Linear Analogues of Acid- and Ester-Terminated Polyamido Dendrimers: Design, Syntheses, and Physical Properties

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Keywords: Hydrogenation / Amines / Dendrimers / Peptides

The synthesis of linear, unnatural amines and carboxylic acids, based on amide connectivity and possessing identical repeat unit architecture to that of analogous dendrimers, was undertaken to assess and compare their physical characteristics. For the series, unexpected insoluble behavior was observed at low molecular weights in contrast to their branched counterparts or other known linear dendritic analogs. Molecular modeling suggests a high degree of intra- and intermolecular H-bonding for the series.

Introduction

The interesting physical properties of dendrimers arise in part from their three-dimensional structures.[1−18] Unlike linear polymers, dendrimers possess a highly branched, "tree-like" architecture with a large number of solvent accessible chain-terminating groups. Following the early stages of dendritic growth, the termini increase in number and become major factors in defining physical properties; in contrast, the end groups of linear polymers remain relatively constant during growth and, thus, play a diminishing role with increasing molecular size. These inherent structural differences lead to many of the observed changes that we see in the chemical and physical properties of dendrimers versus linear polymers. Miller and co-workers[19−21] have demonstrated that 1,3,5-phenylene-based dendrimers are generally more soluble (ca. 10^6 times) than their oligo-*p*-phenylene linear analogs. Likewise, Fréchet et al.[22,23] noticed a similar correlation for their dendritic poly(aryl ester)s. Other physical properties have been monitored such as: size,[24] viscosity,[25] crystallinity,[25] and thermal properties.[26] For example, Fréchet et al.[25] deftly synthesized an exact linear isomer of a 5th-generation polyethereal dendrimer for comparison and showed that the dendrimer's hydrodynamic volume was about 30% smaller than its linear analogue; interestingly, the former was also more reactive toward catalytic hydrogenation than its linear counterpart. More recently, an investigation[27] on the influence of poly(benzyl ether) dendrons vs. their exact linear analogues on a porphyrin core was reported; their "results clearly confirm the anticipation that dendrimers are unique when compared to other architectures".

Recent reports of unnatural peptides[27−42] and the reported helical γ-tetra-, hexa-, and octapeptides,[43] along with the structural relationship between the monomers used in our 1→3 and 1→2 branched dendritic families, have provided the impetus for the creation of the related *gem*-dimethyl γ-amino acid derivatives. We herein report a new class of linear analogues corresponding to our well-defined acid- and ester-terminated polyamido dendrimers.[44,45] An exponential growth strategy[46] was employed to synthesize these monodisperse linear dimers, tetramers, and octamers, using standard peptide [i.e., (DCC and 1-HOBT)[47] and 2-ethoxy-*N*-(ethoxycarbonyl)-1,2-dihydroquinoline (EEDQ)[48]] coupling conditions.[49] Molecular modeling studies, as well as ^{1}H NMR spectroscopic data, of these polyamides suggest that self-aggregation may contribute to the increased insolubility of the larger analogues.

Results and Discussion

Synthesis of Linear Analogs

The controlled Michael-type addition of *tert*-butyl acrylate[50] to 2-nitropropane in refluxing EtOH afforded the desired crystalline nitro ester **1** (Scheme 1), which was supported (^{13}C NMR) by the single carbonyl peak at δ = 171.3 ppm and two peaks at δ = 87.4 ($O_2NC^{4°}$) and δ = 80.7 ($Me_3C^{4°}$) ppm as well as the correct mass (ESI MS) at *m*/*z* = 240.6 $[M + Na]^+$. Hydrogenation of **1** with T-1 Raney nickel[51] at 25 °C afforded (95%) the amino ester monomer **2**, which was characterized by an upfield shift of the nitro quaternary carbon (^{13}C NMR) resonance from δ = 87.4 ppm to δ = 48.7 ppm ($H_2NC^{4°}$); no other signifi-

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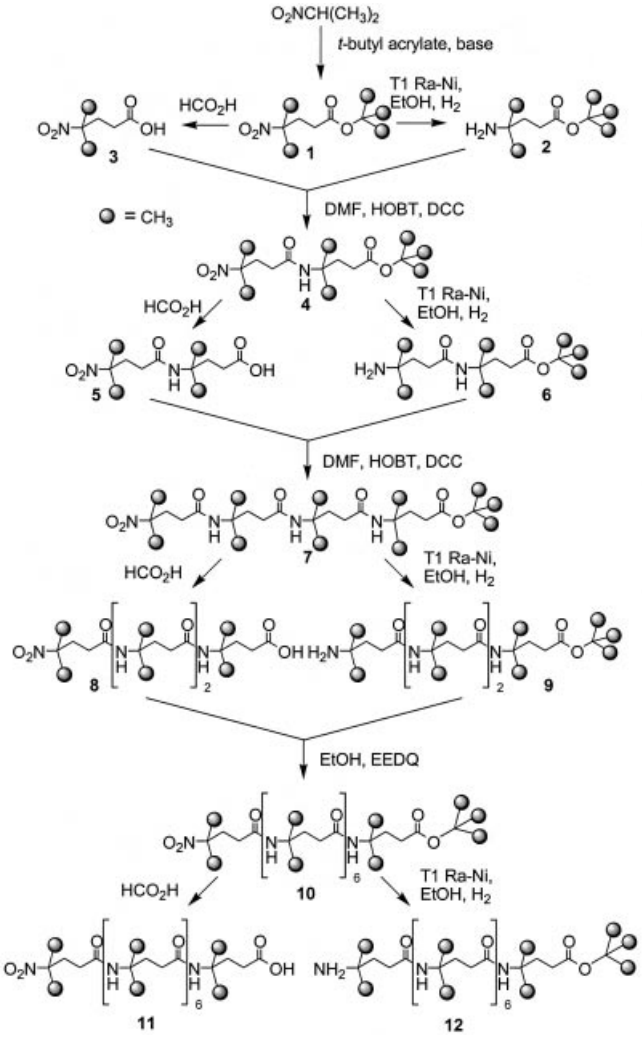
  DOI: 10.1002/ejoc.200300238



