Modular Approach to the Accelerated Convergent Growth of Laser Dye-Labeled Poly(aryl ether) Dendrimers Using a Novel Hypermonomer

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The synthesis of novel dendrimers functionalized with laser dyes both at the periphery and at the core, along with all relevant model compounds necessary for accurate photophysical studies, is described. The utilized synthetic strategy involves a modular approach in which a variety of peripheral and core moieties can be placed on a dendritic structure bearing electrophilic peripheral groups and a nucleophilic core. Specifically, the target macromolecules required functionalization with the laser dyes coumarin 2 (periphery) and coumarin 343 (core) due to the possibility of energy transfer from the former to the latter dye. In addition, the preparation of a novel, highly soluble and reactive hypermonomer utilized in the rapid and efficient synthesis of high-generation dye-labeled dendrimers and model compounds is outlined.

Introduction

As the field of dendrimers rapidly grows,[1] a few key architectures clearly stand out as the most attractive and best documented ones within the highly diverse pool of branched polymers described so far. Poly(aryl ether) dendrimers belong to this class: the simplicity, reliability, and flexibility of their convergent synthesis,[2] together with the commercial availability of the monomer itself, strongly contribute to the prominent role of this structure within the dendrimer literature. Indeed, poly(aryl ether) dendritic macromolecules have been widely used by independent groups for a variety of applications,[3,4] and their chemistry[5−9] and properties[10] are now well established.

In the course of our work on energy transfer in dye-labeled poly(aryl ether) dendrimers,[11] we experienced the need for an alternative structure with orthogonal focal and terminal functionalities. The design of our dendritic antenna molecules connects the nucleophilic amino group of coumarin 2 and the electrophilic acid group of coumarin 343 to the chain ends and focal point of the dendrimer, respectively (Table 1). In contrast, with the "classical" convergent approach to poly(aryl ether) dendrimers,[2] it is the terminal group that bears the electrophilic functionality, whereas the focal point displays a nucleophilic coupling site (Table 1).

To remedy this potential shortcoming and also provide easy access to a wider range of surface functionalities, we later introduced ester-terminated poly(aryl ether) dendrimers[12] and showed that they can be readily surface-functionalized[12,13] in high yields by nucleophilic attack of either an alcohol or an amine. However, the electron-withdrawing character of the appended carbonyl

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(1) (a) Fréchet, J. M. J.; Hawker, C. J. In *Synthesis and Properties of Dendrimers and Hyperbranched Polymers, Comprehensive Polym. Sci., 2nd Suppl.*; Aggarwal, S. L., Russo, S., Eds.; Pergamon Press: Oxford, 1996; p 140. (b) Fréchet, J. M. J. *Science* **1994**, *263*, 1710−1715. (c) Issberner, J.; Moors, R.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2413−2420.

(2) (a) Fréchet, J. M. J.; Jiang, Y.; Hawker, C. J.; Philippides, A. E. *Preprints of the IUPAC International Symposium of Functional Polymers;* The Polymer Society of Korea: Seoul, 1989; p 19. (b) Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638−7647.

(3) (a) Jiang, D.-L.; Aida, T. *Nature* **1997**, *388*, 454−456. (b) Kawa, M.; Fréchet, J. M. J. *Chem. Mater.* **1998**, *10*, 286−296. (c) Karthaus, O.; Ijiro, K.; Shimomura, M.; Hellmann, J.; Irie, M. *Langmuir* **1996**, *12*, 6714−6716. (d) Junge, D. M.; McGrath, D. V. *Chem. Commun.* **1997**, 857−858. (e) Stewart, G. M.; Fox, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 4354−4360. (f) Serroni, S.; Campagna, S.; Juris, A.; Venturi, M.; Balzani, V.; Denti, G. *Gazz. Chim. Ital.* **1994**, *124*, 423−427. (g) Kremers, J. A.; Meijer, E. W. *J. Org. Chem.* **1994**, *59*, 4262−6266. (h) Hudson, S. D.; Jung, H.-T.; Percec, V.; Cho, W.-D.; Johansson, G.; Ungar, G.; Balagurusamy, V. S. *Science* **1997**, *278*, 449−452. (i) Amabilino, D. B.; Ashton, P. R. Balzani, V.; Brown, C. L.; Credi, A.; Fréchet, J. M. J.; Leon, J. W.; Raymo, F. M.; Spencer, N.; Stoddart, J. F.; Venturi, M. *J. Am. Chem. Soc.* **1996**, *118*, 12012−12020. (j) Zimmerman, S. C.; Zeng, F. W.; Reichert, D. E. C.; Kolotuchin, S. V. *Science* **1996**, *271*, 1095−1098. (k) Butz, T.; Murer, P.; Seebach, D. *Polym. Mater. Sci. Eng.* **1997**, *77*, 132−133. (l) Seebach, D.; Lapierre, J.-M.; Greiveldinger, G.; Skrobridis, K. *Helv. Chim. Acta* **1994**, *77*, 1673−1688. (m) Hawker, C. J.; Wooley, K. L. Fréchet J. M. J. *J. Chem. Soc., Chem. Commun.* **1994**, 925. (n) Ferguson, G.; Gallagher, J. F.; McKervey, M. A.; Madigan, E. *J. Chem. Soc., Perkin Trans. 1* **1996**, 599−602. (o) Camps, X.; Schönberg, H.; Hirsch, A. *Chem. Eur. J.* **1997**, *3*, 561−567. (p) Klopsch, R.; Franke, P.; Schlüter, A.-D. *Chem. Eur. J.* **1996**, *2*, 1330−1334. (q) Wooley, K. L.; Hawker, C. J.; Fréchet, J. M. J.; Wudl. F.; Srdanov, G.; Shi, S.; Li, C.; Kao, M. *J. Am. Chem. Soc.* **1993**, *115*, 9836−9837. (r) Gitsov, I.; Fréchet, J. M. J. *Macromolecules* **1993**, *26*, 6536−6546.

(4) (a) Sadamoto, R.; Tomioka, N.; Aida, T. *J. Am. Chem. Soc.* **1996**, *118*, 3978−3979. (b) Jiang, D.-L.; Aida, T. *J. Chem. Soc., Chem. Commun.* **1996**, 1523−1524. (c) Tomoyose, Y.; Jiang, D.; Jin, R.;. Aida, T.; Yamashita, T.; Horie, K.; Yashima, E.; Okamoto, Y. *Macromolecules* **1996**, *29*, 5236−5238. (d) Jin, R. H.; Aida, T.; Inoue, S. *J. Chem. Soc., Chem. Commun.* **1993**, 1260−1262. (e) Pollak, K. W.; Leon, J. W.; Fréchet, J. M. J.; Maskus, M.; Abruña, H. D. *Chem. Mater.* **1999**, *10*, 30−38. (f) Pollak, K. W.; Leon, J. W.; Fréchet, J. M. J. *Polym. Mater. Sci. Eng.* **1995**, *73*, 333−334.

(5) (a) Hawker, C. J.; Fréchet, J. M. J. *Macromolecules* **1990**, *23*, 4726−4729. (b) Wooley, K. L.; Hawker, C. J.; Fréchet, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1059−1076.

(6) Lochman, L.; Wooley, K. L.; Ivanova, P. T.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1993**, *115*, 7043−7044.

(7) (a) Wooley, K. L.; Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1991**, *113*, 4252−4261. (b) Spindler, R.; Fréchet, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 913−918.

(8) L'Abbé, G.; Forier, B.; Dehaen, W. *J. Chem. Soc., Chem. Commun.* **1996**, 2143-2144. Kawaguchi, T.; Walker, K. L.; Wilkins, C. L.; Moore, J. S. *J. Am. Chem. Soc.* **1995**, *117*, 2159−2165.

(9) (a) Sanford, E. M.; Fréchet, J. M. J.; Wooley, K. L.; Hawker, C. J. *Polym. Prepr.* **1993**, *34*, 654−655. (b) Wooley, K. L.; Hawker, C. J.; Fréchet, J. M. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 82−85.

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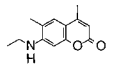
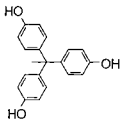
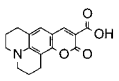
Table 1. Comparison of Peripheral and Core Groups in Classical and "Reversed" Dendrons

	"Classical" strategy	"Reversed" strategy
Terminal group	 electrophilic	 nucleophilic
Focal point or core	 nucleophilic	 electrophilic

group may well affect the electronic properties of the attached chain-end moieties. For example, amidation of the coumarin 2 laser dye would significantly reduce the magnitude of the intramolecular charge transfer which is at the origin of its excellent optical properties. In turn, this would affect our ability to predict the position of absorption and emission maxima, the magnitude of the molar extinction coefficient, and the fluorescence quantum yield.

