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Improved Iterative Synthesis of Linearly Disassembling Dendrons

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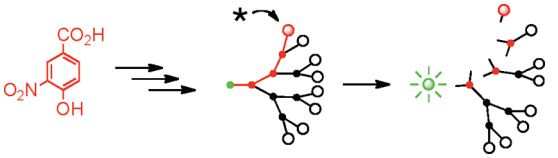

We report a significant improvement in the synthesis of disassembling dendritic structures by using 4-hydroxy-3-nitrobenzoic acid as the building block. We have prepared multigram quantities of first- through third-generation linearly disassembling dendrons containing a [3-*N*,4-*O*]-benzylaryl ether disassembly pathway, capped by a vanillin-derived phenyl allyl ether trigger, and a *p*-nitrophenoxy (PNP) reporter group. The disassembly process of these materials was initiated by allyl deprotection and monitored by the absorbance of the PNP reporter unit in the UV−vis. Modification of the disassembly conditions for the allyl trigger resulted in decreased disassembly times, decreased incubation time for onset of disassembly from minutes to seconds, and allowed observation of indicative rate differences between generations not seen with the previously reported conditions.

Introduction

The use of dendrimer chemistry is an increasingly ubiquitous means to alter the environment of covalently incorporated electro- and/or photoactive moieties.[1] Dendritic encapsulation of core moieties parallels Nature's use of proteins to act as insulation to create tailored microenvironments, the presence of which are critical for function.[2] As in Nature, the presence of this insulation can result in dramatic alterations of the properties of the encapsulated moieties from their nonencapsulated forms.[3] Hence, an ability to degrade dendritic molecular architectures in a controlled manner upon treatment with a discrete chemical or physical stimulus could be a powerful tool to regulate the properties of a system by rapid removal of the dendritic components.

Accordingly, we have developed "disassembling dendrimers"[4] in which varying types of cleavable pathways were engineered into the dendritic architecture (Figure 1a),[5−7] similar in concept to so-called self-immolative dendrimers[8] and polymers.[9,10] Consider compound **A**, an example of a linearly disassembling dendrimer that consists of a phenyl allyl ether trigger group, benzyl ether cleavage vector, and *p*-nitrophenoxy reporter subunit (Figure 1b). Removal of the allyl group triggers an electronic cascade cleavage. A 1,6-elimination mechanism[11] (Figure 1c) results in release of a corresponding *p*-quinone methide (***p*-QM**), which is trapped by an endogenous nucleophile and ultimately liberates the reporter *p*-nitrophenoxide (PNP) ion. Both linear[5] and geometric[6,7] disassembly systems have been realized.

The ability to degrade dendrimers in this fashion has the potential to impact previously established uses of dendrimers as well as introduce a new paradigm for their roles in chemical systems, i.e., as compact reservoirs of releasable active

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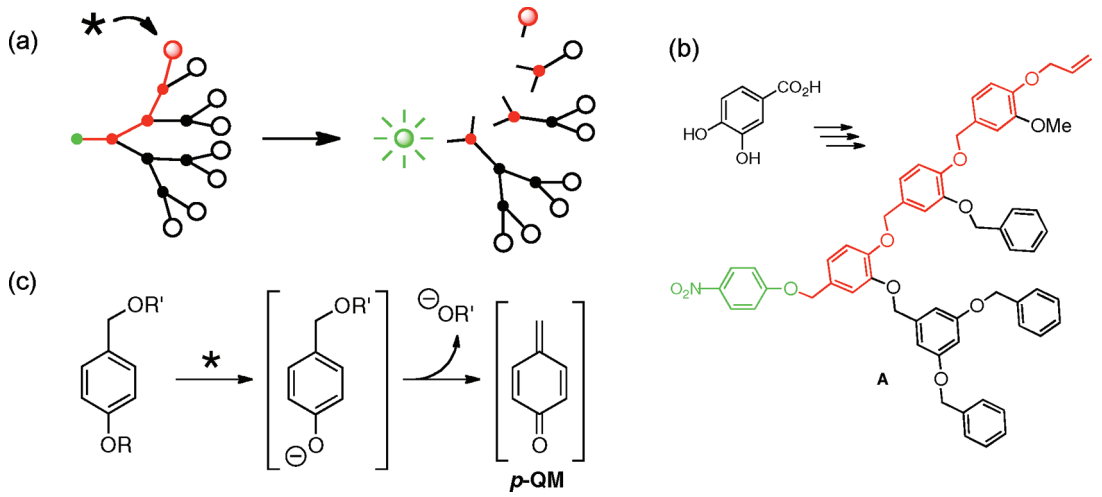

FIGURE 1. (a) Schematic representation of linear disassembly in which a stimulus initiates a linear cascade cleavage through the dendritic structure; (b) 3,4-dihydroxybenzoic acid and a second-generation linear disassembling dendron **A** with a [3-*O*,4-*O*]-benzyl ether cleavage pathway (red) and *p*-nitrophenyl (PNP) reporter group (green) derived therefrom; (c) enabling chemistry for disassembly: upon removal of R by a chemical or physical stimulus, the resulting vinylogous hemiacetal anion undergoes a 1,6-elimination to yield *p*-quinone methide (***p*-QM**) and alkoxide $^{-}$OR′.

species.[4] We find this a powerful construct in that dendrimers and dendritic structures can be made up of a wide variety of subunits, made compatible with many different environments, and incorporated into countless systems, including the biological arena.[12] Indeed, the controlled and precise degradation that is engineered into disassembling/self-immolative systems, both dendritic and polymeric, has demonstrated use as well as expected impact in many fields. For example, these systems have been applied to drug loading and release,[13] detectors,[14] signal amplifiers,[6,15] and degradable nanoparticles.[10]

Our original intent was to construct disassembling dendritic systems that mimicked the design, function, and stability of typical Fréchet-type benzyl(aryl ether) dendrimers, accompanied in particular by a similar ease of large-scale synthesis,[16] a characteristic that has undoubtedly contributed to the ubiquity of benzyl(aryl ether) dendrimers in organic nanoscale systems. Our initial synthesis of linearly disassembling dendrimers such as **A**, however, relied on the selective *O*-alkylation of 3,4-dihydroxybenzoate derivatives at several points throughout the synthesis, resulting in the [3-*O*,4-*O*] benzyl ether cleavage pathway.[5] Despite our efforts, these alkylations proceeded with only limited selectivity and resulted in the undesirable consumption of advanced dendritic intermediates at later stages of the synthesis, even when applying protecting group strategies.[17] There was therefore a need for a synthesis of disassembling dendrons that circumvented this selectivity problem, thus making these materials available in a more straightforward fashion for further incorporation into nanoscale systems.

We report herein an improved synthesis of linearly disassembling dendrons that circumvents previous synthetic limitations and proceeds from readily available starting materials. Our new synthetic approach introduces inherent selectivity in the side-chain installation process and allows for the rapid preparation of gram quantities of disassembling dendrons.

Results and Discussion

The design parameters of disassembling dendrimers contain the following requisites: (1) a stable trigger moiety that is chemically inert throughout the synthesis yet can be readily deprotected on demand to initiate the disassembly process; (2) a coherent linear disassembly pathway that, upon trigger deprotection, results in the cascade cleavage of benzyl ether moieties and the generation of a quinone methide; (3) an overall convergent synthesis with complete regio- and chemoselectivity in order to maintain the integrity of the growing dendritic scaffold; (4) the presence of a hyper-branching molecular architecture rather than an oligomeric chain to provide the insulative and potential energy harvesting properties of typical dendritic materials.

With these parameters in mind, we modified the synthesis of structures such as **A** to adopt 4-hydroxy-3-nitrobenzoic acid, an inexpensive commercially available starting material, as our fundamental building block (Scheme 1). Using the 3-nitro group as a latent amine, 4-*O* alkylation could proceed, followed by nitro reduction and subsequent amine alkylation, to allow for complete regioselective control for each successive generation in the synthetic sequence. The resulting dendrimers would have a [3-*N*,4-*O*]-benzyl ether cleavage pathway, whereby installation of a PNP reporter group on the focal point would give us the envisioned targets **9**, **15**, and **20** (Scheme 1). We chose a vanillin-derived phenyl allyl ether as our trigger moiety because of its particular robustness toward the subsequent synthetic steps of the dendrimer synthesis.