Scheme 1. Synthesis of the linear, amide-based unnatural peptides

cant changes were observed indicating that the rest of the molecule was intact. Its ^{1}H NMR signals corresponding to the methyl and methylene groups adjacent to the nitro quaternary carbon atom also shifted upfield from δ = 1.49 [$O_2NC^{4°}(CH_3)_2$] ppm to δ = 1.21 [$H_2NC^{4°}(CH_3)_2$] ppm and from δ = 2.13 ($O_2NC^{4°}CH_2$) ppm to δ = 1.8 ($H_2NC^{4°}CH_2$) ppm, respectively, upon reduction. Care must be taken to keep **2** below 40 °C to prevent the facile lactam formation that occurs for γ-amino esters;[52] ester **2** was typically stored at 0 °C to minimize cyclization. Treatment of ester **1** with 95% formic acid provided (91%) the monomer **3**, as shown (^{13}C NMR) by the loss of resonances corresponding to the *tert*-butyl group at δ = 171.3 (CO_2R), 80.7 ($C^{4°}Me_3$), and 27.8 [$C^{4°}(CH_3)_3$] ppm and the appearance of a new acid carbonyl peak at δ = 178.6 (CO_2H) ppm.

The two key monomers (amine **2** and acid **3**) were subjected to amidation by standard peptide coupling conditions (DCC and 1-HOBT)[47] to generate (40%) dimer **4**, which was evidenced by the notable peak (^{13}C NMR) shift from δ = 48.7 ($H_2NC^{4°}$) ppm to δ = 53.3 ($CONHC^{4°}$) ppm as well as the correct mass (ESI) value *m*/*z* = 331.06 [M + H]$^+$.

Catalytic (T-1 Raney nickel) hydrogenation of the nitro moiety in dimer **4** gave rise to the terminal amine **6**, structurally characterized (^{13}C NMR) by the shift of the signal at δ = 87.8 ($O_2NC^{4°}$) ppm to δ = 49.4 ($H_2NC^{4°}$) ppm, the upfield (^{1}H NMR) proton shifts at δ = 1.49 [$O_2NC^{4°}(CH_3)_2$] ppm to δ = 1.0 [$NH_2C^{4°}(CH_3)_2$] ppm, and δ = 2.15 ($O_2NC^{4°}CH_2$) ppm to δ = 1.57 ($H_2NC^{4°}CH_2$) ppm, as well as the correct mass (ESI) at *m*/*z* = 301.56 [M + H]$^+$. Deprotection of the ester end group of dimer **4** with formic acid provided (90%) the terminal acid **5**, confirmed by the typical loss of the ^{13}C NMR resonances corresponding to the *tert*-butyl group at δ = 170.8 (CO_2R), 80.6 ($C^{4°}Me_3$), and 28.0 [$C^{4°}(CH_3)_3$] ppm along with the formation of a new signal at δ = 178.2 (CO_2H) ppm.

Combination of amine **6** with acid **5** according to the same coupling conditions (DCC and 1-HOBT) afforded (44%) the desired tetramer **7**, as evidenced by the appropriate ^{13}C NMR shifts caused by amidation: δ = 49.4 ($H_2NC^{4°}$) ppm to δ = 53.15 ($CONHC^{4°}$) ppm. This new tetramer **7** possesses three slightly different $CONHC^{4°}$ peaks at δ = 53.2, 53.15, and 53.1 ppm and exhibits the correct mass (ESI) at *m*/*z* = 557.3 [M + H]$^+$. Two peaks were also detected at *m*/*z* = 501.3 and 454.5 corresponding to the loss of the *tert*-butyl and nitro groups, respectively, which was demonstrated in a related series of building blocks.[53,54] Catalytic hydrogenation (T-1 Raney nickel) of the nitro terminus of tetramer of **7** generated (95%) the terminal amine **9**, whose structural conformation was supported by the shift of the ^{13}C NMR resonance at δ = 87.8 ($O_2NC^{4°}$) ppm to δ = 53.9 ($H_2NC^{4°}$) ppm, the upfield shift (^{1}H NMR) for peaks at δ = 1.49 [$O_2NC^{4°}(CH_3)_2$] ppm to δ = 1.15 [$H_2NC^{4°}(CH_3)_2$] ppm and δ = 2.15 ($O_2NC^{4°}CH_2$) ppm to δ = 1.71 ($H_2NC^{4°}CH_2$) ppm, as well as the observed correct mass (ESI) at *m*/*z* = 527.8 [M + H]$^+$. Deprotection of tetramer **7** with formic acid provided (92%) the acid-terminated tetramer **8**, as denoted by the loss (^{13}C NMR) of peaks corresponding to the *tert*-butyl ester at δ = 170.8 (CO_2R), 80.6 (CMe_3), and 28.0 [$C(CH_3)_3$] ppm along with the appearance of a resonance at δ = 177.8 ppm (CO_2H); the amide groups are stable towards these reaction conditions.

Using diverse variations of the DCC and 1-HOBT coupling procedures, reagents **8** and **9** were recovered in toto, in part because these monomers were not readily soluble in DMF. To circumvent this problem, 2-ethoxy-*N*-(ethoxycarbonyl)-1,2-dihydroquinoline (EEDQ) was used to effect the coupling in EtOH affording (74%) the nitro-terminated octamer **10**; no purification was required, since the product cleanly precipitated. This octamer **10** was generally insoluble in most organic solvents but readily dissolved in 95% formic acid, from which the ^{13}C and ^{1}H NMR spectra could be acquired. As expected, acquisition of the NMR spectroscopic data had to be accomplished rapidly to avoid significant *tert*-butyl ester hydrolysis. Pertinent ^{1}H NMR

peaks for **10** include two broad signals at δ = 2.05 and 1.85 ppm corresponding to the linear chain methylene protons ($C^{4°}CH_2CH_2$), and three distinct methyl proton absorptions at δ = 1.28 [$O_2NC(CH_3)_2$], 1.14 [$C^{4°}(CH_3)_3$], and 1.04 [$HNC^{4°}(CH_3)_2$] ppm in a 2:3:12 ratio. The ESI mass spectrum of octamer **10** exhibited the correct mass at m/z = 1,009.8 $[M + H]^+$.