Another possible option for attaching the dyes onto the dendritic backbone without altering their optical properties involves utilization of appropriately functionalized spacer groups. However, this possibility was eliminated since a key requirement of an efficient dendritic antenna operating through a Förster mechanism is that the interacting chromophores be kept at a minimum distance.[11] Moreover, the increased flexibility resulting from the presence of any spacer might lead to undesired interactions such as aggregation, excimer formation, and dye self-quenching between the numerous terminal groups.

A little known strategy (Figure 1) that still makes use of the efficient coupling reactions that we first introduced with the convergent method but "reverses" focal and terminal functionalities was described by Hanson and coworkers, along with a later variant by Höger.[14] This "reversed" strategy provides an additional entry to poly(aryl ether) dendritic macromolecules, thus adding even more flexibility to the general convergent synthesis of this

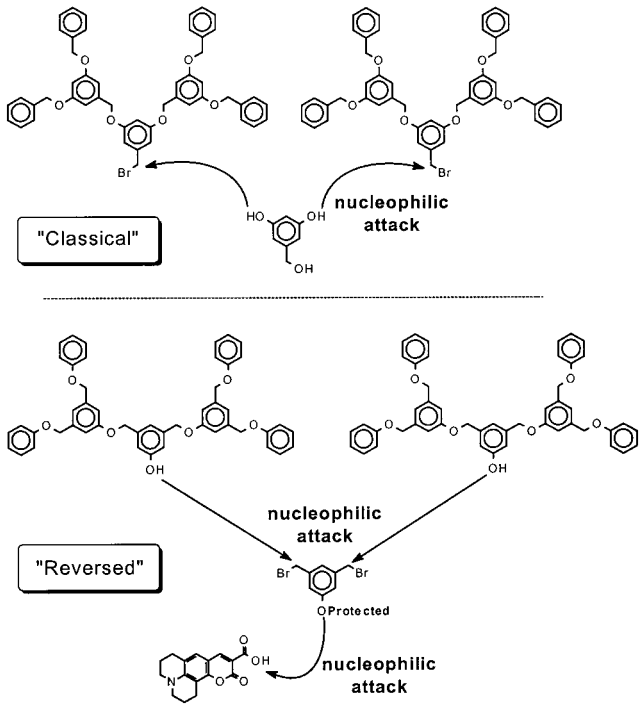


Figure 1. Distribution of the reactive groups in the "classical" and "reversed" poly(aryl ether) dendrimers.

type of architecture. Although the poly(aryl ether) structures resulting from the two strategies are different (Figure 1), it may reasonably be expected that their chemical stability, solubility, and some of their other properties, with the notable exception of the "antenna" effect,[3a,b] will be closely related.[10]

By contrast, this minor skeletal variation results in two surprisingly different synthetic schemes: foremost, the monomer used to build the reversed dendritic structure should be a protected 3,5-bis(bromomethyl)phenol, instead of the widely used 3,5-dihydroxybenzyl alcohol[2] (Figure 1). In the case of the reversed strategy, the additional need to first synthesize the monomer (as opposed to obtaining it directly from commercial sources) is balanced by the great variety of commercially available phenols and amines, which, in turn, provides easy access to a wide range of surface functionalities. The use of a protecting group at the focal point of the growing dendrons is an additional feature that allows the activation step of the classical convergent growth to be replaced by a simple deprotection reaction. The protecting group may be chosen among the numerous phenol protecting groups reported in the literature[15] to ensure that its cleavage is regioselective and compatible with the various functionalities on the dendron. In addition, the absence of a benzyl alcohol functionality either on the monomer or on the dendron (Figure 1) allows for the use of bases stronger than K_2CO_3 for the coupling step, as long as the phenol protecting group is stable under these conditions.

Results and Discussion

Several multistep syntheses of protected 3,5-bis(halogenomethyl)phenols involving protecting groups such as

(10) (a) Hawker, C. J.; Malmström, E. E.; Frank, C. W.; Kampf, J. P. *J. Am. Chem. Soc.* **1997**, *119*, 9903−9904. (b) T. H. Mourey, T. H.; Turner, S. R.; Rubinstein, M.; Fréchet, J. M. J.; Hawker, C. J.; Wooley, K. L. *Macromolecules* **1992**, *25*, 2401−2406. (c) Hawker, C. J.; Wooley, K. L.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1993**, *115*, 4375−4376. (d) Wooley, K. L.; Klug, C. A.; Tasaki, K.; Schaefer, J. *J. Am. Chem. Soc.* **1997**, *119*, 53−58. (e) Wooley, K. L.; Hawker, C. J.; Fréchet, Pochan, J. M.; J. M. J. *Macromolecules* **1993**, *26*, 1514−1519. (f) Saville, P. M.; White, J. W.; Hawker, C. J.; Wooley, K. L.; Fréchet, J. M. J. *J. Phys. Chem.* **1993**, *97*, 293−294. (g) Saville, P. M.; Reynolds, P. A.; White, J. W.; Hawker, C. J.; Fréchet, J. M. J.; Wooley, K. L.; Penfold, J.; Webster, J. R. P. *J. Phys. Chem.* **1995**, *99*, 8283−8289. (h) Hawker, C. J.; Farrington, P. J.; Mackay, M. E.; Wooley, K. L.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1995**, *117*, 4409−4410.

(11) (a) Gilat, S. L.; Adronov, A.; Fréchet, J. M. J. *Polym. Mater. Sci. Eng.* **1997**, *77*, 91−92. (b) Gilat, S. L.; Adronov, A.; Fréchet, J. M. J. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1422−1427.

(12) Leon, J. W.; Kawa, M.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1996**, *118*, 8847−8859.

(13) (a) Leduc, M. R.; Hayes, W.; Fréchet, J. M. J. *J. Polym. Sci. Part A: Polym. Chem.* **1998**, *36*, 1−10. (b) Hayes, W.; Leduc, M. R.; Leon, J. W.; Fréchet, J. M. J. *Polym. Mater. Sci. Eng.* **1997**, *77*, 143−144.

(14) (a) Tyler, T. L.; Hanson, J. E. *Polym. Mater. Sci. Eng.* **1995**, *73*, 356−357. (b) Höger, S. *Synthesis* **1997**, 20−21.

(15) (a) Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley & Sons: New York, 1991. (b) Kocienski, P. J. In *Protecting Groups: Thieme Foundations of Organic Chemistry Series*; Endres, D., Noyori, R., Trost, B. M., Eds.; Georg Thieme Verlag: Stuttgart, 1994.

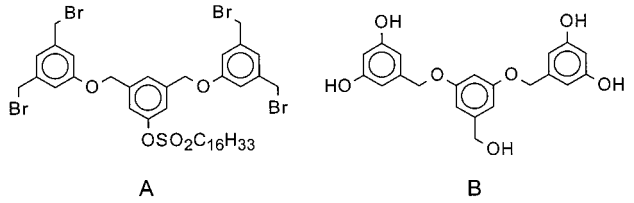


Figure 2. Structure of the current, lipophilic hypermonomer (A) and its previous, hydrophilic analogue (B).

methyl,[16] octadecyl,[17] or *tert*-butyldimethylsilyl[18] (TBDMS) ethers and mesylate or hexadecanesulfonate have been described.[14] The single-step synthesis of 3,5-bis(bromomethyl)anisole (**3**) by bromination of 3,5-dimethylanisole **1** (Figure 2) with NBS has also been described,[19] although characterization of the obtained product is poor and even inconsistent with previous literature data.[16] In fact, more recent work on the bromination of methyl-substituted anisoles with NBS[20] shows that this reaction may be accompanied by side reactions in which ring bromination is favored over side-chain bromination. In the case of 3,5-dimethylanisole **1**, reaction with 2 equiv of NBS under irradiation did not afford the expected 3,5-bis(bromomethyl)anisole (**3**), but gave 4-bromo-3-(bromomethyl)-5-methylanisole instead.

Using 1.8 equiv of NBS in refluxing CCl_4 under irradiation and in the presence of trace amounts of benzoyl peroxide, we obtained both 3-bromomethyl-5-methyl-anisole[21] (**2**) and 3,5-bis(bromomethyl)anisole (**3**) in 18% and 35% yield, respectively (Scheme 1). The two products can be separated by column chromatography, and their characterization is consistent with the assigned structures and literature data.[16] Though 3,5-bis(bromomethyl)anisole is our main target, the product of monobromination, **2**, might also prove useful in the preparation of dendrimers bearing a single terminal dye at the periphery. Reaction of the bis(bromomethyl)anisole (**3**) with 3 equiv of coumarin 2 in refluxing acetonitrile for 3 days, using potassium carbonate as a base,[22] afforded the dye-labeled anisole **4** in 85% yield (Scheme 1). A hydrolysis byproduct, the anisole bearing a single coumarin 2 and a hydroxymethyl group at the 5 position (**5**), was also isolated in 6% yield.

