Synthesis of Functionalized Aromatic Oligomers from a Versatile Diphenylmethane Template

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An efficient synthesis of the functionalized diphenylmethane system **1** is described. Selective unmasking of the latent phenol groups on **1** allowed the introduction of various appendages onto the diphenylmethane scaffold via simple alkylation, Mitsunobu etherification, and transition-metal-mediated C−C bond formation. Conversion of **1** to iodide **18** and benzylic zinc reagent **28** followed by palladium(0)-mediated coupling of these derivatives provided homologue **29**. Repetitive application of this homologation protocol was used to prepare oligomers of chain length up to 16. Several examples of functional group manipulations on these higher order oligomers are presented. Diphenylmethane **1** was also employed as a key building block in the synthesis of the elastase inhibitor **67**. The potential application of extended aromatic oligomers to the field of drug discovery is discussed.

Introduction

In recent years combinatorial chemistry strategies have emerged as widely applicable tools in drug discovery.[1] This has generated considerable interest in versatile molecular platforms capable of supporting the diverse arrays of functionality used to search for new pharmacophores. In choosing suitable platforms for this purpose, careful consideration must be given to a number of parameters, among them ease of preparation, amenability to multiple derivatization, potential for incorporation onto a solid support, and compatibility with the physiological environment. In this paper, we report the synthesis of a functionalized diphenylmethane system which meets the criteria outlined above. We also illustrate the application of this structure to the synthesis of a family of higher order oligomeric systems of chain length up to 16.

A number of small molecule library templates have been reported in the literature to date. These include both amide-based scaffolds,[2] which generate product libraries well suited to interaction with protein frameworks, as well as simple aromatic systems,[3] which produce products most commonly associated with groove or cleft binding. Recently, researchers at Sphinx Pharmaceuticals described a series of versatile biphenyl, diphenylmethane, and diphenylethane platforms,[4] each of which, by selective derivatization of an array of protected phenols, can incorporate various functionalities in a number of relative spatial configurations. Libraries derived from these scaffolds have been designed to search for agonists/antagonists of various 7-transmembrane G-protein coupled receptor systems. The specific system we wish to describe is shown in Figure 1. Like the Sphinx platform, the diphenylmethane framework **1** bears a number of differentially protected phenol groups and so can also accommodate the introduction of diverse appendages in various permutational sets. Besides controlling direct functionalization, the ability to unmask individual phenol groups in **1** also allows selective activation of the corresponding ortho carbon positions to electrophilic attack by halogen. Introduction of bromine or iodine in this manner greatly expands the range and relative orientation of appendages which can be attached to the diphenylmethane framework. The benzylic silyl ether can also be functionalized to provide, among other things, an attachment point for solid phase work or, as discussed below, a chain extension point in the synthesis of higher order aromatic oligomers such as **41**.

Results

Preparation of 1. The synthesis of diphenylmethane **1** is outlined in Scheme 1. The requisite precursors (**8** and **11**) were both prepared from 2,5-dihydroxybenzal-

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(1) For some reviews of this area see (a) Balkenhohl, F.; von dem Bussche-Hunnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288. (b) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. (c) Czarnick, A. W. Ellman, J. A., Eds. *Acc. Chem. Res.* **1996**, *29*, 112−170. (d) Terrett, N. *Drug Discov. Today* **1996**, *1*, 129. (e) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233, 1386. (f) Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *51*, 8135.

(2) For example see (a) Cheng, S.; Comer, D. D.; Williams, J. P.; Myers, P. L.; Boger, D. L. *J. Am. Chem. Soc.* **1996**, *118*, 2567. (b) Carell, T.; Wintner, E. A.; Sutherland, A. J.; Rebek, J.; Dunayevskiy, Y. M.; Vouros, P. *Chem. Biol.* **1995**, *2*, 171. (c) Kocis, P.; Issakova, O.; Sepetov, N. F.; Lebl, M. *Tetrahedron Lett.* **1995**, *36*, 6623. (d) Bray, A. M.; Chiefari, D. S.; Valerio, R. M.; Maeji; N. J. *Tetrahedron Lett.* **1995**, *36*, 5081. (e) Kick, E. K.; Ellman, J. A. *J. Med. Chem.* **1995**, *38*, 1427. (f) Patek, M.; Drake, B.; Lebl, M. *Tetrahedon Lett.* **1994**, *35*, 9169. (g) Hutchins, S. M.; Chapman, K. T. *Tetrahedron Lett.* **1994**, *35*, 4055. (h) Boyce, R.; Li, G.; Nestler, H. P.; Suenaga, T.; Still, W. C. *J. Am. Chem. Soc.* **1994**, *116*, 7955. For the purposes of this discussion we restrict ourselves to the consideration of preformed scaffolds, from which libraries are generated by the introduction of various appendages. This is in contrast to systems in which a common or privileged structure is formed during the diversification stage of library generation. For examples of this strategy, see reference 1c.

(3) For example see (a) Meyers, H. V.; Dilley, G. J.; Durgin, T. L.; Powers, T. S.; Winssinger, N. A.; Zhu, H.; Pavia, M. R. *Molecular Diversity* **1995**, *1*, 13. (b) Rano, T. A.; Chapman, K. T. *Tetrahedron Lett.* **1995**, *36*, 3789. (c) Dankwardt, S. M.; Newman, S. R.; Krstenansky, J. L. *Tetrahedron Lett.* **1995**, *36*, 4923. (d) Frenette, R.; Friesen, R. W. *Tetrahedron Lett.* **1994**, *35*, 9177. See also Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996**, *52*, 4527 and references therein (e) Nugiel, D. A.; Cornelius, L. A. M.; Corbett, J. W. *J. Org. Chem.* **1997**, *62*, 201.

(4) Pavia, M. R.; Cohen, M. P.; Dilley, G. J.; Dubuc, G. R.; Durgin, T. L.; Forman, F. W.; Hediger, M. E.; Milot, G.; Powers, T. S.; Sucholeiki, I.; Zhou, S.; Hangauer, D. G. *Bioorg. Med. Chem. Lett.* **1996**, *4*, 659. See also: Pavia, M. R.; Whitesides, G. M.; Hangauer, D. G.; Hediger, M. E. Patent WO 95/04277, 1995.

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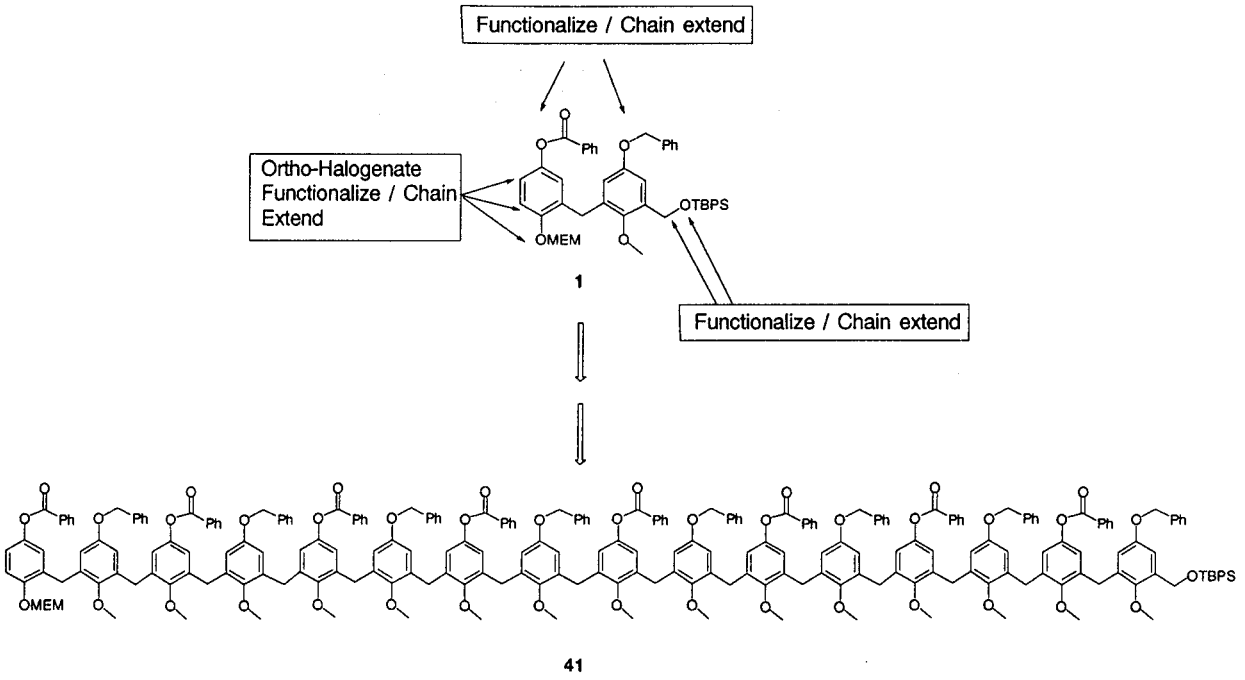


Figure 1. Applications of diphenylmethane **1**.

dehyde, in high yield, using the optimized procedures shown. Coupling of **8** and **11** was effected by preformation of the benzylic zinc reagent **12**[5] and cross-coupling of this species with **8**, under palladium catalysis,[6] to provide **1** in 87% yield. It should be noted that **12**, like several related reagents generated during the course of this project, is stable in THF solution and can be stored for several days without dramatic loss of activity. The synthesis of **1** has been carried out routinely on a 100 g scale with an overall yield of 60% based on dihydroxybenzaldehyde.

Functional Group Manipulation of 1. A representative selection of the chemistry that has been carried out on **1** is summarized in Schemes 2−5. As anticipated, each of the protecting groups can be removed selectively (Scheme 2). The benzyl-protected phenol was liberated cleanly in the presence of the benzylic silyl ether by hydrogenolysis[7] (H_2/Pd/C, 90%) to give **13**. Removal of the MEM ether was accomplished in excellent yield (Pyridinium tosylate/2-propanol, 95%) giving **14**, provided a sterically hindered nucleophile such as 2-propanol was used to effect transketalization. Cleavage of the benzoate was carried out uneventfully by transesterification (NaOMe, 94%) yielding **15**, while desilylation of the benzylic ether was effected using an acetic acid buffered TBAF system (96%)[8] to give **16**.

The phenolic hydroxyl is a versatile functional group capable of undergoing a wide variety of useful transformations.[9] However, within the context of this system, we confined ourselves to three methods of derivatization: Direct alkylation, Mitsunobu etherification, and transition-metal-mediated carbon−carbon bond formation. These three synthetic methods combine to provide access to a wide variety of appendages, but are also mild enough to be tolerated in a multifunctionalized system such as **1**. Simple alkylation (Scheme 3) was accomplished using a range of alkyl halides employing one of two experimental protocols (K_2CO_3, RX, CH_3CN, 70−90% or NaH, RX, THF/DMPU, 85−95%) with the choice of reaction conditions for a particular case being dependent on both the nature of the alkylating agent and the particular phenolic group undergoing reaction. As illustrated by the etherification of **14**, standard Mitsunobu coupling[10] (DEAD/Ph_3P/pyridin-2-ylethanol/THF, rt, 84%) proved an effective alternative to alkylation in situations where the appropriate alkyl halide was unreactive or difficult to access. Transition-metal-mediated carbon−carbon bond formation was effected via aryl triflates[11] such as **20** (NaH/*N*-phenyltriflimide/THF/DMPU, 92% based on **15**) which underwent efficient cross-coupling reaction with acetylenic-zinc reagents (((trimethylsilyl)-ethynyl)zinc chloride/Pd(dba)$_2$/dppf/THF, 91%),[12] as well as palladium-catalyzed methoxycarbonylation (*vide infra*).[13]

As mentioned above, unmasking the latent phenolic groups in **1** activates the corresponding ortho carbons to electrophilic iodination.[14] Optimum reaction conditions for this conversion were found to depend on the other functionality present in the aromatic ring. For example, (Scheme 4) introduction of iodine meta to the benzoate in **14** was effected successfully (79%) using a heteroge-

(5) Berk, S. C.; Knochel, P.; Yeh M. C. P. *J Org. Chem.* **1988**, *53*, 5789. In all cases studied, a small amount of Wurtz type coupling product accompanied the formation of the benzylic zinc reagent. These products were generally isolated and characterized after the cross-coupling reaction (see Experimental Section).

(6) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1823.

(7) Both the benzylic silyl ether and its corresponding benzyl alcohol were completely resistant to hydrogenolysis with palladium catalysts under ambient pressure.

(8) Hoffman, W. F.; Alberts, A. W.; Anderson, P. S.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1986**, *29*, 849.

(9) Whiting, D. A *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Eds.; Pergamon Press: New York, 1979; Vol. 1.

(10) Mitsunobu, O. *Synthesis* **1981**, 1. For an application of this reaction in the derivatization of cyclic aromatic oligomers with various carbohydrates; see Marra, A.; Scherrmann, M.-C.; Dondoni, A.; Casnati, A.; Minari, P.; Ungaro, R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2479.

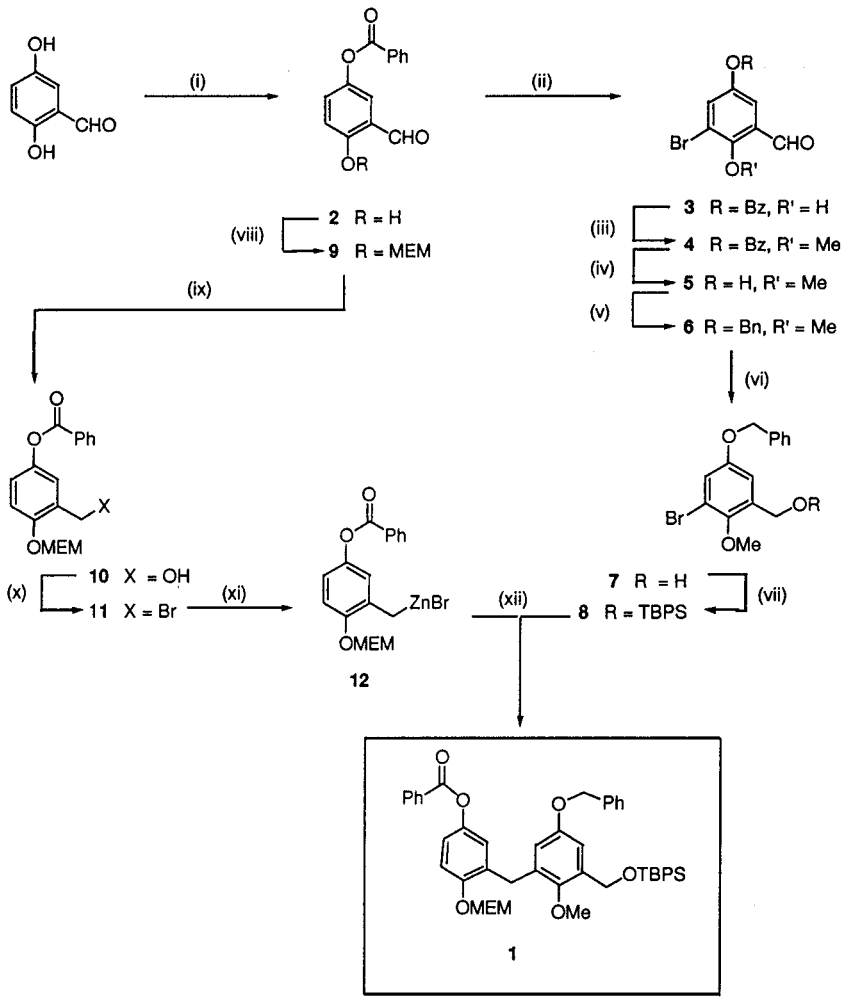
(11) McMurry, J. E.; Scott, W. J. *Acc. Chem. Res.* **1988**, *21*, 47.

(12) Rottlander, M.; Palmer, N.; Knochel, P. *Synlett* **1996**, 573.

(13) Dolle, R. E.; Schmidt, S. J.; Kruse, L. I. *J. Chem. Soc., Chem. Commun.* **1987**, 904.

(14) Merkushev, E. V. *Synthesis* **1988**, 923.

Scheme 1[a]



[a] Reagents, conditions, and yields: (i) Bz_2O/Et_3N then K_2CO_3/methanol then aqueous HCl, 92%; (ii) Br_2/NaOAc; (iii) K_2CO_3/MeI; (iv) NaOMe; (v) K_2CO_3/BnBr, 90% overall from **2**; (vi) $NaBH_4$; (vii) TBPSCl/Imid/DMAP, 94% overall from **6**; (viii) NaH/MEMCl/DMPU; (ix) $NaBH_4$(diglyme)/THF, −35 °C, 84% overall from **2**; (x) NBS/PPh_3, 89%; (xi) Zn 10 equiv, −5 °C; (xii) $(Ph_3P)_4Pd$, 87%.

neous system comprised of iodine and morpholine in dichloromethane at room temperature. However, this system gave poor yields when installing iodine in the presence of the MEM group, as in **15**. In this situation, optimum yields were attained by adding a dilute solution of iodine to a mixture of phenol and morpholine at −10 °C (80%). As one might expect, in the absence of a steric directing group, iodination of **13** resulted in a preparatively useless mixture of mono- and diiodo products. In general, *o*-iodophenol derivatives of these systems were found to be only moderately stable and so were usually further derivatized immediately, as shown for the particular case of **22**, which was efficiently methylated (NaH, MeI/THF/DMPU, 93%) to yield the stable product **18**.

As illustrated in Scheme 5, stepwise oxidation of benzylic alcohol **16** provided aldehyde **24** (Swern, 91%) and the corresponding acid **25**[15] ($NaClO_2$/isobutene, 98%). The latter functionality underwent standard coupling reactions, via a mixed anhydride, to provide amide derivatives such as **26** (isopropyl chloroformate/*N*-methylmorpholine and then L-leucine methyl ester, 96%). In addition to oxidative derivatization, benzylic alcohol **16** was also converted to the corresponding crystalline bromide **27** (NBS/Ph_3P, 97%) furnishing an electrophilic carbon center. Formation of the complementary nucleophilic carbon center was accomplished by conversion of bromide **27** to the benzylic zinc reagent **28**, on treatment with an excess of activated zinc dust (>80%). Such mild nucleophilic reagents are particularly attractive in view of their extensive application in selective carbon−carbon bond-forming reactions.[16]

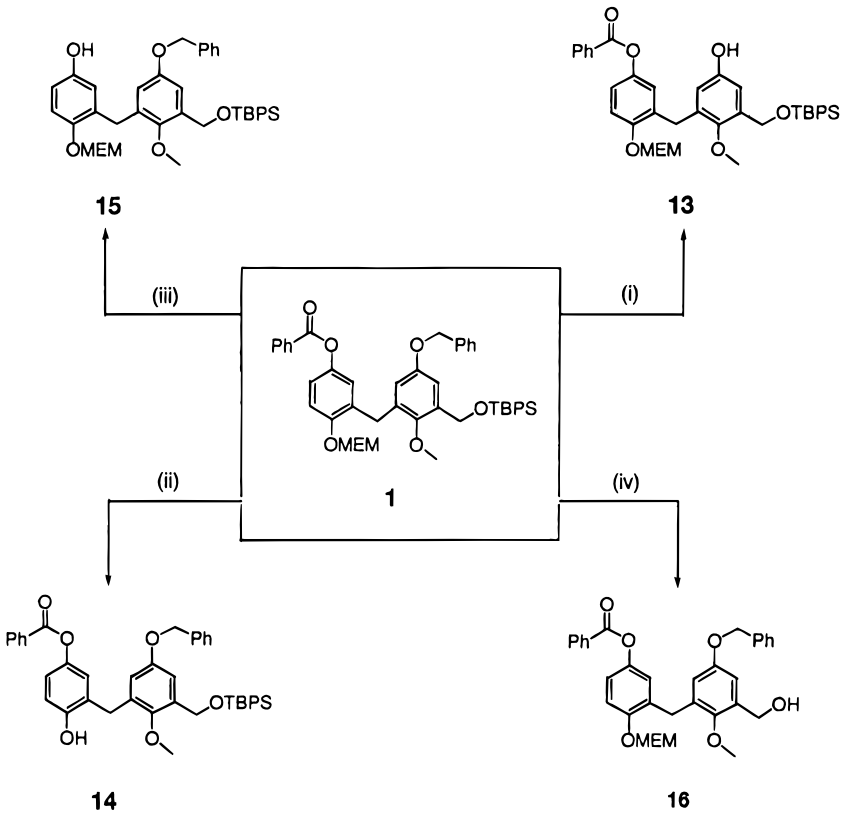
The foregoing chemistry by no means constitutes an exhaustive survey of the manipulations which can be carried out on **1**. Nevertheless, this study does provide a basis for the development of a broad range of useful derivatives in an efficient and cost effective manner and so, we believe, clearly demonstrates that **1** meets the basic criteria of accessibility and versatility set forward earlier for use as a small molecule library platform.

