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Design, Synthesis, and Characterization of Conifer-Shaped Dendritic Architectures

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Abstract: An elongated structural design leading to more conical-shaped dendritic architectures by using a combination of 1→3, 1→(2+1), and 1→(2+1 Me) C-branched monomers is presented. Synthesis of the conifer-shaped macromolecule was achieved by reaction between isocyanate **20** and amine **26** in dry CH_2Cl_2. A resultant extended focal adamantane-modified dendron was deprotected to generate the water-soluble product, which was subsequently complexed with β-cyclodextrin in D_2O to create the desired tree-like product. Host–guest interactions of the adamantane moiety with the β-cyclodextrin cavity were monitored by ^{1}H NMR spectroscopy. All monomers, key intermediates, and final products were fully characterized by ^{1}H and ^{13}C NMR spectroscopy, ESI or MALDI-TOF mass spectrometry, and IR spectroscopy.

Keywords: dendrimers · dendrons · nanostructures · supramolecular chemistry

Introduction

Traditional dendritic growth has generally led to uniform, spherical morphologies, since the monomers used in their construction are generally uniform throughout their infrastructure. In light of the step-wise synthesis associated with the divergent construction of dendrimers, the utilization of different but yet similar branched monomers permits the construction of nonspherical shapes and sizes, thus expanding their applications in the areas of supramolecular chemistry.[1] Also, most of the dendritic architectures reported have a homogeneous surface, and are assembled in a uniform manner, due to the use of identical monomers or dendrons at each successive generation. The design and synthesis of these architectures, including dendronized polymers,[2,3] for various applications in areas such as unimolecular micelles,[4,5] molecular encapsulation,[4,6–9] drug delivery,[10–12] and catalysis[13,14] have become an important part of supramolecular chemistry.[15] The general spherical shape and molecular weight of these unimolecular, nanoscale materials can be controlled by their now well-known step-wise construction, based on either a divergent strategy[16,17] involving an "inside-out" approach or a convergent strategy[18–20] utilizing an "outside-in" methodology. Accelerated procedures such as the orthogonal construction[21,22] and the double-exponential growth method[23] have also been applied to the synthesis of dendrimers to reduce the overall number of steps. The chemical and physical properties of most dendrimers can be tuned by the introduction of appropriate terminal functional groups as well as internal components.

The majority of dendritic constructs have a homogeneous surface, that is, the same functionality appears at each terminus. Although there have been limited examples of combinatorial-type[24] heterogeneous surfaces, Fréchet et al.[25] reported an initial example of the functionalization of a dendron surface by placing a unique functional group on it's periphery; the convergent approach was applied to the construction of first- to fourth-generation dendrons possessing a single cyano group on the surface of each dendron. These dendrons were finally coupled at their focal site to a three-directional core to produce a dendrimer with three unique termini. Schlüter et al.[26] applied a similar strategy to incorporate bromo functionalities at specific locations within their dendritic framework.

More recently, Thayumanavan et al.[27] reported a series of dendrimers with various terminal groups in which the

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Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author. It contains the ^{1}H and ^{13}C NMR data of all the intermediates and products.

branched dendrons were convergently prepared to instill a pattern of substitution into the ultimate dendrimer; multiple approaches involving monomers possessing either different 1→2-branched terminal protecting groups[28] or different terminal reactivities[29] affording varied functional groups on the periphery have been reported. Kozaki and Okada presented[30] the preparation of snowflake-shaped dendrimers by using a combination of Suzuki and Sonogashira cross-coupling reactions.

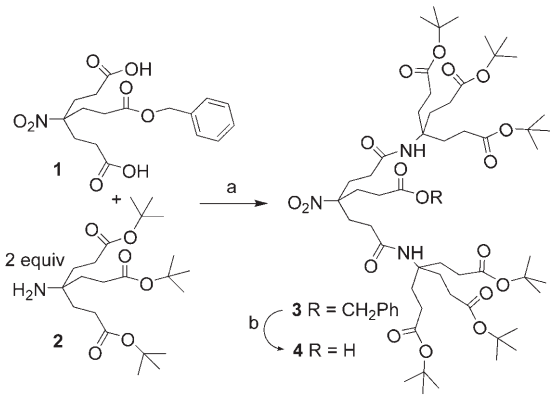
Majoral et al. reported[31–37] the preparation of phosphorus-containing dendrimers with P=N−P=S linkages, followed by internal site-specific functionalization leading to heterogeneous substitution. These authors also selectively functionalized one of the peripheral $P(X)Cl_2$ (X = S, O) moieties by displacement of a single chlorine atom leaving the other chlorine atom for further dendritic growth.[38]

In 2002, we devised a simple, utilitarian series of 1→(2+1) C-branched dendrons[39–42] so that specific functionality could be introduced but branching could still continue by means of the two remaining sites. This permitted access to complex dendritic spherical structures that possessed a single (or a controlled number) unique locus per dendron. This enhanced our general ability to preselect the number of unique sites at each generation of a particular dendrimer. Since these 1→(2+1) C-branched predendrons and related dendrons are easily created, when combined with 1→3 C-branching monomers and dendrons, there is an infinite number of architectural possibilities. Since the vast majority of dendritic structures are spherical, or nearly so depending on the generation, we set the construction of different sizes and forms of nanoscopic macromolecular trees as our goal.

Herein, we describe our initial simple strategy aimed at the synthesis of nonspherical dendrons using the convergent protocol by the selective combination of 1→3, 1→(2+1), and 1→(2+1 Me) C-branching building blocks.

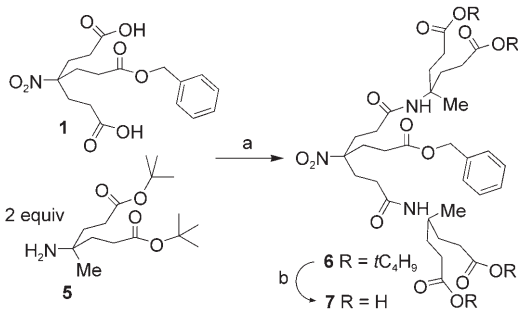
Results and Discussion

Diacid **1**, prepared[39] by treatment of benzyl 4-nitrobutanoate with a slight excess of *tert*-butyl acrylate followed by *tert*-butyl ester hydrolysis (HCO_2H), was treated with two equivalents of 1→3 C-branched amine **2**[43,44] in the presence of dicyclohexyl carbodiimide (DCC) and 1-hydroxy-1*H*-benzotriazole (1-HOBT) to afford heptaester **3** (yield 93%; Scheme 1). The formation of ester **3** is supported by the presence of two new peaks at $\delta = 57.7$ and 170.2 ppm in the ^{13}C NMR spectrum, corresponding to the HN*C* and *C*ONH carbon signals supporting tier assembly; the molecular weight of 1185.3 amu (ESI-MS) further evidenced the structure. Catalytic deprotection of monomer **3** with 10% Pd/C afforded the bis(amido) acid **4** (yield 100%), as shown by the disappearance of the benzyl group absorptions and the observed new peak at $\delta = 174.0$ ppm (CO_2H) in the ^{13}C NMR spectrum. The definitive molecular ion peak (ESI-MS) at $m/z = 1073.33$ $[M-H]^+$ also supported the structure.



Scheme 1. Synthesis of the second-generation predendrons: a) DCC, 1-HOBT, THF, 25 °C, 24 h; b) H_2, 10% Pd/C, EtOH, 25 °C, 7 h.

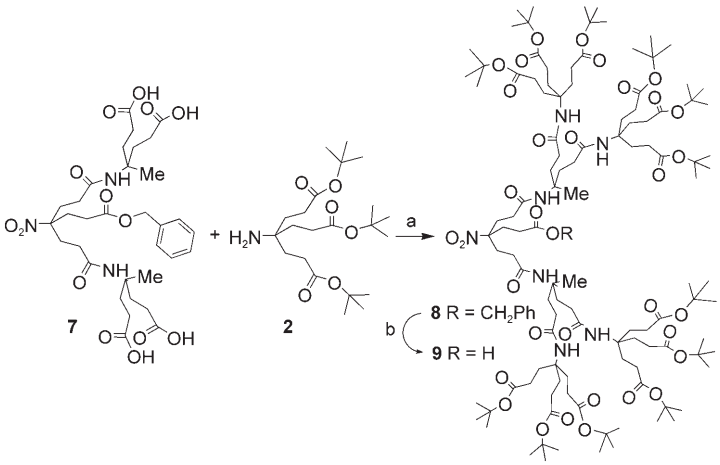
To construct a larger wedge, a 1→(2+1 Me) C-branching pattern was inserted into the synthetic protocol affording a less congested internal environment deemed necessary for later coupling of the components. Treatment of diacid **1** with aminodiester building block **5**[45] using DCC amidation conditions gave pentaester **6** (yield 96%; Scheme 2). The



Scheme 2. Synthesis of predendron **7**: a) DCC, 1-HOBT, THF, 25 °C, 24 h; b) HCO_2H, 25 °C, 15 h.