Cleavage of the methyl ether protecting group of **4** to afford the corresponding phenol **6** was achieved regioselectively in 99% yield by reaction with boron tribromide in dichloromethane[23] (Scheme 1). Finally, acylation of the phenol **6** with an excess of coumarin 343, using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride[24] (EDC) and a catalytic amount of (dimethylamino)-pyridine (DMAP), afforded the first-generation (G-1) dye-labeled dendron **7** in 93% yield (Scheme 1). The same esterification reaction was also carried out with the commercial 3,5-dimethylphenol to afford model compound **8**, the analogue of **7** lacking the donor (coumarin 2) chromophores (Scheme 1). In these and other esterification reactions, EDC was preferred to dicyclohexylcarbodiimide (DCC), since the urea byproduct is water soluble and therefore easier to remove.[24] The use of DPTS, the 1:1 molecular complex between DMAP and *para*-toluenesulfonic acid (PTSA), touted as an efficient catalytic system for esterification reactions,[25] afforded only low yields of product in our case.

Following a standard convergent strategy,[2] coupling of the phenol **6** to the methyl ether protected monomer **3**, under typical Williamson ether synthesis conditions (K_2CO_3 and 18-crown-6 in refluxing acetone), afforded the dye-labeled, methyl ether protected second-generation (G-2) dendron **9** in 81% yield (Scheme 2). However, all our attempts to obtain the corresponding G-2 phenol **10** using BBr_3 under a number of reaction conditions failed. The lack of regioselectivity for cleavage of the methyl ether focal point versus the benzyl ethers of the dendritic structure led to the recovery of only the phenol **6**. Additionally, the use of lithium diphenylphosphine[26] to effect this deprotection proved unsuccessful. Therefore, the methyl ether protecting group is only useful in the preparation of the G-1 dendron **7**, and an alternative protecting group had to be found for the synthesis of dye-labeled dendrons of higher generation.

We consequently employed the hexadecanesulfonate protecting group, since it has been shown[14] that it can be readily cleaved by strong bases without altering the poly(aryl ether) dendritic structure. Moreover, the hexadecane chain introduces a large difference in polarity between the starting phenol and the protected product, facilitating their chromatographic separation, even at higher generations.[14] An added advantage of this protecting group is the extra crystallinity it imparts on all the protected products, allowing their ready isolation and purification. Although coumarins were chosen as the focal and terminal chromophores because of their relatively good solubility, in addition to their excellent optical properties,[11] the solubility enhancement provided by the long alkyl chain represented a decisive advantage since many other dye derivatives tend to be extremely insoluble and hence difficult to use.

Protected monomer **14** was obtained by first reacting the commercially available dimethyl 5-hydroxyisophthalate **11** with 1-hexadecanesulfonyl chloride to give **12** in 91% yield[27] (Scheme 3). Mild reduction of the ester functionalities with KBH_4, in dry THF and in the presence of anhydrous LiCl,[28] afforded the bis(hydroxymethyl) protected phenol **13** in 82% yield. No cleavage

(16) (a) Dewey, T. M.; Du Bois, J.; Raymond, K. N. *Inorg. Chem.* **1993**, *32*, 1729−1738. (b) Zimmerman, H. E.; Jones, G., II. *J. Am. Chem. Soc.* **1970**, *92*, 2753−2761. (c) Boekelheide, V.; Griffin, R. G., Jr. *J. Org. Chem.* **1969**, *34*, 1960−1961.

(17) Murray, M. M.; Kaszynski, P.; Kaisaki, D. A.; Chang, W.; Dougherty, D. A. *J. Am. Chem. Soc.* **1994**, *116*, 8152−8161.

(18) Huck, W. T. S.; van Veggel, F. C. J. M.; Kropman, B. L.; Blank, D. H. A.; Keim, E. G.; Smithers, M. M. A.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1995**, *117*, 8293−8294.

(19) Karlin, K. D.; Nasir, M. S.; Cohen, B. I.; Cruse, R. W.; Kaderli, S.; Zuberbühler, A. D. *J. Am. Chem. Soc.* **1994**, *116*, 1324−1336.

(20) Gruter, G.-J.; Akkerman, O. S.; Bickelhaupt, F. *J. Org. Chem.* **1994**, *59*, 4473−4481.

(21) Kuck, D.; Paisdor, B.; Grützmacher, H.-F. *Chem. Ber.* **1987**, *120*, 589−595.

(22) Bencini, A.; Burguete, M. I.; Garcia-Espana, E.; Luis, S. V.; Miravet, J. F.; Soriano, C. *J. Org. Chem.* **1993**, *58*, 4749−4753.

(23) (a) Grieco, P. A.; Nishizawa, M.; Oguri, T.; Burke, S. D.; Marinovic, N. *J. Am. Chem. Soc.* **1977**, *99*, 5773−5780. (b) Demuynck, M.; De Clercq, P.; Vandewalle, M. *J. Org. Chem.* **1979**, *44*, 4863−4866.

(24) (a) Sheehan, J. C.; Cruickshank, P. A.; Boshart, G. L. *J. Org. Chem.* **1961**, *26*, 2525−2528. (b) Sheehan, J. C.; Preston, J.; Cruickshank, P. A. *J. Am. Chem. Soc.* **1965**, *87*, 2492−2493. (c) Desai, M. C.; Stephens Stramiello, L. M. *Tetrahedron Lett.* **1993**, *34*, 7685−7688.

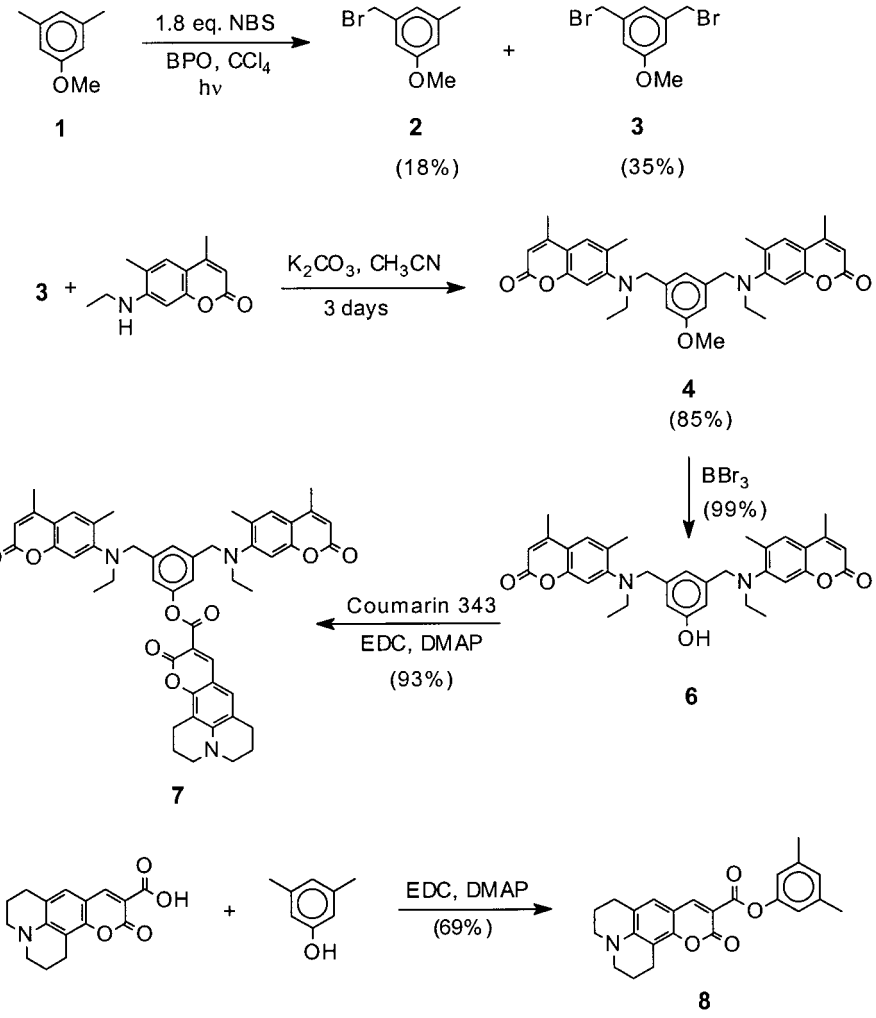
(25) Moore, J. S.; Stupp, S. I. *Macromolecules* **1990**, *23*, 65−70.

(26) Ireland, R. E.; Walba, D. M. *Org. Synth.* **1967**, *IV*, 567−570.

