JOC Article

Sequences in Dendrons and Dendrimers

Kulandaivelu Sivanandan, Britto S. Sandanaraj, and S. Thayumanavan*

Department of Chemistry, University of Massachusetts, 701 LGRT-A, 710 North Pleasant Street, Amherst, Massachusetts 01003

thai@chem.umass.edu

Received January 21, 2004

Sequential incorporation of a variety of functional groups forms the basis for specificity in biomacromolecules. Introduction of such diversity and sequencing ability in artificial macromolecules is fundamentally interesting. In this paper, three different synthetic approaches have been used to build dendrons and dendrimers in which all the monomer units are different from each other. The synthetic strategies described in this paper involve the use of (i) an ABB_p monomer, (ii) an ABB′ monomer, and (iii) an ABB_m monomer. The complementarity and the versatility of these synthetic approaches should render them useful for a variety of applications.

Introduction

The wealth of information storage and function through the ability to sequence polymers is obvious from the versatility of nature's polymers in biology. Proteins and nucleic acids use only few (20 and 4, respectively) different monomers to bring about their impressive structural complexities and functions. With a desire to further expand the scope of these biopolymers in both structure and function, several labs seek to expand functional group variety by manipulating nature's machinery.[1] An alternate pathway to obtaining diversity in macromolecules is a bottom-up approach, in which custom-designed polymers are synthesized with a high degree of control. Nature's functional versatility has served as inspiration to design biomimetic structures for several years.[2] However, most of these structures are small-molecule-based. Although there are a few examples of macromolecular biomimetics, the number is surprisingly low.[3]

Dendrimers are the only class of artificial macromolecules that can be obtained in high molecular weights in a monodisperse form.[4] Therefore, the branched macromolecule is an excellent choice for biomimicry.[5] Several reports exist on the use of a dendrimer as an effective mimic of nature from an encapsulation standpoint.[6] The propensity of dendrimers to adopt a globular conformation at high generations also suggests that these molecules could be pursued as possible globular protein mimics.[7] Dendrimers are composed mainly of three structural components: a core, branching units, and peripheral units. All of these structural components are important for the dendrimers' ability to bind guest molecules. For example, it has been shown that the

(1) (a) Wang, L.; Brock, A.; Herberich, B.; Schultz, P. G. *Science* **2001**, *292*, 498−500. (b) Wang, P.; Tang, Y.; Tirrell, D. A. *J. Am. Chem. Soc.* **2003**, *125*, 6900−6906. (c) Wang, L.; Zhang, Z.; Brock, A.; Schultz, P. G. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 56−61. (d) Kwon, I.; Kishenbaum, K.; Tirrell, D. A. *J. Am. Chem. Soc.* **2003**, *125*, 7512−7513. (e) Hohsaka, T.; Ashizuka, Y.; Sasaki, H.; Murakami, H.; Sisido, M. *J. Am. Chem. Soc.* **1999**, *121*, 12194−12195. (f) Anderson, R. D., III; Zhou, J.; Hecht, S. M. *J. Am. Chem. Soc.* **2002**, *124*, 9674−9675.

(2) (a) Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1304−1319. (b) Conn, M. M.; Rebek, J. *Chem. Rev.* **1997**, *97*, 1647−1668. (c) Rebek, J. *Acc. Chem. Res.* **1999**, *32*, 278−286. (d) Breslow, R.; Dong, S. D. *Chem. Rev.* **1998**, *98*, 1997−2011. (e) Breslow, R. *Acc. Chem. Res.* **1995**, *28*, 146−153. (f) Nowick, J. S. *Acc. Chem. Res.* **1999**, *32*, 287−296.

(3) (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173−180. (b) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893−4012. (c) Liu, L.; Rozenman, M.; Breslow, R. *J. Am. Chem. Soc.* **2002**, *124*, 12660−12661. (d) Liu, L.; Breslow, R. *J. Am. Chem. Soc.* **2003**, *125*, 12110−12111. (e) Liu, L.; Breslow, R. *J. Am. Chem. Soc.* **2002**, *124*, 4978−4979.

(4) (a) Newkome, G. R.; Moorefield, C. N.; Vögtle, F. *Dendrimers and Dendrons: Concepts, Syntheses, Applications*, 2nd ed.; Wiley-VCH: New York, 2001. (b) Bosman, A. W.; Janssen, H. M.; Meijer, E. W. *Chem. Rev.* **1999**, *99*, 1665−1688. (c) Fischer, M.; Vögtle, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 884−905. (d) Fréchet, J. M. J. *Science* **1994**, *263*, 1710−1715. (e) Matthews, O. A.; Shipway, A. N.; Stoddart, J. F. *Prog. Polym. Sci.* **1998**, *23*, 1−56. (f) Moore, J. S. *Acc. Chem. Res.* **1997**, *30*, 402−413. (g) Newkome, G. R.; He, E.; Moorefield, C. N. *Chem. Rev.* **1999**, *99*, 1689−1746. (h) Tomalia, D. A. *Adv. Mater.* **1994**, *6*, 529−539. (i) Tomalia, D. A.; Naylor, A. M.; Goddard, W. A., III. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 138−175. (j) *Dendrimers II: Architecture, Nanostructure and Supramolecular Chemistry*; Vögtle, F., Ed.; Springer: Berlin, 2000; Vol. 210. (l) Zeng, F.; Zimmerman, S. C. *Chem. Rev.* **1997**, *97*, 1681−1712.

(5) (a) Diederich, F.; Felber, B. *Proc. Nat. Acad. Sci. U.S.A.* **2002**, *59*, 4778−4781. (b) Baars, M. W. P. L.; Meijer, E. W. *Top. Curr. Chem.* **2000**, *210*, 131−182. (c) Zimmerman, S. C.; Lawless, L. J. *Top. Curr. Chem.* **2001**, *217*, 95−120. (d) Thayumanavan, S.; Bharathi, P.; Sivanandan, K.; Vutukuri, D. R. *C. R. Acad. Sci., Ser. IIc: Chim.* **2003**, *6*, 767−778.

(6) (a) Hecht, S.; Fréchet, J. M. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 74−91. (b) Gorman, C. B.; Smith, J. C. *Acc. Chem. Res.* **2001**, *34*, 60−71. (c) Stone, D. L.; Smith, D. K.; McGrail, P. T. *J. Am. Chem. Soc.* **2002**, *124*, 856−864. (d) Smith, D. K.; Diederich, F. *Top. Curr. Chem.* **2000**, *210*, 183−227. (e) Crooks, R. M.; Zhao, M.; Sun, L.; Chechik, V.; Yeung, L. K. *Acc. Chem. Res.* **2001**, *34*, 181−190.

