ADMET Synthesis of Polyolefins Targeted for Biological Applications

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ABSTRACT: A series of "*N-terminus*" amino acid and peptide branched, chiral polyolefins, termed bio-olefins, have been prepared using acyclic diene metathesis (ADMET) polycondensation chemistry, using a minimal amount of solvent and Grubbs' second generation catalyst. The carboxylic acid functional groups were protected with methyl, benzyl, and *tert*-butyl esters to enhance both the polymerizability of the monomers themselves and the solubility of the resulting polymers. A number of these polymers are semicrystalline, exhibiting melt transitions of up to 132 and 74 °C for the amino acid and dipeptide branched polymers, respectively. Adding a succinic acid spacer between the amino acid entity and the polymer backbone alters the melting behavior of the polymer, increasing the peak melting point by 27 °C when compared to a polymer having the same amino acid directly attached to the polymer backbone.

Introduction

The incorporation of a high degree of amino acid functionality and chirality in a polymer's repeat unit can increase the solubility of the material that results, in addition to enhancing the potential to form secondary structures such as α-helices and β-sheets.[1,2] Such polymers can be useful as drug-delivery agents, chiral recognition stationary phases, asymmetric catalysts, metal ion absorbents, and biocompatible materials.[3] Advancements in chiral separation and monomer synthesis have led to a wide availability of inexpensive and enantiopure protected amino acids; the field is ripe for exploration.

For example, Endo, Sanda, and co-workers have synthesized a variety of amino acid and peptide branched acrylamides via radical polymerizations,[4,5] North et al. have prepared polyacrylates where the amino acid is attached through the alcohol side chain of a serine moiety leaving the N- and C-termini of the amino acid available for further chemistry,[6,7] and Ayres and co-workers have prepared elastin-based polyolefins via a "living" polymerization technique, atom transfer radical polymerization (ATRP).[8] The subject has even evolved to polymers based on conjugated systems; a variety of amino acid branched polyacetylenes have been prepared.[9,10]

Given the breadth of application based on the metathesis reaction, it is not surprising to find that ring-opening metathesis (ROMP) has been employed to prepare amino acid and peptide branched polymers,[11,12] including the polymerization of norbornene functionalized with the biologically active tripeptide RGD (arginine−glycine−aspartic acid).[13] Copolymerization with a norbornene bearing a penta(ethylene oxide) branch yielded a water-soluble polymer capable of inhibiting cell binding to fibronectin, a property which could be useful for a variety of biomedical applications.[13]

Acyclic diene metathesis (ADMET) chemistry also proves viable for the preparation of amino acid polymers, and recently we presented our first work in this area.[14,15,16] We now report the synthesis and properties of amino acid and peptide-branched polyolefins, termed bio-olefins,[17] where the functionality is attached through the N-terminus rather than the C-terminus. These polymers offer the potential of having carboxylic acids present on the surface of the material. Complete synthetic details and thermal analysis of these polymers are discussed.

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Experimental Section

Chemicals. Reagents and chemicals were purchased and used as received from the Aldrich chemical company, unless otherwise noted. Diethyl ether and THF were used as received from Fisher Scientific unless dry solvents were required, which were obtained from the Aldrich keg system and dried over Al_2O_3. Methylene chloride, methanol, and chloroform were used as purchased from Fisher. Anhydrous DMF (99.8%) was used as purchased in an Aldrich sure seal container equipped with an Aldrich Schlenk cap. The second generation Grubbs Ru catalyst (tricyclohexylphosphine[1,3-bis-(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium(IV) dichloride) was used exclusively and was synthesized as described previously by Grubbs et al.[18] The protected amino acids and peptides were used as purchased from Bachem, except for H−Leu−OMe, which was purchased from Sigma-Aldrich.

Instrumentation. All ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian Associates Gemini 300, Varian Associates VXR 300, or a Varian Associates Mercury 300 spectrometer. All chemical shifts were referenced to TMS (0.00 ppm) for ^{1}H NMR and to $CDCl_3$ (77.23 ppm) or DMSO-d_6 (39.51 ppm) for ^{13}C NMR.

Gel permeation chromatography (GPC) of the unsaturated ADMET polymers was performed using a Waters Associates GPCV2000 liquid chromatography system with an internal differential refractive index detector (DRI), an internal differential viscosity detector (DP), and a Precision 2 angle light scattering detector (LS). The light scattering signal was collected at a 15° angle and corrected at a 90° angle. The three in-line detectors were operated in series in the order LS−DRI−DP. The chromatography was performed at 45 °C using two Waters Styragel HR-5E columns (10 μm PD, 7.8 mm i.d., 300 mm length) with HPLC grade THF as the mobile phase at a flow rate of 1.0 mL/min. Injections were made at 0.05−0.07% w/v sample concentration using a 322.5 μL injection volume. The Precision LS was calibrated using a narrow polystyrene standard having a $\overline{M_w}$ = 65 000 g/mol.

Differential scanning calorimetry (DSC) was performed using a Perkin-Elmer DSC 7 at a heating rate of 10 °C/min using indium and *p*-nitrotoluene as calibration standards with heats of fusion referenced against indium. The samples were

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Table 1. $\bar{M}_w$, PDI, T_m, and T_g Data

polymer	$\bar{M}_w$[a] (g/mol)	PDI[a]	T_m[b] (°C)	T_g[b] (°C)
19	26 000	1.54	*e*	28
20	36 000	1.45	*e*	18
21	73 000	1.55	132	d
22	63 000	1.67	*e*	7
23	21 000	1.62	38[c]	−21
24	25 000	1.91	*e*	5
25	42 000	1.85	*e*	−10
26	29 000	1.59	*e*	3
27	44 000	1.80	79	*d*
28	26 000	1.40	*e*	69
29	73 000	1.50	106	5
30	21 000	1.40	71[c]	*d*
31	38 000	1.64	74	*d*

[a] $\bar{M}_w$ and PDI values were calculated by GPC using LALLS. [b] Data obtained using a Perkin-Elmer DSC 7 at 10 °C/ min. [c] The T_m reported is that of the solvent crystallized sample; no T_m was observed from the melt crystallized sample. [d] No T_g observed over the scanned range of −80 to +180 °C. [e] No T_m observed over the scanned range of −80 to +180 °C.

scanned three times to remove recrystallization differences between samples and when possible the results reported came from the third scan. The results are listed in tabular form (Table 1) as well as within the text as T_m (melting peak) and T_g (glass transition at $^1/_2$ C_p).

Characterization. Strenuous purification was only performed on the final monomers reported herein. Only ^{1}H NMR and ^{13}C NMR spectra are reported for the premonomers (**2**−**6**). All of the monomers were fully characterized by ^{1}H NMR, ^{13}C NMR, EI/HRMS, and elemental analysis with purity confirmed by TLC. The polymers were characterized by ^{1}H NMR, ^{13}C NMR, GPC, and DSC.

Monomer Synthesis. Synthesis of 2-Pent-4-enyl-hept-6-enoic Acid (2).[19] To a 500 mL three neck round-bottom flask equipped with a stir bar, reflux condenser, and addition funnel was added diethyl malonate (12.01 g, 75.0 mmol, 11.3 mL) dropwise to a slurry of NaH (10 g, 60% in mineral oil, 0.250 mol) in THF (30 mL). 5-Bromo-1-pentene (25 g, 167.9 mmol) in THF (10 mL) was then added dropwise. The reaction was stirred at room temperature for 1 h and at reflux for an additional 24 h. The reaction was monitored by TLC using a 3:1 hexanes:ethyl acetate mobile phase. Additional 5-bromo-1-pentene (1.25 g, 8.4 mmol, 1.0 mL) and NaH (1.0 g, 60 % in mineral oil, 25.0 mmol) were added, and the reaction was allowed to stir under reflux. After 5 h, the reaction appeared to be complete by TLC. The mixture was then cooled in an ice bath, and water was added slowly to neutralize the remaining NaH. Then 50 mL of water (total ∼ 100 mL) and ethanol (50 mL) were added along with NaOH (15.0 g, 375.0 mmol) and the reaction was refluxed for 24 h. The reaction was monitored for the disappearance of the diester using TLC (3:1 hexanes: ethyl acetate mobile phase). The solution was neutralized with concentrated HCl and extracted with diethyl ether. Following evaporation of diethyl ether, Decalin (30 mL), and a catalytic amount of *N*,*N*-(dimethylamino)pyridine (DMAP) were added to a 500 mL round-bottom flask equipped with a stir bar and a reflux condenser. The flask was lowered into a 190 °C oil bath, and decarboxylation was monitored by the excess frothing caused by the release of CO_2. After the frothing decreased, the reaction was allowed to cool to room temperature. The crude mixture was flashed through a plug of silica gel using hexane as the initial eluent to remove Decalin and nonpolar impurities—the Decalin could be observed as a clear ring moving through the plug. Once all of the Decalin was removed, the eluent was switched to ethyl acetate to remove the desired product (12.3 g, 68% yield). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.31−1.75 (m, 8H), 2.05 (q, 4H), 2.27−2.43 (br, 1H), 4.89−5.06 (m, 4H), 5.69−5.87 (m, 2H) 10.06−11.22 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 26.75, 31.75, 33.79, 45.52, 114.99, 138.54, 183.24.