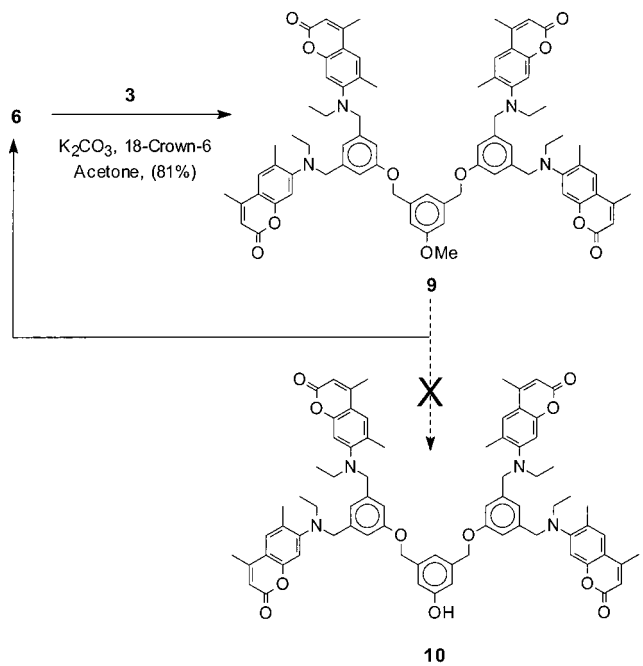
(27) Crossland, R. L.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195−3196.

(28) Hamada, Y.; Shibata, M.; Sugiura, T.; Kato, S.; Shioiri, T. *J. Org. Chem.* **1987**, *52*, 1252−1255.

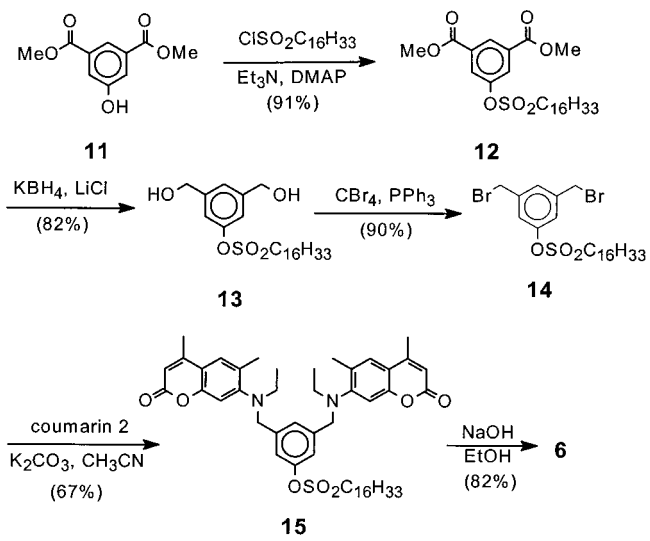
Scheme 1



Scheme 2

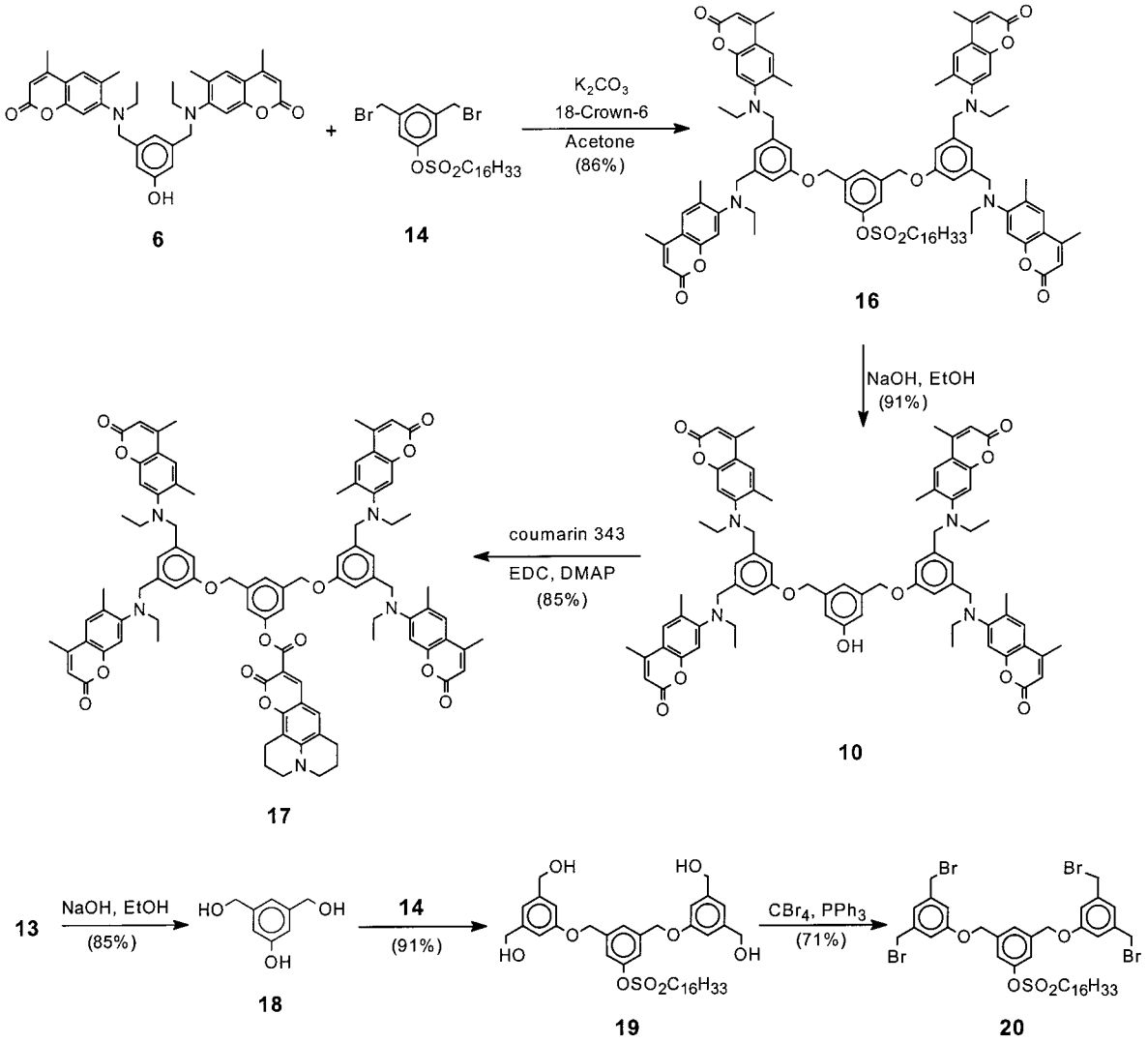


Scheme 3



of the sulfonate group during the reductive step could be detected by ^{1}H NMR. The two benzyl alcohol groups were then converted to the corresponding benzyl bromide functionalities using CBr_4 and PPh_3 in dry THF[2] to afford the hexadecanesulfonate protected monomer **14** in 90% yield. The dye-labeled phenol $(c2)_2$-[G-1]-OH **6** could again be obtained using this new monomer: reaction of **14** with coumarin 2 afforded the dye-labeled hexadecanesulfonate protected phenol **15** in 67% yield, which was

Scheme 4



then regioselectively deprotected in 82% yield with sodium hydroxide in refluxing absolute ethanol (Scheme 3).[29]

The utility of the hexadecanesulfonate protected monomer **14** clearly emerges in the synthesis of the second- and third-generation dendrons. Following a standard convergent strategy,[2] phenol **6** was first coupled to monomer **14**, again under standard Williamson ether synthesis conditions, to afford the protected G-2 dendron **16** in 86% yield (Scheme 4). Separation of the product from the starting phenol proved to be facile as a result of the long alkyl chain introduced by the protecting group. Compound **16** was regioselectively deprotected to the corresponding phenol **10** in 91% yield, using NaOH in refluxing absolute ethanol.[29] Finally, acylation of **10** with coumarin 343, under conditions similar to those used for **7**, afforded the fully labeled G-2 dendron **17** in 85% yield (Scheme 4).

In principle, analogous dendrons of higher generation could further be elaborated using monomer **14** in a standard convergent strategy. However, the time-consuming stepwise synthesis of dendrimers represents a major drawback for this type of polymer architecture and has somewhat hampered their widespread use and applications. As a consequence, several attempts to accelerate the synthesis of poly(aryl ether) dendrimers have been described,[7−9] including the use of a "hypermonomer" of the AB_4 type,[8,9] which allows for the growth of two generations in a single activation/coupling sequence.

