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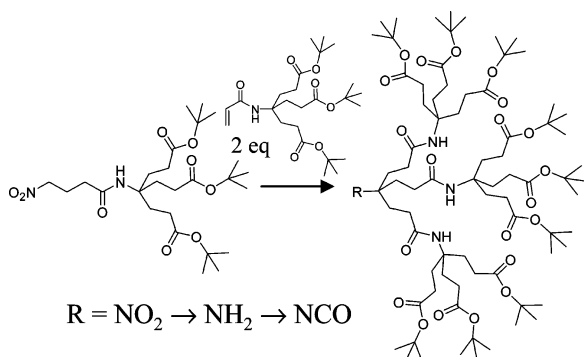
Convenient Synthesis of 1 → 3 C-Branched Dendrons

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A facile, efficient synthesis of 1 → 3 C-branched polyamide dendrons is described. Treatment of acryloyl chloride with 1 → 3 C-branched amines, e.g., di-*tert*-butyl 4-[2-(*tert*-butoxycarbonyl)ethyl]-4-aminoheptanedioate, gave the corresponding acrylamides in high yields, which upon reaction with nitromethane generated the homologated nitroalkane-polyesters. Finally, nitroalkane alkylation with 2 equiv of the acrylamides, followed by nitro group reduction, afforded the desired amino-polyesters.

Both in the convergent construction of dendrimers and the dendrimerization or dendron-coating of materials and surfaces, dendrons of different size and functionality have played a key role in structurally tailored materials.¹ In 1991, we first introduced the 1 → 3 C-branched monomer, di-*tert*-butyl 4-[2-(*tert*-butoxycarbonyl)ethyl]-4-aminoheptanedioate^{2–4} (“Behera’s Amine”; **1**, Scheme 1) and demonstrated its use in the divergent synthesis of a family of dendrimers using amide-based connectivity. The facile conversion of amine **1** to the corresponding isocyanate^{5–7} has further expanded its utilitarian aspects.

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Brettreich and Hirsch⁸ convergently created the related second and third generation dendrons, which were subsequently attached to the C₆₀ surface.^{9–14} These 1 → 3 C-branched monomers have received considerable attention^{15–18} in that they (1) are easily attached to a great variety of starting cores, surfaces¹⁹ and polymers,²⁰ (2) have a specific molecular canopy, and (3) are easily transformed to the corresponding acidic surface for further modification.

The reported divergent and convergent routes⁸ to these higher generation dendrons used the typical amidation coupling reaction in which a combination of DCC (dicyclohexylcarbodiimide) and 1-HOBT (1-hydroxybenzotriazole) in DMF was used. We herein report a new high yield preparation of these 1 → 3 C-branched dendrons, thus eliminating the need to remove high-boiling solvents and multiple byproducts, as well as to circumvent unwanted side reactions, such as that derived from *N*-acylurea formation that can occur in DCC-type amidations.

Behera’s amine **1**, previously synthesized (>95% overall) in two steps^{2,4} from MeNO₂ and *tert*-butyl acrylate, followed by catalytic reduction of the nitro group, was treated with one equivalent of acryloyl chloride in the presence of Et₃N in CH₂Cl₂ to give (>96%) the *N*-substituted amide **2** (Scheme 1), which was confirmed by the new peaks (¹³C NMR) assigned to the new amido carbonyl group at 164.7 ppm (C=O), as well as the expected downfield chemical shift (52.0 to 57.4 ppm) for the newly acylated R₃CNHCO moiety. The ESI-MS further confirmed the assignment by a peak at *m/z* 492.2 [M + Na⁺]. Michael-type addition of MeNO₂ to acrylamide triester **2** in the presence of the water-soluble base TMG (tetramethylguanidine) afforded (93%) the homologated nitrotriester **3**, whose structure was supported (¹³C NMR) by the appearance of a new resonance (74.5 ppm) for the primary CH₂NO₂ group as well as an absence of olefinic signals.