Synthesis of 2-Undec-10-enyltridec-12-enoic acid (3).[19] Premonomer **3** was synthesized using the methodology applied for premonomer **2**, using undecenyl bromide (28.0 g, 112 mmol), NaH (3.22 g, 60% in mineral oil, 134 mmol), and diethyl malonate (7.16 g, 44.7 mmol). The saponification was accomplished as discussed above using ethanol (100 mL) and 6 M NaOH (250 mL) and was worked up by acidification followed by extraction with diethyl ether. Decarboxylation was accomplished as described above using Decalin (25 mL) and catalytic DMAP in a 190 °C oil bath for 1 h. The crude product was purified using hexane to remove Decalin and 3:1 hexanes: ethyl acetate to remove the desired product. The product can be further purified by recrystallization in pentane yielding a white powder (10.5 g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.22−1.55 (br, 28 H), 1.63 (m, 4H), 2.05 (q, 4H), 2.06 (q, br, 4H), 2.37 (m, 1H), 4.98 (m, 4H), 5.82 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 27.58, 29.15, 29.34, 29.65, 29.68, 29.75, 29.77, 32.37, 34.03, 45.75, 114.31, 139.44, 183.14.

Synthesis of 1-Undec-10-enyl-dodec-11-enylamine (4). Synthesis was performed as described in a previous publication, and the characterization matched that previously reported.[16]

Synthesis of *N*-(1-Undec-10-enyl-dodec-11-enyl)succinamic acid (5). To a 100 mL round-bottom flask equipped with a stir bar under nitrogen were added **4** (2.55 g, 7.61 mmol), succinic anhydride (1.90 g, 19.00 mmol), and a catalytic amount of DMAP in 20 mL of dry THF. The reaction was stirred under argon for 12 h. Evaporation of THF yielded a white solid, which was purified by recrystallization from CH_3-CH_2OH/H_2O to give the pure product in a 67% yield. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.14−1.66 (br, 32 H), 2.04 (q, 4H), 2.51 (t, 2H), 2.70 (t, 2H), 3.78−3.96 (br, 1H), 4.88−5.06 (m, 4H), 5.54 (d, br, 1H), 5.72−5.90 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 26.07, 29.16, 29.35, 29.69, 29.76, 29.77, 29.79, 30.42, 31.20, 34.03, 35.28, 50.05, 114.33, 139.43, 172.15, 176.72.

General Coupling Procedure of the Amino Acid/ Dipeptides to 2, 3, or 5. The appropriate amino acid/ dipeptide and 1-hydroxybenzotriazole (HOBt) (2.5−5 equiv to amino acid) were added to a 100 mL round-bottom flask. To the flask, equipped with a stir bar and under argon, was added premonomers **2**, **3**, or **5** (1 equiv), 1,3-diisopropylcarbodiimide (DIC) (1.2−2 equiv to premonomer acid), amino acid/dipeptide (1.2 equiv), and dry THF (just enough to dissolve the compounds). Finally, NEt_3 (1 equiv to amino acid) was added to the solution to neutralize the amino acid salt. The reaction vessel was equipped with a reflux condenser heated at 50−60 °C for 12 h for the amino acids and 48 h for the peptides. The insoluble urea was removed via gravity filtration, followed by extraction (1 × H_2O, 2 × concentrated $NaHCO_3$, 2 × 1 M HCl). The product was purified with three successive recrystallizations using methanol/water (the product was dissolved in hot methanol, and water was added until the solution became cloudy) or by column chromatography.

Synthesis of (*S*)-2-(2-Pent-4-enyl-hept-6-enoylamino)-propionic Acid Benzyl Ester (6). The pure product **6** was obtained using the methodology employed above. Purification was obtained by three recrystallizations from CH_3OH/H_2O to yield 44% of the pure white solid (mp = 71−72 °C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.28−1.49 (m, 7H), 1.53−1.69 (br, 4H), 1.95−2.10 (br, 5H), 4.68 (p, 1H), 4.88−5.04 (m, 4H), 5.11−5.27 (m, 2H), 5.68−5.85 (m, 2H), 5.98 (d, br, 1H) 7.29−7.46 (br, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 18.90, 26.93, 27.01, 32.59, 32.63, 33.92, 33.94, 47.80, 48.09, 67.38, 114.894, 128.38, 128.68, 128.86, 135.54, 138.71, 138.77, 173.24, 175.39. Anal. Calcd for $C_{22}H_{31}NO_3$: C 73.91, H 8.74, N 3.92. Found: C 73.45, H 8.75, N 3.88. EI/HRMS [M + 1]: calcd for $C_{22}H_{31}$-NO_3, 357.2304 g/mol; found, 357.2311 g/mol.

Synthesis of (*S*)-4-Methyl-2-(2-pent-4-enyl-hept-6-enoyl-amino)pentanoic Acid Benzyl Ester (7). The pure product **7** was obtained in 74% yield after purification by column chromatography using 5:1 hexanes:ethyl acetate as the eluent. The product was a wax with a slight yellow tint. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.90 (d, br, 6H), 1.19−1.50 (br, 6H), 1.48−1.70 (br, 5H), 1.91−2.14 (br, 5H), 4.64−4.75 (m, 1H), 4.86−5.02 (m, 4H), 5.07−5.19 (m, 2H), 5.65−5.83 (m, 2H), 5.95 (d, br, 1H), 7.27−7.38 (br, 5H). ^{13}C NMR (75 MHz, $CDCl_3$,

ppm): δ 22.00, 23.07, 25.11, 26.91, 26.98, 32.62, 32.73, 33.85, 33.95, 41.73, 47.79, 50.71, 67.20, 114.83, 114.87, 128.43, 128.59, 128.79, 135.63, 138.65, 138.74, 173.17, 178.74. Anal. Calcd for $C_{25}H_{37}NO_3$: C 75.15, H 9.33, N 3.51. Found: C 74.73, H 9.40, N 3.59. EI/HRMS [M + 1]: calcd for $C_{34}H_{64}N_2O_3$, 399.2773 g/mol; found, 399.2778 g/mol.

Synthesis of (*S*)-4-Methyl-2-(2-pent-4-enyl-hept-6-enoylamino)pentanoic Acid Methyl Ester (8). The pure product **8** was obtained in 80% yield after purification by column chromatography using 5:1 hexanes:THF as the eluent yielding an opaque wax. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.95 (d, br, 6H), 1.27−1.51 (br, 6H), 1.51−1.72 (br, 5H), 1.96−2.17 (br, 5H), 3.73 (s, 3H), 4.62−4.73 (m, 1H), 4.89−5.07 (m, 4H), 5.70−5.87 (m, 2H), 5.92 (d, br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.00, 23.04, 25.10, 26.89, 26.96, 32.62, 32.75, 33.84, 33.94, 41.77, 47.80, 50.56, 52.41, 114.79, 114.82, 138.64, 138.74, 173.79, 175.73. Anal. Calcd for $C_{19}H_{33}NO_3$: C 70.55, H 10.28, N 4.33. Found: C 70.51, H 10.27, N 4.35. EI/HRMS [M + 1]: calcd for $C_{19}H_{33}NO_3$, 323.2460 g/mol; found, 323.2455 g/mol.