(7) (a) Smith, D. K.; Diederich, F. *Chem. Eur. J.* **1998**, *4*, 1353−1361. (b) Dandliker, P. J.; Diederich, F.; Gisselbrecht, J. P.; Louati, A.; Gross, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2725−2728. (c) Mattei, S.; Wallimann, P.; Kenda, B.; Amrein, W.; Diederich, F. *Helv. Chim. Acta* **1997**, *80*, 2391−2417. (d) Habicher, T.; Diederich, F.; Gramlich, V. *Helv. Chim. Acta* **1999**, *82*, 1066−1095. (e) Wallimann, P.; Mattei, S.; Seiler, P.; Diederich, F. *Helv. Chim. Acta* **1997**, *80*, 2369−2390. (f) Jiang, D. L.; Aida, T. *Chem. Commun.* **1996**, 1523−1524. (g) Bharathi, P.; Zhao, H.; Thayumanavan, S. *Org. Lett.* **2001**, *3*, 1961−1964.

10.1021/jo049878p CCC: $27.50
Published on Web 03/26/2004

length of the alkyl chain at the core of an amphiphilic dendrimer could dictate the location of the hydrophobic guest molecule.[8] Similarly, the solubility of dendrimers is dependent on the nature of the peripheral functionalities, which are therefore crucial for binding events based on solvophobic forces. Although there has been much work on varying the core and the periphery of dendrimers, the effect of functional group incorporations within the branching units has not been studied in detail. However, it has been noted that the functionalities present in the branching units have significant effects on binding or catalysis by the dendrimer.[9] The ability to introduce sequences within dendrimers provides the opportunity to systematically vary the core, periphery, and branching units. Also, sequencing methodologies should provide the possibility of presenting a diverse set of functional groups in all these locations. Sequencing dendrimers will open up a number of possibilities for dendrimers in molecular recognition, especially in biomimetics and catalysis. We believe that the synthetic methods outlined here will provide the fundamental tools necessary for those possibilities.

Diversity in functional group display within dendrimers can be achieved through both divergent and convergent approaches. Newkome, Majoral, and others have reported the incorporation of a few different functionalities in dendrimers using divergent methods.[10] The inherent nature of the divergent approach does not allow precise control over the extent and position of functional group incorporation. However, this approach is synthetically much less strenuous and therefore is useful for certain applications. Since excellent control in the placement of functional groups is desirable for biomimetic possibilities, the convergent approach is preferred.[11] In fact, convergent synthesis has been used to incorporate a controlled number of functionalities in the periphery of dendrimers.[12] This was achieved by the stepwise incorporation of functionalities, where the desired monosubstituted product in the first step would be obtained as a statistical mixture with the corresponding undesired disubstituted product. This approach has its obvious drawbacks. To introduce sequences within a dendrimer, the convergent methodology should have the capability of differentiating the two "B" functionalities in an AB_2 monomer as shown in Figure 1.

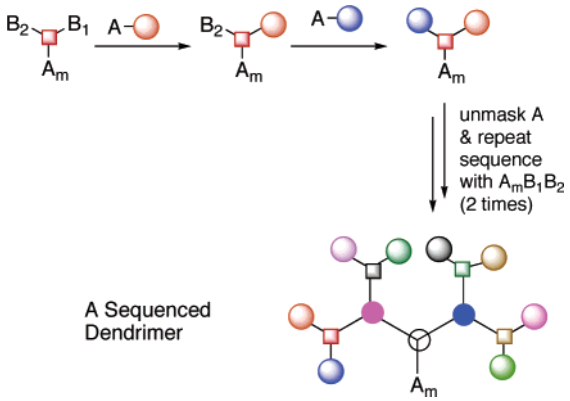


FIGURE 1. Strategy to obtain sequenced dendrimers.

Because sequenced dendrimers with different sets of backbone functionalities and connectivities are likely to emerge in the literature, availability of several complementary methodologies is desirable. We have introduced two complementary methods for the synthesis of dendrons in which the functionalities in the periphery are different from one another:[13] (i) through the stepwise incorporation of two different functional groups to an ABB_p monomer and (ii) through an ABB′ monomer, in which the reactivities of B and B′ are different. These two methodologies can be used to synthesize dendrimers in which each monomer unit is different. In addition, we also introduce here a third complementary synthetic method using ABB_m building block. In this paper, we utilize these methodologies to introduce sequences within dendrimers. To our knowledge, this is the first report in which each monomer unit is different from the other within a dendrimer. The dendrimers reported here are based on arylalkyl ether dendrimers, since one of our long-term goals is to incorporate various functionalities in specific locations of the benzyl ether based amphiphilic dendrimers that we previously reported.[7g] It should be noted, however, that the conceptual aspects of these methodologies could be applied to any set of backbone functionalities.

Results and Discussion

Based on an ABB_p Monomer. In this approach, one of the B functionalities is protected with an easily removable protecting group. To synthesize a G-1 dendron in which all three monomer units are different from each other, three steps are involved: (i) reaction of the first monomer with the unprotected B, (ii) deprotection of the B_p moiety, and (iii) reaction of the second monomer with the newly liberated B. In the case of dihydroxybenzyl alcohol, one of the phenolic groups is protected. The protecting groups that have been used include allyl, benzoyl, and methoxymethyl ether moieties. We have

(8) Watkins, D. M.; Sayed-Sweet, Y.; Klimash, J. W.; Turro, N. J.; Tomalia, D. A. *Langmuir* **1997**, *13*, 3136−3141.

(9) For examples, see: (a) Daniel, M. C.; Ruiz, J.; Astruc, D. *J. Am. Chem. Soc.* **2003**, *125*, 1150−1151. (b) Piotti, M. E., Jr.; F. R.; Bond, R.; Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1999**, *121*, 9471−9472. (c) Koenig, S.; Müller, L.; Smith, D. K. *Chem. Eur. J.* **2001**, *7*, 979−986.