Although the generation of simple derivatives in the manner outlined above is a credible and potentially valuable application, this was not our ultimate goal in preparing **1**. Our main purpose in developing this elaborately functionalized system was to use it as a key building block in the construction of extended aromatic oligomers, from which we planned to develop novel libraries comprised of discrete compounds in the molecular weight range 1000−4000 amu.

(15) (a) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 4825. (b) Lidgren, B. O.; Hilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888.

(16) For a review see Knochel, P.; Singer, D. *Chem. Rev.* **1993**, *93*, 2117.

Scheme 2[a]



[a] Reagents, conditions, and yields: (i) H_2/Pd, 90%; (ii) pyridinium tosylate/2-propanol, 95%; (iii) NaOMe, 94%; (iv) Bu_4NF/AcOH, 96%.

Higher Order Oligomers

Rationale. Historically, pharmaceutical research has been focused on the discovery of small molecule drugs. The reasons for this are far from purely economic, but rather also reflect the very substantial advantages associated with this class of compound regarding oral bioavailability—a crucial factor in defining a practical drug candidate.[17] However, small molecules are intrinsically limited in the amount of chemical information[18] which can be encoded into their structures. Therefore, effective molecular recognition processes involving such compounds rely upon a limited number of extremely precise interactions. Consequently, the discovery of new drug prototypes from unbiased screening sets of small molecules is an inherently low probability event. Indeed, it is this situation which has provided the impetus for the recent intense activity in the fields of combinatorial chemistry and automated high speed synthesis.

For some time, we have been interested in a complementary strategy for new lead generation. In this approach, screening libraries are designed so that the amount of chemical information carried by each member of the library is substantially increased relative to that found in conventional small molecule systems. We speculated that if the number of binding opportunities involved in a molecular recognition process were significantly enlarged, and then the dependence of the associated binding free energy on precise matching of interacting partners could be relaxed,[19] thereby increasing the probability of achieving a measurable association. In adopting this strategy it must be accepted that any enhancement in association probability may come at the expense of specificity. However, once a measurable binding event has been established, the system is then capable of providing the empirical feedback needed to guide an optimization procedure and characterize a *minimum* effective pharmacophore. With this information, issues of selectivity and bioavailability can then be evaluated, and if deemed appropriate, addressed in a separate operation.

Perhaps the simplest way of raising the information content of a molecule is by an increase in molecular size.[20] To accomplish this and realize a significant distinction between conventional libraries, we decided to target structures with molecular weights > 1000 amu. Specif-

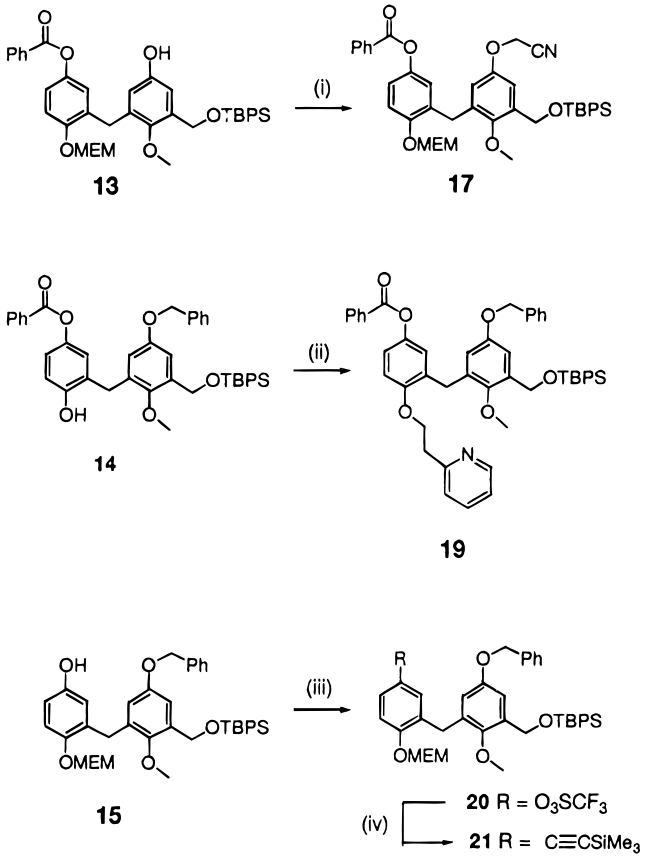
(17) (a) Navia, M. A.; Chaturvedi, P. R. *Drug Dev. Today* **1996**, *1*, 179. (b) Sha'afi, R. I.; Gary-Bobo, C. M.; Solomon, A. K. *J. Gen. Physiol.* **1971**, *58*, 238.

(18) In this context, we use the term chemical information to mean that minimum set of descriptors required to characterize the interaction of a molecule (in its available conformations) with its environment.

(19) This approach emphasizes surface interactions which are less geometrically and sterically constrained than the groove or cleft binding interactions often associated with small molecule ligands. Indeed, there is some support for the idea that substantial binding free energy can result from the cumulative effect of a number of individually weak interactions spread over an extended structure. For example, (a) Cadene, M.; Morel-Desrosiers, N.; Morel, J.-P.; Bieth, J. G. *J. Am. Chem Soc.* **1995**, *117*, 7882 and references therein. (b) van Boeckel, C. A. A.; Petitou, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1671. (c) Lee, Y. C. *FASEB* **1992**, *6*, 3193.

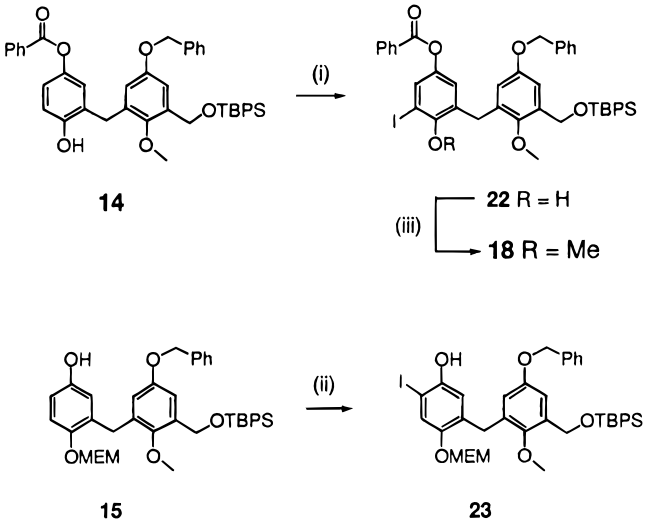
(20) While it seems obvious that increasing the number of atoms in a molecule will increase its information content, at some point, intramolecular interactions will become dominant and, consequently, as secondary structure evolves, interactions between the molecule and its environment will decrease in number and become more precise. We were interested in accessing structures with increased information content over traditional small molecules, but which are not large enough to be completely locked in secondary/tertiary structure motifs. For an interesting discussion on the relationship between size, affinity, and specificity, see Eaton, B. E.; Gold, L.; Zichi, D. A. *Chem. Biol.* **1995**, *2*, 633.

Scheme 3[a]



[a] Reagents, conditions, and yields: (i) K_2CO_3, $BrCH_2CN/CH_3CN$, 81 °C, 72%; (ii) 2-(2-hydroxyethyl)pyridine/DEAD/Ph_3P, rt, 84%; (iii) NaH, *N*-phenyltriflimide, THF/DMPU, 0 °C to rt, 92%; (iv) TMS-acetylene/BuLi, −78 °C then $ZnCl_2$, −78 °C to rt, then $Pd(dba)_2$/dppf/THF, 65 °C, 91%.

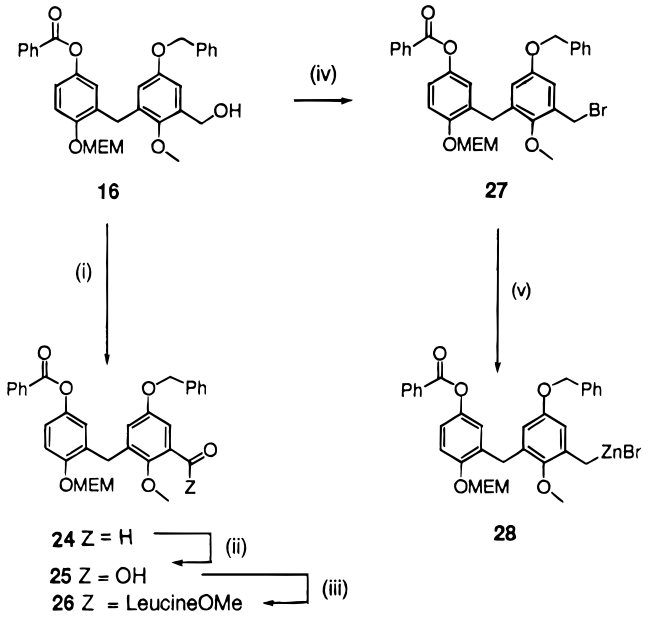
Scheme 4[a]



[a] Reagents, conditions, and yields: (i) I_2 (solid)/morpholine/CH_2Cl_2, rt, 79%; (ii) I_2 (solution)/morpholine, CH_2Cl_2, −10 °C, 80%; (iii) NaH, MeI/THF/DMPU, 0 °C to rt, 93%.

ically, we envisioned that a library based on a flexible aromatic oligomer scaffold would be an attractive system for testing the hypothesis outlined above. Such a platform, we believed, would be both accessible by practical synthetic transformations and amenable to the kind of progressive structural variation needed to map a pharmacophore. Moreover, an oligomer format is capable of encompassing a great deal of structural diversity by combinatorial coupling of even a modest number of building blocks. This traditional combinatorial chemistry approach has, of course, proved highly successful in oligonucleotide and peptide systems.[1e,20] However, in contrast to natural oligomers, the use of a purely synthetic platform to investigate recognition events in biological systems is not complicated or biased by the effects of natural selection. Thus, small molecule libraries, derived from sections of extended synthetic oligomers, provide a valid benchmark from which to evaluate the effects of increased molecular size on association probability. In considering such an undertaking from a practical standpoint, it is important to identify advanced, versatile intermediates capable of elaboration into a range of extended oligomeric structures. In view of its simple preparation, efficient functionalization, and potential for chain extension, diphenylmethane **1** seemed to us particularly well equipped to fulfill such a role.

Scheme 5[a]



[a] Reagents, conditions, and yields: (i) $(COCl)_2$/DMSO/Et_3N, −78 °C to rt, 91%; (ii) $NaClO_2/NaH_2PO_4$/isobutene, rt, 98%; (iii) isopropyl chloroformate/*N*-methylmorpholine, 0 °C then L-leucine methyl ester hydrochloride, 96%; (iv) NBS/Ph_3P/THF, 10 °C to rt, 97%; (v) zinc (powder), 10 equiv, −5 °C, >80%.

Synthesis of a Prototype Scaffold. From the chemistry outlined earlier, it is evident that **1** can be selectively activated to provide the electrophilic (**18**, Scheme 4) and nucleophilic (**28**, Scheme 5) components of a palladium coupling reaction directly analogous to the system used to prepare **1** itself. Coupling of these fragments would then produce a higher order homologue of **1** and complete an iterative cycle of chain elongation. We anticipated that this type of cycle would provide the basic methodology needed to assemble a prototype family of methylene-linked aromatic oligomer scaffolds.[21]

In practice, as outlined in Scheme 6, repetitive application of this activation−coupling strategy provided the corresponding tetramer (**29**) and octamer (**35**) frameworks with little erosion of yields (83 and 70%, respectively, for the coupling step). At the outset, we were concerned that purification of extended oligomer frameworks of this kind could prove to be problematic. How-

ever, these concerns were entirely unfounded. Indeed, even on an octameric framework, the terminal phenol **38**, *o*-iodophenol **39** and *o*-iodomethyl ether **40** were all easily distinguishable by simple TLC analysis. Octameric oligomers in this series are freely soluble in aprotic dipolar solvents such as DMF and DMSO, as well as chlorinated hydrocarbons, particularly chloroform, but are only sparingly soluble in ethereal solvents. In fact, as a result of diminished solubility in THF, the final iteration to the hexadecamer framework required the use of DMF as a cosolvent. With this adjustment, and in deference to the reaction scale (0.3 mmol), using 2 equiv of benzylic zinc, the hexadecamer **41** was formed in 62% yield (based on aryl iodide **40**). With a molecular weight of 4058 amu and, assuming an extended conformation, an overall length of 75 Å, hexadecamer **41** is the largest molecular framework we prepared during this program. The synthesis of **41** underscores the tremendous utility of palladium(0)-mediated chemistry in the construction of large, highly functionalized, organic molecules.[22] Furthermore, by successfully assembling this prototype oligomer family, we were confident that we had identified a synthetic protocol fully capable of furnishing oligomeric structures of any size likely to be of practical use in pharmaceutical research.

Functionalization of Higher Order Oligomers. Derivatization of extended oligomer frameworks was performed employing essentially the same procedures used for the functionalization of **1**. As illustrated in Scheme 7, removal of all four benzoates from **35** (NaOMe), followed by exhaustive alkylation of the crude product ($BrCH_2CO_2Bu^t/K_2CO_3$) provided the partially substituted framework **42** in 84% overall yield. The terminal benzylic silyl ether of **42** was transformed selectively, along the lines previously described, (Bu_4NF/AcOH, 91%, and then Swern, 92%) to yield first aldehyde **44**, and then, by further oxidation ($NaClO_2$/isobutene, 98%), acid **45**. Alternatively, reductive debromination of **37** (Zn/AcOH) provided the end-capped octamer **46** in 86% yield. Sequential removal of the benzyls (H_2/Pd), and then the benzoates (NaOMe) from **46**, followed by alkylation of the resulting octaphenol ($BrCH_2CO_2Bu^t/K_2CO_3$) afforded the fully derivatized framework **49**. The conversion of **46** to **49** involved a total of 16 functional group conversions and was accomplished in an overall yield of 83%. The efficiency of these operations highlights our general observation, that functional groups appended to aromatic oligomers of this kind behave in an entirely predictable manner and are not significantly hindered or perturbed by the extended molecular framework surrounding them.

As shown in Scheme 8, derivatized scaffolds can also be activated for subsequent coupling using the standard procedures already described. Thus, reductive debromination of tetramer **31** (Zn/AcOH, 86%), followed by sequential removal of the benzyl ethers (H_2/Pd), benzoate esters (NaOMe), and sulfonylation of the resulting tetraphenol **52** (NaH/*N*-phenyltriflimide, 88% based on **50**), afforded triflate **53** in high yield. Palladium-mediated methoxycarbonylation of **53** then provided the fully functionalized tetrabenzoate system **54**. Removal of the MEM protecting group from **54** (H_2SO_4/MeOH) followed by iodination (I_2 (solid)/morpholine, 84% based on **54**) and alkylation in the usual manner (NaH/MeI/DMPU, 95%), furnished the activated tetraester building block **57**. Coupling of **57** with 1.2 equiv of benzylic zinc **28** (from a stock solution) afforded the hexamer scaffold **58** in 81% yield. Combinatorial coupling of partial or fully derivatized oligomers, such as **57**, with units containing open functionality such as **28**, provides an obvious mechanism for the generation of diversely functionalized systems from a limited set of advanced intermediates.

Non-Methylene-Linked Oligomers. The linkage between aromatic units is by no means confined to the methylene group employed above. As already demonstrated by both Moore[22a,b] and Tour,[22c,d] extended aromatic oligomers, analogous to **41** but linked by acetylene units, can be assembled with considerable efficiency. In fact, combining common subunits using various linkers represents a particularly economical way of altering the spacial relationship of a given set of functional groups along an oligomer scaffold. A specific example of the construction of a mixed-linkage scaffold is shown in Scheme 9. In this particular instance, the activated diphenylmethane unit **60**[23] was first attached to the salicylate derivative **68**, via an acetylene linkage (CuI/$(Ph_3P)_4$Pd/piperidine, 82%)[24] to produce a trimer **61**. The free phenol of **61** was alkylated ($BrCH_2CO_2Bu^t/K_2CO_3$, 87%) and then the acetylene linkage selectively reduced (H_2/Pd/EtOAc, 73%) to afford **63**. Conversion of the benzylic silyl ether in **63** to the corresponding bromide (Bu_4NF/AcOH and then Ph_3P/NBS, 84% overall) provided **65**, which was subjected to a benzylic homocoupling reaction ($Zn/NiBr_2(Ph_3P)_2/Bu_4NI$, 71%)[25] to furnish the hexamer framework **66**. The assembly of **66** from diphenylmethane **60** requires only six steps (30% overall) and illustrates how alterations in the length (ethylene vs methylene), orientation (para vs meta), and order (head to head vs head to tail) of linkages between the aromatic units can be achieved employing a standard set of terminally functionalized intermediates (aryl iodide and benzyl bromide). The ability to easily alter linkages in this way confers an additional manifold of variability to the aromatic oligomer system which is not readily avail-

(21) Polyanionic, methylene-linked aromatic polymers and oligomers have been shown to exhibit a wide range of interesting biological activities. For examples see (a) Wang, P.; Kozlowski, J.; Cushman, M. *J. Org. Chem.* **1992**, *57*, 3861 and references therein. (b) Regan, J. R.; Bruno, J. G.; Sabatino, R.; D'Alisa, R.; Ben-Sasson, S. A.; Eilat, D. *J. Bioact. Compat. Polym.* **1993**, *8*, 317. (c) Benezra, M.; Vlodavsky, I.; Yayon, A.; Bas-Shavit, R.; Regan, J.; Chang, M.; Ben-Sasson, S. A. *Cancer Res.* **1992**, *52*, 5656. (d) Benezra, M.; Ben-Sasson, S. A.; Regan, J.; Chang, M.; Bar-Shavit, R.; Vlodavsky, I. *Arterioscler. Thromb.* **1994**, *14*, 1992. (e) Weinstein, M.; Vosburgh, E.; Phillips, M.; Terner, N.; Chute-Rose, L.; Moake, J. *Blood* **1991**, *78*, 2291. In addition, there are several natural product families which are based on a methylene-linked aromatic oligomer backbone. For examples see (a) Hufford, C. D.; Lasswell, W. L., Jr.; Hirotsu, K. Clardy, J. *J. Org. Chem.* **1979**, *44*, 4709. (b) Carte, B. K.; Troupe, N.; Chan, J. A.; Westley, J. W.; Faulkner, D. J. *Phytochemistry* **1989**, *28*, 2917. (c) Euw, J. V.; Reichstein, T.; Widen, C.-J. *Helv. Chim. Acta* **1985**, *68*, 1251. There is also an extensive literature covering cyclic aromatic oligomers, known as calixarenes. For a review see Stoddart, J. F., Ed. *Calixarenes, monographs in supramolecular chemistry*; Royal Society of Chemistry: Cambridge, 1989; Vol. 1.