Synthesis of (*S*)-6-Benzyloxycarbonylamino-2-(2-pent-4-enyl-hept-6-enoylamino)hexanoic Acid Methyl Ester (9). The pure product **9** was obtained in 55% yield after purification by three recrystallizations from CH_3OH/H_2O (mp = 77−79 °C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.19−1.94 (br, 14H), 1.95−2.14 (br, 5H), 3.17 (q, br, 2H), 3.74 (s, 3H), 4.54−4.66 (m, 1H), 4.75−4.88 (br, 1H), 4.89−5.84 (m, 4H), 5.06−5.16 (br, 2H), 5.68−5.86 (m, 2H), 6.05 (d, br, 1H), 7.27−7.42 (br, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.57, 26.92, 27.08, 29.58, 32.20, 32.60, 32.69, 33.87, 33.94, 40.74, 47.80, 51.83, 52.61, 66.87, 114.88, 114.92, 128.34, 128.75, 136.78, 138.71, 138.76, 156.76, 173.20, 175.87. Anal. Calcd for $C_{27}H_{40}N_2O_5$: C 68.62, H 8.53, N 5.93. Found: C 68.33, H 8.66, N 5.88. EI/HRMS [M + 1]: calcd for $C_{27}H_{40}N_2O_5$, 472.2937 g/mol; found, 472.2937 g/mol.

Synthesis of (*S*)-2-(2-Undec-10-enyltridec-12-enoylamino)propionic Acid Benzyl Ester (10). The pure product **10** was obtained in 74% yield and purified by three recrystallizations from CH_3OH/H_2O (mp = 87−89 °C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 1.19−1.46 (br, 32H), 1.48−1.69 (br, 3H), 1.92−2.10 (br, 5H), 4.68 (p, 1H), 4.85−5.04 (m, 4H), 5.10−5.26 (m, 2H), 5.71−5.89 (m, 2H), 5.99 (d, br, 1H) 7.26−7.40 (br, 5H).^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 19.13, 27.96, 28.02, 29.38, 29.39, 29.56, 29.57, 29.90, 29.93, 29.97, 30.00, 30.08, 30.12, 33.41, 33.44, 34.25, 48.27, 48.30, 67.52, 114.50, 128.50, 128.83, 129.02, 135.78, 139.63, 139.64, 173.44, 175.88. Anal. Calcd for $C_{34}H_{55}NO_3$: C 77.66, H 10.54, N 2.66. Found: C 77.46, H 10.53, N 2.66. EI/HRMS [M + 1]: calcd for $C_{34}H_{55}NO_3$, 525.4182 g/mol; found, 525.4190 g/mol.

Synthesis of (*S*)-4-Methyl-2-(2-undec-10-enyltridec-12-enoylamino)pentanoic Acid *tert*-Butyl Ester (11). The pure product **11** was obtained in 78% yield and purified by column chromatography using 3:1 hexanes:ethyl acetate as the eluent.^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.94 (d, br, 6H), 1.13−1.74 (br, 44H), 1.92−2.09 (br, 5H), 4.50−4.61 (m, 1H), 4.88−5.05 (m, 4H), 5.72−5.90 (br, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.31, 23.05, 25.21, 27.78, 27.85 28.21, 29.16, 29.35, 29.71, 29.74, 29.84, 29.92, 33.24, 33.37, 34.03, 42.42, 48.29, 51.18, 81.92, 114.31, 139.47, 172.66, 175.76. Anal. Calcd for $C_{34}H_{63}NO_3$: C 76.49, H 11.89, N 2.62. Found: C 76.45, H 12.07, N 2.54. EI/HRMS [M + 1]: calcd for $C_{34}H_{63}NO_3$, 533.4808 g/mol; found, 533.4809 g/mol.

Synthesis of (*S*)-4-Methyl-2-(2-undec-10-enyltridec-12-enoylamino)pentanoic Acid Benzyl Ester (12). The pure product **12** was obtained in 78% yield and purified by column chromatography using a 5:1 hexanes:THF mobile phase (mp = 46−48 °C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.75−1.00 (br, 6H), 1.08−1.47 (br, 30H), 1.47−1.75 (br, 5H), 1.90−2.12 (br, 5H), 4.63−4.79 (br, 1H), 4.85−5.06 (br, 4H), 5.08−5.23 (br, 2H), 5.67−5.94 (m, 2H), 5.95 (d, br, 1H), 7.27−7.46 (br, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.05, 23.08, 25.12, 27.76, 27.85, 29.16, 29.36, 29.71, 29.79, 29.84, 29.92, 33.22, 33.34, 34.04, 41.90, 48.22, 50.65, 67.21, 114.33, 128.41, 128.59, 128.80, 135.63, 139.44, 173.27, 176.02. Anal. Calcd for $C_{37}H_{61}NO_3$: C 78.25, H 10.83, N 2.47. Found: C 78.12, H 10.91, N 2.49. EI/HRMS [M + 1]: calcd for $C_{37}H6_1NO_3$, 567.4651 g/mol; found, 567.4654 g/mol.

Synthesis of (*S*)-4-Methyl-2-(2-undec-10-enyltridec-12-enoylamino)pentanoic acid methyl ester (13). The pure product **13** was obtained in 74% yield and purified via column chromatography using a 5:1 hexanes:THF mobile phase (mp = 42−44 °C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.94 (d, br, 6H), 1.10−1.48 (br, 30H), 1.48−1.73 (br, 5H), 1.93−2.14 (br, 5H), 3.72 (s, 3H), 4.61−4.77 (br, 1H), 4.87−5.11 (m, 4H), 5.71−5.93 (br, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.04, 23.08, 25.12, 27.75, 27.84, 29.15, 29.35, 29.72, 29.76, 29.83, 29.92, 33.25, 33.37, 34.03, 41.92, 48.20, 50.52, 52.40, 114.31, 139.42, 139.44, 173.87, 176.03. Anal. Calcd for $C_{31}H_{57}NO_3$: C 75.71, H 11.68, N 2.85. Found: C 75.62, H 11.75, N 2.84. EI/HRMS [M + 1]: calcd for $C_{31}H_{57}NO_3$, 491.4338 g/mol; found, 491.4341 g/mol.

Synthesis of (*S*)-6-benzyloxycarbonylamino-2-(2-undec-10-enyltridec-12-enoyl-amino)-hexanoic acid methyl ester (14). The pure product **14** was obtained in 78% yield after purification by three recrystallizations from CH_3OH/H_2O (mp = 109−111 °C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.14−1.45 (br, 32H), 1.47−1.94 (br, 6H), 1.96−2.11 (br, 5H), 3.17 (q, br, 2H), 3.73 (s, 3H), 4.56−4.66 (m, 1H), 4.77−4.88 (br, 1H), 4.89−5.84 (m, 4H), 5.06−5.16 (br, 2H), 5.68−5.86 (m, 2H), 6.03 (d, br, 1H), 7.29−7.41 (br, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.56, 27.76, 27.91, 29.16, 29.37, 29.57, 29.70, 29.73, 29.78, 29.86, 29.92, 32.38, 33.17, 33.27, 34.04, 40.75, 48.11, 51.76, 52.57, 66.85, 114.33, 128.32, 128.74, 136.79, 139.46, 156.73, 173.25, 176.19. Anal. Calcd for $C_{39}H_{64}N_2O_5$: C 73.08, H 10.06, N 4.37. Found: C 73.01, H 10.07, N 4.32. EI/HRMS [M + 1]: calcd for $C_{39}H_{64}N_2O_5$, 640.4815 g/mol; found, 640.4831 g/mol.

Synthesis of Arginine-Branched Monomer (15).[20] The pure product **15** was obtained as a yellow tinted oil in 78% yield after purification by column chromatography using ethyl acetate as the eluent. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.14−1.76 (br, 41H), 1.82−1.97 (m, br, 1H), 1.98−2.17 (br, 8H), 2.54 (s, 3H), 2.60 (s, 3H), 2.97 (s, 2H), 3.13−3.29 (br, 1H), 3.30−3.46 (br, 1H), 3.76 (s, 3H), 4.52−4.64 (br, 1H), 4.89−5.07 (m, 4H), 5.73−5.92 (m, 2H), 6.13−6.23 (br, 2H), 6.30−6.40 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 12.68, 18.07, 19.46, 25.21, 27.70, 27.83, 28.82, 29.15, 29.36, 29.69, 29.78, 29.84, 29.89, 30.96, 33.06, 33.15, 34.03, 40.84, 43.49, 47.95, 52.82, 86.54, 114.34, 117.64, 124.76, 132.51, 133.35, 138.56, 139.43, 156.33, 158.90, 172.88, 177.31. Anal. Calcd for $C_{44}H_{74}N_4O_6S$: C 67.14, H 9.48, N 7.12. Found: C 67.56, H 9.73, N 6.80. EI/HRMS [M + 1]: calcd for $C_{44}H_{74}N_4O_6S$, 786.5329 g/mol; found, 786.5360 g/mol.

