6 H, J = 7.13 Hz, CH_3), 4.41 (q, 4 H, J = 7.11 Hz, OCH_2), 4.54 (s, 2 H, benzylic), 8.23 (s, 2 H, aromatic), 8.59 (s, 1 H, aromatic). Anal. Calcd for $C_{13}H_{15}BrO_4$: C, 49.54; H, 4.80. Found: C, 49.80; H, 4.96.

(D) (m-$EtO_2C)_4$-[G-1]-OH (7). Diethyl 5-(bromomethyl)isophthalate (**5**) (594.0 g, 1.74 mol) was combined with 3,5-dihydroxybenzyl alcohol (**6**) (119.1 g, 8.5 × 10 $^{-1}$ mol), K_2CO_3 (371.3 g, 2.7 mol), 18-crown-6 (20.2 g, 7.6 ×10^{-2} mol), and acetone (4 L) in a 6 L three-necked round-bottomed flask equipped with a mechanical stirrer, reflux condenser, heating mantle, and N_2 inlet. The mixture was heated at reflux for 48 h, at which point the reaction was found to be at completion by HPLC analysis (9:1 CH_3CN/H_2O, reverse phase). The reaction mixture was filtered, the solution was concentrated to 60% of the original volume, and absolute EtOH (500 mL) was added. The mixture was brought to reflux, at which point a homogeneous solution formed and the flask was cooled in an ice-salt bath to precipitate a white, crystalline solid. The solid was washed with MeOH (2 × 500 mL) and dried overnight in a vacuum oven at 50 °C to afford the product **7** as a white powder (482.9 g, 90.1%): mp 105−108 °C) FT-IR (KBr) ν_{max} cm^{-1} 3530, 2986, 1723, 1596, 1448, 1370, 1327, 1238, 1203, 1166, 1107, 1030, 753; ^{1}H NMR ($CDCl_3$) δ 1.40 (t, 12 H, J = 7.08 Hz, CH_3), 2.15 (s, 1 H, OH), 4.39 (q, 8 H, J = 7.11 Hz, OCH_2), 4.64 (s, 2 H, benzylic), 5.09 (s, 4 H, benzylic), 6.54 (t, 1 H, J = 2.03 Hz, aromatic), 6.64 (d, 2 H, J = 1.94 Hz, aromatic), 8.27 (s, 4 H, aromatic), 8.61 (s, 2 H, aromatic); MALDI-TOF MS, *m/z* calcd for $C_{33}H_{36}O_{11}$ 631.6 (M + Na), found 631.1 (M + Na). Anal. Calcd for $C_{33}H_{36}O_{11}$: C, 65.12; H, 5.96. Found: C, 65.21; H, 6.02.

(E) (m-$EtO_2C)_4$-[G-1]-Br (8). (m-$EtO_2C)_4$-[G-1]-OH **(7)** (462.9 g, 7.6 × 10^{-1} mol) was dissolved in THF (900 mL) in a 6 L three-necked round-bottomed flask equipped with a mechanical stirrer, reflux condenser, heating mantle, and N_2 inlet. The mixture was heated to 50 °C, at which point homogeneity was achieved. CBr_4 (306.2 g, 9.2 ×10^{-1} mol) was added, followed by PPh_3 (219.3 g, 8.4 × 10^{-1} mol), which was added in four equal-sized portions spaced over 40 min. After the third addition, a white precipitate formed. The fourth addition was accompanied by a mild exotherm, at which point the reaction turned deep yellow. The reaction was quenched with H_2O (1 L), and then CH_2Cl_2 (1.5 L) was added. The resulting mixture was worked up in three "portions" of roughly equal volume. The organic layers were washed with water (1 L × 2), dried over $MgSO_4$, recombined, and concentrated to a yellowish oil on a rotary evaporator. The crude product was recrystallized twice from absolute EtOH (1 L) and dried overnight in a vacuum oven at 50 °C to afford **8** as a white powder (423.7 g, 83%): mp 124−125 °C; FT-IR (KBr) ν_{max} cm^{-1} 2986, 1721, 1597, 1448, 1370, 1325, 1244, 1202, 1169, 1031, 754; ^{1}H NMR ($CDCl_3$) δ 1.41 (t, 12 H, J = 7.06 Hz, CH_3), 4.41 (q, 8 H, J = 7.17 Hz, OCH_2), 4.42 (s, 2 H, benzylic), 5.11 (s, 4 H, benzylic), 6.57 (t, 1 H, J = 1.98 Hz, aromatic), 6.67 (d, 2 H, J = 1.99 Hz, aromatic), 8.29 (s, 4 H, aromatic), 8.64 (s, 2 H, aromatic); MALDI-TOF MS, *m/z* calcd for $C_{33}H_{35}BrO_{10}$ 694.5 (M + Na), found 695.5 (M + Na). Anal. Calcd for $C_{33}H_{35}BrO_{10}$: C, 59.02; H, 5.25. Found: C, 59.27; H, 5.35.

