Molecularly Defined (L)-Lactic Acid Oligomers and Polymers: Synthesis and Characterization

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ABSTRACT: The synthesis of (L)-lactide oligomers from dimer to 64mer via an exponential growth strategy is described. By careful selection of orthogonal protective groups, the synthesis were conducted using a *t*-butyldimethylsilyl (TBDMS) ether as the protective group of the hydroxyl group and benzyl (Bn) ester as the protective group of the carboxylic acid group. The yields of both the deprotection steps and coupling reactions using 1,3-dicyclohexylcarbodiimide or 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride were high (70–100%) and the absence of a requirement for conducting the majority of reactions under an inert atmosphere permitted a robust and efficient synthetic strategy to be developed. This allowed monodisperse dimer, tetramer, octamer, 16mer, 32mer, and 64mer materials to be prepared in gram quantities and fully characterized using mass spectrometry and size exclusion chromatography. Evaluation of the thermal and physical properties using thermogravimetric analysis, differential scanning calorimetry, and small angle X-ray scattering demonstrated a close correlation between the molecular structure of the well-defined Poly(lactide) oligomers and their physical properties. © 2008 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 46: 5977–5990, 2008
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INTRODUCTION

The emergence of well-defined macromolecular structures as a major focus in polymer science has coincided with a renewed focus on both biodegradable materials for medicinal applications as well as polymers derived from renewable resources.[1,2] Polymers obtained from lactic acid fulfill both of these criteria and are currently used in a number of biomedical applications, such as sutures, stents, dialysis media, and drug delivery devices. Poly(lactide) is prepared from renewable resources, such as corn starch (in the U.S.) or sugarcane (rest of world) and is commercially available on a large scale from a variety of manufacturers.

Traditionally, Poly(lactide) has been prepared via ring opening polymerization of cyclic lactide dimers using a catalyst such as stannous

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octanoate with significant effort in recent years being devoted to the development of both controlled polymerization processes[3] and the self-assembly of lactide derived materials.[4] Although there is a growing academic and industrial interest in poly(lactide) and biodegradable polyesters in general, there have been no studies on the synthesis of well-defined oligomers based on poly(lactide) with only a recent report from this group detailing the synthesis and characterization of well-defined poly(caprolactone) oligomers.[5] As in the poly(caprolactone) case, the preparation of these monodisperse oligomers would enable a wide range of structure property studies to fully understand, predict, and tune the degradation rate, crystal structure, self assembly, and performance of these materials in a variety of applications.[6]

The availability and detailed study of dimers, tetramers, octamers, and larger oligomers offers an unprecedented opportunity to impact material design and at the same time develop a fundamental understanding of the parent polymer. Previous work has demonstrated the power of this approach with molecularly defined oligomers being produced in both cellular systems[7] as well as in step-wise synthetic strategies such as the foldamers from Moore and coworkers[8] where the conformation structure and associated physical/chemical properties change dramatically with oligomer length. Similarly, Meijer and coworkers[9] has shown that molecularly controlled π-conjugated oligomers, such as sexithiophene gives rise to well-defined electronic properties and tunable intermolecular solid state organization which is critical in the expanding field of organic electronics. These and other studies demonstrating the synthesis of molecular rods of precise length[10] have conclusively revealed the dramatic insights that can be gained from the study of well-defined oligomers, especially if these materials are related to scientifically and industrially important macromolecules. Herein, we report the development of a synthetic strategy for the synthesis of well-defined poly(lactide) oligomers up to the 64mer and the use of these materials to develop a fundamental insight into the structure–property relationships for the widely studied parent polymer.

EXPERIMENTAL

Materials

4-(Dimethylamino)pyridinium *p*-toluenesulfonate (DPTS) was synthesized according to the previously reported procedure.[11] All the other chemicals and solvents were purchased from Aldrich, of reagent grade, and used without further purification. All reactions were carried out under ambient conditions unless specified.