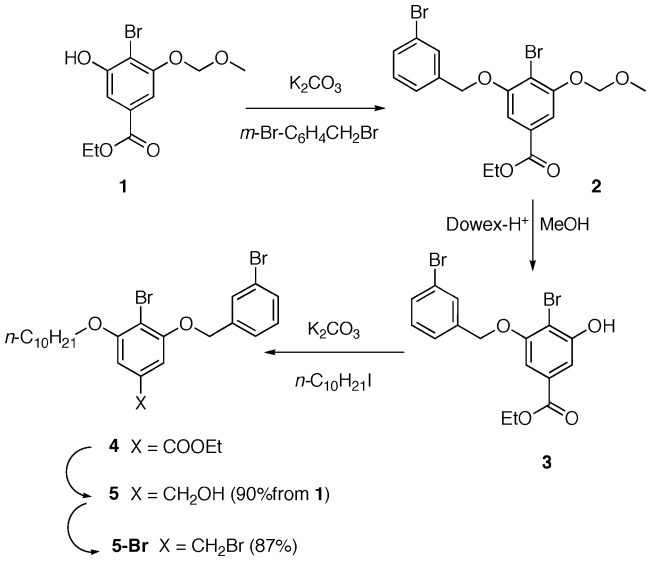
(10) (a) Newkome, G. R.; Weis, C. D.; Moorefield, C. N.; Baker, G. R.; Childs, B. J.; Epperson, J. *Angew. Chem., Int. Ed.* **1998**, *37*, 307−310. (b) Newkome, G. R.; Kim, H. J.; Moorefield, C. N.; Maddi, H.; Yoo, K.-S. *Macromolecules* **2003**, *36*, 4345−4354. (c) Newkome, G. R.; Yoo, K. S.; Hwang, S.-H.; Moorefield, C. N. *Tetrahedron* **2003**, *59*, 3955−3964. (d) Larré, C.; Donnadieu, B.; Caminade, A.-M.; Majoral, J.-P. *J. Am. Chem. Soc.* **1998**, *120*, 4029−4030. (e) Latigue, M.-L.; Slany, M.; Caminade, A.-M.; Majoral, J.-P. *Chem. Eur. J.* **1996**, *2*, 1417−1426. (f) Woller, E. K.; Walter, E. D.; Morgan, J. R.; Singel, D. J.; Cloninger, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 8820−8826.

(11) Grayson, S. M.; Fréchet, J. M. J. *Chem. Rev.* **2001**, *101*, 3819−3868.

(12) (a) Wooley, K. L.; Hawker, C. J.; Fréchet, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1059−1076. (b) Bo, Z.; Schäfer, A.; Franke, P.; Schlüter, A. D. *Org. Lett.* **2000**, *2*, 1645−1648. (c) Ganesh, R. N.; Shraberg, J.; Sheridan, P. G.; Thayumanavan, S. *Tetrahedron Lett.* **2002**, *43*, 7217−7220. (d) For differential substitutions in layer by layer, see: Freeman, A. W.; Chrisstoffels, L. A. J.; Fréchet, J. M. J. *J. Org. Chem.* **2000**, *65*, 7612−7617. (e) For synthesis of dendrimers using different branching structures in one pot, see: Okaniwa, M.; Takeuchi, K.; Asai, M.; Ueda, M. *Macromolecules* **2002**, *35*, 6224−6231; 6232−6238.

(13) (a) Sivanandan, K.; Vutukuri, D.; Thayumanavan, S. *Org. Lett.* **2002**, *4*, 3751−3753. (b) Vutukuri, D.; Sivanandan, K.; Thayumanavan, S. *Chem. Commun.* **2003**, 796−797. (c) Simanek and co-workers reported a methodology in which the differential reactivities of di-, mono-, and unsubstituted cyanuric chloride have been utilized. See: Zeng, W.; Nowlan, D. T., III; Thomson, L. M.; Lackowski, W. M.; Simanek, E. E. *J. Am. Chem. Soc.* **2001**, *123*, 8914−8922.

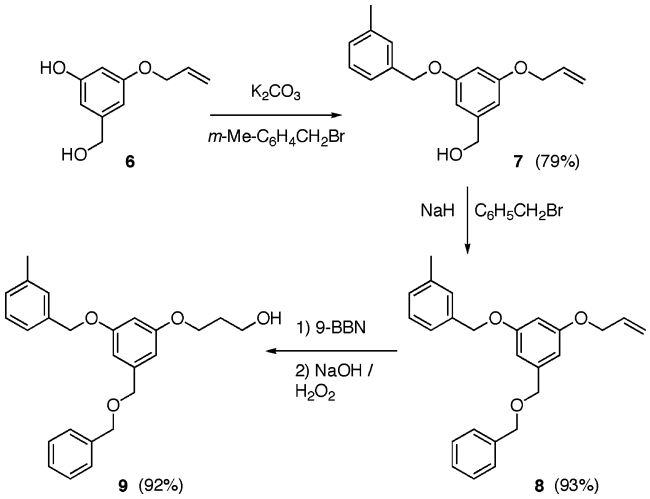
SCHEME 1



developed facile deprotection strategies for all these protecting groups. An example is shown in Scheme 1, in which a methoxymethyl ether (MOM) functionality is used as the protecting group. Treatment of **1** with *m*-bromobenzyl bromide in the presence of potassium carbonate provides the monosubstituted product **2**. Treatment of **2** with Dowex resin in methanol resulted in the cleavage of the MOM group, and the reaction of the resulting phenolic compound **3** with a second electrophile, decyl iodide, provides the unsymmetrically substituted first generation dendron **4**. The ester moiety in **4** was reduced to the alcohol **5** using borane−dimethyl sulfide complex. The overall yield of **5** from **1** was 90%. Note that the intermediates shown in this scheme were not isolated. The overall yield of the 3-mer from the ABB_p monomer compares favorably with the classical synthesis of reacting 2 equiv of benzyl bromide with 3,5-dihydroxybenzyl alcohol.[14] The hydroxymethyl group of compound **5** was converted to a bromomethyl moiety using triphenylphosphine and *N*-bromosuccinimide (NBS) to afford **5-Br** in 87% yield.

Based on an ABB′ Monomer. The inherently differential reactivities of two different functional groups within a monomer unit under certain reaction conditions can also be used to achieve multifunctional dendrons. In this approach, the active form of A can readily react with B under a set of reaction conditions. Under this condition, B′ is either unreactive or much less reactive. This affords the selective incorporation of the first monomer unit on to B. Incorporation of the second monomer unit is then carried out under a different set of conditions in which B′ is reactive with A. An example is outlined in Scheme 2, where the differential reactivity of the phenolic and the hydroxyalkyl functionalities toward the alkyl halide electrophiles is exploited. Treatment of **6** with *m*-methylbenzyl bromide with potassium carbonate as the base affords the monosubstituted product **7** in 79% yield. Under these conditions, the hydroxymethyl group is unreactive toward the alkyl halide electrophile. Treatment of the monosubstituted compound **7** with sodium