(F) (m-$EtO_2C)_8$-[G-2]-OH (9). (m-$EtO_2C)_4$-[G-1]-Br **(8)** (284.0 g, 4.2 × 10^{-1} mol) was combined with 3,5-dihydroxybenzyl alcohol **(6)** (30.2 g, 2.2 × 10^{-1} mol), K_2CO_3 (211.3 g, 1.53 mol), 18-crown-6 (45.2 g, 1.7 × 10^{-1} mol), and acetone (2.5 L) in a 6 L three-necked round-bottomed flask equipped with a mechanical stirrer, reflux condenser, heating mantle, and N_2 inlet. The reaction mixture was allowed to stir at 40 °C and monitored closely by reverse phase HPLC (9:1 CH_3CN/H_2O). After 48 h, a large amount of white precipitate was evident. The reaction mixture was cooled to room temperature, and the solids were collected by suction filtration. The crude product was dissolved in 700 mL of hot CH_2Cl_2 and filtered to remove residual inorganic salts. The solution was then concentrated to dryness on a rotary evaporator, and the product was recrystallized three times from 3:1 acetone/THF. The pure product was dried overnight in a vacuum oven at 50 °C. A total of 200.1 g of pure **9** was retrieved after the recrystallization residues were further concentrated (200.1 g, 68.8%): mp 100−101 °C; FT-IR (KBr) ν_{max} cm^{-1} 3535, 2983, 1723, 1596, 1447, 1369, 1324, 1237, 1199, 1160, 1029, 831, 754; ^{1}H NMR ($CDCl_3$) δ 1.40 (t, 24 H, J = 7.14 Hz, CH_3), 2.00 (t, 1 H, J = 5.81 Hz, OH), 4.40 (q, 16 H, J = 7.11 Hz, OCH_2), 4.62 (d, 2 H, J = 5.80 Hz, benzylic), 4.98 (s, 4 H, benzylic), 5.12 (s, 8 H, benzylic), 6.49 (t, 1 H, J = 2.16 Hz, aromatic), 6.59 (m, 4 H, aromatic), 6.69 (d, 4 H, J = 2.20 Hz, aromatic), 8.28 (d, 8 H, J = 1.46 Hz, aromatic), 8.62 (t, 4 H, J = 1.61 Hz aromatic); MALDI-TOF MS, *m/z* calcd for $C_{73}H_{76}O_{23}$ 1344.1 (M + Na), found 1345.4 (M + Na). Anal. Calcd for $C_{73}H_{76}O_{23}$: C, 66.35; H, 5.80. Found: C, 66.29; H, 5.86.

(G) (m-$EtO_2C)_8$-[G-2]-Br (10). (m-$EtO_2C)_8$-[G-2]-OH **(9)** (198.4 g, 1.5 × 10^{-1} mol) was combined with THF (375 mL) in a 2 L three-necked round-bottomed flask equipped with a condenser, N_2 inlet, and mechanical stirrer. The mixture was heated to 60 °C, at which point all of the solids were dissolved and the heating power was lowered. CBr_4 (87.07 g, 2.62 × 10^{-1} mol) and PPh_3 (68.86 g, 2.62 × 10^{-1} mol) were added in equimolar amounts over 45 min, at which point a white precipitate formed and the reaction mixture turned bright yellow. The reaction was quenched with water (250 mL), and then CH_2Cl_2 (600 mL) was added. The mixture was poured into a separatory funnel, the organic layer was washed twice with equal volumes of water and dried over magnesium sulfate, and the solvents were concentrated *in vacuo*

(24) Collman, J. P.; Zhang, X.; Wong, K.; Brauman, J. I. *J. Am. Chem. Soc.* **1994**, *116*, 6245.

to yield a yellowish oil. The crude product was recrystallized twice from 1200 mL of 3:1 THF/acetone and dried overnight in a vacuum oven at 50 °C to afford **10** as a fine, white powder (184.1 g, 88.7%): mp 132−133 °C; FT-IR (KBr) ν_{max} cm^{-1} 2982, 1723, 1595, 1446, 1369, 1323, 1241, 1199, 1160, 1108, 1029, 831, 754; ^{1}H NMR ($CDCl_3$) δ 1.40 (t, 24 H, J = 7.13 Hz, CH_3), 4.37−4.44 (m, 18H, overlapping OCH_2 and focal point benzylic CH_2), 4.99 (s, 4 H, benzylic), 5.12 (s, 8 H, benzylic), 6.54 (t, 1 H, J = 2.20 Hz, aromatic), 6.60 (t, 2 H, J = 2.23 Hz, aromatic), 6.63 (d, 2 H, J = 2.21 Hz, aromatic), 6.70 (d, 4 H, J = 2.23 Hz, aromatic), 8.29 (d, 8 H, J = 1.58 Hz, aromatic), 8.63 (t, 4 H, J = 1.62 Hz, aromatic); MALDI-TOF MS, *m/z* calcd for $C_{73}H_{75}BrO_{22}$ 1407.2 (M + Na), found 1407.7 (M + Na). Anal. Calcd for $C_{73}H_{75}BrO_{22}$: C, 63.34; H, 5.46. Found: C, 63.09; H, 5.31.

(H) (*m*-EtO$_2$C)$_{16}$-[G-3]-OH (11). (*m*-EtO$_2$C)$_8$-[G-2]-Br **(10)** (135.7.0 g, 9.8 × 10^{-2} mol) was combined with 3,5-dihydroxybenzyl alcohol **(6)** (6.70 g, 4.78 × 10^{-2} mol), K_2CO_3 (27.02 g, 1.96 × 10^{-1} mol), 18-crown-6 (8.13 g, 3.10 × 10^{-2} mol), and THF (1.2) in a 2 L three-necked round-bottomed flask equipped with a mechanical stirrer, reflux condenser, heating mantle, and N_2 inlet. The mixture was heated at 45−50 °C for 72 h, at which point the reaction was at >90% completion by HPLC analysis (CH_3CN, reverse phase). CH_2Cl_2 (500 mL) was added, and the reaction mixture was filtered to remove insoluble inorganic salts. The solvents were stripped on a rotary evaporator until a final volume of 800 mL was reached, and the solution was placed in a freezer overnight. The precipitates were recrystallized once from 2:1 THF/CH_2Cl_2 (700 mL) and again from 4:3 THF/CH_2Cl_2 (700 mL). The product was dried overnight in a vacuum oven at 50 °C to afford **11** as a white powder (100.6 g, 76.7%): mp 113−115 °C; FT-IR (KBr) ν_{max} cm^{-1} 3522, 2982, 2938, 2905, 2874, 1723, 1596, 1447, 1369, 1324, 1242, 1199, 1159, 1108, 1029, 831, 754; ^{1}H NMR ($CDCl_3$) δ 1.39 (t, 48 H, J = 7.12 Hz, CH_3), 2.05 (t, 1 H, J = 6.11 Hz, OH), 4.38 (q, 32 H, J = 7.12 Hz, OCH_2), 4.60 (d, 2 H, J = 6.04 Hz, benzylic), 4.95 (s, 4 H, benzylic), 4.98 (s, 8 H, benzylic), 5.07−5.09 (m, 16 H, benzylic), 6.52−6.71 (m, 21 H, aromatic), 8.24−8.27 (m, 16 H, aromatic), 8.58−8.61 (m, 8 H, aromatic); MALDI-TOF MS, *m/z* calcd for $C_{153}H_{156}O_{47}$ 2769.8 (M + Na), found 2769.6 (M + Na). Anal. Calcd for $C_{153}H_{156}O_{47}$: C, 66.90; H, 5.72. Found: C, 67.09; H, 5.59.