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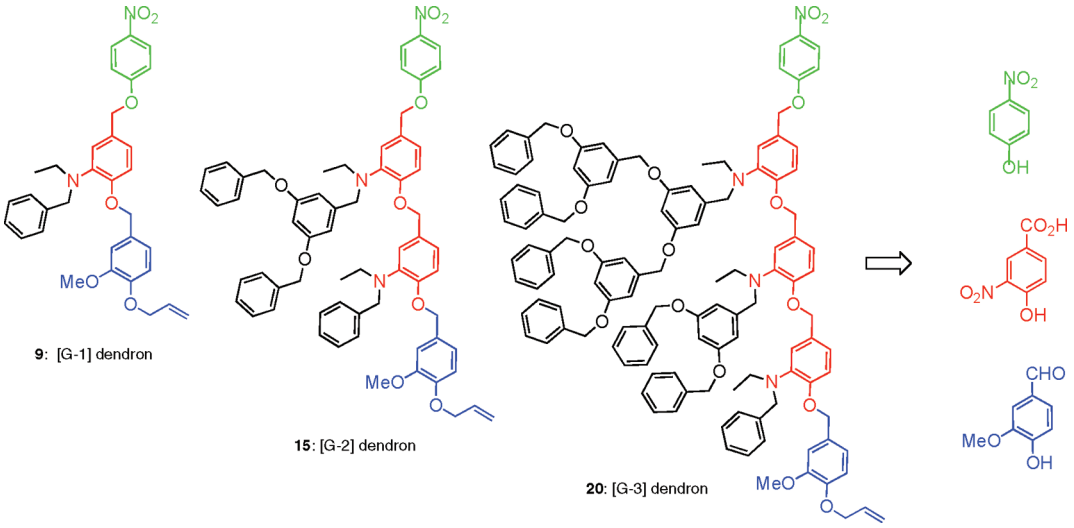
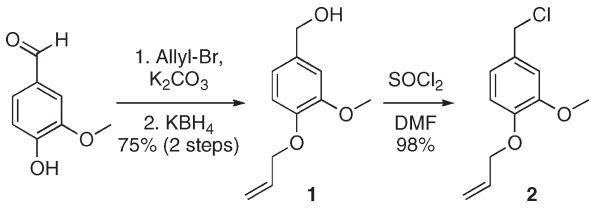
SCHEME 1. Retrosynthetic Analysis of Disassembling Dendrons 9, 15, and 20



SCHEME 2. Synthesis of Vanillin-Derived Trigger Moiety

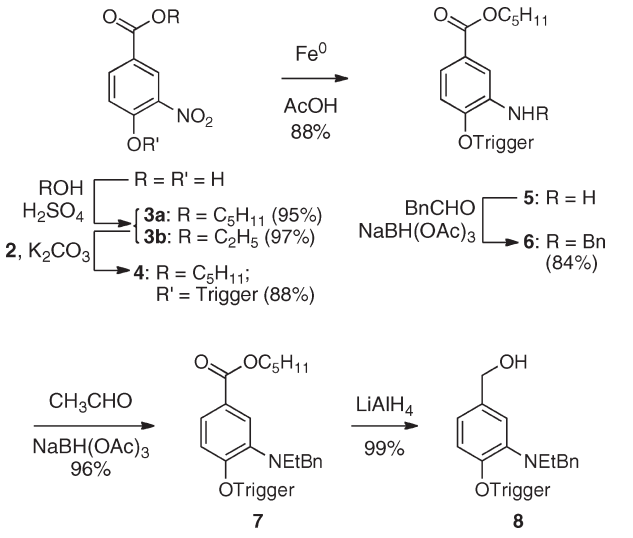


To obtain the trigger, vanillin was *O*-allylated and the resulting aldehyde reduced without purification to give **1**[18] (Scheme 2). Subsequent chlorination provided benzyl chloride **2** as a colorless solid in a 72% yield (three steps).

Dendron Synthesis. With **2** in hand, we turned our attention to the regioselective functionalization of 4-hydroxy-3-nitrobenzoic acid (Scheme 3). Fischer esterification of 4-hydroxy-3-nitrobenzoic acid was carried out with both 1-pentanol and EtOH to give the respective esters **3a** and **3b** in 95% and 97% yield, respectively. Installation of the trigger moiety was accomplished by alkylation of pentyl ester **3a** with benzyl chloride **2** under Williamson etherification conditions to afford nitroester **4** in 88% yield. Reduction of the nitro group required dissolving metal conditions to prevent concomitant reduction of the allyl trigger. For this reason, Fe^0 and AcOH[19] were employed, resulting in aniline **5** in 84% yield.

Side chains were installed by *N*-alkylation of the aniline function at each generational stage. Reductive amination conditions using $NaBH(OAc)_3$ and AcOH in DCE[20] were employed for all *N*-alkylation reactions. With these conditions employed for the alkylation of **5** using 1 equiv of benzaldehyde, a mixture of the desired *N*-benzyl along with *N*,*N*-dibenzyl side product was obtained. Formation of this side product was minimal, however, and **6** was still obtained in 84% yield. The subsequent ethylation of **6** with acetaldehyde, under identical reductive amination conditions, served to remove any protic sites from the compound to prevent any undesirable reactions later in the synthesis. Reduction of **7** with $LiAlH_4$ resulted in the corresponding benzyl alcohol **8**, the first-generation disassembling dendron, in 98% yield.

SCHEME 3. Synthesis of [3-*N*,4-*O*] Disassembling Dendron 8



Homologation of **8** followed by a sequence of transformations similar to that of Scheme 3 was used in an iterative fashion to prepare dendrons **13** and **19** (Scheme 4). Coupling benzyl alcohol **8** with ethyl ester **3b** under Mitsunobu conditions gave nitroester **10** in 89% yield. Nitroester **10** was reduced via a modified protocol using $NaBH_4$ and $SnCl_2$[21] to yield aniline **11** in 74% yield. At this juncture, we anticipated that sterics might play a role in the successive monoalkylation of two different substituents on the 3-position aniline. This indeed worked to our advantage, as alkylation with

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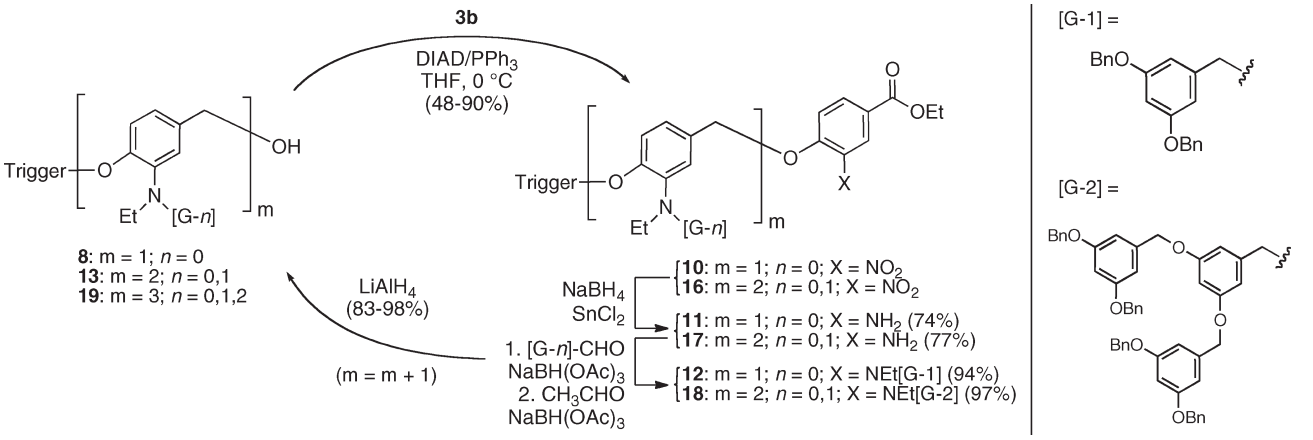
SCHEME 4. Synthesis of [3-*N*, 4-*O*] Disassembling Dendrons 13 and 19



dendritic aldehydes from this point in the cycle forward gave the mono-*N*-alkylated product as the predominant or exclusive product obtained. Reductive amination of **11** with a slight excess of [G-1]-CHO resulted in the *N*-[G-1]-mono-alkylated product almost exclusively (ca. 4% *N,N*-di[G-1] byproduct). Utilizing the knowledge that sterics largely suppressed dialkylation of the dendritic adduct, the alkylation procedure was modified so that a two-step, "one-pot" reaction could be conducted successively alkylating the aniline with both [G-1]-CHO and acetaldehyde using the same reductant [$NaBH(OAc)_3$] to give **12** in 94% yield and with minimal production of the *N,N*-di[G-1] side product. Reduction of **12** with $LiAlH_4$ gave benzyl alcohol **13**, the second-generation disassembling dendron, in 97% yield.

A second sequence around the cycle led to the third-generation dendron **19**, starting with Mitsunobu coupling of benzyl alcohol **13** with ethyl ester **3b** to provide nitroester **16** in 90% yield. Sonication during this coupling step resulted in reaction completion in a matter of minutes rather than hours, which has been reported to be an effective technique for the coupling of sterically hindered or deactivated substrates in the Mitsunobu reaction.[22] Nitro reduction using similar conditions for the preparation of **11** gave aniline **17** in 77% yield. The subsequent reductive aminations were again carried out by the two-step, "one-pot" procedure to efficiently yield *N*-[G-2]-*N*-ethyl tertiary aniline **18** in 97% yield. Ester reduction using standard conditions resulted in the production of a deallylated byproduct as seen by NMR. Formation of the byproduct was eliminated by allowing the reaction mixture to warm slowly from −78 °C until full conversion was determined by TLC. Benzyl alcohol **19**, the third-generation disassembling dendron, was thus obtained in 83% yield.