Subsequent reaction of two equivalents of acrylamide **2** with the nitroalkane reagent **3** in the presence of TMG

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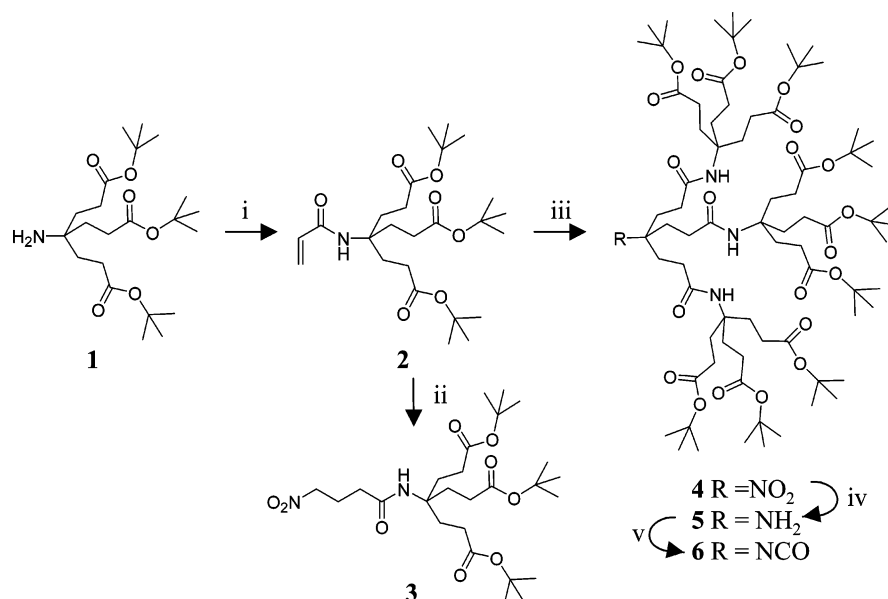
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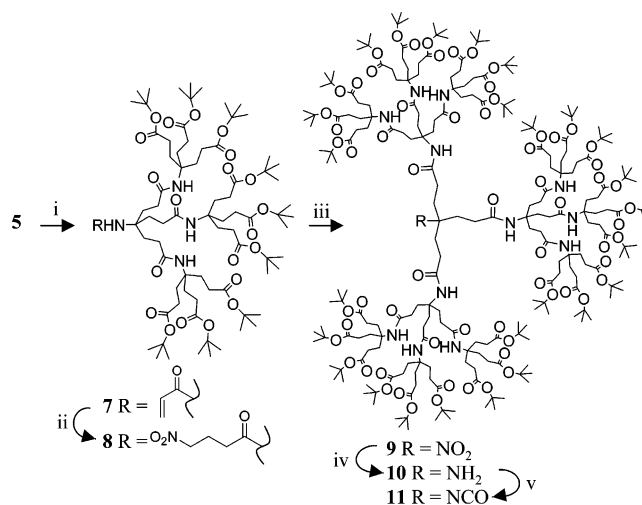
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SCHEME 1^a

^a Key: (i) Et₃N, CH₂Cl₂, CH₂=CHCOCl, 0 °C, 3 h; (ii) Excess CH₃NO₂, CHCl₃, TMG, 25 °C, 24 h; (iii) **3**, THF, TMG, 50 °C, 15 h; (iv) EtOH, H₂ (65 psi), 50 °C, 12 h; (v) Et₃N, triphosgene, THF, 25 °C, 3 h.

(THF, 50 °C, 15 h) gave (91%) the desired second generation nitro-nonaester predendron **4**. A notable downfield chemical shift (¹³C NMR) for the resonance assigned to the R₃CNO₂ group from 74.5 to 92.1 ppm supported the coupling procedure. Different acrylamide monomers derived from other branched monomers can also be attached to afford easy access to heterogeneously functionalized higher generation dendrons. One-step treatment of MeNO₂ with three equivalents of the acrylamide **2** in the presence of TMG in THF afforded a near quantitative yield of the predendron **4**. Reduction of the focal nitro group with Raney-Ni²¹ in absolute EtOH at 40 °C smoothly afforded (>95%) the desired amino-nonaester dendron **5**, as evidenced by the upfield chemical shift (¹³C NMR) of the signal assigned to the R₃CNH₂ moiety from 92.1 to 52.3 ppm; this sample is identical in all respects to one prepared by the convergent acrylamide alkylation coupling procedure.