(I) (*m*-EtO$_2$C)$_{16}$-[G-3]-Br (12). (*m*-EtO$_2$C)$_{16}$-[G-3]-OH **(11)** (81.47 g, 2.97 × 10^{-2} mol) was combined with THF (160 mL) in a 1 L three-necked round-bottomed flask equipped with a condenser, N_2 inlet, and mechanical stirrer. The mixture was heated to 60 °C, at which point all of the solids were dissolved and the heating power was lowered. CBr_4 (10.33 g, 3.11 × 10^{-2} mol) and PPh_3 (15.58 g, 5.94 × 10^{-2} mol) were added all at once. After 10 min, a white precipitate formed and the reaction mixture turned bright yellow. The reaction was quenched with water (200 m), and then CH_2Cl_2 (200 mL) was added. The mixture was poured into a separatory funnel, the organic layer was washed twice with equal volumes of water and dried over magnesium sulfate, and the solvents were stripped on a rotary evaporator to yield a yellowish oil. The crude product was recrystallized twice from THF (700 mL) and once from 5:3 THF/methanol (800 mL). The product was dried overnight in a vacuum oven at 50 °C to afford **12** as a fine, white powder (68.63 g, 82.2%): mp 110−111 °C; FT-IR (KBr) ν_{max} cm^{-1} 2982, 2939, 2906, 2874, 1723, 1596, 1447, 1369, 1324, 1238, 1198, 1160, 1108, 1029, 834, 754; ^{1}H NMR ($CDCl_3$) δ 1.39 (t, 48 H, J = 7.10 Hz, CH_3), 4.38 (q, 32 H, J = 7.13 Hz, OCH_2), 4.42 (s, 2 H, benzylic), 4.96 (s, 4 H, benzylic), 4.98 (s, 8 H, benzylic), 5.05−5.10 (m, 16 H, benzylic), 6.56−6.71 (m, 21 H, aromatic), 8.26−8.29 (m, 16 H, aromatic), 8.60−8.62 (m, 8 H, aromatic); MALDI-TOF MS, *m/z* calcd for $C_{153}H_{155}BrO_{46}$ 2848.7 (M + K), found 2848.3 (M + K). Anal. Calcd for $C_{153}H_{155}BrO_{46}$: C, 65.41; H, 5.56. Found: C, 65.60; H, 5.69.

(J) (*m*-EtO$_2$C)$_{32}$-[G-4]-OH (13). (*m*-EtO$_2$C)$_8$-[G-3]-Br **(12)** (7.34 g, 2.61 × 10^{-3} mol) was combined with 3,5-dihydroxybenzyl alcohol (0.18 g, 1.28 × 10^{-3} mol), K_2CO_3 (1.10 g, 8.02 × 10^{-3} mol), 18-crown-6 (0.13 g, 5.10 × 10^{-4} mol), and THF (70 mL) in a 250 mL round-bottomed flask equipped with a magnetic stirrer, reflux condenser, heating mantle, and N_2 inlet. The reaction was heated at 60 °C for 184 h, at which point the starting material was no longer evident by TLC. The reaction mixture was partitioned between CH_2Cl_2 and water, and the organic layer was washed three times with water and dried over $MgSO_4$. The solvent was then stripped on a rotary evaporator to afford a yellowish oil. The crude product was purified by column chromatography (1% Et_2O in CH_2Cl_2 increasing slowly to 15%) three times to give the product **13** as a clear glass (4.49 g, 62.9%): FT-IR (neat, NaCl) ν_{max} cm^{-1} 3420, 3060, 2991, 2938, 2907, 2875, 1722, 1596, 1447, 1369, 1324, 1238, 1203, 1163, 1115, 1029, 834, 758; ^{1}H NMR ($CDCl_3$) δ 1.37 (t, 96 H, J = 7.12 Hz, CH_3), 4.36 (q, 64 H, J = 7.13 Hz, OCH_2), 4.55 (s, 2 H, benzylic), 4.93−5.00 (s, 28 H, benzylic), 5.04−5.15 (s, 32 H, benzylic), 6.56−6.71 (m, 45 H, aromatic), 8.26−8.29 (m, 32 H, aromatic), 8.60−8.62 (m, 16 H, aromatic); MALDI-TOF MS, *m/z* calcd for $C_{313}H_{316}O_{95}$ 5621.0 (M + Na), found 5623.4 (M + Na). Anal. Calcd for $C_{313}H_{316}O_{95}$: C, 67.16; H, 5.69. Found: C, 66.96; H, 5.80.