General Procedures/Characterization

Freeze drying was conducted using LABCONCO 1 Liter Benchtop Freeze Dry Systems. Analytical TLC was performed on commercial Merck Plates coated with silica gel GF254 (0.24 mm thick). Silica gel for Flash Column Chromatography was Merck Kieselgel 60 (230–400 mesh, ASTM). ^{1}H NMR and ^{13}C NMR measurements were performed on a Bruker AC 500 and/or AC 200 spectrometer at room temperature. $CDCl_3$ was used as NMR solvent if not otherwise specified. Matrix Assisted Laser Desorption/Ionization (MALDI-TOF-MS) was carried out at room temperature on DYNAMO THERMO BIOANALYSIS using Dithranol in THF as the Matrix and Sodium trifluoroacetate in THF as the ionizing agent. Size exclusion chromatography (SEC) was carried out at room temperature on a Waters Alliance HPLC System (Waters 2695 Separation Module) connected to Waters Styragel® HR columns (0.5, 2, 4, and % INT'L HAZA) using THF as eluent (flow rate: 1 mL/min). A Waters 2414 differential refractometer and a 2996 photodiode array detector were employed. The molecular weights of the polymers were calculated relative to linear polystyrene standards. ThermoGravimetric Analysis was conducted using METTLER TGA/sDTA851e under N_2 atmosphere. Differential scanning calorimetry (DSC) measurements were performed with a TA Instruments DCS 2920 and a ramp rate of 5°/min with data collected during third cycle in the selected temperature ranges if not otherwise specified. Calibrations were made using indium as a standard for both temperature transitions and the heats of fusion. Melting transition temperatures (T_m) were determined as the peak maxima of the transition. Small angle X-ray scattering measurements were carried out in quartz capillary cells using Ultra-SAXS (X-ray Source; Fine focus (0.2 mm) Rigaku rotating anode generator, wavelength; 1.54 Å, sample-to-detector distance; 172.5 cm, Interface; Bruker SAXS software and SPEC) and Intermediate-SAXS (X-ray Source; 18 kW Rigaku rotating anode generator, Wavelength; 1.54 Å, Sample to Detector Distance; 75.8 cm, Interface; SPEC). Also, WAXS (four circle wide angle X-ray spectrometer: X-ray source;

18 kW Rigaku rotating anode generator, wavelength; 1.54 Å, monochromator; OSMIC confocal maxflux focusing multilayer mirror, Detector; MAR345 image plate area detector, Goniometer; Large Huber 4-circle, typical range of length scale probed; 2–20 Å, software for data collection; SPEC, software for data processing; CPLOT and Fit2D) was used. UV–Vis measurements were performed in quartz cells (inside dimension; 1 cm) using PERKIN ELMER Lambda20. Optical rotation and chirality were evaluated using JASCO Digital Polarimeter DIP-1000 (Cell length; 100 mm, Light source; Na 589 nm) and OLIS RSM Circular Dichroism Spectrometer at room temperature, respectively. Single crystal diffraction measurements were conducted using Bruker 3-axis platform diffractometer (X-ray Source and Optics; Sealed 2.4 kW Mo tube, graphite monochromator, Detector; SMART 1000 CCD detector, Cryostream System; OXFORD-600, operating temperature from 90 to 300 K, Software; Windows version SMART, Saint, SHELXTL, Cambridge Structure Database, Microscope: Nikon SMZ-U, magnification range 7×–75×, Sample requirement; typically 0.1–0.3 mm single crystal).

Benzyl (L)-lactate, 2

A 500-mL round bottom flask was charged with 20.57 g (0.18 mol) of Sodium L-lactate, **1**, 30.85 g (0.18 mol) of benzyl bromide, 0.10 g of 15-Crown-5, and 170 mL of DMF. This reaction mixture was stirred overnight at 100 °C. The majority of the DMF (~ 160 mL) was then removed by evaporation under reduced pressure at 80 °C and the crude product was purified via flash column chromatography using 1:1 Hexanes:Ethyl acetate as eluent to yield 29.98 g (91% yield) of **2** as a clear oil.

^{1}H NMR ($CDCl_3$): δ 7.37 (m, Ar, 5H), 5.22 (s, CO_2CH_2Ph, 2H), 4.32 (m, CH_2OH, 2H), 2.84 (b, HO, 1H), 1.43 (d, J = 7.0 Hz, CH_3, 3H). ^{13}C NMR ($CDCl_3$): δ 175.75 (CO, 1C), 135.44 (Ar, CH_2AC, 1C) 128.87 (Ar-*meta*, 2C), 128.76 (Ar-*para*, 1C), 128.44 (Ar-*ortho*, 2C), 67.52 (HO$CH(CH_3)CO$, 1C), 67.06 (CO_2CH_2Ph, 1C), 20.58 (CH_3, 1C). Mass Spec for $C_{10}H_{12}O_3$ Calculated: 203.07; Found $(M+Na)^+$: 203.07.