Catalytic hydrogenation (T-1 Raney nickel) of the nitro terminus in octamer **10** afforded (48%; presumably, increasing chain length might necessitate the use of higher pressures and longer reaction times) the desired terminal amine **12**, whose structural conformation was supported by the ^{13}C NMR shift of the peak at δ = 87.8 ($O_2NC^{4°}$) ppm to δ = 53.9 ($H_2NC^{4°}$) ppm and by the observation of the ^1H NMR upfield shifts for the signals at δ = 1.28 [$O_2NC^{4°}(CH_3)_2$] ppm to δ = 1.05 [$H_2NC^{4°}(CH_3)_2$] ppm and δ = 2.05 ($O_2NC^{4°}CH_2$) ppm to δ = 1.61 ($H_2NC^{4°}CH_2$) ppm. The correct mass (ESI) for the amino ester **12** at m/z = 980.2 $[M + H]^+$ was also obtained. Treatment of octamer **10** with formic acid provided (90%) acid-terminated octamer **11**, as confirmed by the loss (^1H NMR) of the signals corresponding to the *tert*-butyl group, as noted above, and the correct parent ion (ESI) at m/z = 953.6 $[M + H]^+$.

In general, these linear analogs of the acid- and ester-terminated polyamidoamine dendrimers[44,45] are less soluble and more crystalline than their dendritic counterparts. This is in good agreement with the previous studies presented by Fréchet[22] and Miller[19–21] in aryl, convergently generated dendrimers; however, the physical properties of these linear analogs presented here are quite dramatic. For example, the linear octamer **10**, possessing only 8 repeat units (1,009 Da) corresponding to an intermediate size between a first (4 repeats) and second (12 repeats) generation polyamido dendrimer (Figure 1), was insoluble in all nonpolar organic solvents and formed a thermally reversible gel in polar solvents such as DMF and nitrobenzene.

In contrast, the physical properties of the polyethereal linear analogs[25] do not change significantly until they are as large as a 5th-generation polyethereal dendrimer (31 repeats) with a molecular weight of 6,680 Da. This confirms that the physical behavior of acid- and ester-terminated polyamidoamine dendrimers is quite different from their respective linear analogs. Figure 2 shows elongated ball-and-stick models, with exaggerated methyl groups, of the nitro acid tetramer **8** (Figure 2, a) and the nitro acid octamer **11** (Figure 2, b) with measured extended lengths of 27.3 and 53.5 Å, respectively. Figure 2 (c) represents two octamers (i.e., **11**; they are shaded differently to aid in visualizing the intertwined chains) minimized together starting from an elongated and perpendicular overlapping conformation. Notably, much of the exterior is occupied by the lipophilic methyl groups; whereas, the heteroatom connectivity is oriented inward. This suggests that the unexpected insolubility at even these low molecular weights might be due to extensive intra- and intermolecular H-bonding. Other data supporting this conclusion includes the downfield shift and broadening of the amide proton absorption (δ = 5.85 ppm to δ = 6.05 ppm) for amino ester **6** when progressing from a dilute to a concentrated sample; this fits with literature precedence.[55]

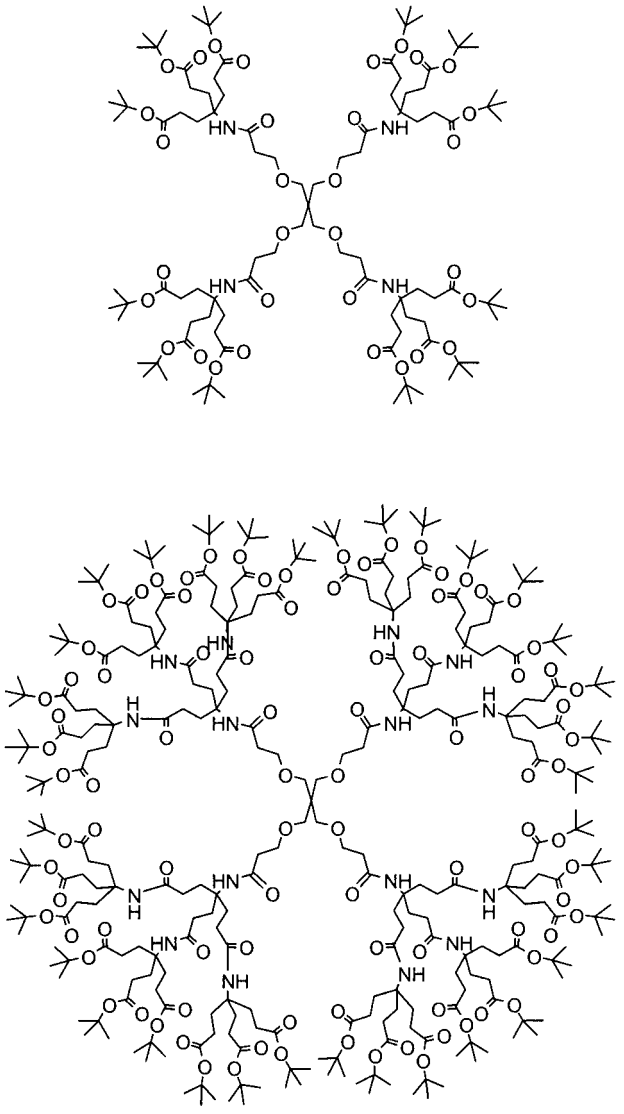


Figure 1. Idealized representations of 1st- and 2nd-generation polypeptide dendrimers for comparison to the linear analogs