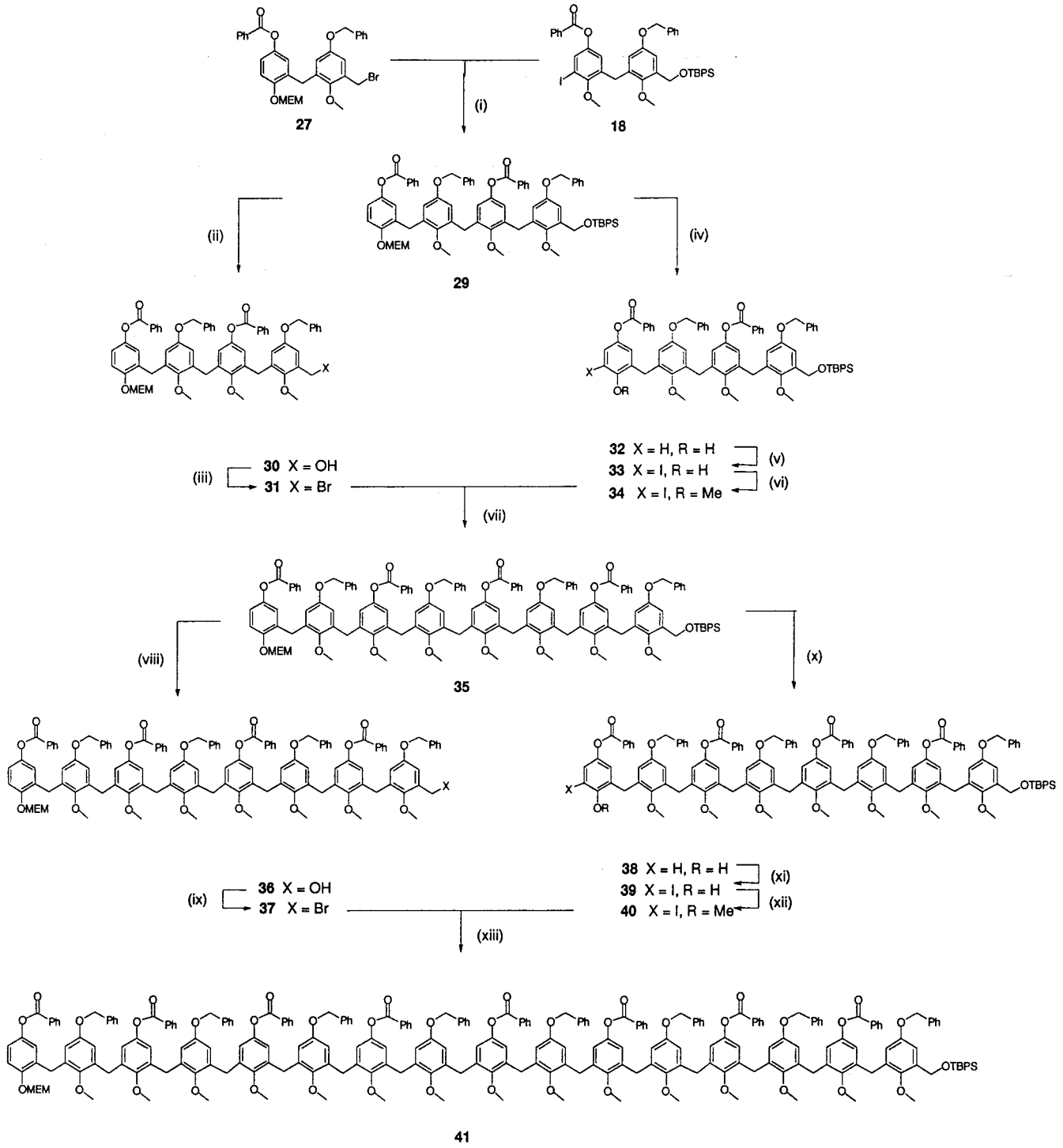
(22) (a) Zhang, J.; Moore, J. S.; Zhifu Xu; Aguirre, R. A. *J. Am. Chem. Soc.* **1992**, *114*, 2273. (b) Nelson, J. C.; Young, J. K.; Moore, J. S. *J. Org. Chem.* **1996**, *61*, 8160. (c) Schumm, J. S.; Pearson, D. L.; Tour, J. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1360. (d) Pearson, D. L.; Tour, J. M. *J. Org. Chem.* **1997**, *62*, 1367. (e) Jones, L., II; Schumm, J. S.; Tour, J. M. *J. Org. Chem.* **1997**, *62*, 1388 and references therein. For a review of this field see Tour, J. M. *Chem. Rev.* **1996**, *96*, 537.

(23) **59** was prepared by alkylation of **14** with benzyl bromide and then removal of the benzoate using conditions described in the Experimental Section. **68** was prepared from 5-iodosalicylic acid, in four steps.

(24) Rossi, R.; Carpita, A.; Bellina, F. *Org. Prep. Proc. Int.* **1995**, *27*, 127.

(25) Iyoda, M.; Sakaitani, M.; Hiroki, O.; Oda, M. *Chem. Lett.* **1985**, 127.

Scheme 6[a]



[a] Reagents, conditions, and yields: (i) Zn then $(Ph_3P)_4Pd$, 83%. (ii) TBAF/AcOH, 83%. (iii) NBS/Ph_3P, 96%. (iv) Py Tos/IPA. (v) I_2/morpholine, 82% overall from **29**. (vi) NaH/MeI/DMPU, 92%, (vii) as in (i) , 70%. (viii) as in (ii), 93%. (ix) as in (iii), 82%. (x) as in (iv). (xi) as in (v), 79% overall from **35**. (xii) as in (vi), 92%. (xiii) as in (i), 62% based on **40**.

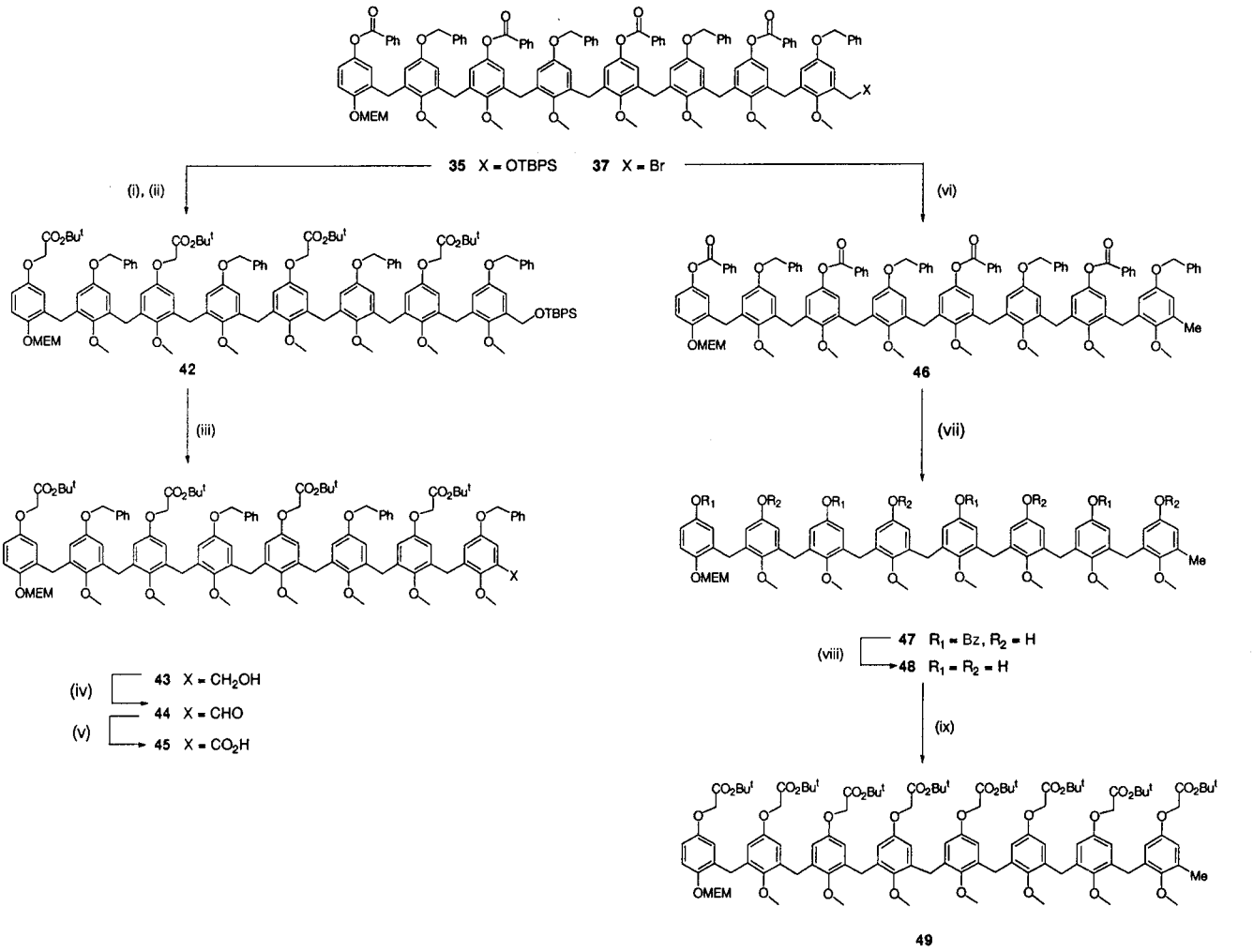
able to many other oligomeric platforms. Final deprotection of **66** (PPTS and then NaOH, 57%) provided the target hexamer **67**. This rather simple structure was one of a group of extended, anionic oligomers found to be potent inhibitors of human neutrophil elastase (**67**, K_i = 18 nM). Interestingly, oligomers in this series with chain lengths less than five were at least two orders of magnitude less active.[26]

(26) A more detailed account of the interaction of this class of compound with HNE will appear elsewhere.

Conclusion

Diphenylmethane **1** can function as the progenitor of a variety of low molecular weight structures by selective derivatization of its appended functionality. In addition, this versatile building block can be used as an advanced intermediate in the synthesis of a wide range of extended aromatic scaffolds, thereby greatly reducing the investment of time and effort required to prepare any individual structure. A subset of these extended oligomers, exemplified by hexamer **67**, were found to be effective

Scheme 7[a]



[a] Reagents, conditions, and yields: (i) NaOMe. (ii) $BrCH_2CO_2Bu^t/K_2CO_3$, 84% overall from **35**. (iii) Bu_4NF/AcOH, 91%. (iv) Swern, 92%. (v) $NaClO_2$/isobutene, 98%. (vi) Zn/AcOH, 86%. (vii) H_2/Pd. (viii) as in (i). (ix) as in (ii), 83% overall from **46.**

inhibitors of human neutrophil elastase, while substantially smaller oligomer fragments were almost inactive. These observations illustrate the type of result that can be obtained by including higher molecular weight compounds in screening libraries. However, this represents only one case and the likelihood of observing such trends in other systems remains to be determined. Indeed, relatively little is known about the detailed biological interactions, metabolism, or pharmacokinetics of non-natural oligomers in this molecular weight range.[27] The chemistry outlined in this paper, and elsewhere,[22] shows that such structures are readily accessible and provides a basis for the development of the more extensive libraries needed to test the ideas regarding association probability outlined above. We believe that synthetic oligomers of this kind have an important role to play in the study of basic molecular recognition, as well as in the field of drug discovery, particularly in areas where the search for leads from small molecule libraries has not been successful.

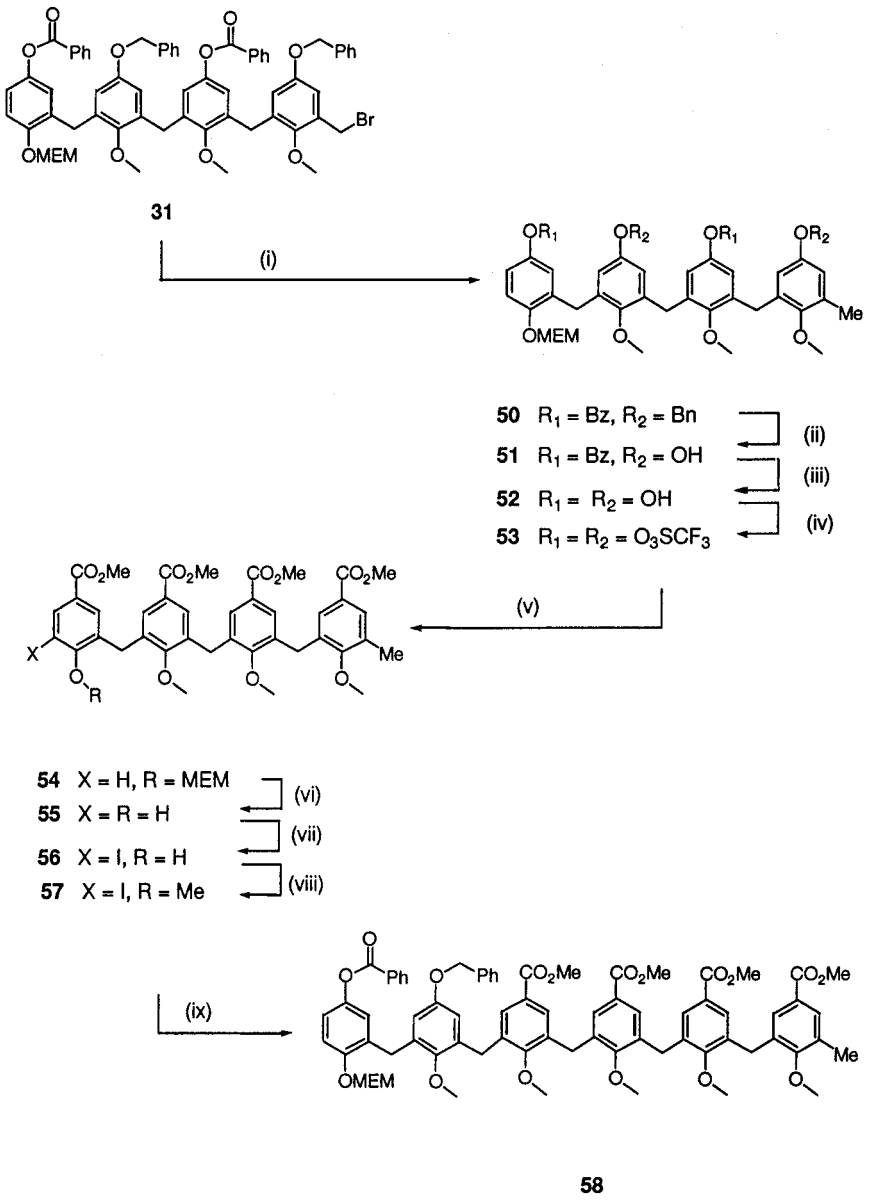
(27) Preliminary studies on the biological properties of oligocarbamates and peptoids suggest that these systems may possess significant advantages over natural peptide sequences. Oligocarbamates: Cho, C. Y.; Moran, E. J.; Cherry, S. R.; Stephans, J. C.; Fodor, F. P. A.; Adams, C. L.; Sundaram, A.; Jacobs, J. W.; Schultz, P. G. *Science* **1993**, *261*, 1303. Peptoids: Miller, S. M.; Simon, R. J.; Ng, S.; Zuckermann, R. N.; Kerr, J. M.; Moos, W. H. *Bioorg. Med. Chem. Lett.* **1994**, 2657. For other examples of extended, non-natural oligomers of biological relevance see (a) Koert, U.; Harding, M. M.; Lehn, J.-M. *Nature* **1990**, *346*, 339. (b) Bannwarth, W.; Bergmann, F. *Tetrahedron Lett.* **1995**, *36*, 1839. (c) Shao, J.; Tam, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 3893. (d) Richert, C.; Roughton, A. L.; Benner, S. A. *J. Am. Chem. Soc.* **1996**, *118*, 4518 and references therein. (e) Parks, P. E.; Baird, E. E.; Dervan, P. B. *J. Am. Chem. Soc.* **1996**, *118*, 6141, 6147, and 6153. (f) Kogan, M.; Valasinas, A.; Frydman, B. *Tetrahedron. Lett.* **1996**, *37*, 763. (g) Zanini, D.; Roy, R. *J. Org. Chem.* **1996**, *61*, 7348. (h) Gauler, R.; Risch, N.; *Tetrahedron Lett.* **1997**, *38*, 223. (i) Hoger, S. *Synthesis* **1997**, 20. (j) Mulders, S. J. E.; Brouwer, A. J.; van der Meer, P. G. J.; Liskamp, R. M. J. *Tetrahedron Lett.* **1997**, *38*, 631.

Experimental Section

^1H NMR spectra were recorded at a frequency of 300 MHz. Plasma desorption mass spectra were recorded at Purdue University. Unless otherwise specified, materials were obtained from commercial suppliers and were used without further purification. Piperidine and morpholine were distilled from calcium hydride prior to use. NBS was recrystallized from water and dried over P_2O_5. Anhydrous solvents were obtained from Aldrich. Column chromatography was performed on Merck silica gel (230−400 mesh).

Benzoic Acid 3-Formyl-4-hydroxyphenyl Ester (2). To a solution of 2,5-dihydroxybenzaldehyde (25.5 g, 185 mmol) in CH_2Cl_2 (500 mL) was added Et_3N (57 mL, 413 mmol) followed by benzoic anhydride (87.9 g, 389 mmol) and DMAP (2.26 g, 18.5 mmol) . The resulting solution was stirred for 5 h and then diluted with ether and washed, sequentially, with saturated $NaHCO_3$ solution and brine. The organic phase was dried over $MgSO_4$ and then concentrated under reduced pressure. The residue was dissolved in 4:1 MeOH:THF (500

Scheme 8[a]



[a] Reagents, conditions, and yields: (i) Zn/AcOH, 86%; (ii) H_2/Pd/MeOH/THF, (iii) NaOMe; (iv) NaH/*N*-phenyltriflimide/DMPU, 88% from **50**; (v) CO/MeOH/Et_3N/Pd(OAc)$_2$/bdpp, 74%; (vi) MeOH/H_2SO_4; (vii) I_2/morpholine, 84% overall from **54**; (viii) NaH/MeI/DMPU, 95%; (ix) **28**/$(Ph_3P)_4Pd$, 81%.

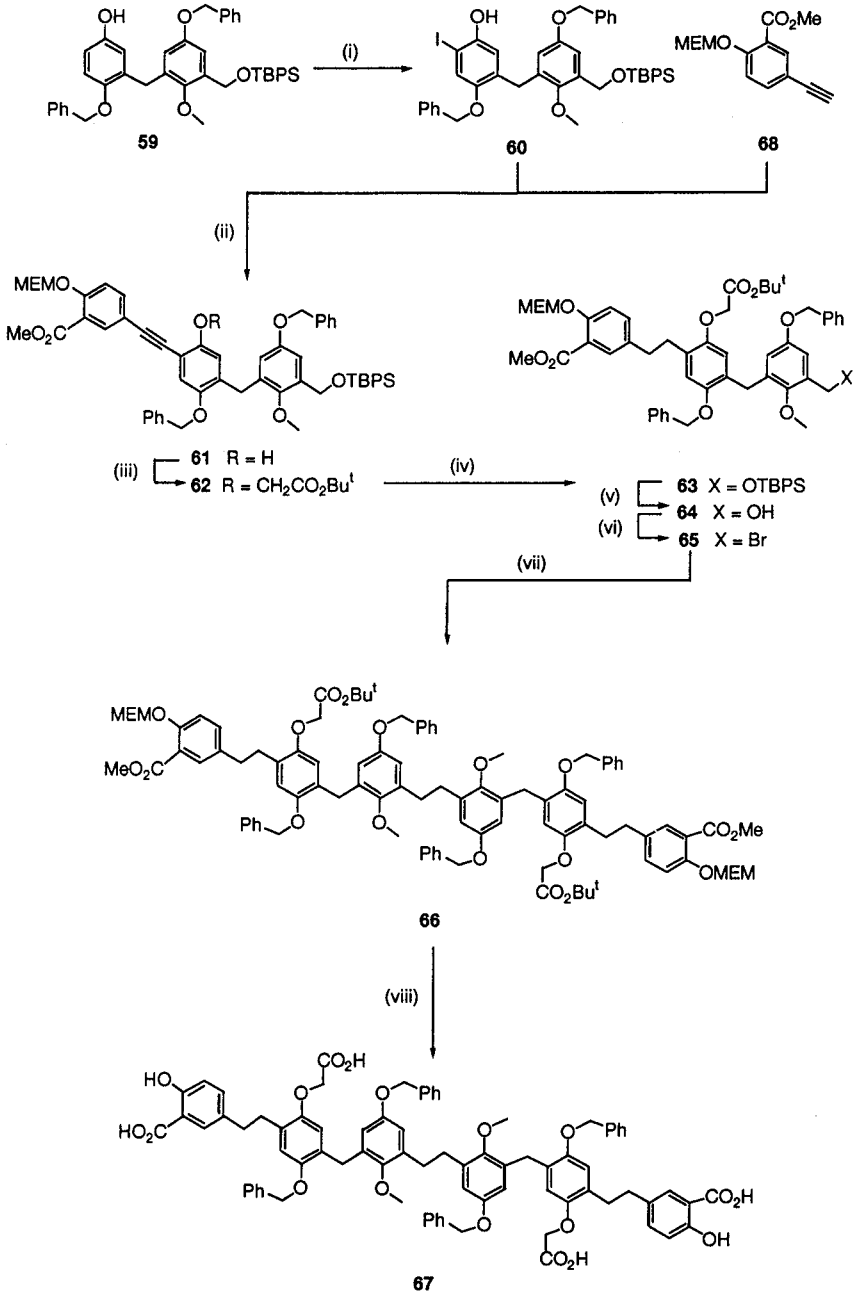
mL), and then anhydrous K_2CO_3 (25.6 g, 185 mmol) was added. The resulting mixture was stirred for 1 h and then diluted with ether and acidified with HCl (250 mL, 2 M). The organic phase was washed with a saturated solution of Na_2HPO_4. This wash was repeated several times until most of the benzoic acid had been removed (TLC analysis). The ether solution was then dried over $MgSO_4$ and concentrated under reduced pressure. The residual solid was recrystallized from 30% EtOAc in hexane to give (from two crops) 41.3 g of **2** (92%), mp 107−108 °C (lit. 107 °C).[28] ^{1}H NMR ($CDCl_3$) δ 7.05 (d, J = 9 Hz, 1H), 7.40 (dd, J = 9.0, 2.9 Hz, 1H), 7.46 (d, J = 2.9 Hz, 1H), 7.53 (m, 2H), 7.66 (m, 1H), 8.20 (d, J = 7.4 Hz, 2H), 9.88 (s, 1H), 10.9 (s, 1H). Anal. $C_{14}H_{10}O_4$ requires C 69.4, H 4.2. Found C 69.2, H 4.3.