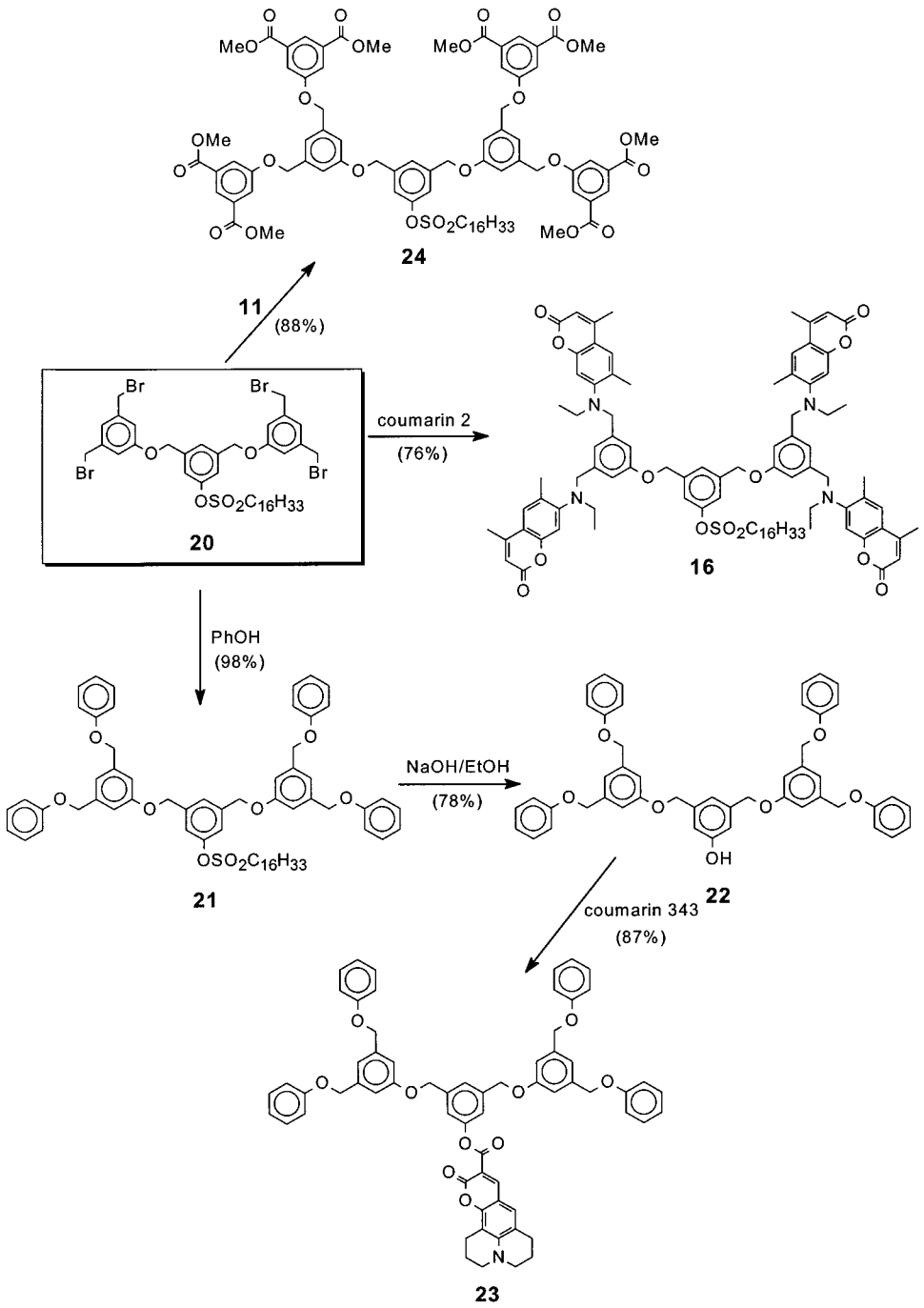
Accelerated Synthesis of Higher Generation Dendrons. Our approach to the accelerated synthesis of laser dye-labeled dendrons involved the novel tetrabromide hypermonomer **20** (Scheme 4). Deprotection of precursor **13** using NaOH in refluxing ethanol afforded the bis(hydroxymethyl)phenol[30] **18** in 82% yield, which was then coupled to the protected monomer **14** obtained previously from the same parent compound. The second-generation dendron **19** was thus obtained in 97% yield. Conversion to the tetrabromide **20** was achieved with CBr_4 and PPh_3 in dry THF (71% yield). In this scheme, all three products **18**, **19**, and the hypermonomer **20** itself were isolated by crystallization.

Because of the very nature of the "reversed" strategy, this novel hypermonomer **20** displays five lipophilic groups and is therefore extremely soluble in common organic solvents. In contrast, the corresponding hyper-

(29) Looker, J. H.; Thatcher, D. N. *J. Am. Chem. Soc.* **1954**, *76*, 4−788.

(30) Lee, S. M.; Fréchet, J. M. J.; Willson, C. G. *Macromolecules* **1994**, *27*, 5154−5159.

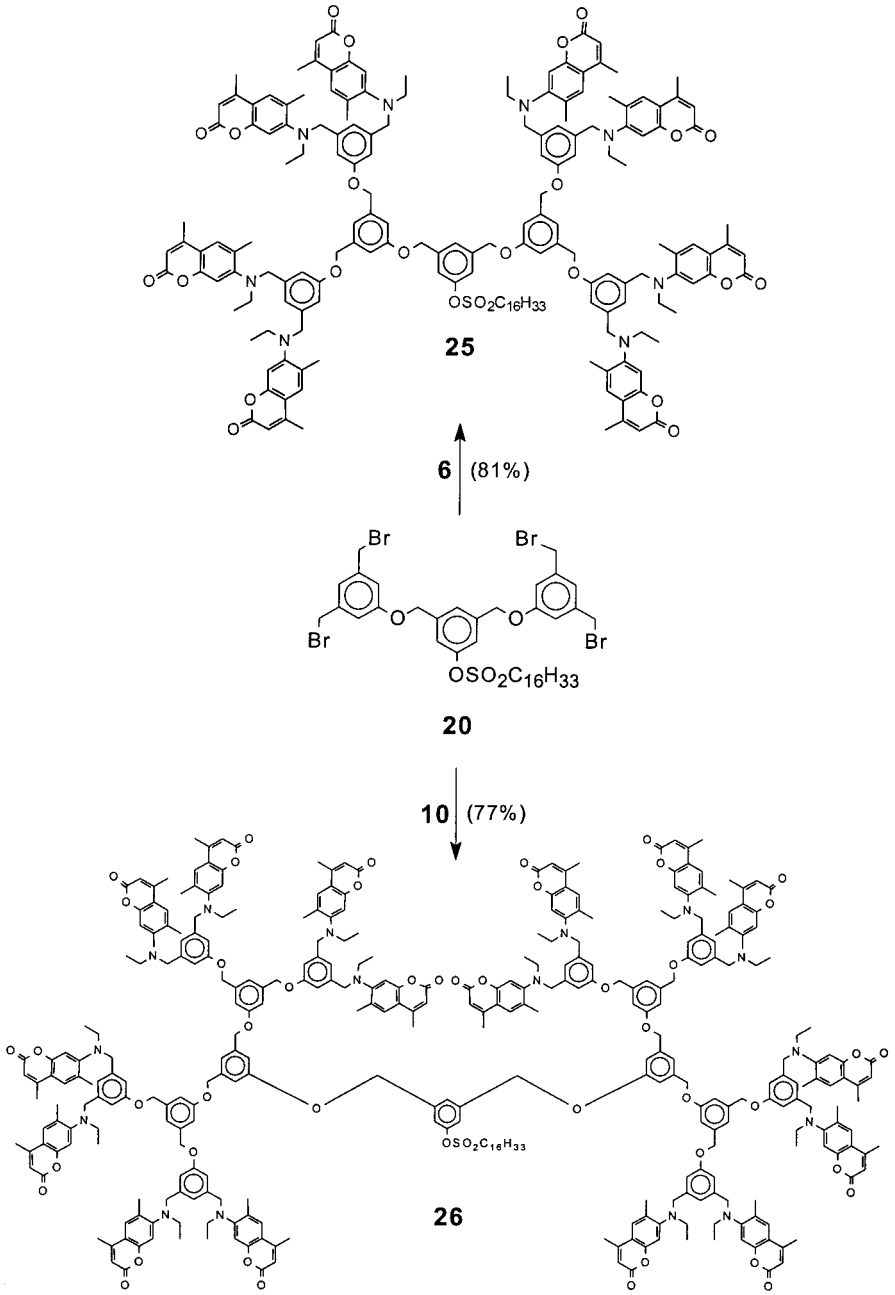
Scheme 5



monomer (Figure 2, B) used in the classical convergent strategy presents an array of five hydrophilic groups and, not surprisingly, was found to display poor solubility in organic solvents. As a consequence, its synthesis and handling were reported to be relatively difficult.[9]

The ready availability of the versatile hypermonomer **20** enables a simple modular approach to a great variety of dendrons of various generations bearing different surface functionalities. For example, Scheme 5 outlines the single-step preparation of a broad array of generation 2 dendrons from hypermonomer **20**. Functionalization of the four benzyl bromide functionalities by phenol under standard Williamson ether synthesis conditions afforded the phenyl-terminated dendron **21** in 98% yield. Compound **21** could easily be deprotected to the corresponding phenol **22** (78% yield) and coupled to coumarin 343 using EDC and DMAP to give the second-generation model dendron **23** (87%) containing the acceptor dye, but no donors. Reaction of the hypermonomer **20** with the hydroxyisophthalate **11** afforded the ester-terminated second-generation dendron **24** (88% yield). As demonstrated previously in the case of the classical poly(aryl ether) structure, ester-terminated dendrimers are of great significance since they provide easy access to a number of surface functionalities (namely, carboxylic acid, acid chloride, benzyl alcohols, amides, and other esters by transesterification).[12,13] Most importantly, functionalization of the four benzyl bromide groups by coumarin 2, under strictly anhydrous conditions and using CaH_2 as a base,[22] afforded the dye-labeled second-generation dendron **16** in 76% yield (Scheme 5), previously obtained in three steps from monomer **14**.