^{13}C NMR spectral data for **6** showed two carbonyl groups [$\delta = 170.4$ (amide) and 173.2 ppm (ester)] as well as an ESI-MS peak at $m/z = 957.3$ $[M+Na]^+$. Pentaester **6** was then deprotected with 95% formic acid at 25 °C for 15 h to quantitatively give the tetraacid **7**, which was confirmed by the disappearance of the *tert*-butyl absorptions in the ^{13}C NMR spectrum, as well as the expected downfield shift for the carboxylic carbonyl group to $\delta = 174.0$ ppm; the ESI-MS revealed a molecular ion peak at $m/z = 708.3$ $[M-H]^+$.

The tetraacid **7** was coupled with Behera's amine **2** under similar amidation conditions to afford (85%) predendron **8** (Scheme 3), which was identified by the appearance of a singlet at $\delta = 24.0$ ppm for the unique methyl groups and four distinctive carbonyl absorptions at $\delta = 170.9$, 172.2, 172.9, and 173.0 ppm in the ^{13}C NMR spectrum, as well as the appropriate MALDI-TOF MS peak at $m/z = 2321.6$ $[M+Na]^+$. Hydrogenolysis of the benzyl group with 10% Pd/C at 60 psi and 25 °C for 48 h liberated the unique internal acid moiety generating the desired dodecaester **9** as demonstrat-

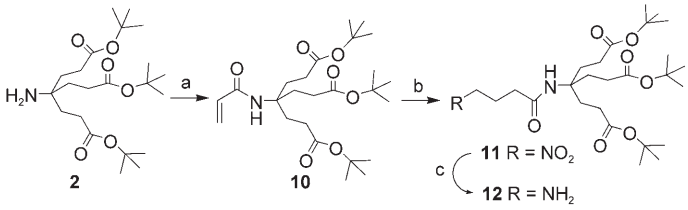


Scheme 3. Synthesis of third-generation predendron **9**: a) DCC, 1-HOBT, DMF, 25 °C, 24 h; b) H_2, 10 % Pd/C, 25 °C, 48 h.

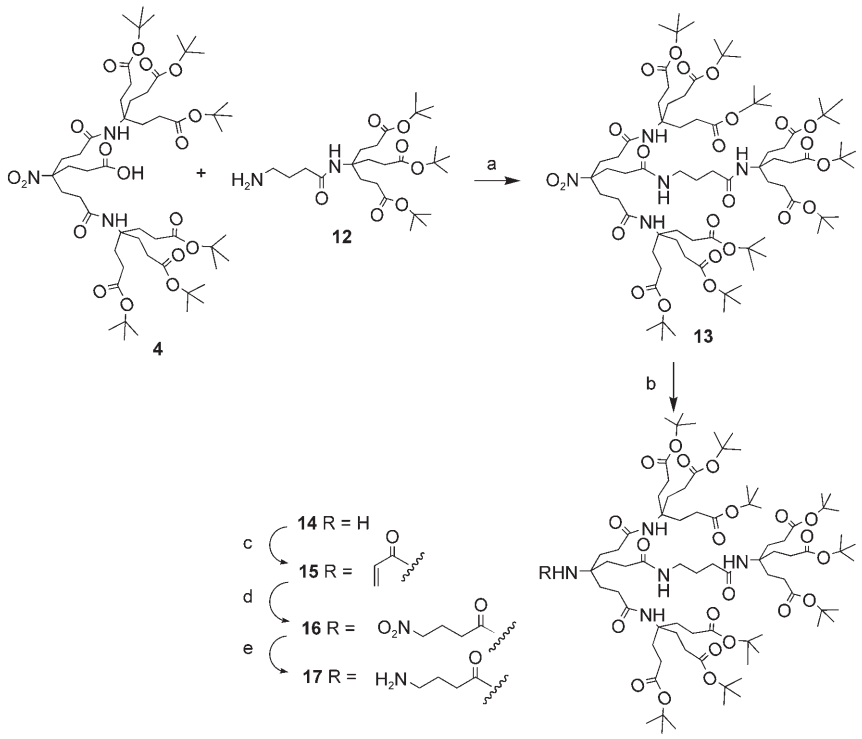
ed by the appearance of a new peak at $\delta = 174.9$ ppm for this carbonyl group, while still retaining all other core functionality as verified by ^{13}C NMR spectroscopy. A shift ($1730 \rightarrow 1700\ cm^{-1}$) of the C=O adsorption (IR spectroscopy) as well as observed broad peak for the OH stretching ($3660–3000\ cm^{-1}$) further confirmed the transformation. The combination of these different monomers in the assembly process ensures a high outer surface density while leaving the internal infrastructure open for subsequent elaboration.

To instill the elongated component into the framework, Behera's amine **2**, when treated with one equivalent of acryloyl chloride in the presence of Et_3N in dry THF, gave the N-substituted amide **10** (yield > 96 %; Scheme 4), which was subsequently subjected to a 1:1 Michael-type addition with $MeNO_2$ in the presence of the water-soluble base tetramethylguanidine (TMG) to generate the homologated nitrotriester **11** (ca. 90 % overall yield).[46] Reduction of the nitro moiety with Raney Ni catalyst in absolute EtOH at 50 °C afforded the desired extended amine dendron **12** (yield 98 %), whose structure was identified by the anticipated upfield chemical shift from $\delta = 74.5$ to 41.0 ppm (O_2NCH_2 and H_2NCH_2, respectively) in the ^{13}C NMR spectrum and the molecular ion peak (ESI-MS) at $m/z = 523.1$ $[M+Na]^+$.

With most of the key components of this elongated molecular structure in-hand, assembly of the sections started with the top tier **12**, which is connected to the middle tier **4**, then to the bottom tier **9**, and lastly is extended with a novel focal section. Thus, the DCC-mediated coupling of monoacid **4** and amine **12** afforded top-section predendron **13** (yield 92 %; Scheme 5), which was characterized by the appearance of peaks at $\delta = 80.6$ and 80.7 ppm for two different *tert*-butyl quaternary carbon atoms and the presence of three peaks for the three different amide carbonyl moieties in the ^{13}C NMR spectrum, and a definitive molecular ion (ESI-MS) peak at $m/z = 1577.8$ $[M+Na]^+$. The focal nitro group of this predendron **13** was then reduced quantitatively to the corresponding amine group by catalytic hydrogenation to generate the (1+2)-polyfunctional dendron **14**. Formation of amine **14** was demonstrated by the upfield shift (^{13}C NMR spectroscopy) of the peak assigned to the focal quaternary carbon from $\delta = 93.1$ to 55.3 ppm and a molecular ion peak (ESI-MS) at $m/z = 1547.8$ $[M+Na]^+$.



Scheme 4. Synthesis of the extended amine dendron **12**: a) H_2C=CHCOCl, Et_3N, CH_2Cl_2, 25 °C, 2 h; b) CH_3NO_2, $CHCl_3$, 25 °C, 24 h; c) H_2, Raney Ni, EtOH, 50 °C, 15 h.

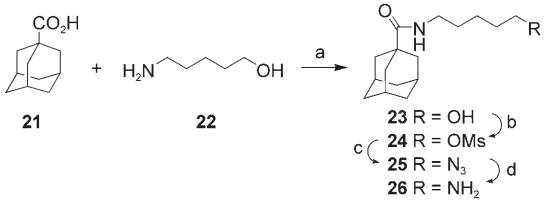


Scheme 5. Synthesis of the second-generation extended dendron **17**: a) DCC, 1-HOBT, THF, 25 °C, 24 h; b) H_2, T1-Raney Ni, EtOH, 50 °C, 15 h; c) H_2C=CHCOCl, Et_3N, THF, 25 °C, 5 h; d) CH_3NO_2, TMG, 50 °C, 15 h; e) H_2, Raney Ni, EtOH, 50 °C, 15 h.

To instill the extended focal functionality necessary to penetrate into and attach the lower tier 3, the synthesis of acrylamide **15** (yield 93%; Scheme 5) was achieved by the treatment of amine **14** with acryloyl chloride in the presence of Et_3N in dry THF. The new acrylamide signal (^{13}C NMR spectrum) at $\delta = 165.5$ ppm (*C*ONH) and olefinic peaks at $\delta = 125.5$, 132.1 ppm, as well as a molecular ion peak (ESI-MS) at $m/z = 1602.1$ $[M+Na]^+$, provided evidence for the initial extension stage. Treating the acrylamide **15**[46] with $MeNO_2$ in the presence of TMG in refluxing THF for 24 h gave predendron **16** (yield 82%), which was structurally established by ^{13}C NMR spectroscopy with a new signal ($\delta =$ 74.9 ppm) for the O_2NCH_2R moiety and by the molecular ion peak (ESI-MS) at $m/z = 1662.9$ $[M+Na]^+$. Reduction of the nitro moiety with Raney Ni catalyst in absolute EtOH at 50°C created the desired extended amino dendron **17** (yield 95%), which was supported by the spectral similarity to the previous predendrons in this synthetic series with the exception of the notable chemical shift (^{13}C NMR spectroscopy) from $\delta = 74.9$ to 39.9 ppm (O_2NCH_2 and H_2NCH_2, respectively) and the molecular ion peak (ESI-MS) at $m/z =$ 1633.0 $[M+Na]^+$.