SCHEME 2



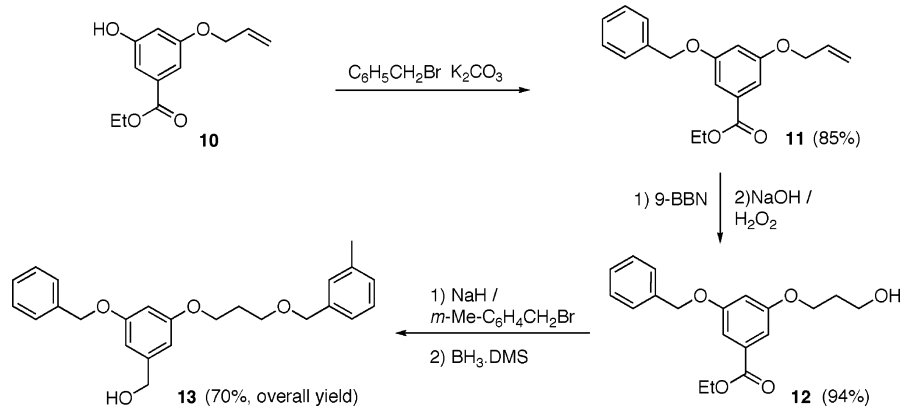
hydride followed by benzyl bromide affords the product **8** in 93% yield. The allyl functionality of **8** was then converted to hydroxypropyl by hydroboration to afford **9**. Conversion of the hydroxyalkyl group to the corresponding bromomethyl moiety was achieved using triphenylphosphine and NBS. Further elaboration to higher generations can be carried out by repeating these steps with different sets of monomer units.

Based on an ABB_m Monomer. In this approach, the B or B′ moiety is masked as a different functionality until the first reaction between A and B is completed. This allows for flexibility in the reaction conditions that could be used to react A with the first B. The second B moiety is then unmasked to install the second monomer unit. An example of this approach is outlined in Scheme 3. To demonstrate the possibility, we utilized the monomer **10** as the starting material. Treatment of **10** with potassium carbonate and an electrophilic alkyl halide provided the monosubstituted product **11** in 85% yield. The allyl moiety was then hydroborated in order to unmask it as a hydroxyalkyl group. The resultant product **12** was then treated with sodium hydride and a second alkyl halide to afford the unsymmetrically substituted product. The ester moiety of this compound was then reduced to the corresponding hydroxymethyl moiety to obtain **13**. Elaboration of this dendron to higher generation could then be carried out through the benzyl alcohol moiety of **13**.

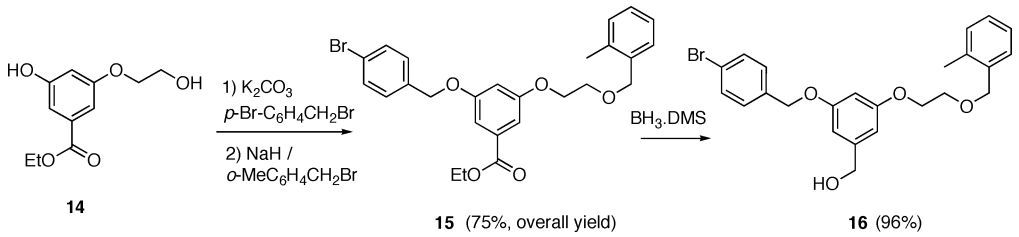
Comparison of the Three Methodologies. It is immediately obvious that the number of steps involved in all three methodologies described above is more than the classical synthesis of dendrimers. However, we rationalized that if the synthetic steps are achieved in high yields, then the benefits of being able to differentiate each monomer within a dendrimer far outweigh the rather small increase in the number of synthetic steps. Note also that even the well-known syntheses of polypeptides involve protection-deprotection strategies to introduce an appropriate sequence. Within the three methods described above, the ABB′ method is capable of providing the products with one less step per iteration. In the particular set of functionalities that we have chosen, it requires two steps to unmask the functionality A from an ester moiety to a bromomethyl group. This is mainly due to our particular interest in arylalkyl ether dendrim-

(14) Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638−7647.

SCHEME 3



SCHEME 4



ers for the reasons mentioned above. However, note that with a judicial choice of functionalities, it is easily imaginable to reduce the number of unmasking steps to one. Despite one more step per iteration in the other two methodologies, those approaches are useful complements to the ABB′ methodology.

The difference between the ABB_p and ABB_m methodologies is subtle. In the former case, the two B functionalities are the same and one of them is protected. In the latter case, the only requirement is that both B and the unmasked form of B_m are reactive toward A. The two B functionalities (from B and the unmasked form of B_m) can be exactly the same or different. In the particular example outlined above, the reactivity of the unmasked form B_m is very different from that of B.

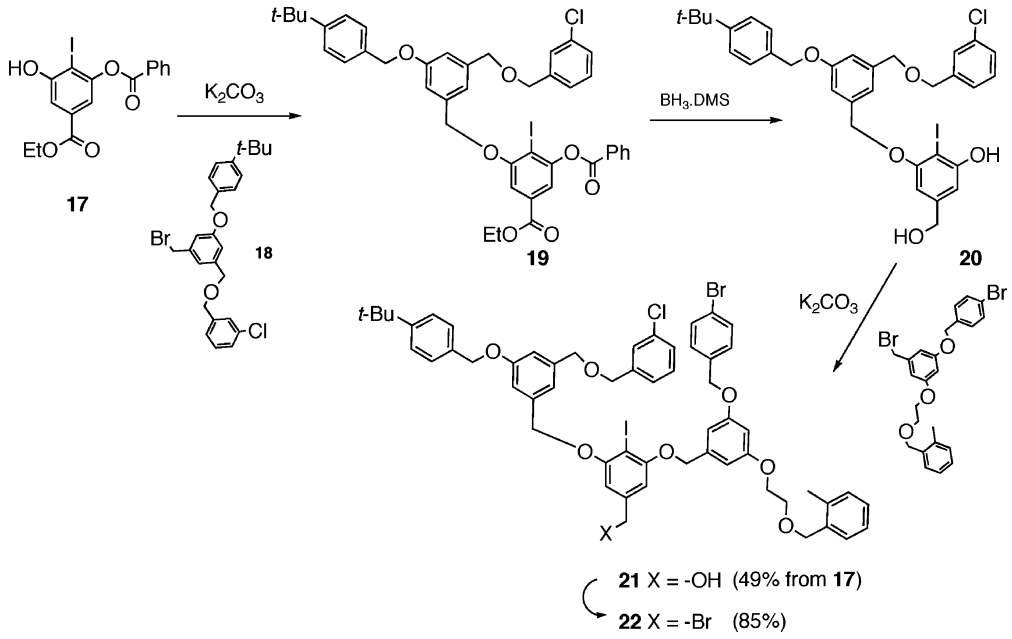
The preference for which methodology one should choose for sequencing a dendrimer depends on a few factors. If one prefers identical linkages between the monomer units and if efficient protection-deprotection strategies have been developed, then the ABB_p monomer-based methodology is the preferred approach. If differences in linkages could be tolerated or if the number of steps per iteration is an important criteria, then the ABB′ method should be chosen. If different linkages could be tolerated but two different reaction conditions in which B and B′ react with A could not be identified, then the preferred method should be based on an ABB_m monomer. Additionally, the choice of the method will depend on the nature of the linkages that connect the building blocks, other functional groups present in various monomers, and the compatibility of the dendrimer assembly reaction conditions to those functional groups. Considering the variables that could dictate the choice, the availability of three complementary synthetic methodologies should prove useful.