(K) (*m*-EtO$_2$C)$_{32}$-[G-4]-Br (14). (*m*-EtO$_2$C)$_{32}$-[G-4]-OH **(13)** (3.48 g, 6.21 × 10^{-4} mol) was dissolved in refluxing THF (10 mL) in a 50 mL round-bottomed flask equipped with a magnetic stirrer, reflux condenser, and N_2 inlet. CBr_4 (0.62 g, 1.87 × 10^{-3} mol) and PPh_3 (0.49 g, 1.87 × 10^{-3} mol) were added in rapid succession. Within 2 min, a white precipitate appeared and the reaction mixture turned bright yellow. The reaction was then quenched with water and partitioned between water and CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography (1% Et_2O in CH_2Cl_2 increasing slowly to 10%) to afford the product **14** as a clear glass (2.70 g, 76.7%): FT-IR (KBr) ν_{max} cm^{-1} 2981, 2937, 2906, 2875, 1721, 1595, 1447, 1369, 1325, 1238, 1196, 1157, 1108, 1049, 1028, 953, 928, 859, 832, 753; ^{1}H NMR ($CDCl_3$) δ 1.36 (t, 96 H, J = 7.13 Hz, CH_3), 4.36 (q, 64 H, J = 7.13 Hz, OCH_2), 4.42 (s, 2 H, benzylic), 4.93−5.00 (s, 28 H, benzylic), 5.04−5.15 (s, 32 H, benzylic), 6.53−6.71 (m, 16 H, aromatic), 8.26−8.29 (m, 16 H, aromatic), 8.60−8.62 (m, 8 H, aromatic); MALDI-TOF MS, *m/z* calcd for $C_{313}H_{315}BrO_{94}$ 5683.8 (M + Na), found 5685.5 (M + Na). Anal. Calcd for $C_{313}H_{315}BrO_{94}$: C, 66.41; H, 5.61. Found: C, 66.21; H, 5.74.

(L) {(*m*-EtO$_2$C)$_{16}$-[G-3]}$_2$-[C] (24). (*m*-EtO$_2$C)$_{16}$-[G-3]-Br **(12)** (4.62 g, 1.64 × 10^{-3} mol) was combined with 4,4′-biphenol (0.15 g, 8.06 × 10^{-4} mol), K_2CO_3 (1.11 g, 8.03 × 10^{-3} mol), 18-crown-6 (0.204 g, 7.62 × 10^{-4} mol), and THF (45 mL) in a 100 mL round-bottomed flask equipped with a magnetic stirrer, reflux condenser, and N_2 inlet. The mixture was heated at reflux for 24 h, at which point MALDI-TOF analysis indicated the complete disappearance of the starting material. The solvents were stripped *in vacuo*, and the crude material was loaded directly onto a silica gel column. Elution with 2% methanol in CH_2Cl_2 followed by precipitation from THF into pentane afforded **24** as a fine powder (4.07 g, 89.5%): FT-IR (KBr) ν_{max} cm^{-1} 2952, 1725, 1596, 1498, 1455, 1374, 1324, 1237, 1192, 1048, 973, 830, 752; ^{1}H NMR ($CDCl_3$) δ 1.37 (t, 96 H, J = 7.12 Hz, CH_3), 4.37 (q, 64 H, J = 7.12 Hz, OCH_2), 4.98 (s, 28 H, benzylic), 5.08 (s, 32 H, benzylic), 6.57 (m, 14 H, aromatic), 6.70 (m, 28 H, aromatic), 6.96 (d, 4 H, J = 9.00 Hz, aromatic), 7.40 (d, 4 H, J = 8.77 Hz, aromatic), 8.26 (m, 32 H, aromatic), 8.60 (m, 16 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 14.28, 61.40, 69.04, 69.82, 101.58, 106.53, 114.95, 127.62, 130.16, 131.26, 132.50, 133.57, 137.63, 139.22, 139.40, 139.48, 157.81, 159.76, 159.97, 160.05, 165.50; MALDI-TOF MS, *m/z* calcd for $C_{318}H_{318}O_{94}$ 5645.0 (M + H), found 5648.2 (M + H). Anal. Calcd for $C_{318}H_{318}O_{94}$: C, 67.67; H, 5.68. Found: C, 67.77; H, 5.88.

(M) {(*m*-EtO$_2$C)$_{32}$-[G-4]}$_2$-[C] (25). (*m*-EtO$_2$C)$_{32}$-[G-4]-Br **(14)** (1.40 g, 2.47 × 10^{-4} mol) was combined with 4,4′-biphenol (2.25 × 10^{-2} g, 1.21 × 10^{-4} mol), K_2CO_3 (5.02 × 10^{-2} g, 3.63 × 10^{-4} mol), 18-crown-6 (1.60 × 10^{-2} g, 6.05 × 10^{-5} mol), and THF (10 mL) in a 25 mL round-bottomed flask equipped with a magnetic stirrer, reflux condenser, and N_2 inlet. The mixture was heated at reflux for 28 h, at which point MALDI-TOF analysis indicated the complete disappearance of the starting material. The solvents were stripped *in vacuo*, and the crude material was loaded directly onto a silica gel column. Elution with a slow solvent gradient (10−13% Et_2O in CH_2Cl_2) followed by precipitation from THF to methanol afforded **25** as a fine powder, which was dried overnight in a vacuum oven at 50 °C (1.29 g, 94.0%): FT-IR (KBr) ν_{max} cm^{-1} 2982, 1723, 1596, 1447, 1369, 1324, 1237, 1198, 1160, 1108, 1029, 833, 754, 719; ^{1}H NMR ($CDCl_3$) δ 1.34 (t, 192 H, J = 7.12 Hz, CH_3), 4.33 (q, 128 H, J = 7.11 Hz, OCH_2), 4.92 and 5.03 (bs, 124 H, benzylic), 6.51−6.53 and 6.64−6.73 (m, 90 H, aromatic), 6.93 (d, 4 H, J = 8.56 Hz, aromatic), 7.36 (d, 4 H, J = 8.57 Hz, aromatic), 8.21 (d, 64 H, J = 1.50 Hz, aromatic), 8.55 (d, 32 H, J = 1.53 Hz, aromatic); ^{13}C NMR ($CDCl_3$) δ 14.19, 61.31, 68.86, 69.66, 96.84, 101.41, 106.28, 106.39, 114.76, 127.46, 129.99, 131.11, 132.35, 133.36, 137.57, 139.12, 139.16, 139.25, 139.40, 157.71, 159.63, 165.37;