Synthesis of (*S*)-6-Benzyloxycarbonylamino-2-[3-(1-undec-10-enyl-dodec-11-enylcarbamoyl)propionylamino]-hexanoic Acid Methyl Ester (16). The pure product **16** was obtained in 72% yield as a white solid after purification by three recrystallizations using CH_3CH_2OH/H_2O (mp = 131−133 °C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.10−1.75 (br, 38H), 1.75−1.88 (br, 1H), 1.90−1.96 (br, 1H), 2.02 (q, 4H), 2.36−2.61 (br, 4H), 3.06−3.27 (br, 2H), 3.71 (s, 3H), 3.75−3.90 (br, 1H), 4.46−4.61 (br, 1H), 4.86−5.04 (m, 4H), 5.06−5.22 (br, 3H), 5.58 (d, br, 1H), 5.71−5.91 (m, 2H), 6.68 (d, br, 1H), 7.29−7.39 (br, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.38, 26.06, 26.09, 29.16, 29.36, 29.71, 29.80, 29.87, 31.82, 31.92, 34.03, 35.30, 35.39, 40.62, 49.69, 52.19, 52.55, 66.77, 114.33, 128.28, 128.73, 136.91, 139.45, 156.83, 171.67, 172.46, 172.96. Anal. Calcd for $C_{42}H_{69}N_3O_6$: C 70.85, H 9.77, N 5.90. Found: C 70.65, H 9.90, N 5.74. EI/HRMS [M + 1]: calcd for $C_{42}H_{69}N_3O_6$, 711.5186 g/mol; found, 711.5252 g/mol.

Synthesis of (*S*)-2-[2-(2-Undec-10-enyltridec-12-enoylamino)propionylamino]propionic Acid Methyl Ester (17). The pure product **17** was obtained in 72% yield after purification by three recrystallizations from CH_3OH/H_2O (mp = 99−100 °C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.12−1.50 (br, 35H), 1.51−1.67 (br, 3H), 1.94−2.12 (br, 5H), 3.75 (s, 3H), 4.55 (m, 2H), 4.88−5.06 (br, 2H), 5.80 (m, 2H), 5.98 (d, 1H), 6.70 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 18.26, 18.51, 27.81, 29.15, 19.35, 29.69, 29.76, 29.79, 29.86, 29.93, 33.24, 34.03, 48.00, 48.30, 48.54, 52.67, 114.33, 139.45, 172.15,

173.21 176.28. Anal. Calcd for $C_{31}H_{56}N_2O_4$: C 71.49, H 10.84, N 5.38. Found: C 71.47, H 10.80, N 5.33. EI/HRMS [M + 1]: calcd for $C_{31}H_{56}N_2O_4$, 520.4240 g/mol; found, 520.4232 g/mol.

Synthesis of (*S*)-4-Methyl-2-[4-methyl-2-(2-undec-10-enyltridec-12-enoylamino)pentanoylamino]pentanoic Acid Methyl Ester (18). The pure product **18** was obtained in 71% yield after purification by three recrystallizations from CH_3OH/H_2O (mp = 57−59 °C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.85−1.01 (m, 12H), 1.12−1.47 (br, 30H), 1.48−1.72 (br, 8H), 1.94−2.08 (br, 5H), 3.73 (s, 3H), 4.43−4.64 (br, 2H), 4.88−5.06 (m, 4H), 5.72−5.92 (br, 3H), 6.51 (d, br, 1H).^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.03, 22.24, 23.03, 23.16, 24.91, 24.96, 27.85, 29.16, 29.35, 29.70, 29.73, 29.83, 29.97, 33.16, 33.34, 34.06, 40.92, 41.67, 48.22, 50.93, 51.40, 52.51, 114.35, 139.46, 171.99, 173.24, 176.49. Anal. Calcd for $C_{37}H_{68}N_2O_4$: C 73.46, H 11.33, N 4.63. Found: C 73.27, H 11.41, N 4.49. EI/HRMS [M + 1]: calcd for $C_{37}H_{68}N_2O_4$, 604.5179 g/mol; found, 604.5178 g/mol.

Polymer Synthesis. General Synthesis. Polymerization of the monomers containing amino acid and peptide entities differs somewhat from a typical ADMET polymerization. These monomers are solids at or near room temperature, and so a small amount of solvent is necessary to conduct the chemistry in the liquid state under mild polymerization conditions. The procedure is described as follows. Monomer is placed in a 50 or 100 mL Schlenk tube equipped with a stir bar and a septum, followed by the addition of second generation Grubbs' Ru catalyst (**1**) (100:1/monomer:catalyst); both additions are done while maintaining a positive Ar flow throughout the system, followed by flushing with Ar for 30 min after the additions are complete. A minimal amount of dry THF then is added via syringe to produce a homogeneous solution, and the reaction mixture is allowed to stir for 144 h at 50 °C. This lengthy reaction time is done to ensure complete conversion, which is necessary during a step polymerization; shorter reaction times likely are feasible. Dry THF was added periodically to replace solvent lost to evaporation. The reaction then is sampled and assessed for complete conversion via ^{1}H NMR, and if necessary, additional catalyst is added and the solution is allowed to stir for a longer period of time. Once conversion is complete, the ruthenium catalyst is removed via complexation by treatment with tris(hydroxymethyl)phosphine (THP). Doing so is accomplished by dissolving the reaction mixture in chloroform (∼30 mL), combining this solution with a tris(hydroxymethyl) phosphine solution (1 M in 2-propanol, 30 equiv. to catalyst) and then extracting this solution with 1 M HCl (1 × 20 mL), concentrated $NaHCO_3$ (1 × 20 mL), and concentrated NaCl (1 × 20 mL). The polymer solution that remains is dried over $MgSO_4$, followed by rotary evaporation to yield the pure polymer. These polymers can then be solvent-cast from chloroform on a Teflon plate to yield a thin film.

Characterization of 19. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.07−1.73 (br, 7H), 1.74−2.19 (br, 5H), 4.53−4.74 (p, 1H), 5.04−5.39 (br, 4H), 5.94−6.56 (br, 1H), 7.27−7.41 (br, 5H).^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 18.82, 26.80, 27.75, 32.55, 32.84, 48.07, 48.42, 67.30, 67.40, 128.33, 128.40, 128.65, 128.85, 130.42, 131.47, 135.59, 173.21, 175.62.

Characterization of 20. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.77−0.97 (br, 6H), 1.10−1.45 (br, 6H), 1.45−1.74 (br, 5H), 1.78−2.18 (br, 5H), 4.59−4.77 (br, 1H), 5.03−5.20 (br, 2H), 5.20−5.39 (br, 2H), 5.80−6.05 (br, 1H), 7.27−7.41 (br, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.06, 23.09, 25.10, 27.74, 32.74, 41.73, 47.89, 50.71, 67.19, 128.41, 128.60, 128.81, 130.34, 135.63, 173.28, 175.90.

Characterization of 21. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.94 (d, br, 6H), 1.18−1.49 (br, 6H), 1.50−1.78 (br, 5H), 1.82−2.27 (br, 5H), 3.72 (s, 3H), 4.58−4.73 (br, 1H), 5.26−5.50 (br, 2H), 5.94−6.18 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$-d_6, ppm): δ 22.01, 23.08, 25.09, 27.58, 27.67, 30.52, 32.70, 41.69, 47.80, 50.56, 52.39, 130.40, 130.70, 173.78, 175.85.

Characterization of 22. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.08−1.74 (br, 13H), 1.74−2.20 (br, 6H), 3.00−3.22 (br, 2H), 3.67 (s, br, 3H), 4.46−4.66 (m, 1H), 4.95−5.16 (br, 2H), 5.16−5.43 (m, 3H), 6.11−6.67 (br, 1H), 7.23−7.40 (br, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.68, 27.64, 29.54, 29.92, 30.54, 31.94, 32.79, 40.74, 47.58, 51.89, 52.54, 66.74, 128.21, 128.27, 128.56, 128.71, 130.36, 136.85, 156.86, 173.23, 176.13.

Characterization of 23. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.07−1.49 (br, 32H), 1.50−1.69 (br, 3H), 1.84−2.13 (br, 5H), 4.58−4.76 (p, 1H), 5.09−5.26 (br, 2H), 5.28−5.49 (br, 2H), 6.01−6.21 (br, 1H), 7.24−7.40 (br, 5H).^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 18.85, 27.78, 27.84, 29.44, 29.78, 29.91, 32.86, 33.26, 48.05, 67.29, 128.32, 128.63, 128.84, 130.58, 135.61, 173.25, 175.77.