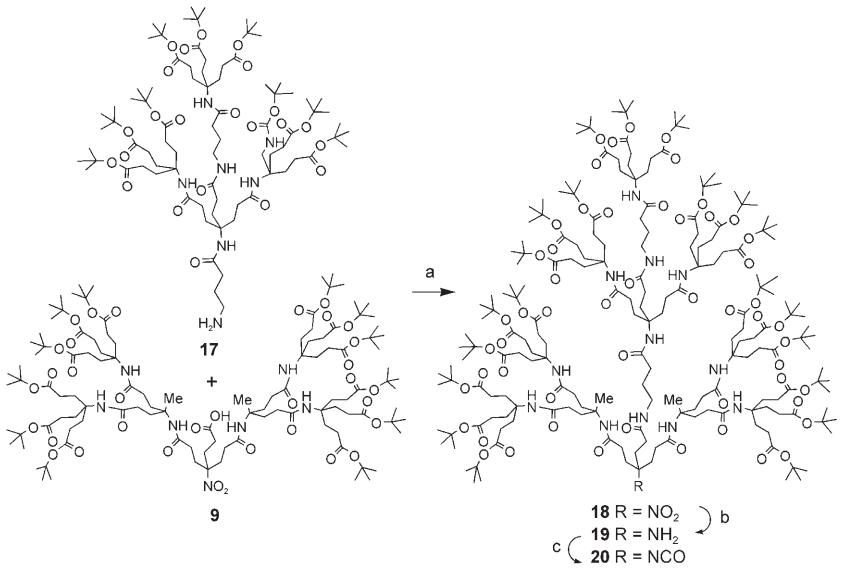
The assembly of the combined tiers 1 and 2 in extended amine **17** with the lower (tier 3) portion was accomplished by treatment of the acid **9** with amine **17** by the DCC coupling procedure to generate the desired predendron **18** (yield 65%; Scheme 6). The structure of **18** was confirmed by the observation of the peaks assigned to the ten different carbonyl groups in the ^{13}C NMR spectrum and the molecular ion at $m/z = 3825.5$ $[M+Na]^+$ in the MALDI-TOF MS. Reduction of the nitro moiety with Raney Ni in absolute EtOH at 50°C for 36 h afforded the corresponding amine **19** (yield 85%) that was characterized by the chemical shift (^{13}C NMR spectroscopy) for the H_2NC carbon atom from $\delta = 92.3$ to 55.6 ppm and the molecular ion peak in MALDI-TOF MS at m/z = 3796.2 $[M+Na]^+$. Amino dendron **19** was next treated with triphosgene in the presence of Et_3N to afford (75%) the desired isocyanate dendron **20**. New peaks at $\delta = 62.3$ (OCN*C*), 123.2 ppm (O*C*N) supported the assigned structure of **20**; in addition, a $[M+Na]^+$ peak at $m/z = 3819.6$ (calcd mass: 3820.9) and appearance of the unique peak at 2210 cm^{-1} (FTIR) further characterized the proposed structure.

Construction of the adamantane-based focal molecular anchor was undertaken next; the strategy for the synthesis of alkyl amine modified adamantane **26** is shown in Scheme 7. Using the standard amidation conditions, 1-adamantanecarboxylic acid was treated with aminopentanol to



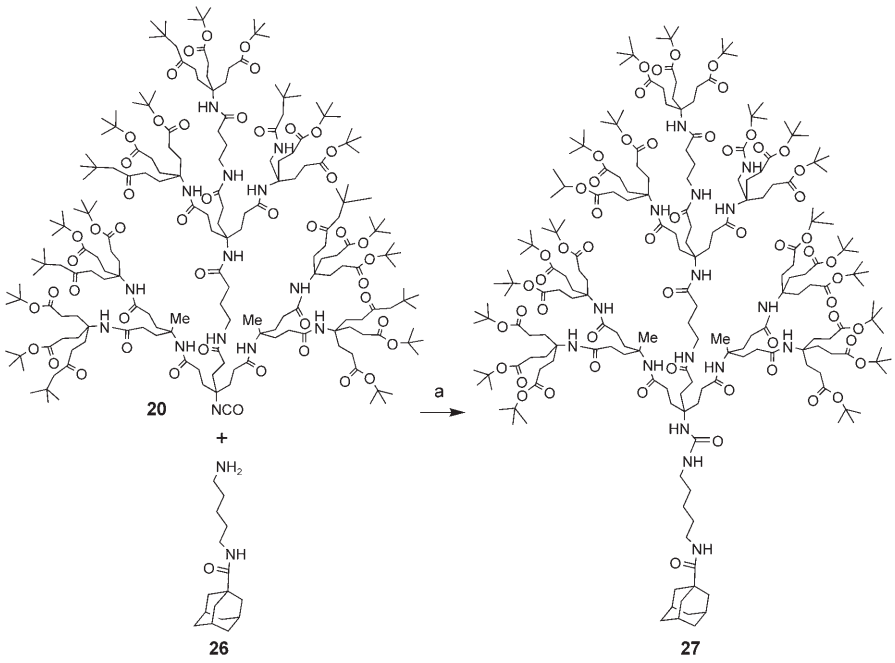
Scheme 7. Selective amidation of **21** allowing construction of adamantane amine **26**: a) DCC, 1-HOBT, THF, 25°C, 5 h; b) Et_3N, MsCl, THF, 25°C, 3 h; c) NaN_3, DMF, 50°C, 7 h; d) H_2, 10% Pd/C, EtOH, 25°C, 12 h.

generate alcohol **23** (yield 87%), as evidenced by the appearance of a carbonyl peak at $\delta = 178.2$ ppm in the ^{13}C NMR spectrum for the amide and the ESI-MS data revealing the expected molecular ion at $m/z = 288.1$ $[M+Na]^+$. Alcohol **23** was subsequently treated with mesyl chloride in the presence of Et_3N in THF to produce mesylate **24** (yield 90%); the downfield shift ($\delta = 62.2$ to 69.9 ppm) for OCH_2 and the appearance of a peak at $\delta = 37.3$ ppm for the SO_2CH_3 moiety in the ^{13}C NMR spectrum, as well as the molecular ion peak (ESI-MS) at $m/z = 366.2$ $[M+Na]^+$, confirmed the transformation. Nucleophilic substitution of the mesyl group with NaN_3 in DMF at 60°C afforded azide **25** (yield 93%), which was catalytically hydrogenated to give the corresponding amine **26** (yield 95%), the structure of which was supported by an upfield shift ($\delta = 51.2 \rightarrow 40.8$ ppm; ^{13}C NMR spectrum) of the absorption corresponding to the CH_2NH_2 moiety and a molecular ion peak (ESI-MS) at $m/z =$ 287.3 $[M+Na]^+$.



Scheme 6. Synthesis of elongated dendron **20**: a) DCC, 1-HOBT, DMF, 25°C, 24 h; b) H_2, Raney Ni, EtOH, 50°C, 48 h; c) triphosgene, Et_3N, THF, 25°C, 12 h.

Synthesis of the desired elongated macromolecule **27** was achieved (yield 95%; Scheme 8) by the reaction between isocyanate **20** and amine **26** in dry CH_2Cl_2. Evidence for the formation of **27** was supported by the appearance of the new urea carbonyl group at $\delta = 158.3$ ppm (^{13}C NMR spectroscopy) and the molecular ion peak (MALDI-TOF) at $m/z =$



Scheme 8. Construction of the conifer-shaped dendrimer and its complexation with β-cyclodextrin: a) CH_2Cl_2, 25 C, 5 h.