Sequencing Dendrons. A G-3 monodendron in which each monomer unit is different from the other has been synthesized. To assemble this macromolecule, four different 3-mer dendrons are needed, and they have been assembled using the methodologies described above. For example, the 3-mer dendron **16** was assembled using the ABB′ methodology, as outlined in Scheme 4. The starting material **14** was synthesized from dihydroxybenzyl alcohol and bromoethanol. Treatment of this compound with potassium carbonate and *p*-bromobenzyl bromide, followed by sodium hydride and *o*-methylbenzyl bromide, affords the unsymmetrically substituted product **15** with 75% overall yield. Note that these two alkylation steps above were carried out in one pot, although the alkylation conditions are very different from each other. Reduction of the ester moiety of **15** affords the 3-mer dendron **16** in 96% yield.

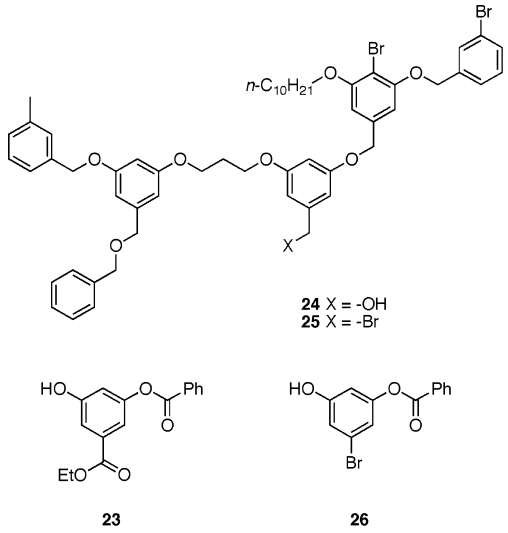
Treatment of the benzoyl-protected monomer unit **17** with potassium carbonate and the G-1 dendron **18** afforded the corresponding 4-mer dendron **19**. The synthesis of the 3-mer dendron **18** was achieved using an ABB′ repeating unit. Reaction of **19** with BH_3·DMS provided the corresponding benzyl alcohol while simultaneously deprotecting the benzoyl protecting group to afford **20**. Because of some inseparable impurities in **19** and **20**, these compounds were taken to the next step without further characterization. Reaction of compound **20** with potassium carbonate and the bromomethyl version of the 3-mer dendron **16** provided the 7-mer dendron **21** in 49% overall yield. The hydroxymethyl group at the focal point of **21** was converted to the corresponding bromomethyl moiety using triphenylphosphine and NBS to afford the compound **22**. The synthetic protocol is outlined in Scheme 5.

Synthesis of the 7-mer dendron **25** was achieved using a reaction sequence similar to that outlined in Scheme 5. The 3-mer dendrons used in this case were the bromoalkyl versions of **5** and **9**. The bromoalkyl compounds were synthesized from the corresponding hydroxymethyl compounds using triphenylphosphine and NBS as the reagent. The core unit for this dendron was

SCHEME 5



derived from the monomer **23**, which was easily synthesized from 3,5-dihydroxybenzoic acid.



The 15-mer dendron **27** was synthesized using the protocols similar to those outlined in Scheme 5. The 7-mer dendron **22** was treated with **26** in the presence of potassium carbonate to afford the corresponding 8-mer dendron.[15] Reduction followed by the incorporation of the second 7-mer dendron **25** afforded the 15-mer dendron **27** in 90% yield. All 15 monomer units within the G-3 dendron **27** are different from each other. The variations within the monomer units is due either to the functionality present in the aryl ring or to the linker that is used to attach to the next monomer unit. The different monomer units within the dendron **27** are identified with different colors for each monomer unit in Figure 2. The size exclusion chromatography (SEC) elution profiles of G-1, G-2, and G-3 dendrons are shown in Figure 3, to illustrate that these molecules are clean and monodisperse macromolecules.

Sequencing Dendrimers. In addition to synthesizing multifunctional monodendrons, the synthetic approaches outlined above can also be used to bring about functional group diversity in didendrons and tridendrons. To demonstrate this possibility, we synthesized didendrons or tridendrons with different monomer units. To synthesize a didendron, we used 4,4′-biphenol as the core unit. The sequential introduction of two different monodendrons onto the biaryl core was accomplished using the protection-deprotection methodology. One of the phenolic groups of 4,4′-biphenol was protected with a MOM group to afford the core unit **28**. Treatment of **28** with potassium carbonate and **25** afforded the corresponding monosubstituted 8-mer compound in 96%yield. The MOM group was then deprotected using catalytic amount of PTSA in