Synthesis of the 2nd generation acrylamide **7** (Scheme 2) was achieved (93%) by treatment of acryloyl chloride with second generation amine **5** in the presence of Et₃N in dry CH₂Cl₂. The appearance of three different carbonyl signals in its ¹³C NMR spectrum and the molecular peak at *m/z* 1516.2 [M + Na⁺] in the ESI-MS support the amidation. Subjecting the second generation acrylamide **7** to MeNO₂ alkylation in the presence of TMG in refluxing THF for 24 h lead (82%) to predendron **8**, which was structurally established (¹³C NMR) by the new signal (74.8 ppm) for RH₂CNO₂ and the molecular ion peak (ESI MS) at *m/z* 1577.9 [M + Na⁺]. Alkylation of **8** using two equivalents of the acrylamide **7** then gave (70%) the fully substituted quaternary carbon center of nitro-polyester **9**. The presence of (¹³C NMR) a new absorption at 92.7 ppm attributed to the R₃CNO₂ moiety along with the mass peak (MALDI-TOF MS) at *m/z* 4567.2 [M + Na⁺]

SCHEME 2^a

^a Key: (i) Et₃N, CH₂Cl₂, CH₂=CHCOCl, 0 °C; (ii) excess CH₃NO₂, THF, TMG, 50 °C, 24 h; (iii) 2 equiv of **7**, THF, TMG, 50 °C, 24 h; (iv) Raney Ni, EtOH, H₂ (65 psi), 50 °C, 24 h; (v) Et₃N, triphosgene, THF, 25 °C, 8 h.

provided evidence for the structure. Reduction of the nitro moiety of **9** with Raney Ni catalyst in absolute ethanol at 50 °C then afforded (85%) the 3rd generation amino-polyester dendron **10**, which was supported by the chemical shift (¹³C NMR) for the quaternary carbon from 92.7 to 52.3 ppm (R₃CNO₂ and R₃CNH₂, respectively) and the molecular ion peak (MALDI-TOF MS) at *m/z* 4537.3 [M + Na⁺].

Subsequent treatment of amines **5** and **10** with 0.5 equiv of triphosgene (*Caution*: poisonous phosgene gas is generated) in the presence of Et₃N in dry THF gave the desired isocyanates **6** and **11**, respectively. Their structures were evidenced by their ¹³C NMR spectra that exhibited chemical shifts for the R₃CNCO signals from 52.3 and 52.4 ppm to 62.3 and 59.9 ppm, respectively,

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as well as the presence of new absorptions at 122.4 and 125.5 ppm assigned to the NCO group. In addition, the IR spectra of both displayed isocyanate peaks (**6**, 2261 cm^{-1} ; and **11**, 2256 cm^{-1}) and signals (ESI MS and MALDI-TOF MS) at m/z 1512.1 [$\text{M} + \text{Na}^+$] (**6**: calc. m/z 1510.9 [$\text{M} + \text{Na}^+$]) and m/z 4565.2 [$\text{M} + \text{Na}^+$] (**11**: calc. m/z 4561.9 [$\text{M} + \text{Na}^+$]) further characterized the transformation of the amine group. As well, the ^1H and ^{13}C NMR data for dendron **11**, along with that of **9** and **10**, was identical to previously reported spectra.²²

The 1 \rightarrow 3 C-branched amine dendrons have been synthesized by a new, high yield route, then transformed to the corresponding isocyanate derivatives. The structures of these monomers were characterized by means of ^1H and ^{13}C NMR, as well as mass spectrometry. Use of this protocol facilitates the purification of the dendrons at each stage of the synthesis and removes the potential for unwanted byproducts, such *N*-acylureas, that are commonly observed in DCC-based amidations, as well as provides high yield access to new multifunctional dendrons.

Experimental Section

Synthesis of Di-*tert*-butyl 4-Acryloylamino-4-(2-*tert*-butoxycarbonylethyl)heptanedioate (2**).** To a stirred solution of Behera's amine⁴ (**1**; 4.6 g, 11 mmol) and Et_3N (3.1 mL, 22 mmol) in dry CH_2Cl_2 (100 mL) at 0 $^\circ\text{C}$, acryloyl chloride (1 g, 11 mmol) dissolved in CH_2Cl_2 (20 mL) was added dropwise over a period of 15 min. After stirring for 2 h at 25 $^\circ\text{C}$, the reaction mixture was washed with water then satd. brine, dried (MgSO_4), filtered, and concentrated in vacuo to give a crude solid. Following chromatography (SiO_2) using $\text{EtOAc}/\text{CHCl}_3$ (1:9 v/v) as the eluent, amide **3** was obtained (96%), as a white solid: 5.3 g; mp 144–145 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 1.44 (27 H, s), 2.04 (6 H, t, $J = 7.5$ Hz), 2.26 (6 H, t, $J = 7.5$ Hz), 5.59 (1 H, dd, $J = 12, 1.5$ Hz), 6.03 (1 H, dd, $J = 19.0, 10.0$ Hz), 6.20 (1 H, s), 6.22 (1 H, dd, $J = 18.0, 1.5$ Hz); ^{13}C NMR (CDCl_3) δ 27.9, 29.6, 29.9, 57.4, 80.3, 125.5, 131.7, 164.7, 172.7; IR 3290, 1710, 1654, 1622 cm^{-1} ; MS (ESI) m/z 492.2 [$\text{M} + \text{Na}^+$]; calcd 492.3 [$\text{M} + \text{Na}^+$]. Anal. Calcd for $\text{C}_{25}\text{H}_{43}\text{NO}_7$: C, 63.94; H, 9.23; N, 2.98. Found: C, 63.68; H, 9.30; N, 2.84.