To assay the disassembly of these [3-*N*,4-*O*] cleavage pathway dendrons, installation of a PNP reporter moiety was necessary, whereupon disassembly of the dendritic system the liberated PNP anion (λ_{max} = 421 nm) could by tracked using time-course UV−vis experiments. Two methods were used to install this group. Coupling dendron **8** to *p*-nitrophenol using a Mitsunobu protocol was used to prepare first-generation PNP ether **9** in 48% yield. The preparation of **20** using the same conditions was accompanied by the formation of a *C*-alkylated side product, in addition to the *O*-alkylated **20**. These were easily separated by flash chromatography by eluting with 1:6:3 NEt_3−EtOAc−hexanes, which yielded the third-generation PNP ether **20** in a moderate 57% yield. In an attempt to prepare the PNP ethers in higher yield, we assayed the alternate Williamson etherification for the preparation of second-generation **15** via the corresponding chloride **14**, prepared from **13** with $SOCl_2$. Although conversion of **13** to **14** proceeded in an excellent 97% yield, second-generation PNP ether **15** was only obtained in 47% yield.

Disassembly Studies. The disassembly of dendrons **9**, **15**, and **20** was expected to take place under standard reductive allyl deprotection conditions since the triggers used for the previously reported disassembling systems[5,6] utilized the same phenolic allyl group. In these prior systems, the disassembly was initiated by reductive deprotection of the phenyl allyl ether trigger with catalytic $Pd(PPh_3)_4$ and $NaBH_4$ in DMF. During the course of the current work, we modified our original conditions in an attempt to eliminate the several-minute incubation period that we had observed before the disassembly event initiated. We found that by switching the palladium source to $PdCl_2(PPh_3)_2$ and adding MeOH to the reaction mixture, disassembly took place after an initial incubation period of mere seconds following catalyst addition. Smooth disassembly was observed in the UV−vis by a rapid increase in the absorption of PNP ion at 421 nm. This spectral evolution takes place within 200 s under the newly modified disassembly conditions (Figure 2). The final absorbance values observed at 421 nm indicated complete disassembly (i.e., disassembly proceeding to the focal point) of **9**, **15**, and **20** in 88%, 93%, and 82% yield, respectively, based on the measured absorptivity of PNP under the reaction conditions.

There are two clear benefits to these modified disassembly conditions. First, these conditions are optimal for rapid disassembly. Disassembly experiments with the previous conditions proceeded to completion within 15 min including a 10-min incubation period, whereas disassembly with the current modified conditions were completely disassembled within 200 s requiring an incubation period of roughly 15 s. Second, they are sensitive to the generation of dendrimer being disassembled in that the rate of complete disassembly (release of PNP) under these conditions is dependent on the

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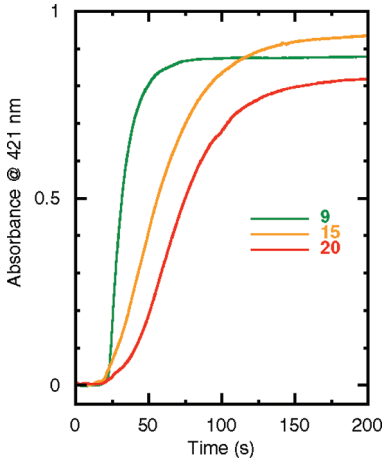

FIGURE 2. UV absorbance at 421 nm as a function of time during the disassembly of **9**, **15**, and **20**. Concentrations of **9**, **15**, and **20** were normalized such that quantitative disassembly would result in the same concentrations of released PNP.

cleavage pathway length, with the initial rate approximately proportional to $1/n$ where n is the number of benzyl groups in the pathway.[23] Work is currently underway in our laboratory on the kinetics of disassembly and will be reported in due course.

Summary

A new class of disassembling dendrons that have a [3-*N*,4-*O*] benzyl ether cleavage pathway were prepared by an iterative pathway using 4-hydroxy-3-nitrobenzoic acid as the building block. Disassembly proceeded smoothly under modified disassembly conditions with a markedly reduced incubation period relative to previous reports.[5,6] The complete regiochemical control afforded by the use of 4-hydroxy-3-nitrobenzoic acid in the synthesis eliminated the undesirable consumption of advanced dendritic intermediates at later stages of the synthesis. Gram quantities of disassembling dendrons are now readily available using the synthesis reported herein, making the incorporation of these structures in nanoscopic systems more feasible.

Experimental Section

4-Allyloxy-3-methoxybenzyl Alcohol (1). A mixture of vanillin (63.06 g, 414.4 mmol), allyl bromide (75.21 g, 621.6 mmol), K_2CO_3 (114.5 g, 828.8 mmol), and DMF (500 mL) was stirred and heated to 60 °C for 24 h. The mixture was poured over H_2O (500 mL) and extracted into ether (3 × 200 mL). The ethereal layer was washed with brine (3 × 100 mL), dried ($MgSO_4$), filtered, and concentrated to a yellow oil. To this crude aldehyde in THF−MeOH (2:1, 450 mL) at 25 °C was added KBH_4 (33.5 g, 620 mmol). The resulting reaction mixture was then heated to 55 °C (24 h). The reaction mixture cooled to rt, quenched by reverse addition into 1 M HCl (500 mL), and extracted with ether (3 × 200 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo and recrystallized from hexanes yielding **1** (58.91 g, 75%) as white crystals: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (s, 1 H), 6.88 (s, 2 H), 6.08 (m, 1 H), 5.42 (dd, J = 17.4, 1.5 Hz, 1 H), 5.30 (dd, J = 10.5, 1.5 Hz, 1 H), 4.62 (dt, J = 5.4, 1.2 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.6, 147.5, 133.9, 133.3, 119.3, 118.0, 113.3, 110.8, 69.9, 65.3, 55.9; MS (FAB$^+$) m/z 194.26 (M^+, $C_{11}H_{14}O_3$ requires 194.09).

4-Allyloxy-3-methoxybenzyl Chloride (2). To a stirred solution of **1** (21.41 g, 112.2 mmol) in CH_2Cl_2 (300 mL) at 25 °C were added, in succession, DMF (1 mL) and $SOCl_2$ (19.67 g, 165.3 mmol) dropwise (over a period of 30 min). The solution was stirred for an additional 30 min and was quenched by the careful addition of satd aqueous $NaHCO_3$ (ca. 50 mL) and stirred for 1 h. The resulting mixture was extracted with CH_2Cl_2 (3 × 50 mL), dried ($MgSO_4$), filtered through a short silica gel plug, and concentrated in vacuo to yield **2** (22.80 g, 98%) as a colorless crystalline solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (s, 1 H), 6.90 (dd, J = 10.8, 2.4 Hz, 1 H), 6.83 (d, J = 7.8 Hz, 1 H), 6.07 (m, 1 H), 5.40 (dd, J = 17.4, 1.5 Hz, 1 H), 5.29 (dd, J = 10.5, 1.5 Hz, 1 H), 4.61 (dt, J = 5.4, 1.2 Hz, 2 H), 4.56 (s, 2 H), 3.89 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5, 148.2, 133.1, 130.3, 121.0, 118.1, 113.1, 112.1, 69.8, 55.9, 46.6; MS (FAB$^+$) m/z 212.23 (M^+, $C_{11}H_{13}O_2Cl$ requires 212.06).

Pentyl 4-Hydroxy-3-nitrobenzoate (3a). A solution of 4-hydroxy-3-nitrobenzoic acid (100 g, 546 mmol), 1-pentanol (500 mL), and concentrated H_2SO_4 (1 mL) was refluxed for 72 h in a 1 L round-bottom flask fitted with a Dean−Stark trap and a jacketed water condenser. Upon completion of the reaction based on TLC analysis, the excess 1-pentanol was removed from the reaction via vacuum distillation, and the resulting red oil was dissolved in hexanes−CH_2Cl_2 (2:1, 80 mL) and filtered through a short silica gel plug. The filtrate was concentrated in vacuo to afford compound **3a** (131 g, 95%) as a red oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 (d, J = 2.1 Hz, 1 H), 8.24 (dd, J = 8.7, 1.8 Hz, 1 H), 7.22 (d, J = 9.0 Hz, 1 H), 4.34 (t, J = 6.9 Hz, 2 H), 1.84 − 1.74 (m, 2 H), 1.44 − 1.39 (m, 4 H), 0.94 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 164.3, 158.0, 137.9, 133.2, 127.2, 123.1, 120.1, 65.8, 28.3, 28.1, 22.3, 13.9; MS (FAB$^+$) m/z 254.30 (M^+, $C_{12}H_{15}O_5N$ requires 254.10). Anal. Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.52; H, 6.11; N, 5.51.