Characterization of 24. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.95 (d, br, 6H), 1.13−1.77 (br, 44H), 1.87−2.11 (br, 5H), 4.50−4.63 (m, 1H), 5.28−5.47 (br, 2H), 5.83 (d, br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.28, 23.05, 25.18, 27.43, 27.79, 27.86, 28.19, 29.42, 29.54, 29.76, 29.80, 29.89, 32.83, 33.26, 33.39, 42.36, 48.26, 51.16, 81.86, 130.54, 172.63, 175.75.

Characterization of 25. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.0.92 (d, br, 6H), 1.09−1.47 (br, 30H), 1.48−1.70 (br, 5H), 1.85−2.11 (br, 5H), 4.72 (m, br, 1H), 5.10−5.21 (br, 2H), 5.29−5.41 (br, 2H), 5.86 (d, br, 1H), 7.29−7.40 (br, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.04, 23.10, 25.12, 27.80, 27.89, 29.44, 29.77, 29.88, 32.85, 33.27, 33.39, 41.85, 48.22, 50.65, 67.18, 128.40, 128.57, 128.79, 130.56, 135.65, 173.24, 176.02.

Characterization of 26. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.94 (d, br, 6H), 1.14−1.47 (br, 30H), 1.49−1.72 (br, 5H), 1.89−2.12 (br, 5H), 3.73 (s, 3H), 4.68 (br, m, 1H), 5.28−5.46 (br, 2H), 5.78−5.96 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.03, 23.08, 25.11, 27.43, 27.77, 27.87, 29.42, 29.55, 29.77, 29.82, 29.89, 32.83, 33.28, 33.41, 41.88, 48.20, 50.52, 52.39, 130.56, 173.86, 176.03.

Characterization of 27. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.09−1.76 (br, 38H), 1.90−2.16 (br, 5H), 3.02−3.23 (br, 2H), 3.71 (s, 3H), 4.52−4.66 (br, 1H), 4.99−5.25 (br, 3H), 5.28−5.45 (br, 2H), 6.26−6.44 (br, 1H), 7.24−7.40 (br, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.59, 25.81, 27.74, 27.89, 29.40, 29.53, 29.76, 29.86, 31.98, 32.82, 33.17, 33.29, 40.65, 47.89, 51.81, 52.43, 66.69, 128.18, 128.22, 128.66, 130.52, 136.85, 156.82, 173.21, 176.29.

Characterization of 28. ^{1}H NMR (300 MHz, DMSO-d_6, 70 °C, ppm): δ 0.96−1.81 (br, 42H), 1.84−2.29 (br, 8H), 2.39−2.66 (br, 6H overlapping with DMSO-d_6 resonance), 2.89−3.19 (br, 4H), 3.61 (s, br, 3H), 4.14−4.33 (br, 1H), 4.23−4.46 (br, 2H), 6.48−7.33 (br, 3H), 8.12−8.32 (br, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, 70 °C, ppm): δ 12.70, 18.03, 19.36, 26.26, 27.30, 27.49, 28.89, 29.14, 29.61, 31.18, 32.54, 32.98, 33.16, (note some peaks under DMSO-d_6 resonance) 43.36, 46.06, 52.01, 52.25, 86.75, 116.84, 124.87, 130.65, 132.15, 137.84, 156.93, 158.20, 173.06, 175.87.

Characterization of 29. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.09−1.77 (br, 36H), 1.77−2.06 (br, 6H), 2.40−2.63 (br, 4H), 3.06−326 (br, 2H), 3.72 (br, s, 3H), 3.79−3.90 (br, 1H), 4.47−4.61 (br, 1H), 5.04−5.17 (br, 2H), 5.22−5.47 (br, 3H), 5.69−6.13 (br, 1H), 6.69−7.02 (br, 1H) 7.20−7.40 (br, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.69, 26.37, 29.62, 29.97, 30.09, 32.05, 33.04, 35.64, 40.86, 49.90, 52.44, 52.69, 66.94, 128.43, 128.88, 130.76, 137.14, 157.00, 171.86, 172.66, 173.10.

Characterization of 30. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.10−1.46 (br, 35H), 1.47−1.68 (br, 3H), 1.89−2.13 (br, 5H), 3.74 (s, 3H), 4.52 (br, m, 1H), 4.59−4.76 (br, 1H), 5.07 (m, 4H), 5.72−5.91 (m, 2H), 5.98 (d, br, 1H), 6.70 (d, br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 17.97, 18.79, 25.82, 27.39, 27.80, 29.35, 29.75, 29.86, 32.80, 33.24, 47.83, 48.29, 48.49, 52.57, 130.56, 172.54, 173.22, 176.26.

Characterization of 31. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.92 (m, 12H), 1.10−1.47 (br, 30H), 1.47−1.73 (br, 8H), 1.86−2.13 (br, 5H), 3.73 (s, 3H), 4.47−4.66 (br, 2H), 5.28−5.47 (br, 2H), 6.02−6.39 (br, 1H), 6.79−7.09 (br, 1H).^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.06, 22.38, 22.99, 23.12, 24.88, 24.96, 27.83, 29.39, 29.74, 29.86, 32.80, 33.16, 33.34, 41.10, 41.41, 48.04, 50.94, 51.44, 52.37, 130.08, 130.54, 172.25, 173.18, 176.39.

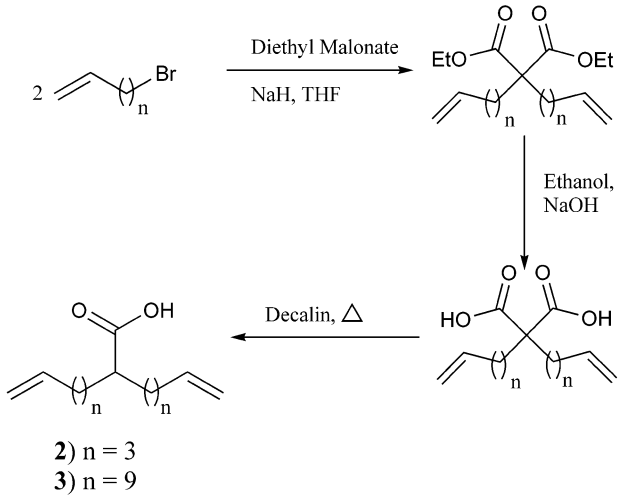


Figure 1. General synthetic scheme for the preparation of premonomers **2** and **3**.

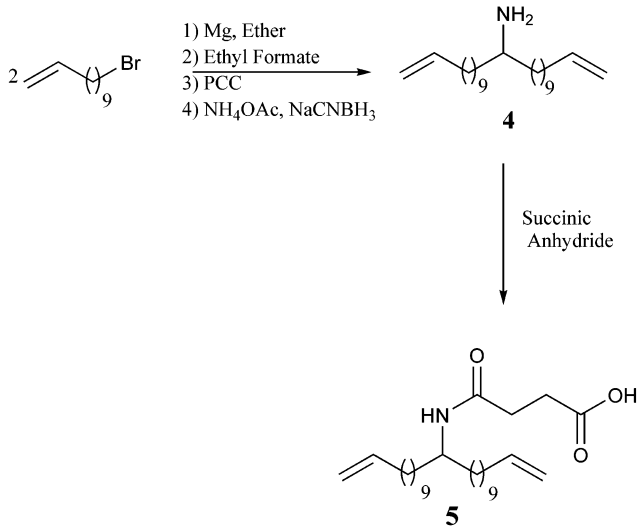


Figure 2. The synthesis of the succinic acid branched premonomer **5**.

Results and Discussion

Monomer Synthesis. All of the monomers in this study were synthesized using routine peptide coupling chemistry to attach the appropriate amino acid/peptide to the premonomers **2**, **3**, or **5**.[21] The synthesis of premonomers **2** and **3** was accomplished via two consecutive S_N2 reactions between the deprotonated diethyl malonate and the corresponding alkenyl halide to form the diester (Figure 1). The reaction mixture was allowed to stir overnight under reflux and was easily monitored for complete conversion by TLC. In most cases, excess NaH and alkenyl bromide were added to force the reaction to completion, and in the case of premonomer **3**, undecenyl iodide was used as well. Doing so gave similar overall yields as the bromide; however, the initial diester synthesis was completed after only 4 h as determined by TLC. Neutralization of the NaH with water, addition of ethanol and NaOH, and refluxing overnight resulted in successful saponification to the desired diacid. The crude product was dissolved in a minimal amount of Decalin—just enough to dissolve the diacid when hot—a procedure that led to rapid decarboxylation at 190 °C as evidenced by the vigorous bubbling. The large difference in polarity of the product, starting material, and Decalin permitted easy purification by flash chromatography. Decalin can be removed using hexane as the eluent, a procedure simplified by the fact that Decalin is observed as a clear band in the silica gel. Switching to a more polar eluent, i.e., adding ethyl acetate, removed the desired product. Further purification of premonomer **3** is possible via recrystallization in pentane.