Synthesis of Nitro Amide **3.** To a stirred solution of acrylamide **2** (2 g, 4.2 mmol) in a $\text{MeNO}_2/\text{CHCl}_3$ mixture (1:1 v/v; 100 mL) was added TMG (200 μL) and the temperature maintained at 25 $^\circ\text{C}$ for 24 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 aq HCl (5%), water, and satd brine. The organic phase was then dried (Na_2SO_4), filtered, and concentrated in vacuo to give a crude oil, which was column chromatographed (SiO_2 , $\text{EtOAc}/\text{hexane}$, 1:3 v/v) to obtain (93%) amide **3** as a white solid: 2.1 g; mp 140–141 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 1.45 (27 H, s), 1.99 (6 H, t, $J = 7.5$ Hz), 2.24 (6 H, t, $J = 7.5$ Hz), 2.26 (4 H, m), 4.47 (2 H, t, $J = 6$ Hz), 6.19 (1 H, s); ^{13}C NMR (CDCl_3) δ 22.8, 27.7, 29.6, 29.8, 32.4, 57.3, 74.5, 80.2, 170.1, 172.4; IR 3300, 1710, 1670, 1552 cm^{-1} ; MS (ESI) m/z 553.3 [$\text{M} + \text{Na}^+$], calcd 553.3 [$\text{M} + \text{Na}^+$].

Synthesis of Second-Generation Nitro Predendron **4.** Acrylamide **2** (1.9 g, 4.0 mmol) and TMG (250 μL) were added to a stirred solution of amide **3** (1 g, 1.9 mmol) in dry THF (100 mL). After being stirred for 15 h at 50 $^\circ\text{C}$, the solution was concentrated in vacuo to give a solid residue, which was dissolved in CHCl_3 and then sequentially washed with dilute aq HCl (5%), water, and satd brine. The organic phase was then dried (Na_2SO_4), filtered, and concentrated in vacuo to give a oil. Following column chromatography (SiO_2 , $\text{EtOAc}/\text{hexane}$, 1:2 v/v), **4** was obtained (91%) as a white solid: 2.5 g; mp 157–158 $^\circ\text{C}$;

^1H NMR (CDCl_3) δ 1.44 (81 H, s), 1.93 (18 H, t, $J = 7.0$ Hz), 2.12 (30 H, t, $J = 7.0$ Hz), 6.20 (3 H, s); ^{13}C NMR (CDCl_3) δ 28.2, 29.8, 29.9, 31.4, 57.7, 80.8, 92.6, 170.6, 172.9; IR 3360, 2979, 1731, 1681 cm^{-1} ; MS (ESI) m/z 1493.4 [$\text{M} + \text{Na}^+$], calcd 1492.9 [$\text{M} + \text{Na}^+$].

Second-generation amine dendron **5** was generated by a catalytic hydrogenation of the predendron **4** (1.0 g, 220 μmol) with T-1 Raney Ni (~ 2.0 g) in absolute EtOH at 65 psi at 50 $^\circ\text{C}$ for 15 h. The solution was cautiously filtered through Celite to remove the pyrophoric catalyst, and then the filtrate was concentrated in vacuo to give (>95%) pure amine dendron **5** (940 mg): mp 193–194 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 1.51 (81 H, s), 2.01 (18 H, t, $J = 7.0$ Hz), 2.12 (30 H, t, $J = 7.0$ Hz), 6.22 (3 H, s), 6.31 (2 H, s); ^{13}C NMR (CDCl_3) δ 28.2, 29.8, 29.9, 31.4, 57.7, 52.3, 80.8, 170.6, 172.9; IR 3360, 2979, 1731, 1681 cm^{-1} ; MS (ESI) m/z 1463.2 [$\text{M} + \text{Na}^+$], calcd 1462.8 [$\text{M} + \text{Na}^+$].