Ethyl 4-Hydroxy-3-nitrobenzoate (3b).[24] A solution of 4-hydroxy-3-nitrobenzoic acid (100 g, 546 mmol), ethanol (500 mL), and concentrated H_2SO_4 (1 mL) were refluxed for 72 h in a 1 L round-bottom flask fitted with a Dean−Stark trap and a jacketed water condenser. Upon completion of the reaction, Et_2O (500 mL) was added, and the resulting phases were separated. The organic phase was then washed with brine (4 × 300 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Subsequent recrystallization from 9:1 hexanes−Et_2O yielded **3b** (112 g, 97%) as yellow crystals: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (d, J = 2.4 Hz, 1 H), 8.25 (dd, J = 9.0, 1.8 Hz, 1 H), 7.22 (d, J = 8.7 Hz, 1 H), 4.41 (q, J = 7.5 Hz, 2 H), 1.42 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 164.2, 158.0, 137.9, 133.2, 127.2, 123.1, 120.1, 61.6, 14.3; MS (ESI$^+$) m/z 212.80 (M + H$^+$, $C_9H_{10}O_5N$ requires 212.06).

Pentyl 4-(4-Allyloxy-3-methoxybenzyloxy)-3-nitrobenzoate (4). To a stirred solution of **3** (79.6 g, 314.3 mmol) in DMF (500 mL) at 25 °C were added benzyl chloride **2** (79.4 g, 373.3 mmol) and K_2CO_3 (86.5 g, 625.9 mmol). The reaction mixture was then maintained at 50 °C with stirring for 72 h. After the reaction mixture was allowed to cool to rt, the reaction was quenched by reverse addition to H_2O (500 mL) and the mixture extracted with Et_2O (4 × 300 mL). The combined organic extracts were then washed with 1 M HCl (200 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Pure pentyl ester **4** could be obtained by recrystallization from Et_2O−hexanes (7:1), providing **4** (119 g, 88%) as light yellow crystals: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J = 2.4 Hz, 1 H), 8.18

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(dd, J = 8.7, 2.4 Hz, 1 H), 7.17 (d, J = 8.7 Hz, 1 H), 7.05 (d, J = 2.1 Hz, 1 H), 6.93 (dd, J = 8.4, 2.1 Hz, 1 H), 6.87 (d, J = 7.8 Hz, 1 H), 6.14 − 6.02 (m, 1 H), 5.41 (dd, J = 17.1, 1.5 Hz, 1 H), 5.29 (dd, J = 10.5, 1.5 Hz, 1 H), 5.24 (s, 2 H), 4.62 (dt, J = 5.4, 1.3 Hz, 2 H), 4.32 (t, J = 6.6 Hz, 2 H), 3.90 (s, 3 H), 1.81 − 1.72 (m, 2 H), 1.43 − 1.38 (m, 4 H), 0.93 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 164.5, 154.9, 149.8, 148.1, 139.8, 135.1, 133.1, 127.6, 127.1, 123.1, 119.4, 118.1, 114.6, 113.1, 110.6, 71.4, 69.9, 65.7, 56.0, 28.4, 28.1, 22.3, 14.0; MS (FAB^+) m/z 429.57 (M^+, $C_{23}H_{27}O_7N$ requires 429.18). Anal. Calcd for $C_{23}H_{27}NO_7$: C, 64.32; H, 6.34; N, 3.26. Found: C, 64.30; H, 6.74; N, 3.44.

Pentyl 3-Amino-4-(4-allyloxy-3-methoxybenzyloxy)benzoate (5). A mixture of compound **4** (59.6 g, 139 mmol), AcOH−EtOH (1:1, 1 L), and Fe^0 powder (55.9 g, 1000 mmol) was maintained at 55 °C under Ar for 9 h with stirring. After the reaction was allowed to cool to rt, it was poured over H_2O (700 mL) and extracted with Et_2O (3 × 300 mL). The combined organics were then washed with satd $NaHCO_3$ (500 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to provide the crude product as a light brown oil. Crystallization of the oil from hexanes/CH_2Cl_2 (9:1) yielded **5** (49.0 g, 88%) as a white crystalline solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (dd, J = 8.4, 1.8 Hz, 1 H), 7.41 (d, J = 2.1 Hz, 1 H), 6.97 − 6.86 (m, 4 H), 6.16 − 6.03 (m, 1 H), 5.42 (dd, J = 17.1, 1.5 Hz, 1 H), 5.30 (dd, J = 10.5, 1.2 Hz, 1 H), 5.05 (s, 2 H), 4.63 (d, J = 3.9 Hz, 2 H), 4.26 (t, J = 6.9 Hz, 2 H), 3.90 (s, 2 H), 3.89 (s, 3 H), 1.79 − 1.70 (m, 2 H), 1.43 − 1.35 (m, 4 H), 0.93 (t, J = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 150.0, 149.6, 148.0, 136.1, 133.2, 129.2, 123.5, 120.8, 120.3, 118.1, 115.7, 113.2, 111.5, 110.9, 70.5, 69.9, 64.8, 56.0, 28.5, 28.2, 22.4, 14.0; MS (FAB^+) m/z 400.61 ($M + H^+$, $C_{23}H_{30}O_5N$ requires 400.21). Anal. Calcd for $C_{23}H_{29}NO_5$: C, 69.15; H, 7.32; N, 3.51. Found: C, 69.15; H, 7.33; N, 3.63.

Pentyl 4-(4-Allyloxy-3-methoxybenzyloxy)-3-(*N*-benzylamino)benzoate (6). To a stirred solution of **5** (31.1 g, 77.9 mmol) in DCE (200 mL) at 25 °C were added benzaldehyde (7.92 mL, 78.0 mmol) and AcOH (3 mL), the resulting mixture was stirred at this temperature for 30 min before $NaBH(OAc)_3$ (24.6 g, 116 mmol) was added, and stirring was continued for an additional 12 h. The reaction was quenched by the addition of equal portions of CH_2Cl_2 (200 mL) and H_2O (200 mL). The layers were separated, and the organic phase was washed with brine (3 × 100 mL), dried ($MgSO_4$), filtered, and concentrated to a light yellow oil. Purification of the oil via flash column chromatography (SiO_2, 6:1 hexanes/EtOAc) and subsequent crystallization from CH_2Cl_2−hexanes (1:9) afforded **6** (32.2 g, 84%) as a colorless, crystalline solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−6.84 (m, 11 H), 6.15−6.02 (m, 1 H), 5.41 (dd, J = 17.1, 1.5 Hz, 1 H), 5.29 (dd, J = 10.5, 1.2 Hz, 1 H), 5.06 (s, 2 H), 4.69 (t, J = 6.0 Hz, 1 H), 4.62 (dt, J = 5.4, 1.5 Hz, 2 H), 4.39 (d, J = 5.4 Hz, 2 H), 4.24 (t, J = 6.6 Hz, 2 H), 3.83 (s, 3 H), 1.77−1.68 (m, 2 H), 1.41−1.36 (m, 4 H), 0.92 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 166.9, 149.5, 149.5, 148.0, 139.1, 137.9, 133.1, 129.1, 128.5, 127.5, 127.2, 123.6, 120.2, 119.2, 118.0, 113.1, 111.3, 110.7, 110.0, 70.5, 69.8, 64.7, 55.9, 47.8, 28.4, 28.2, 22.3, 14.0; MS (FAB^+) m/z 490.69 ($M + H^+$, $C_{30}H_{36}O_5N$ requires 490.26). Anal. Calcd for $C_{30}H_{35}NO_5$: C, 73.59; H, 7.21; N, 2.86. Found: C, 73.31; H, 7.60; N, 3.18.

Pentyl 4-(4-Allyloxy-3-methoxybenzyloxy)-3-(*N*-benzyl-*N*-ethylamino)benzoate (7). Following the procedure for the preparation of **6**, a mixture of **6** (12.6 g, 25.7 mmol), acetaldehyde (1.70 mL, 51.4 mmol), AcOH (3 mL), DCE (60 mL), and $NaBH(OAc)_3$ (6.53 g, 30.8 mmol) was allowed to react to yield **7** (12.9 g, 96%) as white crystals after recrystallization from hexanes−CH_2Cl_2 (9:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (dd, J = 8.4, 2.4 Hz, 1 H), 7.62 (d, J = 1.8 Hz, 1 H), 7.24 (m, 6 H), 6.92 (m, 3 H), 6.83 (d, J = 8.4 Hz, 1 H), 6.08 (m, 1 H), 5.41 (dd, J = 17.4, 1.5 Hz, 1 H), 5.29 (dd, J = 10.5, 1.5 Hz, 1 H), 5.11 (s, 2 H), 4.62 (dt, J = 5.4, 1.2 Hz, 2 H), 4.28 (s, 2 H), 4.26 (t, J = 6.9 Hz, 2 H), 3.77 (s, 3 H), 3.15(q, J = 7.5 Hz, 2 H), 1.74 (m, 2 H), 1.40 (m, 4 H), 1.00 (t, J = 6.9 Hz, 3 H), 0.92 (t, J = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 156.2, 149.5, 147.8, 140.0, 139.2, 133.2, 129.4, 128.4, 128.0, 126.8, 124.5, 123.1, 122.6, 120.0, 118.0, 113.1, 112.5, 111.2, 70.5, 69.9, 64.8, 56.6, 55.8, 44.9, 28.5, 28.2, 22.4, 14.0, 12.2; MS (FAB^+) m/z 518.78 ($M + H^+$, $C_{32}H_{40}O_5N$ requires 518.29). Anal. Calcd for $C_{32}H_{39}O_5N$: C, 74.25; H, 7.59; N, 2.71. Found: C, 74.17; H, 7.86; N, 3.10.