The diminished solubility of the octamer **12** prevented its addition to the acid-terminated dendrimers; however, the tetramer **9** was covalently linked to members of the acid-terminated dendrimers as demonstrated by the coupling of the known tetraacid chloride[56] **13** with a slight excess of amine **9** in THF in the presence of Et_3N to afford (62%) the 1st-generation dendritic core **14** (Scheme 2). The presence (^{13}C NMR) of two carbonyl peaks at δ = 173.2 (*C*ONH) and 170.9 ppm (*C*O_2R); three quaternary carbon peaks at δ = 80.1 (Me_3C), 52.8 (four overlapped $HNC^{4°}$), and 45.2 ppm ($C^{4°}CH_2$); seven distinct methylene peaks at δ = 68.9 ($C^{4°}CH_2O$), 67.4 (OCH_2CH_2), 37.0 (OCH_2CH_2), 36.1 and 34.7 ($C^{4°}CH_2CH_2$), 31.8 and 30.5 ($C^{4°}CH_2CH_2$) ppm; and three methyl peaks at δ = 27.9 [$C^{4°}(CH_3)_3$], 26.5 and 26.4 [$C^{4°}(CH_3)_2$] ppm as well as ESI MS possessing m/z = 1230.7 corresponding to the doubly charged parent ion

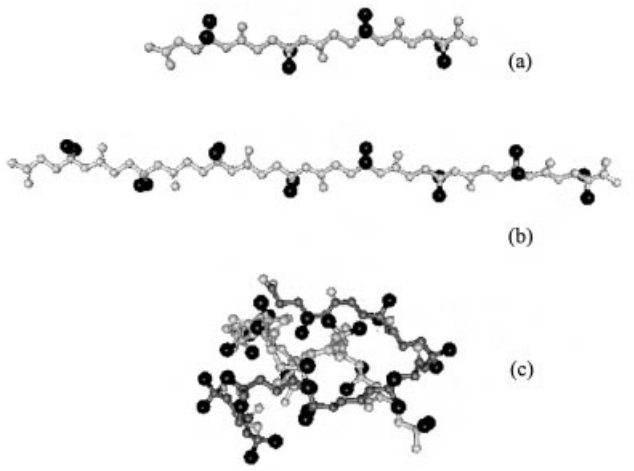
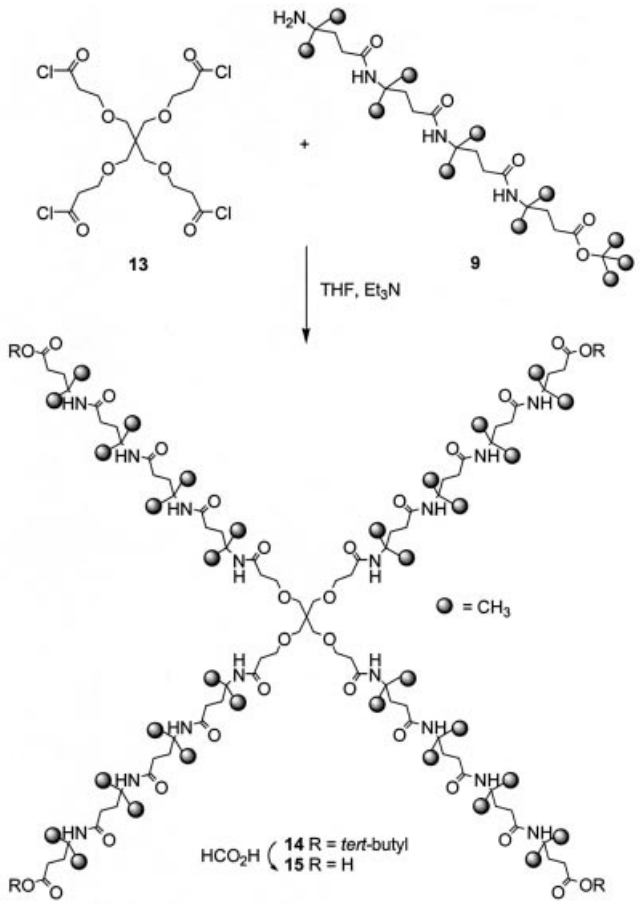


Figure 2. Ball-and-stick representations of the nitro acids **8** (a) and **11** (b) with measured lengths of 27.3 and 53.5 Å, respectively, and two octamers **11** (c) minimized together resulting in aggregation (modeling, minimization, and dynamics were performed with Cerius2 version 4.6 software by Accelrys, Inc.)



Scheme 2. Facile attachment of the tetramer **9** to a poly(acid chloride)

$[M + 2 H]^{2+}$ supported the transformation. Ester **14** was subsequently hydrolyzed with formic acid to give (92%) the tetraacid **15**, as suggested by the loss of the signature absorptions corresponding to the *tert*-butyl groups along with the formation of a new acid peak at δ = 177.5 ppm (CO_2H). The tetraacid **15** also showed (ESI) the parent ion peak at m/z = 1117.7 $[M + 2 H]^{2+}$.

Conclusion

These simple, linear polyamides are but new members of a growing family of extended, unnatural polypeptides, which are physically interesting as related to either their highly branched or natural, well-known counterparts. Even at low molecular weights and low repeat unit number, these materials show unexpectedly poor solubility in nonpolar solvents due to H-bonding interactions, an attribute of structural self-assembly. The complementary amine and ester functionalities make these materials ideal for use as spacer moieties in dendritic constructs.

Experimental Section

General Remarks: Melting point data were obtained in capillary tubes with an Electrothermal 9100 melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$, except where noted, and are recorded at 250.13 MHz. The ^1H and ^{13}C NMR spectra of samples dissolved in formic acid were obtained without a lock signal and were shimmed on the FID. Infrared spectra (IR) were obtained (KBr pellet, unless otherwise noted) and recorded with an ATI Mattson Genesis Series FTIR spectrometer. Mass spectrometric data were obtained using an Esquire electron ionization mass spectrometer (ESI) and are reported as: (relative intensity) [assignment]. 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. The 8-mer nitro/ester, nitro/acid, and amino/ester samples were all first dissolved in 95% formic acid and then diluted 1:10 in $MeOH/H_2O$ (4:1) before loading into the ESI.