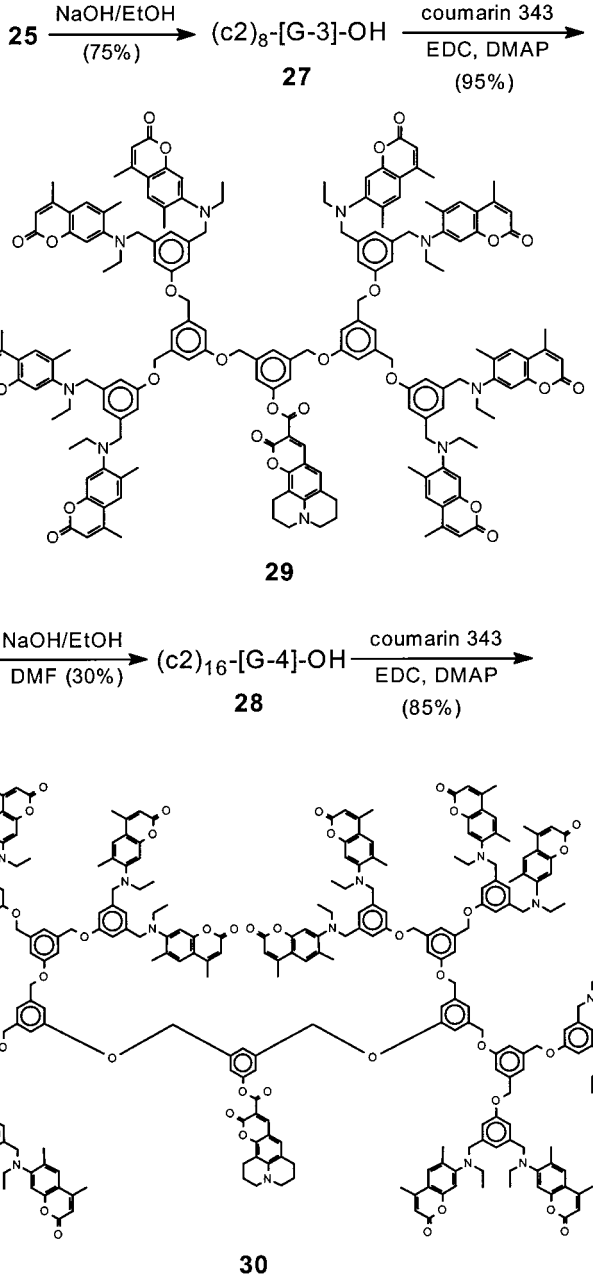
Scheme 6



Finally, coupling of the deprotected G-2 phenol **10** to hypermonomer **20** quickly afforded the protected fourth-generation (G-4) dendron **26** (77%, Scheme 6), thus demonstrating the accelerating effect generated by the use of the hypermonomer in this modular approach. Similarly, reaction of the G-1 phenol **6** with hypermonomer **20** gave the protected third-generation (G-3) dendron **25** in 81% yield (Scheme 6).

In line with the results obtained for the previous generations, deprotection of the G-3 dendron **25** with NaOH proceeded smoothly to yield the corresponding phenol **27** (77%, Scheme 7). However, starting at generation 4, cleavage of the sulfonate protecting group using the same conditions proved to be more difficult. At this stage, the protected dendron **26**, bearing 16 laser dyes on its periphery, turned out to be completely insoluble in refluxing ethanol. All our attempts to achieve the deprotection in this solvent or in higher alcohols, using different bases in excess, failed. One possible explanation for this lack of reactivity is the collapse of the dendrimer on its focal point, prohibiting access of the base to the buried sulfonate. Alternatively, since a nucleophilic base is required for the deprotection, attack at the lactone rings of the multiple and accessible coumarins may be more likely than at the single sulfonate group of the focal point. By trying a variety of solvents to "expand" the dendritic structure, while also monitoring the disappearance of the starting material and the appearance of the deprotected product by MALDI-TOF spectrometry, the best conditions for the deprotection were found to involve the addition of a NaOH solution in ethanol to a DMF solution of the dendrimer. Though clearly not ideal, this process could be used to transform the G-4 dendron **26** into the corresponding phenol **28** in 30% yield (Scheme 8). Evidence for lactone ring opening on the peripheral coumarins was observed through color changes from light yellow to darker yellow-brown upon addition of base, which may account for the poor yield of the reaction.

Scheme 7

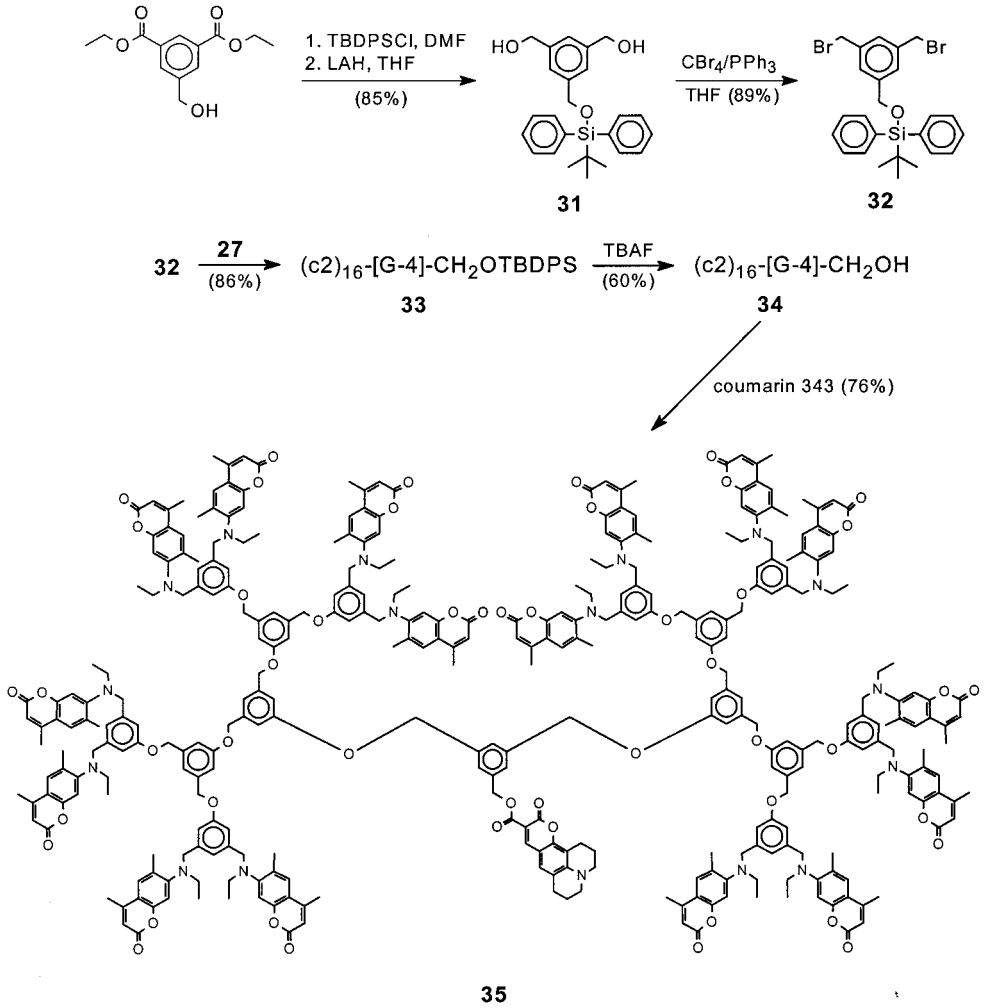


Finally, acylation of the dendritic phenols **27** and **28** with coumarin 343 afforded the fully dye-labeled dendrons **29** and **30**, in 95% and 85% yield, respectively.