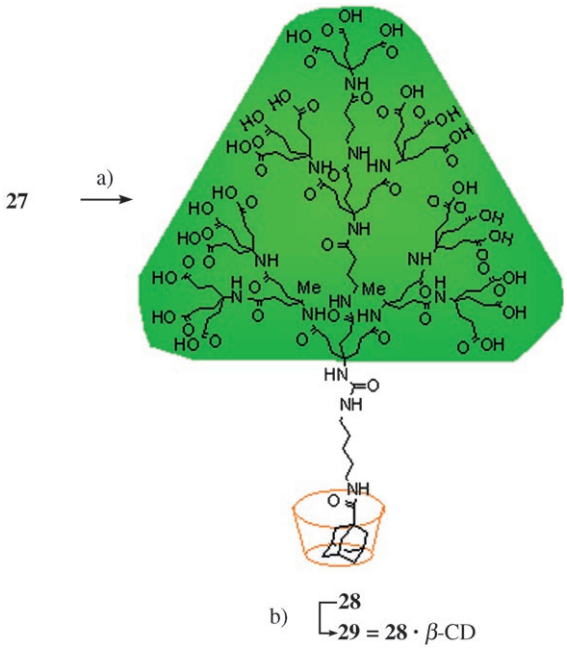
4085.0 $[M \rightarrow Na]^+$. The *tert*-butyl groups of the adamantane-terminated dendron were removed by using formic acid to generate the desired water-soluble admantane-terminated acid dendron **28**, which was "planted" into a suitable molecular container, β-cyclodextrin (β-CD), by treatment of a 1:1 mixture of **28** and β-CD in D_2O at ambient temperature. The host–guest interactions of the adamantane moiety within the β-cyclodextrin cavity were monitored by ^{1}H NMR spectroscopy. The H-3 peak of the uncomplexed cyclodextrin at $\delta = 4.01$ ppm was shifted upfield ($\Delta\delta = -0.13$ ppm) upon complexation with the acid-terminated adamantane-modified dendron, which compares well with other proton data reported in the literature for this phenomenon.[42,47,48]

In summary, new types of dendritic frameworks possessing different, branched layers were synthesized from the key intermediates **9** and **17**, which in turn were readily prepared from a combination of 1→(2+1 Me), 1→(2+1), and 1→3 C-branched building blocks. The amine dendron **18** has been synthesized, and then transformed to the corresponding isocyanate dendron by using triphosgene. Treatment of isocyanate **20** with amine **26** afforded conical-shaped dendron **27**, which was subsequently treated with formic acid to generate the water-soluble, acid-based dendron **28**. Finally, the dendron **28** was planted in β-cyclodextrin and the resulting complex (i.e., **29**) was confirmed by ^{1}H NMR spectroscopy.

All the new dendrons were isolated as either white solids or clear viscous liquids, which were soluble in common organic solvents such as $CHCl_3$, CH_2Cl_2, THF, and MeOH and were fully characterized by ^{1}H and ^{13}C NMR spectroscopy, ESI or MALDI-TOF MS, and IR spectroscopy. Today when one buys an evergreen tree in a nursery, the balled root system is in a plastic bucket, thus the creation of coniferous-shaped molecular trees and their protected sites for attachment is possible and may be available in the future to build molecular gardens and forests. One realizes that two-dimensional representations do not accurately depict three-dimensional molecular assemblies, but having appropriate branched monomers permits the construction of novel non-uniform, tree-shaped structures (Scheme 9).

Experimental Section

General remarks: Melting point data were obtained in capillary tubes with an Electrothermal 9100 melting point apparatus and are uncorrected. All of chemicals were purchased from Aldrich except for Behera's amine.[49] Tetrahydrofuran (THF) was dried by refluxing over benzophenone/Na under N_2. Dichloromethane was dried over CaH_2. All other commercially available solvents were used without further purification. Column chromatography was conducted by using silica gel (60–200 mesh) from Fisher Scientific with the stipulated solvent mixture. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ (setting the reference peak at $\delta = 77.23$ ppm) except where noted, and were recorded at 300 and 75 MHz, respectively. Infrared spectra (IR) were obtained (KBr pellet, unless otherwise noted)



Scheme 9. Removal of the ester groups of **27** to afford the water-soluble adamantane-terminated acid dendron followed by complexation with β-cyclodextrin: a) HCO_2H, 25 °C, 15 h; b) β-CD, D_2O, 25 °C, 1 h.

and recorded on an ATI Mattson Genesis Series FTIR spectrometer. Mass spectral data were obtained by using an Esquire electron ionization mass spectrometer (ESI); ESI samples were typically prepared in MeOH/H_2O/TFA (70:30:01) for positive ion mode or Me_2CHOH/H_2O/NH_3 (70:30:1) for negative ion mode and matrix assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometer.

Preparation of activated Raney nickel catalyst:[50] In a beaker with distilled water (2 L), NaOH (300 g) was added carefully with stirring. After dissolution, Al-Ni alloy (120 g) was added in small portions. The temperature suddenly increased with the evolution of hydrogen gas. The beaker was covered with a watch glass and the temperature was maintained at 80–90 °C by warming on a hot plate/stirrer for one hour. The supernatant solution was then decanted; the catalyst was washed several times with distilled water and then three times with EtOH. *Throughout this process, caution must be taken to keep the catalyst wet; the activated catalyst is highly pyrophoric.*

Heptaester 3 and bis(amido)acid 4: These compounds were both prepared by literature procedures.[39]

Synthesis of pentaester 6: DCC (1.2 g, 5.7 mmol) and 1-HOBT (770 mg, 5.7 mmol) were added at 25 °C to a stirred solution of acid **1**[39] (mp 96–97 °C; 1 g, 2.7 mmol) in dry DMF (30 mL); after 2 h, diester amine **5**[45] (1.7 g, 5.7 mmol) was added. The mixture was stirred for 24 h, after which the white precipitate was filtered. The filtrate was concentrated in vacuo to give a crude oil, which was subjected to column chromatography (SiO_2) eluting with 15 % EtOAc in hexane to afford (96 %) **6**, as viscous oil. Yield: 2.5 g; ^{1}H NMR: δ = 1.27 (s, 6H; CH_3), 1.43 (s, 36H; C-(CH_3)$_3$), 1.89 (t, J = 7.5 Hz, 8H; CH_2CH$_2$CO$_2$), 2.01 (t, J = 7.5 Hz, 4H; CH_2CH$_2$CO$_2$CH$_2$), 2.08 (t, J = 6 Hz, 8H; CH_2CO$_2$), 2.23 (t, J = 7.5 Hz, 6H; CH_2CH$_2$CONH, CH_2CH$_2$CO$_2$CH$_2$), 2.39 (t, J = 8.4 Hz, 2H; CH_2COCH$_2$), 5.11 (s, 2H; OCH_2), 6.05 (s, 2H; NH), 7.35 ppm (s, 5H; Ph); ^{13}C NMR: δ = 23.5 (CH_3), 27.9 (C(CH_3)$_3$), 28.5 (CH_2CH$_2$CO$_2$CH$_2$), 29.9 (CH_2CH$_2$CONH), 30.1 (CH_2CH$_2$CO$_2$), 30.9 (CH_2CO$_2$CH$_2$), 31.0 (CH_2CONH), 33.1 (CH_2CO$_2$), 55.3 (NHC), 66.5 (H$_2$CO), 80.3 (CMe_3), 92.6 (O$_2$NC), 128.1 (4-PhC), 128.2 (3-PhC), 128.4 (2-PhC), 135.5 (1-PhC), 170.2 (CONH), 171.7 (CO$_2$CH$_2$), 173.0 ppm (CO$_2$); IR: $\tilde{\nu}$ = 1725 (C=O), 1715 (C=O), 1530 cm^{-1} (NO$_2$); ESI-MS: m/z calcd: 957.16 [M+Na]$^+$; found: 956.8.

Synthesis of tetraacid 7: A solution of pentaester **6** (5 g, 5.3 mmol) in HCO$_2$H (100 mL, 95 %) was stirred at 25 °C for 15 h. After concentration in vacuo, toluene (2 × 50 mL) was added, and the solution was again evaporated in vacuo to afford (95 %) pure tetraacid **7** as viscous liquid. Yield: 3.6 g; ^{1}H NMR: δ = 1.29 (s, 6H; CH_3), 1.93 (br m, 8H; CH_2CH$_2$CO$_2$), 2.10 (t, J = 7.5 Hz, 2H; CH_2CO$_2$CH$_2$), 2.15 (t, J = 6 Hz, 8H; CH_2CO$_2$), 2.35 (t, J = 7.5 Hz, 6H; CH_2CH$_2$CONH, CH_2CO$_2$CH$_2$), 2.43 (t, J = 8.4 Hz, 4H; CH_2CONH), 5.19 (s, 2H; OCH_2), 6.18 (s, 2H; NH), 7.41 ppm (s, 5H; Ph); ^{13}C NMR: δ = 23.8 (CH_3), 26.5 (CH_2CH$_2$CO$_2$CH$_2$), 29.6 (CH_2CH$_2$CONH), 29.9 (CH_2CH$_2$CO$_2$), 31.3 (CH_2CO$_2$CH$_2$), 31.7 (CH_2CONH), 34.4 (CH_2CO$_2$), 56.4 (NHC), 67.7 (H$_2$CO), 94.1 (O$_2$NC), 129.3 (4-PhC), 129.4 (3-PhC), 129.6 (2-PhC), 137.4 (1-PhC), 173.7 (CONH), 173.9 (CO$_2$CH$_2$), 177.5 ppm (CO$_2$); IR: $\tilde{\nu}$ = 3400–3000 (OH), 1725 (C=O), 1700 (C=O), 1535 cm^{-1} (NO$_2$); ESI-MS: m/z calcd: 708.74 [M−H]$^+$; found: 708.30.