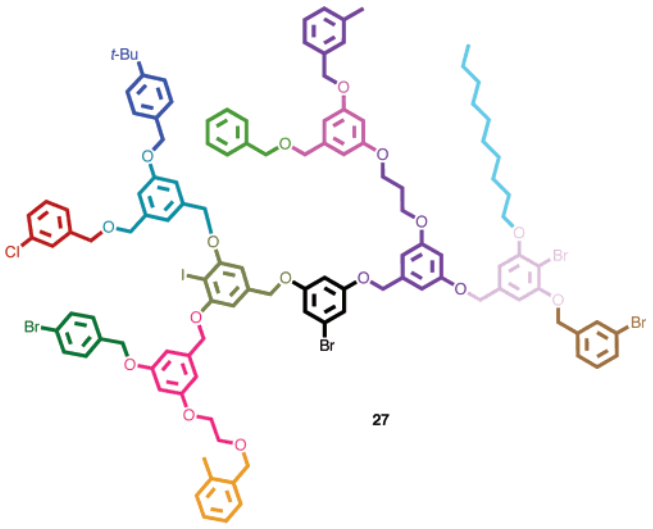
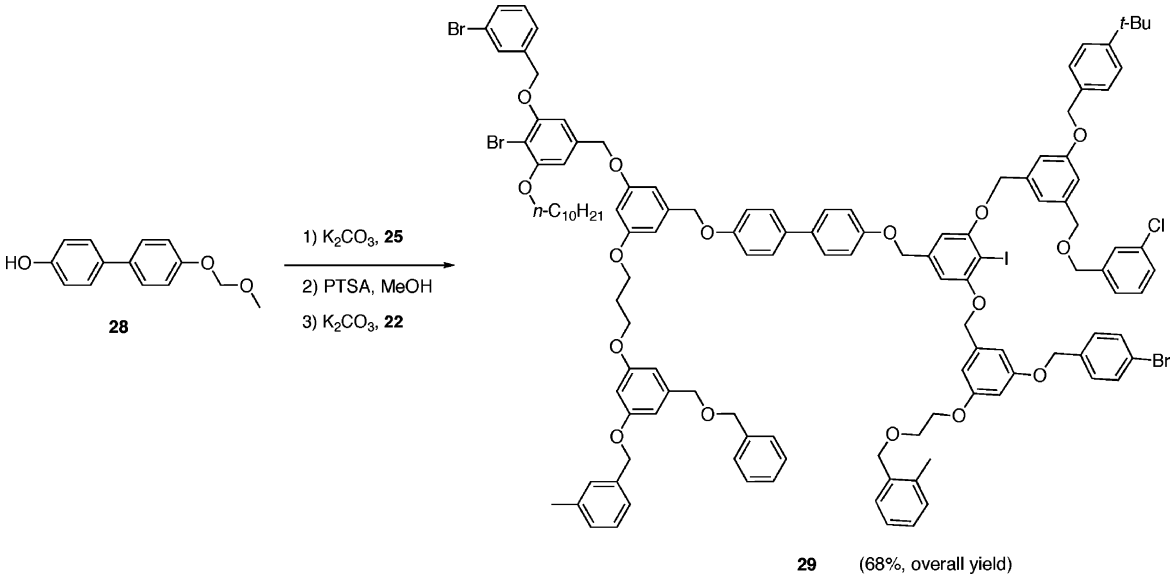


FIGURE 2. Structure of a multifunctional 15-mer monodendron.

(15) Compound **26** was obtained from 5-bromo-resorcinol, which was synthesized from 3,5-dimethoxybenzoic acid using the procedures reported in: Dol, G. C.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Eur. J. Org. Chem.* **1998**, *359*, 9−364.

SCHEME 6



methanol and dioxane in 80% yield. The resultant product was then treated with the 7-mer dendron **22** to afford the didendron **29** in 89% yield, as outlined in Scheme 6.

To synthesize a tridendron, we need to introduce three different monodendrons sequentially on to a central core unit. The core unit chosen was ethyl-3-hydroxy-5-hydroxymethylbenzoate (**30**). Here, we used both the differential reactivity of phenolic and hydroxyalkyl functionalities along with the unmasking of another hydroxyalkyl group from an ester functionality. The phenolic moiety of **30** was first reacted with a 3-mer dendron **31** to afford the corresponding 4-mer **32**.[16] Compound **32** was then treated with sodium hydride followed by the bromomethyl version of the 3-mer dendron **16** to afford the corresponding 7-mer **33**. Reduction of the ester moiety with BH_3·DMS followed by the alkylation of the resultant hydroxymethyl moiety with the 3-mer dendron **34** afforded the 10-mer tridendron **35** in 74% yield. The synthetic approach is outlined in Scheme 7. The SEC elutions of compounds **32** (one dendron installed on the trifunctional core), **33** (two dendrons installed) and **34** (tridendron) are shown in Figure 4.

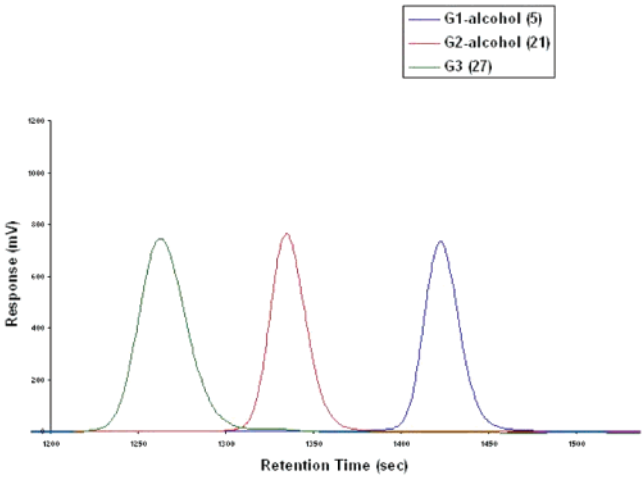


FIGURE 3. Elution profiles in size exclusion chromatography for G-1, G-2, and G-3 monodendrons.

Summary

Three complementary synthetic strategies for differentially substituting B units of an AB_2 monomer are reported. These methodologies encompass the variations that are desirable for designing dendrimers with different sets of functional groups and connectivities. These methodologies were then used to introduce sequences in dendrons. We have also demonstrated that dendrons can be sequentially introduced onto a core to synthesize didendrons and tridendrons. Note that these methodologies are not limited to tridendrons, since the combination of the above-mentioned strategies do provide the opportunity to introduce several dendrons onto a multifunctional core. The ability to vary the monomer units within dendrimers provides the opportunity to introduce a variety of functional groups within these macromolecules with excellent control. Such capabilities should have implications in a variety of areas, especially in biomimetics. The ability of proteins to selectively bind guest molecules is often attributed to its ability to converge multiple functionalities that are complementary to those present in the guest molecule. The methodologies outlined here could provide the basis for synthesizing artificial macromolecules with the controlled spatial disposition of functional groups.[17] Efforts toward such goals are part of the ongoing studies in our laboratories.

Experimental Section

This section describes the general procedures for the key steps involved in sequencing the dendrimers. Each general procedure is followed by an example. Details of synthesis and

(16) Synthesis of **31** is illustrated in Scheme 11 within Supporting Information.

(17) For an interesting example in which copies of the same functionality are incorporated in the dendritic interior, see: Zimmerman, S. C.; Wendland, M. S.; Rakow, N. A.; Zharov, I.; Suslick, K. S. *Nature* **2002**, *418*, 399−403. (b) Zimmerman, S. C.; Zharov, I.; Wendland, M. S.; Rakow, N. A.; Suslick, K. S. *J. Am. Chem. Soc.* **2003**, *125*, 13504−13518.