Alternative Protecting Group. The low yield of the deprotection step in the fourth generation demonstrates the difficulty in balancing the need for a highly reactive nucleophile for core deprotection with the need for preserving the somewhat fragile coumarin dyes at the periphery. The poor yield achieved in the deprotection step prompted us to look for an alternative strategy for the assembly of the G-4 dendron. We eventually chose to use the more classical *tert*-butyldiphenylsilyl (TBDPS) protecting group, since its deprotection with tetrabutylammonium fluoride (TBAF) is well documented and highly selective.[15] However, to implement this protecting group, a significant change in the dendrimer focal point had to be made. The protected phenolic core functionality was replaced by a protected benzyl alcohol that confers greater stability to the chosen protecting group.[15a] Attachment of two G-3 deprotected dendrons **27** to the 3,5-bis(bromomethyl)benzyl alcohol **32**, obtained in three steps from the commercially available diethyl-5-methoxyisophthalate (Scheme 8), afforded the G-4 protected dendron **33**. Deprotection of **33** proceeded smoothly with TBAF to yield the alcohol **34** in 60% yield (Scheme 8). This molecule could be coupled to coumarin 343 using the same EDC/DMAP conditions, to yield the slightly modified G-4 fully dye-labeled dendrimer **35** in 76% yield. Compound **35** is extremely similar to **30** and is altered only by the presence of a methylene group at the core.

Preliminary steady-state fluorescence measurements indicate that energy transfer from the peripheral donor coumarins (coumarin 2) to the core acceptor (coumarin 343) is highly efficient. Energy-transfer efficiencies at each dendrimer generation were calculated by studying fluorescence quenching of the donor dyes in the presence of the acceptor. It was found that, for the first three generations, energy transfer is greater than 97% efficient.

Scheme 8



With the larger fourth-generation dendrimer, this efficiency of energy transfer drops to approximately 90% as a result of increased distance between donor and acceptor dyes.[31] However, to fully quantify the photoprocesses occurring in these dendritic assemblies, it is necessary to carry out careful quantum yield calculations, as well as time-resolved measurements. These measurements will be presented in a subsequent publication.[32]

Conclusion

To carry out accurate photophysical studies on multichromophoric macromolecules, it is necessary to gain access to a variety of model compounds in order to deconvolute the contribution of each individual type of chromophore. In the case of dendrimers, it is also necessary to identify the effects of increasing the dendrimer generation. Hence, to carry out the necessary studies on dendritic systems, a large number of different structures are required. Our modular approach to the synthesis of multichromophoric dendrimers, involving a novel and versatile hypermonomer, allows for the preparation of not only the target molecules but also the necessary model compounds. This novel, "reversed" strategy allows for the utilization of the previously described high-yielding Williamson ether synthesis reactions to assemble dendrimers with appropriate functionality for coupling nucleophilic peripheral chromophores and an electrophilic core chromophore. The hexadecanesulfonate protecting group was found to have several advantages, namely, improved solubility, crystallinity, and ease of purification. However, its usefulness is greatly reduced at the fourth generation, where solubility problems hampered its efficient removal. The optical properties, including the light-harvesting and energy-transfer capacity, of the various dendrimers described in this article will be reported separately.[32]

Experimental Section

All reagents were used as received and without further purification, unless otherwise noted. THF was distilled under N_2 over sodium/benzophenone immediately prior to use. NBS was recrystallized in water, and 3,5-dimethylanisole was distilled prior to use. Coumarin 2 and coumarin 343 (laser grade) were purchased from Acros. Potassium carbonate and lithium chloride were ground and dried in an oven (170 °C) overnight. Column chromatography was carried out with Merck silica gel for flash columns, 230−400 mesh. Preparative TLC plates were 1 or 2 mm thick Merck silica gel 60 F_{254} glass backed plates. Spinning band chromatography was done using rotors coated with 1 or 2 mm thick TLC grade silica (Aldrich) layers. IR spectra were recorded on a Mattson Genesis Series FTIR. NMR spectra were recorded on a Bruker AMX-300,

(31) T. Förster, *Z. Naturforsch.* **1949**, *4A*, 319−27. Förster, T. *Discuss. Faraday Soc.* **1959**, *27*, 7−17. Stryer, L. *Annu. Rev. Biochem.* **1978**, *47*, 819−846.

(32) Adronov, A.; Gilat, S. L.; Fréchet, J. M. J. Manuscript in preparation.

Bruker AMX-400, or Bruker DRX-500 instrument with TMS or solvent carbon signal as the standards. Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry was performed on a PerSeptive Biosystems Voyager-DE spectrometer using delayed extraction mode and with an acceleration voltage of 20 keV. Samples were prepared[33] by using a 1:20 ratio of analyte (5 mg/mL in THF) to matrix solution (*trans*-indoleacrylic acid, 10 mg/mL in THF). Fluorescence spectra were recorded on an SPEX/ISA Fluorolog 3.22 equipped with double excitation and emission monochromators and a digital photon-counting photomultiplier. Excitation correction was achieved with a solid-state silicon photodiode. UV/vis spectra were recorded in toluene (maximum OD < 0.2) on a Uvicon 933 spectrophotometer, using standard 1 cm quartz UV cells. Samples for fluorescence measurements were degassed by bubbling N_2 through the solution for 5 min. Melting points were measured on a Gallenkamp melting point apparatus. Elemental analyses were performed by MHW laboratories. Electron impact (EIMS) mass spectra were obtained using a VG Prospec mass spectrometer operated in positive ion mode. Detailed NMR data for all compounds are available in the Supporting Information.

3,5-Bis(bromomethyl)anisole (3). A yellow, heterogeneous solution of 3,5-dimethylanisole (5.01 g, 36.8 mmol), *N*-bromosuccinimide (1.80 equiv, 66.2 mmol, 11.8 g), and traces of benzoyl peroxide (0.04 mol %, 15.0 mmol, 3.50 mg) in CCl_4 (90.0 mL) was heated at reflux with vigorous stirring for 14 h under irradiation (120 W standard white bulb). The resulting brownish heterogeneous mixture was filtered, and the filtrate was washed with water (100 mL), saturated aqueous $NaHCO_3$ (100 mL), and again with water (100 mL), dried on Na_2SO_4, and concentrated in vacuo. Column chromatography on silica gel (9:1 hexanes/chloroform) afforded two major products. After evaporation of the solvent in vacuo, the first ($R_f = 0.35$) was a clear oil that crystallized slowly at room temperature to give colorless crystals of 3-(bromomethyl)-5-methylanisole (1.46 g, 19% based on the anisole). The second product ($R_f = 0.2$) was a white powder, which was further recrystallized in cyclohexane to yield 3,5-bis(bromomethyl)anisole (3.713 g, 35%): white needles; mp 75−76 °C (lit.[20] 76−76.5 °C); Anal. Calcd for $C_9H_{10}Br_2O$ (293.98): C, 36.77; H, 3.43. Found: C, 36.85; H, 3.60.

3,5-Bis(*N*-(4,6-dimethyl-7-ethylaminocoumarin)methyl)-anisole (or (c2)$_2$-[G-1]-OMe) (4). 3,5-Bis(bromomethyl)-anisole (690 mg, 2.35 mmol) in CH_3CN (10 mL) was added over 4 h to a mixture of 4,6-dimethyl-7-ethylaminocoumarin (coumarin 2, 3 equiv, 7.04 mmol, 1.53 g) and K_2CO_3 (6 equiv, 14.08 mmol, 1.95 g) in CH_3CN (60 mL). The reaction mixture was heated at reflux under argon with vigorous stirring for 3 days. The cooled solution was then filtered, evaporated to dryness in vacuo, taken up in CH_2Cl_2, and chromatographed on silica gel (20:1 CH_2Cl_2/ethyl acetate), first affording recovered coumarin 2 (530 mg, 1.04 equiv, 35%), then (c2)$_2$-[G-1]-OMe as a white powder (1.14 g, 85%), and finally 3-hydroxymethyl-5-(*N*-(4,6-dimethyl-7-ethylaminocoumarin)-methyl)anisole (52.0 mg, 6%). An analyticalsample of (c2)$_2$-[G-1]-OMe was provided by recrystallization in acetonitrile: white crystals, mp 195−196 °C; MS (EI) *m*/*z* 566 (M^+), calcd *m*/*z* 566.69. Anal. Calcd for $C_{35}H_{38}N_2O_5$ (566.69): C, 74.18; H, 6.76; N, 4.94. Found: C, 73.93; H, 6.55; N, 4.85.