MALDI-TOF MS, *m/z* calcd for $C_{638}H_{638}O_{190}$ 11384 (M + K), found 11408 (M + K). Anal. Calcd for $C_{638}H_{638}O_{190}$: C, 67.54; H, 5.67. Found: C, 67.34; H, 5.90.

(N) {(HO$_2$C)$_{16}$-[G-3]}$_2$-[C] (26). To a solution of {(*m*-EtO$_2$C)$_{16}$-[G-3]}$_2$-[C] **(25)** (1.00 g, 1.77×10^{-4} mol) in THF (45 mL) was added KOH (1.93 g, 3.45×10^{-2} mol) dissolved in water (5 mL). Methanol (20 mL) was then added to the two-phase mixture to afford a homogeneous solution. The reaction was heated at reflux for 1 h, at which point a large amount of white precipitate had formed. The reaction mixture was then evaporated to dryness, and water (33 mL) was added resulting in a homogeneous solution which was heated at reflux for 2 h. After the solution was cooled to room temperature, glacial acetic acid (3 mL) was added to precipitate the product **2b**, which was isolated by filtration on a nylon membrane filter, washed with water (50 mL × 3), and dried overnight in a vacuum oven at 50 °C (0.82 g, 97.6%): FT-IR (KBr) ν_{max} cm^{-1} 3700−2050 (br, CO$_2$H), 1711, 1593, 1448, 1372, 1297, 1266, 1207, 1145, 1046, 802, 756; ^{1}H NMR (DMSO-d_6) δ 4.0−5.5 (br, 32 H, CO$_2$H), 5.00 (s, 28 H, benzylic), 5.22 (s, 32 H, benzylic), 6.63−6.74 (m, 42 H, aromatic), 6.91 (d, 4 H, J = 8.30 Hz, aromatic), 7.36 (d, 4 H, J = 8.93 Hz, aromatic), 8.18 (s, 32 H, aromatic), 8.41 (s, 16 H, aromatic); ^{13}C NMR (DMSO-d_6) δ 68.57, 69.17, 101.19, 106.79, 115.10, 127.20, 129.52, 131.75, 132.71, 137.94, 139.43, 139.63, 159.47, 159.58, 167.07; MALDI-TOF MS, *m/z* calcd for $C_{254}H_{190}O_{94}$ 4785.2 (M + K), found 4780.6 (M + K).

(O) {(BzNHCO)$_{16}$-[G-3]}$_2$-[C] (27). A mixture of {(*m*-EtO$_2$C)$_{16}$-[G-3]}$_2$-[C] **(24)** (0.20 g, 3.54×10^{-5} mol), benzylamine (7 mL, excess), and NaCN (0.016 g, 3.26×10^{-4} mol) was heated at 130−160 °C for 72 h under a constant stream of nitrogen. The temperature was raised to 190 °C for 0.5 h, and then the reaction was cooled to room temperature. The benzylamine was removed by vacuum distillation, and the crude product was precipitated from DMF into CH_2Cl_2 resulting in a milky suspension. Filtration using a teflon membrane filter resulted in the retrieval a small amount of a very fine, white powder of **24** (0.15 g, 55.6%): FT-IR (KBr) ν_{max} cm^{-1} 3306 (br, N−H stretch), 3059, 2928, 1655, 1596, 1536, 1452, 1368, 1294, 1153, 1056, 834, 746; ^{1}H NMR (DMSO-d_6) δ 4.44 (s, 28 H, benzylic), 4.99 (s, 32 H, benzylic), 5.15 (s, 64 H, benzylic), 6.50−6.75 (m, 42 H, aromatic), 6.90 (m, 4 H, aromatic), 7.05−7.30 (m, 160 H, aromatic), 7.36 (m, 4 H, aromatic), 8.11 (s, 32 H, aromatic), 8.42 (s, 16 H, aromatic); MALDI-TOF MS, *m/z* calcd for $C_{478}H_{414}O_{62}$ 7600 (M + H), found 7398 (M + H).

(P) {(BzO$_2$C)$_{16}$-[G-3]}$_2$-[C] (28). (*m*-EtO$_2$C)$_{16}$-[G-3]$_2$-[C] **(24)** (0.15 g, 2.66×10^{-5} mol) and dibutyltin dilaurate (0.05 g, 8.00×10^{-5} mol) were dissolved in benzyl alcohol (10 mL) and heated at 160 °C for 24 h, at which point MALDI-TOF analysis of the reaction mixture showed complete disappearance of the starting material. The benzyl alcohol was removed by vacuum distillation, and the product was purified by precipitation three times from CH_2Cl_2 into Et_2O to give the product **24** as a white powder (0.18 g, 90.0%): FT-IR (KBr) ν_{max} cm^{-1} 2952, 1725, 1596, 1498, 1374, 1324, 1237, 1192, 1048, 973, 830, 752; ^{1}H NMR ($CDCl_3$) δ 4.91 (s, 28 H, benzylic), 5.00 (s, 32 H, benzylic), 5.31 (s, 64 H, benzylic), 6.50 (m, 14 H, aromatic), 6.64 (m, 28 H, aromatic), 6.91 (d, 4 H, J = 9.21 Hz, aromatic), 7.24−7.41 (m, 164 H, overlapping end group and core aromatic), 8.25 (s, 32 H, aromatic), 8.64 (s, 16 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 67.06, 68.87, 69.78, 99.39, 101.53, 106.52, 114.97, 127.61, 128.22, 128.32, 128.58, 130.41, 130.98, 132.77, 135.62, 137.81, 139.25, 139.43, 139.51, 157.79, 159.66, 159.95, 160.04, 165.22; MALDI-TOF MS, *m/z* calcd for $C_{478}H_{382}O_{94}$ 7669.2 (M + K), found 7681 (M + K). Anal. Calcd for $C_{478}H_{382}O_{94}$: C, 75.24; H, 5.05. Found: C, 75.13; H, 5.01.