Monomer ((*S*)-Benzyl 2-(*tert*-butyldimethylsilyloxy)propanoate), 6

50.07 g (0.33 mol) of *tert*-butyldimethylsilyl chloride was added to a DMF (50 mL) solution of **2** (28.73 g, 0.16 mol) and imidazole (43.90 g, 0.64 mol). This reaction mixture was stirred overnight at room temperature under an argon atmosphere and the resulting mixture was poured into a separatory funnel containing 300 mL of saturated aqueous $NaHCO_3$ followed by extraction with 300 mL of hexanes for four times. The organic fractions were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was then purified via flash column chromatography using 5:1 hexane:ethyl acetate as eluent to yield 45.31 g (97% yield) of **6** as a clear, colorless oil.

^{1}H NMR ($CDCl_3$): δ 7.35 (b, Ar, 5H), 5.16 (m, CH_2Ph, 2H), 4.38 (q, J = 6.7 Hz, SiOC$H(CH_3)CO$, 1H), 1.43 (d, J = 6.8 Hz, $SiOCH(CH_3)CO$, 3H), 0.92 (s, $(CH_3)_3CSi$, 9H), 0.10 (s, $(CH_3)_2Si$, 3H), 0.08 (s, $(CH_3)_2Si$, 3H). ^{13}C NMR ($CDCl_3$): δ 173.97 (CO_2CH_2Ph, 1C), 135.93 (Ar, CH_2AC, 1C), 128.66 (Ar-*meta*, 2C), 128.41 (Ar-*ortho*, *para*, 3C), 68.60 ($SiOCH(CH_3)CO$, 1C), 66.61 (CO_2CH_2Ph, 1C), 25.86 ($(CH_3)_3CSi$, 3C), 21.46 ($SiOCH(CH_3)CO$, 1C), 18.43 ($(CH_3)_3CSi$, 1C), −4.79 ($(CH_3)_2Si$, 1C), −5.14 ($(CH_3)_2Si$, 1C). Mass Spec for $C_{16}H_{26}O_3Si$ Calculated: 317.17; Found $(M+Na)^+$: 317.16. $[\alpha]^{23}_D = -28°$ (c = 1.11 cg/mL $CHCl_3$)

Dimer-OH-CO_2H ((*S*)-2-((*S*)-2-Hydroxypropanoyloxy)propanoic acid), 10

A suspension of 20.16 g (0.14 mol) of (3*S*,6*S*)-3,6-dimethyl-1,4-dioxane-2,5-dione, **9**, in water (120 mL) was stirred at 40 °C for 4 h. The clear reaction mixture was then dried by freeze drying to yield 20.40 g (90% yield) of **10** as a clear colorless oil.

^{1}H NMR (MeOD-d_4): δ 5.22 (b, OH, 2H), 5.07 (q, J = 7.0 Hz, $CO_2CH(CH_3)CO_2H$, 1H), 4.32 (q, J = 7.0 Hz, $HOCH(CH_3)CO_2$, 1H), 1.49 (d, J = 7.0 Hz, $CO_2CH(CH_3)CO_2H$, 3H), 1.43 (d, J = 7.0 Hz, $HOCH(CH_3)CO_2$, 3H). ^{13}C NMR (MeOD-d_4): δ 175.74 (CO_2H, 1C), 173.99 (CO_2C, 1C), 70.17 ($CO_2CH(CH_3)CO_2H$, 1C) 67.57 (HO$CH(CH_3)CO_2$, 1C), 20.57 ($HOCH(CH_3)CO_2$, 1C) 17.28 ($CO_2CH(CH_3)CO_2H$, 1C). Mass spec for $C_6H_{10}O_5$ calculated: 185.04; Found $(M+Na)^+$: 185.03.

Dimer-OH ((*S*)-Benzyl 2-((*S*)-2-hydroxypropanoyloxy)propanoate), 11

A 1 L round bottom flask was charged with 20.30 g (0.13 mol) of **10**, 38.46 g (0.22 mol) of benzyl bromide, 44.63 g (0.44 mol) of triethylamine, and CH_2Cl_2 (200 mL). This reaction mixture

was then stirred overnight at room temperature and the CH_2Cl_2 and triethylamine removed under reduced pressure. The crude product was then redissolved in CH_2Cl_2 (100 mL), the solvent removed again *in vacuo* and the residue dissolved in CH_2Cl_2 (200 mL) and washed with saturated aqueous NH_4Cl (2 × 100 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure with the residue being purified via flash column chromatography using 1:1 hexane:ethyl acetate as eluent to yield 21.11 g (67% yield) of **11** as a colorless clear oil.