Synthesis of predendron 8: DCC (1.2 g, 5.7 mmol) and 1-HOBT (780 mg, 5.7 mmol) were added at 25 °C to a stirred solution of tetraacid **7** (1 g, 1.4 mmol) in dry DMF (30 mL); after 2 h, Behera's amine[49] **2** (2.4 g, 5.7 mmol) was added. The mixture was stirred for 24 h, after which the white precipitate was filtered. The filtrate was concentrated in vacuo to give a crude oil, which was subjected to column chromatography (SiO_2) eluting with 40 % EtOAc in $CHCl_3$ to afford **8** as a white solid. Yield: 2.8 g (85 %); m.p. 127–128 °C; ^{1}H NMR: δ = 1.24 (s, 6H; CH_3), 1.43 (s, 108H; C(CH_3)$_3$), 1.53 (br m, 12H; CH_2CH$_2$CONH), 1.67 (br m, 12H; CH_2CONH), 1.95 (t, J = 7.8 Hz, 24H; CH_2CH$_2$CO$_2$), 2.02 (br m, 2H; CH_2CH$_2$CO$_2$CH$_2$), 2.20 (t, J = 7.5 Hz, 24H; CH_2CO$_2$), 2.41 (br m, 2H; CH_2CO$_2$CH$_2$), 5.12 (s, 2H; OCH_2), 6.12 (s, 4H; NH), 6.88 (s, 2H; NH), 7.35 ppm (s, 5H; Ph); ^{13}C NMR: δ = 24.0 (CH_3), 28.2 (C(CH_3)$_3$), 28.9 (CH_2CH$_2$CO$_2$CH$_2$), 29.9 (CH_2CH$_2$CO$_2$), 30.1 (CH_2CO$_2$), 30.4 (CH_2COCH$_2$), 30.8 (CH_2CH$_2$CONH), 31.3 (CH_2CONH), 32.1 (CH_2CH$_2$CONH), 34.6 (CH_2CONH), 55.7 (HNC), 57.5 (HNC), 66.8 (H$_2$CO), 80.7 (CMe_3), 92.8 (O$_2$NC), 128.4 (4-PhC), 128.7 (3-PhC), 128.8 (2-PhC), 135.8 (1-PhC), 170.9 (CONH), 172.2 (CO$_2$CH$_2$), 172.9 (CONH), 173.0 ppm (CO$_2$); IR: $\tilde{\nu}$ = 1730 (C=O), 1725 (C=O), 1535 cm^{-1} (NO$_2$); ESI-MS: m/z calcd: 2322.33 [M+Na]$^+$; found: 2322.0.

Synthesis of acid 9: A solution of ester **8** (1 g, 430 μmol) in absolute EtOH (100 mL) in the presence of 10 % Pd on activated carbon (1 g) was hydrogenated at 60 psi at 25 °C for 12 h. The solution was cautiously filtered through Celite and the solvent was reduced in vacuo to give monoacid **9** as a white solid. Yield: 860 mg (90 %); m.p. 135–137 °C; ^{1}H NMR: δ = 1.26 (s, 6H; CH_3), 1.44 (s, 108H; C(CH_3)$_3$), 1.96 (t, J = 7.2 Hz, 64H; CH_2CH$_2$CO$_2$, CH_2CH$_2$CONH), 2.19 (br m, 8H; CH_2CH$_2$CONH), 2.39 (br m, 4H; CH_2CH$_2$CO$_2$CH$_2$), 6.25 (s, 4H; NH), 6.59 ppm (s, 2H; NH); ^{13}C NMR: δ = 23.8 (CH_3), 28.0 (C(CH_3)$_3$), 28.4 (CH_2CH$_2$CO$_2$CH$_2$), 29.7 (CH_2CH$_2$CO$_2$), 30.1 (CH_2CO$_2$), 30.8 (CH_2CH$_2$CONH), 31.2 (CH_2CO$_2$CH$_2$), 31.9 (CH_2CONH), 34.5 (CH_2CH$_2$CONH), 34.8 (CH_2CONH), 55.5 (HNC), 57.4 (HNC), 80.5 (CMe_3), 93.3 (O$_2$NC), 171.1 (CONH), 172.7 (CONH), 173.1 (CO$_2$), 174.9 ppm (CO$_2$H); IR: $\tilde{\nu}$ = 1735 (C=O), 1720 (C=O), 1700 (C=O), 1535 cm^{-1} (NO$_2$); ESI-MS: m/z calcd: 2232.81 [M+Na]$^+$; found: 2231.41.

Synthesis of amine 12: A suspension of nitro amide **11**[46] (3 g, 5.6 mmol) and T-1 Raney Ni (2 g) in absolute EtOH (100 mL) was hydrogenated at 60 psi at 50 °C for 15 h. The solution was cautiously filtered (*Pyrophoric*) through Celite, after which the solvent was removed in vacuo to afford **12** as a white solid. Yield: 2.7 g (96 %); m.p. 110–112 °C; ^{1}H NMR: δ = 1.44 (s, 27H; CH_3), 1.88 (t, J = 6.6 Hz, 2H; CH_2CO), 1.96 (t, J = 7.5 Hz, 6H; CH_2CH$_2$CO), 2.22 (t, J = 7.5 Hz, 6H; CH_2CO), 2.33 (t, J = 6 Hz, 2H; CH_2CONH), 2.89 (t, J = 6 Hz, 2H; H$_2$NCH_2), 4.27 (s, 2H; NH_2), 6.19 ppm (s, 1H; NH); ^{13}C NMR: δ = 22.8 (CH_2CO), 28.2 [C(CH_3)$_3$], 30.0 (CH_2CO, CH_2CH$_2$CO), 34.7 (H$_2$NCH$_2$CH_2), 41.0 (H$_2$NCH_2), 57.6 (HNC), 80.8 (CMe_3), 172.3 (CONH), 173.1 ppm (CO$_2$); IR: $\tilde{\nu}$ = 3300–3000 (NH$_2$), 1710 (C=O), 1670 cm^{-1} (C=O); ESI-MS: m/z calcd: 523.67 [M+Na]$^+$; found: 523.12.

Synthesis of the extended predendron 13: DCC (385 mg, 1.8 mmol) and 1-HOBT (255 mg, 1.8 mmol) at 25 °C were added to a stirred solution of acid **4**[39] (2 g, 1.8 mmol) in dry DMF (50 mL); after 2 h, extended amine **12** (930 mg, 1.8 mmol) was added. The mixture was stirred for 24 h, after which the white precipitate was filtered. The filtrate was concentrated in vacuo to give a crude oil, which was subjected to column chromatography (SiO_2) eluting with 20 % EtOAc in hexane to afford **13** as a white solid. Yield: 1.8 g (91 %); ^{1}H NMR: δ = 1.43 (s, 81H; CH_3), 1.78 (t, J = 5.1 Hz, 2H; CH_2CO), 1.96 (br m, 36H; CH_2CH$_2$CO, CH$_2$CH_2CO), 2.09 (t, J = 4.5 Hz, 2H; CH_2CH$_2$CO), 2.19 (m, 12H; CH_2CH$_2$CONH, CH$_2$CH_2CONH), 3.25 (t, J = 4.8 Hz, 2H; NHCH_2), 6.12 (s, 2H; NH), 6.21 (s, 1H; NH), 6.40 ppm (t, J = 3.9 Hz, 1H; NHCH$_2$); ^{13}C NMR: δ = 25.71 (CH_2CO), 28.1 (CH_3), 29.8 (CH_2CH$_2$CO$_2$), 29.9 (CH_2CO$_2$), 29.99 (CH_2CH_2CO$_2$), 30.4 (CH_2CH$_2$CONH), 30.8 (CH_2CONH), 31.4 (CH_2CO$_2$), 34.5 (HNCH$_2$CH_2), 39.1 (HNCH_2), 57.5 (HNC), 57.6 (HNC), 80.6, 80.7 (2CMe_3), 93.1 (O$_2$NC), 170.6, 171.7, 172.2 (3CONH), 172.8, 172.9 ppm (2CO$_2$); IR: $\tilde{\nu}$ = 3300 (NH), 1730 (C=O), 1720 (C=O), 1550 cm^{-1} (NO$_2$) cm^{-1}; ESI-MS: m/z calcd: 1577.98 [M+Na]$^+$; found: 1577.80.