Synthesis of Second-Generation Isocyanate **6.** The second-generation amine **5** (500 mg, 340 μmol) was dissolved in dry THF (20 mL), Et_3N (50 μL , 680 μmol) was added under nitrogen atmosphere, and then the mixture was cooled to 0 $^\circ\text{C}$. A solution of triphosgene (51 mg, 170 μmol) in THF (5 mL) was added dropwise at 0 $^\circ\text{C}$ over 20 min. After the addition was completed, the stirred reaction mixture was allowed to warm to 25 $^\circ\text{C}$; after 3 h, the white precipitate was filtered and the filtrate was concentrated in vacuo to give a residue, which was dissolved in CHCl_3 washed with water, dried (MgSO_4), and then concentrated in vacuo to give a solid, which was column chromatographed (SiO_2) eluting with $\text{EtOAc}/\text{hexane}$ (1:3 v/v) to obtain (70%) the second-generation isocyanate **6** as a white solid: 710 mg; mp 163–164 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 1.49 (81 H, s), 2.0 (18 H, br m), 2.12 (30 H, br m), 6.33 (3 H, s); ^{13}C NMR (CDCl_3) δ 27.5, 29.3, 29.6, 31.1, 31.7, 57.4, 62.3, 80.2, 122.4, 171.2, 172.9; IR 3363, 2978, 2936, 2260, 1730, 1680 cm^{-1} ; MS (ESI) m/z 1489.3 [$\text{M} + \text{Na}^+$], calcd 1488.9 [$\text{M} + \text{Na}^+$].

Synthesis of Amide **7.** To a stirred solution of second-generation amine **5** (5 g, 3.5 mmol) and Et_3N (1.0 mL, 9.8 mmol) in anhydrous THF (50 mL) was added acryloyl chloride (310 mg, 3.5 mmol) in THF (20 mL) under nitrogen atmosphere at 0 $^\circ\text{C}$. After stirring for 3 h at 25 $^\circ\text{C}$, the reaction mixture was filtered and concentrated in vacuo to give the crude product, which was dissolved in CHCl_3 , washed with satd brine, dried (MgSO_4), filtered, and concentrated in vacuo. Following chromatography (SiO_2 , $\text{EtOAc}/\text{hexane}$, 1:2 v/v), **6** was obtained (93%) as a white solid: mp 169–170 $^\circ\text{C}$; 4.8 g; ^1H NMR (CDCl_3) δ 1.44 (81 H, s), 1.95 (18 H, t, $J = 6.9$ Hz), 2.04 (12 H, br m), 2.20 (18 H, t, $J = 6.9$ Hz), 5.54 (1 H, dd, $J = 12, 1.5$ Hz), 6.06 (1 H, dd, $J = 19.0, 10.0$ Hz), 6.11 (2 H, br), 6.21 (1 H, dd, $J = 18.0, 1.5$ Hz); ^{13}C NMR (CDCl_3) δ 27.9, 29.7, 29.9, 31.6, 32.0, 57.3, 57.7, 80.4, 125.4, 132.1, 165.5, 172.5, 172.9; IR 3280, 1710, 1654, 1622 cm^{-1} ; MS (ESI) m/z 1516.2 [$\text{M} + \text{Na}^+$], calcd 1515.9 [$\text{M} + \text{Na}^+$]. Anal. Calcd for $\text{C}_{79}\text{H}_{136}\text{N}_4\text{O}_{22}$: C, 63.51; H, 9.18; N, 3.75. Found: C, 63.04; H, 9.13; N, 3.74.