^{1}H NMR ($CDCl_3$): δ 7.35 (m, Ar, 5H), 5.21 (m, $CO_2C\mathbf{H}(CH_3)CO_2C\mathbf{H}_2Ph$, 3H), 4.34 (m, $HOC\mathbf{H}(CH_3)CO_2CH(CH_3)CO_2Ph$, 1H), 2.72 (d, J = 6.0 Hz, **H**O, 1H), 1.54 (d, J = 7.0 Hz, $CO_2CH(C\mathbf{H}_3)CO_2CH_2Ph$, 3H), 1.43 (d, J = 7.0 Hz, $HOCH(C\mathbf{H}_3)CO_2$, 3H). ^{13}C NMR ($CDCl_3$): δ 175.33 ($\mathbf{C}O_2C$, 1C), 170.22 ($\mathbf{C}O_2C$, 1C), 135.30 (Ar, $CH_2A\mathbf{C}$, 1C) 128.86 (Ar-*meta*, 2C), 128.77 (Ar-*ortho*, 1C), 128.47 (Ar-*para*, 2C), 69.63 ($CO_2\mathbf{C}H(CH_3)CO_2CH_2Ph$, 1C), 67.48 ($CO_2CH(CH_3)CO_2\mathbf{C}H_2Ph$, 1C), 66.93 ($HO\mathbf{C}H(CH_3)CO_2$, 1C), 20.65 ($HOCH(\mathbf{C}H_3)CO_2$, 1C) 17.04 ($CO_2CH(\mathbf{C}H_3)CO_2CH_2Ph$, 1C). Mass spec for $C_{13}H_{16}O_5$ calculated: 275.09; Found $(M+Na)^+$: 275.09.

Dimer ((*S*)-Benzyl 2-((*S*)-2-(*tert*-butyldimethylsilyloxy)propanoyloxy)propanoate), 5

25.67 g (0.17 mol) of *tert*-butyldimethylsilyl chloride was added to a DMF (25 mL) solution of **11** (21.08 g, 0.08 mol) and imidazole (22.65 g, 0.33 mol). This reaction mixture was then stirred overnight at room temperature under an argon atmosphere. The resulting mixture was poured into a separatory funnel containing 150 mL of saturated aqueous $NaHCO_3$ and extracted four times with 150 mL of hexane. The organic fractions were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was then purified via flash column chromatography using 5:1 hexane:ethyl acetate as eluent to yield 24.93 g (81% yield) of **5** as a clear, colorless oil.

^{1}H NMR ($CDCl_3$): δ 7.34 (b, Ar, 5H), 5.16 (m, $CO_2C\mathbf{H}(CH_3)CO_2C\mathbf{H}_2Ph$, 3H), 4.38 (q, J = 6.8 Hz, $SiOC\mathbf{H}(CH_3)CO$, 1H), 1.43 (d, J = 6.8 Hz, $SiOCH(C\mathbf{H}_3)CO$, 3H), 0.90 (s, $(C\mathbf{H}_3)_3CSi$, 9H), 0.10 (s, $(C\mathbf{H}_3)_2Si$, 3H), 0.08 (s, $(C\mathbf{H}_3)_2Si$, 3H). ^{13}C NMR ($CDCl_3$): δ 173.56 ($\mathbf{C}O_2C$, 1C), 170.45 ($\mathbf{C}O_2C$, 1C), 135.44 (Ar, $CH_2A\mathbf{C}$, 1C), 128.72 (Ar-*meta*, 2C), 128.54 (Ar-*para*, 1C), 128.34 (Ar-*ortho*, 2C), 68.95 ($CO_2\mathbf{C}H(CH_3)CO_2CH_2Ph$, 1C), 68.21 ($SiO\mathbf{C}H(CH_3)CO_2$, 1C), 67.14 ($CO_2\mathbf{C}H_2Ph$, 1C), 25.84 ($(\mathbf{C}H_3)_3CSi$, 3C), 21.32 ($SiOCH(\mathbf{C}H_3)CO$, 1C), 18.41 ($(CH_3)_3\mathbf{C}Si$, 1C), 17.01 ($CO_2CH(\mathbf{C}H_3)CO_2CH_2Ph$, 1C), -4.78 ($(\mathbf{C}H_3)_2Si$, 1C), -5.14 ($(\mathbf{C}H_3)_2Si$, 1C). Mass spec for $C_{19}H_{30}O_5Si$ calculated: 389.18; Found $(M+Na)^+$: 389.17.

General Procedure of Deprotection of Benzyl Ester (hydrogenation): Synthesis of Dimer-CO_2H ((*S*)-2-((*S*)-2-(*tert*-Butyldimethylsilyloxy)propanoyloxy) propanoic acid), 12, Depicted

1.39 g of palladium on activated carbon (10 wt %) was added to a solution of the dimer, **5**, (12.09 g, 32.99 mmol) in ethyl acetate (150 mL) and the reaction mixture was stirred overnight at room temperature under hydrogen. The resulting mixture was filtered through celite and the cake was washed with 100 mL of ethyl acetate. The combined filtrates were concentrated under reduced pressure to yield 9.12 g (100% yield) of **12** as a clear, colorless oil.