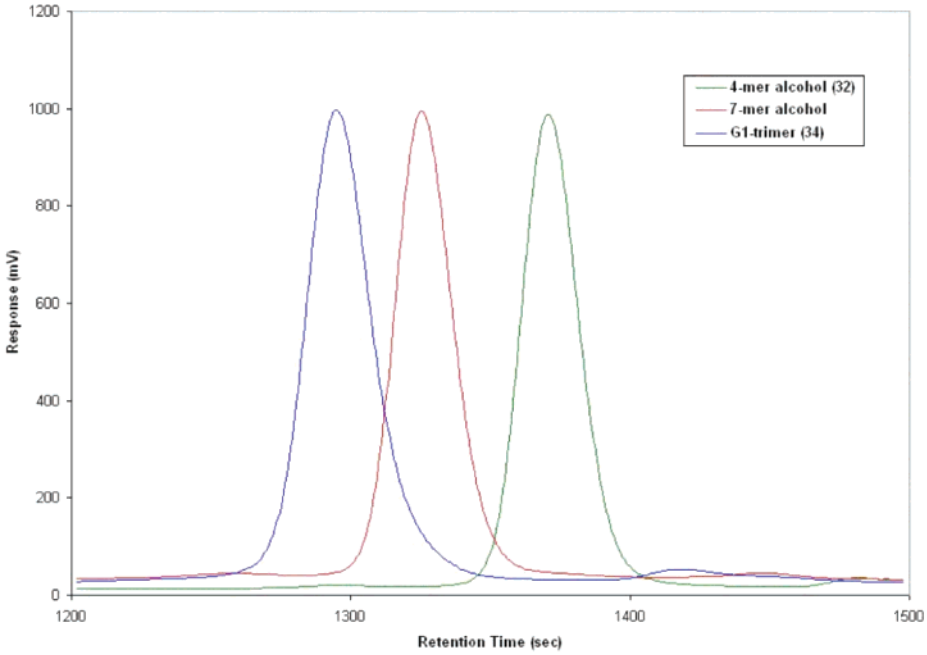
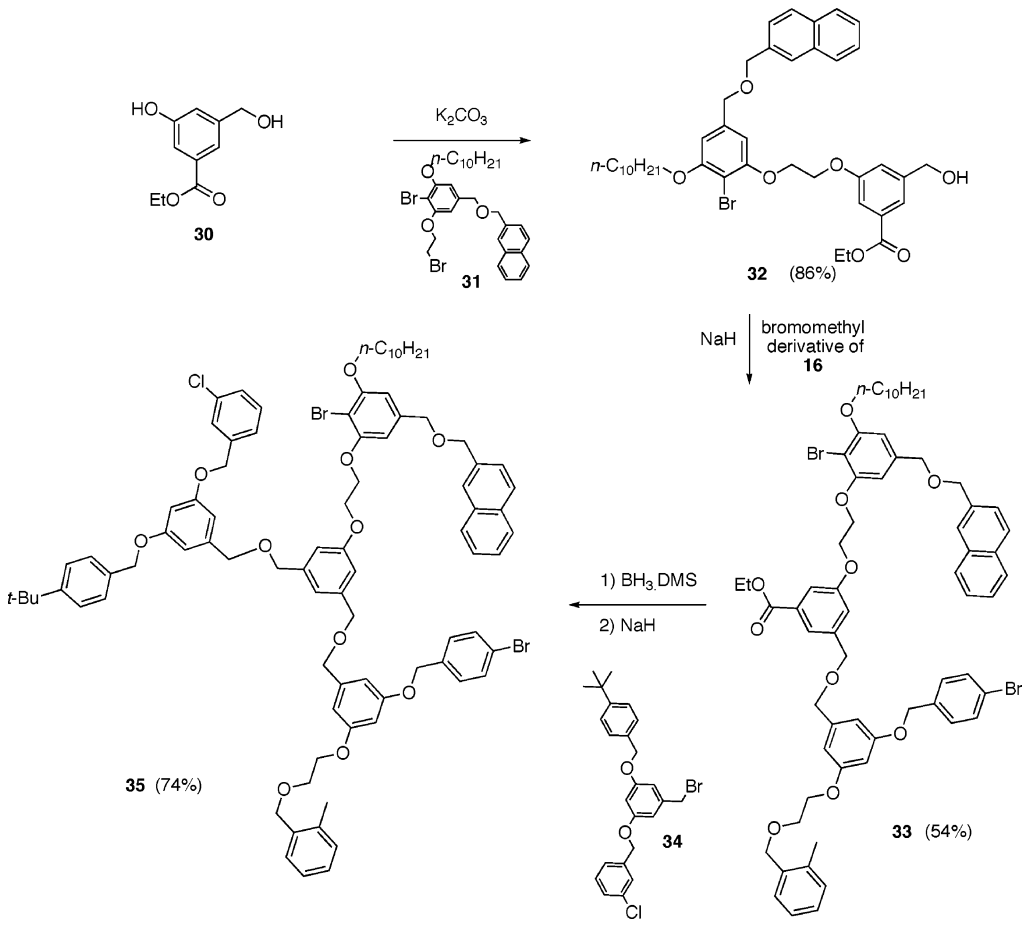


FIGURE 4. Elution profiles in size exclusion chromatography for mono-, di-, and tridendrons.

SCHEME 7



characterization of all other compounds are outlined in Supporting Information.

General Procedure for Ether Synthesis using Phenol and Alkyl Halides. A mixture of phenol (1.00 equiv), appropriate bromomethyl compound (1.0−1.2 equiv), dry K_2CO_3 (3.00 equiv), and 18-crown-6 (0.1 equiv) in acetone or THF (THF was the solvent of choice in the presence of benzoyl protecting groups) was heated at reflux and stirred vigorously under nitrogen for 12 h. The reaction mixture was allowed to cool, and solvent was evaporated to dryness. The residue was

partitioned between water and CH_2Cl_2. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by silica gel column chromatography.

Synthesis of 3-(*m*-Methylbenzyloxy)-5-allyloxy-benzyl Alcohol (7). Phenol **6**[13a] (1.84 g, 10.22 mmol), 3-methylbenzyl bromide (1.6 mL, 12.2 mmol), K_2CO_3 (1.14 g, 30.0 mmol), 18-crown-6 (0.27 g, 1.0 mmol), and acetone (30 mL) were refluxed under nitrogen for 12 h. The reaction mixture was allowed to cool, and solvent was evaporated to dryness. The residue was partitioned between water and CH_2Cl_2. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and evaporated to dryness. The crude product was isolated by silica gel column chromatography using ethyl acetate /hexane (30:70). Yield 2.30 g (79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32−7.14 (m, 4H), 6.62 (bs, 1H), 6.56 (bs, 1H), 6.50 (t, J = 2.2 Hz, 1H), 6.11−6.00 (m, 1H), 5.41 (m, 1H), 5.29 (m, 1H), 5.01 (s, 2H), 4.52 (m, 2H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 159.8, 143.3, 138.2, 136.6, 133.0, 128.7, 128.4, 128.2, 124.6, 117.7, 105.5, 105.4, 101.07, 70.0, 68.8, 65.2, 21.3. EI/MS *m*/*z*(relative intensity): 284(M^+, 17), 106(11), 105(100), 81(8), 79(6), 77(6), 69(15).