(Q) {([G-1]-O$_2$C)$_{16}$-[G-3]}$_2$-[C] (30). (*m*-EtO$_2$C)$_{16}$-[G-3]$_2$-[C] **(24)** (0.090 g, 1.59×10^{-5} mol) and dibutyltin dilaurate (0.030 g, 4.75×10^{-5} mol) were combined with 3,5-di(benzyloxy)benzyl alcohol ([*G*-1]-OH) (3.00 g, 9.36×10^{-3} mol) and heated in the melt under a steady stream of nitrogen for 24 h at 160 °C and then for 12 h at 170 °C. The yellowish solution was allowed to cool to room temperature and purified by column chromatography with 2.5% EtOAc/CH_2Cl_2 followed by precipitation three times from CH_2Cl_2 into methanol to afford the product **30** as a white powder (0.20 g, 87.0%): FT-IR (KBr) ν_{max} cm^{-1} 3032, 2872, 1725, 1596, 1497, 1451, 1372, 1322, 1227, 1191, 1157, 1054, 1048; ^{1}H NMR ($CDCl_3$) δ 4.90 (m, 188 H, benzylic), 5.22 (s, 64 H, benzylic), 6.50 (s, 46 H, aromatic), 6.63 (m, 92 H, aromatic), 6.91 (d, 4 H, J = 9.21 Hz, aromatic), 7.18−7.32 (m, 324 H, overlapping end group and core ArH), 8.24 (s, 32 H, aromatic), 8.64 (s, 16 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 66.84, 68.80, 69.97, 101.43, 106.54, 107.10, 114.87, 127.04, 127.46, 127.60, 127.91, 128.48, 130.42, 130.85, 132.85, 136.60, 137.84, 137.94, 139.15, 139.35, 139.49, 159.65, 159.87, 160.04, 165.14; MALDI-TOF MS, *m/z* calcd for $C_{926}H_{766}O_{158}$ 14422 (M + H), found 14386 (M + H). Anal. Calcd for $C_{926}H_{766}O_{158}$: C, 77.12; H, 5.35. Found: C, 77.12; H, 5.18.

(R) {(HO$_2$C)$_{32}$-[G-4]}$_2$-[C] (31). To a solution of {(*m*-EtO$_2$C)$_{32}$-[G-4]}$_2$-[C] **(25)** (0.57 g, 5.02×10^{-5} mol) in THF (20 mL) was added KOH (1.00 g, 1.80×10^{-2} mol) dissolved in water (2 mL). The reaction was heated at reflux for 90 min, at which point a white precipitate had formed. The reaction mixture was then evaporated to dryness, and water (30 mL) and methanol (25 mL) were added resulting in a homogeneous solution which was then heated at reflux for 7 h. After being cooled to room temperature, the reaction solution was added dropwise to a solution of concentrated HCl (1.85 g) and water (200 mL), resulting in a milky suspension which was concentrated *in vacuo* to 15 mL. Brine (30 mL) was added, and the suspension was extracted with THF (7 mL × 5). The combined THF layers were washed with brine (5 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo*, and dried overnight in a vacuum oven at 50 °C to yield the product **31** as a fine, white powder (0.47 g, 98%): FT-IR (KBr) ν_{max} cm^{-1} 3700−2050 (br, CO_2H), 1710, 1598, 1450, 1371, 1161, 1059, 898, 830; ^{1}H NMR (pyridine-d_5/D_2O/CD_3OD) δ 4.96 (bs, 124 H, benzylic), 6.55−6.90 (bm, 98 H, aromatic), 8.33 (s, 64 H, aromatic), 8.78 (s, 32 H, aromatic); MALDI-TOF MS, *m/z* calcd for $C_{510}H_{382}O_{190}$ 9572.5 (M + Na), found 9566.3 (M + Na).

(S) {(BzO$_2$C)$_{32}$-[G-4]}$_2$-[C] (32). This compound was prepared from {(*m*-EtO$_2$C)$_{32}$-[G-4]}$_2$-[C] (25) using the same procedure as **28**. The product was purified by precipitation twice from THF into methanol followed by column chromatography (CH_2Cl_2 increasing slowly to 6% Et_2O in CH_2Cl_2) to give the product **32** as a colorless glass (88%): FT-IR (KBr) ν_{max} cm^{-1} 3034, 1725, 1596, 1499, 1455, 1374, 1325, 1238, 1192, 1160, 1047, 933, 832, 753; ^{1}H NMR ($CDCl_3$) δ 4.84 and 4.91 (bs, 124 H, benzylic), 5.26 (s, 128 H, benzylic), 6.44−6.64 (m, 94 H, aromatic), 6.87 (d, 4 H, J = 8.64 Hz, aromatic), 7.22−7.35 (m, 324 H, overlapping end group and biphenyl ArH), 8.20 (d, 64 H, J = 1.43 Hz, aromatic), 8.59 (t, 32 H, J = 1.47 Hz, aromatic); ^{13}C NMR ($CDCl_3$) δ 66.99, 68.70, 69.67, 101.38, 106.43, 114.79, 127.52, 128.18, 128.27, 128.53, 130.31, 130.85, 132.68, 133.36, 135.57, 137.77, 139.20, 139.42, 157.76, 159.57, 159.87, 159.97, 165.14; MALDI-TOF MS, *m/z* calcd for $C_{958}H_{766}O_{190}$ 15357.5 (M + K), found 15357 (M + K). Anal. Calcd for $C_{958}H_{766}O_{190}$: C, 75.12; H, 5.04. Found: C, 75.46; H, 5.40.