Synthesis of amino dendron 14: A solution of nitro ester **13** (2 g, 1.3 mmol) in absolute EtOH (150 mL) with T-1 Raney Ni (3 g) was hydrogenated (60 psi) at 50 °C for 15 h. The solution was cautiously filtered, as in the above procedure, through Celite, then concentrated in vacuo to give the amino ester **14** as a viscous oil. Yield: 1.86 g (95 %); ^{1}H NMR: δ = 1.41 (s, 81H; CH_3), 1.81 (t, J = 5.1 Hz, 2H; CH_2CO), 1.96 (br m, 36H; CH_2CH$_2$CO, CH$_2$CH_2CO), 2.22 (m, 2H; CH_2CH$_2$CO), 2.35 (m, 12H; CH_2CH$_2$CONH, CH_2CONH), 3.27 (t, J = 4.8 Hz, 2H; NHCH_2), 6.42 (s, 2H; NH), 6.51 (s, 1H; NH), 6.41 (br s, J = 3.9 Hz, 1H; NHCH$_2$), 7.35 ppm (s, 2H; NH_2); ^{13}C NMR: δ = 25.7 (CH_2CO), 28.0 (CH_3), 29.6 (CH_2CH$_2$CO$_2$), 29.7 (CH_2CO$_2$), 30.2 (CH_2CH$_2$CONH), 30.8 (CH_2CONH), 32.4 (CH_2CH$_2$CONH, CH_2CONH), 34.3 (HNCH$_2$CH_2), 38.7 (HNCH_2), 55.3 (H$_2$NC), 57.4, 57.7 (3HNC), 80.3, 80.4 (2CMe_3), 172.5, 172.6, 172.8 (3CONH), 172.9, 173.2 ppm (2CO$_2$); IR: $\tilde{\nu}$ = 3400–3000 (NH$_2$), 1730 (C=O), 1725 cm^{-1} (C=O); ESI-MS: m/z calcd: 1548.0 [M+Na]$^+$; found: 1547.8.

Synthesis of acrylamide 15: Acryloyl chloride (60 mg, 650 μmol) was added to a stirred solution of amine **14** (1 g, 650 μmol) and Et_3N (184 μL, 1.3 mmol) in dry THF at 0 °C. After 5 h at 25 °C, the reaction mixture was washed with water, then saturated brine. The organic solution was dried ($MgSO_4$), filtered, and concentrated in vacuo to give a crude solid, which was subjected to chromatography (SiO_2) eluting with a 30% EtOAc in $CHCl_3$ mixture to afford amide **15** as a white solid. Yield: 990 mg (96%); ^{1}H NMR: δ = 1.44 (s, 81H; CH_3), 1.79 (t, J = 5.1 Hz, 2H; CH_2CO), 1.98 (br m, 36H; CH_2CH$_2$CO, CH_2CO), 2.21 (t, J = 4.5 Hz, 2H; CH_2CH$_2$CO), 2.27 (m, 12H; CH_2CH$_2$CONH, CH_2CONH), 3.25 (t, J = 4.8 Hz, 2H; NHCH_2), 5.58 (br m, 1H; CH_2=CH), 6.12 (br m, 1H; CH$_2$=CH), 6.21 (br m, 1H; CH_2=CH), 6.41 (s, 2H; NH), 6.51 (s, 2H; NH), 6.41 (s, 1H; NHCH$_2$), 7.35 ppm (s, 2H; NH_2); ^{13}C NMR: δ = 25.7 (*C*H$_2$CO), 28.0 (*C*H$_3$), 29.5 (*C*H$_2$CH$_2$CO$_2$), 29.7 (*C*H$_2$CO$_2$), 30.9 (*C*H$_2$CH$_2$CO), 31.6 (*C*H$_2$CH$_2$CONH), 31.9 (*C*H$_2$CO$_2$), 33.1 (*C*H$_2$CH$_2$CONH), 34.3 (*C*H$_2$CONH), 35.3 (HNCH$_2$*C*H$_2$), 38.8 (HN*C*H$_2$), 57.3, 57.9 (3HN*C*), 80.3, 80.4 (2*C*Me$_3$), 125.5 (CH$_2$=CH), 132.1 (*C*H$_2$=CH), 165.5, 172.1, 172.6, 172.7 (4*C*ONH), 172.9, 173.7 ppm (2*C*O$_2$); IR: $\tilde{\nu}$ = 3350 (NH), 1730 (C=O), 1720 (C=O), 1620 (C=C), 1670 cm^{-1} (C=O); ESI-MS: m/z calcd: 1602.4 [M+Na]$^+$; found: 1602.1.

Synthesis of extended nitroamide 16: TMG (250 μL) was added to a stirred solution of acryl amide **15** (1 g, 630 μmol) in a $MeNO_2$/$CHCl_3$ mixture (1:1; 50 mL), and the resulting solution was maintained at 50 °C for 15 h. The mixture was then concentrated in vacuo to give a crude solid, which was dissolved in $CHCl_3$ and then sequentially washed with dilute aqueous HCl, water, and saturated brine. The organic solution was dried (Na_2SO_4), filtered, and concentrated in vacuo to give a crude oil, which was subjected to column chromatography (SiO_2) eluting with 40% EtOAc in $CHCl_3$ to give amide **16** as a white solid. Yield: 900 mg (87%); ^{1}H NMR: δ = 1.44 (s, 81H; CH_3), 1.79 (t, J = 5.1 Hz, 2H; CH_2CO), 1.96 (br m, 36H; CH_2CH$_2$CO, CH$_2$CH_2CO), 2.15 (br s, 2H; CH_2CO), 2.21 (quint, J = 4.5 Hz, 2H; CH$_2$CH_2CH$_2$CO), 2.27 (m, 12H; CH_2CH$_2$CONH, CH_2CONH), 2.30 (m, 4H; CH_2CH$_2$), 3.27 (t, J = 4.8 Hz, 2H; NHCH_2), 4.51 (t, J = 4.8 Hz, 2H; O$_2$NCH_2), 6.09 (s, 2H; NH), 6.25 (s, 2H; NH), 6.43 ppm (t, J = 3.9 Hz, 1H; NHCH$_2$); ^{13}C NMR: δ = 22.8 (*C*H$_2$CO), 25.7 (*C*H$_2$CO), 27.9 (*C*H$_3$), 29.6 (*C*H$_2$CH$_2$CO$_2$, *C*H$_2$CO), 31.3 (*C*H$_2$CH$_2$CONH), 31.4 (*C*H$_2$CONH), 32.6 (O$_2$NCH$_2$*C*H$_2$), 34.3 (HNCH$_2$*C*H$_2$), 34.7 (*C*H$_2$CONH), 38.8 (HN*C*H$_2$), 57.2, 57.7 (4HN*C*), 74.9 (O$_2$N*C*H$_2$), 80.3, 80.4 (2*C*Me$_3$), 170.8, 172.0, 172.5, 172.7 (4*C*ONH), 172.7, 173.5 ppm (2*C*O$_2$); IR: $\tilde{\nu}$ = 3350 (NH), 1735 (C=O), 1720 (C=O), 1550 cm^{-1} (NO$_2$); ESI-MS: m/z calcd: 1663.08 [M+Na]$^+$; found: 1662.90.

Synthesis of aminoamide 17: A solution of predendron **16** (1 g, 610 μmol) in absolute EtOH (150 mL) with T-1 Raney Ni (3 g) was hydrogenated (60 psi) at 50 °C for 24 h. The solution was cautiously filtered, as in the above procedure, through Celite, then concentrated in vacuo to give the amino ester **17**. Yield: 930 mg (95%); ^{1}H NMR: δ = 1.44 (s, 81H; CH_3), 1.79 (t, J = 5.1 Hz, 2H; CH_2CO), 1.96 (br m, 36H; CH_2CH$_2$CO, CH$_2$CH_2CO), 2.15 (br s, 2H; CH_2CO), 2.21 (br m, 2H; CH_2CH$_2$CO), 2.27 (m, 12H; CH_2CH$_2$CONH, CH_2CONH), 2.30 (m, 4H; CH_2CH$_2$), 2.80 (t, J = 4.8 Hz, 2H; NHCH_2), 3.25 (m, 2H; H$_2$NCH_2), 6.09 (s, 2H; NH), 6.25 (s, 2H; NH), 6.96 ppm (t, J = 3.9 Hz, 1H; NHCH$_2$); ^{13}C NMR: δ = 23.1 (*C*H$_2$CO), 26.0 (*C*H$_2$CO), 28.0 (*C*H$_3$), 29.7 (*C*H$_2$CH$_2$CO$_2$, *C*H$_2$CO$_2$), 30.7 (*C*H$_2$CH$_2$CONH), 31.0 (*C*H$_2$CONH), 31.2 (*C*H$_2$CH$_2$CONH), 31.3 (*C*H$_2$CONH), 33.9 (HNCH$_2$*C*H$_2$), 34.3 (H$_2$NCH$_2$*C*H$_2$), 38.4 (HN*C*H$_2$), 39.9 (H$_2$N*C*H$_2$), 57.3, 57.4, 57.7 (4HN*C*), 80.3, 80.4 (2*C*Me$_3$), 172.7, 172.8, 172.9, 173.0 (4*C*ONH), 173.3, 173.9 ppm (2*C*O$_2$); IR: $\tilde{\nu}$ = 3400–3000 (NH$_2$), 1735 (C=O), 1720 cm^{-1} (C=O); ESI-MS: m/z calcd: 1633.10 [M+Na]$^+$; found: 1633.0.