General Procedure for Reaction of Hydroxyalkyl Groups with Alkyl Halides. To a stirred solution of NaH (2.0 equiv) in dry THF was added appropriate benzyl alcohol in THF under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 15 min. A mixture of 18-crown-6 (0.1 equiv) and appropriate bromomethyl compound (1−1.2 equiv) in dry THF was added dropwise to the above solution. The reaction was monitored by TLC (thin-layer chromatography). After completion of the reaction, the reaction mixture was quenched by slow addition of water and extracted with ether. The organic layer was washed with brine and dried over Na_2SO_4. The organic layer was evaporated and purified by silica gel column chromatography.

Synthesis of 3-mer Dendron 8. To a stirred solution of NaH (0.61 g, 15.3 mmol) in dry THF was added **7** (2.18 g, 7.66 mmol) in THF under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 15 min. A mixture of 18-crown-6 (0.22 g, 0.7 mmol) and benzyl bromide (1.1 g, mL, 9.2 mmol) in dry THF was added dropwise to the above solution. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched by slow addition of water and extracted with ether. The organic layer was washed with brine and dried over Na_2SO_4. The organic layer was evaporated and purified by silica gel column chromatography using ethyl acetate/hexane (10:90) as the eluent. Yield 2.65 g (93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.11 (m, 9H), 6.61 (bs, 1H), 6.55 (bs, 1H), 6.49 (t, J = 2.4 Hz, 1H). 6.09−5.98 (m, 1H), 5.39 (m, 1H), 5.26 (m, 1H), 4.98 (s, 2H), 4.53 (s, 2H), 4.50 (t, J = 1.6 Hz, 2H), 4.51−4.48 (m, 2H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 159.7, 140.6, 138.2, 138.1, 136.6, 133.1, 128.7,128.4, 128.3, 128.2, 127.7, 127.6, 124.6, 117.6, 106.4, 106.3, 101.1, 71.9, 71.9, 70.0, 68.7, 21.3. EI/MS *m*/*z*(relative intensity): 374(M^+, 2), 268(56), 147-(26), 105(100), 91(32).

General Procedure for Conversion of Ester to Alcohol and Deprotection of Benzoyl Group. To the ester (1.00 equiv) in dry THF was added borane−dimethyl sulfide complex (4.00−8.00 equiv), and the resulting mixture was stirred at refluxing condition under nitrogen atmosphere for 8 h. The reaction was monitored by TLC. The reaction mixture was slowly added to aqueous ammonium chloride solution and was extracted twice with dichloromethane. The combined organic layer was dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by silica gel column chromatography.

Synthesis of 3-mer Alcohol 16. The ester **15** (0.5 g, 1.1 mmol) was treated with 2.0 M solution of BH_3:SMe_2 (2.9 mL, 6.0 mmol) and refluxed overnight in THF (20 mL) to obtain the corresponding alcohol. The reaction mixture was added to a cold solution of ammonium chloride and extracted with CH_2Cl_2. The crude mixture was purified by silica gel column chromatography using ethyl acetate/hexane (20:80) as the eluent. Yield 0.5 g (96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (s, 1H), 7.42 (s, 1H), 7.32 − 7.12 (m, 6H), 6.50 (bs, 1H), 6.47 (bs, 1H), 6.39 (t, J = 2.2 Hz, 1H), 4.85 (s, 2H), 4.55 (s, 2H), 4.48 (s, 2H), 4.03 (t, J = 4.6 Hz, 2H), 3.74 (t, J = 4.6 Hz, 2H), 2.73 (bs, 1H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 159.4, 143.4, 136.6, 135.7, 135.5, 131.4, 130.1, 128.9, 128.5, 127.7, 125.5, 121.6, 105.3, 105.2, 100.7, 71.5, 68.9, 68.2, 67.2, 64.6, 18.6. EI/MS *m*/*z*(relative intensity): 459(M + 3, 25), 458(M + 2, 25), 457(M + 1,6), 456(M^+, 25), 170(97), 168(100), 105(92), 91(14), 90(10).

General Procedure for Conversion of Benzylic Alcohol into Corresponding Bromide. To a stirred solution of the appropriate benzyl alcohol (1.00 equiv) and PPh_3 (1.1−1.3 equiv) in minimal dry THF was added *N*-bromosuccinimide (1.1−1.3 equiv) under nitrogen atmosphere. The reaction mixture was stirred at room temperature and was monitored by TLC (all reactions completed within 1−5 min). The reaction mixture was treated with water and extracted two times with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by silica gel column chromatography.

Synthesis of Bromomethyl Derivative of 16. Alcohol **16** (0.4 g, 1.0 mmol) was dissolved in THF (10 mL) followed by addition of PPh_3 (0.3 g, 1.2 mmol). After 5 min, NBS (0.2 g, 1.2 mmol) was added. After completion of the reaction, the reaction mixture was quenched with water and extracted with CH_2Cl_2. The crude mixture was purified by silica gel column chromatography using ethyl acetate/hexane (2:98) as the eluent. Yield 0.4 g (77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (s, 1H), 7.33 (s, 1H), 7.19 (d, J = 7.2 Hz, 1H), 7.14−7.00 (m, 5H), 6.44 (d, J = 2.0 Hz, 1H), 6.43 (d, J = 2.0 Hz, 1H), 6.32 (t, J = 2.2 Hz, 1 H), 4.77 (s, 2H), 4.46 (s, 2H), 4.23 (s, 2H), 3.95 (t, J = 4.8 Hz, 2H), 3.65 (t, J = 4.8 Hz, 2H), 2.21 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 159.4, 139.5, 136.6, 135.6, 135.4, 131.4, 130.1, 128.9, 128.4, 127.7, 125.5, 121.7, 107.8, 107.8, 101.7, 71.6, 69.0, 68.2,67.3, 33.4, 18.6. EI/MS *m*/*z*(relative intensity): 521(M + 3, 7), 519(M + 1, 15), 517(M^+, 7), 170-(97), 168(100), 105(96), 91(24), 90(11).

Acknowledgment. This work is supported by the NIGMS of the National Institutes of Health (GM-065255-01). Part of this work was carried out at Tulane University.

Supporting Information Available: Synthesis and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO049878P