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Synthesis and Characterization of Fluorescent Poly(aromatic amide) Dendrimers

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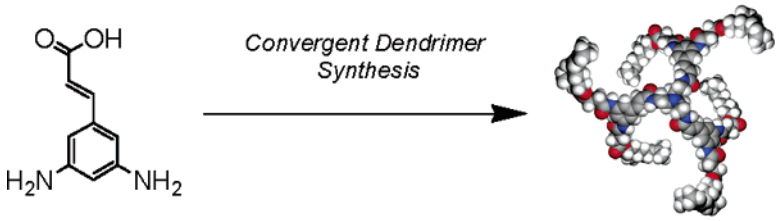

The synthesis of a series of poly(aromatic amide) dendrimers up to the second generation is described herein. The AB_2 building block used throughout the synthesis of the dendrimers was the allyl ester of 3,5-diaminocinnamic acid, which has been synthesized from 3,5-dinitrobenzoic acid in good yield with use of a four-step procedure. Dendron synthesis was achieved via a convergent approach with use of a sequence of deprotection/coupling steps. Two commercially available alcohols, L-menthol and citronellol, were coupled to the AB_2 monomer by using an alkyl diacid spacer and two core units; 1,7-diaminoheptane and tris(2-aminoethyl)amine have been used to produce the final dendrimers. Characterization was carried out by NMR and IR spectroscopies, MALDI-TOF mass spectrometry, GPC, and DSC. The novel monomer and dendritic derivatives exhibited a strong fluorescence emission in the visible region ($\lambda \approx 500$ nm) of the spectrum and a weak emission in the near-infrared ($\lambda \approx 850$ nm) upon excitation in the near-UV region. The fluorescence emission characteristics were found to be solvent and dendrimer generation dependent.

Introduction

Linear aromatic polyamides exhibit high tensile strength, elasticity, and high melting points and are thus suited for use as high-performance fiber materials.[1] These properties are attributable to the rigidity of the polymer backbone and to the presence of polar groups which give rise to dipolar interactions and the formation of extended hydrogen bonding networks between aligned polymer chains. However, the semicrystalline nature of aromatic polyamides often renders them insoluble in common organic solvents and hence these polymers are difficult to process.[2] One approach to circumvent the problem of poor processability has been the introduction of flexible spacers into the polymer backbone that then separate the rigid polyamide moieties. Although this method improves the processability of the polyamide material, the desirable mechanical properties suffer as a consequence.

The incorporation of branched structures[3] has also been proposed to disrupt the polyamide chain alignments and ultimately lead to a reduction of the semicrystalline nature of these systems.[2,4] For example, Kim reported[5] the preparation of the first hyperbranched poly(aromatic amide)s via homopolymerization of AB_2 monomers in the form of the amine diacid chlorides. The resultant hyperbranched poly(aromatic amide)s possessed excellent solubility characteristics in organic solvents such as *N,N*-dimethylformamide, *N*-methylpyrrolidinone, and *N,N*-dimethylacetamide. Dendritic poly(aromatic amide)s have

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also been investigated in the light of the interesting physical properties of dendrimers[6]—a notable development in this field was reported[7] by Miller and Neenan in 1990, who described the use of the convergent approach[8] to construct a poly(aromatic amide) dendrimer from 5-nitroisophthaloyl dichloride. Feast et al. have reported[9] an alternative synthesis of dendrimers of this type via a related convergent method. Since these early studies, numerous dendritic poly(aromatic amide) systems that feature modifications within the main poly(aromatic amide) backbone have been constructed by employing a variety of synthetic approaches.[10,11] For example, incorporation of a variety of linker moieties (such as aliphatic and amino acid units,[12,13] esters,[14] ethers,[15,16] and urea linkages[17]) has been utilized to improve further the solubility and viscosity characteristics of these systems.

The use of cinnamic acids in dendrimer synthesis has been reported by several research groups.[18,19] For example, Wang et al. described[18] the synthesis of cinnamoyl-coated PAMAM dendrimers and the subsequent photocyclization of the cinnamoyl residues by irradiation with UV light to obtain cyclobutane derivatives on the dendrimers' outer shell. Neubert et al. have outlined[19] the solid-phase synthesis of polyamide dendrimers up to the second generation that have potential applications in MALDI-TOF mass spectrometric analysis.

In this paper we describe the synthesis, characterization, and photophysical properties of a series of novel poly(aromatic amide) dendrimers that are based upon the branched repeat unit 3,5-diaminocinnamic acid. These dendritic systems were found to be soluble in a wide range of organic solvents and exhibited a strong fluorescence emission in the visible region ($\lambda \approx 500$ nm) of the spectrum in addition to a weaker emission in the near-infrared ($\lambda \approx 850$ nm) upon excitation in the near-UV region. The fluorescence emission characteristics were found to be solvent dependent, indicating a strong dependence of solvent polarity and hydrogen bonding character on both the excited-state energies and the nonradiative relaxation rates in these compounds.

Results and Discussion

Synthesis of the Poly(aromatic amide) Dendrimers. The cinnamic acid derivative 3,5-diaminocinnamic acid **1** was chosen as a suitable building block for the construction of a novel series of poly(aromatic amide) dendrimers. However, the selection of a convergent approach to these dendrimers via selective coupling between the orthogonal amine and carboxylic acid functionalities necessitated the use of protecting group chemistries. Initial studies encompassed the use of ethyl or *tert*-butyl esters as the protecting groups for the acid functionality. However, selective hydrolysis of these protecting groups was found not to be compatible with the convergent dendrimer synthesis and led to degradation of the monomer. In light of these results, the allyl ester protecting group was utilized. This protecting group has been shown to be stable under mild basic or acidic conditions and can be cleaved readily with high selectivity by an allyl-transfer reaction in the presence of a palladium catalyst and a nucleophilic allyl acceptor or hydride transfer agents.[20] The fully protected/masked monomer **2** was obtained in two synthetic steps from the commercially available 3,5-dinitrobenzoic acid **3** (Scheme 1). This synthetic route involved the selective reduction of 3,5-dinitrobenzoic acid **3** to 3,5-dinitrobenzaldehyde **4** via a one-pot reduction−oxidation process with borane−dimethyl sulfide (BMS) followed by treatment with pyridinium chlorochromate (PCC).[21] The resultant aldehyde **4** was then reacted with allyl diethylphosphonoacetate under Wadsworth−Horner−Emmons conditions to achieve the dinitrocinnamate **2** in 67% yield.[22]

The dinitrocinnamate **2** was isolated as single white crystals that were subjected to X-ray crystallographic analysis (see Figure 1a). Reduction of the two nitro groups was achieved with tin(II) chloride[23] in a mixture of THF/H_2O 50:50 to afford the desired 3,5-diaminocinnamic acid allyl ester **5** in good yield (85%) as yellow crystals that were also subjected to X-ray crystallographic analysis. Solid-state analysis revealed clearly that, in contrast to the dinitrocinnamate **2**, in which the phenyl ring and the allyl ester moiety were not coplanar, the extensive conjugation of diaminocinnamate **5** was maintained throughout the structure by adopting a coplanar conformation (Figure 1b). This result is in agreement with the solid-state structures of related cinnamic acid derivatives reported in the literature,[24] whereby the phenyl and the carboxyl groups are almost always coplanar. However, the solid-state structure of 3,5-

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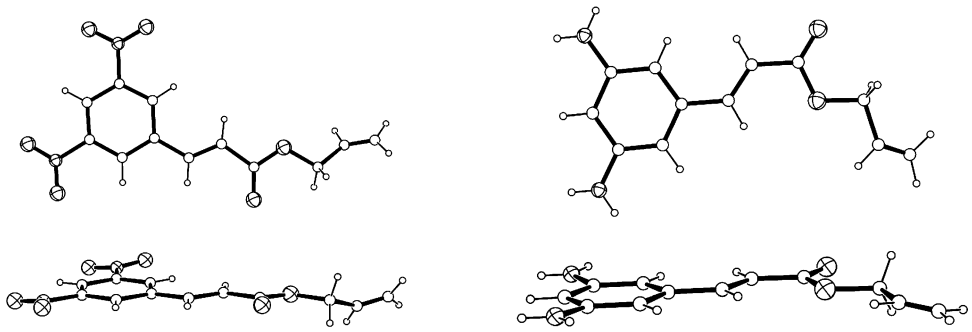
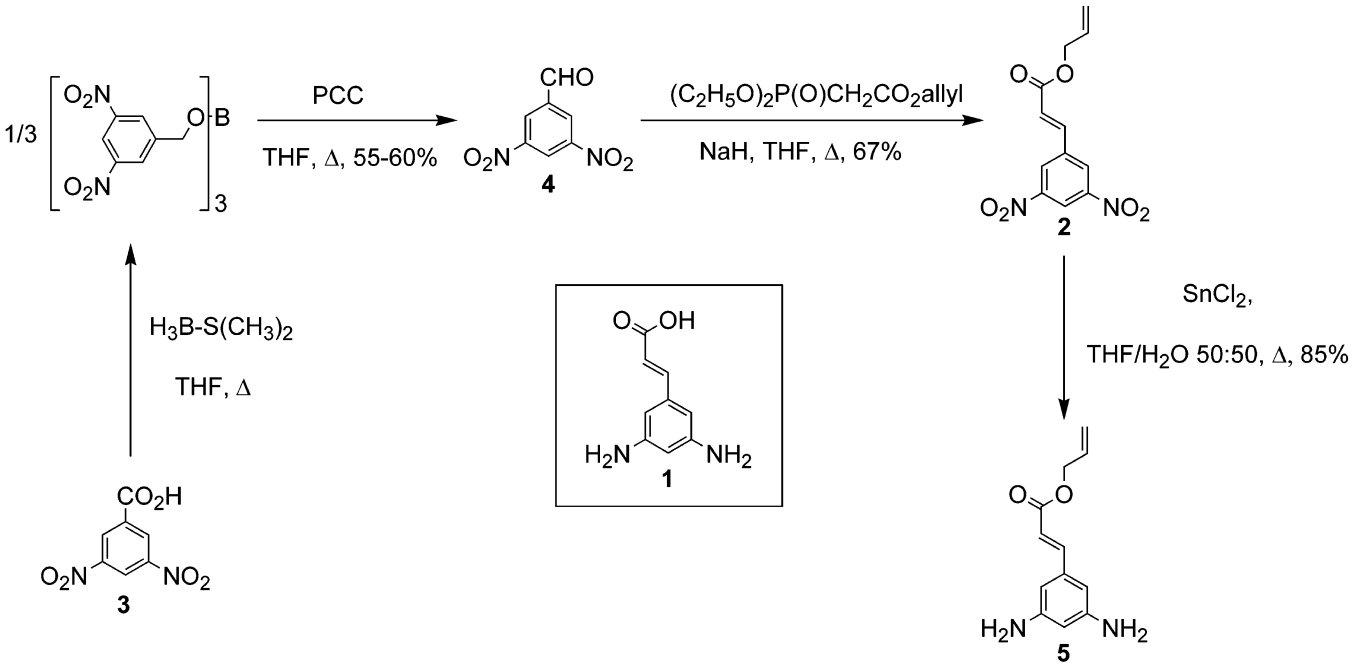


FIGURE 1. (a) Two views of the solid-state structure of the 3,5-dinitrocinnamic acid allyl ester **2**. (b) Two views of the solid-state structure of the 3,5-diaminocinnamic acid allyl ester **5**. (Atom labels: clear circles, medium carbon, small hydrogen; hashed circles, large oxygen, medium nitrogen).

SCHEME 1. Synthesis of 3,5-Diaminocinnamic Acid Allyl Ester 5, a Novel AB_2 Monomer



dinitrocinnamic acid reported[25] by Desiraju et al. exhibited a 28° intramolecular twist between carboxy and aromatic groups. Interestingly, this compound was found to crystallize as an O−H···O dimer wherein the hydrogen-bonded molecules are related by a 2-fold rotation axis rather than by an inversion center—more typical for this class of compounds. The diaminocinnamate **5**, a novel AB_2 monomer, was then employed successfully as the key building block in the convergent synthesis of the desired poly(aromatic amide) dendrimers.

The solubility of the dendritic systems was a major requirement to obtain materials that could be further modified and processed under a wide range of reaction conditions. It was envisaged that the synthesis of the monomer-linker-solubilizing group as the first step in the convergent synthesis of the dendrons would improve the solubility of the aromatic amide systems and render the synthesis facile. Bulky terpene derived units (citronellol and L-menthol, respectively) were thus coupled to the spacer molecule chosen, succinic acid, via an ester linkage.[26] The ester bond was obtained by ring opening succinic anhydride under basic conditions thus affording a transparent oil **6** and a white solid **7** in yields of 90% and 95%, respectively. The carboxylic acid derivatives **6** and **7** were then reacted onto the amine groups of monomer **5**, thereby leading to the first generation dendrons **8** and **9** respectively with ester groups at the periphery and at the focal point. Synthesis of the dendron C_2-[G-1]-CO_2Allyl **8** involved the use of a combination of the coupling reagents 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) and 4-hydroxyazabenzotriazole (HOAt)[27] and high yields (ca. 90%) were obtained although complete conversion of the starting materials required significant reaction times (up to 4