3,5-Bis(*N*-(4,6-dimethyl-7-ethylaminocoumarin)methyl)phenol (or (c2)$_2$-[G-1]-OH) (6). Method 1: To a clear, homogeneous solution of 3,5-bis(*N*-(4,6-dimethyl-7-ethylaminocoumarin)methyl)anisole (1.18 g, 2.08 mmol) in CH_2Cl_2 (100 mL) was added dropwise under an Ar atmosphere a solution of BBr_3 in CH_2Cl_2 (1.0 M, 20.0 mL, 20.0 mmol, 10 equiv). The solution initially turned green and then pale yellow, with a white precipitate. After 2 h of vigorous stirring at room temperature, the mixture was carefully poured in water (200 mL). The clear, colorless organic phase was washed with $NaHCO_3$ (200 mL) and water (200 mL) and then dried over Na_2SO_4. The solvent was evaporated in vacuo, and the yellow-brown powder obtained was recrystallized in ethyl acetate, yielding a fine, yellowish powder (1.09 g, 95%). Method 2: To a solution of (c2)$_2$-[G-1]-OHds (**15**) (475 mg, 5.65×10^{-4} mol) in 200 mL of absolute ethanol was added a solution of NaOH (250 mg, 6.25×10^{-3} mol, 11 equiv) in 150 mL of absolute ethanol. The mixture was stirred and heated to reflux for 3 h, after which it was brought to pH 5 using dilute (2 M) HCl. The solvent was evaporated in vacuo, and the residue was taken up in CH_2Cl_2, filtered, and chromatographed on silica gel (8:2 CH_2Cl_2/ethyl acetate). Yield: 257 mg (82%). MS (EI): *m*/*z* 552 (M^+), calcd *m*/*z* 552.67. Anal. Calcd for $C_{34}H_{36}N_2O_5 \cdot H_2O$ (570.68): C, 71.56; H, 6.71; N, 4.91. Found: C, 71.58; H, 6.92; N, 4.72.

(c2)$_2$-[G-1]-C343 (7). An orange solution of (c2)$_2$-[G-1]-OH (100 mg, 0.181 mmol), coumarin 343 (2 equiv, 0.361 mmol, 103 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (2.5 equiv, 0.454 mmol, 87.0 mg), and (dimethylamino)pyridine (DMAP) (0.2 equiv, 36.19 mmol, 5.4 mg) in CH_2Cl_2 (2 mL) was stirred for 72 h at room temperature. After addition of water (2 mL), the organic phase was separated, washed with aqueous HCl (0.5N, 4 × 2 mL), saturated $NaHCO_3$ (4 × 2 mL), and water (2 × 2 mL), dried over Na_2SO_4, and chromatographed twice on silica gel (preparative TLC, 9:1 CH_2Cl_2/EtOAc, then 9:1 CH_2Cl_2/Et_2O) to give an orange powder (138 mg, 93%). MS (MALDI): *m*/*z* 816.9 (M^+), calcd *m*/*z* 819.9. UV/vis (CH_2Cl_2): λ_{max} (ϵ) = 343, 437 nm (25 000, 46 000, respectively). Anal. Calcd for $C_{50}H_{53}N_3O_{10} \cdot 2H_2O$ (855.98): C, 70.16; H, 6.24; N, 4.91. Found: C, 70.15; H, 5.86; N, 4.91.

3,5-Bis(bromomethyl)phenol hexadecanesulfonate, (Br)$_2$-[G-1]-OHds (14). Compound **13** (1.50 g, 3.39 mmol) and CBr_4 (2.5 equiv, 8.47 mmol, 2.25 g) were dissolved in dry THF (50 mL), and triphenylphosphine (2.5 equiv, 8.47 mmol, 2.22 g) was added in two parts. The reaction mixture was stirred at room temperature under N_2 for 2 h. The solvent was evaporated in vacuo and the residue was filtered over a short plug of silica gel (eluted with 6:4 hexanes/CH_2Cl_2), affording a white solid (1.636 g; 85%), mp 81−83 °C. HRMS (EI): *m*/*z* calcd for $C_{24}H_{40}O_3S^{81}Br_2$ 570.1024, found 570.1016.

(c2)$_4$-[G-2]-OHds (16). Method 1: A yellow, heterogeneous solution of **14** (0.905 g, 1.59×10^{-3} mol), **6** (1.90 g, 3.44×10^{-3} mol, 2.2 equiv), K_2CO_3 (1.33 g, 9.62×10^{-3} mol, 6.0 equiv), and 18-crown-6 (0.255 g, 9.65×10^{-4} mol, 0.6 equiv) in acetone (250 mL) was heated at reflux under Ar with vigorous stirring for 20 h. The cooled solution was evaporated to dryness in vacuo, taken up in CH_2Cl_2, and filtered. The light yellow solution was then concentrated and purified by chromatography on silica gel (9:1 CH_2Cl_2/ethyl acetate). Yield: 2.35 g (98%). Method 2: The heterogeneous mixture of **20** (92.0 mg, 9.52×10^{-5} mol), coumarin 2 (124 mg, 5.71×10^{-4} mol, 6 equiv), and CaH_2 (29 mg, 6.89×10^{-4} mol, 7.2 equiv) in 25 mL of dry CH_3CN was stirred and heated to reflux for 85 h. The solution was then cooled and filtered, and the solvent was evaporated in vacuo. The resulting residue was taken up in CH_2Cl_2 and purified by preparative TLC (95:5 CH_2Cl_2/ethyl acetate). Yield: 109 mg (76%). MS (MALDI): *m*/*z* 1509.4 (M^+), calcd *m*/*z* 1511.96. Anal. Calcd for $C_{92}H_{110}N_4O_{13}S$ (1511.96): C, 73.08; H, 7.33; N, 3.71. Found: C, 72.85; H, 7.48; N, 3.55.

(Br)$_4$-[G-2]-OHds (20). The solution of **19** (1.000 g, 1.399 mmol) and CBr_4 (6 equiv, 8.392 mmol, 2.783 g) in dry THF (50 mL) was cooled to 0 °C, and PPh_3 (6 equiv, 8.392 mmol, 2.201 g) was added in two parts. The reaction mixture was stirred at room temperature under N_2 for 4 h. The pH was then adjusted to 7 with saturated Na_2CO_3 (5 mL), and brine (50 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL), and the organic fractions were combined and concentrated in vacuo. The concentrate was loaded on a short plug of silica, washed with hexanes (300 mL), and eluted with 8:2 hexanes/ethyl acetate (300 mL). The product was then crystallized in hexanes, yielding white crystals (960 mg; 71%), mp 78−79 °C. Anal. Calcd for $C_{40}H_{54}Br_4O_5S$ (966.54): C, 49.71; H, 5.63. Found: C, 49.79; H, 5.52.

(c2)$_8$-[G-3]-OHds (25). The mixture of **20** (0.380 g, 3.93×10^{-4} mol), **6** (1.00 g, 1.811×10^{-3} mol, 4.6 equiv), K_2CO_3 (0.691 g, 5.00×10^{-3} mol, 12.7 equiv), and 18-crown-6 (0.150 g,

(33) (a) Leon, J. W.; Fréchet, J. M. J. *Polym. Bull.* **1995**, *35*, 449. (b) Hayes, W.; Freeman, A.; Fréchet, J. M. J. *Polym. Mater. Sci. Eng.* **1997**, *77*, 136−137.

5.675×10^{-4} mol, 1.4 equiv) in 25 mL of dry acetone was stirred and heated at reflux under argon for 24 h. It was then cooled and evaporated to dryness in vacuo to yield a yellow powder that was taken up in CH_2Cl_2, filtered, and purified by chromatography on silica gel (8:2 CH_2Cl_2/ethyl acetate). Yield: 0.910 g (81%). MS (MALDI): *m*/*z* 2849.0 (M^+), calcd *m*/*z* 2853.57. Anal. Calcd for $C_{176}H_{194}N_8O_{25}S \cdot 4H_2O$ (2925.63): C, 72.26; H, 6.96; N, 3.83. Found: C, 72.33; H, 7.24; N, 3.77.

$(c2)_{16}$-[G-4]-OHds (26). The heterogeneous mixture of **20** (0.226 g, 2.34×10^{-4} mol), **10** (1.30 g, 1.06×10^{-3} mol, 4.5 equiv), K_2CO_3 (0.394 g, 2.85×10^{-3} mol, 12 equiv), and 18-crown-6 (0.076 g, 2.88×10^{-4} mol, 1.2 equiv) in dry acetone (150 mL) was stirred and heated to reflux under argon for 40 h. The reaction mixture was cooled and evaporated to dryness in vacuo. The residue was then taken up in CH_2Cl_2, filtered, and concentrated. The product was purified by column chromatography on silica gel (100:4 CH_2Cl_2/methanol) yielding a light yellow solid (1.00 g, 77%). MS (MALDI): *m*/*z* 5530.3 (M^+), calcd *m*/*z* 5536.79. Anal. Calcd for $C_{344}H_{362}N_{16}O_{49}S$ (5536.79): C, 74.62; H, 6.59; N, 4.05. Found: C, 75.00; H, 6.51; N, 3.96.

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Supporting Information Available: ^1H and ^{13}C NMR data for all compounds and full experimental details for compounds **2**, **5**, **8**−**13**, **15**, **17**−**19**, **21**−**24**, and **27**−**35**. This material is available free of charge via the Internet at http://pubs.acs.org.

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