^{1}H NMR ($CDCl_3$): δ 11.76 (b, CO_2H, 1H), 5.11 (q, J = 7.1 Hz, $CO_2C\mathbf{H}(CH_3)CO_2H$, 1H), 4.38 (q, J = 6.8 Hz, $SiOC\mathbf{H}(CH_3)CO$, 1H), 1.52 (d, J = 7.2 Hz, $SiOCH(CH_3)CO_2CH(C\mathbf{H}_3)CO_2H$, 3H), 1.42 (d, J = 6.8 Hz, $SiOCH(C\mathbf{H}_3)CO_2CH(CH_3)CO_2H$, 3H), 0.88 (s, $(C\mathbf{H}_3)_3CSi$, 9H), 0.08 (s, $(C\mathbf{H}_3)_2Si$, 3H), 0.06 (s, $(C\mathbf{H}_3)_2Si$, 3H). ^{13}C NMR ($CDCl_3$): δ 176.70 ($\mathbf{C}O_2H$, 1C), 173.68 ($\mathbf{C}O_2C$, 1C), 68.56 ($CO_2\mathbf{C}H(CH_3)CO_2H$, 1C), 68.25 ($SiO\mathbf{C}H(CH_3)CO_2$, 1C), 25.83 ($(\mathbf{C}H_3)_3CSi$, 3C), 21.29 ($SiOCH(\mathbf{C}H_3)CO$, 1C), 18.42 ($(CH_3)_3\mathbf{C}Si$, 1C), 16.88 ($CO_2CH(\mathbf{C}H_3)CO_2H$, 1C), −4.81 ($(\mathbf{C}H_3)_2Si$, 1C), −5.20 ($(\mathbf{C}H_3)_2Si$, 1C). Mass spec for $C_{12}H_{24}O_5Si$ calculated: 299.13; Found $(M+Na)^+$: 299.12.

General Procedure of Deprotection of TBDMS (Desilylation): Synthesis of Dimer-OH, 11, Depicted

Acetic acid, 25.20 g (419.6 mmol), was added to a solution of the dimer, **5**, (12.09 g, 32.99 mmol) in THF (75 mL). To this was gradually added 65.82 g (72.89 mmol) of tetrabutylammonium fluoride (TBAF) (1.0 M solution in THF) and the reaction mixture was stirred overnight at room temperature. The resulting mixture was poured into a separatory funnel containing 300 mL of ethyl acetate and 300 mL of H_2O and the organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 200 mL), 5 wt % aqueous citric acid (2 × 200 mL), and H_2O (1 × 200 mL). The organic layer

was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure with the crude product being purified via flash column chromatography using 1:1 hexane:ethyl acetate as eluent to yield 7.44 g (89% yield) of **11** as a clear, colorless oil.

General Procedure of Coupling Reaction: Synthesis of Tetramer, 13, Depicted

A mixture of **11** (7.43 g, 29.45 mmol), **12** (8.66 g, 31.33 mmol), 1,3-dicyclohexylcarbodiimide (DCC) (7.63 g, 36.9 mmol), and 4-(dimethylamino)pyridinium *p*-toluenesulfonate (DPTS) (1.74 g, 5.92 mmol) was dissolved in CH_2Cl_2 (50 mL) and stirred overnight at room temperature. The reaction mixture was then filtered and washed with 100 mL of saturated aqueous $NaHCO_3$ and 100 mL of H_2O. The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product which was then purified via gradient flash column chromatography (eluting with 20:1 hexane:ethyl acetate gradually increasing to 4:1 hexane:ethyl acetate) to yield 13.99 g (93% yield) of **13** as a colorless solid.