Benzoic Acid 3-Bromo-5-formyl-4-hydroxyphenyl Ester (3). To a solution of **2** (48.7 g, 201 mmol) in acetic acid (250 mL) was added sodium acetate (18.3 g, 223 mmol), and the resulting mixture was cooled to 15 °C. To this mixture was added, dropwise, a solution of bromine (10.4 mL, 201 mmol) in acetic acid (35 mL). On complete addition, the reaction mixture was stirred for a further 15 min and then allowed to warm to room temperature over 1.5 h. The product was isolated by pouring the reaction mixture into 1.5 L of water and filtering the precipitated solid. The solid was washed thoroughly with water, dried azeotropically using toluene, and used without further purification. ^{1}H NMR ($CDCl_3$) δ 7.49 (d, J = 2.8 Hz, 1H), 7.53 (m, 2H), 7.67 (m, 1H), 7.70 (d, 2.8 Hz, 1H), 8.18 (d, J = 7.5 Hz, 2H), 9.8 (s, 1H), 11.5 (s, 1H); MS (EI) m/z 320/322 Br pattern $(M)^+$.

Benzoic Acid 3-Bromo-5-formyl-4-methoxyphenyl Ester (4) To a solution of **3** (64.2 g, 200 mmol) in CH_3CN (450 mL) was added anhydrous K_2CO_3 (29.2 g, 212 mmol) and iodomethane (62 mL, 1 mol). The resulting mixture was stirred at 45−50 °C for 18 h and then cooled to room temperature, and the excess iodomethane was removed by distillation under reduced pressure. The residue was diluted with EtOAc and then acidified with 1 M HCl. The organic phase was separated, washed, sequentially, with water and brine, dried over $MgSO_4$, and then concentrated under reduced pressure to give 64.9 g of solid. This product was dried azeotropically with toluene and used without further purifica-

(28) Kawai, S.; Nakamura, T.; Yoshida, M. *Chem. Ber.* **1940**, *70*, 581.

Scheme 9[a]



[a] Reagents conditions and yields: (i) I_2/morpholine, 89%; (ii) $(Ph_3P)_4Pd/CuI$/piperidine, 82%; (iii) $BrCH_2CO_2Bu^t/K_2CO_3$, 87%; (iv) H_2/Pd/EtOAc, 73%; (v) Bu_4NF/AcOH, 93%; (vi) NBS/Ph_3P, 90%; (vii) $Zn/NiBr_2(Ph_3P)_2/Bu_4NI$, 71%; (viii) PyTos then NaOH, 57%.

tion. ^{1}H NMR ($CDCl_3$) δ 4.02 (s, 3H), 7.52 (m, 2H), 7.65 (m, 1H), 7.67 (d, J = 2.9 Hz, 1H), 7.74 (d, J = 2.9 Hz, 1H), 8.16 (d, J = 7.5 Hz, 2H), 10.35 (s, 1H); MS (EI) m/z 335/337 Br pattern $(MH)^+$.

3-Bromo-5-hydroxy-2-methoxybenzaldehyde (5). A solution of **4** (64.9 g, 193 mmol) in anhydrous THF (550 mL) was cooled to −45 °C. To this solution was added sodium methoxide (46.5 mL, 25 wt % in methanol, 203 mmol). The resulting solution was stirred for 1.25 h and then quenched with HCl (205 mL, 1 M). The reaction mixture was then diluted with ether and washed, sequentially, with water (3×) and brine, dried over $MgSO_4$, and concentrated. The crude, solid product was triturated with hexanes and then dried azeotropically with toluene and used without further purification. ^{1}H NMR ($CDCl_3$) δ 3.94 (s, 3H), 5.6 (bs, 1H), 7.28 (d, J = 3.0 Hz, 1H), 7.38 (d, J = 3.0 Hz, 1H), 10.29 (s, 1H); MS (EI) m/z 230/232 Br pattern $(M)^+$.

5-(Benzyloxy)-3-bromo-2-methoxybenzaldehyde (6). The crude **5** from the previous step was dissolved in anhydrous CH_3CN (500 mL), and then K_2CO_3 (28.0 g 203 mmol) and benzyl bromide (26.4 mL, 221 mmol) were added. The resulting mixture was stirred at 81 °C for 3 h, cooled to room temperature, and diluted with ether. The ether solution was washed, sequentially, with water (3×) and brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (eluting with 10% ether/10% CH_2Cl_2 in hexanes) to give 58.6 g of **6** (90% based on **2**), mp 61−62.5 °C. ^{1}H NMR ($CDCl_3$) δ 3.94 (s, 3H), 5.06 (s, 2H), 7.37 (d, J = 3.0 Hz, 1H), 7.4 (m, 5H), 7.48 (d, J = 3 Hz, 1H), 10.3 (s, 1H); IR (KBr) ν 3073 (w), 2868 (w), 1688 (s), 1594 (m), 1384 (m), 1227 (s), 1103 (m), 1026 (s), 986 (m) cm^{-1}; MS (FAB nitrobenzyl alcohol) m/z 321/323 Br pattern $(MH)^+$. Anal. $C_{15}H_{13}O_3Br$ requires C 56.1, H 4.1. Found C 56.2, H 4.0.

The following compounds were prepared using essentially the same procedure:

***tert*-Butyl-(5-(cyanomethoxy)-2-methoxy-3-(2-((2-methoxyethoxy)methoxy)-5-(benzoyloxy)benzyl)benzyloxy)-diphenyl-silane (17).** Purified by flash chromatography

(eluting with 30% Et_2O/20% CH_2Cl_2 in hexanes): 484 mg of **13** gave 363 mg of **17** (72%). ^1H NMR ($CDCl_3$) δ 1.10 (s, 9H), 3.36 (s, 3H), 3.50 (m, 2H), 3.51 (s, 3H), 3.73 (m, 2H), 3.98 (s, 2H), 4.65 (s, 2H), 4.83 (s, 2H), 5.27 (s, 2H), 6.60 (d, J = 3 Hz, 1H), 6.89 (d, J = 3 Hz, 1H), 7.02 (dd, J = 9, 3 Hz, 1H), 7.12 (d, J = 3 Hz, 1H), 7.20 (d, J = 9 Hz, 1H), 7.40 (m, 6H), 7.48 (m, 2H), 7.62 (m, 1H), 7.69 (m, 4H), 8.16 (m, 2H); IR (KBr) ν 3013 (m), 2932 (m), 2859 (w), 1732 (s), 1600 (w), 1496 (s), 1265 (s), 1200 (s), 1152 (s), 1112 (s), 1077 (s), 1063 (s) cm^{-1}; MS (FAB nitrobenzyl alcohol) m/z 746 $(MH)^+$.

2-((2-Methoxyethoxy)methoxy)-5-(5-(benzyloxy)-3-(5-(benzyloxy)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-methoxybenzyl)-2-(((*tert*-butyloxycarbonyl)methyl)oxy)-phenyl)ethynyl)benzoic Acid Methyl Ester (62). Purified by flash chromatography (eluting with 20% EtOAc/20% CH_2Cl_2 in hexanes): 750 mg of **61** gave 703 mg of **62** (87%). ^1H NMR (C_6D_6) δ 1.20 (s, 9H), 1.30 (s, 9H), 3.01 (s, 3H), 3.20 (m, 2H), 3.24 (s, 3H), 3.49 (s, 3H), 3.60 (m, 2H), 4.08 (s, 2H), 4.32 (s, 2H), 4.52 (s, 2H), 4.84 (s, 2H), 4.96 (s, 2H), 5.04 (s, 2H), 6.76 (s, 1H), 6.82 (d, J = 3 Hz, 1H), 6.97 (d, J = 9 Hz, 1H), 7.05−7.30 (m, 17H), 7.47 (d, J = 3 Hz, 1H), 7.60 (dd, J = 9, 2 Hz, 1H), 7.80 (m, 4H), 8.29 (d, J = 2 Hz, 1H); IR ($CHCl_3$) ν 3011 (w), 2932 (w), 1748 (m), 1725 (s), 1604 (w), 1506 (s), 1242 (s), 1158 (s), 1112 (s) 1078 (s) cm^{-1}; MS (ion spray) m/z 1071 $(MH)^+$. Anal. $C_{65}H_{70}O_{12}Si$ requires C 72.9, H 6.6. Found C 72.7, H 6.5.

(5-(Benzyloxy)-3-bromo-2-methoxyphenyl)methanol (7). A solution of **6** (58.6 g 182 mmol) in THF (500 mL) was cooled to −60 °C, and then $NaBH_4$ (200 mL, 0.5 M in diglyme) was added. On complete addition, the solution was warmed to −25 °C and stirred at this temperature for 1 h. The reaction was quenched with HCl (250 mL, 2 M) and the product extracted with EtOAc. The combined organic extracts were washed, sequentially, with water (5 × 500 mL) and brine, dried over $MgSO_4$, and concentrated. The residue was further dried azeotropically with toluene and then used for the next step without further purification. ^1H NMR ($CDCl_3$) δ 2.04 (t, J = 6.2 Hz, 1H), 3.83 (s, 3H), 4.71 (d, J = 6.2 Hz, 2H), 5.02 (s, 2H), 6.98 (d, J = 3.1 Hz, 1H), 7.11 (d, J = 3.1 Hz, 1H), 7.4 (m, 5H); MS (EI) m/z 322/324 Br pattern $(M)^+$.

((5-(Benzyloxy)-3-bromo-2-methoxyphenyl)methoxy)-*tert*-butyldiphenylsilane (8). The crude **7** from the previous step was dissolved in CH_2Cl_2 (600 mL), and imidazole (18.7 g, 275 mmol) was added, followed by *tert*-butyldiphenylsilyl chloride (49.4 mL, 190 mmol). The resulting mixture was stirred for 30 min and then diluted with ether. The ether solution was washed, sequentially, with water and brine, dried over $MgSO_4$, filtered, and then concentrated. The residue was purified by flash chromatography (eluting with 5% and then 10% Et_2O in hexanes) to give 96.1 g of product which solidified on standing (94%), mp 51−53 °C. ^1H NMR ($CDCl_3$) δ 1.07 (s, 9H), 3.58 (s, 3H), 4.77 (s, 2H), 5.0 (s, 2H), 7.05 (d, J = 3.0 Hz, 1H), 7.17 (d, J = 3.0 Hz, 1H), 7.3−7.44 (m, 11H), 7.67 (m, 4H); IR (KBr) ν 3066 (w), 2948 (m), 2928 (m), 2855 (m), 1597 (w), 1471 (s), 1453 (s), 1424 (s), 1208 (m), 1117 (s), 1046 (m), 699 (s) cm^{-1}; MS (FAB nitrobenzyl alcohol) m/z 559/561 Br pattern $(MH)^+$. Anal. $C_{31}H_{33}O_3BrSi$ requires C 66.3, H 5.9. Found C 66.3, H 6.0.

Benzoic Acid 3-Formyl-4-((2-methoxyethoxy)methoxy)phenyl Ester (9). To a chilled (−10 °C) suspension of NaH (10.1 g, 60% dispersion in mineral oil, 252 mmol) in THF (250 mL) was added, over 45 min, a solution comprised of **2** (54.2 g, 224 mmol), MEM chloride (30 mL, 263 mmol), and DMPU (30 mL) in THF (300 mL). The cold bath was then removed and stirring continued for 4 h. The reaction was quenched with HCl (30 mL, 1 M) and then diluted with ether. The ether solution was washed sequentially with water and brine, dried over $MgSO_4$, and concentrated. The residue was further dried by toluene azeotrope and the resulting white solid used without further purification. ^1H NMR ($CDCl_3$) δ 3.39 (s, 3H), 3.59 (m, 2H), 3.89 (m, 2H), 5.42 (s, 2H), 7.36 (d, J = 9 Hz, 1H), 7.41 (dd, J = 9.0, 2.6 Hz, 1H), 7.52 (m, 2H), 7.64 (m, 1H), 7.67 (d, J = 2.6 Hz, 1H), 8.18 (m, 2H), 10.48 (s, 1H); MS (ion spray) m/z 331 $(MH)^+$.

Benzoic Acid 3-(Hydroxymethyl)-4-((2-methoxyethoxy)-methoxy)phenyl Ester (10). The crude product **9** from the previous step was dissolved in THF (250 mL) and then cooled to −78 °C. To this solution was added $NaBH_4$ (150 mL, 0.5 M in diglyme). The resulting solution was warmed to −45 °C and stirred for 20 min. The reaction was then quenched with HCl (75 mL, 1 M) and diluted with EtOAc, washed with water (until no diglyme shows on TLC of organic fraction) and then brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (eluting with 30% EtOAc/10% CH_2Cl_2 in hexanes) to yield 63.1 g of **10** (84% based on **2**) which solidified on standing, mp 43.5−45 °C. ^1H NMR ($CDCl_3$) δ 2.38 (bt, J = 6.4 Hz, 1H), 3.37 (s, 3H), 3.56 (m, 2H), 3.85 (m, 2H), 4.71 (d, J = 6.4 Hz, 2H), 5.33 (s, 2H), 7.09 (dd, J = 8.8, 2.9 Hz, 1H), 7.19 (d, J = 8.8 Hz, 1H), 7.22 (d, J = 2.8 Hz, 1H), 7.50 (m, 2H), 7.61 (m, 1H), 8.19 (d, J = 7 Hz, 2H); IR (KBr) ν 3328 (bm), 3239 (bw), 3075 (w), 2930 (m), 2889 (m), 1735 (s), 1602 (w), 1496 (s), 1454 (m), 1266 (s), 1189 (s), 1106 (s), 1064 (s), 1027 (s), 996 (s) 905 (m), 850 (w) cm^{-1}; MS (ion spray) m/z 333 $(MH)^+$. Anal. $C_{18}H_{20}O_6$ requires C 65.0, H 6.1. Found C 65.0, H 6.0.

Benzoic Acid 3-(Bromomethyl)-4-((2-methoxyethoxy)-methoxy)phenyl Ester (11). A solution of **10** (56.0 g, 169 mmol) in THF (450 mL) was cooled to 5 °C and Ph_3P (50.0 g, 191 mmol) added, followed by NBS (33.0 g, 185 mmol). The resulting mixture was stirred for 15 min and then concentrated under reduced pressure, and the residue was purified by flash chromatography (eluting with 25% EtOAc in hexanes) to give 59.3 g of **11** (89%), mp 60−61 °C. ^1H NMR ($CDCl_3$) δ 3.39 (s, 3H), 3.58 (m, 2H), 3.89 (m, 2H), 4.55 (s, 2H), 5.37 (s, 2H), 7.12 (dd, J = 8.9, 2.7 Hz, 1H), 7.20 (d, J = 2.7 Hz, 1H), 7.23 (d, J = 8.9 Hz, 1H), 7.51 (t, J = 7.5 Hz, 2H), 7.64 (t, J = 7.5 Hz, 1H), 8.18 (d, J = 7.5 Hz, 2H); IR (KBr) ν 3074 (w), 2987 (w), 2888 (m), 1731 (s), 1603 (w), 1451 (m), 1269 (s), 1203 (s), 1156 (s), 1137 (s), 1061 (s), 988 (s), 707 (s) cm^{-1}; MS (EI) m/z 394/396 Br pattern $(M)^+$. Anal. $C_{18}H_{19}O_5Br$ requires C 54.7, H 4.8. Found C 54.8, H 4.6.

Benzoic Acid 3-(5-(Benzyloxy)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-methoxybenzyl)-4-((2-methoxyethoxy)-methoxy)phenyl Ester (1). To a suspension of zinc powder (100 g, 1.53 mol, 325 mesh) in THF (50 mL) was added 1,2-dibromoethane (3.25 mL, 38 mmol). The resulting mixture was heated to reflux, stirred vigorously for 1.5 min, and then allowed to cool to room temperature. The activated zinc suspension was then further cooled to −5 °C (external temp), and then a solution **11** (57.0 g, 144 mmol) in THF (130 mL) was added, dropwise, over 4.75 h. On complete addition, the mixture was stirred a further 15 min, and then stirring was stopped and the excess zinc allowed to settle. The supernatant solution was transferred to a separate reaction flask containing a solution of $(Ph_3P)_4Pd$ (2.80 g, 2.4 mmol) and **8** (75.0 g, 134 mmol) in THF (20 mL). The zinc was washed with THF (2 × 200 mL), and these washings also transferred to the reaction flask. The reaction mixture was stirred at 60 °C for 17 h and then cooled to room temperature, diluted with ether, and washed, sequentially, with saturated NH_4Cl solution, 5% NH_3 solution, water, and brine. The ether solution was then dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (eluting with 40% EtOAc in hexanes) to give 92.7 g of **1** as an oil (87%). ^1H NMR ($CDCl_3$) δ 1.08 (s, 9H), 3.43 (s, 3H), 3.58 (m, 2H), 3.59 (s, 3H), 3.78 (m, 2H), 4.02 (s, 2H), 4.90 (s, 2H), 5.05 (s, 2H), 5.31 (s, 2H), 6.69 (d, J = 2.7Hz , 1H), 6.95 (d, J = 2.7 Hz, 1H), 7.10 (dd, J = 8.6, 2.6 Hz, 1H), 7.2 (d, J = 2.6 Hz, 1H), 7.25 (d, J = 8.6 Hz, 1H), 7.3−7.5 (m, 11H), 7.55 (t, J = 7.9 Hz, 2H), 7.68 (t, J = 7.9 Hz, 1H), 7.77 (d, J = 7.0 Hz, 4H), 8.24 (d, J = 7.9 Hz, 2H); IR (KBr) ν 3055 (m), 2952 (s) 2930 (s), 2890 (s), 2857 (s), 1733 (s), 1576 (m), 1496 (m), 1262 (s), 1061 (s) cm^{-1}; MS (FAB nitrobenzyl alcohol) m/z 797 $(MH)^+$. Anal. $C_{49}H_{52}O_8Si$ requires C 73.8, H 6.6. Found C 73.5, H 6.6. Also isolated was 5.80 g of the homocoupled product[5] **1,2-bis(5-(benzoyloxy)-2-((2-methoxyethoxy)methoxy)phenyl)ethane** as a white solid, mp 118−119 °C. ^1H NMR ($CDCl_3$) δ 2.90 (s, 4H), 3.35 (s, 6H), 3.55 (m, 4H), 3.81 (m, 4H), 5.26 (s, 4H), 6.97 (dd, J = 8.8, 2.8 Hz, 2H), 7.0 (d, J = 2.8 Hz, 2H), 7.18 (d, J = 8.8 Hz, 2H), 7.48 (t, J = 7.7 Hz, 4H), 7.61 (t, J = 7.7 Hz, 2H), 8.17 (d, J = 7.7 Hz, 4H); IR (KBr) ν 3055 (w), 2928 (m), 1741 (s), 1593 (m), 1465 (s), 1263 (s), 1061 (s) cm^{-1}; MS (FAB nitrobenzyl

alcohol) *m*/*z* 630 $(M)^+$. Anal. $C_{36}H_{38}O_{10}$ requires C 68.55, H 6.1. Found C 68.3, H 6.1.