***tert*-Butyl 4,4-Dimethyl-4-nitropentanoate (1):** A total of 1.2 equiv. (0.2 equiv. excess) of *tert*-butyl acrylate (172.6 g, 1.35 mol) was added portionwise over 10 min to a refluxing solution of 2-nitropropane (100 g, 1.12 mol) and Triton B (2.2 mL, 40% in MeOH) in refluxing abs. EtOH (500 mL). After the *tert*-butyl acrylate was added, additional Triton B (2.2 mL) was added and the mixture was refluxed for 14 h. The solvent was removed in vacuo to afford a crude light-yellow solid, which was recrystallized with $EtOH/H_2O$ to give (60%) the desired ester: 146 g; m.p. 63.7−65.1 °C. ^{13}C NMR: δ = 171.3 (C=O), 87.4 ($O_2NC^{4°}$), 80.7 (CMe_3), 35.3 ($C^{4°}CH_2$), 30.3 ($C^{4°}CH_2CH_2$), 27.8 [$C(CH_3)_3$], 25.6 [$C^{4°}(CH_3)_2$]. ^1H NMR: δ = 2.13 (br., 4 H, CH_2CH_2), 1.49 [s, 6 H, $C^{4°}(CH_3)_2$], 1.34 [s, 9 H, $C^{4°}(CH_3)_3$] ppm. IR (KBr): $\tilde{\nu}$ = 1730 (ester C=O), 1540 (NO_2), 1373 (NO_2) cm^{-1}. MS (ESI): m/z (%) = 240.6 (100) $[M + Na]^+$.

***tert*-Butyl 4,4-Dimethyl-4-aminopentanoate (2):** A solution of nitro ester **1** (40 g, 184 mmol) in abs. EtOH (300 mL) with T-1 Raney Ni (30 g, 50:50% Al/Ni) was hydrogenated (3.79×10^5 Pa) at 25 °C for 12 h. The solution was filtered through Celite to remove the catalyst, using care to not let the filter pad become dry due to the pyrophoric nature of the catalyst, and the solvent was removed in vacuo to give (95%) the amino ester **2**, as a clear liquid: 32.7 g. ^{13}C NMR: δ = 173.1 (C=O), 79.6 (CMe_3), 48.7 ($H_2NC^{4°}$), 39.1 ($C^{4°}CH_2$), 30.8 ($C^{4°}CH_2CH_2$), 30.0 [$C^{4°}(CH_3)_2$], 27.7 [$C(CH_3)_3$]. ^1H NMR: δ = 2.35 (t, J = 8.3 Hz, 2 H, $C^{4°}CH_2CH_2$), 1.8 (t, J = 8.3 Hz, 2 H, $C^{4°}CH_2CH_2$), 1.55 [s, 9 H, $C(CH_3)_3$], 1.44 (s, 2 H,

NH_2), 1.21 [s, 6 H, $C^{4°}(CH_3)_2$] ppm. IR (neat): $\tilde{\nu}$ = 3355 (NH_2), 3287 (NH_2), 1729 (ester C=O) cm^{-1}. MS (ESI): *m*/*z* (%) = 188.2 (41.2) $[M + H]^+$, 132.3 (100) $[M + H - CMe_3]^+$.

4,4-Dimethyl-4-nitropentanoic Acid (3): Ester **1** (40 g, 184 mmol) was dissolved in formic acid (95%, 200 mL) and stirred at 25 °C for 12 h. The excess formic acid was removed in vacuo, water was added (200 mL), and the solution was again concentrated in vacuo to ensure the absence of any residual formic acid affording (91%) the acid **3**, as a white solid: 27 g; m.p. 150−151 °C. ^{13}C NMR: δ = 178.6 (CO_2H), 87.2 ($O_2NC^{4°}$), 34.8 ($C^{4°}CH_2$), 29.1 ($C^{4°}CH_2CH_2$), 25.7 [$C^{4°}(CH_3)_2$] ppm. ^1H NMR: δ = 11.2 (br., 1 H, CO_2H), 2.29 (m, 2 H, $C^{4°}CH_2$), 2.16 (m, 2 H, $C^{4°}CH_2CH_2$), 1.47 [s, 6 H, $C^{4°}(CH_3)_2$] ppm. IR (KBr): $\tilde{\nu}$ = 3500−3000 (CO_2H), 1674 (C=O), 1563 (NO_2), 1367 (NO_2) cm^{-1}. MS (ESI): *m*/*z* (%) = 160.8 (100) $[M - H]^+$.

2-mer 4: A stirred mixture of nitro acid **3** (10.95 g, 68 mmol), 1-HOBT (9.18 g, 68 mmol), and DCC (14.0 g, 68 mmol) in DMF (100 mL) was maintained at 25 °C for 30 min, before amine **2** (12.71 g, 68 mmol) was added. The mixture was stirred for 18 h, then filtered through Celite to remove the dicyclohexylurea. The solvent was removed in vacuo to give the crude product, which was dissolved in CH_2Cl_2 (100 mL) and washed with water (3 ×, 200 mL). After concentration in vacuo, the residue was recrystallized (cyclohexane) to give (40%) the desired amide **4**, as colorless crystals: 8.9 g; m.p. 83−84.5 °C. ^{13}C NMR: δ = 173.5 (*C*ONH), 170.8 (CO_2R), 87.8 ($O_2NC^{4°}$), 80.6 (CMe_3), 53.3 ($HNC^{4°}$), 35.9 ($O_2NC^{4°}CH_2$), 35.1 ($HNC^{4°}CH_2$), 31.8 (CH_2CONH), 30.6 (CH_2CO_2R), 28.0 [$C(CH_3)_3$], 26.5 [$NHC^{4°}(CH_3)_2$], 25.7 [$O_2NC^{4°}(CH_3)_2$] ppm. ^1H NMR: δ = 5.84 (N*H*), 2.15 (m, 4 H, $O_2NC^{4°}CH_2$, CH_2CO_2R), 2.01 (m, 2 H, $HNC^{4°}CH_2$), 1.84 (t, *J* = 7.4 Hz, 2 H, $HNC^{4°}CH_2$), 1.49 [s, 6 H, $O_2NC^{4°}(CH_3)_2$], 1.35 [s, 9 H, $C^{4°}(CH_3)_3$], 1.22 [s, 6 H, $HNC^{4°}(CH_3)_2$] ppm. IR (KBr): $\tilde{\nu}$ = 3333 (NH), 1689, 1667 (ester/amide C=O), 1538 (NO_2), 1366 (NO_2) cm^{-1}. MS (ESI): *m*/*z* (%) = 353.19 (10.3) $[M + Na]^+$, 275.13 (100) $[M + H - CMe_3]^+$.