Premonomer **5** (Figure 2) was prepared by reacting amine **4**, which was synthesized as reported previously,[16] with succinic anhydride and a catalytic amount of 4-(dimethylamino)pyridine (DMAP). The reaction occurred rapidly, and the product was purified by recrystallization from CH_3CH_2OH/H_2O giving the desired acid in 67% yield. Succinic anhydride was used without purification, which could have led to a lower reaction yield do to the presence of unreactive succinic acid.

The protected monomers were prepared using the 1,3-diisopropylcarbodiimide (DIC)(1.5−2 equiv)/1-hydroxybenzatriazole (HOBt) (2.5−5 equiv) peptide coupling method with THF as the solvent (Figure 3). Triethylamine (1 equiv) was added to neutralize the amino acid salt, and the reactions were stirred at 50−60 °C for 12 to 48 h; the dipeptides were given more time to react, as previously determined to be necessary.[16] Once finished, the triethylamine hydrochloride and urea salts were removed by gravity filtration, and the THF was removed by rotary evaporation. The crude product was dissolved in methylene chloride, and washings were performed to remove excess triethylamine, premonomer, amino acid/dipeptide, and HOBt. The order of the washings proved important—a solid precipitated in the separatory funnel if HCl was added first, while no problems were encountered when concentrated $NaHCO_3$ was used for the initial washing. The monomers were purified either by recrystallization or column chromatography, characterized by elemental analysis, HRMS, ^1H NMR, and ^{13}C NMR and assessed for purity by TLC prior to polymerization.

The amino acid branched dienes **6**, **7**, **8**, and **9**, which possess three methylene units between the olefin and branch point, were prepared by coupling premonomer **2** with H−Ala−OBz·HCl, H−Leu−OBz·*p*-tosylate, H−Leu−OMe·HCl, and H−Lys(CBz)−OMe·HCl, respectively (Figure 3). Monomers **6** and **9** were purified via three recrystallizations using CH_3OH/H_2O to give the pure compounds in 44% and 55% yield. These yields were low due to the rather high solubility of the compounds in methanol. Monomers **7** and **8** are waxy solids and were thus purified by column chromatography using 5:1 hexanes:ethyl acetate and 5:1 hexanes:THF as the eluents, respectively. The compounds were recovered in 74% yield for **7** and 80% yield for **8**, which also suggests that the recrystallization method used for monomers **6** and **9** was the cause of the lower yields.

Monomers **10**, **11**, **12**, **13**, **14**, and **15** were synthesized by coupling premonomer **3** to H−Ala-OBz·HCl, H−Leu−OtBu·HCl, H−Leu−OBz·HCl, H−Leu−OMe·HCl, H−Lys(CBz)−OMe·HCl, and H−Arg(PBf)−OMe·HCl (Figure 3). Monomers **10** and **11** were purified by recrystallization using the CH_3OH/H_2O method in high yields, 74% and 78%, respectively. Monomer **11** was purified by flash chromatography using 3:1 hexanes:ethyl acetate as the eluent giving the pure product as a yellow-tinted oil in 78% yield. In the case of monomers

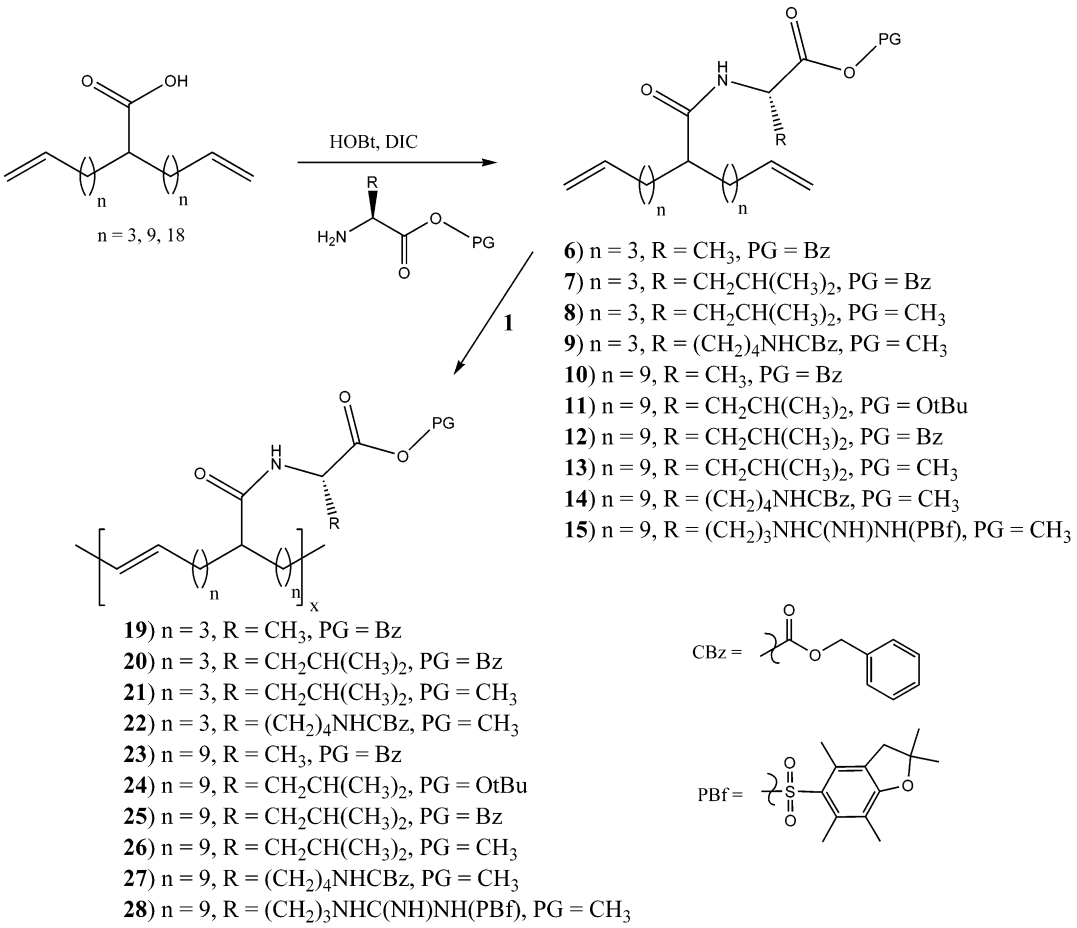


Figure 3. Synthesis of the protected amino acid branched monomers and polymers.

12 and **13**, 5:1 hexanes:THF was employed as the mobile phase, which gave pure products as opaque waxes in 78% and 74% yields, respectively. Monomer **15** was recovered in pure form as an oil in 78% yield—the liquid nature of the monomer is probably due to the PBf protecting group—after purification by flash column chromatography using ethyl acetate as the eluent.

Monomer **16** was synthesized having a succinic acid linkage between the polymer backbone and the amino acid in order to investigate the effect of a "spacer" between the amino acid functionality and the polymer backbone (Figure 4). Premonomer **5** was coupled to H−Lys(CBz)−OMe·HCl using the same methodology discussed above, and purification by recrystallization from CH_3OH/H_2O gave the desired product as a white powder in 72% yield.

The dipeptide branched monomers, **17** and **18**, were prepared by coupling premonomer **3** to H−Ala-Ala−OMe·HCl and H−Leu-Leu−OMe·HBr, respectively (Figure 5). The reactions were allowed to stir 48 h, the time being previously determined to give high yields for dipeptide branched monomers.[16] These monomers were obtained as white solids after purification using the recrystallization method described above, and recovered in good yields, 72% and 71%, respectively.

Polymer Synthesis. Acyclic diene metathesis (ADMET) is a simple step polymerization that allows for precise branch and/or functionality placement along the polymer backbone, where this structural feature is "built in" prior to polymerization by way of appropriate monomer design. Thus, ADMET permits the synthesis of polymers incapable of being prepared by common polymerization methods.[22] Since all of the monomers described herein are solids or become solids after minimal couplings, the polymerizations were run in a minimal amount of solvent (THF) under an Ar purge to aid in the removal of ethylene.