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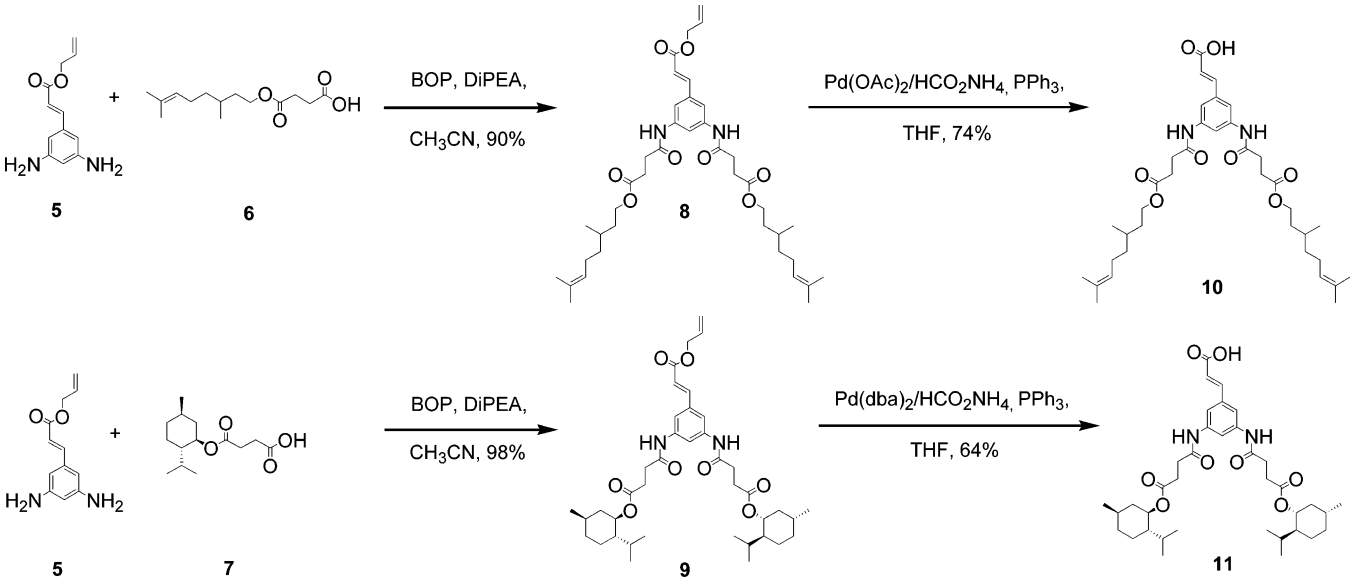
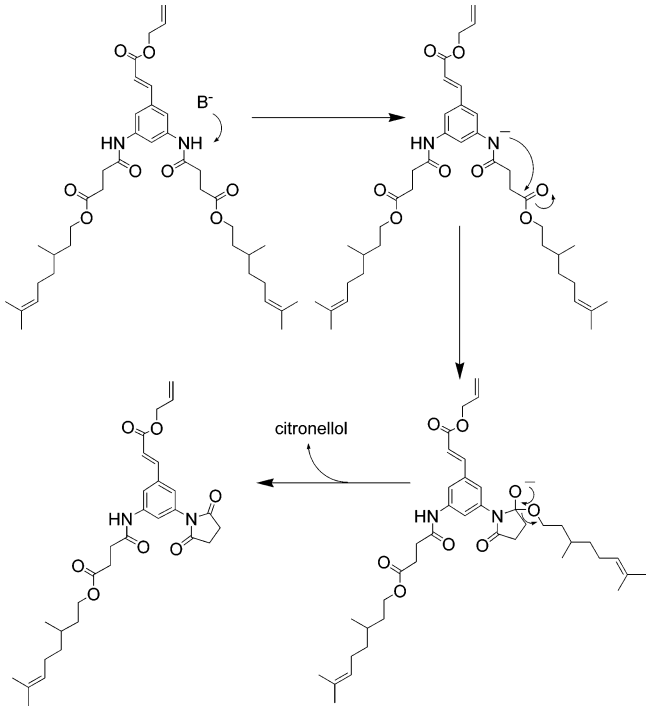
SCHEME 2. Synthesis of the First Generation Dendrons 8−11



days). More efficient coupling of **6** with the diaminocinnamate **5** was obtained when benzotriazol-1-yloxytris-(dimethylamino)phosphonium hexafluorophosphate (BOP) was used in acetonitrile.[28] As a consequence the use of the BOP coupling agent was adopted in the synthesis of the dendron M_2-[G-1]-CO_2Allyl **9** and excellent yields (up to 98%) were obtained (Scheme 2).

The cleavage of the allyl ester at the dendron focal point of dendron **8** was attempted initially with $Pd(PPh_3)_4$ and morpholine in THF at room temperature.[29] Under these conditions morpholine behaves as a reversible allyl scavenger thereby promoting the reductive elimination of Pd^0 with subsequent formation of the byproduct *N*-allyl morpholine. However, when subjected to these conditions detrimental degradation of the starting material **8** was observed after a short period (ca. 1 h), while insignificant cleavage of the allyl ester occurred. An improvement was observed when the more stable palladium source, $Pd(OAc)_2$, was used in the presence of PPh_3; however, the yield of the C_2-[G-1]-CO_2H **10** was poor (27%) and significant decomposition of the monomer was again observed. A closer understanding of this phenomenon was obtained by evaluating the effect of the base upon the substrate by stirring a solution of the dendron **8** in the presence of morpholine in THF at room temperature. Thin layer chromatographic analysis revealed a progressive decrease in the concentration of the starting material **8** with the simultaneous increase in concentration of citronellol. Therefore, it was proposed that the base was responsible for the deprotonation of the amide proton that in turn triggered an intramolecular nucleophilic condensation onto the other carboxyl unit of the succinate moiety with the result of the elimination of citronellol as the leaving group (Scheme 3). Kunz et al.[30] have observed similar substrate decomposition during the cleavage of allyl groups from dipeptides. Therefore, the

SCHEME 3. Proposed Succinimide Formation under Basic Conditions



base-sensitivity of dendron **8** encouraged the trial of milder deprotection conditions. Some of the first allyl scavenger systems used in palladium-catalyzed allylic cleavage were formic acid or ammonium formate.[31] Under these conditions, allyl cleavage for the dendron **8** occurred smoothly with no evidence of detrimental side reactions. A range of palladium catalysts was examined to optimize this deprotection procedure (see Table 1) and the use of $Pd(OAc)_2$ afforded the optimum results. This optimized allyl protection/deprotection method at the focal point of the aromatic amide dendrons proved to be an efficient

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TABLE 1. The Different Reaction Conditions Employed To Cleave Selectively the Allyl Ester Functionality of the Dendron C_2-[G-1]-CO_2Allyl 8

entry	catalyst	base	solvent	yield, %
1[29]	$P[PPh_3]_4$	morpholine	THF	
2[32]	$Pd(OAc)_2$, PPh_3	morpholine	THF	27
3[33]	$Pd[PPh_3]_4$	HCO_2NH_4	THF	56
4	$Pd(dba)_2$, PPh_3	HCO_2NH_4	THF	47
5	$Pd(OAc)_2$, PPh_3	HCO_2NH_4	THF	74

synthetic strategy and was, therefore, employed to generate the desired poly(aromatic amide) dendrimers bearing either citronellol or L-menthol as the peripheral groups.

The synthesis of M_2-[G-1]-CO_2H **11** was carried out according to the procedures described in the case of the synthesis of C_2-[G-1]-CO_2H **10**. Cleavage of the allyl group of **9** was achieved with $Pd(OAc)_2$ or $Pd(dba)_2$ in the presence of PPh_3 and ammonium formate in reasonable yield (from 45% to 64%). Interestingly, the reaction yields were lower than those reported for the allyl cleavage of **8**, and the optimum results were obtained when $Pd(dba)_2$ was employed.

Synthesis of citronellol and L-menthol second generation dendrons C_4-[G-2]-CO_2Allyl **12** and M_4-[G-2]-CO_2-Allyl **13** was carried out by coupling the dendrons **10** and **11** with monomer **5**. BOP was used initially as the coupling reagent. However, the poor yields and prolonged reaction times observed in the coupling of the cinnamate **5** with **10** and **11** suggested the use of more active coupling agents such as *O*-(7-azabenzotriazol-1-yl-)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate, (HATU) (a so-called "second generation" uronium coupling reagent).[34] Uronium salts of this type are employed widely in peptide chemistry for amide bond formation in solution or in the solid phase; however, there are only a few examples reported in polyamide dendrimer synthesis.[15] The use of HATU in the presence of HOAt allowed the successful synthesis of the second generation dendrons as white solids in excellent yields (69% in the case of C_4-[G-2]-CO_2Allyl **12** and 95% in the case of M_4-[G-2]-CO_2Allyl **13**). Treatment of these compounds under the palladium-promoted allyl cleavage conditions (vide supra) led to the formation of the desired dendrons **14** and **15** as pale yellow solids in reasonable yields (39−69%) (Scheme 4).

A range of catalyst systems was tested to achieve optimum allyl cleavage conditions for the second generation dendrons and the results are reported in Table 2. Cleavage of the allyl group from M_4-[G-2]-CO_2Allyl **13** with a combination of $Pd(PPh_3)_4$ and ammonium formate led to higher yield (69%) of the desired acid product than when the reaction was performed on M_2-[G-1]-CO_2Allyl **9** (64%). There was no definite trend to describe the reactivity of the allyl scavenger catalysts as each allyl-protected dendron required different catalyst combinations to attain the optimum cleavage of the carboxylic acid focal point protecting group.

The dendrimers were constructed from [G-0] to [G-2] by the coupling of each dendritic wedge to either bifunctional or trifunctional central core units. The synthesis of the simple zero generation species was carried out by direct coupling of the citronellol/L-menthol-spacer moieties to the central units to afford simple aliphatic skeletons. In contrast, however, the higher generation dendritic species all featured highly conjugated polyaromatic structures. The syntheses of the zero generation dendrimers possessing a bifunctional core unit were carried out with EDCI/HOAt as the coupling agent and co-reagent, respectively. The products were isolated as either a solid (C_2-[G-0]$_2$-C **16**) or as oil (M_2-[G-0]$_2$-C **17**) in good yields (55−86%) following purification via column chromatography. Synthesis of the zero generation with the trifunctional core C_3-[G-0]$_3$-N **18** and M_3-[G-0]$_3$-N **19** was also achieved in respectable yields (41−70%).

Synthesis of the first generation dendrimers was carried out initially with EDCI/HOAt as the coupling reagent system, but the yields were very poor. In particular, the synthesis of M_4-[G-1]$_2$-C **20** was achieved in only 10% yield while formation of M_6-[G-1]$_3$-N **21** was not observed even after prolonged reaction times. Amides possess high rotational barriers around the amide C−N bond and thereby "lock" the conformation of bulky dendritic structures rendering the coupling step very difficult.[35] However, use of more efficient coupling reagents such as BOP afforded M_4-[G-1]$_2$-C **20** as a white solid in excellent yield (96%) and M_6-[G-1]$_3$-N **21** as a pale yellow solid in moderate yield (48%) over a prolonged reaction time (48 h). The BOP reagent was also used in the synthesis of C_4-[G-1]$_2$-C **22** and C_6-[G-1]$_3$-N **23**. These dendrimers were obtained after purification by column chromatography as pale yellow solids in acceptable yields (98% and 28%, respectively), in agreement with the results obtained for the series of L-menthol first generation dendrimers (Scheme 5). Synthesis of the second-generation dendrimers was achieved by using the coupling reagent combination of HATU/HOAt leading to the desired dendrimers C_8-[G-2]$_2$-C **24** and M_8-[G-2]$_2$-C **25**. However, in the case of these bulkier and more rigid dendrimers successful isolation of the pure products required the use of repetitive silica gel column chromatography.

Molecular Modeling Studies. Although dendrimers are represented typically as symmetrical, globular structures with the end groups evenly distributed in the outer shell, several theoretical studies have investigated the end group positions, potential intermolecular interactions, and dendritic conformations under vacuum and in different solvent types.[36] Knowledge of the dendritic architecture is of great importance to establish and "tune" the physical properties of the macromolecule. Bhalgat and Roberts, for example, have carried out molecular dynamics studies[37] on a series of PAMAM dendrimers up to the third and fourth generation and demonstrated that as the molecular size increased the structures adopted more dense and spherical conformations.

In this study, the electronic structure of the first generation dendrimer C_6-[G-1]$_3$-N **23** was investigated

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SCHEME 4. Synthesis of the Second Generation Dendrons

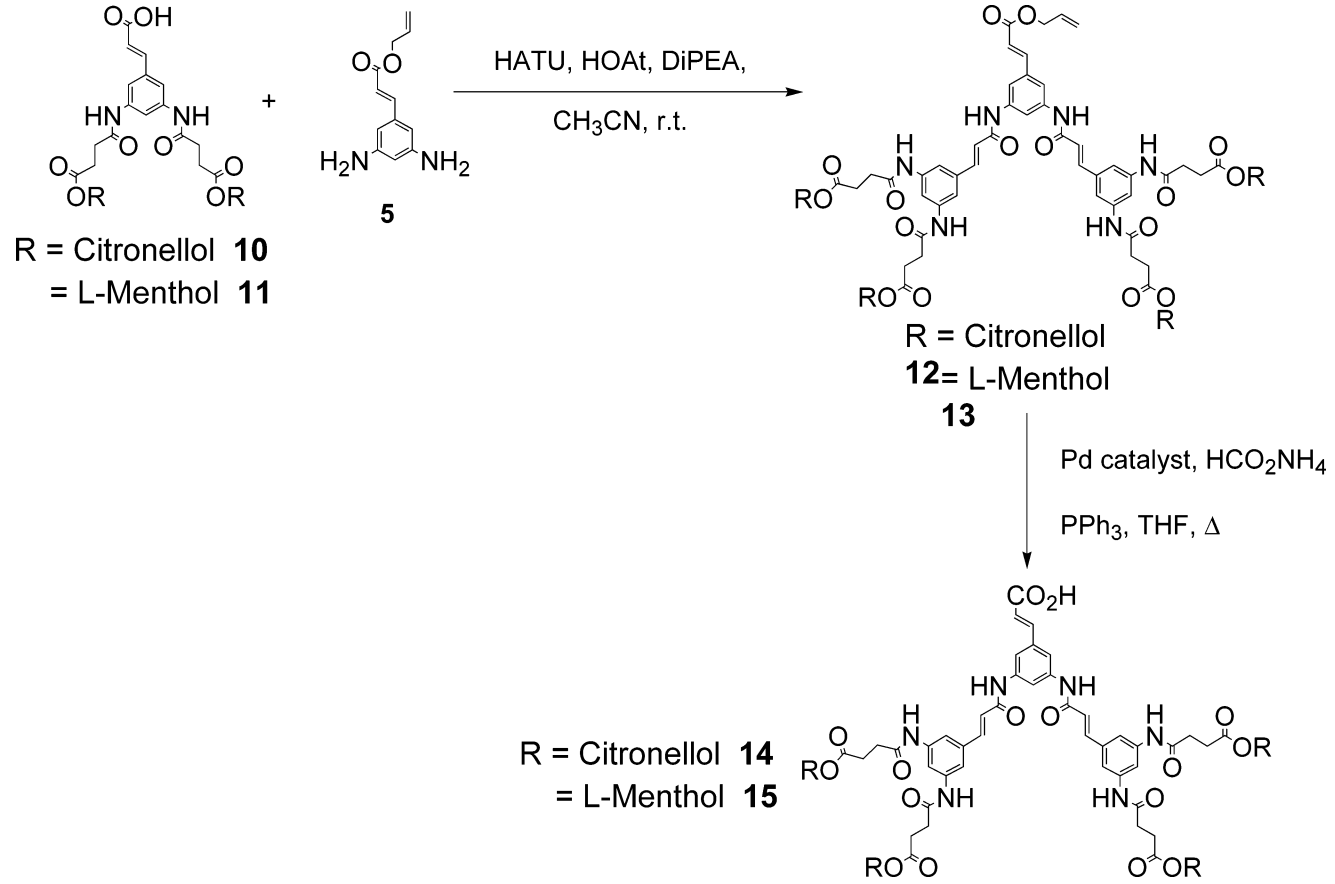

TABLE 2. Different Catalytic Systems Used for the Cleavage of the Allyl Ester of Second Generation Dendrons (12 and 13)

substrate	catalyst	additives, solvent	yield, %
C_4-[G-2]-CO_2Allyl **12**	$Pd(PPh_3)_4$	THF	67
	$Pd(OAc)_2$	PPh_3, THF	58
M_4-[G-2]-CO_2Allyl **13**	$Pd(PPh_3)_4$	THF	69
	$Pd(OAc)_2$	PPh_3, THF	39
	$Pd(dba)_2$	PPh_3, THF	56

with ab initio methods in conjunction with preliminary molecular mechanics (MM) treatment. The structure was built within Cerius2[38] and was subjected to MM energy minimization, using the Universal Force Field[39] with calculated QEq atomic charges.[40] Several successive "agitations" to this configuration were made, each consisting of a short, elevated-temperature (1000 K) molecular dynamics (MD) simulation in the NVT ensemble in the gas phase, accompanied by subsequent MM energy minimizations. These stages are employed to locate a suitable low-energy conformation of the system, such that the intended ab initio minimization has a suitable starting point. Conformational analysis cannot be used to this end as a consequence of the high flexibility of the molecule, resulting in the number of possible conformers being too numerous to digest with current computational methods. Several conformers located in this manner suggested that the system may exhibit C_3 symmetry, and atomic coordinates were adjusted in order that the molecular framework contained this symmetry. Without this approximation, any ab initio calculations on the system become rather unfeasible. In these studies, a stable conformation in which the dendrimer assumed a "spheroidal" structure was calculated (Figure 2), whereby the flexible citronellol aliphatic arms were backfolded and the aromatic rings are twisted by approximately 45° with respect to each other. This twisting of the arms and the rigidity of the conjugated double bond places the aromatic rings at a distance of 13.3 Å from each other, which disfavor intramolecular interactions between the π-systems of the cinnamate residues.[41]