The following compounds were prepared employing essentially the same procedure:

Benzoic Acid 3-(5-(Benzyloxy)-3-(5-(benzoyloxy)-3-(5-(benzyloxy)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-methoxybenzyl)-2-methoxybenzyl)-2-methoxybenzyl)-4-((2-methoxyethoxy)methoxy)phenyl Ester (29). Purified by flash chromatography (30% and then 40% EtOAc in hexanes): 34.0 g of **18** gave 41.72 g of **29** as a colorless oil (83%). ^{1}H NMR ($CDCl_3$) δ 1.07 (s, 9H), 3.42 (s, 3H), 3.57 (s, 3H), 3.58 (m, 2H), 3.68 (s, 3H), 3.73 (s, 3H), 3.75 (m, 2H), 4.07 (bs, 4H), 4.14 (s, 2H), 4.88 (s, 2H), 4.93 (s, 2H), 5.04 (s, 2H), 5.31 (s, 2H), 6.61 (d, J = 2.6 Hz, 1H), 6.62 (d, J = 2.7 Hz, 1H), 6.70 (d, J = 2.8 Hz, 1H), 6.80 (d, J = 2.8 Hz, 1H), 6.85 (d, J = 2.8 Hz, 1H), 6.99 (d, J = 2.7 Hz, 1H), 7.10 (dd, J = 9.4, 2.8 Hz, 1H), 7.20 (d, J = 2.8 Hz, 1H), 7.25 (d, J = 9.4 Hz, 1H), 7.26−7.5 (m, 16H), 7.5−7.58 (m, 4H), 7.63−7.70 (m, 2H), 7.85 (d, J = 7.9 Hz, 4H), 8.16−8.27 (m, 4H); IR (KBr) ν 3059 (w), 3026 (w), 2930 (m), 2878 (m), 2817 (w), 1737 (s), 1599 (m), 1496 (m), 1469 (s), 1451 (m), 1428 (m), 1262 (s), 1207 (s), 1174 (m), 1110 (m), 1079 (m), 1061 (s), 1005 (m) cm^{-1}; MS (FAB, nitrobenzyl alcohol) *m*/*z* 1262 $(M)^+$. Anal. $C_{79}H_{78}O_{13}Si$ requires, C 75.1, H 6.2. Found C 74.7, H 6.3. Also obtained was the homocoupled product[5] **1,2-bis(5-(benzyloxy)-3-(5-(benzoyloxy)-2-((2-methoxyethoxy)methoxy)benzyl)-2-methoxyphenyl)ethane** which solidified on standing, mp 102−103 °C. ^{1}H NMR ($CDCl_3$) δ 2.91 (s, 4H), 3.35 (s, 6H), 3.49 (m, 4H), 3.68 (s, 6H), 3.72 (m, 4H), 4.02 (s, 4H), 4.92 (s, 4H), 5.25 (s, 4H), 6.56 (d, J = 2.9 Hz, 2H), 6.74 (d, J = 2.9 Hz, 2H), 6.91 (d, J = 2.8 Hz, 2H), 7.03 (dd, J = 8.8, 2.8 Hz, 2H), 7.18 (d, J = 8.8 Hz, 2H), 7.26−7.37 (m, 10H), 7.46 (t, J = 7.7 Hz, 4H), 7.60 (t, J = 7.7 Hz, 2H), 8.16 (d, J = 7.7 Hz, 4H); IR (KBr) ν 3082 (w), 3054 (w), 3029 (w), 2931 (m), 2878 (m), 2817 (m), 1738 (s), 1601 (m), 1498 (s), 1479 (m), 1467 (m), 1452 (m), 1425 (m), 1315 (m), 1263 (s), 1221 (m), 1201 (s), 1156 (m), 1079 (m), 1058 (s), 1037 (m), 1027 (m), 1004 (s) cm^{-1}; MS (FAB, nitrobenzyl alcohol) *m*/*z* 1082 $(M)^+$. Anal. $C_{66}H_{66}O_{14}$ requires C 73.2, H 6.1. Found C 73.0, H 6.3.

Compound 35. Purified by flash chromatography (30% EtOAc/20% CH_2Cl_2 in hexanes): 12.0 g of **34** gave 14.0 g of **35** (70%) as a white solid, mp 153−154 °C. ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 9H), 3.33 (s, 3H), 3.46 (m, 2H), 3.47 (s, 3H), 3.58 (bs, 9H), 3.65 (s, 6H), 3.66 (s, 3H), 3.68 (m, 2H), 4.00 (s, 2H), 4.02 (s, 2H), 4.06 (bs, 10H), 4.81 (s, 2H), 4.86 (bs, 6H), 4.96 (s, 2H), 5.23 (s, 2H), 6.53 (d, J = 3.0 Hz, 1H), 6.57, (bs, 5H), 6.64 (d, J = 3.0 Hz, 1H), 6.74 (d, J = 2.8 Hz, 1H), 6.79 (bs, 5H), 6.93 (d, J = 2.8 Hz, 1H), 7.02 (dd, J = 8.9, 2.8 Hz, 1H), 7.13 (d, J = 3.0 Hz, 1H), 7.2−7.5 (m, 35H), 7.55−7.6 (m, 4H), 7.67−7.71 (m, 4H), 8.09−8.17 (m, 8H); IR (KBr) ν 3082 (w), 3054 (w), 3026 (w), 2931 (m), 2820 (m), 1736 (s), 1599 (m), 1471 (s), 1452 (m), 1429 (m), 1314 (w), 1263 (s), 1215 (s), 1173 (m), 1062 (s), 1006 (m) cm^{-1}; MS (FAB, nitrobenzyl alcohol) *m*/*z* 2196 $(MH)^+$. Anal. $C_{139}H_{130}O_{23}Si$ requires C 76.0, H 6.0. Found C 75.5, H 6.0. Also obtained was 2.2 g of homocoupled product **1,2-bis-(5-(benzyloxy)-3-(5-(benzoyloxy)-3-(5-(benzyloxy)-3-(5-(benzoyloxy)-2-((2-methoxyethoxy)methoxy)benzyl)-2-methoxybenzyl)-2-methoxybenzyl)-2-methoxyphenyl)-ethane**. ^{1}H NMR ($CDCl_3$) δ 2.91 (s, 4H), 3.33 (s, 6H), 3.47 (m, 4H), 3.60 (s, 6H), 3.67 (s, 12H), 3.69 (m, 4H), 4.01 (s, 4H), 4.07 (s, 4H), 4.08 (s, 4H), 4.86 (s, 4H), 4.91 (s, 4H), 5.23 (s, 4H), 6.54 (d, J = 3.0 Hz, 2H), 6.57 (bs, 4H), 6.74 (d, J = 3.0 Hz, 2H), 6.77 (d, J = 3.0 Hz, 2H), 6.79 (d, J = 2.8 Hz, 2H), 6.92 (d, J = 2.8 Hz, 2H), 7.01 (dd, J = 8.8, 2.8 Hz, 2H), 7.17 (d, J = 8.8 Hz, 2H), 7.15−7.48 (m, 20H), 7.5−7.62 (m, 8H), 7.65−7.75 (m, 4H), 8.08−8.19 (m, 8H); IR (KBr) ν 3082 (w), 3059 (w), 3019 (w), 2932 (m), 2871 (m), 2820 (w), 1735 (s), 1600 (m), 1496 (m), 1472 (s), 1452 (m), 1429 (m), 1314 (w), 1262 (s), 1213 (s), 1174 (m), 1137 (m), 1080 (s), 1062 (s), 1006 (m) cm^{-1}; MS (FAB, nitrobenzyl alcohol) *m*/*z* 2016 $(MH)^+$. Anal. $C_{126}H_{118}O_{24}$ requires C 75.1, H 5.9. Found C 74.7, H 6.0.

Compound 41. Purified by flash chromatography (15% EtOAc/30% CH_2Cl_2 in hexanes): 670 mg of **40** gave 731 mg of **41** (62%) as a white amorphous solid. ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 9H), 3.33 (s, 3H), 3.45 (m, 2H), 3.47 (s, 3H), 3.58 (bs, 21H), 3.64 (bs, 18H), 3.66 (s, 3H), 3.68 (m, 2H), 4.01 (s, 2H), 4.02 (s, 2H), 4.05 (bs, 26H), 4.81 (s, 2H), 4.83 (s, 2H), 4.86 (s, 12H), 4.96 (s, 2H), 5.22 (s, 2H), 6.54 (d, J = 3.0 Hz, 1H), 6.57 (bs, 13H), 6.63 (d, J = 3.1 Hz, 1H), 6.74 (d, J = 2.8 Hz, 1H), 6.78 (bs, 13H), 6.91 (d, J = 2.8 Hz, 1H), 7.00 (dd, J = 8.7, 2.8 Hz, 1H), 7.13 (d, J = 3.0 Hz, 1H), 7.16−7.5 (m, 63H), 7.5−7.62 (m, 8H), 7.65−7.75 (m, 4H), 8.04−8.16 (m, 16H); IR (KBr) ν 3053 (w), 3023 (w), 2965 (m), 2936 (m), 2863 (m), 2823 (m), 1738 (s), 1600 (m), 1468 (s), 1452 (m), 1429 (m), 1314 (w), 1263 (s), 1233 (s), 1215 (s), 1172 (m), 1137 (m), 1080 (m), 1062 (s), 1038 (m), 1025 (m), 1006 (m) cm^{-1}; MS (plasma desorption) average mass measured 4064. Calculated $(M)^+$ for $C_{259}H_{234}O_{43}Si$ = 4063. Anal. $C_{259}H_{234}O_{43}Si$ requires C 76.56, H 5.81. Found C 76.1, H 6.1. Also obtained was the homocoupled product[5] **1,2-bis(5-(benzyloxy)-3-(5-(benzoyloxy)-3-(5-(benzyloxy)-3-(5-(benzoyloxy)-3-(5-(benzyloxy)-3-(5-(benzoyloxy)-3-(5-(benzyloxy)-3-(5-(benzoyloxy)-2-((2-methoxyethoxy)methoxy)benzyl)-2-methoxybenzyl)-2-methoxybenzyl)-2-methoxybenzyl)-2-methoxybenzyl)-2-methoxybenzyl)-2-methoxybenzyl)-2-methoxybenzyl)-2-methoxyphenyl)ethane**. ^{1}H NMR ($CDCl_3$) δ 2.92 (bs, 4H), 3.32 (s, 6H), 3.47 (m, 4H), 3.60 (bs, 18H), 3.67 (bs, 28H), 4.02 (s, 4H), 4.08 (bs, 24H), 4.86 (bs, 12H), 4.92 (s, 4H), 5.23 (s, 4H), 6.55 (d, J = 2.9 Hz, 2H), 6.59 (bs, 12H), 6.74 (d, J = 3 Hz, 2H), 6.80 (bs, 10H), 6.94 (d, J = 2.7 Hz, 2H), 7.02 (dd, J = 9.0, 2.7 Hz, 2H), 7.20−7.38 (m, 44H), 7.4−7.52 (m, 16H), 7.52−7.63 (m, 8H), 8.03−8.20 (m, 16H); IR (KBr) ν 3054 (w), 3020 (w), 2965 (w), 2930 (m), 2863 (m), 2823 (m), 1741 (s), 1600 (m), 1467 (s), 1452 (m), 1429 (m), 1314 (w), 1263 (s), 1233 (s), 1214 (s), 1172 (m), 1137 (m), 1080 (m), 1062 (s), 1037 (m), 1025 (m), 1004 (m) cm^{-1}; MS (plasma desorption) average mass measured 3884. Calculated $(M)^+$ for $C_{246}H_{222}O_{44}$ = 3882. Anal. $C_{246}H_{222}O_{44}$ requires C 76.1, H 5.8. Found C 75.7, H 5.8.

Compound 58. Purified by flash chromatography (eluting with 40 and then 50% EtOAc/10% CH_2Cl_2 in hexanes): 378 mg of **57** gave 449 mg of **58** as a foam (81%). ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H), 3.36 (s, 3H), 3.51 (m, 2H), 3.59 (s, 3H), 3.65 (s, 3H), 3.66 (s, 3H), 3.67 (s, 3H), 3.68 (s, 3H), 3.73 (m, 2H), 3.77 (s, 3H), 3.79 (s, 3H), 3.80 (s, 3H), 3.84 (s, 3H), 4.03 (s, 2H), 4.08 (s, 2H), 4.09 (s, 2H), 4.10 (s, 2H), 4.12 (s, 2H), 4.84 (s, 2H), 5.28 (s, 2H), 6.44 (d, J = 3 Hz, 1H), 6.55 (d, J = 3 Hz, 1H), 6.92 (d, J = 3 Hz, 1H), 7.03 (dd, J = 8, 3 Hz, 1H), 7.20 (d, J = 8 Hz, 1H), 7.27 (m, 5H), 7.48 (t, J = 9 Hz, 2H), 7.63 (m, 7H) 7.71 (d, J = 2.2 Hz, 1H), 7.79 (d, J = 2 Hz, 1H), 8.17 (d, J = 9 Hz, 2H); MS (ion spray) *m*/*z* 1255 $(MH)^+$, 1272 $(MNH_4)^+$. Anal. $C_{73}H_{74}O_{19}$ requires C 69.8, H 5.9. Found C 69.6, H 6.1.

Benzoic Acid 3-(5-(Benzyloxy)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-methoxybenzyl)-4-hydroxy-5-iodophenyl Ester (22). To a solution of **1** (35.18 g, 44 mmol) in 2-propanol:THF (4:1, 150 mL) was added pyridinium tosylate (11.1 g, 44 mmol). The resulting solution was stirred at 70 °C for 32 h, cooled to room temperature, diluted with ether, washed, sequentially, with water and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was further dried, azeotropically, with toluene to give **benzoic acid 3-(5-(benzyloxy)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-methoxybenzyl)-4-hydroxyphenyl ester (14)**. ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 9H), 3.70 (s, 3H), 3.80 (s, 2H), 4.78 (s, 2H), 4.97 (s, 2H), 6.80 (d, J = 3 Hz, 1H), 6.84 (d, J = 9 Hz, 1H), 6.95 (dd, J = 9, 3 Hz, 1H), 7.04 (d, J = 3 Hz, 1H), 7.09 (d, J = 3 Hz, 1H), 7.30 (s, 1H), 7.30−7.45 (m, 11H), 7.50 (m, 2H), 7.64 (m, 1H), 7.70 (m, 4H), 8.18 (m, 2H); IR (KBr) ν 3433 (m), 3068 (w), 2955 (m), 2931 (m), 2856 (m), 1733 (s), 1599 (m), 1496 (s), 1478 (s), 1452 (s), 1429 (s), 1267 (s), 1176 (s), 1145 (s), 1109 (s), 1063 (s) 704 (s) cm^{-1}; MS (ion spray) *m*/*z* 709 $(MH)^+$. Anal. $C_{45}H_{44}O_6Si$ requires C 76.2, H 6.3. Found C 76.2, H 6.3. This residue was then dissolved in CH_2Cl_2 (150 mL) and morpholine added (8.7 mL, 100 mmol) followed by iodine (10.1 g, 40 mmol). The resulting mixture was stirred at room temperature for 3 h, diluted with ether, and washed, sequentially, with HCl (60 mL, 1 M), saturated sodium thiosulfate solution, and brine. The ether solution was then dried over $MgSO_4$, filtered, and concentrated and the residue purified by crystallization (20% ethyl acetate in hexanes) to give 27.6 g of **14** as a white solid (75% based on **1**), mp 133−134 °C. ^{1}H NMR ($CDCl_3$) δ 1.09 (s, 9H), 3.67 (s, 3H), 3.85 (s, 2H), 4.79 (s, 2H), 4.97 (s, 2H),

6.75 (d, J = 2.6 Hz, 1H), 7.0 (d, J = 2.6 Hz, 1H), 7.1 (d, J = 2.6 Hz, 1H), 7.35−7.46 (m, 12H), 7.5 (t, J = 7.9 Hz, 2H), 7.58−7.7 (m, 5H), 8.17 (d, J = 7.9 Hz, 2H); IR (KBr) ν 3284 (bm), 3051 (w), 2930 (m), 2855 (m), 1731 (s), 1601 (w), 1472 (m), 1268 (m), 1216 (m), 1105 (m), 1081 (m), 1055 (m) cm^{-1}; MS (FAB nitrobenzyl alcohol) m/z 834 (M)$^+$.

The following compounds were prepared using essentially the same procedure:

Benzoic Acid 3-(5-(Benzyloxy)-3-(5-(benzoyloxy)-3-(5-(benzyloxy)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-methoxybenzyl)-2-methoxybenzyl)-2-methoxybenzyl)-4-hydroxy-5-iodophenyl Ester (33). Purified by flash chromatography (20% EtOAc/10% CH_2Cl_2 in hexanes): 20.7 g of **29** gave 17.9 g of **33** as a colorless oil (82%). ^{1}H NMR ($CDCl_3$) δ 1.06 (s, 9H), 3.46 (s, 3H), 3.56 (s, 3H), 3.79 (s, 3H), 3.89 (s, 2H), 3.99 (s, 2H), 4.06 (s, 2H), 4.79 (s, 2H), 4.88 (s, 2H), 4.95 (s, 2H), 6.56 (d, J = 3 Hz, 1H), 6.61 (d, J = 3 Hz, 1H), 6.69 (d, J = 3 Hz, 1H), 6.73 (m, 2H), 7.02 (d, J = 2.7 Hz, 1H), 7.11 (d, J = 3 Hz, 1H), 7.2−7.5 (m, 22H), 7.58 (m, 2H), 7.66 (m, 4H), 8.13 (m, 4H); IR (KBr) ν 3438 (bs), 3051 (w), 2930 (m), 2856 (m), 1734 (s), 1599 (m), 1471 (s), 1428 (m), 1262 (s), 1216 (s), 1174 (m), 1062 (s) cm^{-1}; MS (FAB nitrobenzyl alcohol) m/z 1300 (M)$^+$.

Compound 39. Purified by flash chromatography (15% EtOAc/20% CH_2Cl_2 in hexanes): 2.19 g of **35** gave 1.76 g of **39** as a white solid, mp 153−156 °C dec (79%). ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 9H), 3.46 (s, 3H), 3.59 (bs, 9H), 3.65 (bs, 6H), 3.80 (s, 3H), 3.92 (s, 2H), 4.01 (s, 2H), 4.07 (bs, 10H), 4.82 (s, 2H), 4.87 (s, 4H), 4.90 (s, 2H), 4.96 (s, 2H), 6.57 (bs, 4H), 6.59 (d, J = 3.0 Hz, 1H), 6.63 (d, J = 3.0 Hz, 1H), 6.70 (d, J = 3.0 Hz, 1H), 6.73 (d, J = 3.0 Hz, 1H), 6.77 (bs, 3H), 6.80 (d, J = 3.0 Hz, 1H), 7.04 (d, J = 3.0 Hz, 1H), 7.13 (d, J = 3.0 Hz, 1H), 7.15−7.64 (m, 40H), 7.66−7.71 (m, 4H), 8.05−8.19 (m, 8H); IR (KBr) ν 3443 (b), 3059 (w), 3020 (w), 2929 (m), 2874 (m), 2859 (m), 2816 (m), 1742 (s), 1591 (m), 1465 (s), 1452 (s), 1428 (s), 1315 (w), 1263 (s), 1250 (s), 1233 (s), 1214 (s), 1160 (m), 1136 (m), 1079 (m), 1061 (s), 1036 (s), 1025 (s), 1002 (m) cm^{-1}; MS (FAB nitrobenzyl alcohol) m/z 2235 (MH)$^+$.

(5-(Benzyloxy)-3-(5-hydroxy-4-iodo-2-((2-methoxyethoxy)methoxy)benzyl)-2-methoxybenzyloxy)-*tert*-butyldiphenylsilane (23). To a solution comprised of morpholine (0.66 mL, 7.6 mmol) and **15** (2.0 g, 2.9 mmol) in CH_2Cl_2 (9 mL), cooled to −10 °C, was added, dropwise, a solution of iodine (0.75 g, 2.95 mmol) in CH_2Cl_2 (20 mL) over 15 min. The resulting mixture was stirred at −10 °C for 7 h, diluted with ether, and washed, sequentially, with HCl (4.5 mL, 1 M), water, sodium bisulfite solution, and brine. The ether solution was dried over $MgSO_4$, filtered, and concentrated. The residue was then purified by flash chromatography (eluting with 20% EtOAc in hexanes) to give 1.90 g of **23** as a viscous oil (80%). ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 9H), 3.35 (s, 3H), 3.48 (s, 3H), 3.49 (m, 2H), 3.68 (m, 2H), 3.84 (s, 2H), 4.81 (s, 2H), 4.95 (s, 2H), 4.97 (s, 1H), 5.11 (s, 2H), 6.52 (d, J = 3 Hz, 1H), 6.64 (s, 1H), 7.13 (d, J = 3 Hz, 1H), 7.35 −7.42 (m, 12H), 7.69 (m, 4H); IR (KBr) ν 3507 (w), 3009 (m), 2931 (m), 1482 (s), 1106 (s), 1008 (s), 702 (m) cm^{-1}; MS (ion spray) m/z 819 (MH)$^+$.

Also prepared using essentially the same procedure:

5-(Benzyloxy)-3-(2-(benzyloxy)-5-hydroxy-4-iodobenzyl)-2-methoxybenzyloxy)-*tert*-butyldiphenylsilane (60). Purified by flash chromatography (10% ethyl acetate in hexanes): 608 mg of **59** gave 632 mg of **60** (89%).^{1}H NMR ($CDCl_3$) δ 1.11 (s, 9H), 3.39 (s, 3H), 3.89 (s, 2H), 4.80 (s, 2H), 4.89 (s, 2H), 4.93 (s, 2H), 6.55 (d, J = 3 Hz, 1H), 6.67 (s, 1H), 7.13 (s, 1H), 7.14 (d, J = 3 Hz, 1H), 7.2−7.45 (m, 16H), 7.67 (m, 4H); MS (CI) m/z 820 (MH)$^+$.