^{1}H NMR ($CDCl_3$): δ 7.32 (b, Ar, 5H), 5.15 (m, $CH(CH_3)CO_2[C\mathbf{H}(CH_3)CO_2]_3C\mathbf{H}_2Ph$, 5H), 4.38 (q, J = 6.8 Hz, $SiOC\mathbf{H}(CH_3)CO$, 1H), 1.57 (d, J = 6.8 Hz, $CH(C\mathbf{H}_3)CO_2CH_2Ph$, 3H), 1.51 (m, $CH(CH_3)CO_2[CH(C\mathbf{H}_3)CO_2]_2CH(CH_3)CO_2CH_2Ph$, 6H), 1.44 (d, J = 6.8 Hz, $SiOCH(C\mathbf{H}_3)CO$, 3H), 0.90 (s, $(C\mathbf{H}_3)_3CSi$, 9H), 0.10 (s, $(C\mathbf{H}_3)_2Si$, 3H), 0.08 (s, $(C\mathbf{H}_3)_2Si$, 3H). ^{13}C NMR ($CDCl_3$): δ 173.61 ($\mathbf{C}O_2C$, 1C), 170.08 ($\mathbf{C}O_2C$, 2C), 169.76 ($\mathbf{C}O_2C$, 1C), 135.25 (Ar, $CH_2A\mathbf{C}$, 1C), 128.73 (Ar-*meta*, 2C), 128.62 (Ar-*para*, 1C), 128.36 (Ar-*ortho*, 2C), 69.35 ($CO_2\mathbf{C}H(CH_3)CO_2$, 1C), 68.94 ($CO_2\mathbf{C}H(CH_3)CO_2$, 1C), 68.66 ($CO_2\mathbf{C}H(CH_3)CO_2$, 1C), 68.11 ($SiO\mathbf{C}H(CH_3)CO_2$, 1C), 67.28 ($CO_2\mathbf{C}H_2Ph$, 1C), 25.82 ($(\mathbf{C}H_3)_3CSi$, 3C), 21.34 ($SiOCH(\mathbf{C}H_3)CO$, 1C), 18.38 ($(CH_3)_3\mathbf{C}Si$, 1C), 16.85 ($CO_2CH(\mathbf{C}H_3)CO_2$, 2C), 16.71 ($CO_2CH(\mathbf{C}H_3)CO_2$, 1C), −4.78 ($(\mathbf{C}H_3)_2Si$, 1C), −5.17 ($(\mathbf{C}H_3)_2Si$, 1C). Mass spec for $C_{25}H_{38}O_9Si$ calculated: 533.22; Found $(M+Na)^+$: 533.21.

Tetramer-CO_2H, 14

The monoprotected, acid-functionalized tetramer-CO_2H, **14**, was prepared using the general procedure described earlier for deprotection of benzyl esters (hydrogenation), starting from the protected tetramer, **13**. The crude product was then purified via gradient flash column chromatography (eluting with 2:1 hexane:ethyl acetate gradually increasing to 2:1 ethyl acetate:MeOH) to yield **14** as a colorless oil (93% yield).

^{1}H NMR ($CDCl_3$): δ 11.70 (b, $CO_2\mathbf{H}$, 1H), 5.15 (m, $CH(CH_3)CO_2[C\mathbf{H}(CH_3)CO_2]_3H$, 3H), 4.37 (q, J = 6.8 Hz, $SiOC\mathbf{H}(CH_3)CO$, 1H), 1.47 (m, $SiO[CH(C\mathbf{H}_3)CO_2]_4H$, 12H), 0.87 (s, $(C\mathbf{H}_3)_3CSi$, 9H), 0.07 (s, $(C\mathbf{H}_3)_2Si$, 3H), 0.05 (s, $(C\mathbf{H}_3)_2Si$, 3H). ^{13}C NMR ($CDCl_3$): δ 176.00 ($\mathbf{C}O_2H$, 1C), 173.76 ($\mathbf{C}O_2C$, 1C), 170.20 ($\mathbf{C}O_2C$, 2C), 169.90 ($\mathbf{C}O_2C$, 1C), 69.59 ($CO_2\mathbf{C}H(CH_3)CO_2$, 1C), 69.08 ($CO_2\mathbf{C}H(CH_3)CO_2$, 1C), 68.74 ($CO_2\mathbf{C}H(CH_3)CO_2$, 1C), 68.13 ($SiO\mathbf{C}H(CH_3)CO_2$, 1C), 25.82 (($\mathbf{C}H_3)_3CSi$, 3C), 21.34 ($SiOCH(\mathbf{C}H_3)CO$, 1C), 18.38 ($(CH_3)_3\mathbf{C}Si$, 1C), 16.83 ($CO_2CH(\mathbf{C}H_3)CO_2$, 2C), 16.69 ($CO_2CH(\mathbf{C}H_3)CO_2$, 1C), −4.79 (($\mathbf{C}H_3)_2Si$, 1C), −5.18 (($\mathbf{C}H_3)_2Si$, 1C). Mass spec for $C_{18}H_{32}O_9Si$ calculated: 443.17; Found $(M+Na)^+$: 443.17.