4-(4-Allyloxy-3-methoxybenzyloxy)-3-(*N*-benzyl-*N*-ethylamino)benzyl Alcohol (8). To a stirred slurry of LAH (0.950 g, 25.0 mmol) and freshly distilled THF (100 mL) at 25 °C was added ester **7** (10.8 g, 20.9 mmol) as a solid in 10 equal portions. Upon completion, the reaction was quenched by successive dropwise addition of H_2O (0.95 mL), aq NaOH (15% w/w, 0.95 mL), and then H_2O (2.85 mL). The resulting slurry was stirred for an additional 20 min, dried ($MgSO_4$), filtered through a short silica gel plug, and concentrated to yield alcohol **8** (9.0 g, 99%) as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (m, 6 H), 6.97 (d, J = 2.1 Hz, 1 H), 6.92 (m, 3 H), 6.83 (d, J = 8.4 Hz, 1 H), 6.08 (m, 1 H), 5.40 (dd, J = 17.2, 1.5 Hz, 1 H), 5.29 (dd, J = 10.2, 0.9 Hz, 1H), 5.06 (s, 2 H), 4.61 (dt, J = 5.4, 1.2 Hz, 2 H), 4.57 (d, J = 6.0 Hz, 2 H), 4.29 (s, 2 H), 3.77 (s, 3 H), 3.14 (q, J = 6.5 Hz, 2 H), 1.51 (t, J = 5.7 Hz, 1 H), 1.26 (t, J = 7.5 Hz, 2 H), 1.00 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.0, 149.4, 147.6, 140.7, 139.3, 133.7, 133.3, 130.2, 128.4, 128.0, 126.7, 121.0, 120.6, 119.9, 117.9, 114.1, 113.1, 111.2, 70.8, 69.9, 65.4, 56.6, 55.8, 44.8, 12.2; MS (FAB^+) m/z 434.64 ($M + H^+$, $C_{27}H_{32}O_4N$ requires 434.23). Anal. Calcd for $C_{27}H_{31}O_4N$: C, 74.80; H, 7.21; N, 3.23. Found: C, 74.95; H, 7.60; N, 3.20.

4-(4-Allyloxy-3-methoxybenzyloxy)-3-(*N*-benzyl-*N*-ethylamino)benzyl Alcohol, 4-Nitrophenyl Ether (9). To a stirred solution of alcohol **8** (1.06 g, 2.44 mmol) in freshly distilled THF (25 mL) at 0 °C were successively added *p*-nitrophenol (0.41 g, 3.0 mmol), PPh_3 (0.77 g, 2.9 mmol), and diisopropyl azodicarboxylate (0.56 mL, 2.8 mmol) dropwise via syringe. The reaction was then allowed to warm to ambient temperature, and upon completion of the reaction (2 h), based on TLC analysis (SiO_2, 4:1 hexanes−EtOAc), the reaction mixture was diluted with Et_2O (100 mL) and quenched with satd $NaHCO_3$ (5 × 50 mL). The ethereal layer was dried ($MgSO_4$), filtered, and concentrated to a light yellow oil. Purification of the crude oil was carried out by crystallization from CH_3OH which provided compound **9** (0.65 g, 48%) as a light yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 9.3 Hz, 2 H), 7.22 (m, 5 H), 6.95 (m, 6 H), 6.84 (d, J = 7.8 Hz, 1 H), 6.09 (m, 1 H), 5.40 (dd, J = 17.1, 1.8 Hz, 1H), 5.29 (dd, J = 10.2, 1.5 Hz, 1 H), 5.07 (s, 2 H), 5.03 (s, 2 H), 4.62 (dt, J = 5.4, 1.2 Hz, 2 H), 4.30 (s, 2 H), 3.78 (s, 3 H), 3.15 (q, J = 6.5 Hz, 2 H), 1.00 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8, 152.5, 149.5, 147.7, 141. 5, 140.6, 139.1, 133.3, 129.9, 128.3, 128.0, 127.9, 126.7, 125.8, 121.5, 121.0, 120.0, 118.0, 114.9, 114.0, 113.1, 111.3, 70.8, 70.7, 69.9, 56.4, 55.8, 45.1, 12.3; MS (FAB^+) m/z 555.77 ($M + H^+$, $C_{33}H_{35}O_6N_2$ requires 555.25). Anal. Calcd for $C_{33}H_{34}O_6N_2$: C, 71.46; H, 6.18; N, 5.05. Found: C, 71.55; H, 6.50; N, 5.22.

Ethyl 4-(4-(4-Allyloxy-3-methoxybenzyloxy)-3-(*N*-benzyl-*N*-ethylamino)benzyloxy)-3-nitrobenzoate (10). Following the procedure for the preparation of **9**, alcohol **8** (17.5 g, 40.4 mmol) in THF (350 mL) was reacted with compound **3b** (8.56 g, 40.5 mmol), PPh_3 (11.7 g, 44.6 mmol), and diisopropyl azodicarboxylate (8.61 mL, 43.7 mmol) to afford the crude product as a yellow solid following precipitation from CH_3OH−CH_2Cl_2 (9:1). Subsequent purification by recrystallization from 5:1 hexanes−Et_2O provided **10** (22.6 g, 89%) as yellow needles: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (d, J = 2.4 Hz, 1 H), 8.12 (dd, J = 8.7, 2.4 Hz, 1H), 7.21 (m, 5 H), 7.07 (d, J = 8.7 Hz, 1 H), 6.94

(m, 5 H), 6.83 (d, J = 8.4 Hz, 1 H), 6.09 (m, 1 H), 5.40 (dd, J = 17.1, 1.5 Hz, 1 H), 5.29 (dd, J = 10.8, 0.9 Hz, 1 H), 5.19 (s, 2 H), 5.06 (s, 2 H), 4.62 (dt, J = 5.4, 1.5 Hz, 2 H), 4.38 (q, J = 6.9 Hz, 2 H), 4.30 (s, 2 H), 3.77 (s, 3 H), 3.15(q, J = 6.9 Hz, 2 H), 1.40 (t, J = 6.9 Hz, 3 H), 1.00 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5, 155.0, 152.4, 149.4, 147.7, 140.6, 139.7, 139.1, 134.9, 133.3, 129.9, 128.3, 128.0, 127.2, 127.0, 126.7, 122.8, 120.9, 120.3, 120.0, 118.0, 114.6, 113.9, 113.1, 111.3, 71.5, 70.7, 69.9, 61.5, 56.3, 55.8, 45.1, 14.3, 12.2; MS (FAB$^+$) m/z 627.83 (M + H$^+$, $C_{36}H_{39}O_8N_2$ requires 627.27). Anal. Calcd for $C_{36}H_{38}O_8N_2$: C, 68.99; H, 6.11; N, 4.47. Found: C, 69.15; H, 6.46; N, 4.44.

Ethyl 3-Amino-4-(4-(4-allyloxy-3-methoxybenzyloxy)-3-(*N*-benzyl-*N*-ethylamino)benzyloxy)benzoate (11). To a stirred solution of **10** (14.7 g, 23.5 mmol) in absolute ethanol (300 mL) and freshly distilled THF (50 mL) at 50 °C was added $SnCl_2 \cdot 2H_2O$ (26.4 g, 117 mmol) followed by slow addition (25 min) of a suspension of finely ground $NaBH_4$ (0.88 g, 23 mmol) in absolute ethanol (50 mL). The reaction mixture was maintained at this temperature for 20 min before being allowed to cool to ambient temperature and quenched by the successive addition of H_2O (150 mL) and aq NaOH (15% w/w, 10 mL). The resulting mixture was then extracted with Et_2O (3 × 200 mL), and the combined organic layer was washed with aq satd $NaHCO_3$ (4 × 200 mL) solution, dried ($MgSO_4$), filtered, and concentrated in vacuo. Crystallization of the crude residue from hexanes−CH_2Cl_2 (9:1) furnished compound **11** (10.4 g, 74%) as a white, crystalline solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (dd, J = 8.1, 1.8 Hz, 1 H), 7.39 (d, J = 1.8 Hz, 1 H), 7.22 (m, 5 H), 6.94 (m, 5 H), 6.84 (d, J = 6.3 Hz, 1 H), 6.81 (d, J = 6.3 Hz, 1 H), 6.09 (m, 1 H), 5.41 (dd, J = 17.1, 1.5 Hz, 1 H), 5.30 (dd, J = 10.8, 0.9 Hz, 1 H), 5.08 (s, 2 H), 5.00 (2 H), 4.62 (dt, J = 5.4, 1.5 Hz, 2 H), 4.33 (q, J = 6.9 Hz, 2 H), 4.31 (s, 2 H), 3.82 (s, 2 H), 3.78 (s, 3 H), 3.15 (q, J = 7.2 Hz, 2 H), 1.37 (t, J = 7.5 Hz, 3 H), 1.01 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 152.4, 150.1, 149.5, 147.7, 140.5, 139.1, 136.2, 133.3, 130.1, 128.9, 128.4, 128.0, 126.7, 123.3, 121.7, 121.2, 120.8, 120.0, 118.0, 115.6, 113.9, 113.1, 111.3, 110.9, 70.7, 70.6, 69.9, 60.5, 56.5, 55.8, 45.1, 14.4, 12.3; MS (FAB$^+$) m/z 597.76 (M + H$^+$, $C_{36}H_{41}O_6N_2$ requires 597.30). Anal. Calcd for $C_{36}H_{40}O_6N_2$: C, 72.46; H, 6.76; N, 4.69. Found: C, 72.85; H, 7.16; N, 4.58.