Characterization of the Polyaromatic Dendrons and Dendrimers: Solubility Properties of the Dendrons and the Dendrimers. An important characteristic of dendritic molecules is the high solubility in a large number of organic solvents, thereby permitting improved processability characteristics and a wider range of applications than their linear polymeric analogous. Several studies have compared[15,42,43] the physical and chemical properties of different dendrimers with their linear

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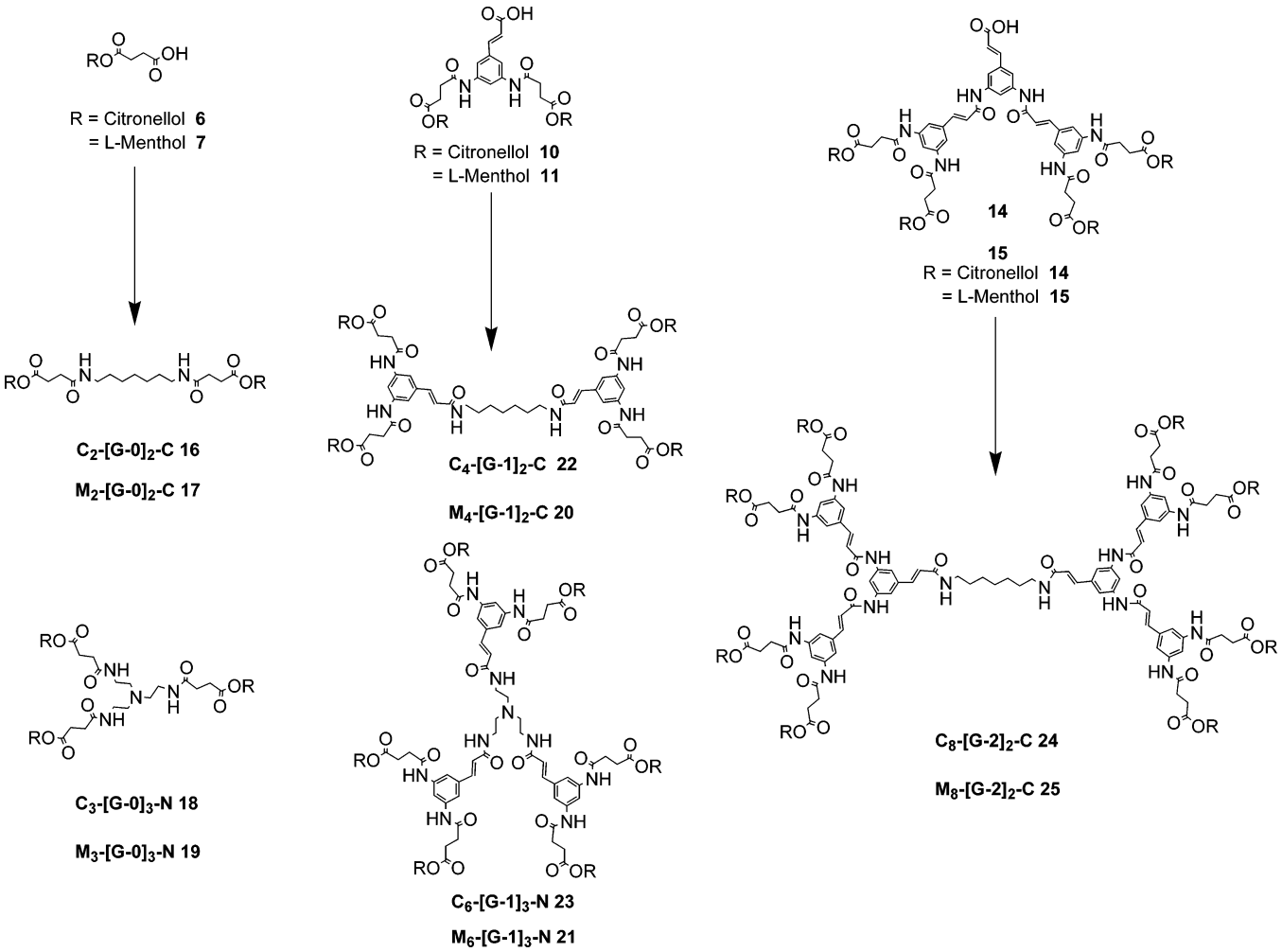
SCHEME 5. Synthesis of the Zero, First, and Second Generation Dendrimers 16–25



polymer analogues and found enhanced solubility properties for the branched systems.

Different solubility properties were found in the polyamide dendrons (**8**–**15**) and the dendrimers (**16**–**25**). In general, dendrons bearing an ester at the focal point were soluble in solvents of medium to high polarity such as halogenated solvents, THF, alcohols, acetone, and amidic solvents. However, very low solubilities were observed for these substrates in nonpolar solvents such as *n*-hexane. The dendrons bearing a carboxylic acid at the focal point were soluble in polar solvents such as THF, ethanol, and acetone. First generation dendrimers exhibited similar solubility properties to the dendrons with protected focal points, although increasing the generation limited the solubility to solvents such as acetone, DMF, and DMSO. At low concentrations, the C_8-[G-2]$_2$-C **24** dendrimer was also soluble in THF and ethanol. A comparison of the solubility properties of these systems with analogous dendrimers built via a divergent approach and possessing nitro groups at the periphery[44] confirmed that the introduction of flexible and more lipophilic groups on the external layer of the dendritic structure disrupted partially the network of noncovalent interations such as hydrogen bonding and $\pi-\pi$ stacking, and thus enhanced greatly the solubility of these polyamide dendrimers.

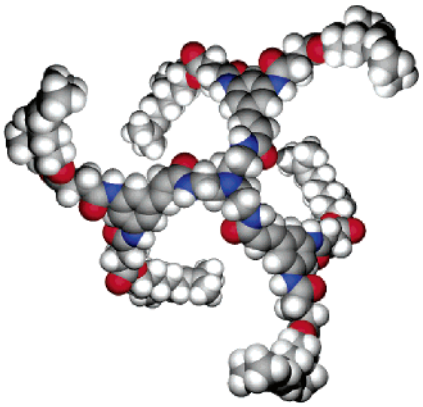


FIGURE 2. Molecular model of C_6-[G-1]$_3$-N **23** generated with molecular mechanics energy minimization and ab Initio calculations.

NMR Spectroscopic Analysis. NMR spectroscopy provides useful information toward the structural identification of dendritic macromolecules as well as the degree of purity and in some extent furnishes important information upon the solution state properties of these polyamide dendrimers. As the molecular weights of the dendrons and dendrimers synthesized were not especially

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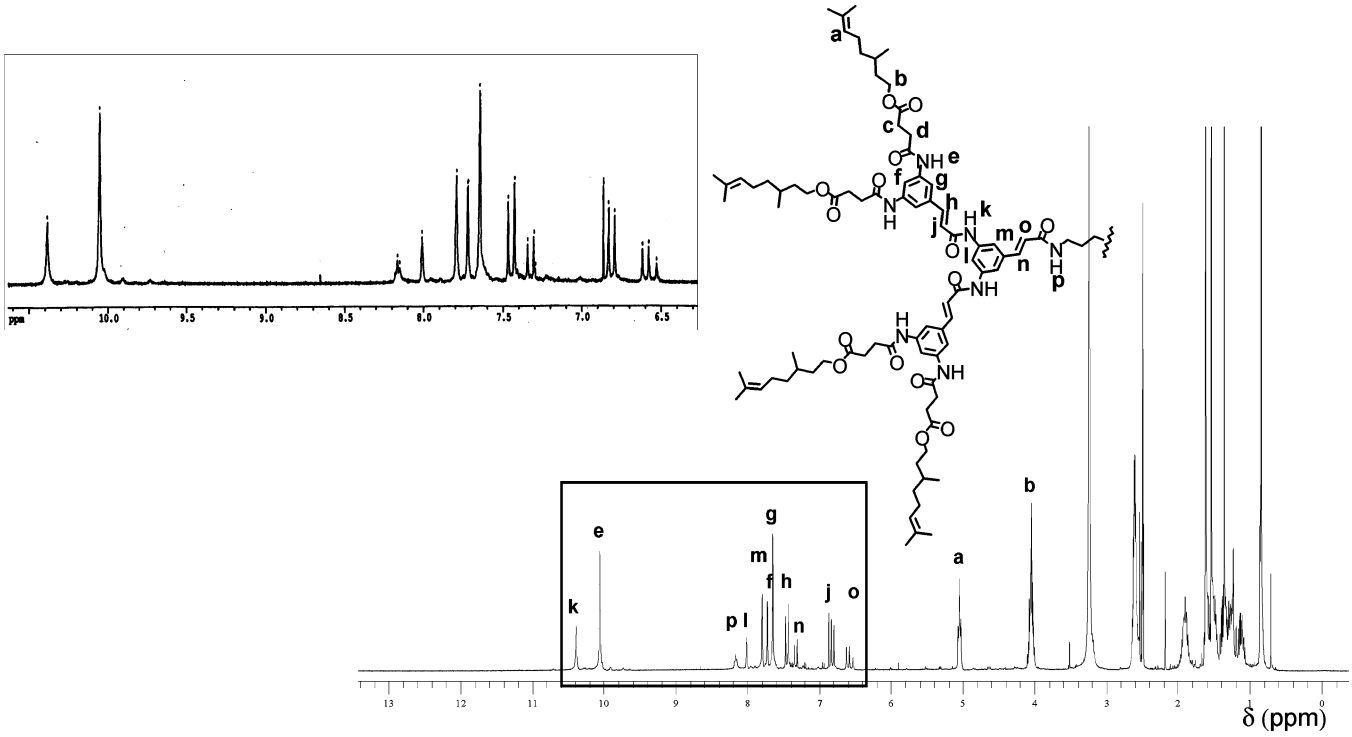

FIGURE 3. The ^{1}H NMR spectra of C_8-[G-2]$_2$-C **24** Recorded at 40 °C.

high (606 to 2997 Dalton) the ^{1}H NMR resonances of the protons of these compounds were well resolved. Several important features emerged from the ^{1}H NMR spectroscopic analysis. A significant solvent effect was observed on the series of dendrons and dendrimers bearing citronellol surface groups. Replacement of strongly hydrogen bonding solvents such as d_6-DMSO with $CDCl_3$ led to significant peak broadening, noticeable particularly in the case of the resonances of the protons in close proximity with the N−H bonds. Upon changing the solvent from d_6-DMSO to $CDCl_3$, considerable shifts to higher fields of the NH protons were also observed (0.7 ppm for the more external NH) caused by the removal of the hydrogen bonding interactions with the solvent.[45] This phenomenon is also indicative of self-aggregation (e.g., via $\pi-\pi$ aromatic stacking, hydrogen bonding) generated by the presence of a "poor" solvent, whereby the highly polar dendritic structures tend to aggregate to minimize the interactions with the solvent. In contrast, in a "good" solvent (such as d_6-DMSO), the dendrons and dendrimers were solvated readily and aggregation phenomena occurred only to a small extent.[13] The ^{1}H NMR spectra of the polyamide dendrimers and dendrons of different generations revealed significant similarities in the chemical shifts of the aliphatic moieties. However, it was noted that as the generation number increased the signals of the protons of the external aromatic rings and of the conjugated double bonds were subjected to upfield shifts (0.2 ppm) (Figure 3). Stoddart and co-workers[16] and Chow and co-workers[13] reported similar upfield shifts of proton atoms of peripheral units of polyamide dendrimer systems, which were attributed to microenviromental changes within the dendritic structure. The chemical shifts of the olefinic protons of C_8-[G-2]$_2$-C revealed an interesting feature—when the spectrum was recorded at 400 MHz and at 40 °C the resonances of the protons (j and o, Figure 3) corresponding to the trans olefins appeared unexpectedly as two sets of overlapped doublets whereas when the spectrum was recorded at 250 MHz and at room temperature these resonances appeared as normal doublets—a more common feature for trans-disubstituted olefins. These differing multiplicities may be rationalized as a "twist" of the dendritic structure to generate units that are no longer symmetrical in nature and therefore experience different microenvironments.

MALDI-TOF Mass Spectrometry, GPC, and DSC Characterization. MALDI-TOF mass spectrometry was used[46] to analyze the polyamide dendrons and dendrimers described above. The optimum spectra were obtained when α-cyano-4-hydroxycinnamic acid was used as the matrix and the detector was used in linear mode. Under these conditions all the compounds analyzed afforded excellent signal/noise ratios without the addition of cationization agents. However, in conjunction with the molecular ion peak, the corresponding sodiated and potassiated adducts were also detected (these cations are present as impurities in glassware), indicating relatively high cation affinities of the dendritic molecules. At high laser powers, molecular ion-matrix aggregates were also observed. MALDI-TOF mass spectrometric analysis was also used to assess the relative purity of the molecules synthesized, as in all of the dendrimers described peaks attributable to fragmentation of the sample were not observed (Figure 4).

Gel permeation chromatography (GPC) was also carried out to further confirm the purity of all dendrons and

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(46) (a) Hayes, W.; Freeman A. W.; Fréchet, J. M. J. *Polym. Mater. Sci. Eng.* **1997**, *77*(2), 136. (b) Yu D.; Vladimirov N.; Fréchet J. M. J. *Macromolecules* **1999**, *32*, 5186.