Synthesis of Asymmetric Dimethyl Phthalate-Terminated Dendrons. (A) Dimethyl 4-Methylphthalate. 4-Methylphthalic anhydride (50.0 g, 0.308 mol) was stirred in methanol (110 mL) at reflux in the presence of *p*-toluenesulfonic acid monohydrate (0.5 g) for 2 days. The solution was then allowed to cool to room temperature, and CH_2Cl_2 (400 mL) was added. The resulting solution was washed with saturated aqueous $NaHCO_3$ and water followed by drying (Na_2SO_4) and filtration, and the solvent was removed *in vacuo*. The crude product was purified further by vacuum distillation (110−112 °C at 0.07 mmHg) to afford the product as a clear oil (37.0 g, 57.7%): ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3 H, methyl), 3.89 and 3.90 (s, 3 H each, methoxy), 7.31 (dt, 1 H, J = 0.78 and 7.88 Hz, aromatic), 7.45 (d, 1 H, J = 1.41 Hz, aromatic), 7.66 (d, 1 H, J = 7.90 Hz, aromatic).

(B) Dimethyl 4-(Bromomethyl)phthalate (15). Dimethyl 4-methylphthalate (180.68 g, 0.868 mol) and *N*-bromosuccinimide (156.0 g, 0.877 mol) were combined in carbon tetrachloride (810 mL) and stirred at reflux under the irradiation of a sunlamp (120 W, GE) for 3.5 h. The solids were removed by filtration, and the solvent was stripped *in vacuo*. The crude product, consisting of the desired product, starting material, and dimethyl 4-(dibromomethyl)phthalate, was purified by fractional vacuum distillation (three times) to afford **15** as a clear oil of 95% purity (115 g, 46%): ^{1}H NMR ($CDCl_3$) δ 3.88 and 3.90 (s, 3 H each, C*H*$_3$), 4.47 (s, 2 H, benzylic), 7.54 (dd, 2 H, J = 1.84 and 7.98 Hz, aromatic), 7.69 (d, 1 H, J = 7.96 Hz, aromatic), 7.54 (d, 1 H, J = 1.80 Hz, aromatic).

(C) General Procedure for the Synthesis of Dendritic Benzyl Alcohols with Asymmetric Dimethyl Phthalate Terminal Units. 3,5-Dihydroxybenzyl alcohol **(6)** (1.00 equiv), the appropriate dendritic benzyl bromide (2.05 equiv), 18-crown-6 (0.2 equiv), and potassium carbonate (2.5 equiv) were combined and stirred vigorously in boiling acetone under nitrogen until the disappearance of the benzyl bromide

was evident by TLC (typically about 1 day). The acetone was then removed *in vacuo* and the resulting residue was partitioned between methylene chloride and water. The aqueous layer was extracted with methylene chloride twice, and the combined organic layers were washed with water and dried over Na_2SO_4, and the solvent was removed *in vacuo*. The crude products were further purified as outlined in the following text.

(D) General Procedure for the Synthesis of the Dendritic Benzyl Bromides with Asymmetric Dimethyl Phthalate Terminal Units. The appropriate dendritic benzyl alcohol (1.00 equiv) and carbon tetrabromide (1.25 equiv) were dissolved in the minimum amount of dry THF (typically 2 mL/g) under nitrogen at room temperature. Triphenylphosphine (1.25 equiv) was then added portionwise (to avoid an exotherm) with stirring, and the reaction was monitored by TLC. For an incomplete reaction, additional amounts of the both reagents (typically portions of 0.25 equiv) were added as needed. When the reaction reached completion, water (excess) was added and the reaction mixture was extracted three times with methylene chloride. The combined organic layers were washed once with water and dried over Na_2SO_4, and the solvents were removed *in vacuo*. The crude products were further purified as noted in the following text.

(E) (*o*-$MeO_2C)_4$-[G-1]-OH (16). This compound was prepared from dimethyl 4-(bromomethyl)phthalate **(15)**. The crude product was purified by silica gel column chromatography eluting with hexanes/ethyl acetate (1:1 increasing slowly to 1:2) to afford the product **16** as a clear oil (93.2%): ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 12 H, CH_3), 4.53 (s, 2 H, benzylic), 4.98 (s, 4 H, benzylic), 6.41 (t, 1 H, J = 2.21 Hz, aromatic), 6.53 (d, 2 H, J = 2.20 Hz, aromatic), 7.49 (dd, 2 H, J = 1.94 and 7.94 Hz, aromatic), 7.67 (d, 2 H, J = 8.09 Hz, aromatic), 7.69 (s, 2 H, aromatic). Anal. Calcd for $C_{29}H_{28}O_{11}$: C, 63.04; H, 5.11. Found: C, 62.87; H, 5.02.