Ethyl 4-(4-(4-Allyloxy-3-methoxybenzyloxy)-3-(*N*-benzyl-*N*-ethylamino)benzyloxy)-3-(*N*-3,5-dibenzyloxybenzyl-*N*-ethylamino)benzoate (12). To a stirred solution of **11** (12.1 g, 20.3 mmol) in DCE (120 mL) at 25 °C were added 3,5-dibenzyloxybenzaldehyde (8.36 g, 26.3 mmol) and AcOH (3 mL). The resulting mixture was stirred for 30 min before $NaBH(OAc)_3$ (5.54 g, 26.1 mmol) was added, and stirring was continued for an additional 32 h. Acetaldehyde (2.55 mL, 45.4 mmol) and an additional portion of $NaBH(OAc)_3$ (5.54 g, 26.1 mmol) were then added to the reaction mixture, and stirring was continued for 1 h. The reaction solution was then diluted with Et_2O (200 mL), washed with brine (2 × 200 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Subsequent purification of the crude product by flash column chromatography (SiO_2, 4:1 hexanes−EtOAc) yielded compound **12** (17.6 g, 94%) as a colorless glass: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (dd, J = 9.0, 1.8 Hz, 1H), 7.63 (s, 1 H), 7.26 (m, 15 H), 6.46 (t, J = 2.4 Hz, 1 H), 6.08 (m, 1 H), 5.40 (dd, J = 17.1, 1.5 Hz, 1H), 5.29 (dd, J = 10.2, 1.5 Hz, 1 H), 5.05 (s, 2 H), 4.92 (s, 2 H), 4.86 (s, 4 H), 4.60 (dt, J = 5.4, 1.5 Hz, 2 H), 4.33 (q, J = 7.2 Hz, 2 H), 4.21 (s, 2 H), 4.15 (s, 2 H), 3.74 (s, 3 H), 3.11 (q, J = 7.2 Hz, 2 H), 3.01 (q, J = 7.2 Hz, 2 H), 1.36 (t, J = 6.9 Hz, 3 H), 0.97 (t, J = 6.9 Hz, 3 H), 0.90 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 159.7, 156.3, 152.2, 149.4, 147.6, 142.0, 140.6, 139.8, 139.2, 137.0, 133.3, 130.1, 129.0, 128.5, 128.3, 127.9, 127.8, 127.5, 126.7, 124.6, 122.9, 122.7, 121.5, 120.8, 120.0, 118.0, 113.7, 113.1, 112.3, 111.3, 107.3, 100.8, 70.6, 70.5, 69.9, 69.9, 60.6, 56.8, 56.4, 55.8, 44.8, 44.6, 14.4, 12.3, 12.1; MS (MALDI) m/z 925.46 (M − H, $C_{59}H_{61}O_8N_2$ requires 925.44). Anal. Calcd for $C_{59}H_{62}O_8N_2$: C, 76.43; H, 6.74; N, 3.02. Found: C, 76.8; H, 6.91; N, 3.23.

4-(4-(4-Allyloxy-3-methoxybenzyloxy)-3-(*N*-benzyl-*N*-ethylamino)benzyloxy)-3-(*N*-3,5-dibenzyloxybenzyl-*N*-ethylamino)benzyl Alcohol (13). Following the procedure for the preparation of **6**, a mixture of ester **11** (1.45 g, 1.56 mmol) in freshly distilled THF (40 mL) was allowed to react with LAH (0.12 g, 3.2 mmol) to afford alcohol **13** (1.35 g, 98%) as a colorless glass after purification by flash column chromatography (SiO_2, 2:1 hexanes−EtOAc): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 15 H), 6.92 (m, 6 H), 6.81 (d, J = 8.1 Hz, 1 H), 6.60 (d, J = 2.1 Hz, 2 H), 6.47 (t, J = 2.4 Hz, 1 H), 6.09 (m, 1 H), 5.41 (dd, J = 17.1, 1.5 Hz, 1H), 5.29 (dd, J = 10.2, 1.5 Hz, 1 H), 5.01 (s, 2 H), 4.94 (s, 2 H), 4.87 (s, 4 H), 4.61 (dt, J = 5.4, 1.5 Hz, 2 H), 4.23 (s, 2 H), 4.17 (s, 2 H), 3.74 (s, 3 H), 3.11 (q, J = 7.5 Hz, 2 H), 3.03 (q, J = 7.2 Hz, 2 H), 1.50 (t, J = 5.7 Hz, 1 H), 0.98 (t, J = 7.5 Hz, 3 H), 0.91 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7, 152.1, 152.0, 149.4, 147.6, 142.1, 140.5, 140.4, 139.3, 137.0, 133.5, 133.3, 130.1, 129.7, 128.5, 128.4, 127.9, 127.8, 127.5, 126.6, 121.5, 121.1, 120.9, 120.7, 119.9, 118.0, 113.9, 113.7, 113.1, 111.3, 107.3, 100.7, 70.7, 70.6, 69.9, 69.8, 65.4, 56.9, 56.5, 55.7, 44.8, 44.6, 12.3, 12.1; MS (MALDI) m/z 885.00 (M + H$^+$, $C_{57}H_{61}O_7N_2$ requires 885.45). Anal. Calcd for $C_{57}H_{60}O_7N_2$: C, 77.35; H, 6.83; N, 3.17. Found: C, 76.96; H, 7.11; N, 3.19.

4-(4-(4-Allyloxy-3-methoxybenzyloxy)-3-(*N*-benzyl-*N*-ethylamino)benzyloxy)-3-(*N*-3,5-dibenzyloxybenzyl-*N*-ethylamino)benzyl Chloride (14). Following the procedure for the preparation of **2**, a mixture of alcohol **13** (2.10 g, 2.37 mmol) in freshly distilled CH_2Cl_2 (50 mL) was allowed to react with $SOCl_2$ (0.19 mL, 2.6 mmol) and DMF (0.5 mL) to provide chloride **14** (2.10 g, 98%) as a colorless glass: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 15 H), 6.88 (m, 9 H), 6.57 (d, J = 1.8 Hz, 2 H), 6.47 (t, J = 2.1 Hz, 1 H), 6.08 (m, 1 H), 5.40 (dd, J = 1.5, 17.1 Hz, 1H), 5.29 (dd, J = 1.5, 10.2 Hz, 1 H), 5.00 (s, 2 H), 4.94 (s, 2 H), 4.86 (s, 4 H), 4.60 (dt, J = 1.5, 5.4 Hz, 2 H), 4.51 (s, 2 H), 4.23 (s, 2 H), 4.16 (s, 2 H), 3.74 (s, 3 H), 3.09 (q, J = 6.9 Hz, 2 H), 3.02 (q, J = 6.9 Hz, 2 H), 0.98 (t, J = 7.5 Hz, 3 H), 0.90 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 159.7, 152.5, 152.1, 149.4, 147.6, 141.9, 140.5, 140.4, 139.3, 137.0, 133.3, 130.1, 129.9, 129.5, 128.5, 128.4, 127.9, 127.8, 127.5, 126.6, 122.5, 121.9, 121.5, 120.9, 120.0, 118.0, 113.7, 113.6, 113.1, 111.3, 107.3, 100.8, 70.7, 70.6, 69.9, 69.9, 56.8, 56.5, 55.8, 46.8, 44.7, 44.6, 12.4, 12.1; MS (MALDI) m/z 901.43 (M − H, $C_{57}H_{58}O_6N_2Cl$ requires 901.40). Anal. Calcd for $C_{57}H_{59}ClO_6N_2$: C, 75.77; H, 6.58; N, 3.10. Found: C, 75.72; H, 6.97; N, 3.17.