Synthesis of Extended Nitro Dendron **8.** Acrylamide **7** (2 g, 1.3 mmol) was dissolved in anhydrous THF/ MeNO_2 mixture (1:1; 100 mL), and TMG (250 μL) was added to the above solution at 25 $^\circ\text{C}$. The reaction mixture was then stirred for 24 h at 50 $^\circ\text{C}$. Concentration of the mixture in vacuo gave a crude solid, which was dissolved in CHCl_3 and then sequentially washed with dilute aq HCl, water, and satd brine. The organic phase was then dried (Na_2SO_4), filtered, and concentrated to give a crude oil, which was column chromatographed (SiO_2) eluting with a solvent mixture of $\text{EtOAc}/\text{CHCl}_3$ (1:3 v/v) to give (88%) amide **8** as a white solid: 1.83 g; mp 122–123 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 1.44 (81 H, s), 1.95 (18 H, t, $J = 5.4$ Hz), 2.01 (2 H, t, $J = 5.1$ Hz), 2.20 (30 H, t, $J = 5.4$ Hz), 2.30 (2 H, m), 4.51 (2 H, t, $J = 4.8$ Hz), 6.04 (3 H, s), 7.94 (1 H, s); ^{13}C NMR (CDCl_3) δ 22.8, 27.92, 29.6, 29.7, 31.4, 32.5, 57.2, 57.6, 74.8, 80.3, 170.7, 172.5, 172.7; IR 3320, 1715, 1670, 1550 cm^{-1} ; MS (ESI) m/z 1577.9 [$\text{M} + \text{Na}^+$], calcd 1577.9 [$\text{M} + \text{Na}^+$]. Anal. Calcd for $\text{C}_{80}\text{H}_{139}\text{N}_5\text{O}_{24}$: C, 61.80; H, 8.96; N, 4.62. Found: C, 61.79; H, 9.01; N, 4.50.

Synthesis of Third-Generation Predendron **9.** Nitroamide **8** (500 mg, 0.32 μmol) and TMG (100 μL) were dissolved in anhydrous THF (25 mL), and the second-generation acryl-

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amide **7** (960 mg, 0.064 μ mol) in THF (50 mL) was added. The mixture was refluxed under nitrogen for 12 h, cooled, and concentrated in vacuo to give the crude product, which was dissolved in CHCl_3 , washed with water, dried (MgSO_4), filtered, and concentrated in vacuo to give the crude product. Following column chromatography (SiO_2) using EtOAc/hexane (1:2 v/v) as the eluent, the third-generation predendron **7** was obtained (70%) as a white solid: 1.0 g; mp 161–162 °C; ^1H NMR (CDCl_3) δ 1.42 (243 H, s), 1.93 (78 H, br m), 2.12 (78 H, br m), 6.19 (12 H, s); ^{13}C NMR (CDCl_3) δ 27.3, 29.2, 33.6, 56.7, 57.5, 80.1, 92.7, 170.5, 170.9, 172.5; IR 3358, 2978, 2936 1730, 1654 cm^{-1} ; MALDI-TOF MS m/z = 4567.2 [$\text{M} + \text{Na}^+$], calcd m/z = 4565.8 [$\text{M} + \text{Na}^+$].

Third-Generation Dendron 10. The predendron **8** (1 g, 220 μ mol) in absolute EtOH (50 mL) and T-1 Raney Ni was hydrogenated at 65 psi at 50 °C for 24 h. The solution was cautiously filtered through Celite being careful not to allow the catalyst to become dry due to its *pyrophoric* nature. The filtrate was concentrated in vacuo to give the crude product, which was then chromatographed (SiO_2) eluting with EtOAc to give (73%) **9** as a white solid: 720 mg; mp 206–207 °C; ^1H NMR (CDCl_3) δ 1.22 (243 H, s), 1.77 (78 H, br m), 2.00 (78 H, br m), 6.14 (12 H, s); ^{13}C NMR (CDCl_3) δ 27.6, 29.5, 31.3, 52.4, 57.0, 57.5, 80.1, 172.3, 172.9; IR 3361, 3334, 2978, 2934, 1730, 1653 cm^{-1} ; MALDI-TOF MS m/z = 4537.3 [$\text{M} + \text{Na}^+$], calcd m/z = 4535.8 [$\text{M} + \text{Na}^+$].

Synthesis of third-generation isocyanate 11 followed that of **6** in which the crude reaction mixture was column chromatographed (SiO_2) eluting with EtOAc/hexane (1:1 v/v) to obtain (57%) the pure isocyanate **10**: 0.57 g; mp 147–148 °C; ^1H NMR (CDCl_3) δ 1.24 (243 H, s), 1.75 (78 H, br m), 2.01 (78 H, br m), 6.21 (12 H, s); ^{13}C NMR (CDCl_3) δ 28.0, 29.6, 31.5, 57.3, 57.7, 59.9, 80.2, 125.5, 171.9, 172.8; IR 3324, 2978, 2933, 2256, 1731, 1655 cm^{-1} ; MS (MALDI-TOF) m/z 4565.2 [$\text{M} + \text{Na}^+$], calcd 4561.9 [$\text{M} + \text{Na}^+$].

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Supporting Information Available: General remarks concerning the experimental procedures and ^1H , ^{13}C , and 2D HETCOR NMRs and mass spectra for compounds **2**, **3**, **7**, and **8**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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