Synthesis of predendron 18: DCC (93 mg, 450 μmol) and 1-HOBT (61 mg, 450 μmol) were added at 25 °C to a stirred solution of acid **9** (1 g, 450 μmol) in dry DMF (30 mL); after 2 h, extended amine **17** (930 mg, 450 μmol) was added. The mixture was stirred for 24 h, after which the white precipitate was filtered. The filtrate was concentrated in vacuo to give a crude oil, which was subjected to column chromatography (SiO_2) eluting with EtOAc to afford predendron **18** as a white solid. Yield: 1.1 g (65%); ^{1}H NMR: δ = 1.23 (s, 6H; CH_3), 1.44 (s, 189H; CH_3), 1.95 (br m, 84H; CH_2CH_2CO$_2$), 2.20 (br m, 48H; CH_2CH_2CONH), 3.24 (br m, 4H; HNCH_2), 6.10 (s, 6H; NH), 6.52 (s, 3H; NH), 6.55 ppm (s, 2H; NH); ^{13}C NMR: δ = 23.8 (*C*H$_3$), 24.1 (*C*H$_2$CO), 26.2 (*C*H$_2$CH$_2$), 28.5 (*C*H$_3$), 29.8, 31.0, 31.3, 32.1, 33.9, 34.4, 34.9 (*C*H$_2$CH$_2$CO, *C*H$_2$CH$_2$CONH), 38.8 (HNCH$_2$), 55.5, 55.6, 57.3, 57.4 (4HN*C*), 80.4, 80.5, 80.6 (3*C*Me$_3$), 93.4 (O$_2$N*C*), 171.0, 171.8, 172.2, 172.4, 172.7, 172.8, 172.9 (7*C*ONH), 173.0, 173.1, 173.7 ppm (3*C*O$_2$); IR: $\tilde{\nu}$ = 3350 (NH), 1730 (C=O), 1720 (C=O), 1550 cm^{-1} (NO$_2$); MALDI-TOF MS: m/z calcd: 3824.9 [M+Na]$^+$; found: 3825.5.

Synthesis of amine 19: A suspension of **18** (1 g, 263 μmol) and T-1 Raney-Ni (3 g) in absolute EtOH (50 mL) was hydrogenated at 60 psi at 50 °C for 48 h. The solution was cautiously filtered (pyrophoric) through Celite, after which the solvent was concentrated in vacuo to afford of amine **19** as a white solid. Yield: 770 mg (78%); ^{1}H NMR: δ = 1.24 (s, 6H; CH_3), 1.43 (s, 189H; CH_3), 1.91 (br s, 84H; CH_2CH_2CO$_2$), 2.20 (br s, 48H; CH_2CH_2CONH), 3.20 (br s, 2H; HNCH_2), 4.18 (br s, 2H; HNCH_2), 6.15 (s, 6H; NH), 6.52 (s, 3H; NH), 6.55 ppm (s, 4H; NH, H_2N); ^{13}C NMR: δ = 24.1 (*C*H$_3$), 24.5 (*C*H$_2$CO), 26.4 (*C*H$_2$CH$_2$), 28.3 (*C*H$_3$), 29.7, 31.0, 31.5, 32.3, 33.9, 34.4, 34.9 (*C*H$_2$CH$_2$CO, *C*H$_2$CH$_2$CONH), 38.8 (NH*C*), 53.2 (H$_2$N*C*), 55.6, 57.3, 57.4, (3HN*C*), 80.4, 80.5, 80.6 (3*C*Me$_3$), 171.3, 172.4, 173.5 (3*C*ONH), 173.9 ppm (*C*O$_2$); IR: $\tilde{\nu}$ = 3400–3000 (NH$_2$), 1730 (C=O), 1720 cm^{-1} (C=O); MALDI-TOF MS: m/z calcd: 3794.9 [M+Na]$^+$; found: 3794.6.

Synthesis of isocyanate dendron 20: Triphosgene (23 mg, 79 μmol) in THF (10 mL) was added to a stirred solution of amine **19** (500 mg, 132 μmol), Et_3N (26 μL, 264 μmol) in dry THF (25 mL) at 0 °C. The solution was stirred for 12 h, was filtered, and concentrated in vacuo to afford crude solid. This solid was subjected to column chromatography (SiO_2) eluting with EtOAc to afford isocyanate **20** as a solid. Yield: 380 mg (75%); ^{1}H NMR: δ = 1.25 (s, 6H; CH_3), 1.44 (s, 189H; CH_3), 1.95 (br s, 84H; CH_2CH_2CO$_2$), 2.20 (br s, 48H; CH_2CH_2CONH), 3.24 (br s, HNCH_2), 3.52 (br s, HNCH_2), 6.10 (s, NH), 6.52 (s, NH), 6.55 ppm (s, NH); ^{13}C NMR: δ = 23.8 (*C*H$_3$), 24.1 (*C*H$_2$CO), 26.2 (*C*H$_2$CH$_2$), 28.5 (*C*H$_3$), 29.8, 31.0, 31.3, 32.1, 33.9, 34.4, 34.9, 38.8 (*C*H$_2$CH$_2$CO, *C*H$_2$CH$_2$CONH), 55.6, 57.3, 57.4 (3HN*C*), 62.3 (OCN*C*), 80.4, 80.5, 80.6 (3*C*Me$_3$), 123.2 (O*C*N), 171.2, 172.4, 172.7 (3*C*ONH), 172.8 ppm (*C*O$_2$); IR: $\tilde{\nu}$ = 3300 (NH), 2210 (OCN), 1730 (C=O), 1720 cm^{-1} (C=O); MALDI-TOF MS: m/z calcd: 3820.91 [M+Na]$^+$; found: 3822.87.

Synthesis of amide 23: DCC (2.3 g, 11 mmol) and 1-HOBT (1.5 g, 11 mol) were added to a stirred solution of adamantane acid **21** (2 g, 11 mmol) in dry DMF (50 mL) at 25 °C; after 2 h, aminopentanol **22** (1.15 g, 11 mmol) was added. The mixture was stirred for 5 h, after which the white precipitate was filtered. The filtrate was concentrated in vacuo to give a crude oil, which was subjected to column chromatography (SiO_2) eluting with 20% EtOAc in hexane to afford the amide **23** as a white solid. Yield: 2.5 g (87%); m.p. 103–104 °C; ^{1}H NMR: δ = 1.37–1.51 (br m, 6H; CH_2CH_2CH_2), 1.72–1.85 (br m, 15H; adamantane), 2.01 (s, 1H; OH), 3.25 (t, J = 6.9 Hz, 2H; HNCH_2), 3.65 (t, J = 6.3 Hz, 2H; HOCH_2), 5.60 ppm (s, 1H; NH); ^{13}C NMR: δ = 23.0 (CH$_2$), 28.1 (*C*H of adamantane), 29.4 (CH$_2$), 32.2 (*C*H$_2$CH$_2$NH), 36.5 (*C*H$_2$ of adamantane), 36.7 (*C*H$_2$CH$_2$OH), 39.1 (*C*^{4o} of adamantane), 39.2 (*C*H$_2$ of adamantane), 40.5 (HN*C*H$_2$), 62.2 (HO*C*H$_2$), 178.2 ppm (*C*ONH); IR: $\tilde{\nu}$ = 3450–3000 (OH), 1720 cm^{-1} (C=O); ESI-MS: m/z calcd: 288.39 [M+Na]$^+$; found: 288.0.