4-(4-(4-Allyloxy-3-methoxybenzyloxy)-3-(*N*-benzyl-*N*-ethylamino)benzyloxy)-3-(*N*-3,5-dibenzyloxybenzyl-*N*-ethylamino)benzyl Alcohol, 4-Nitrophenyl Ether (15). A mixture of **14** (0.79 g, 0.87 mmol), *p*-nitrophenol (0.15 g, 1.0 mmol), K_2CO_3 (0.25 g, 1.7 mmol), and DMF (30 mL) was maintained at 50 °C under argon for 24 h. Et_2O (60 mL) was added, and the mixture was washed with satd aqueous $NaHCO_3$ solution (5 × 100 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford a light yellow oil. Purification of the crude oil was conducted by flash column chromatography (SiO_2, 4:1, hexanes−EtOAc) to afford **15** (0.41 g, 47%) as a light yellow glass: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, J = 9.3 Hz, 2 H), 7.27 (m, 17 H), 6.88 (m, 11 H), 6.56 (d, J = 2.7 Hz, 2 H), 6.47 (t, J = 2.4 Hz, 1 H), 6.09 (m, 1 H), 5.40 (dd, J = 17.1, 2.1 Hz, 1 H), 5.29 (dd, J = 10.8, 0.9 Hz, 1 H), 5.02 (s, 4 H), 4.95 (s, 2 H), 4.86 (s, 4 H), 4.61 (dt, J = 5.4, 1.5 Hz, 2 H), 4.24 (s, 2 H), 4.17 (s, 2 H), 3.74 (s, 3 H), 3.12 (q, J = 6.9 Hz, 2 H), 3.03 (q, J = 6.9 Hz, 2 H), 0.98 (t, J = 6.9 Hz, 3 H), 0.91 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 159.7, 152.5,

152.1, 149.4, 147.6, 141.9, 141.4, 140.5, 140.4, 139.3, 137.00, 133.3, 129.5, 128.4, 127.94, 127.86, 127.7, 127.5, 126.6, 125.8, 121.6, 121.5, 121.0, 120.9, 120.0, 118.0, 114.8, 113.7, 113.7, 113.1, 111.3, 107.3 100.6, 70.9, 70.7, 70.6, 69.9, 69.8, 56.6, 56.5, 55.8, 45.1, 44.6, 12.4, 12.1; MS (MALDI) m/z 1007.26 (M + $2H^+$, $C_{63}H_{65}O_9N_3$ requires 1007.47). Anal. Calcd for $C_{63}H_{63}O_9N_3$: C, 75.20; H, 6.31; N, 4.18. Found: C, 75.10; H, 6.69; N, 3.97.

Ethyl 4-(4-(4-Allyloxy-3-methoxybenzyloxy)-3-(*N*-benzyl-*N*-ethylamino)benzyloxy)-3-(*N*-3,5-dibenzyloxybenzyl-*N*-ethylamino)-3-nitrobenzoate (16). To a stirred solution of **13** (3.63 g, 4.08 mmol) in THF (50 mL) at 25 °C were successively added **3b** (0.79 g, 3.7 mmol), PPh_3 (1.17 g, 4.45 mmol), and diisopropyl azodicarboxylate (0.86 mL, 4.4 mmol) dropwise over 10 min. The reaction mixture was stirred at this temperature for 10 min before being placed in a sonication bath. After completion of the reaction, based on TLC analysis, the reaction mixture was diluted with Et_2O (100 mL), washed with satd aqueous $NaHCO_3$ solution (6 × 200 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to a light yellow oil. The crude oil was purified by flash column chromatography (SiO_2, 3:1 hexanes−EtOAc) to afford **16** (3.49 g, 90%) as a light yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (d, J = 1.8 Hz, 1 H), 8.11 (dd, J = 8.7, 2.1 Hz, 1 H), 7.26 (m, 15 H), 7.06 (d, J = 9.3 Hz, 1 H), 6.90 (m, 9 H), 6.58 (d, J = 2.1 Hz, 2 H), 6.45 (t, J = 2.4 Hz, 1 H), 6.08 (m, 1 H), 5.40 (dd, J = 17.1, 2.1 Hz, 1 H), 5.28 (dd, J = 10.8, 0.9 Hz, 1 H), 5.18 (s, 2 H), 5.00 (s, 2 H), 4.93 (s, 2 H), 4.85 (s, 4 H), 4.60 (dt, J = 5.4, 1.5 Hz, 2 H), 4.36 (q, J = 7.2 Hz, 2 H), 4.24 (s, 2 H), 4.16 (s, 2 H), 3.74 (s, 3 H), 3.13 (q, J = 6.9 Hz, 2 H), 3.02 (q, J = 6.9 Hz, 2 H), 1.38 (t, J = 7.2 Hz, 3 H), 0.97 (t, J = 7.2 Hz, 3 H), 0.90 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4, 159.7, 155.0, 152.4, 152.1, 149.4, 147.6, 142.0, 140.5, 140.4, 139.7, 139.3, 137.0, 134.9, 133.3, 130.1, 129.5, 128.4, 128.3, 127.9, 127.8, 127.5, 127.1, 127.0, 126.6, 122.8, 121.5, 120.9, 120.2, 119.9, 117.9, 114.6, 113.6, 113.1, 111.3, 107.1, 100.7, 71.5, 70.7, 70.6, 69.9, 69.8, 61.4, 56.6, 56.5, 55.7, 45.1, 44.6, 14.3, 12.3, 12.1; MS (MALDI) m/z 1076.44 (M − H, $C_{66}H_{66}O_{11}N_3$ requires 1076.47). Anal. Calcd for $C_{66}H_{67}O_{11}N_3$: C, 73.52; H, 6.26; N, 3.90. Found: C, 73.72; H, 6.65; N, 3.79.

Ethyl 3-Amino-4-(4-(4-allyloxy-3-methoxybenzyloxy)-3-(*N*-benzyl-*N*-ethylamino)benzyloxy)-3-(*N*-3,5-dibenzyloxybenzyl-*N*-ethylamino)benzoate (17). Following the procedure for the preparation of **11**, a solution of **16** (4.15 g, 3.96 mmol) in THF (20 mL) was allowed to react with $SnCl_2 \cdot 2H_2O$ (4.47 g, 19.8 mmol), KBH_4 (0.21 g, 4.0 mmol), and absolute EtOH (75 mL) at 70 °C. Purification of the crude residue by flash column chromatography (SiO_2, 3:1 hexanes−EtOAc) yielded **17** (3.04 g, 77%) as a colorless glass: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (dd, J = 8.1, 1.8 Hz, 1 H), 7.26 (m, 15 H), 6.89 (m, 11 H), 6.57 (d, J = 2.1 Hz, 2 H), 6.46 (t, J = 2.4 Hz, 1 H), 6.08 (m, 1 H), 5.40 (dd, J = 17.1, 2.1 Hz, 1 H), 5.28 (dd, J = 10.8, 0.9 Hz 1H), 5.02 (s, 2 H), 4.99 (s, 2 H), 4.89 (s, 4 H), 4.60 (dt, J = 5.4, 1.5 Hz 2 H), 4.32 (q, J = 6.9 Hz, 2 H), 4.24 (s, 2 H), 4.17 (s, 2 H), 3.79 (s, 2 H), 3.74 (s, 3 H), 3.12 (q, J = 6.9 Hz, 2 H), 3.04 (q, J = 6.9 Hz, 2 H), 1.36 (t, J = 6.6 Hz, 3 H), 0.98 (t, J = 7.5 Hz, 3 H), 0.91 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 159.7, 152.4, 152.1, 150.1, 149.4, 147.6, 142.0, 140.5, 140.2, 139.3, 137.0, 136.2, 133.3, 130.1, 129.6, 128.7, 128.5, 128.3, 127.93, 127.85, 127.5, 126.6, 123.2, 121.8, 121.5, 121.2, 120.9, 120.7, 119.9, 118.0, 115.5, 113.7, 113.6, 113.1, 111.3, 110.8, 107.3, 100.6, 70.7, 70.6, 69.9, 69.8, 60.5, 56.6, 56.5, 55.7, 45.1, 44.6, 14.4, 12.4, 12.1; MS (ESI$^+$) m/z 1048.30 (M + H^+, $C_{66}H_{70}O_9N_3$ requires 1048.51). Anal. Calcd for $C_{66}H_{69}O_9N_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.86; H, 7.02; N, 4.12.)