(F) (*o*-$MeO_2C)_4$-[G-1]-Br (17). This compound was prepared from (*o*-$MeO_2C)_4$-[G-1]-OH **(16)**. The crude product was purified by silica gel column chromatography eluting with hexanes/ethyl acetate (2:1 increasing to 3:2) to afford **17** as a clear oil (94.5%): ^{1}H NMR ($CDCl_3$) δ 3.79 and 3.80 (s, 6 H each, CH_3), 4.31 (s, 2 H, CH_2Br), 4.92 (s, 4 H, benzylic), 6.41 (t, 1 H, J = 2.09 Hz, aromatic), 6.54 (d, 2 H, J = 2.17 Hz, aromatic), 7.44 (dd, 2 H, J = 1.48 and 8.03 Hz, aromatic), 7.63 (d, 2 H, J = 7.94 Hz, aromatic), 7.66 (d, 2 H, J = 1.22 Hz, aromatic). Anal. Calcd for $C_{29}H_{27}BrO_{10}$: C, 56.59; H, 4.42. Found: C, 56.48; H, 4.51.

(G) (*o*-$MeO_2C)_8$-[G-2]-OH (18). This compound was prepared from (*o*-$MeO_2C)_4$-[G-1]-Br **(17)**. The crude product was purified by silica gel column chromatography eluting with 1:2 hexanes/ethyl acetate to afford **18** as a colorless glass (97.3%): ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 24 H, CH_3), 4.54 (s, 2 H, benzylic), 4.89 (s, 4 H, benzylic), 5.01 (s, 8 H, benzylic), 6.43 (t, 1 H, J = 2.14 Hz, aromatic), 6.47 (t, 2 H, J = 2.19 Hz, aromatic), 6.52 (d, 2 H, J = 2.15 Hz, aromatic), 6.60 (d, 4 H, J = 2.19 Hz, aromatic), 7.50 (dd, 4 H, J = 1.69 and 7.98 Hz, aromatic), 7.67−7.71 (m, 8 H, aromatic). Anal. Calcd for $C_{65}H_{60}O_{23}$: C, 64.56; H, 5.00. Found: C, 64.40; H, 4.83.

(H) (*o*-$MeO_2C)_8$-[G-2]-Br (19). This compound was prepared from (*o*-$MeO_2C)_8$-[G-2]-OH **(18)**. The crude product was purified by silica gel column chromatography eluting with 1:1 hexanes/ethyl acetate to afford **19** as a colorless glass (84.5%): ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 24 H, CH_3), 4.38 (s, 2 H, CH_2Br), 4.92 (s, 4 H, benzylic), 5.03 (s, 8 H, benzylic), 6.50−6.52 (m, 3 H, aromatic), 6.61 (d, 2 H, J = 2.11 Hz, aromatic), 6.65 (d, 4 H, J = 2.13 Hz, aromatic), 7.51 (dd, 4 H, J = 1.76 and 7.85 Hz, aromatic), 7.70 (d, 4 H, J = 7.87 Hz, aromatic), 7.75 (d, 4 H, J = 1.22 Hz, aromatic). Anal. Calcd for $C_{65}H_{59}BrO_{22}$: C, 61.37; H, 4.68. Found: C, 61.52; H, 4.86.

(I) (*o*-$MeO_2C)_{16}$-[G-3]-OH (20). This compound was prepared from (*o*-$MeO_2C)_8$-[G-2]-Br **(19)**. The crude product was purified by silica gel column chromatography eluting with 9:1 CH_2Cl_2/Et_2O to afford **20** as a colorless glass (84.9%): ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 48 H, CH_3), 4.50 (s, 2 H, benzylic), 4.86 (s, 12 H, benzylic), 4.96 (s, 16 H, benzylic), 6.42 (bs, 1 H, aromatic), 6.44 (m, 6 H, aromatic), 6.51 (d, 2 H, J = 1.58 Hz, aromatic), 6.59 (m, 12 H, aromatic), 7.47 (dd, 8 H, J = 1.27 and 8.19 Hz, aromatic), 7.64−7.68 (m, 16 H, aromatic). Anal. Calcd for $C_{137}H_{124}O_{47}$: C, 65.23; H, 4.96. Found: C, 65.29; H, 5.08.

(J) (*o*-$MeO_2C)_{16}$-[G-3]-Br (21). This compound was prepared from (*o*-$MeO_2C)_{16}$-[G-3]-OH **(20)**. The crude product was purified by silica gel column chromatography eluting with hexanes/ethyl acetate (1:2 increasing to 1:6) to afford **21** as a colorless glass (98.5%): ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 48 H, CH_3), 4.38 (s, 2 H, CH_2Br), 4.95 (s, 12 H, benzylic), 5.06 (s, 16 H, benzylic), 6.50−6.52 (m, 7 H, aromatic), 6.60−6.69 (m, 14 H, aromatic), 7.54 (d, 8 H, J = 7.94 Hz, aromatic), 7.71−7.74 (m, 16 H, aromatic). Anal. Calcd for $C_{137}H_{123}BrO_{46}$: C, 63.64; H, 4.80. Found: C, 63.84; H, 5.06.

(K) (*o*-$MeO_2C)_{32}$-[G-4]-OH (22). This compound was prepared from (*o*-$MeO_2C)_{16}$-[G-3]-Br **(21)**. The crude product was purified by silica gel column chromatography eluting with hexanes/ethyl acetate (1:9 increasing to pure ethyl acetate) to afford **22** as a colorless glass (63.6%): ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 96 H, CH_3), 4.52 (s, 2 H, benzylic), 4.82−5.00 (m, 60 H, benzylic), 6.40−6.63 (m, 45 H, aromatic), 7.49 (dd, 16 H, J = 1.62 and 7.98 Hz, aromatic), 7.67−7.72 (m, 32 H, aromatic); MALDI-TOF MS, *m/z* calcd for $C_{281}H_{252}O_{95}$ 5150.0 (M + H), found 5146.8 (M + H). Anal. Calcd for $C_{281}H_{252}O_{95}$: C, 65.54; H, 4.93. Found: C, 66.24; H, 5.56.

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