Synthesis of mesylate 24: Mesyl chloride (431 mg, 3.7 mmol) in THF (20 mL) was added to a stirred solution of **23** (1 g, 3.7 mmol), Et_3N (570 μL, 5.6 mmol) in dry THF (50 mL) at 0 °C. The solution was stirred for 3 h at 25 °C. After filtration, the solvent was removed in vacuo to give a residue, which was dissolved in $CHCl_3$ (100 mL) and washed with water (100 mL, 2×) and then saturated brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo to give a solid that was subjected to column chromatography (SiO_2) eluting with 20% EtOAc in hexane to give **24** as a white solid. Yield: 1.15 g (90%); m.p. 108–109 °C; ^{1}H NMR: δ = 1.44–1.67 (br m, 6H; CH_2CH_2CH_2), 1.72–1.85 (br m, 15H; adamantane), 3.01 (s, 3H; O$_2$SCH_3), 3.25 (t, J = 6.6 Hz, 2H; NHCH_2), 4.24 (t, J = 6.3 Hz, 2H; OCH_2), 5.62 ppm (s, 1H; NH); ^{13}C NMR: δ = 22.7, 28.1 (*C*H of adamantane), 28.7 (*C*H$_2$), 29.0 (*C*H$_2$), 36.5 (*C*H$_2$ of adamantane), 37.3 (O$_2$S*C*H$_3$), 38.8 (*C*^{4o} of adamantane), 39.3 (*C*H$_2$ of adamantane), 40.5 (HN*C*H$_2$), 69.9 (O*C*H$_2$), 178.0 ppm (*C*ONH); IR: $\tilde{\nu}$ = 3300 (NH), 1720 cm^{-1} (C=O); ESI-MS: m/z calcd: 366.48 [M+Na]$^+$; found: 366.0.

Synthesis of azide 25: A stirred solution of mesylate **24** (1 g, 2.9 mmol) and NaN_3 (560 mg, 8.7 mmol) in DMF (50 mL) was refluxed for 7 h. After filtration, the solvent was concentrated in vacuo to give a residue, which was dissolved in $CHCl_3$ and then sequentially washed with water and saturated brine. The solution was dried ($MgSO_4$), filtered, and concentrated in vacuo to give a crude solid, which was subjected to column chromatography (SiO_2) eluting with 20% EtOAc in hexane to afford azide **25** as a viscous oil. Yield: 785 mg (93%); ^{1}H NMR: $\delta = 1.36$–1.65 (brm, 6H; CH_2CH_2CH_2), 1.72–1.85 (brm, 15H; adamantane), 3.22 (t, $J =$ 6.9 Hz, 2H; N_3CH_2), 3.30 (t, $J = 6.6$ Hz, 2H; NHCH_2), 5.60 ppm (s, 1H; NH); ^{13}C NMR: $\delta = 24.0$ (CH_2), 28.1 (CH_2), 28.5 (CH of adamantane), 29.2, 36.5 (CH_2 of adamantane), 39.0 ($C^{4\circ}$ of adamantane), 39.3 (CH_2 of adamantane), 40.6 (HNCH_2), 51.2 (N_3CH_2), 178.0 ppm (CONH); IR: $\tilde{\nu} =$ 3300 (NH), 2110 (N_3), 1720 cm^{-1} (C=O); ESI-MS: m/z calcd: 313.40 $[M+Na]^+$; found: 313.2.

Synthesis of amine 26: A suspension of azide **25** (500 mg, 1.7 mmol) and 10% Pd on activated carbon (200 mg) in EtOH (30 mL) was hydrogenated at 60 psi at 25 °C for 12 h. The solution was then cautiously filtered through Celite (*pyrophoric*) and then the solvent was concentrated in vacuo to afford amine **26** as a white solid. Yield: 432 mg (95%); m.p. 82–83 °C; ^{1}H NMR: $\delta = 1.35$–1.63 (brm, 6H; CH_2CH_2CH_2), 1.70–1.83 (brm, 15H; adamantane), 2.70 (t, $J = 6.6$ Hz, 2H; NHCH_2), 3.23 ppm (t, $J =$ 6.6 Hz, 2H; NH_2CH_2); ^{13}C NMR: $\delta = 24.0$ (CH_2), 27.1 (CH_2), 28.2 (CH of adamantane), 29.2 (CH_2), 36.6 (CH_2 of adamantane), 39.4 ($C^{4\circ}$ of adamantane), 39.9 (CH_2 of adamantane), 40.6 (HNCH_2), 40.8 (H_2NCH_2), 179.0 ppm (CONH); IR: $\tilde{\nu} =$ 3400–3000 (NH_2), 1720 cm^{-1} (C=O); ESI-MS: m/z calcd: 265.41 $[M+H]^+$; found: 265.10.

Synthesis of adamantane dendrimer 27: Amine **26** (14 mg, 52 μmol) was added to a stirred solution of isocyanate **20** (200 mg, 52 μmol) in dry CH_2Cl_2 at 25 °C. The reaction mixture was stirred for 6 h, after which the solvent was concentrated in vacuo to quantitatively afford **27** as a viscous liquid. Yield: 210 mg; ^{1}H NMR: $\delta = 1.44$ (s, 189H; CH_3), 1.5–1.67 (brm, 15H; adamantane), 1.71 (s, 6H; CH_3), 1.84 (brm, 36H; CH_2CH_2CO_2), 1.95 (brm, 48H; CH_2CH_2CO_2), 2.20 (brm, 36H; CH_2CH_2CONH, CH_2CH_2CO) 2.50 (brm, 12H; CH_2CH_2CONH), 3.24 (brm, 2H; HNCH_2), 3.52 (brm, 2H; HNCH_2), 6.10 (s, 6H; NH), 6.52 (s, 3H; NH), 6.55 ppm (s, 4H; NH, H_2N); ^{13}C NMR: $\delta = 23.8$ (CH_3), 24.1 (CH_2CO), 26.0 (CH_2CH_2CO), 26.2 (CH of adamantane), 28.5 (CH_3), 29.8, 31.0, 31.3, 32.1, 33.9, 34.4, 34.9, 38.8, 53.2, 55.6, 57.3, 57.4 (4HNC), 80.4, 80.5, 80.6 (3CMe$_3$), 158.3 (HNCONH), 172.4, 172.9, 173.0, 173.4 (4CONH), 174.2 (CO_2), 178.4 ppm (CONH, adamantane); IR: $\tilde{\nu} =$ 3400 (NH), 1730 (C=O), 1720 (C=O), 1650 cm^{-1} (C=O); MALDI-TOF MS: m/z calcd. 4085.31 $[M+Na]^+$; found: 4085.0.

Synthesis of adamantane-modified acid dendron 28: A solution of adamantane dendrimer **27** (80 mg, 19.6 μmol) in HCO_2H (5 mL) was stirred at 25 °C for 15 h. After concentration in vacuo, toluene (2 × 5 mL) was added and the solution was again evaporated in vacuo to afford pure acid dendron **28** as a viscous liquid. Yield: 48 mg (85%); ^{1}H NMR (CD_3OD): $\delta = 1.24$ (s, 6H; CH_3), 1.29–1.68 (brm, 15H; adamantane), 1.99 (brm, 36H; CH_2CH_2CO_2), 2.22 (brm, 36H; CH_2CH_2CONH, CH_2CH_2CO), 2.33 (brm, 48H; CH_2CH_2CO_2), 2.67 (brm, 12H; CH_2CH_2CONH), 3.12 (brm, 2H; HNCH_2), 3.17 (brm, 2H; HNCH_2), 4.80 (s, 6H; NH), 4.91 (s, 7H; NH, H_2N), 8.29 ppm (s, 21H; CO_2H); ^{13}C NMR: $\delta = 25.2$ (CH_3), 26.8 (CH of adamantane), 29.3 (CH_2CO), 29.6 (CH_2CH_2CO), 30.3, 30.5, 30.9, 31.6, 32.1, 32.7, 32.9, 35.0, 37.6, 40.2, 40.7, 41.8, 57.7, 58.6, 58.7 (4HNC), 164.7 (HNCONH), 173.1, 175.2, 175.7 (4CONH), 177.2 (CO_2H), 180.9 ppm (CONH, adamantane); IR: $\tilde{\nu} =$ 3500–3300 (OH), 1730 (C=O), 1720 (C=O), 1650 cm^{-1} (C=O); MALDI-TOF MS: m/z calcd: 2883.08 $[M-H]^+$; found: 2880.47.

Preparation of dendron 28·β-cyclodextrin complex 29: Dendron **28** (20 mg, 7.1 μmol) was added to a solution of β-cyclodextrin (8 mg, 7.1 μmol) in D_2O. Then the mixture was ultrasonicated for 1 h to afford a clear solution of the **28**·β-CD complex. ^{1}H NMR (D_2O): $\delta = 1.24$ (s, 6H; CH_3), 1.49–1.92 (brm, 15H; adamantane), 1.99 (brm, 36H; CH_2CH_2CO_2), 2.17 (brm, 48H; CH_2CH_2CO_2), 2.34 (brm, 36H; CH_2CH_2CONH, CH_2CH_2CO), 2.60 (brm, 2H; HNCH_2), 2.68 (brs, 12H; CH_2CH_2CONH), 3.17 (t, $J = 7.2$ Hz, 2H; HNCH_2), 3.58, 3.75, 3.85, 5.05 (CH_2, CH of cyclodextrin), 7.95 (s, 6H; NH, NH_2), 8.30 ppm (s, 21H; CO_2H).

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