This methodology produces polymers of approximately the same molecular weight as those obtained under typical ADMET conditions using high vacuum (Table 1).[14−16] Dry THF was chosen as the solvent since it has been shown to be best for polymerizing amino acid and peptide branched monomers. Apparently the solvent participates in the polymerization mechanism itself by shifting the dynamic equilibrium complex of monomer functionality and catalyst toward the free catalyst state; thus, the catalyst is available for polymerization chemistry.

Previously we described the synthesis of polyolefins containing amino acids attached through the C-terminus, which have interesting thermal and mechanical properties.[16] We also synthesized polymers with a leucine methyl ester branch attached through the N-terminus, on every ninth carbon, a polymer which had good mechanical properties and a high melting temperature. Consequently, we felt it advantageous to investigate further the synthesis and properties of polymers with amino acids/dipeptides attached through the N-terminus on every 9th and 21st carbon of the backbone and to compare these results with those polymers prepared previously having amino acid/peptide moieties attached through the C-terminus.

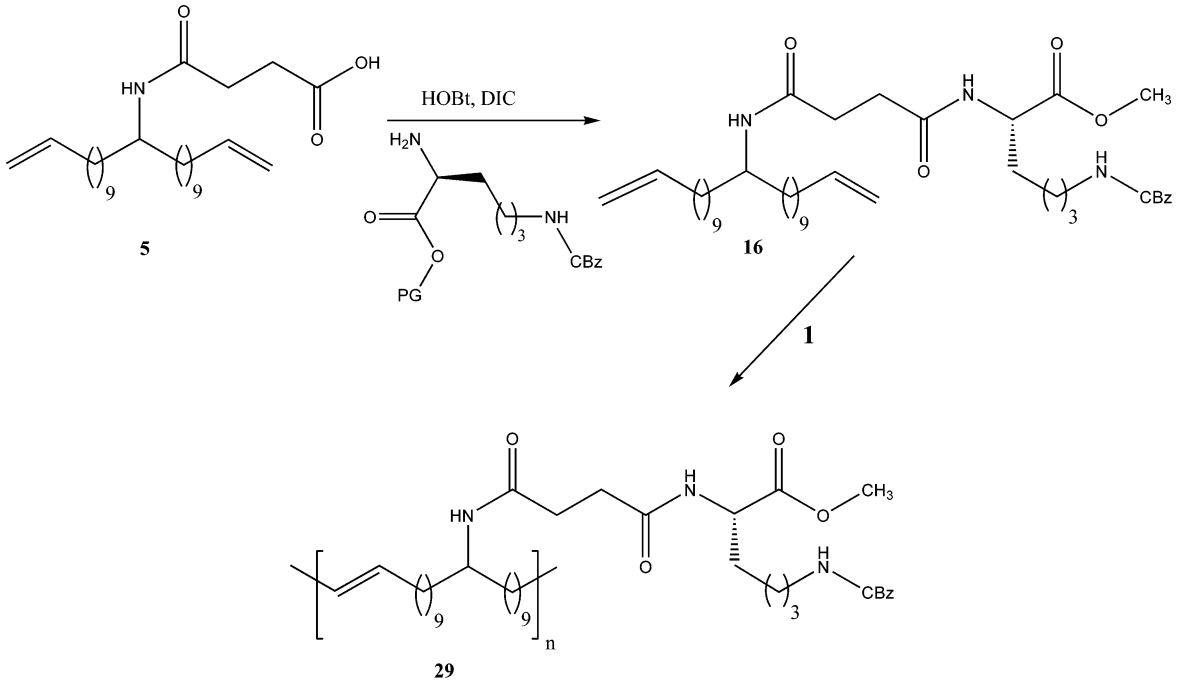


Figure 4. Synthesis of the lysine branched monomer separated from the diene with a succinic acid spacer.

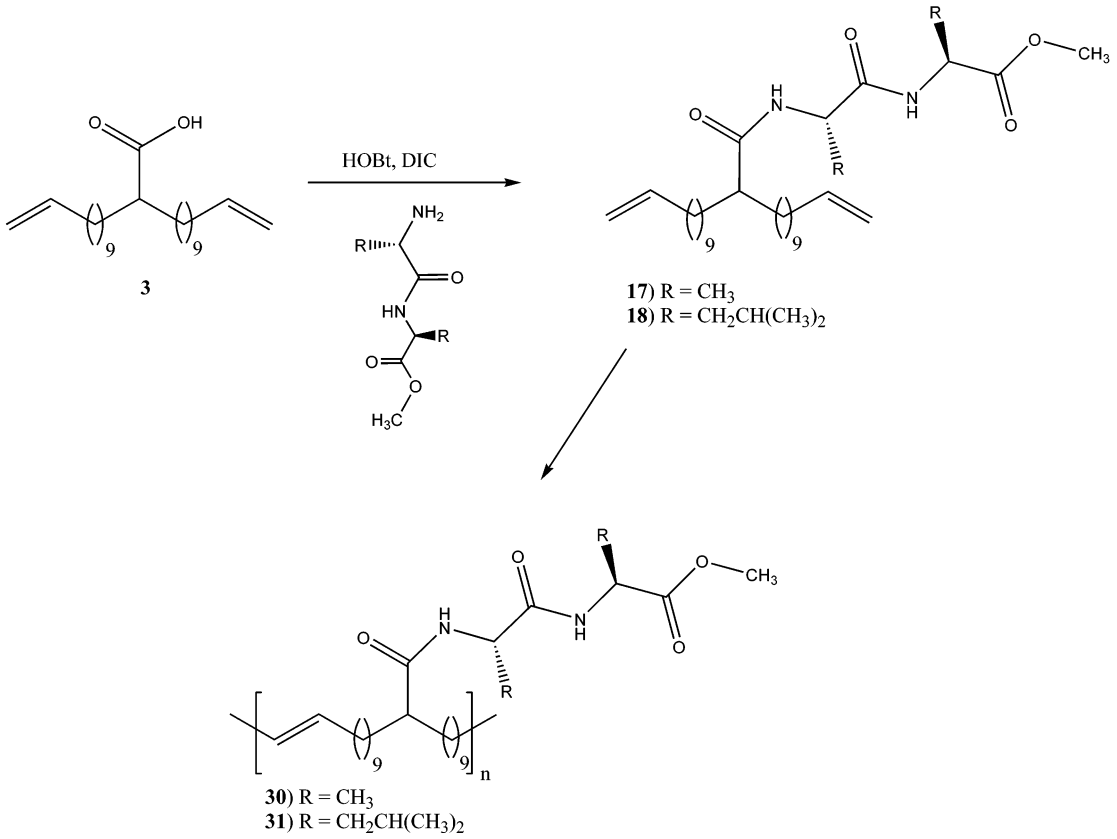
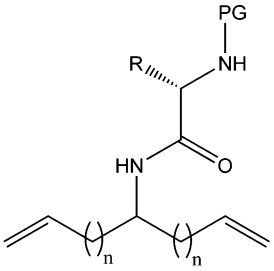


Figure 5. Synthesis of the dipeptide branched monomers and polymers.

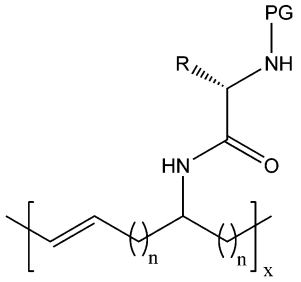
Monomer **6** was polymerized to polymer **19** having a molecular weight (M_w obtained by light scattering) of 26 000 (Table 1 and Figure 3). After only a few hours, the growing polymer became insoluble resulting in a gellike mixture; however, the polymerization continues to occur even in a gellike state, suggesting that a high degree of polymer/monomer solubility may not be required for high polymer preparation. This observation could become important when applying this methodology to larger peptides, which tend to lack solubility in common organic solvents. The resulting polymer **19** was only slightly soluble in common organic solvents, which led to easy purification of the polymer by precipitation in hexanes.

Monomer **7** was converted to polymer **20**, but with some difficulty. End groups were detectable in the ^{1}H NMR after the first polymerization attempt, a sign of incomplete conversion, so the polymer was dissolved in



32) n = 3, R = CH_3, PG = BOC
33) n = 3, R = $CH_2CH(CH_3)_2$, PG = BOC
34) n = 9, R = $(CH_2)_3NHCN(CBz)NHCBz$, PG = CBz

Figure 6. "C-terminus" amino acid branched monomers incapable of being polymerized using catalyst **1**.