Tetramer-OH, 15

The monoprotected, hydroxyl-functionalized tetramer-OH, **15**, was prepared using the general procedure described earlier for deprotection of TBDMS groups (desilylation), starting from the tetramer, **13**. The crude product was purified via gradient flash column chromatography (eluting with 1:1 hexane:ethyl acetate gradually increasing to ethyl acetate) to yield **15** as a colorless oil (88% yield).

^{1}H NMR ($CDCl_3$): δ 7.34 (b, Ar, 5H), 5.18 (m, $CH(CH_3)CO_2[C\mathbf{H}(CH_3)CO_2]_3C\mathbf{H}_2Ph$, 5H), 4.36 (m, $SiOC\mathbf{H}(CH_3)CO$, 1H), 3.10 (b, O**H**, 1H), 1.50 (m, $CH(C\mathbf{H}_3)CO_2$, 12H). ^{13}C NMR ($CDCl_3$): δ 175.06 ($\mathbf{C}O_2C$, 1C), 169.96 ($\mathbf{C}O_2C$, 1C), 169.80 ($\mathbf{C}O_2C$, 1C), 169.61 ($\mathbf{C}O_2C$, 1C), 135.16 (Ar, $CH_2\mathbf{C}$, 1C), 128.66 (Ar-*meta*, 2C), 128.56 (Ar-*para*, 1C), 128.30 (Ar-*ortho*, 2C), 69.35 ($CO_2\mathbf{C}H(CH_3)CO_2$, 1C), 69.08 ($CO_2\mathbf{C}H(CH_3)CO_2$, 1C), 69.00 ($CO_2\mathbf{C}H(CH_3)CO_2$, 1C), 67.24 ($CO_2\mathbf{C}H_2Ph$, 1C), 66.73 ($HO\mathbf{C}H(CH_3)CO_2$, 1C), 20.48 ($HOCH(\mathbf{C}H_3)CO$, 1C), 16.77 ($CO_2CH(\mathbf{C}H_3)CO_2$, 2C), 16.62 ($CO_2CH(\mathbf{C}H_3)CO_2$, 1C). Mass spec for $C_{19}H_{24}O_9$ calculated: 419.14; Found $(M+Na)^+$: 419.13.

Octamer, 16

The doubly protected octamer, **16**, was prepared using the general procedure described above for coupling, from the tetramers, **14** and **15**. The crude product was purified via gradient flash column chromatography (eluting with 4:1 hexane:ethyl acetate gradually increasing to 1:1

hexane:ethyl acetate) to give **16** as a colorless sticky oil (92% yield).

^{1}H NMR ($CDCl_3$): δ 7.33 (b, Ar, 5H), 5.17 (m, $CH(CH_3)CO_2[CH(CH_3)CO_2]_7CH_2Ph$, 9H), 4.38 (q, J = 6.8 Hz, $SiOCH(CH_3)CO$, 1H), 1.55 (m, $CH(CH_3)CO_2$, 24H), 0.90 (s, $(CH_3)_3CSi$, 9H), 0.10 (s, $(CH_3)_2Si$, 3H), 0.08 (s, $(CH_3)_2Si$, 3H). ^{13}C NMR ($CDCl_3$): δ 173.69 (CO_2C, 1C), 170.16 (CO_2C, 2C), 170.06 (CO_2C, 1C), 169.89 (CO_2C, 1C), 169.81 (CO_2C, 1C), 169.77 (CO_2C, 2C), 169.70 (CO_2C, 1C), 135.26 (Ar, CH_2AC, 1C), 128.80 (Ar-*meta*, 2C), 128.70 (Ar-*para*, 1C), 128.42 (Ar-*ortho*, 2C), 69.45 ($CO_2CH(CH_3)CO_2$, 1C), 69.17 ($CO_2CH(CH_3)CO_2$, 4C), 68.98 ($CO_2CH(CH_3)CO_2$, 1C), 68.71 ($CO_2CH(CH_3)CO_2$, 1C), 68.17 ($SiOCH(CH_3)CO_2$, 1C), 67.38 (CO_2CH_2Ph, 1C), 25.87 ($(CH_3)_3CSi$, 3C), 21.39 ($SiOCH(CH_3)CO$, 1C), 18.44 ($(CH_3)_3CSi$, 1C), 16.92 ($CO_2CH(CH_3)CO_2$, 2C), 16.81 ($CO_2CH(CH_3)CO_2$, 4C), 16.74 ($CO_2CH(CH_3)CO_2$, 1C), −4.74 ($(CH_3)_2Si$, 1C), −5.12 ($(CH_3)_2Si$, 1C). Mass spec for $C_{37}H_{54}O_{17}Si$ calculated: 821.30; Found $(M+Na)^+$: 821.30.