Benzoic Acid 3-(5-(Benzyloxy)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-methoxybenzyl)-4-methoxy-5-iodophenyl Ester (18). To a suspension of NaH (1.89 g, 60% dispersion in mineral oil, 47 mmol) in THF (50 mL), cooled to −15 °C, was added a solution comprised of **22** (37.7 g, 45 mmol) and iodomethane (7.1 mL, 114 mmol) in DMPU/THF (1:7, 100 mL). The resulting solution was allowed to warm to room temperature and stirred for 2.5 h. The reaction was quenched with HCl (2 mL, 2 M) and then diluted with ether. The ether solution was washed, sequentially, with water (3×) and brine, dried over $MgSO_4$, filtered, and concentrated and the residue purified by flash chromatography (30% Et_2O in hexanes) to give 35.4 g of **18** as a colorless oil (92%): ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 9H), 3.48 (s, 3H), 3.70 (s, 3H), 4.02 (s, 2H), 4.81 (s, 2H), 4.99 (s, 2H), 6.58 (d, J = 3 Hz, 1H), 6.85 (d, J = 2.8 Hz, 1H), 7.14 (d, J = 3 Hz, 1H), 7.24−7.40 (m, 12H), 7.52 (t, J = 7.5 Hz, 2H), 7.63 (t, J = 7.5 Hz, 1H), 7.68 (d, J = 6 Hz, 4H), 8.14 (d, J = 7.5 Hz, 2H); IR (KBr) ν 3055 (w), 2950 (m), 2929 (m), 2855 (m), 1735 (s), 1593 (m), 1463 (s), 1426 (s), 1259 (s), 1206 (s), 1110 (s), 1077 (m), 1059 (s), 1001 (m) cm^{-1}; MS (FAB nitrobenzyl alcohol) m/z 849 (MH)$^+$, 848 (M)$^+$.

The following compounds were prepared using essentially the same procedure:

Benzoic Acid 3-(5-(Benzyloxy)-3-(5-(benzoyloxy)-3-(5-(benzyloxy)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-methoxybenzyl)-2-methoxybenzyl)-2-methoxybenzyl)-4-methoxy-5-iodophenyl Ester (34). Purified by flash chromatography (10% EtOAc/10% CH_2Cl_2 in hexanes): 17.9 g of **33** gave 16.6 g of **34.** ^{1}H NMR ($CDCl_3$) δ 1.09 (s, 9H), 3.48 (s, 3H), 3.60 (s, 3H), 3.65 (s, 3H), 3.70 (s, 3H), 4.0 (s, 2H), 4.07 (s, 2H), 4.08 (s, 2H), 4.81 (s, 2H), 4.90 (s, 2H), 4.96 (s, 2H), 6.51 (d, J = 3.0 Hz, 1H), 6.60 (d, J = 3.0 Hz, 1H), 6.63 (d, J = 3.0 Hz, 1H), 6.74 (d, J = 3.0 Hz, 1H), 6.77 (d, J = 3.0 Hz, 1H), 6.90 (d, J = 3.0 Hz, 1H), 7.12 (d, J = 3.0 Hz, 1H), 7.16−7.4 (m, 16H), 7.4−7.5 (m, 4H), 7.52 (d, J = 3.0 Hz, 1H), 7.60 (m, 2H), 7.69 (m, 4H), 8.13 (m, 4H); IR (KBr) ν 3055 (w), 3021 (w), 2929 (m), 2847 (m), 2824 (w), 1740 (s), 1593 (m), 1465 (s), 1428 (m), 1261 (s), 1247 (s), 1212 (s), 1169 (m), 1060 (s), 1002 (m) cm^{-1}; MS (FAB nitrobenzyl alcohol) m/z 1314 (M)$^+$.

Compound 40. Purified by flash chromatography (10% EtOAc/30% CH_2Cl_2 in hexanes): 1.45 g of **39** gave 1.34 g of **40**. ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 9H), 3.47 (s, 3H), 3.58 (bs, 9H), 3.64 (bs, 9H), 3.68 (s, 3H), 4.01 (s, 2H), 4.05 (s, 12H), 4.81 (s, 2H), 4.86 (bs, 4H), 4.88 (s, 2H), 4.96 (s, 2H), 6.51 (d, J = 3.0 Hz, 1H), 6.57 (bs, 4H), 6.60 (d, J = 2.7 Hz, 1H), 6.63 (d, J = 3.0 Hz, 1H), 6.73 (d, J = 3.0 Hz, 1H), 6.78 (bs, 5H), 6.91 (d, J = 2.7 Hz, 1H), 7.13 (d, J = 3.0 Hz, 1H), 7.15−7.50 (m, 34H), 7.52 (d, J = 3.0 Hz, 1H), 7.53−7.60 (m, 4H), 7.65−7.71 (m, 4H), 8.05−8.15 (m, 8H); IR (KBr) ν 3082 (w), 3054 (w), 3024 (w), 2930 (m), 2863 (m), 2820 (w), 1737 (s), 1599 (s), 1470 (s), 1452 (m), 1428 (m), 1314 (w), 1262 (s), 1215 (s), 1172 (m), 1138 (m), 1080 (s), 1062 (s), 1025 (m), 1007 (m) cm^{-1}; MS (FAB nitrobenzyl alcohol) m/z 2284 (MH)$^+$.

3-Iodo-4-methoxy-5-(2-methoxy-4-(methoxycarbonyl)-3-(2-methoxy-4-(methoxycarbonyl)-3-(3-(methoxycarbonyl)-5-methylbenzyl)benzyl)benzyl)benzoic Acid Methyl Ester (57). Purified by flash chromatography (20% EtOAc in hexanes): 402 mg of **56** gave 388 mg of **57** (95%). ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H), 3.65 (s, 3H), 3.66 (s, 3H), 3.67 (s, 3H), 3.76 (s, 3H), 3.79 (s, 3H), 3.80 (s, 3H), 3.84 (s, 6H), 4.09 (s, 2H), 4.13 (bs, 4H), 7.63 (bs, 4H), 7.66 (d, J = 2 Hz, 1H), 7.72 (d, J = 2 Hz, 1H), 7.79 (d, J = 2 Hz, 1H), 8.36 (d, J = 2 Hz, 1H); IR (KBr) ν 3028 (w), 3011 (w), 2952 (w), 1716 (s), 1603 (w), 1438 (m), 1310 (s), 1287 (s), 1231 (m), 1205 (s), 1165 (m), 1006 (s) cm^{-1}; MS (FAB nitrobenzyl alcohol) m/z 841 (MH)$^+$.

Benzoic Acid 3-(5-(Benzyloxy)-3-(hydroxymethyl)-2-methoxybenzyl)-4-((2-methoxyethoxy)methoxy)phenyl Ester (16). To a solution of **1** (92.7 g, 116 mmol) in THF (150 mL) was added acetic acid (10.0 mL, 175 mmol) followed by Bu_4NF (162 mL, 1 M in THF). The resulting solution was stirred for 1 h, diluted with ether, washed with water and then brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (60% EtOAc in hexanes) to give 61.98 g of product as an oil which solidified on standing (95%), mp 57−58 °C. ^{1}H NMR ($CDCl_3$) δ 2.1 (bs, 1H), 3.34 (s, 3H), 3.49 (m, 2H), 3.68 (m, 2H), 3.72 (s, 3H), 4.0 (s, 2H), 4.7 (s, 2H), 4.95 (s, 2H), 5.23 (s, 2H), 6.64 (d, J = 3 Hz, 1H), 6.87 (d, J = 3 Hz, 1H), 6.89 (d, J = 2.8 Hz, 1H), 7.02 (dd, J = 8.8, 2.8 Hz, 1H), 7.16 (d, J = 8.8 Hz, 1H), 7.2−7.4 (m, 5H), 7.5 (t, J = 7.6 Hz, 2H), 7.61 (m, 1H), 8.15 (m, 2H); IR (KBr) ν 3432 (bs), 3051 (m), 3019 (m), 2925 (s), 2886 (s), 2828 (s), 1730 (s), 1574 (m), 1466 (s), 1364 (m), 1302 (s), 1231 (s), 1168 (s) cm^{-1}; MS (FAB nitrobenzyl alcohol), m/z 558 (M)$^+$. Anal. $C_{33}H_{34}O_8$ requires C 70.9, H 6.1. Found C 70.6, H 6.1.

The following compounds were prepared using essentially the same procedure:

Benzoic Acid 3-(5-(Benzyloxy)-3-(5-(benzoyloxy)-3-(5-(benzyloxy)-3-(hydroxymethyl)-2-methoxybenzyl)-2-methoxybenzyl)-2-methoxybenzyl)-4-((2-methoxyethoxy)-methoxy)phenyl Ester (30). Purified by flash chromatography (50% EtOAc in hexanes): 16.8 g of **29** gave 11.29 g of **30** (83%). ^{1}H NMR ($CDCl_3$) δ 1.6 (bs, 1H), 3.33 (s, 3H), 3.48 (m, 2H), 3.61 (s, 3H), 3.66 (s, 3H), 3.67 (m, 2H), 3.70 (s, 3H), 4.01 (s, 2H), 4.05 (s, 2H), 4.07 (s, 2H), 4.70 (s, 2H), 4.86 (s, 2H), 4.96 (s, 2H), 5.22 (s, 2H), 6.54 (d, J = 3.0 Hz, 1H), 6.56 (d, J = 3.0 Hz, 1H), 6.68 (d, J = 3.0 Hz, 1H), 6.75 (d, J = 3.0 Hz, 1H), 6.79 (d, J = 3.0 Hz, 1H), 6.92 (d, J = 3.0 Hz, 1H), 7.03 (dd, J = 7.9, 3.0 Hz, 1H), 7.18 (d, J = 7.9 Hz, 1H), 7.2−7.4 (m, 10H), 7.47 (m, 4H), 7.60 (m, 2H), 8.13 (m, 4H); IR (KBr) ν 3443 (bm), 3056 (w), 3021 (w), 2932 (m), 2876 (m), 2817 (m), 1734 (s), 1600 (m), 1496 (m), 1472 (s), 1452 (s), 1430 (m), 1314 (w), 1262 (s), 1207 (s), 1173 (m), 1080 (s), 1062 (s), 1025 (s), 1004 (s) cm^{-1}; MS (FAB nitrobenzyl alcohol) m/z 1024 $(M)^+$.

Compound 36. Purified by flash chromatography (40% EtOAc/30% CH_2Cl_2 in hexanes): 2.0 g of **35** gave 1.66 g of **36** as a white solid, mp 153−155 °C (93%). ^{1}H NMR ($CDCl_3$) δ 3.33 (s, 3H), 3.46 (m, 2H), 3.58 (bs, 9H), 3.63 (bs, 9H), 3.66 (m, 2H), 3.67 (s, 3H), 4.00 (s, 2H), 4.04 (s, 2H), 4.05 (s, 10H), 4.71 (s, 2H), 4.86 (bs, 6H), 4.96 (s, 2H), 5.22 (s, 2H), 6.54 (d, J = 3.0 Hz, 1H), 6.57 (bs, 5H), 6.68 (d, J = 3.0 Hz, 1H), 6.74 (d, J = 3.0 Hz, 1H), 6.80 (bs, 5H), 6.88 (d, J = 2.8 Hz, 1H), 6.91 (d, J = 3.0 Hz, 1H), 7.03 (dd, J = 8.8, 3.0 Hz, 1H), 7.18 (d, J = 8.8 Hz, 1H), 7.18−7.50 (m, 28H), 7.51−7.62 (m, 4H), 8.06−8.18 (m, 8H); IR (KBr) ν 3436 (b), 3082 (w), 3059 (w), 3024 (w), 2936 (m), 2874 (m), 2823 (m), 1736 (s), 1590 (m), 1469 (s), 1452 (s), 1429 (m), 1315 (w), 1262 (s), 1215 (s), 1173 (s), 1137 (m), 1080 (s), 1062 (s), 1025 (m), 1006 (m) cm^{-1}; MS (FAB nitrobenzyl alcohol) m/z 1959 $(MH)^+$.

Compound 43. Purified by flash chromatography (30% EtOAc/30% CH_2Cl_2 in hexanes): 1.5 g of **42** gave 1.22 g of **43** as a white solid, mp 78−80 °C (91%). ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9H), 1.41 (s, 18H), 1.45 (s, 9H), 1.7 (bs, 1H), 3.34 (s, 3H), 3.50 (m, 2H), 3.57 (bs, 9H), 3.65 (s, 9H), 3.70 (m, 2H), 3.71 (s, 3H), 3.96 (s, 2H), 4.01 (s, 2H), 4.02 (s, 10H), 4.30 (s, 2H), 4.31 (s, 4H), 4.40 (s, 2H), 4.71 (s, 2H), 4.81 (s, 6H), 4.94 (s, 2H), 5.16 (s, 2H), 6.46 (m, 2H), 6.49 (m, 10H), 6.62 (d, J = 3 Hz, 1H), 6.69 (m, 2H), 6.85 (d, J = 3 Hz, 1H), 7.06 (m, 1H), 7.15−7.36 (m, 20H); IR ($CHCl_3$) ν 3011 (w), 2935 (w), 1749 (s), 1594 (w), 1474 (s), 1370 (m), 1230 (s), 1213 (s), 1147 (s), 1082 (m), 1009 (m) cm^{-1}; MS (ion spray) m/z 1999 $(MH)^+$. Anal. $C_{119}H_{136}O_{27}$ requires C 71.5, H 6.9. Found C 71.6, H 7.0.

2-((2-Methoxyethoxy)methoxy)-5-((5-(benzyloxy)-3-(5-(benzyloxy)-3-(hydroxymethyl)-2-methoxybenzyl)-2-((((*tert*-butyloxycarbonyl)methyl)oxy)phenyl)ethyl)-benzoic Acid Methyl Ester (64). Purified by flash chromatography (40% EtOAc/20% CH_2Cl_2 in hexanes): 500 mg of **63** gave 365 mg of **64** (93%). ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H), 2.23 (t, J = 7 Hz, 1H), 2.90 (m, 4H), 3.37 (s, 3H), 3.52 (m, 2H), 3.62 (s, 3H), 3.87 (m, 2H), 3.87 (s, 3H), 3.93 (s, 2H), 4.48 (s, 2H), 4.68 (d, J = 7 Hz, 2H), 4.90 (s, 2H), 4.91 (s, 2H), 5.30 (s, 2H), 6.51 (s, 1H), 6.57 (d, J = 3 Hz, 1H), 6.69 (s, 1H), 6.86 (d, J = 3 Hz, 1H), 7.15 (d, J = 8 Hz, 1H), 7.20−7.40 (m, 11H), 7.64 (d, J = 2 Hz, 1H); MS (ion spray) m/z 854 $(MNH_4)^+$.

Benzoic Acid 3-(5-(Benzyloxy)-3-(bromomethyl)-2-methoxybenzyl)-4-((2-methoxyethoxy)methoxy)phenyl Ester (27). To a solution of benzylic alcohol **16** (27.85 g, 50 mmol) in THF (250 mL), cooled to 10 °C, was added Ph_3P (14.41 g, 55 mmol) followed by NBS (9.61 g, 54 mmol). On complete addition, the reaction mixture was allowed to warm to room temperature, stirred for 20 min, and then concentrated under reduced pressure. The residue was purified by flash chromatography (40% EtOAc in hexanes) to give 30.12 g of **27** as a colorless oil, which solidified on standing (97%), mp 73−74 °C. ^{1}H NMR ($CDCl_3$) δ 3.38 (s, 3H), 3.46 (m, 2H), 3.66 (m, 2H), 3.80 (s, 3H), 3.98 (s, 2H), 4.54 (s, 2H), 4.92 (s, 2H), 5.22 (s, 2H), 6.62 (d, J = 3 Hz, 1H), 6.83 (d, J = 3 Hz, 1H), 6.90 (d, J = 3 Hz, 1H), 7.03 (dd, J = 8.7, 3 Hz, 1H), 7.18 (d, J = 8.7 Hz, 1H), 7.25−7.4 (m, 5H), 7.49 (t, J = 8.5 Hz, 2H), 7.61 (t, J = 8.5 Hz, 1H), 8.17 (d, J = 8.5 Hz, 2H); IR (KBr) ν 3041 (w), 2931 (m), 2876 (m), 2822 (w), 1733 (s), 1489 (m), 1456 (m), 1264 (s), 1198 (s), 1150 (m), 1061 (s) cm^{-1}; MS (FAB nitrobenzyl alcohol) m/z 622, 620 $(M)^+$.

The following compounds were prepared using essentially the same procedure:

Benzoic Acid 3-(5-(Benzyloxy)-3-(5-(benzoyloxy)-3-(5-(benzyloxy)-3-(bromomethyl)-2-methoxybenzyl)-2-methoxybenzyl)-4-((2-methoxyethoxy)-methoxy)phenyl Ester (31). Purified by flash chromatography (20% EtOAc/10% CH_2Cl_2 in hexanes): 11.29 g of **30** gave 11.48 g of **31** (96%). ^{1}H NMR ($CDCl_3$) δ 3.33 (s, 3H), 3.49 (m, 2H), 3.60 (s, 3H), 3.67 (s, 3H), 3.70 (m, 2H), 3.80 (s, 3H), 4.01 (s, 2H), 4.05 (s, 2H), 4.08 (s, 2H), 4.55 (s, 2H), 4.86 (s, 2H), 4.95 (s, 2H), 5.23 (s, 2H), 6.55 (d, J = 2.8 Hz, 1H), 6.56 (d, J = 2.8 Hz, 1H), 6.69 (d, J = 2.7 Hz, 1H), 6.75 (d, J = 2.7 Hz, 1H), 6.80 (d, J = 2.8 Hz, 1H), 6.88 (d, J = 2.7 Hz, 1H), 6.92 (d, J = 2.7 Hz, 1H), 7.02 (dd, J = 8.7, 2.7 Hz, 1H), 7.19 (d, J = 8.7 Hz, 1H), 7.2−7.38 (m, 10H), 7.42−7.51 (m, 4H), 7.57−7.64 (m, 2H), 8.1−8.2 (m, 4H); MS (FAB nitrobenzyl alcohol) m/z 1088, 1086 $(M)^+$.

Compound 37. Purified by flash chromatography (30% EtOAc/30% CH_2Cl_2 in hexanes): 1.8 g of **36** gave 1.66 g of **37** as a white solid, mp 151−152 °C (89%). ^{1}H NMR ($CDCl_3$) δ 3.31 (s, 3H), 3.46 (m, 2H), 3.56 (bs, 9H), 3.64 (bs, 9H), 3.68 (m, 2H), 3.80 (s, 3H), 4.00 (s, 2H), 4.05 (s, 2H), 4.06 (bs, 10H), 4.54 (s, 2H), 4.85 (bs, 6H), 4.93 (s, 2H), 5.23 (s, 2H), 6.54 (d, J = 2.9 Hz, 1H), 6.57 (bs, 5H), 6.68 (d, J = 2.7 Hz, 1H), 6.74 (d, J = 2.7 Hz, 1H), 6.75 (bs, 5H), 6.87 (d, J = 2.7 Hz, 1H), 6.91 (d, J = 2.7 Hz, 1H), 7.01 (dd, J = 8.8, 2.7 Hz, 1H), 7.16 (d, J = 8.8 Hz, 1H), 7.18−7.38 (m, 20H), 7.38−7.5 (m, 8H), 7.5−7.62 (m, 4H), 8.07−8.18 (m, 8H); IR (KBr) ν 3051 (w), 3024 (w), 2929 (m), 2867 (m), 2823 (m), 1742 (s), 1593 (m), 1465 (s), 1452 (m), 1425 (m), 1314 (w), 1264 (s), 1233 (s), 1213 (s), 165 (m), 1136 (m), 1061 (s), 1036 (m), 1025 (m), 1003 (m) cm^{-1}; MS (FAB nitrobenzyl alcohol) m/z 2022, 2020 $(M)^+$.

2-((2-Methoxyethoxy)methoxy)-5-((5-(benzyloxy)-3-(5-(benzyloxy)-3-(bromomethyl)-2-methoxybenzyl)-2-((((*tert*-butyloxycarbonyl)methyl)oxy)phenyl)ethyl)benzoic Acid Methyl Ester (65). Purified by flash chromatography (30% EtOAc/20% CH_2Cl_2 in hexanes): 360 mg of **64** gave 343 mg of **65** (89%). ^{1}H NMR (C_6D_6) δ 1.28 (s, 9H), 2.94 (m, 2H), 3.00 (m, 2H), 3.02 (s, 3H), 3.23 (m, 2H), 3.50 (s, 3H), 3.54 (s, 3H), 3.66 (m, 2H), 4.05 (s, 2H), 4.16 (s, 2H), 4.30 (s, 2H), 4.57 (s, 2H), 4.61 (s, 2H), 5.03 (s, 2H), 6.53 (s, 1H), 6.56 (s, 1H), 6.75 (d, J = 3 Hz, 1H) 7.0−7.22 (m, 12H), 7.83 (d, J = 2.1 Hz, 1H); IR ($CHCl_3$) ν 3011 (m), 2983 (w), 2948 (w), 2932 (w), 1749 (s), 1718 (s), 1600 (w), 1505 (s), 1499 (s), 1477 (m), 1465 (m), 1437 (m), 1232 (s), 1203 (s), 1154 (s), 1077 (s), 1002 (s) cm^{-1}; MS (ion spray) m/z 916, 918 $(MNH_4)^+$ Br pattern.