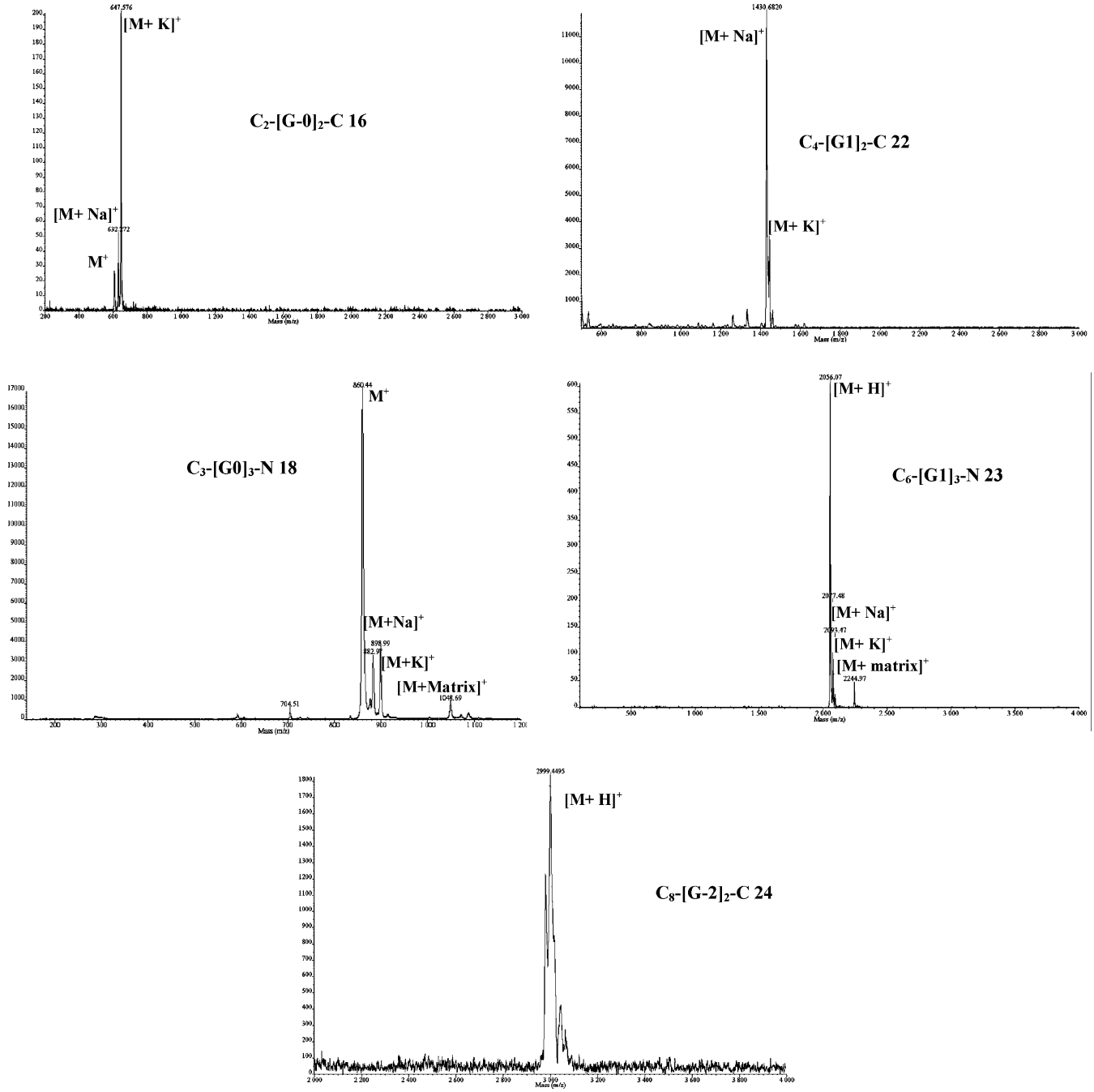

FIGURE 4. MALDI-TOF mass spectra of the citronellol dendritic family.

dendrimers and to analyze the structural changes that occur by varying the generation number and degree of branching of the core. GPC analyses of all the dendritic molecules were carried out with THF as the eluent and the retention times were compared to a set of polystyrene standards used as calibrants, to determine the average molecular weight (M_w) of the species eluted.[43a,47] The GPC traces obtained for the citronellol and L-menthol dendrimer families are shown in Figure 5. A similar trend was observed in the two families of dendrimers, whereby the M_w was found to be greater than the predicted values in the case of dendrimers possessing the bifunctional core. However, increasing the multiplicity of the core from two to three resulted in an increase in the retention time, hence M_w values that were closer to the predicted values for $[G\text{-}0]_3$-N but lower than that determined for the $[G\text{-}1]_3$-N dendrimer. This behavior indicates clearly that the dendrimers possessing a bifunctional core assumed a more open conformation in solution, resembling a random coil, whereas the dendrimers with a trifunctional core assumed a more condensed conformation in solution. Although this feature is found commonly in dendritic

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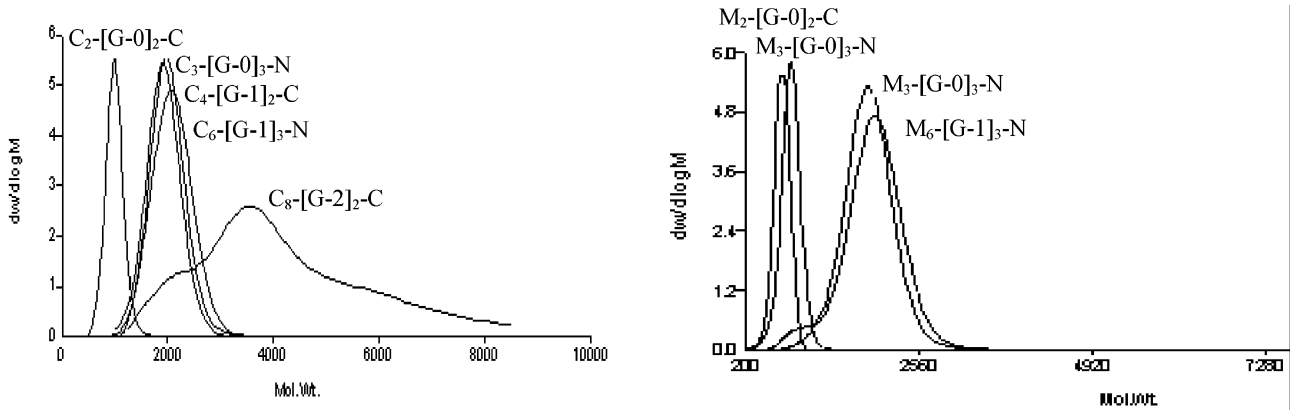

FIGURE 5. GPC traces of the citronellol and L-menthol dendritic families. (Note: Linear polymers and dendritic systems possess very different retention volumes and therefore the use of linear polystyrene calibrants will generate lower molecular weights for the dendritic samples.[43a,47])

systems, whereby the generation number of surface groups increases exponentially eventually leading to a globular conformation,[48] in the dendrimers described this phenomenon was observed at low generations, and most likely arose as a consequence of the rigidity of the dendritic amide backbone. GPC analysis of C_8-[G-2]$_2$-C **24** in THF revealed evidence for self-aggregation and interaction of the dendrimers with the solid support. The chromatograms possessed not only a long tail at high molecular weight but also shoulders corresponding to high molecular weight species were clearly visible. This behavior can be attributed to the poor solubility of these dendrimers in THF, which resulted in the formation of aggregates (note that MALDI-TOF mass spectrometric and NMR spectroscopic analyses confirmed the purity of this compound).

Differential scanning calorimetric analysis (DSC) (Supporting Information) revealed the melting ranges for the majority of the dendritic species bearing citronellol residues at the peripheral surfaces (with the exception of C_3-[G-0]$_3$-N **18**, which is an oil) thereby indicating partial crystallinity of these compounds. The zero generation aliphatic species exhibited a very low melting point (44.4−43.4 °C) as expected by consideration of the very flexible structure. However, the higher generation species possessed much higher and broader melting ranges, generally between 170 and 250 °C, as a consequence of the progressive increased rigidity of the compounds and the presence of intermolecular hydrogen bonding. Interestingly, although the two series of dendrons featured an identical cinnamic amide backbone, significant differences in the melting point characteristics were observed. For example, the dendron C_2-[G-1]-CO_2-Allyl **8** exhibited a broad melting range at high temperature (240−260 °C), typical of amide-type compounds, whereas the L-menthol dendron derivative M_2-[G-1]-CO_2-Allyl **9** revealed a well-defined melting point at low temperature (50.3−52.3 °C). The highly crystalline nature of the citronellol-derived dendrimers was demonstrated in particular by C_4-[G-2]-CO_2Allyl **12**, which possessed a very sharp melting peak between 259 and 261 °C. The corresponding dendron C_4-[G-2]-CO_2H **14** that featured a carboxyl group at the focal point exhibited a broad melting peak at a higher temperature (258−296 °C) as a consequence of the extended hydrogen bonded network involving the acid moiety and the amide groups of the dendritic backbone. However, very different melting point characteristics were exhibited by the series of L-menthol dendrimers—these systems were amorphous solids that did not exhibit detectable melting points. Furthermore, these compounds did not reveal any glass transitions (T_g) within the interval examined even after repeated scans and cooling to low temperatures.

Steady-State and Time-Resolved Fluorescence Spectroscopic Studies. In parallel with the synthetic development of novel dendrimers, attention has shifted in recent times more toward novel applications of these perfectly hyperbranched species. Although efficient photocycloaddition reactions in the solid state[49] and photoisomerization of the double bond when electronically excited by UV radiation in solution[50] of species of this type are well documented, cinnamic acid derivatives do not tend to exhibit fluorescence emissions. However, Jia and co-workers have reported[18] recently that cinnamoyl shell-modified PAMAM dendrimers did exhibit strong fluorescence emissions.

To verify if the novel cinnamic acid derivatives developed in this synthetic study revealed similar photochemical characteristics, preliminary absorption and emission spectroscopic studies of the 3,5-diaminocinnamic acid allyl ester **5** and the dendritic derivatives (**8**−**25**) that feature the diaminocinnamate moiety within the building block were carried out. Steady-state fluorescence experiments were carried out by irradiating the molecules at different wavelengths to evaluate the dependence of the emission with the excitation wavelength used. Five solutions of concentrations ranging from 0.0001 to 0.0150 mM were investigated and the emission characteristics analyzed in a solvent of low polarity such as hexane, and higher polarity such as acetonitrile (a hydrogen bond acceptor solvent) and methanol (a hydrogen bond donor and acceptor solvent). It was envisaged that these three parameters would furnish the information necessary to identify the photophysical characteristics of the species

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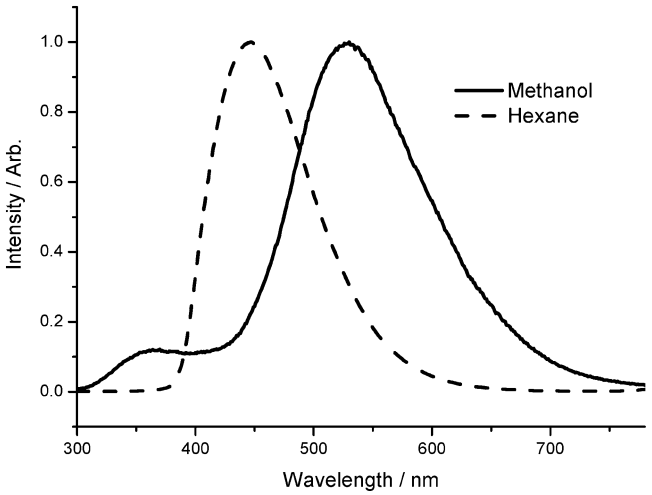

FIGURE 6. Normalized emission spectra of 3,5-diaminocinnamic acid allyl ester **5** recorded in hexane and methanol at $\lambda_{ex} = 273$ nm.

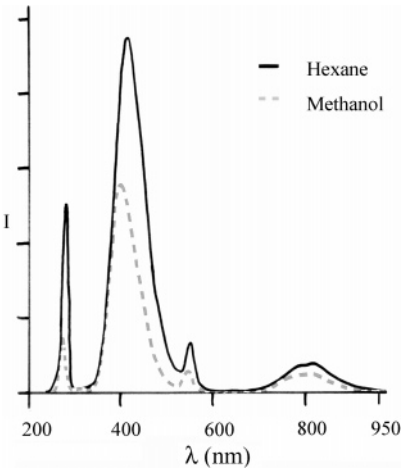

FIGURE 7. The fluorescent emission of M_6-[G-1]$_3$-N **21** recorded in hexane and methanol, upon excitation at $\lambda = 273$ nm.

involved and to determine whether molecular aggregation also played an important role in the emission properties. 3,5-Diaminocinnamate **5** was irradiated at three different wavelengths, two of which correspond to absorption maxima (210 and 330 nm) with the third (273 nm) corresponding to the λ_{max} of unsubstituted cinnamic acid. The emission spectra were recorded between 200 and 950 nm. The spectra obtained were not normalized and the fluorimeters' sensitivity was adjusted for each analysis to obtain responses within the scale limits, therefore, in many cases direct and precise comparison of the emission intensities was not possible. However, interesting results were obtained when the diaminocinnamate **5** was excited at 273 nm (Figure 6). In the hexane solutions, the fluorescence emission was detectable even in the case of very diluted solutions (10^{-4} mM) and the intensity increased almost 6-fold for the solution with a concentration of 0.015 mM. In this solvent a major emission with a maximum at 425 nm was observed. However, this emission decreased in intensity by 50% and a bathochromic shift of 75 nm was observed in acetonitrile, and almost complete fluorescence quenching was revealed in methanolic solution. These large solvent shifts may be indicative of profound solvent interactions with the excited states, resulting in significant excited state stabilization. Additionally the possibility of excimer formation in these solvents cannot be ruled out, and is the subject of ongoing investigations. Fluorescence lifetime data show a decrease in lifetime in deoxygenated solution from approximately 4.8 ns in hexane solution to 1.74 nm in methanol solution. The concomitant decrease in fluorescence yield is indicative of the solvent-promoting nonradiative relaxation in compound **5** as the solvent polarity and hydrogen bonding ability increase.

The effect of different substituents on the benzene ring of the molecule has proven to have a significant impact on the fluorescent properties. The presence of two nitro groups in the meta position quenched the radiative emission completely, whereas interconversion of the amine groups into amides with alkyl chains of different rigidity not only increased the fluorescence yield but also resulted in a hypsochromic shift for the main maximum fluorescence band. This behavior was consistent throughout the series of [G-1] dendrons and dendrimers **8**−**23** (Figure 7—note some artifacts appearing in the spectrum arising from second-order reflections in the emission gratings from the excitation wavelength (at 546 nm) and from the main emission band, appearing around 800 nm; careful use of filters has established that there are no emission bands in these regions), although increasing the generation number up to two yet again affected this emission characteristic (vide infra).