Ethyl 4-(4-(4-(4-Allyloxy-3-methoxybenzyloxy)-3-(*N*-benzyl-*N*-ethylamino)benzyloxy)-3-(*N*-3,5-dibenzyloxybenzyl-*N*-ethylamino)benzyloxy)-3-((*N*-3,5-bis-(3,5-dibenzyloxybenzyloxy)-benzyl)-*N*-ethylamino)benzoate (18). Following the procedure for the preparation of **12**, a solution of **16** (3.15 g, 2.99 mmol) in DCE (50 mL) was allowed to react with [G-2]-CHO (2.90 g, 3.89 mmol), $NaBH(OAc)_3$ (1.52 g, 7.16 mmol), acetaldehyde (0.63 mL, 15 mmol), and AcOH (2 mL) to yield **18** (5.03 g, 97%) as a colorless oil after purification via flash column chromatography (3:1 hexanes−EtOAc): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 2 H), 7.25 (m, 35 H), 6.85 (m, 10 H), 6.63 (d, J = 2.7 Hz, 4 H), 6.60 (d, J = 2.1 Hz, 2 H), 6.54 (d, J = 1.8 Hz, 2 H), 6.52 (t, J = 2.4 Hz, 2 H), 6.43 (t, J = 3.3 Hz, 1 H), 6.41 (t, J = 2.4 Hz, 1 H), 6.08 (m, 1 H), 5.40 (dq, J = 17.1, 2.1 Hz, 1 H), 5.28 (dq, J = 10.8, 0.9 Hz, 1 H), 5.04 (s, 2 H), 4.96 (s, 8 H), 4.87 (s, 2 H), 4.85 (s, 2 H), 4.78 (s, 4 H), 4.78 (s, 4 H), 4.59 (dt, J = 5.4, 1.5 Hz, 2 H), 4.30 (q, J = 7.2 Hz, 2 H), 4.21 (s, 2 H), 4.11 (s, 2 H), 4.07 (s, 2 H), 3.10 (q, J = 7.2 Hz, 2 H), 2.98 (m, 4 H), 1.34 (t, J = 7.5 Hz, 3H), 0.96 (t, J = 7.5 Hz, 3 H), 0.86 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 160.1, 159.7, 159.6, 156.3, 152.3, 152.0, 149.4, 147.6, 142.2, 142.0, 140.5, 140.4, 139.8, 139.5, 139.4, 137.0, 136.8, 133.3, 130.1, 129.6, 128.7, 128.5, 128.4, 128.3, 127.9, 127.8, 127.53, 127.50, 126.6, 124.6, 122.9, 122.7, 121.6, 121.5, 120.8, 119.9, 118.0, 113.5, 113.4, 113.1, 112.3, 111.3, 107.3, 107.2, 106.4, 101.5, 100.8, 100.6, 70.6, 70.5, 70.0, 69.9, 69.7, 60.6, 56.9, 56.6, 56.5, 55.7, 44.8, 44.6, 44.5, 31.6, 22.7, 14.4, 14.1, 12.3, 12.2, 12.1; MS (ESI$^+$) m/z 1803.20 (M + H^+, $C_{117}H_{116}O_{15}N_3$ requires 1803.84). Anal. Calcd for $C_{117}H_{115}O_{15}N_3$: C, 77.93; H, 6.43; N, 2.33. Found: C, 77.58; H, 6.60; N, 2.41.

4-(4-(4-(4-Allyloxy-3-methoxybenzyloxy)-3-(*N*-benzyl-*N*-ethylamino)benzyloxy)-3-(*N*-3,5-dibenzyloxybenzyl-*N*-ethylamino)-benzyloxy)-3-((*N*-3,5-bis-(3,5-dibenzyloxybenzyloxy)benzyl)-*N*-ethylamino)benzyl Alcohol (19). Following a modified procedure for the preparation of **8**, a mixture of **18** (2.45 g, 1.5 mmol), LAH (0.11 g, 2.9 mmol), and THF (10 mL) was allowed to react by slowly warming the initial suspension from −78 °C to rt and worked up as described previously to yield **19** (2.15 g, 83%) as a colorless glass after purification via flash column chromatography (3:1 hexanes−EtOAc): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 35 H), 6.87 (m, 12 H), 6.62 (d, J = 2.5 Hz, 4 H), 6.57 (d, J = 2.5 Hz, 2 H), 6.54 (d, J = 2.5 Hz, 2 H), 6.52 (t, J = 2.5 Hz, 2 H), 6.42 (t, J = 2.5 Hz, 1 H), 6.41 (t, J = 2.5 Hz, 1 H), 6.08 (m, 1 H), 5.40 (dq, J = 17.1, 2.1 Hz, 1 H), 5.28 (dq, J = 10.8, 0.9 Hz, 1 H), 5.00 (s, 2 H), 4.96 (s, 8 H), 4.87 (s, 2 H), 4.78 (s, 8 H), 4.59 (dt, J = 5.4, 1.5 Hz, 2 H), 4.51 (d, J = 6 Hz, 4 H), 4.21 (s, 2 H), 4.12 (s, 4 H), 4.09 (s, 4 H), 3.72 (s, 3 H), 3.09 (q, J = 7 Hz, 2 H), 2.99 (m, 6 H), 1.45 (t, J = 6 Hz, 1 H; ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.1, 159.63, 159.57, 152.12, 152.07, 152.0, 149.4, 147.6, 142.22, 142.16, 140.5, 140.4, 140.3, 139.5, 139.4, 137.0, 136.8, 133.5, 133.3, 130.1, 129.7, 129.5, 128.5, 128.4, 128.3, 127.9, 127.8, 127.5, 127.5, 126.6, 121.6, 121.5, 121.1, 120.9, 120.7, 119.9, 117.9, 113.9, 113.6, 113.4, 113.1, 111.3, 107.3, 107.2, 106.4, 101.5, 100.74, 100.67, 70.8, 70.6, 70.0, 69.9, 69.8, 69.7, 65.4, 57.0, 56.7, 56.5, 55.7, 44.9, 44.7, 44.6, 12.4, 12.2, 12.1; MS (ESI$^+$) m/z 1761.20 (M + H^+, $C_{115}H_{114}O_{14}N_3$ requires 1761.83). Anal. Calcd for $C_{115}H_{113}O_{14}N_3$: C, 78.43; H, 6.47; N, 2.39. Found: C, 78.09; H, 6.32; N, 2.39.

4-(4-(4-(4-Allyloxy-3-methoxybenzyloxy)-3-(*N*-benzyl-*N*-ethylamino)benzyloxy)-3-(*N*-3,5-dibenzyloxybenzyl-*N*-ethylamino)-benzyloxy)-3-((*N*-3,5-bis-(3,5-dibenzyloxybenzyloxy)benzyl)-*N*-ethylamino)benzyl Alcohol, 4-Nitrophenyl Ether (20). Following the procedure used for the preparation of **9**, a mixture of **19** (1.06 g, 0.60 mmol), *p*-nitrophenol (0.17 g, 1.2 mmol), PPh_3 (0.31 g, 1.2 mmol), THF (15 mL), and diethyl azodicarboxylate (0.19 mL, 1.2 mmol) yielded, after recrystallization from ether−hexanes (1:5), **20** (0.644 g, 57%) as yellow needle-like crystals: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (m, 4 H), 7.25 (m, 35 H), 6.88 (m, 10 H), 6.61 (d, J = 2.3 Hz, 4 H), 6.55 (d, J = 2.1 Hz, 2 H), 6.52 (m, 4 H), 6.43 (t, J = 3.1 Hz, 1 H), 6.41 (t, J = 2.2 Hz, 1 H), 6.08 (m, 1 H), 5.40 (dq, J = 17.1, 2.1 Hz, 1 H), 5.28 (dq, J = 10.8, 0.9 Hz, 1 H), 5.00 (s, 2 H), 4.95 (s, 8 H), 4.88 (s, 2 H),

4.87 (s, 2 H), 4.79 (s, 4 H), 4.78 (s, 4 H), 4.59 (dt, J = 5.4, 1.5 Hz, 2 H), 4.24 (s, 2 H), 4.12 (s, 2 H), 4.10 (s, 2 H), 3.72 (s, 3 H), 3.10 (q, J = 7.0 Hz, 2 H), 3.00 (m, 4 H), 0.96 (t, J = 7.0 Hz, 3 H), 0.87 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7, 160.0, 159.6, 159.5, 152.5, 152.1, 152.0, 149.3, 147.5, 142.1, 141.8, 141.3, 140.4, 140.2, 139.4, 139.3, 137.0, 136.7, 133.3, 130.1, 129.6, 129.2, 130.1, 129.6, 129.2, 126.6, 125.7, 128.5, 128.4, 128.3, 127.90, 127.88, 127.73, 127.68, 127.5, 127.4, 121.7, 121.6, 121.5, 121.1, 120.9, 119.9, 117.9, 114.8, 113.7, 113.5, 113.3, 113.0, 111.2, 107.3, 107.1, 106.3, 101.3, 100.6, 70.8, 70.7, 70.53, 70.51, 70.0, 69.8, 69.7, 69.6, 56.64, 56.57, 56.5, 55.7, 45.1, 44.7, 44.5, 12.4, 12.2, 12.1; MS (ESI$^+$) m/z 1882.20 (M + H$^+$, $C_{121}H_{117}O_{16}N_4$ requires 1882.85). Anal. Calcd for $C_{121}H_{116}O_{16}N_4$: C, 77.21; H, 6.21; N, 2.98. Found: C, 77.60; H, 6.60; N, 2.85.

General Conditions for Disassembly. All disassembly experiments (compounds **9**, **15**, **20**) were performed under identical conditions. Stock solutions of the substrate (2.17 mM in DMF), KBH_4 (1 mg/mL in DMF), and $PdCl_2(PPh_3)_2$ (1 mg/mL in DMSO) were prepared. Disassembly trials were performed by adding 30 μL of the stock substrate solution to 1.7 mL of the stock KBH_4 solution in a UV cuvette and shaking vigorously. MeOH (100 μL) was then added to the mixture, and again the mixture was mixed thoroughly via shaking. The UV instrument was then autozeroed to this mixture, after which 20 μL of the stock catalyst solution was added. A final mixing of the solution by shaking the cuvette preceded initiation of the UV time−course experiment. Absorbance data points were collected at 421 nm every 0.1 s.

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Supporting Information Available: General experimental methods and NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.