Benzoic Acid 3-(5-(Benzyloxy)-3-(5-(benzoyloxy)-3-(5-(benzyloxy)-3-methyl-2-methoxybenzyl)-2-methoxybenzyl)-2-methoxybenzyl)-4-((2-methoxyethoxy)methoxy)-phenyl Ester (50). To a suspension of zinc dust (3.6 g, 55 mmol, 325 mesh) in THF (10 mL) was added 1,2-dibromoethane (112 μL, 1.3 mmol). The resulting mixture was heated to reflux and then stirred vigorously for 1.5 min. Upon cooling to room temperature, a solution comprised of **31** (3.3 g, 3 mmol) and acetic acid (1.2 mL, 19.5 mmol) in DMF (15 mL) was added. This mixture was stirred for 17 h, diluted with EtOAc, and filtered to remove excess zinc. The filtrate was washed with water and brine, dried over $MgSO_4$, filtered, and then concentrated. The residue was purified by flash chromatography (30% EtOAc/20% CH_2Cl_2 in hexanes) to give 2.61 g of **50** (86%) as a viscous oil. ^{1}H NMR ($CDCl_3$) δ 2.27 (s, 3H), 3.33 (s, 3H), 3.47 (m, 2H), 3.61 (s, 3H), 3.63 (s, 3H), 3.67 (s, 3H), 3.69 (m, 2H), 4.01 (s, 2H), 4.04 (s, 2H), 4.08 (s, 2H), 4.86 (s, 2H), 4.93 (s, 2H), 5.22 (s, 2H), 6.55 (m, 3H), 6.66 (d, J = 2.9 Hz, 1H), 6.75 (d, J = 2.9 Hz, 1H), 6.78 (d, J = 2.9 Hz, 1H), 6.92 (d, J = 2.9 Hz, 1H), 7.17 (dd, J = 8.8, 2.9 Hz, 1H), 7.25 (d, J = 8.8 Hz, 1H), 7.25−7.40 (m, 10H), 7.40−7.51 (m, 4H), 7.54−7.63 (m, 2H), 8.05−8.18 (m, 4H); IR (KBr) ν 3063 (w), 3035 (w), 2935 (m), 2830 (w), 1731 (s), 1598 (m), 1494 (s), 1452 (s), 1250 (s), 1209 (s), 1059 (s) cm^{-1}; MS (FAB nitrobenzyl alcohol) m/z 1008, $(M)^+$. Anal. $C_{63}H_{60}O_{12}$ requires C 75.0, H 5.6. Found C 74.7, H 5.8.

The following compounds were prepared using essentially the same procedure:

Compound 46. Purified by flash chromatography (15% EtOAc/30% CH_2Cl_2 in hexanes): 500 mg of **37** gave 464 mg of **46** as a white solid, mp 154−155 °C (86%). ^{1}H NMR ($CDCl_3$) δ 2.27 (s, 3H), 3.33 (s, 3H), 3.47 (m, 2H), 3.59 (s, 3H), 3.60 (s, 3H), 3.61 (s, 3H), 3.63 (s, 3H), 3.65 (s, 3H), 3.69 (m, 2H), 4.01 (s, 2H), 4.04 (s, 2H), 4.08 (s, 10H), 4.86 (s, 6H), 4.93 (s, 2H), 5.22 (s, 2H), 6.55 (m, 7H), 6.66 (d, J = 2.9 Hz, 1H), 6.75 (d, J = 2.9 Hz, 1H), 6.78 (m, 6H), 6.92 (d, J = 2.9 Hz, 1H), 7.02 (dd, J = 9, 2.8 Hz, 1H), 7.12−7.38 (m, 21H), 7.38−7.5 (m, 8H), 7.58 (m, 4H), 8.05−8.18 (m, 8H); IR (KBr) ν 3054 (w), 2928 (w), 1741 (s), 1593 (m), 1466 (s), 1314 (w), 1263 (s), 1214 (s), 1061 (s) cm^{-1}; MS (ion spray) m/z 1943 $(MH)^+$. Anal. $C_{123}H_{112}O_{22}$ requires C 76.1, H 5.8. Found C 75.9, H 6.0.

Compound 53. To a solution of **50** (1.91 g 1.89 mmol) dissolved in DMF:MeOH (1:1, 10 mL) was added 10% palladium on carbon (400 mg). The resulting suspension was stirred under a hydrogen atmosphere for 18 h. The catalyst was then filtered and the filtrate concentrated. The residue was dissolved in THF:MeOH (1:1, 10 mL) and cooled to −10 °C and sodium methoxide (2.1 mL, 25 wt % in methanol, 10 mmol) added. The resulting solution was stirred for 40 min and then quenched with HCl (10 mL, 1 M). The product was extracted with EtOAc/CH_2Cl_2, washed with brine (3×), dried over $MgSO_4$, and concentrated. The residue was further dried by toluene azeotrope and then added to a solution comprised of *N*-phenyltriflimide (3.46 g, 9.7 mmol) and DMPU (1 mL) in THF (5 mL). This solution was then added to a slurry of NaH (400 mg, 60% dispersion in mineral oil, 10 mmol) in THF (3 mL) which had been cooled to 0 °C. The resulting mixture was allowed to come to room temperature and stirred for 1 h. The reaction mixture was then concentrated and the residue purified by flash chromatography (eluting with 30% CH_2Cl_2/5% EtOAc in hexanes) to give 1.907 g of **53** as a viscous oil (88%). ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H), 3.35 (s, 3H), 3.51 (m, 2H), 3.65 (s, 3H), 3.66 (bs, 6H), 3.68 (m, 2H), 4.01 (s, 2H), 4.04 (s, 2H), 4.09 (s, 2H), 5.27 (s, 2H), 6.78 (d, J = 3 Hz, 1H), 6.81 (d, J = 3 Hz, 1H), 6.84 (bs, 3H), 6.99 (d, J = 3 Hz, 1H), 7.01 (d, J = 3 Hz, 1H), 7.12 (dd, J = 9, 3 Hz, 1H), 7.23 (d, J = 9 Hz, 1H); IR (KBr) ν 2946 (w), 2937 (w), 2837 (w), 1591 (w), 1471 (m), 1422 (s), 1212 (s), 1140 (s), 842 (m) cm^{-1}; MS (ion spray) m/z 1149 $(MH)^+$.

By using essentially the same procedure for sulfonylation, there were prepared the following compounds:

3-(5-(Benzyloxy)-3-((*tert*-butyldiphenylsiloxy)methyl)-2-methoxybenzyl)-4-((2-methoxyethoxy)methoxy)phenyl Trifluoromethane Sulfonate (20). Purified by flash chromatography (eluting with 5% EtOAc/CH_2Cl_2 in hexanes): 825 mg of **15** gave 900 mg of **20** (92%). ^{1}H NMR ($CDCl_3$) δ 1.09 (s, 9H), 3.32 (s, 3H), 3.46 (m, 2H), 3.48 (s, 3H), 3.67 (m, 2H), 3.92 (s, 2H), 4.80 (s, 2H), 4.95 (s, 2H), 5.22 (s, 2H), 6.51 (d, J = 3 Hz, 1H), 6.93 (d, J = 3 Hz, 1H), 7.05 (dd, J = 9, 3 Hz, 1H), 7.13 (d, J = 3 Hz, 1H), 7.14 (d, J = 9 Hz, 1H), 7.2−7.45 (m, 11H), 7.7 (m, 4H); IR (KBr) ν 3011 (w), 2981 (w), 2892 (w), 2859 (w), 1600 (w), 1492 (m), 1426 (m), 1221 (s), 1213 (s), 1141 (s), 1112 (m), 1002 (m), 851 (m), 701 (m) cm^{-1}; MS (ion spray) m/z 825 $(MH)^+$. Anal. $C_{43}H_{48}O_9SSiF_3$ requires C 62.5, H 5.9. Found C 62.4, H 5.7.

4-((2-Methoxyethoxy)methoxy)-3-(2-methoxy-4-(methoxycarbonyl)-3-(2-methoxy-4-(methoxycarbonyl)-3-(3-(methoxycarbonyl)-5-methylbenzyl)benzyl)benzyl)benzoic Acid Methyl Ester (54). To a solution of **53** (850 mg, 0.74 mmol) in DMSO (2 mL) was added MeOH (1.5 mL) followed by 1,3-bis(diphenylphosphino)propane (80 mg, 0.193 mmol) and $Pd(OAc)_2$ (41 mg, 0.185 mmol). The resulting solution was flushed with carbon monoxide and then Et_3N (1.0 mL, 7.25 mmol) added. The resulting solution was heated to 75 °C and stirred at this temperature for 3 h. The reaction mixture was then cooled to room temperature, diluted with EtOAc, and then washed with water and brine. The organic fraction was dried over $MgSO_4$, filtered, and then concentrated. The residue was purified by flash chromatography (eluting with 30% EtOAc/20% CH_2Cl_2 in hexanes) to give 429 mg of **54** as a viscous oil (74%). ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H), 3.31 (s, 3H), 3.42 (m, 2H), 3.61 (m, 2H), 3.64 (s, 3H), 3.66 (s, 3H), 3.67 (s, 3H), 3.76 (s, 3H), 3.77 (s, 3H), 3.82 (s, 3H), 3.83 (s, 3H), 4.04 (s, 2H), 4.07 (s, 2H), 4.10 (s, 2H), 5.30 (s, 2H), 7.15 (d, J = 9 Hz, 1H), 7.60 (m, 4H), 7.61 (d, J = 3 Hz, 1H), 7.76 (d, J = 2.1 Hz, 1H), 7.79 (d, J = 2.2 Hz, 1H), 7.89 (dd, J = 9, 2.2Hz 1H); IR (KBr) ν 2988 (w), 2949 (w), 2833 (w), 1716 (s), 1603 (w), 1434 (m), 1307 (s), 1267 (m), 1236 (m), 1203 (s), 1163 (s), 1003 (s) cm^{-1}; MS (FAB nitrobenzyl alcohol) m/z 789 $(MH)^+$. Anal. $C_{43}H_{48}O_{14}$ requires C 65.5, H 6.1. Found C 65.5, H 6.3.

3-Iodo-4-hydroxy-5-(2-methoxy-4-(methoxycarbonyl)-3-(2-methoxy-4-(methoxycarbonyl)-3-(3-(methoxycarbonyl)-5-methylbenzyl)benzyl)benzyl)benzoic Acid Methyl Ester (56). To a solution of **54** (470 mg, 0.596 mmol) in MeOH (3 mL) was added 1 drop of concd sulfuric acid. The resulting solution was heated to 60 °C and stirred at this temperature for 2 h. The reaction mixture was diluted with EtOAc, washed with water and then brine, dried over $MgSO_4$, and concentrated. The residue was taken up in CH_2Cl_2 (2.0 mL) and cooled to 10 °C. To this solution was added morpholine (120 μL, 1.4 mmol) followed by iodine (150 mg, 0.59 mmol). The cold bath was removed and stirring continued for 3 h, HCl (1.0 mL, 1 M) was added, and the resulting mixture was diluted with EtOAc, washed with water and then brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (eluting with 30% EtOAc/10% CH_2Cl_2 in hexanes to give 411 mg of **56** (84% based on **54**). ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3H), 3.65 (s, 3H), 3.66 (s, 3H), 3.79 (s, 3H), 3.81 (s, 6H), 3.84 (s, 3H), 3.87 (s, 3H), 4.04 (s, 2H), 4.08 (s, 2H), 4.13 (s, 2H), 7.52 (s, 1H), 7.62 (m, 3H), 7.65 (d, J = 2 Hz, 1H), 7.78 (bs, 2H), 7.89 (d, J = 2 Hz, 1H), 8.28 (d, J = 2 Hz, 1H); IR ($CHCl_3$) ν 3250 (bw), 3026 (w), 3013 (w), 2952 (w), 1716 (s), 1603 (w), 1436 (m), 1303 (bs), 1234 (m), 1206 (s), 1007 (m) cm^{-1}; MS (FAB nitrobenzyl alcohol) m/z 827 $(MH)^+$.

5-(Benzyloxy)-2-methoxy-3-(2-((2-methoxyethoxy)-methoxy)-5-(benzoyloxy)benzyl)benzaldehyde (24). To a solution of $(COCl)_2$ in CH_2Cl_2 (2.7 mL, 2 M, 5.4 mmol) cooled to −78 °C was added, dropwise, DMSO (0.5 mL, 7.05 mmol). The resulting mixture was stirred for 5 min and then a solution of **16** (1.49 g, 2.67 mmol) in CH_2Cl_2 (4.0 mL) added dropwise. This solution was stirred for 5 min and then Et_3N (2.5 mL, 18 mmol) added. The cold bath was removed and stirring continued for 20 min. The reaction mixture was then diluted with ether, washed with water and then brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (eluting with 30% EtOAc/10% CH_2Cl_2 in hexanes) to give 1.36 g of **24** as a white solid (91%), mp 70−71.5 °C. ^{1}H NMR ($CDCl_3$) δ 3.35 (s, 3H), 3.48 (m, 2H), 3.70 (m, 2H), 3.86 (s, 3H), 5.00 (s, 2H), 5.25 (s, 2H), 6.93 (d, J = 2.9 Hz, 1H), 7.00 (d, J = 2.9 Hz, 1H), 7.04 (dd, J = 8.8, 2.9 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 7.25 (d, J = 2.9 Hz, 1H), 7.4 (m, 5H), 7.5 (m, 2H), 7.62 (m, 1H), 8.18 (d, J = 7 Hz, 2H), 10.36 (s, 1H); IR (KBr) ν 3074 (w), 3035, 2925 (w), 2875 (w), 1727 (s), 1682 (s), 1599 (m), 1496 (s), 1470 (m), 1267 (s), 1206 (s), 1152 (s), 1064 (s) cm^{-1}; MS (FAB nitrobenzyl alcohol) m/z 556 $(M)^+$. Anal. $C_{33}H_{32}O_8$ requires C 71.2, H 5.7. Found C 71.2, H 5.7.

By using essentially the same procedure there were prepared the following compounds:

Compound 44. 399 mg of **43** gave 372 mg of **44** (92%) used without purification. ^{1}H NMR (C_6D_6) δ 1.22 (s, 9H), 1.25 (s, 18H), 1.27 (s, 9H), 3.04 (s, 3H), 3.26 (m, 2H), 3.33 (s, 3H), 3.35 (s, 3H), 3.45 (bs, 6H), 3.50 (s, 3H), 3.51 (s, 3H), 3.52 (s, 3H), 3.58 (m, 2H), 3.94 (s, 2H), 4.11 (s, 4H), 4.15 (bs, 12H), 4.20 (s, 2H), 4.30 (s, 2H), 4.58 (s, 2H), 4.69 (bs, 6H), 4.95 (s, 2H), 6.65 (d, J = 3 Hz, 1H), 6.69 (dd, J = 9, 3 Hz, 1H), 6.75 (m, 12H), 6.90 (d, J = 3 Hz, 1H), 7.0−7.2 (m, 21H), 7.47 (d, J = 3 Hz, 1H), 10.4 (s, 1H); IR (KBr) ν 2976 (m), 2933 (m), 1750 (s), 1728 (m), 1685 (m), 1599 (m), 1473 (s), 1432 (m), 1308 (bm), 1218 (s), 1145 (s), 1080 (s) cm^{-1}; MS (ion spray) m/z 1997 $(MH)^+$.

5-(Benzyloxy)-2-methoxy-3-(2-((2-methoxyethoxy)-methoxy)-5-(benzoyloxy)benzyl)benzoic Acid (25). To a suspension of **24** (1.22 g, 2.19 mmol) in *tert*-butyl alcohol (22 mL) was added 2-methylbut-2-ene (2.2 mL, 19 mmol). To this mixture was added a solution comprised of 2.16 g of $NaH_2PO_4 \cdot H_2O$ (2.16 g, 16 mmol) and 2.16 g of $NaClO_2$ (2.16 g, technical grade, 19 mmol) in water (22 mL). This solution was stirred for 15 min and then diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to give 1.25 g of **25** as a viscous oil (99%). ^{1}H NMR ($CDCl_3$) δ

3.35 (s, 3H), 3.49 (m, 2H), 3.67 (m, 2H), 3.90 (s, 3H), 4.03 (s, 2H), 5.01 (s, 2H), 5.24 (s, 2H), 6.92 (d, J = 2.7 Hz, 1H), 6.93 (d, J = 2.9 Hz, 1H), 7.07 (dd, J = 8.9, 2.7 Hz, 1H), 7.24 (d, J = 8.9 Hz, 1H), 7.3−7.4 (m, 5H), 7.50 (m, 2H), 7.56 (d, J = 2.9 Hz, 1H), 7.62 (m, 1H), 8.17 (d, J = 7.2 Hz, 2H); MS (FAB nitrobenzyl alcohol) m/z 573 $(MH)^+$. Anal. $C_{33}H_{32}O_9$ requires C 69.2, H 5.6. Found C 69.5, H 5.9.

By using essentially the same procedure there were prepared the following compounds:

Compound 45. 370 mg of **44** gave 370 mg of **45** (98%). ^{1}H NMR (C_6D_6) δ 1.23 (s, 9H), 1.25 (s, 18H), 1.27 (s, 9H), 3.04 (s, 3H), 3.26 (m, 2H), 3.32 (s, 6H), 3.43 (s, 6H), 3.50 (s, 3H), 3.51 (s, 3H), 3.52 (s, 3H), 3.58 (m, 2H), 3.86 (s, 2H), 4.10 (s, 2H), 4.15 (m, 18H), 4.57 (s, 2H), 4.65 (bs, 6H), 4.93 (s, 2H), 6.60 (d, J = 3 Hz, 1H), 6.70 (dd, J = 9, 3 Hz, 1H), 6.73 (m, 12H), 6.90 (d, J = 3 Hz, 1H), 6.97 (s, J = 3 Hz, 1H), 7.0−7.2 (m, 20H), 7.75 (d, J = 3 Hz, 1H), MS (ion spray) m/z 2013 $(MH)^+$. Anal. $C_{119}H_{134}O_{28}$ requires C 71.0, H 6.7. Found C 70.6, H, 7.1.

***N*-(3-(5-(Benzoyloxy)-2-((2-methoxyethoxy)methoxy)-benzyl)-5-(benzyloxy)-2-methoxybenzoyl)-(L)-leucine Methyl Ester (26).** To a solution of **25** (570 mg, 1 mmol) in CH_2Cl_2 (3 mL), cooled to 0 °C, was added *N*-methylmorpholine (360 μL, 3.3 mmol) followed by isopropyl chloroformate (1.05 mL of a 1 M solution in CH_2Cl_2 1.05 mmol). This solution was stirred for 10 min, and then L-leucine methyl ester hydrochloride (200 mg, 1.1 mmol) was added. The resulting mixture was stirred for 20 min, diluted with ether, washed, sequentially, with water and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (eluting with 30% EtOAc/20% CH_2Cl_2 in hexanes to give 671 mg of **26** as a viscous oil (96%). ^{1}H NMR ($CDCl_3$) δ 0.89 (m, 1H), 0.97 (d, J = 5 Hz, 3H), 0.99 (d, J = 5 Hz, 3H), 1.72 (m, 2H), 3.34 (s, 3H), 3.48 (m, 2H), 3.68 (m, 2H), 3.76 (s, 3H), 3.79 (s, 3H), 4.02 (s, 2H), 4.86 (m, 1H), 5.0 (s, 2H), 5.24 (s, 2H), 6.82 (d, J = 3.0 Hz, 1H), 6.92 (d, J = 3 Hz, 1H), 7.05 (dd, J = 9, 3 Hz, 1H), 7.24 (d, J = 9 Hz, 1H), 7.25 −7.4 (m, 5H), 7.49 (m, 2H), 7.52 (d, J = 3 Hz, 1H), 7.62 (m, 1H), 8.17 (d, J = 7.7 Hz, 2H), 8.32 (bd, J = 8 Hz, 1H); IR (KBr) ν 3375 (bm), 3026 (w), 3013 (w), 2958 (w), 1738 (s), 1653 (m), 1600 (w), 1522 (m), 1497 (m), 1464 (m), 1265 (s), 1063 (s) cm^{-1}; MS (FAB nitrobenzyl alcohol), m/z 700 $(MH)^+$. Anal. $C_{40}H_{45}O_{10}N$ requires C 68.7, H 6.5, N 2.0. Found C 68.9, H 6.5, N 2.3.