2-mer Acid 5: Amide **4** (4 g, 12 mmol) was dissolved in formic acid (95%, 200 mL) and stirred at 25 °C for 12 h. The workup was as for **3** above to give (90%) **5**, as a pure white solid: 3.0 g; m.p. 120−122 °C. ^{13}C NMR: δ = 178.2 (CO_2H), 171.7 (*C*ONH), 87.9 ($O_2NC^{4°}$), 53.4 ($HNC^{4°}$), 36.0, 34.7 ($C^{4°}CH_2$), 31.7, 29.2 ($C^{4°}CH_2CH_2$), 26.5, 25.6 [$C^{4°}(CH_3)_2$] ppm. ^1H NMR: δ = 11.0 (br., 1 H, CO_2H), 6.15 (br., 1 H, CON*H*) 2.21 (t, *J* = 7.2 Hz, 2 H, CH_2CO_2), 2.05 (m, 2 H, $O_2NC^{4°}CH_2$), 1.95 (m, 2 H, CH_2NH), 1.88 (t, *J* = 7.4 Hz, 2 H, $HNC^{4°}CH_2$), 1.43 [s, 6 H, $O_2NC^{4°}(CH_3)_2$], 1.17 [s, 6 H, $HNC^{4°}(CH_3)_2$] ppm. IR (KBr): $\tilde{\nu}$ = 3384 (NH), 3200−2900 (CO_2H), 1738 (acid C=O), 1538 (NO_2) cm^{-1}. MS (ESI): *m*/*z* (%) = 297.1 (55.7) $[M + Na]^+$, 275.2 (100) $[M + H]^+$.

2-mer Amine 6: A solution of the ester **4** (4 g, 12 mmol) in abs. EtOH (300 mL) with T-1 Raney Ni [10 g, Al/Ni (1:1)] was hydrogenated (3.79 × 10^5 Pa) at 25 °C for 12 h. The solution was carefully filtered, as in the procedure for compound **2**, through Celite, then concentrated in vacuo to give (92%) the amino ester **6**: 3.4 g; m.p. 68.5−70 °C. ^{13}C NMR: δ = 173.6 (*C*ONH), 172.9 (CO_2R), 80.6 (CMe_3), 53.1 ($CONHC^{4°}$), 49.4 ($H_2NC^{4°}$), 39.9 ($H_2NC^{4°}CH_2$), 35.2 ($NHC^{4°}CH_2CH_2$), 33.0 (CH_2CONH), 30.7 (CH_2CO_2R), 30.4 [$H_2NC^{4°}(CH_3)_2$], 28.1 [$C(CH_3)_3$], 26.7 [$NHC^{4°}(CH_3)_2$] ppm. ^1H NMR: δ = 5.88 (CON*H*), 2.1 (m, 4 H, $C^{4°}CH_2CH_2$), 1.84 (t, *J* = 7.8 Hz, 2 H, $HNC^{4°}CH_2$), 1.61 (s, 2 H, NH_2), 1.57 (t, *J* = 7.9 Hz, 2 H, $H_2NC^{4°}CH_2$), 1.33 [s, 9 H, $C^{4°}(CH_3)_3$], 1.21 [s, 6 H, $HNC^{4°}(CH_3)_2$], 1.0 [s, 6 H, $H_2NC^{4°}(CH_3)_2$] ppm. IR (neat): $\tilde{\nu}$ = 3313 (NH_2), 1726 (ester C=O), 1646 (amide C=O) cm^{-1}. MS (ESI): *m*/*z* (%) = 323.28 (6.1) $[M + Na]^+$, 301.56 (100) $[M + H]^+$.

4-mer 7: A stirred mixture of acid **5** (6.35 g, 23 mmol), 1-HOBT (3.13 g, 23 mmol), and DCC (4.8 g, 23 mmol) in DMF (100 mL) was maintained at 25 °C for 30 min, then amine **6** (6.95 g, 23 mmol) was added. The mixture was stirred for an additional 18 h. The solution was subsequently filtered through Celite and concentrated in vacuo to give the crude product, which was dissolved in CH_2Cl_2 (100 mL) and washed with 5% HCl (3 × 200 mL), then aq. NaOH (5%, 200 mL). The solvent was removed in vacuo to afford the tetramer **7**, which was recrystallized (EtOAc) to give (44%) the desired product: 5.6 g; m.p. 189.3−190.3 °C. ^{13}C NMR: δ = 173.5, 173.4, 173.3 (*C*ONH), 170.8 (CO_2R), 87.8 ($O_2NC^{4°}$), 80.6 (CMe_3), 53.2, 53.15, 53.1 ($HNC^{4°}$), 35.9, 35.1 ($C^{4°}CH_2$), 31.8, 30.6 ($C^{4°}CH_2CH_2$), 28.0 [$C(CH_3)_3$], 26.5, 25.7 [$C^{4°}(CH_3)_2$] ppm. ^1H NMR: δ = 7.00, 6.92 (br., N*H*), 2.14 (m, 8 H, CH_2CH_2), 2.05 (m, 2 H, $O_2NC^{4°}CH_2$), 1.85−1.75 (m, *J* = 7.4 Hz, 6 H, $HNC^{4°}CH_2$) 1.48 [s, 6 H, $O_2NC^{4°}(CH_3)_2$], 1.35 [s, 9 H, $C(CH_3)_3$], 1.22 [br, 18 H, $HNC^{4°}(CH_3)_2$] ppm. IR (KBr): $\tilde{\nu}$ = 3284 (NH), 1729 (ester C=O), 1642 (amide C=O), 1546 (NO_2), 1369 (NO_2) cm^{-1}. MS (ESI): *m*/*z* (%) = 557.3 (45.6) $[M + H]^+$, 501.3 (100) $[M + H - CMe_3]^+$.