The second generation dendrons **12**−**15** revealed a drastic decrease in both the emission intensity and lifetime, with, for example, the lifetime for M_4-[G-2]-CO_2-Allyl **13** in methanol solution being below the time resolution of the apparatus used (<100 ps). However, the dendrimer C_8-[G-2]$_2$-C **24** exhibited again an increase in fluorescence. Detailed investigations of the photophysical properties of these dendritic poly(aromatic amide) materials are currently underway and the results of these studies will be reported soon.

Conclusions. The syntheses of a series of novel poly(aromatic amide) dendrimers have been described in this article. The dendrimers were based on a novel AB_2 monomer, 3,5-diaminocinnamic acid, and were constructed via convergent approach with the dendritic growth starting from the peripheral surface groups (the terpene solubilizing moieties), followed by addition of the internal branched layers and final coupling with a multifunctional core. The solubilizing units used, citronellol and L-menthol, were conjugated on the dendritic surface by means of a spacer, whose presence introduced a degree of flexibility in the dendritic backbone as indicated by molecular modeling studies. The dendrimers were synthesized up to the second generation by coupling of the dendrons to two types of cores, a bifunctional and a trifunctional core, respectively. These compounds exhibited good solubility properties in a variety of organic solvents such as DMF, DMSO, CH_2Cl_2, $CHCl_3$, MeOH, acetone, and THF. Furthermore, this novel building block and its dendritic derivatives displayed interesting fluorescence emissions in the visible region ($\lambda \approx 500$ nm) of the spectrum upon excitation at 273 nm. The fluorescence spectra and emission lifetimes of the monomer were

found to be strongly solvent dependent. Increasing the dendritic generations also generally resulted in a decrease in emission lifetime and quantum yield.

Experimental Section

Sample Preparations for UV−Vis and Fluorescence Spectroscopies. General procedure: Samples were prepared by carefully transferring a fixed aliquot of sample into a volumetric flask (100 mL, or otherwise stated) and diluting to volume with HPLC-grade hexane, acetonitrile, or methanol, respectively, to obtain 0.5000 mM solutions (or otherwise stated). The solutions were subjected to ultrasound irradiation for a period of 10 min prior to use. Known aliquots of the 0.5000 mM stock solutions were transferred carefully into volumetric flasks and diluted to volumes to obtain solutions of concentrations 0.0150, 0.0100, 0.0050, 0.0010, and 0.0001 mM, respectively. Each flask was subjected to ultrasound irradiation for 10 min prior to use.

Molecular Modeling Study. Dendrimer C_6-[G-1]$_3$-N **23** was built and subjected to initial molecular mechanics energy minimization with the Universal force-field, using the Cerius2 software.[38] Geometry optimizations were carried out on the system with the Gaussian03 software. From the symmetric, pseudo-low-energy configuration generated via the described molecular mechanics (MM)/molecular dynamics (MD) treatment, a preliminary low-level ab initio calculation was performed with the STO-3G basis set at the Hartree−Fock level. Once suitable convergence parameters had been achieved, the calculation was restarted employing the 3-21G basis set, this being followed by a third calculation at the 6-31G(d) level. All optimizations were carried out in the gas phase at a standard temperature and pressure of 298.15 K and 1 atm. C_3 symmetry was imposed at all points in the optimization.

Synthesis of 4. Part 1: Synthesis of 3,5-Dinitrobenzoyloxyboroxine. 3,5-Dinitrobenzoic acid **3** (6.36 g, 30.00 mmol) and dry THF (38 mL) were placed into a dry, round-bottomed flask equipped with a septum inlet, magnetic stirring bar, and a reflux condenser, under a stream of argon. The mixture was stirred vigorously and borane−dimethyl sulfide (BMS) (3.06 mL, 30.00 mmol) was added dropwise from a syringe. Following the addition of an initial aliquot of BMS (1−1.5 mL), when the gas evolution ceased, the mixture was heated under gentle reflux to complete the evolution of gas. The remaining BMS was added at such a rate as to maintain a gentle reflux. Following completion of the addition, the mixture was heated under reflux for 12 h. The solvent and the dimethyl sulfide were then removed under reduced pressure and THF (50 mL) was added to dissolve the residue. The progress of the reaction was monitored by TLC analysis (CH_2Cl_2-EtOAc 80:20, R_f 0.77). 3,5-Dinitrobenzoyloxyboroxine was not isolated but was oxidized directly in the second step to yield the desired compound.

Part Two: Oxidation of 3,5-Dinitrobenzoyloxyboroxine to 3,5-Dinitrobenzaldehyde. To a well-stirred solution of PCC (7.80 g, 36.00 mmol) in dry THF (50 mL) was added dropwise the solution of 3,5-dinitrobenzoyloxyboroxine in THF (50 mL). The stirred mixture was heated under reflux overnight and then diluted with CH_2Cl_2 (50 mL). The supernatant and the solid residue were then filtered through Florisil (50.00 g) contained in a sintered-glass funnel. The filtrate was concentrated under reduced pressure and the crude product purified by column chromatography (CH_2Cl_2−hexane 90:10) to yield a yellow powder (3.10 g, 52% yield, mp 78−80 °C (lit.[51] mp 76−80 °C)). The progress of the reaction was monitored by TLC analysis (CH_2Cl_2−EtOAc 90:10, R_f 0.79). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.98 (2 H, s), 9.23 (1 H, s), 10.15 (1 H, s) ppm.^{13}C NMR (62.8 MHz, $CDCl_3$) δ 123.7, 129.1, 138.8, 149.9, 187.6 ppm. IR ν_{max} cm^{-1} 3075, 1706, 1625, 1541. CI-MS: $C_7H_4N_2O_5$, *m/z* calcd for $(M - H)^+$ 195.00, found $(M - H)^+$ 195.00.

Synthesis of 2. To a suspension of NaH (0.65 g, 16.00 mmol) in dry THF (20 mL) was added allyl diethylphosphonoacetate (4.00 g, 15.90 mmol) in a dropwise fashion and the mixture was stirred at room temperature for 15 min. A solution of 3,5-dinitrobenzaldehyde **4** (2.00 g, 10.00 mmol) in dry THF (5 mL) was then added and the reaction gently refluxed under argon for 12 h. The progress of the reaction was monitored by TLC analysis (CH_2Cl_2−EtOAc 98:2, R_f 0.68). The excess NaH was quenched by careful addition of a few drops of methanol and then by addition of water (10 mL). The product was then extracted in EtOAc (3 × 20 mL), washed with brine, dried ($MgSO_4$), and filtered and the solvent was removed under reduced pressure to leave the crude product, which was further purified by column chromatography (CH_2Cl_2−EtOAc 98:2) to afford a light brown solid (0.15 g, in 54% yield, mp 147−149 °C). ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.23 (2 H, d, $^3J_{HH}$ = 5.8 Hz), 5.28 (2 H, m), 5.90 (1 H, m), 6.96 (1 H, d, $^3J_{HH\ Trans}$ = 16.0 Hz), 7.75 (1 H, $^3J_{HH\ Trans}$ = 16.0 Hz), 8.61 (2 H, s), 8.97 (1 H, s) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 66.3, 119.4, 119.7, 124.4, 127.7, 131.9, 138.5, 140.0, 149.4, 165.31 ppm. IR ν_{max} 2350, 1708, 1650, 1538 cm^{-1}. CI-MS: $C_{12}H_{10}N_2O_6$, *m/z* calcd for M$^+$ 278.05, found M$^+$ 278.05. Anal. Calcd for $C_{12}H_{10}N_2O_6$: C 51.80, H 3.62, N 10.06. Found: C 51.22, H 3.63, N 9.91.

Synthesis of 5. To a solution of 3,5-dinitrocinnamic acid allyl ester **2** (1.20 g, 4.32 mmol) in THF (10 mL) and distilled water (10 mL) was added $SnCl_2$ (9.00 g, 48.10 mmol) and the reaction was heated under reflux for 2 h. The reaction profile was monitored by TLC analysis ($CHCl_3$−EtOH 9:1, R_f 0.27). After cooling to room temperature, the solution was poured onto ice contained in a beaker and then treated with a solution of 5% $NaHCO_3$ in water (200 mL) until the pH was 7−8. EtOAc (80 mL) was then added and the white precipitate filtered off. The product was then extracted with EtOAc (3 × 100 mL). The combined organic layers were then dried ($MgSO_4$) and filtered and the solvent was removed under reduced pressure to leave the crude product, which was further purified by column chromatography ($CHCl_3$−EtOH 99:1) to afford the desired product as a yellow solid (0.80 g, 86% yield, mp 70−72 °C). ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.57 (4 H, s), 4.63 (2 H, d, $^3J_{HH}$ = 5.6 Hz), 5.26 (2 H, m), 5.88 (1 H, m), 5.95 (1 H, s), 6.20 (2 H, s), 6.30 (1 H, d, $^3J_{HH\ Trans}$ = 15.9 Hz), 7.48 (1 H, d, $^3J_{HH\ Trans}$ = 15.9 Hz) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 64.0, 102.7, 104.6, 116.4, 117.3, 131.3, 135.2, 144.6, 146.8, 165.8 ppm. IR ν_{max} 3500, 3361, 2315, 1701, 1631, 1597 cm^{-1}. CI-MS: $C_{12}H_{14}N_2O_2$, *m/z* calcd for $(M + H)^+$ 219.11, found $(M + H)^+$ 219.11. Anal. Calcd for $C_{12}H_{14}N_2O_2$: C 66.04, H 6.47, N 12.83. Found: C 66.05, H 6.54, N 12.69.

Synthesis of 6. A mixture of citronellol (4.06 g, 26.00 mmol), succinic anhydride (3.00 g, 30.00 mmol), and DiPEA (4.50 mL, 26 mmol) in ether (10 mL) was stirred for 2 days at room temperature. Conversion of the reaction was followed by TLC analysis ($CHCl_3$−EtOH 90:10, R_f 0.27). The solvent was removed under reduced pressure, and the residue dissolved in CH_2Cl_2 (50 mL) and washed with an aqueous solution of 5% w/w citric acid (2 × 30 mL). The organic layer was dried ($MgSO_4$) and filtered and the solvent was removed under reduced pressure to give the crude product that was purified by column chromatography ($CHCl_3$−EtOH 98:2) to afford **6** as a transparent oil (6.00 g, 90% yield). ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.86 (3 H, d, $^3J_{HH}$ = 6.4 Hz), 1.17 (1 H, m), 1.37 (4 H, m), 1.56 (3 H, s), 1.64 (3 H, s), 1.94 (2 H, m), 2.48 (4 H, m), 4.01 (2 H, m), 5.07 (1 H, m) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 18.0, 19.7, 25.7, 26.1, 29.3, 29.8, 35.7, 37.3, 63.8, 124.9, 131.7, 172.5, 178.7 ppm. IR ν_{max} 2924, 1739, 1716, 1436 cm^{-1}. CI-MS: $C_{14}H_{24}N_{22}O_{33}$, *m/z* calcd for $(M + H)^+$ 257.17, found $(M + H)^+$ 257.17.

Synthesis of 8. To a solution of succinic acid mono(3,7-dimethyl-oct-6-enyl) ester **6** (7.00 g, 27.30 mmol), 3,5-diaminocinnamic acid allyl ester **5** (0.30 g, 1.35 mmol), and DiPEA

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(5.18 mL, 27.00 mmol) in dry CH_3CN (70 mL) was added benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) (10.13 g, 27.00 mmol) (0.68 g, 3.50 mmol) and the reaction was left stirring at room temperature overnight. The reaction profile was monitored by TLC analysis ($CHCl_3$−EtOH 9:1, R_f 0.74). The reaction was quenched by the addition of water (70 mL) and the desired product was extracted with $CHCl_3$ (3 × 30 mL). The organic layers were dried ($MgSO_4$) and filtered and the solvent was removed under reduced pressure to leave the crude product that was purified further by column chromatography ($CHCl_3$−EtOH 98:2) to afford a yellowish waxy material (6.10 g, 96% yield). ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.83 (6 H, d, $^3J_{HH}$ = 6.3 Hz), 1.18 (2 H, m), 1.24 (2 H, m), 1.34 (2 H, m), 1.40 (2 H, m), 1.51 (6 H, s), 1.57 (2 H, m), 1.62 (6 H, s), 1.88 (4 H, m), 2.63 (8 H, m), 4.05 (4 H, m), 4.62 (2 H, d, $^3J_{HH}$ = 5.6 Hz), 4.99 (1 H, m), 5.20 (2 H, m), 5.88 (1 H, m), 6.32 (1 H, d, $^3J_{HH\ Trans}$ = 16.0 Hz), 7.37 (2 H, s), 7.46 (1 H, d, $^3J_{HH\ Trans}$ = 16.0 Hz), 7.96 (1 H, s), 8.25 (2 H, s) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 18.0, 19.7, 25.7, 29.6, 29.1, 32.2, 35.7, 36.9, 37.3, 63.9, 65.5, 112.9, 115.1, 118.5, 119.0, 124.9, 131.7, 132.5, 135.9, 139.3, 144.9, 166.8, 170.6, 173.7 ppm. IR ν_{max} 3342, 3090, 1734, 1718, 1639, 1601, 1555 cm^{-1}. CI-MS: $C_{40}H_{58}N_2O_8$, *m/z* calcd for 695.42 $(M + H)^+$, found $(M + H)^+$ 695.42. FAB MS: *m/z* calcd for $(M + Na)^+$ 717.41, $(M + K)^+$ 733.38, found $(M + Na)^+$ 717.40, $(M + K)^+$ 733.41.