(5-(Benzyloxy)-3-(5-hydroxy-2-((2-methoxyethoxy)-methoxy)benzyl)-2-methoxybenzyloxy)-*tert*-butyldiphenylsilane (15). To a solution of **1** (1.6 g, 2.0 mmol) in THF (10 mL), cooled to −40 °C, was added NaOMe (450 μL, 25 wt % in methanol, 2 mmol). The resulting solution was stirred for 25 min, and then the reaction was quenched with HCl (2.5 mL, 1 M), diluted with ether, washed with water and then brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (eluting with 40% EtOAc in hexanes) to give 1.304 g of **15** as a colorless oil (94%). ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 9H), 3.34 (s, 3H), 3.48 (m, 2H), 3.49 (s, 3H), 3.71 (m, 2H), 3.89 (s, 2H), 4.46 (s, 1H), 4.82 (s, 2H), 4.96 (s, 2H), 5.15 (s, 2H), 6.46 (d, J = 3.0 Hz, 1H), 6.57 (d, J = 2.9 Hz, 1H), 6.60 (dd, J = 8.6, 2.9 Hz, 1H), 6.99 (d, J = 8.6 Hz, 1H), 7.13 (d, J = 3 Hz, 1H), 7.3−7.45 (m, 11H), 7.70 (m, 4H); IR (KBr) ν 3958 (w), 2962 (w), 2933 (m), 1598 (w), 1498 (s), 1478 (s), 1147 (s), 1112 (s), 1087 (s), 1010 (s) cm^{-1}; MS (FAB nitrobenzyl alcohol) m/z 692 $(M)^+$. Anal. $C_{42}H_{48}O_7Si$ requires C 72.8, H 7.0. Found C 72.4, H 7.0.

Benzoic Acid 3-(3-((*tert*-Butyldiphenylsiloxy)methyl)-5-hydroxy-2-methoxybenzyl)-4-((2-methoxyethoxy)-methoxy)phenyl Ester (13). To a solution of **1** (960 mg, 1.2 mmol) in THF:MeOH (1:1, 20 mL) was added 10% palladium on carbon (100 mg). The resulting suspension was stirred under hydrogen until all the starting material was consumed (TLC analysis). The catalyst was then removed by filtration and the filtrate concentrated to give 769 mg of **13** as a foam (90%). ^{1}H NMR ($CDCl_3$) δ 1.09 (s, 9H), 3.39 (s, 3H), 3.53 (s, 3H), 3.59 (m, 2H), 3.77 (m, 2H), 3.95 (s, 2H), 4.79 (s, 2H), 5.28 (s, 2H), 5.61 (s, 1H), 6.45 (d, J = 3 Hz, 1H), 6.97 (d, J = 3 Hz, 2H), 7.03 (dd, J = 9, 3 Hz, 1H), 7.14 (d, J = 9 Hz, 1H), 7.36 (m, 6H), 7.48 (m, 2H), 7.62 (m, 1H), 7.71 (m, 4H), 8.17 (m, 2H); IR (KBr) ν 3374 (bm), 3074 (w), 2951 (m), 2931 (m), 2893 (m), 2857 (m), 1737 (s), 1599 (m), 1495 (s), 1462 (s), 1262 (s), 1203 (s), 1151 (s), 1110 (s), 1062 (s), 1005 (s) cm^{-1}; MS (FAB nitrobenzyl alcohol) m/z 706 $(M)^+$.

2-((2-Methoxyethoxy)methoxy)-5-((5-(benzyloxy)-3-(5-(benzyloxy)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-methoxybenzyl)-2-hydroxyphenyl)ethynyl)benzoic Acid Methyl Ester (61). To a mixture of $(Ph_3P)_4Pd$ (100 mg, 0.087 mmol) and CuI (12 mg, 0.06 mmol) was added a solution comprised of iodide **60** (1.5 g, 1.83 mmol) and **68** (570 mg, 2.16 mmol) in THF (6 mL). Piperidine (450 μL, 4.5 mmol) was added and the resulting mixture stirred for 3 h, diluted with EtOAc, washed, sequentially, with 1 M HCl and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (eluting with 30% EtOAc/20% CH_2Cl_2 in hexanes) to give 1.44 g of **61** as a viscous oil (82%). ^{1}H NMR ($CDCl_3$) δ 1.09 (s, 9H), 3.36 (s, 3H), 3.40 (s, 3H), 3.55 (m, 2H), 3.86 (m, 2H), 3.88 (s, 3H), 3.94 (s, 2H), 4.81 (s, 2H), 4.94 (s, 2H), 4.95 (s, 2H), 5.37 (s, 2H), 5.50 (s, 1H), 6.57 (d, J = 3 Hz, 1H), 6.68 (s, 1H), 6.94 (s, 1H), 6.93 (s, 1H), 7.14 (d, J = 3 Hz, 1H), 7.25−7.5 (m, 17H), 7.59 (dd, J = 8.8, 2.2 Hz, 1H), 7.71 (m, 4H), 7.96 (d, J = 2.2 Hz, 1H); IR ($CHCl_3$) ν 3300 (bm), 3031 (w), 3010 (m), 2952 (m), 2932 (m), 2893 (w), 1724 (s), 1604 (w), 1505 (s), 1436 (s), 1429 (s), 1301 (s), 1242 (s), 1146 (s), 1106 (s), 1075 (s) cm^{-1}; MS (ion spray) m/z 957 $(MH)^+$.

2-((2-Methoxyethoxy)methoxy)-5-((5-(benzyloxy)-3-(5-(benzyloxy)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-methoxybenzyl)-2-(((*tert*-butyloxycarbonyl)methyl)oxy)-phenyl)ethyl)benzoic Acid Methyl Ester (63). To a solution of **62** (700 mg, 0.65 mmol) in EtOAc (4.0 mL) was added 10% palladium on carbon (150 mg). The resulting mixture was stirred under a hydrogen atmosphere for 3 h, diluted with EtOAc, and filtered through Celite. The filtrate was concentrated and the residue purified by flash chromatography (eluting with 20% EtOAc/20% CH_2Cl_2 in hexanes) to give 507 mg of **63** (73%). ^{1}H NMR (C_6D_6) δ 1.29 (s, 9H), 1.39 (s, 9H), 3.05 (m, 2H), 3.10 (m, 2H), 3.11 (s, 3H), 3.32 (m, 2H), 3.36 (s, 3H), 3.65 (s, 3H), 3.78 (m, 2H), 4.20 (s, 2H), 4.25 (s, 2H), 4.75 (s, 2H), 4.94 (s, 2H), 5.17 (s, 4H), 6.65 (s, 1H), 6.71 (s, 1H), 6.97 (d, J = 3 Hz, 1H), 7.1−7.35 (m, 18H), 7.53 (d, J = 3 Hz, 1H), 7.90 (m, 4H), 7.97 (d, J = 2 Hz, 1H); IR ($CHCl_3$) ν 3011 (w), 2931 (w), 1749 (s), 1733 (s), 1605 (w), 1498 (s), 1234 (s), 1202 (s), 1112 (s), 1078 (s) cm^{-1}; MS (ion spray) m/z 1075 $(M)^+$. Anal. $C_{65}H_{74}O_{12}Si$ requires C 72.6, H 6.9. Found C 72.9, H 7.0.

Benzoic Acid 3-(5-(Benzyloxy)-3-((*tert*-butyldiphenylsiloxy)methyl)-2-methoxybenzyl)-4-(2-(pyridin-2-yl)-ethoxy)phenyl Ester (19). To a solution of **14** (708 mg, 1.0 mmol) in THF (3 mL) were added, sequentially, 2-(2-hydroxyethyl)pyridine (225 μL, 2 mmol), Ph_3P (524 mg 2.0 mmol), and DEAD (320 μL, 2.0 mmol). The resulting solution was stirred for 3 h and then concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with 20% EtOAc in toluene) to give 684 mg of product **19** as oil (84%). ^{1}H NMR ($CDCl_3$) δ 1.09 (s, 9H), 3.19 (t, J = 6 Hz, 2H), 3.42 (s, 3H), 3.87 (s, 2H), 4.32 (t, J = 6 Hz, 2H), 4.81 (s, 2H), 4.93 (s, 2H), 6.52 (d, J = 3 Hz, 1H), 6.82 (d, J = 3 Hz, 1H), 6.87 (d, J = 9 Hz, 1H), 7.01 (dd, J = 9, 3 Hz, 1H), 7.04 (m, 1H), 7.08−7.5 (m, 16H), 7.57 (m, 1H), 7.70 (m, 4H), 8.15 (m, 2H), 8.49 (m, 1H); IR ($CHCl_3$) ν 3011 (w), 2958 (w), 2932 (w), 2859 (w), 1732 (s), 1594 (w), 1498 (s), 1473 (s), 1264 (s), 1150 (m), 1081 (s), 1065 (s) cm^{-1}; MS (FAB, nitrobenzyl alcohol) m/z 814 $(MH)^+$. Anal. $C_{52}H_{51}O_4SiN$ requires C 76.7, H 6.3, N 1.7. Found C 76.9, H 6.6, N 1.8.

1,2-Bis(5-(benzyloxy)-3-(5-(benzyloxy)-2-((*tert*-butyloxycarbonyl)methoxy)-3-(2-(3-(methoxycarbonyl)-4-((2-methoxyethoxy)methoxy)phenyl)ethyl)benzyl)-2-methoxyphenyl)ethane (66). To a suspension of zinc powder (72 mg 1.1 mmol) in benzene (0.5 mL) was added 1,2-dibromoethane (6 μL, 0.07 mmol). The resulting slurry was heated to reflux, stirred at this temperature for 1 min, and then allowed to cool to room temperature. To this mixture were added Bu_4NI (140 mg, 0.38 mmol) and $(Ph_3P)_2NiCl_2$ (24 mg, 0.037 mmol). The resulting red mixture was stirred for 30 min and then a solution of **65** (335 mg, 0.37 mmol) in benzene (0.6 mL) added. This mixture was stirred for 45 min and then diluted with EtOAc. The EtOAc solution was washed, sequentially, with

5% NH_3 solution and brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (eluting with 40% EtOAc/20% CH_2Cl_2 in hexanes) to give 215 mg of **66** as an oil (71%). ^1H NMR ($CDCl_3$) δ 1.47 (s, 18H), 2.83 (m, 8H), 2.93 (s, 4H), 3.36 (s, 6H), 3.54 (m, 4H), 3.66 (s, 6H), 3.85 (m, 4H), 3.86 (s, 6H), 4.04 (s, 4H), 4.42 (s, 4H), 4.89 (s, 4H), 4.92 (s, 4H), 5.30 (s, 4H), 6.56 (s, 2H), 6.61 (d, J = 3 Hz, 2H), 6.64 (s, 2H), 6.75 (d, J = 3 Hz, 2H) 7.12 (d, J = 8 Hz, 2H), 7.19 (dd, J = 8, 2 Hz, 2H), 7.25−7.40 (m, 20H), 7.59 (d, J = 2 Hz, 2H); IR ($CHCl_3$) ν 3029 (w), 3010 (w), 2981 (w), 2948 (w), 1749 (s), 1718 (s), 1604 (w), 1505 (s), 1498 (s), 1304 (bm), 1233 (s), 1202 (s), 1155 (s), 1077 (s) cm^{-1}; MS (ion spray), m/z 1657 $(MNH_4)^+$. Anal. $C_{98}H_{110}O_{22}$ requires C 71.8, H 6.8. Found C 71.7, H 6.4.

1,2-Bis(5-(benzyloxy)-3-(5-(benzyloxy)-2-((carboxymethyl)oxy)-3-(2-(3-carboxy-4-hydroxyphenyl)ethyl)benzyl)-2-methoxyphenyl)ethane (67). To a solution of **66** (192 mg, 0.117 mmol) in 2-propanol (2.0 mL) was added pyridinium tosylate (251 mg, 1.0 mmol). The resulting mixture was heated to 70 °C and stirred at this temperature for 24 h. The reaction mixture was cooled and then concentrated under reduced pressure. The residue was suspended in THF (2.0 mL) and then MeOH (1.0 mL) added, followed by NaOH solution (2.0 mL, 2 M, 4.0 mmol). The reaction mixture was stirred for 18 h, acidified with 2 M HCl, diluted with ethyl acetate, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (eluting with 2% formic acid/18% THF in $CHCl_3$)[21a] to give 89 mg of product **67** as a white solid (57%). ^1H NMR (DMSO) δ 2.80 (m, 12H), 3.58 (s, 6H), 3.84 (s, 4H), 4.55 (s, 4H), 4.85 (s, 4H), 4.90 (s, 4H), 6.33 (d, J = 2 Hz, 2H), 6.70 (s, 2H), 6.75 (d, J = 2 Hz, 2H), 6.84 (d, J = 8 Hz, 2H), 6.90 (s, 2H), 7.12−7.32 (m, 20H), 7.34 (dd, J = 8, 2 Hz, 2H), 7.63 (d, J = 2 Hz, 2H); IR (KBr) ν 3500−2500 (bm), 3421 (bm), 3033 (w), 2927 (w), 2866 (w), 1729 (m), 1647 (m), 1589 (m), 1506 (m), 1454 (m), 1433 (m), 1218 (s), 1209 (s), 1039 (m), 698 (m) cm^{-1}; MS (FAB nitrobenzyl alcohol) m/z 1323 $(MH)^+$. Anal. $C_{80}H_{74}O_{18}$ requires C 72.6, H 5.6. Found C 72.6, H 5.7.

Compound 42. To a solution of **35** (3.0 g 1.366 mmol) in THF (5.0 mL), cooled to −15 °C, was added sodium methoxide (1.3 mL, 25 wt % in methanol, 6.4 mmol). This solution was stirred for 3 h, and then HCl (6.0 mL, 1 M) was added. The reaction mixture was diluted with EtOAc, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was azeotroped with toluene, and then 1.72 g of this product was dissolved in DMF (10 mL) and K_2CO_3 (1.1 g, 8 mmol) added followed by *tert*-butyl bromoacetate (1.3 mL, 8.0 mmol). The resulting mixture was heated to 80 °C and stirred at this temperature for 24 h. The reaction mixture was diluted with EtOAc and then washed, sequentially, with 0.1 M HCl, water (3×), and brine. The EtOAc solution was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (eluting with 20% EtOAc/20% CH_2Cl_2 in hexanes) to give 1.88 g of **42** (84%).^1H NMR (C_6D_6) δ 1.17 (s, 9H), 1.24 (s, 9H), 1.25 (s, 18H), 1.27 (s, 9H), 3.04 (s, 3H), 3.26 (m, 2H), 3.27 (s, 3H), 3.37 (s, 3H), 3.42 (s, 6H), 3.50 (s, 3H), 3.51 (s, 3H), 3.52 (s, 3H), 3.56 (m, 2H), 4.07 (s, 2H), 4.09 (s, 2H), 4.12 (s, 6H), 4.15 (s, 6H), 4.16 (s, 6H), 4.65 (bs, 6H), 4.82 (s, 2H), 4.93 (s, 2H), 5.04 (s, 2H), 6.69 (dd, J = 8, 3 Hz, 1H), 6.71 (d, J = 3 Hz, 1H), 6.72−6.8 (m, 12H), 6.84 (d, J = 3 Hz, 1H), 6.90 (s, J = 3 Hz, 1H), 7.0−7.25 (m, 26H), 7.46 (d, J = 3 Hz, 1H), 7.80 (m, 4H); IR ($CHCl_3$) ν 3012 (w), 2994 (w), 1748 (s), 1594 (m), 1474 (s), 1430 (s), 1230 (s), 1147 (s), 1088 (s), 1010 (s) cm^{-1}; MS (ion spray) m/z 2237 $(MH)^+$. Anal. $C_{135}H_{154}O_{27}Si$ requires C 72.5, H 6.9. Found C 72.6, H 6.9.

Compound 49. To a solution of **46** (370 mg, 0.191 mmol) in a 1:1:1 mixture of MeOH:DMF:THF (6.0 mL) was added 10% palladium on carbon (150 mg). The resulting suspension was stirred under an atmosphere of hydrogen for 14 h and then filtered through Celite and the filtrate concentrated under reduced pressure. The residue was dissolved in a 1:1 mixture of MeOH:THF (4.0 mL). This solution was cooled to −10 °C and then sodium methoxide (370 μL, 25 wt % in methanol, 1.82 mmol) added. The resulting solution was stirred for 1 h and then acetic acid (105 μL, 8.0 mmol) added. The reaction mixture was then concentrated under reduced pressure and the residue dissolved in DMF (2.0 mL). To this solution was added K_2CO_3 (396 mg, 2.9 mmol) and *tert*-butyl bromoacetate (396 μL, 2.4 mmol). The resulting mixture was warmed to 78 °C and stirred at this temperature for 1 h. At this point a further batch of both K_2CO_3 (396 mg) and of *tert*-butyl bromoacetate (396 μL) was added. This mixture was stirred for 2 h, cooled to room temperature, diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (eluting with 30% CH_2Cl_2/20% EtOAc in hexanes) to give 328 mg of **49** as an oil (83%). ^1H NMR ($CDCl_3$) δ 1.41 (s, 54H), 1.46 (s, 9H), 1.47 (s, 9H), 2.28 (s, 3H), 3.36 (s, 3H), 3.52 (m, 2H), 3.62 (s, 3H), 3.64 (bs, 18H), 3.73 (m, 2H), 3.97 (s, 2H), 4.00 (s, 2H), 4.04 (bs, 10H), 4.31 (s, 2H), 4.32 (s, 2H), 4.33 (s, 8H), 4.40 (s, 2H), 4.42 (s, 2H), 5.20 (s, 2H), 6.41 (d, J = 3 Hz, 1H), 6.44 (d, J = 3 Hz, 1H), 6.49 (m, 11H), 6.59 (d, J = 3 Hz, 1H), 6.69 (m, 2H), 7.08 (m, 1H); IR ($CHCl_3$) ν 3024 (w), 3011 (w), 2983 (w), 2934 (w), 1748 (s), 1595 (m), 1475 (s), 1231 (s), 1147 (s), 1083 (s), 1010 (m) cm^{-1}; MS (ion spray) m/z 2079 $(MH)^+$. Anal. $C_{115}H_{152}O_{34}$ requires C 66.5, H 7.4. Found C 66.9, H 7.4.

(5-(Benzyloxy)-3-(2-methoxy-5-((trimethylsilyl)ethynyl)-benzyl)-2-methoxybenzyloxy)-*tert*-butyldiphenylsilane (21). A solution of (trimethylsilyl)acetylene (176 μL, 1.25 mmol) in THF (2.0 mL) was cooled to −78 °C, and then n-BuLi (0.5 mL, 2.5 M in hexanes, 1.25 mmol) was added dropwise. The resulting solution was stirred for 15 min, and then a solution of $ZnCl_2$ (1.3 mL, 0.5 M in THF, 0.65 mmol) added. The cold bath was removed and stirring continued for 10 min. To this mixture was added a solution comprised of **20** (400 mg, 0.485 mmol), 1,1′-bis(diphenylphosphino)ferrocene (14 mg, 0.025 mmol), and bis(dibenzylideneacetone)palladium (14 mg, 0.025 mmol) in THF (3 mL). The reaction mixture was heated to 65 °C and stirred at this temperature for 18 h, cooled to room temperature, diluted with EtOAc, washed, sequentially, with saturated NH_4Cl solution and brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (eluting with 10% EtOAc in hexanes) to give 342 mg of **21** as a viscous oil (91%). ^1H NMR ($CDCl_3$) δ 0.23 (s, 9H), 1.10 (s, 9H), 3.30 (s, 3H), 3.42 (m, 2H), 3.50 (s, 3H), 3.60 (m, 2H), 3.89 (s, 2H), 4.82 (s, 2H), 4.93 (s, 2H), 5.21 (s, 2H), 6.50 (d, J = 3 Hz, 1H), 7.02 (d, J = 8.5 Hz, 1H), 7.10 (s, 3 Hz, 1H), 7.19 (d, J = 1 Hz, 1H), 7.28−7.4 (m, 12H), 7.69 (m, 4H); IR ($CHCl_3$) ν 3010 (w), 2960 (w), 2931 (w), 2148 (w), 1602 (w), 1495 (s), 1473 (s), 1250 (s), 1105 (s), 1081 (s), 1004 (s) cm^{-1}; MS (ion spray) m/z 773 $(MH)^+$. Anal. $C_{47}H_{56}O_6Si_2$ requires C 73.0, H 7.3. Found C 72.9, H, 7.7.

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Supporting Information Available: ^1H NMR of compounds **1, 3**−**5**, **7**, **9**, **18**, **22**, **23**, **27**, **29**−**31**, **33**−**37**, **39**−**42**, **44**, **49**, **53**, **56**, **57**, **60**, **61**, **64**, and **67** (31 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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