35) n = 9, R = $(CH_2)_4NHCBz$, PG = CBz

Figure 7. Previously reported lysine branched polymer attached through the C-terminus.[16]

THF and exposed to additional catalyst (100:1 initial monomer: catalyst), which yielded high polymer with a $\overline{M}_w$ of 36 000 (Table 1). Monomers **8** and **9** were easily converted to high polymers **21** and **22** having $\overline{M}_w$s of 73 000 and 63 000, respectively (Figure 3). In addition, several "N-terminus" polymers (**23**−**27** in Figure 3) were prepared possessing an amino acid branch on every 21st carbon, and all of these polymers are high in molecular weight (Table 1).

The orientation of the amino acid entity with respect to the polymer backbone influences the reactivity of the diene toward ADMET chemistry, regardless of the frequency of appearance of the amino acid along the hydrocarbon polymer backbone. For example, "N-terminus" polymers **19** and **20** (those which have the amino acid attached via the N-terminus), and which have the amino acid attached on every ninth carbon, can be synthesized in high molecular weight, whereas the previously reported "C-terminus" monomers **32** and **33** (Figure 6) only yield oligomers. This phenomenon is even observed when the amino acid appears on every 21st carbon; the highly polar arginine-based "*C* terminus" monomer **34** (Figure 6) does not polymerize to high molecular weight, whereas the similar "N-terminus" monomer **15 (**Figure 3) does. This observation likely is a result of the intramolecular complexation, mentioned above, being more of a factor in the mechanism for "C-terminus" monomer polymerization than for "N-terminus" polymerization. Furthermore, the arginine moiety of the biologically active peptide sequence arginine−glycine−aspartic acid (RGD),[11,23] which is a target molecule for the preparation of a biologically active bio-olefin, is the most polar entity making the polymerizability of monomer **15** an important result.

Interesting solubility characteristics were observed for polymer **28**. Although the monomer was soluble in a variety of solvents, e.g. $CHCl_3$, CH_2Cl_2, and THF, the polymer was only slightly soluble in hot THF and DMSO. During the removal of the catalyst using the methodology described previously, a white coating of polymer formed on the glassware, which upon addition of ethyl acetate formed a tacky aggregate that was easily isolated. Furthermore, addition of concentrated $NaHCO_3$ solution broke up the aggregation producing a granular material that was easily filtered and purified by washing with DI H_2O to yield polymer **28** as a white fibrous material.

We also investigated the effect of inserting a "spacer" molecule between the hydrocarbon backbone and lysine. The monomer synthesis and polymerization are trivial (Figure 4), yielding a high molecular weight bio-olefin, **29**. In addition, the lysine branched polymers **27** (Figure 3) and **35** (Figure 7), which have lysine branches directly attached to the polymer backbone, are semicrystalline; therefore, polymer **29** should give an interesting insight on the effect of a spacer on the semicrystallinity of the resulting polymer.

Dipeptide monomers also are amenable to this polymerization methodology, which converts monomers **17** and **18** (Figure 5) into polymers **30** and **31**, both high in molecular weight as well (Table 1). Peptides, of course, are of interest since the goal of this research is to generate high strength materials possessing surfaces designed for biological activity. The fact that highly polar monomers such as **17** and **18** are capable of ADMET polymerization speaks well of the utility of the ruthenium-based metathesis catalysts.

Thermal Characterization. Generating durable materials capable of being shaped into useful biologically active structures usually means working with polymers that either have a high glass temperature or a reasonably high degree of crystallization. A considerable number of these biopolymers indeed crystallize, which likely is a result of both the regularity of spacing of the amino acid group along the hydrocarbon backbone, coupled with the strong interactions between amino acid and peptide groups.

The crystallinity within these materials is manifested in terms of tensile strength and toughness, which for some of the polymers roughly matches that of low-density polyethylene.[16] Our work in understanding the nature of the crystallinity present in these bio-olefins remains under investigation and will be published elsewhere. At this point we report only the thermal data collected by differential scanning calorimetry. The data can be found in Table 1.

Roughly half of the bio-olefins made to date crystallize; those which appear to be completely amorphous exhibit glass transitions in the range of −10 to +69 °C, while those which are semicrystalline exhibit melting points between 40 and 130 °C. Both of the dipeptide bioolefins are semicrystalline. Furthermore, the initial wide-angle X-ray work on many of these polymers suggests they possess a high degree of crystallinity. It appears that the size and polarity of the amino acid and dipeptide entities influence the nature of the crystallization that we observe.

Only one of the leucine-containing polymers is semicrystalline (**21**, the methyl ester branched polymer); this polymer exhibits the highest melting point as well. It is interesting to compare it with polymer **26**, which differs only in the location of the branch—polymer **21** possesses leucine on every ninth carbon of the backbone, while **26** places leucine on every 21st carbon.

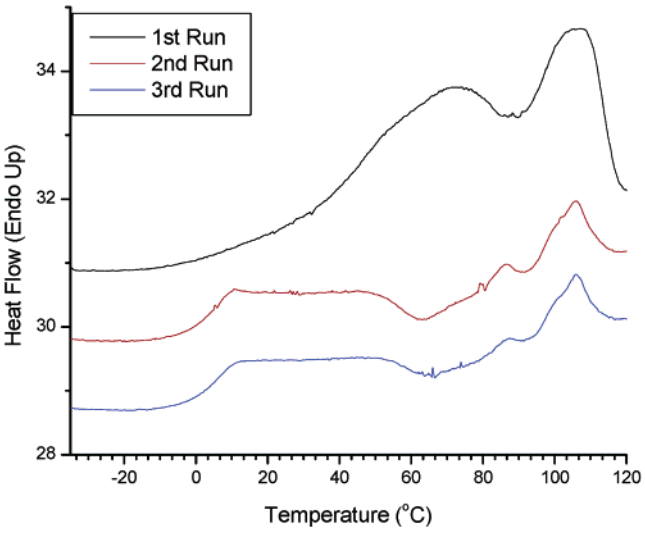


Figure 8. DSC scans of polymer **29**, demonstrating cold crystallization phenomena.

One might predict that polymer **26** should be semicrystalline as well, but that is not the case. Also interesting is the comparison of polymers **22** and **27**, which again are identical in structure with the exception of the distance between points of attachment of the amino acid. This time the order is reversed: the longer spaced bio-olefin (amino acid on every 21st carbon) crystallizes while the other does not.

The lysine branched polymer **29** possessing a succinic acid "spacer" separating the amino acid from the backbone is semicrystalline; its DSC curve exhibits what may be a cold crystallization (Figure 8). The first scan reveals an isomorphic response, with a "premelt" appearing at about 60 °C, followed by a higher melting response at about 105 °C. The cold crystallization phenomenon, if indeed that is what we observe, is apparent at around 60 °C followed by a melt at 106 °C in the second and third scans on the same sample. Adding the succinic acid "spacer" increases the melting point of a bio-olefin, an observation evident through comparison of polymer **29** (Figure 4) with the lysine branched polymers **27** (Figure 3) and **35** (Figure 7), which lack the spacer and melt (T_m) 27 and 10 °C lower, respectively. It may be that the spacer provides additional freedom for the amino acid moiety to order.

Although both dipeptide branched polymers **30** and **31** crystallize and possess similar melting points, they appear to do so at different crystallization rates, with the alanine−alanine polymer (**31**) being the slower of the two. In fact the semicrystalline form of polymer **31** can be generated only by casting from solution, whereas polymer **30** recrystallized from the melt. Similar responses were observed for the N-terminus polymer, **23**, and several of the C-terminus polymers as well. At this point we are unable to offer full explanations for the thermal behavior that is observed; the X-ray scattering experiments that are underway should provide us with a better view.

Conclusions

Bio-olefins have been prepared using ADMET chemistry to give high molecular weight materials having melting points of up to 132 °C and 74 °C for amino acid and dipeptide branched polymers, respectively. Monomers with amino acids/peptides attached through the N-terminus of the amino acid polymerize more readily than monomers with amino acids/peptides attached through the C-terminus.

Other than the result obtained for polymer **21**, the thermal data support our previous suggestion[16] that the amino acid moiety and not the polymer backbone is responsible for the semicrystalline nature of the polymer, with the more polar amino acids tending to be semicrystalline (lysine) and the nonpolar amino acids (leucine) being amorphous. In addition, results for the arginine branched polymer **28** and dipeptide branched polymers **30** and **31** are encouraging when contemplating the polymerization of ADMET monomers possessing biologically active peptides such as the RGD sequence.

These bio-olefins described in this paper have properties uncharacteristic of typical branched polyolefins, leading to many questions regarding structure property relationships. At present we are studying the X-ray scattering, mechanical properties, and surface properties of these materials.

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