Synthesis of 9. To a solution of succinic acid mono(5-isopropyl-2-methylcyclohexyl) ester **7** (7.00 g, 27.30 mmol), 3,5-diaminocinnamic acid allyl ester **5** (0.30 g, 1.35 mmol), and DiPEA (5.18 mL, 27.00 mmol) in dry CH_3CN (70 mL) was added BOP (10.13 g, 27.00 mmol) and the reaction was left stirring at room temperature overnight. The reaction profile was monitored by TLC analysis ($CHCl_3$−EtOH 9:1, R_f 0.70). The reaction was quenched by the addition of water (70 mL) and the desired product was extracted with $CHCl_3$ (3 × 30 mL). The organic layers were dried ($MgSO_4$) and filtered and the solvent was removed under reduced pressure to leave the crude product, further purified by column chromatography ($CHCl_3$−EtOH 98:2) to afford a yellowish solid (6.23 g, 98% yield, mp 50.3−52.3 °C) ($[\alpha]^{20}_D$ −46.20 (*c* 1.00 in $CHCl_3$)). ^{1}H NMR (250 MHz, d_6-DMSO) δ 0.67 (6 H, d, $^3J_{HH}$ = 6.9 Hz), 0.77 (6 H, d, $^3J_{HH}$ = 6.9 Hz), 0.83 (6 H, d, $^3J_{HH}$ = 6.9 Hz), 0.91 (2 H, m), 1.26 (4 H, m), 1.38 (4 H, m), 1.60 (4 H, m), 1.81 (2 H, m), 1.86 (2 H, m), 2.59 (8 H, m), 4.57 (2 H, m), 4.69 (2 H, d, $^3J_{HH}$ = 5.3 Hz), 5.31 (2 H, m), 6.33 (1 H, m), 6.39 (1 H, d, $^3J_{HH\ Trans}$ = 15.9 Hz), 7.59 (1 H, d, $^3J_{HH\ Trans}$ = 15.7 Hz), 7.60 (2 H, s), 7.90 (1 H, s), 10.11 (2 H, s) ppm. ^{13}C NMR (62.8 MHz, d_6-DMSO) 16.5, 20.8, 22.2, 26.0, 29.3, 31.1, 31.4, 34.0, 46.7, 64.9, 73.6, 112.1, 113.6, 118.0, 133.0, 134.6, 140.4, 145.2, 165.8, 170.4, 172.0, 173.7 ppm. IR ν_{max} 3343, 2300, 1726, 1650, 1601, 1555 cm^{-1}. MALDI-TOF MS: $C_{37}H_{54}N_2O_8$ *m/z* calcd for $(M + Na)^+$ 717.41, $(M + K)^+$ 733.38, found $(M + Na)^+$ 717.33, $(M + K)^+$ 733.30.

Synthesis of 10. C_2-[G-1]-CO_2Allyl **8** (9.30 g, 13.39 mmol) was dissolved in THF (200 mL). The solution was then treated with HCO_2NH_4 (9.50 g, 152.00 mmol), PPh_3 (1.88 g, 7.23 mmol), and $Pd(OAc)_2$ (0.65 g, 2.89 mmol) and the mixture was heated under reflux under an argon atmosphere for 8 h. The reaction was monitored by TLC analysis ($CHCl_3$−EtOH 9:1, R_f 0.23). The reaction mixture was then cooled and filtered and the solvent was removed under reduced pressure. The solid residue was dissolved in EtOAc (100 mL), washed with water (3 × 50 mL), dried ($MgSO_4$), and filtered and the solvent was removed under reduced pressure. The progress of the reaction was monitored by TLC analysis ($CHCl_3$−EtOH 9:1, R_f 0.23) and the crude product purified by column chromatography, using a gradient elution (from $CHCl_3$−EtOH 98:2 to $CHCl_3$−EtOH 20:80), to afford the desired product as a pale yellow powder (6.50 g, 74% yield). ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.84 (6 H, d, $^3J_{HH}$ = 6.4 Hz), 1.18 (2 H, m), 1.23 (2 H, m), 1.33 (2 H, m), 1.36 (2 H, m), 1.52 (6 H, s), 1.56 (2 H, m), 1.64 (6 H, s), 1.89 (4 H, m), 2.66 (8 H, m), 4.08 (4 H, m), 5.00 (2 H, m), 6.23 (1 H, d, $^3J_{HH\ Trans}$ = 16.0 Hz), 7.17 (2 H, s), 7.32 (1 H, d, $^3J_{HH\ Trans}$ = 16.0 Hz), 7.66 (1 H, s), 8.37 (2 H, s) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 16.6, 18.3, 24.7, 28.4, 30.4, 34.3, 36.0, 62.7, 112.0, 114.1, 123.5, 130.3, 132.4, 134.0, 137.7, 137.8, 169.4, 170.6, 172.7 ppm. IR ν_{max} 3291, 2963, 2345, 1734, 1701, 1672, 1636, 1555, 1429, 1261 cm^{-1}. MALDI TOF MS: $C_{37}H_{54}N_2O_8$, *m/z* calcd for $(M + H)^+$ 655.39, $(M + Na)^+$ 677.38, $(M + K)^+$ 693.35, found $(M + H)^+$ 655.10, $(M + Na)^+$ 677.90, $(M + K)^+$ 693.40.

Synthesis of 11. M_2-[G-1]-CO_2Allyl **9** (6.00 g, 8.64 mmol) was dissolved in THF (100 mL). The solution was then treated with HCO_2NH_4 (6.43 g, 99.40 mmol), PPh_3 (1.13 g, 4.34 mmol), and $Pd(dba)_2$ (1.12 g, 1.94 mmol) and the mixture was heated under reflux under an argon atmosphere for 8 h. The reaction was monitored by TLC analysis ($CHCl_3$−EtOH 98:2, R_f 0.52). The reaction mixture was then cooled and filtered and the solvent was removed under reduced pressure. The solid residue was dissolved in EtOAc (50 mL), washed with water (3 × 20 mL), dried ($MgSO_4$), and filtered and the solvent was removed under reduced pressure. The progress of the reaction was monitored by TLC analysis ($CHCl_3$−EtOH 9:1) and the crude product purified by column chromatography in gradient elution (from $CHCl_3$ to $CHCl_3$−EtOH 95:5) to afford the desired product as a white solid (3.89 g, 69% yield, mp 198.9−200.9 °C) ($[\alpha]^{20}_D$ −41.00 (*c* 1 in MeOH)).^{1}H NMR (250 MHz, $CDCl_3$) δ 0.68 (6 H, d, $^3J_{HH}$ = 6.8 Hz), 0.80 (6 H, d, $^3J_{HH}$ = 6.9 Hz), 0.85 (6 H, d, $^3J_{HH}$ = 6.9 Hz), 0.95 (4 H, m), 1.26 (4 H, m), 1.35 (4 H, m), 1.60 (2 H, m), 1.86 (2 H, m), 2.58 (8 H, m), 4.57 (2 H, m), 6.31 (1 H, d, $^3J_{HH\ Trans}$ = 15.9 Hz), 7.44 (1 H, d, $^3J_{HH\ Trans}$ = 15.9 Hz), 7.55 (2 H, s), 7.89 (1 H, s), 10.10 (2 H, s) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 16.4, 20.8, 22.1, 23.6, 26.6, 30.2, 31.7, 32.2, 34.5, 40.9, 47.2, 75.2, 112.9, 115.0, 135.6, 138.5, 147.4, 159.8, 165.1, 173.1, 174.5 ppm. IR ν_{max} 3259, 3021, 2869, 1727, 1699, 1657, 1597, 1423, 1293 cm^{-1}. MALDI-TOF MS: *m/z* calcd for $(M + Na)^+$ 677.38, $(M + K)^+$ 693.33, found $(M + Na)^+$ 677.40, $(M + K)^+$ 693.40.

Synthesis of 12. To a solution of C_2-[G-1]-CO_2H **10** (0.11 g, 0.168 mmol), 3,5-diaminocinnamic acid allyl ester **5** (0.02 g, 0.07 mmol), 4-hydroxyazabenzotriazole (HOAt) (0.02 g, 0.17 mmol), and DiPEA (0.06 mL, 0.34 mmol) in dry CH_3CN (2.5 mL) was added *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) (0.06 g, 0.17 mmol) and the reaction was left stirring at room temperature for 24 h. Progress of the reaction was followed by MALDI-TOF MS and TLC analysis ($CHCl_3$−EtOH 9:1, R_f 0.39). The reaction was quenched by the addition of water (3 mL) and the desired product was extracted with $CHCl_3$ (3 × 5 mL). The organic layers were dried ($MgSO_4$) and filtered and the solvent was removed under reduced pressure to leave the crude product, which was purified further by column chromatography ($CHCl_3$−EtOH 95:5) to afford a white solid (0.07 g, 69% yield, mp 259−261 °C). ^{1}H NMR (250 MHz, d_6-DMSO) δ 0.87 (12 H, d, $^3J_{HH}$ = 6.4 Hz), 1.13 (4 H, m), 1.25 (4 H, m), 1.33 (4 H, m), 1.42 (4 H, m), 1.49 (4 H, m), 1.52 (12 H, s), 1.66 (12 H, s), 1.94 (4 H, m), 2.66 (16 H, m), 4.09 (8 H, m), 4.76 (2 H, m), 5.09 (4 H, m), 5.39 (2 H, m), 6.05 (1 H, m), 6.52 (1 H, d, $^3J_{HH\ Trans}$ = 15.9 Hz), 6.90 (2 H, d, $^3J_{HH\ Trans}$ = 15.6 Hz), 7.54 (2 H, d, $^3J_{HH\ Trans}$ = 15.4 Hz), 7.64 (1 H, d, $^3J_{HH\ Trans}$ = 15.9 Hz), 7.73 (4 H, s), 7.83 (2 H, s), 7.85 (2 H, s), 8.19 (1 H, s), 10.19 (4 H, s), 10.70 (2 H, s) ppm. ^{13}C NMR (62.8 MHz, d_6-DMSO) δ 17.8, 19.5, 25.2, 25.8, 29.2, 31.2, 35.3, 36.8, 62.6, 65.0, 111.3, 112.4, 113.3, 114.1, 118.1, 122.5, 124.9, 130.9, 133.0, 134.9, 135.5, 140.4, 140.6, 140.9, 146.0, 164.0, 165.8, 170.5, 172.6. IR ν_{max} 3328, 1731, 1716, 1686, 1676, 1614, 1556 cm^{-1}. MALDI-TOF-MS: $C_{86}H_{118}N_6O_{16}$, *m/z* calcd.for M^+ 1490.86, $(M + Na)^+$ 1513.85, $(M + K)^+$ 1529.82, found M^+ 1490.01, $(M + Na)^+$ 1513.01, $(M + K)^+$ 1529.74.

Synthesis of 13. To a solution of M_2-[G-1]-CO_2H **11** (0.60 g, 0.97 mmol), 3,5-diaminocinnamic acid allyl ester **5** (0.90 g, 0.41 mmol), DiPEA (0.3 mL, 1.55 mmol), and HOAt (0. 14 g, 1.00 mmol) in dry CH_3CN (20 mL) was added HATU (0. 38 g, 1.00 mmol) and the reaction mixture was left stirring at room temperature for 2 days. The progress of the reaction was

monitored by TLC analysis ($CHCl_3$−EtOH 9:1, R_f 0.5) and MALDI-TOF MS. The reaction was then quenched with water (20 mL) and the product extracted in $CHCl_3$ (3 × 10 mL). The organic solvent was dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography ($CHCl_3$−EtOH 96:4) to afford a yellowish waxy material (0.58 g, 95%) ($[\alpha]^{20}_D$ −63.90 (*c* 0.50 in $CHCl_3$)). ^{1}H NMR (400 MHz, d_6-DMSO) δ ppm 0.70 (12 H, d, $^3J_{HH}$ = 6.9 Hz), 0.83 (12 H, d, $^3J_{HH}$ = 7.0 Hz), 0.89 (12 H, d, $^3J_{HH}$ = 7.0 Hz), 1.06 (12 H, m), 1.32 (8 H, m), 1.64 (8 H, m), 1.88 (8 H, m), 2.64 (16 H, m), 4.62 (4 H, m), 4.75 (2 H, d, $^3J_{HH}$ = 5.3 Hz), 5.39 (2 H, m), 6.05 (1 H, m), 6.46 (1 H, d, $^3J_{HH\ Trans}$ = 16.0 Hz), 6.88 (2 H, d, $^3J_{HH\ Trans}$ = 15.5 Hz), 7.51 (2 H, d, $^3J_{HH\ Trans}$ = 15.5 Hz), 7.51 (1 H, d, $^3J_{HH\ Trans}$ = 15.8 Hz), 7.73 (4 H, s), 7.82 (2 H, s), 7.83 (2 H, s), 8.17 (1 H, s), 10.18 (4 H, s), 10.56 (2 H, s) ppm. ^{13}C NMR (100 MHz, d_6-DMSO) δ 15.7, 20.0, 21.4, 22.4, 25.1, 28.6, 30.3, 30.6, 33.2, 39.6, 45.9, 64.2, 72.8, 110.4, 112.4, 113.3, 117.3, 121.6, 132.2, 134.1, 134.5, 139.6, 139.7, 140.2, 145.0, 163.1, 165.0, 169.6, 171.2 ppm. IR ν_{max} 3446, 1635 cm^{-1}. MALDI-TOF MS: $C_{86}H_{118}N_6O_{16}$, *m/z* calcd for $(M + Na)^+$ 1513.85, $(M + K)^+$ 1529.82, found $(M + Na)^+$ 1514.41, $(M + K)^+$ 1529.59.

Synthesis of 14. C_4-[G-2]-CO_2Allyl **12** (0.07 g, 0.05 mmol) was dissolved in THF (4 mL). The solution was then treated with HCO_2NH_4 (0.03 g, 0.50 mmol) and $Pd(PPh_3)_4$ (0.02 g, 0.01 mmoL) and the mixture was heated under reflux under an argon atmosphere for 4 h. The reaction mixture was then cooled and filtered and the solvent was removed under reduced pressure. The solid residue was dissolved in EtOAc (5 mL), washed with water (3 × 5 mL), dried ($MgSO_4$), and filtered and the solvent was removed under reduced pressure. The progress of the reaction was monitored by TLC analysis ($CHCl_3$−EtOH 9:1, R_f 0.25) and the crude product purified by column chromatography employing a gradient elution (from $CHCl_3$−EtOH 95:5 to $CHCl_3$−EtOH 20:80), to afford the desired product as a pale yellow solid (0.05 g, 67% yield, mp (broad) 258−296 °C). ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.77 (12 H, d, $^3J_{HH}$ = 6.4 Hz), 1.02 (4 H, m), 1.10 (4 H, m), 1.26 (4 H, m), 1.39 (4 H, m), 1.45 (12 H, s), 1.48 (4 H, m), 1.53 (12 H, s), 1.79 (4 H, m), 2.52 (16 H, m), 3.99 (8 H, m), 4.99 (4 H, m), 6.35 (1 H, d, $^3J_{HH\ Trans}$ = 15.5 Hz), 6.80 (2 H, d, $^3J_{HH\ Trans}$ = 15.8 Hz), 7.39 (2 H, d, $^3J_{HH\ Trans}$ = 15.5 Hz) 7.51 (2 H, d, $^3J_{HH\ Trans}$ = 15.8 Hz), 7.60 (4 H, s), 7.64 (2 H, s), 7.73 (2 H, s), 7.93 (1 H, s), 10.16 (4 H, s) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 17.8, 19.5, 25.1, 25.8, 29.2, 31.3, 35.3, 36.8, 62.6, 113.1, 113.3, 122.5, 124.9, 129.0, 130.9, 131.9, 135.5, 137.0, 140.4, 140.9, 142.0, 164.0, 165.8, 170.5, 172.6 ppm. IR ν_{max} 3324, 2963, 1716, 1678, 1613, 1425 cm^{-1}. MALDI-TOF MS: $C_{83}H_{114}N_6O_{16}$, *m/z* calcd for $(M + Na)^+$ 1473.82, $(M + K)^+$ 1489.79, found $(M + Na)^+$ 1473.40, $(M + K)^+$ 1488.3.