4-mer Acid 8: Tetramer **7** (5 g, 90 mmol) was dissolved in formic acid (95%, 200 mL) and stirred at 25 °C for 14 h. The workup was similar to that of **3**, and afforded (92%) acid **8**, as a pure white solid: 4.1 g; m.p. 176.3−177.7 °C. ^{13}C NMR (CD_3OD): δ = 177.8 (CO_2H), 175.8, 173.8 (*C*ONH), 89.0 ($O_2NC^{4°}$), 54.3, 54.2, 54.0 ($HNC^{4°}$), 37.5, 37.3, 37.2, 35.7 ($C^{4°}CH_2$), 33.1, 33.0, 32.6, 30.5 ($C^{4°}CH_2CH_2$), 27.2, 27.1, 26.1 [$C^{4°}(CH_3)_2$] ppm. ^1H NMR (CD_3OD): δ = 11.0 (br., 1 H, CO_2H), 6.15 (br., 3 H, CON*H*) 2.2 (m, 12 H), 1.9 (m, 4 H), 1.58 [s, 6 H, $O_2NC^{4°}(CH_3)_2$], 1.28 [s, 18 H, $HNC^{4°}(CH_3)_2$] ppm. IR (KBr): $\tilde{\nu}$ = 3500−3300 (CO_2H), 3279 (NH), 1711 (acid C=O), 1642 (amide C=O), 1544 (NO_2) cm^{-1}. MS (ESI): *m*/*z* (%) = 501.2 (100) $[M + H]^+$.

4-mer Amine 9: A solution of nitro ester **7** (5 g, 90 mmol) in abs. EtOH (300 mL) with T-1 Raney Ni [10 g, Al/Ni (1:1)] was hydrogenated (3.79 × 10^5 Pa) at 25 °C for 14 h. The solution was filtered, as in the procedure for compound **2**, through Celite and the solvent was removed in vacuo to give (95%) the amino ester **9**, as a white solid: 4.5 g; m.p. 209.7−210.7 °C. ^{13}C NMR (CD_3OD): δ = 175.8, 175.7, 174.9 (*C*ONH), 81.4 (CMe_3), 54.1, 53.9 ($NHC^{4°}$), 41.4, 37.3, 37.2, 35.7 ($C^{4°}CH_2$), 33.5, 33.1, 31.8 ($C^{4°}CH_2CH_2$), 29.8, 28.7, 28.5, 27.3 [$C^{4°}(CH_3)_2$], 27.1 [$C(CH_3)_3$] ppm. ^1H NMR (CD_3OD): δ = 7.6, 7.5, 7.4 (CON*H*), 2.15 (m, 8 H, CH_2CO), 1.95 (m, 6 H, $HNC^{4°}CH_2$), 1.71 (m, 2 H, $H_2NC^{4°}CH_2$), 1.48 [s, 9 H, $C(CH_3)_3$], 1.33, 1.32 [s, 18 H, $HNC^{4°}(CH_3)_2$], 1.15 [s, 6 H, $H_2NC^{4°}(CH_3)_2$] ppm. IR (KBr): $\tilde{\nu}$ = 3274 (NH), 1726 (ester C=O), 1642 (amide C=O), 1566 (NO_2) cm^{-1}. MS (ESI): *m*/*z* (%) = 527.8 (100) $[M + H]^+$.

8-mer 10: Nitro acid **8** (100 mg, 2 mmol) and amine **9** (105 mg, 2 mmol) were dissolved in EtOH (ca. 5 mL) and refluxed, then cooled and 2-ethoxy-*N*-(ethoxycarbonyl)-1,2-dihydroquinoline (EEDQ; 54 mg, 22 mmol) was added; the mixture was stirred at 50 °C for 14 h. The mixture was subsequently cooled to 25 °C and the resultant white precipitate was filtered and washed with EtOH (3 × 5 mL) to yield (74%) the desired 8-mer **10**: 150 mg; m.p. 250−251.5 °C. ^{13}C NMR (HCO_2H): δ = 176.9 (*C*ONH), 173.6 (CO_2R), 87.8 ($O_2NC^{4°}$), 82.5 (CMe_3), 54.6 ($HNC^{4°}$), 35.8, 35.0 ($C^{4°}CH_2$), 31.2, 30.3 ($C^{4°}CH_2CH_2$), 26.8 [$C(CH_3)_3$], 25.4, 24.4, 19.7 [$C^{4°}(CH_3)_2$] ppm. ^1H NMR (HCO_2H): δ = 7.18, 7.16, 7.1, 6.95 (br., 7 H, N*H*), 2.05, 1.85 (br., 32 H, CH_2CH_2), 1.28 [s, 6 H, $O_2NC^{4°}(CH_3)_2$], 1.14 [s, 9 H, $C(CH_3)_3$], 1.04 [s, 42 H, $HNC^{4°}(CH_3)_2$] ppm. IR (KBr): $\tilde{\nu}$ = 3280 (NH), 1730 (ester C=O),

1641 (amide C=O), 1552 (NO_2) cm^{-1}. MS (ESI): *m/z* (%) = 1047.7 (100) $[M + K]^+$, 1009.8 (34.1) $[M + H]^+$.

8-mer Acid 11: A stirred mixture of ester **8** (120 mg, 12 mmol) in formic acid (95%, 10 mL) was maintained at 25 °C for 14 h, then worked up as for **3** affording (90%) the desired acid **11**, as a pure white solid: 100 mg; m.p. 246−248 °C. ^{13}C NMR (HCO_2H): δ = 179.1 (*C*O_2H), 176.9 (*C*ONH), 87.8 ($O_2NC^{4°}$), 54.6, 54.3 (HN*C*$^{4°}$), 35.8, 35.0, 33.3 ($C^{4°}CH_2$), 31.1, 28.6 ($C^{4°}CH_2CH_2$), 25.4, 24.4, 19.7 [$C^{4°}(CH_3)_2$] ppm. ^1H NMR (HCO_2H): δ = 7.18, 7.20, 6.95 (br., 7 H, N*H*), 2.07, 1.85 (br., 32 H, CH_2CH_2), 1.28 [s, 6 H, $O_2NC^{4°}(CH_3)_2$], 1.04 [s, 42 H, $HNC^{4°}(CH_3)_2$] ppm. IR (KBr): $\tilde{\nu}$ = 3500−3300 (CO_2H), 3280 (NH), 1717 (acid C=O), 1641 (amide C=O), 1552 (NO_2) cm^{-1}. MS (ESI): *m/z* (%) = 975.4 (5.3) $[M + Na]^+$, 953.6 (100) $[M + H]^+$.