Synthesis of 15. M_4-[G-2]-CO_2Allyl ester **13** (0.04 g, 0.03 mmol) was dissolved in THF (2.5 mL). The solution was then treated with HCO_2NH_4 (0.02 g, 0.34 mmol) and $Pd(PPh_3)_4$ (0.01 g, 0.01 mmol) and the mixture was heated under reflux under an argon atmosphere for 4 h. The reaction mixture was then cooled and filtered and the solvent was removed under reduced pressure. The solid residue was dissolved in EtOAc (5 mL), washed with water (2 × 3 mL), dried ($MgSO_4$), and filtered and the solvent was removed under reduced pressure. The reaction was monitored by MALDI-TOF MS and TLC analysis ($CHCl_3$−EtOH 9:1, R_f 0.2) and the crude product purified by gradient column chromatography (from $CHCl_3$−EtOH 85:15 to $CHCl_3$−EtOH 10:90) to afford a white solid (30.00 mg, 69% yield, mp (broad) 250−285 °C) ($[\alpha]^{20}_D$ −24.9 (*c* 0.285 in $CHCl_3$)). ^{1}H NMR (400 MHz, d_6-DMSO) δ ppm 0.67 (12 H, d, $^3J_{HH}$ = 6.9 Hz), 0.78 (12 H, d, $^3J_{HH}$ = 7.0 Hz), 0.84 (12 H, d, $^3J_{HH}$ = 7.0 Hz), 1.00 (8 H, m), 1.22 (4 H, m), 1.30 (12 H, m), 1.59 (8 H, m), 1.88 (8 H, m), 2.59 (16 H, m), 4.56 (4 H, m), 6.35 (1 H, d, $^3J_{HH\ Trans}$ = 16.0 Hz), 6.83 (2 H, d, $^3J_{HH\ Trans}$ = 15.5 Hz), 7.40 (1 H, br d), 7.42 (1 H, d, $^3J_{HH\ Trans}$ = 15.8 Hz), 7.68 (6 H, s), 7.63 (2 H, s), 8.30 (1 H, s), 10.14 (4 H, s), 10.45 (2 H, s) ppm. ^{13}C NMR (100 MHz, d_6-DMSO) δ 16.5, 20.8, 22.2, 23.2, 25.9, 29.4, 31.2, 31.4, 34.0, 38.8, 46.7, 73.6, 111.2, 113.3, 122.6, 135.4, 136.5, 137.5, 140.4, 140.8, 163.9, 170.5, 172.0 ppm. IR ν_{max} 3430, 2959, 1713, 1631, 1557 cm^{-1}. MALDI-TOF MS: $C_{83}H_{114}N_6O_{16}$, *m/z* calcd for $(M + Na)^+$ 1473.82, $(M + K)^+$ 1489.79, found $(M + Na)^+$ 1473.82, $(M + K)^+$ 1489.79.

Synthesis of 16. To a solution of 1,7-diaminoheptane (0.16 g, 1.25 mmol), succinic acid mono(3,7-dimethyl-oct-6-enyl) ester **6** (0.77 g, 3.00 mmol), HOAt (0.41 g, 3.00 mmol), and *N*-methylmorpholine (NMM) (0.33 mL, 3.00 mmol) in dry DMF (8 mL) was added EDCI (0.58 g, 3.00 mmol) at 0 °C, and the reaction was left stirring at room temperature for 24 h. The reaction profile was monitored by TLC analysis ($CHCl_3$−EtOH 90:10, R_f 0.58). The reaction was quenched by the addition of HCl (1 M, 10 mL) and the desired product was extracted with $CHCl_3$ (3 × 10 mL). The organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure to leave the crude product, whcih was further purified by column chromatography ($CHCl_3$−EtOH 96:4) to afford a white solid (0.65 g, 86% yield, mp 41.4−43.4 °C). ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.84 (6 H, d, $^3J_{HH}$ = 6.3 Hz), 1.11 (2 H, m), 1.23 (4 H, m), 1.28 (6 H, m), 1.40 (4 H, m), 1.43 (4 H, m), 1.53 (6 H, s), 1.60 (6 H, s), 1.93 (4 H, m), 2.38 (4 H, m), 2.58 (4 H, m), 3.16 (4 H, m), 4.04 (4 H, m), 5.01 (2 H, m), 5.78 (2 H, m) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 16.6, 18.3, 24.3, 24.7, 25.6, 28.3, 28.4, 28.7, 30.1, 34.3, 35.9, 38.4, 62.3, 123.5, 130.3, 170.3, 172.1 ppm. IR ν_{max} 3326, 2932, 1723, 1640, 1539 cm^{-1}. CI MS: $C_{35}H_{62}N_2O_6$, *m/z* calcd for $(M + H)^+$ 607.47, found $(M + H)^+$ 607.47. MALDI-TOF MS: *m/z* calcd for $(M + H)^+$ 607.47, $(M + Na)^+$ 629.45, $(M + K)^+$ 645.42, found $(M + H)^+$ 606.97, $(M + Na)^+$ 629.56, $(M + K)^+$ 645.21. Anal. Calcd for $C_{35}H_{62}N_2O_6$: C 69.27, H 10.30, N 4.61. Found: C 68.97, H 10.42, N 4.53.

Synthesis of 17. To a solution of 1,7-diaminoheptane (0.16 g, 1.25 mmol), succinic acid mono(5-isopropyl-2-methylcyclohexyl) ester **7** (0.77 g, 3.00 mmol), HOAt (0.41 g, 3.00 mmol), and NMM (0.33 mL, 3.00 mmol) in dry DMF (8 mL) was added EDCI (0.580 g, 3.00 mmol) at 0 °C, and the reaction was left stirring at room temperature for 24 h. The reaction profile was monitored by TLC analysis ($CHCl_3$−EtOH 90:10, R_f 0.59). The reaction was quenched by the addition of HCl (1 M, 10 mL) and the desired product was extracted with $CHCl_3$ (3 × 10 mL). The organic layers were dried ($MgSO_4$) and filtered and the solvent was removed under reduced pressure to leave a crude product that was further purified by column chromatography ($CHCl_3$−EtOH 95:5) to afford the desired product as a transparent oil (1.00 g, 55% yield) ($[\alpha]^{20}_D$ −60.4 (*c* 1.00 in $CHCl_3$)). ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.65 (6 H, d, $^3J_{HH}$ = 6.9 Hz), 0.80 (2 H, m), 0.81 (12 H, m), 0.87 (4 H, m), 1.25 (8 H, m), 1.40 (2 H, m), 1.43 (2 H, m), 1.57 (4 H, m), 1.62 (2 H, m), 1.85 (2 H, m), 2.35 (8 H, m), 3.13 (4 H, m), 4.62 (2 H, m) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 16.7, 21.1, 22.4, 23.8, 26.6, 27.0, 29.0, 29.8, 30.4, 31.7, 34.6, 39.8, 41.2, 47.3, 75.0, 171.8, 173.1 ppm. IR ν_{max} 3303, 2953, 1731, 1649, 1552, 1454 cm^{-1}. CI-MS: $C_{35}H_{62}N_2O_6$, *m/z* calcd.for $(M + H)^+$ 607.47, found $(M + H)^+$ 607.47. MALDI-TOF MS: $(M + Na)^+$ 629.45, $(M + K)^+$ 645.42, $(M + Na)^+$, found $(M + K)^+$ 629.36, 645.26. Anal. Calcd for $C_{35}H_{62}N_2O_6$: C 69.27,, H 10.30, N 4.62. Found: C 68.44, H 10.35, N 4.55.

Synthesis of 18. To a solution of tris(2-ethylamino)amine (TREN) (0.17 mL, 1.10 mmol), succinic acid mono(3,7-dimethyl-oct-6-enyl) ester **6** (1.00 g, 3.90 mmol), HOAt (0.54 g, 3.90 mmol), and NMM (0.43 mL, 3.90 mmol) in dry DMF (12 mL) was added EDCI (0.75 g, 3.90 mmol) at 0 °C, and the reaction was left stirring at room temperature for 24 h. The reaction profile was monitored by TLC analysis ($CHCl_3$−EtOH 95:5, R_f 0.49). The reaction was quenched by the addition of HCl (1 M, 12 mL) and the desired product was extracted with $CHCl_3$ (3 × 10 mL). The organic layers were dried ($MgSO_4$) and filtered and the solvent was removed under reduced pressure to leave the crude product, which was further purified by column chromatography ($CHCl_3$−EtOH 98:2) to afford a transparent oil (0.66 g, 70% yield). ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.84 (9 H, d, $^3J_{HH}$ = 6.4 Hz), 1.14 (3 H, m), 1.27 (3 H, m),

1.33 (3 H, m), 1.39 (3 H, m), 1.52 (9 H, s), 1.58 (3 H, m), 1.63 (9 H, s), 1.92 (6 H, m), 2.45 (6 H, m), 2.55 (6 H, m), 2.68 (6 H, m), 3.25 (6 H, m), 4.05 (6 H, m), 5.03 (3 H, m), 6.85 (3 H, m) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 17.7, 19.4, 25.4, 29.3, 29.5, 30.5, 35.4, 37.0, 38.0, 54.3, 63.4, 124.5, 131.4, 172.1, 173.5 ppm. IR ν_{max} 3290, 3099, 1734, 1651, 1546, 1455 cm^{-1}. MALDI-TOF MS: $C_{48}H_{84}N_4O_9$, *m/z* calcd for M^+ 860.62, $(M + Na)^+$ 883.61, $(M + K)^+$ 899.59, found M^+ 860.19, $(M + Na)^+$ 882.91, $(M + K)^+$ 898.93. Anal. Calcd for $C_{48}H_{84}N_4O_9 \cdot 3DMF \cdot 4H_2O$: C 59.40, H 9.88, N 8.51. Found: C 59.18, H 9.61, N 8.61.

Synthesis of 19. To a solution of TREN (0.17 mL, 1.10 mmol), succinic acid mono(5-isopropyl-2-methylcyclohexyl) ester **7** (1.00 g, 3.87 mmol), HOAt (0.54 g, 3.90 mmol), and NMM (0.43 mL, 3.90 mmol) in dry DMF (12 mL) was added EDCI (0.75 g, 3.90 mmol) at 0 °C, and the reaction was left stirring at room temperature for 24 h. The reaction profile was monitored by TLC analysis ($CHCl_3$−EtOH 90:10, R_f 0.60). The reaction was quenched by the addition of HCl (1 M, 12 mL) and the desired product was extracted with $CHCl_3$ (3 × 10 mL). The organic layers were dried ($MgSO_4$) and filtered and the solvent was removed under reduced pressure to leave the crude product, whcih was further purified by column chromatography ($CHCl_3$−EtOH 98:2) to afford a transparent oil (0.39 g, 41% yield) ($[\alpha]^{20}_D$ −60.05 (*c* 1.00 in $CHCl_3$)). ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.65 (9 H, d, $^3J_{HH}$ = 6.9 Hz), 0.80 (3 H, m), 0.82 (18 H, m), 0.98 (6 H, m), 1.31 (3 H, m), 1.35 (3 H, m), 1.57 (6 H, m), 1.72 (3 H, m), 1.84 (3 H, m), 2.43 (12 H, m), 2.63 (6 H, m), 3.27 (6 H, m), 4.59 (3 H, m), 6.87 (3 H, m) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 20.7, 22.0, 23.4, 26.2, 29.6, 30.6, 31.4, 34.2, 38.3, 40.9, 46.9, 54.3, 74.6, 172.2, 173.0 ppm. IR ν_{max} 3291, 2953, 1729, 1651, 1456 cm^{-1}. FAB MS: $C_{48}H_{84}N_4O_9$, *m/z* calcd for $(M + H)^+$ 861.63, $(M + Na)^+$ 883.61, found $(M + H)^+$ 861.63, $(M + Na)^+$ 883.62. MALDI-TOF MS: $(M + H)^+$ 861.63, found $(M + H)^+$ 863.21. Anal. Calcd for $C_{48}H_{84}N_4O_9 \cdot 3H_2O$: C 62.99, H 9.91, N 6.12. Found: C 62.78, H 9.35, N 6.10.

Synthesis of 20. To a solution of 1,7-diaminoheptane (0.05 g, 0.40 mmol), M_2-[G-1]-CO_2H **11** (0.65 g, 0.99 mmol), and DiPEA (0.31 mL, 1.79 mmol) in dry CH_3CN (20 mL) was added BOP (0.46 g, 1.20 mmol) and the reaction was left stirring at room temperature for 24 h. The reaction profile was monitored by TLC analysis ($CHCl_3$−EtOH 9:1, R_f 0.61). The reaction was quenched by the addition of distilled water (20 mL) and the product was extracted with $CHCl_3$ (3 × 20 mL). The organic layers were dried ($MgSO_4$) and filtered and the solvent was removed under reduced pressure to leave the crude product, whcih was further purified by column chromatography ($CHCl_3$−EtOH 97:3) to afford a white amorphous solid (0.54 g, 96% yield) ($[\alpha]^{20}_D$ −35.00 (*c* 1.00 in $CHCl_3$)). ^{1}H NMR (400 MHz, d_6-DMSO) δ 0.66 (12 H, d, $^3J_{HH}$ = 6.9 Hz), 0.77 (12 H, d, $^3J_{HH}$ = 6.9 Hz), 0.85 (4 H, m), 0.88 (12 H, d, $^3J_{HH}$ = 6.9 Hz), 0.98 (4 H, m), 1.07 (4 H, m), 1.33 (10 H, m), 1.46 (8 H, m), 1.64 (8 H, m), 1.86 (8 H, m), 2.54 (16 H, m), 3.18 (4 H, m), 4.60 (4 H, m), 6.58 (1 H, d, $^3J_{HH\ Trans}$ = 15.7 Hz), 7.28 (2 H, d, $^3J_{HH\ Trans}$ = 15.6 Hz), 7.60 (4 H, s), 7.82 (2 H, s), 8.25 (2 H, s), 10.10 (4 H, s) ppm. ^{13}C NMR (100 MHz, d_6-DMSO) 17.2, 21.5, 22.9, 23.9, 26.6, 27.5, 29.5, 30.1, 31.8, 32.1, 34.7, 41.1, 47.4, 74.2, 111.5, 113.7, 123.3, 136.4, 140.0, 141.0, 165.9, 172.7 ppm. IR ν_{max} 3446, 1713, 1661, 1618, 1557, 1454 cm^{-1}. MALDI-TOF MS: $C_{81}H_{122}N_6O_{14}$, *m*/z calcd for $(M + Na)^+$ 1425.89, $(M + K)^+$ 1441.87, found $(M + Na)^+$ 1426.42, $(M + K)^+$ 1442.89. Anal. Calcd for $C_{81}H_{122}N_6O_{14} \cdot 2H_2O$: C 67.57, H 8.82, N 5.84. Found: C 67.54, H 8.81, N 5.94. GPC (THF): M_w 1812, M_n 1740, M_w/M_n 1.04.

Synthesis of 21. To a solution of TREN (0.02 mL, 0.15 mmol) and M_2-[G-1]-CO_2H **11** (0.33 g, 0.48 mmol), in dry CH_3CN (7 mL) was added BOP (0.19 g, 0.50 mmol) followed by triethylamine (0.14 mL, 0.96 mmol), then the mixture was left stirring at room temperature for 4 days, and the conversion of the starting material was monitored by TLC ($CHCl_3$−EtOH 9:1, R_f 0.68) and MALDI-TOF MS. The reaction was quenched by addition of water (10 mL), and the product was extracted in $CHCl_3$ (3 × 10 mL) and washed with brine (3 × 10 mL). The organic layer was then dried ($MgSO_4$) and filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography ($CHCl_3$−EtOH 99:1) to afford a white amorphous solid (0.147 g, 48% yield) ($[\alpha]^{20}_D$ −36.2 (*c* 0.25 in $CHCl_3$)). ^{1}H NMR (400 MHz, d_6-DMSO) δ 0.70 (18 H, d, $^3J_{HH}$ = 6.9 Hz), 0.83 (18 H, d, $^3J_{HH}$ = 7.0 Hz), 0.84 (6 H, m), 0.88 (18 H, d, $^3J_{HH}$ = 7.0 Hz), 0.94 (6 H, m), 1.04 (6 H, m), 1.27 (12 H, m), 1.30 (12 H, m), 1.42 (12 H, m), 1.62 (12 H, m), 2.62 (24 H, m), 3.10 (6 H, m), 3.28 (6 H, m), 4.59 (6 H, m), 6.68 (3 H, d, $^3J_{HH\ Trans}$ = 15.7 Hz), 7.32 (3 H, d, $^3J_{HH\ Trans}$ = 15.5 Hz), 7.58 (6 H, s), 7.85 (3 H, s), 8.32 (3 H, s), 10.10 (6 H, s) ppm. ^{13}C NMR (100 MHz, d_6-DMSO) δ 17.2, 21.5, 22.9, 23.9, 26.6, 30.1, 31.8, 32.1, 34.7, 38.3, 47.4, 54.6, 74.2, 111.5, 113.7, 123.3, 136.4, 140.0, 141.0, 165.9, 172.7, 172.7 ppm. IR ν_{max} 3349, 1727, 1661, 1618, 1555, 1453 cm^{-1}. MALDI-TOF MS: $C_{117}H_{174}N_{10}O_{21}$, *m/z* calcd for $(M + H)^+$ 2056.29, $(M + Na)^+$ 2078.28, $(M + K)^+$ 2094.25, found $(M + H)^+$ 2055.96, $(M + Na)^+$ 2078.25, $(M + K)^+$ 2094.49. GPC (THF): M_w 1766, M_n 1729, M_w/M_n 1.02.

Synthesis of 22. To a solution of C_2-[G-1]-CO_2H **10** (0.21 g, 0.32 mmol) and 1,7-diaminoheptane (0.02 g, 0.14 mmol) in dry CH_3CN (5 mL) was added BOP (0.15 g, 0.40 mmol) followed by DiPEA (0.03 mL, 0.15 mmol), and the mixture was stirred at room temperature for 48 h and the conversion of the starting material was monitored by TLC ($CHCl_3$−EtOH 9:1, R_f 0.37) and MALDI-TOF MS. The reaction was quenched by addition of water (5 mL) and the product was extracted in $CHCl_3$ (3 × 5 mL). The organic layer was then dried ($MgSO_4$) and filtered and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography ($CHCl_3$−EtOH 96:4) to afford a pale yellow solid (0.19 g, 98% yield, mp (broad) 240−280 °C). ^{1}H NMR (250 MHz, d_6-DMSO) δ 0.82 (12 H, d, $^3J_{HH}$ = 6.3 Hz), 1.23 (8 H, m), 1.25 (4 H, m), 1.33 (10 H, m), 1.36 (4 H, m), 1.39 (4 H, m), 1.41 (12 H, s), 1.47 (4 H, m), 1.55 (12 H, s), 1.89 (8 H, m), 2.59 (16 H, m), 3.17 (4 H, m), 4.03 (8 H, m), 5.04 (4 H, m), 6.57 (2 H, d, $^3J_{HH\ Trans}$ = 15.6 Hz), 7.28 (1 H, d, $^3J_{HH\ Trans}$ = 15.5 Hz), 7.54 (4 H, s), 7.81 (2 H, s), 8.31 (2 H, s), 10.08 (4 H, s) ppm. ^{13}C NMR (62.8 MHz, d_6-DMSO) δ 17.8, 19.5, 25.1, 25.8, 26.8, 28.9, 29.1, 29.4, 31.2, 35.3, 36.7, 36.8, 62.5, 79.5, 111.0, 113.0, 122.8, 124.9, 130.9, 135.8, 138.7, 140.3, 164.9, 170.3, 172.6 ppm. IR ν_{max} 3270, 3099, 1735, 1690, 1663, 1617, 1558, 1452 cm^{-1}. FAB MS: $C_{81}H_{122}N_6O_{14}$, *m/z* calcd for $(M + Na)^+$ 1425.89, found $(M + Na)^+$ 1425.89. MALDI-TOF MS: *m/z* calcd for M^+ 1402.90, $(M + Na)^+$ 1425.89, $(M + K)^+$ 1441.87, found M^+ 1401.34, $(M + Na)^+$ 1424.25, $(M + K)^+$ 1440.39. Anal. Calcd for $C_{81}H_{122}N_6O_{14}$: C 69.30, H 8.76, N 5.98. Found: C 69.20, H 8.73, N 5.62. GPC (THF): M_w 1645, M_n 1631, M_w/M_n 1.01.

Synthesis of 23. To a solution of TREN (0.03 mL, 0.23 mmol) and C_2-[G-1]-CO_2H **10** (0.51 g, 0.77 mmol) in dry CH_3CN (10 mL) was added BOP (0.30 g, 0.80 mmol) followed by DiPEA (0.06 mL, 0.30 mmol). The reaction mixture was left stirring at room temperature for 4 days, and conversion of the starting material was monitored by TLC ($CHCl_3$−EtOH 9:1, R_f 0.66) and MALDI-TOF MS. The reaction was quenched by addition of water (10 mL), extracted with $CHCl_3$ (3 × 10 mL), and then washed with brine (3 × 10 mL). The organic layer was then dried ($MgSO_4$) and filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography ($CHCl_3$−EtOH 99:1) to afford a white solid (0.13 g, 28% yield, mp (broad) 183−201 °C). ^{1}H NMR (250 MHz, d_6-DMSO) δ 0.84 (18 H, d, $^3J_{HH}$ = 6.3 Hz), 1.13 (6 H, m), 1.26 (6 H, m), 1.33 (6 H, m), 1.38 (6 H, m), 1.49 (3 H, m), 1.53 (18 H, s), 1.61 (18 H, s), 1.92 (12 H, m), 2.58 (30 H, m), 3.08 (6 H, m), 4.02 (12 H, m), 5.06 (6 H, m), 6.60 (3 H, d, $^3J_{HH\ Trans}$ = 15.8 Hz), 7.31 (3 H, d, $^3J_{HH\ Trans}$ = 15.4 Hz), 7.54 (6 H, s), 7.81 (3 H, s), 8.25 (6 H, m), 10.07 (3 H, m) ppm. ^{13}C NMR (62.8 MHz, d_6-DMSO) δ 17.06, 19.4, 25.2, 25.8, 29.1, 34.3, 35.2, 36.8, 42.2, 62.4, 111.0, 113.1, 124.8, 130.9, 135.7, 138.0, 140.3, 165.2, 170.4, 172.7 ppm. IR ν_{max} 3337, 3092, 1733, 1713, 1639, 1601, 1556, 1452 cm^{-1}. MALDI-TOF MS:

$C_{117}H_{174}N_{10}O_{21}$, *m/z* calcd for M^+ 2055.29, $(M + Na)^+$ 2078.28, $(M + K)^+$ 2094.25, found M^+ 2055.90, $(M + Na)^+$ 2077.90, $(M + K)^+$ 2095.30. Anal. Calcd for $C_{117}H_{174}N_{10}O_{21}\cdot 7H_2O$: C 64.38, H 8.68, N 6.42. Found: C 64.27, H 8.57, N 5.92. GPC (THF): M_w 1944, M_n 1884, M_w/M_n 1.03.

Synthesis of 24. To a solution of 1,7-diaminoheptane (0.04 g, 0.05 mmol), C_4-[G-2]-CO_2H **14** (0.20 g, 0.14 mmol), HOAt (0.03 g, 0.20 mmol), and DiPEA (0.04 mL, 0.22 mmol) in dry CH_3CN (10 mL) and dry DMF (2 mL) was added HATU (0.09 g, 0.20 mmol), and the reaction was left stirring at room temperature for 24 h. The reaction profile was monitored by TLC analysis ($CHCl_3$−EtOAc 9:1, R_f 0.30) and MALDI-TOF MS. The reaction was quenched by the addition of water (10 mL) and the product was extracted with $CHCl_3$ (3 × 10 mL). The organic layers were dried ($MgSO_4$) and filtered and the solvent was removed under reduced pressure to leave the crude product. Purification was carried out by column chromatography utilizing a gradient elution (from CH_2Cl_2−EtOAc 80:20 to EtOAc−EtOH 95:5), to afford the desired product as a pale brown solid (30.00 mg, 20% yield, mp (broad) 200−230 °C). ^{1}H NMR (400 MHz, d_6-DMSO, 40 °C) δ 0.84 (24 H, d, $^3J_{HH}$ = 6.6 Hz), 1.10 (8 H, m), 1.13 (8 H, m), 1.26 (8 H, m), 1.31 (10 H, m), 1.40 (8 H, m), 1.53 (24 H, s), 1.57 (8 H, m), 1.67 (24 H, s), 1.88 (4 H, m), 2.63 (32 H, m), 3.17 (4 H, m), 4.05 (16 H, m), 5.06 (8 H, m), 6.54 (2 H, d, $^3J_{HH\ Trans}$ = 15.6 Hz), 6.86 (4 H, d, $^3J_{HH\ Trans}$ = 15.6 Hz), 7.29 (2 H, d, $^3J_{HH\ Trans}$ = 15.3 Hz), 7.41 (4 H, d, $^3J_{HH\ Trans}$ = 15.4 Hz), 7.68 (8 H, s), 7.75 (4 H, s), 7.80 (4 H, s), 8.02 (2 H, s), 10.17 (8 H, s), 10.50 (4 H, s) ppm. ^{13}C NMR (100 MHz, d_6-DMSO) δ 26.8, 28.5, 34.2, 34.7, 35.8, 37.8, 38.2, 38.4, 40.4, 43.7, 44.3, 71.6, 120.6, 122.5, 131.8, 133.9, 134.2, 139.0, 144.6, 145.0, 148.5, 149.8, 173.0, 175.0, 179.4, 181.6 ppm. IR ν_{max} 3425, 1722, 1666, 1617, 1555, 1453 cm^{-1}. MALDI-TOF MS: $C_{83}H_{114}N_6O_{16}$, *m/z* calcd for $(M + Na)^+$ 3018.77, $(M + K)^+$ 3034.75, found $(M + Na)^+$ 3017.90, $(M + K)^+$ 3034.87. GPC (THF): M_w 3054, M_n 2770, M_w/M_n 1.10.

Synthesis of 25. To a solution of 1,7-diaminoheptane (1.37 mg, 0.087 mmol), M_4-[G-2]-CO_2H **15** (0.35 g, 0.245 mmol), HOAt (0.041 g, 0.30 mmol), and DiPEA (0.07 mL, 0.40 mmol) in dry CH_3CN (15 mL) and dry DMF (2 mL) was added HATU (0.137 g, 0.30 mmol), and the reaction was left stirring at room temperature for 24 h. The reaction profile was monitored by TLC analysis ($CHCl_3$−EtOH 9:1, R_f 0.82). The reaction was quenched by the addition of water (10 mL) and the product was extracted with $CHCl_3$ (3 × 10 mL). The organic layers were dried ($MgSO_4$) and filtered and the solvent was evaporated under reduced pressure to leave the crude product as pale brown amorphous solid (76.00 mg, 29% yield). ^{1}H NMR (250 MHz, d_6-DMSO) δ 0.68 (24 H, d, $^3J_{HH}$ = 6.8 Hz), 0.80 (24 H, d, $^3J_{HH}$ = 6.8 Hz), 0.83 (8 H, m), 0.91 (24 H, d, $^3J_{HH}$ = 6.8 Hz), 0.97 (8 H, m), 1.05 (8 H, m), 1.31 (10 H, m), 1.43 (16 H, m), 1.61 (16 H, m), 1.87 (16 H, m), 2.54 (32 H, m), 3.17 (4 H, m), 4.61 (8 H, m), 6.61 (2 H, d, $^3J_{HH\ Trans}$ = 15.5 Hz), 6.85 (4 H, d, $^3J_{HH\ Trans}$ = 15.5 Hz), 7.29 (2 H, d, $^3J_{HH\ Trans}$ = 15.7 Hz), 7.48 (4 H, $^3J_{HH\ Trans}$ = 15.4 Hz), 7.69 (8 H, s), 7.75 (4 H, s), 7.78 (4 H, s), 8.02 (2 H, s), 8.31 (2 H, s), 10.14 (8 H, s), 10.49 (4 H, s) ppm. ^{13}C NMR (100 MHz, d_6-DMSO) δ 15.8, 20.0, 21.4, 22.4, 25.1, 28.0, 28.6, 29.9, 30.3, 30.6, 33.2, 45.9, 72.8, 110.4, 112.4, 121.8, 122.0, 123.0, 124.4, 134.6, 135.1, 137.9, 139.6, 140.0, 163.1, 164.1, 169.6, 171.2 ppm. IR ν_{max} 3310, 3099, 1729, 1708, 1669, 1615, 1557, 1453 cm^{-1}. MALDI-TOF MS: $C_{83}H_{114}N_6O_{16}$, *m/z* calcd for $(M + Na)^+$ 3018.77, $(M + K)^+$ 3034.75, found $(M + Na)^+$ 3018.36, $(M + K)^+$ 3033.26. GPC (THF): M_w 3967, M_n 3510, M_w/M_n 1.13.

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Supporting Information Available: General methods used, DSC data for compounds **8**, **10**, **12**, **14**, **13**, **15**, **16**, **20**, **21**, **22**, **23**, and **24** (Figures 1s−6s), ^{1}H NMR spectroscopic data for **12**, **16**, **17**, **18**, **19**, **20**, **22**, and **23** (Figures 7s−15s), MALDI-TOF mass spectrometric data for **17**, **19**, **20**, and **21** (Figure 16s), and X-ray crystallographic files for **2** and **5** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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