8-mer Amine 12: A stirred solution of ester **10** (150 mg, 15 mmol) in abs. EtOH (100 mL) with T-1 Raney Ni [2 g, Al/Ni (50:50)] was hydrogenated (1.38×10^6 Pa) at 115 °C for 14 h in a metal bomb. The solution was filtered, as in the procedure for compound **2**, through Celite and the solvent was removed in vacuo to give (48%) the amino ester **12**, as a white solid: 70 mg; m.p. 245−246.5 °C. ^{13}C NMR (HCO_2H): δ = (*C*ONH), 81.4 ($C^{4°}Me_3$), 54.1, 53.9 (HN*C*$^{4°}$), 41.4, 37.3, 37.2, 35.7 ($C^{4°}CH_2$), 33.5, 33.1, 31.8 ($C^{4°}CH_2CH_2$), 29.8, 28.7, 28.5, 27.3 [$C^{4°}(CH_3)_2$], 27.1 [$C(CH_3)_3$] ppm. ^1H NMR (HCO_2H): δ = 7.5, 7.4, 7.3 (CON*H*), 2.05 (m, 8 H, CH_2CO), 1.85 (m, 6 H, $HNC^{4°}CH_2$), 1.61 (m, 2 H, $H_2NC^{4°}CH_2$), 1.38 [s, 9 H, $C(CH_3)_3$], 1.23, 1.22 [s, 18 H, $HNC^{4°}(CH_3)_2$], 1.05 [s, 6 H, $H_2NC^{4°}(CH_3)_2$] ppm. IR (KBr): $\tilde{\nu}$ = 3279 (NH), 1731 (ester C=O), 1641 (amide C=O), 1553 (NO_2) cm^{-1}. MS (ESI): *m/z* (%) = 1008.0 (77.0) $[M + Na]^+$, 980.2 (100) $[M + H]^+$.

4 × 4 Ester 14: To a refluxing solution of amine **9** (1.53 g, 2.9 mmol) and Et_3N (300 mg, 2.9 mmol) in dry THF (50 mL) was added dropwise, the tetraacid chloride **13** (320 mg, 646 mol), prepared from the corresponding tetracarboxylic acid,[57] in THF (10 mL) over 30 min. The solution was then refluxed for 14 h then the solvent was removed in vacuo to give the crude product, which was dissolved in MeOH (5 mL) and dialyzed against MeOH (3 × 1000 mL) using a 1000 MWCO dialysis membrane (regenerated cellulose) to afford (62%) the ester **14**: 980 mg; m.p. 177−179 °C. ^{13}C NMR: δ = 173.2 (*C*ONH), 170.9 (*C*O_2R), 80.1 (*C*Me_3), 68.9 ($C^{4°}CH_2O$), 67.4 (OCH_2CH_2), 52.8 (HN*C*$^{4°}$), 45.2 ($C^{4°}CH_2$), 37.0 (OCH_2CH_2), 36.1, 34.7 ($C^{4°}CH_2CH_2$), 31.8, 30.5 ($C^{4°}CH_2CH_2$), 27.9 [$C(CH_3)_3$], 26.5, 26.4 [$C^{4°}(CH_3)_2$] ppm. ^1H NMR: δ = 7.0, 6.97, 6.32 (br., 12 H, CON*H*), 3.52 (br., 8 H, OCH_2CH_2), 3.22 (br., 8 H, $C^{4°}CH_2O$), 2.23 (br., 8 H, OCH_2CH_2), 2.1 (m, 32 H, $C^{4°}CH_2CH_2$), 1.85 (m, 32 H, $C^{4°}CH_2CH_2$), 1.32 [s, 36 H, $C^{4°}(CH_3)_3$], 1.20 [s, 96 H, $C^{4°}(CH_3)_2$] ppm. IR (KBr): $\tilde{\nu}$ = 3307 (NH), 1732 (ester C=O), 1647 (amide C=O), 1547 cm^{-1}. MS (ESI): *m/z* (%) = 1230.7 (100) $[M + 2H]^{2+}$.

4 × 4 Acid 15: A stirred mixture of ester **14** (880 mg, 36 mmol) in formic acid (95%, 10 mL) was maintained at 25 °C for 15 h, then worked up as described above for **3**, to yield (92%) the desired acid **15**, as a pure white solid: 730 mg; m.p. 159−161 °C. ^{13}C NMR (CD_3OD): δ = 177.5 (*C*O_2H), 175.6, 173.4 (*C*ONH), 70.6 ($C^{4°}CH_2O$), 68.9 (OCH_2), 54.2, 54.1 (HN*C*$^{4°}$), 46.6 ($C^{4°}CH_2$), 38.5 (OCH_2CH_2), 37.2, 35.6 ($C^{4°}CH_2$), 33.1, 30.4 ($C^{4°}CH_2CH_2$), 27.2, 27.1 [$C^{4°}(CH_3)_2$]. ^1H NMR (CD_3OD): δ = 7.58 (br., 16 H, CON*H*), 3.65 (br., 8 H, OCH_2CH_2), 3.4 (br., 8 H, $C^{4°}CH_2O$), 2.4 (br., 8 H, OCH_2CH_2), 2.2 (br., 32 H, $C^{4°}CH_2CH_2$), 2.05 (br., 32 H, $C^{4°}CH_2CH_2$), 1.30 [s, 96 H, $C^{4°}(CH_3)_2$]. IR (KBr): $\tilde{\nu}$ = 3315 (NH), 3082, 1715 (acid C=O), 1651 (amide C=O) cm^{-1}. MS (ESI): *m/z* (%) = 1117.7 (100) $[M + 2H]^{2+}$.

Acknowledgments

We gratefully thank the National Science Foundation (DMR-9901393 & 0196231), the Office of Naval Research (N00013-99-1-0082), and the Ohio Board of Regents for financial support.

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Received April 15, 2003