Octamer-CO_2H, 17

The monoprotected, acid-functionalized octamer-CO_2H, **17**, was prepared using the general procedure described earlier for deprotection of benzyl esters (hydrogenation), starting from the octamer, **16**. The crude product was purified via gradient flash column chromatography (eluting with 1:1 hexane:ethyl acetate gradually increasing to 2:1 ethyl acetate:MeOH) to give **17** as a colorless sticky oil (94% yield).

^{1}H NMR ($CDCl_3$): δ 6.20 (b, CO_2H, 1H), 5.15 (m, $CH(CH_3)CO_2[CH(CH_3)CO_2]_7H$, 7H), 4.39 (q, J = 6.8 Hz, $SiOCH(CH_3)CO$, 1H), 1.50 (m, $SiO[CH(CH_3)CO_2]_8H$, 24H), 0.89 (s, $(CH_3)_3CSi$, 9H), 0.10 (s, $(CH_3)_2Si$, 3H), 0.07 (s, $(CH_3)_2Si$, 3H). ^{13}C NMR ($CDCl_3$): δ 173.85–169.82 (CO_2, 8C), 69.13–68.73 ($CO_2CH(CH_3)CO_2$, 7C), 68.19 ($SiOCH(CH_3)CO_2$, 1C), 25.89 ($(CH_3)_3CSi$, 3C), 21.41 ($SiOCH(CH_3)CO$, 1C), 18.47 ($(CH_3)_3CSi$, 1C), 16.93–16.83 ($CO_2CH(CH_3)CO_2$, 7C), −4.72 ($(CH_3)_2Si$, 1C), −5.10 ($(CH_3)_2Si$, 1C). Mass spec for $C_{30}H_{48}O_{17}Si$ calculated: 731.26; Found $(M+Na)^+$: 731.25.

Octamer-OH, 18

The monoprotected, hydroxyl-functionalized Octamer-OH, **18**, was prepared using the general procedure described earlier for deprotection of TBDMS groups (desilylation), starting from the octamer, **16**. The crude product was purified via flash column chromatography using 1:1 hexane:ethyl acetate as eluent to give **18** as a white solid (88% yield).

^{1}H NMR ($CDCl_3$): δ 7.33 (m, Ar, 5H), 5.18 (m, $CH(CH_3)CO_2[CH(CH_3)CO_2]_7CH_2Ph$, 9H), 4.33 (m, $SiOCH(CH_3)CO$, 1H), 2.78 (b, OH, 1H), 1.50 (m, $CH(CH_3)CO_2$, 24H). ^{13}C NMR ($CDCl_3$): δ 175.27–169.70 (CO_2, 8C), 135.25 (Ar, CH_2-C, 1C), 128.79 (Ar-*meta*, 2C), 128.69 (Ar-*para*, 1C), 128.41 (Ar-*ortho*, 2C), 69.45-69.19 ($CO_2CH(CH_3)CO_2$, 7C), 67.38 (CO_2CH_2Ph, 1C), 66.86 ($HOCH(CH_3)CO_2$, 1C), 20.67 ($HOCH(CH_3)CO$, 1C), 16.90–16.73 ($CO_2CH(CH_3)CO_2$, 7C). Mass spec for $C_{31}H_{40}O_{17}$ calculated: 707.22; Found $(M+Na)^+$: 707.22.

16mer, 19

The doubly protected 16mer, **19**, was prepared using the general procedure described earlier for coupling, from the octamers, **17** and **18**. The crude product was purified via gradient flash column chromatography (eluting with 4:1 hexane:ethyl acetate gradually increasing to ethyl acetate) followed by precipitation from CH_2Cl_2 into hexane to give **19** as a white solid (77% yield).

^{1}H NMR ($CDCl_3$): δ 7.34 (b, Ar, 5H), 5.17 (m, $CH(CH_3)CO_2[CH(CH_3)CO_2]_{15}CH_2Ph$, 17H), 4.38 (q, J = 6.8 Hz, $SiOCH(CH_3)CO$, 1H), 1.54 (m, $CH(CH_3)CO_2$, 48H), 0.90 (s, $(CH_3)_3CSi$, 9H), 0.10 (s, $(CH_3)_2Si$, 3H), 0.08 (s, $(CH_3)_2Si$, 3H). ^{13}C NMR ($CDCl_3$): δ 173.73–169.80 (CO_2, 16C), 135.27 (Ar, CH_2AC, 1C), 128.82 (Ar-*meta*, 2C), 128.74 (Ar-*para*, 1C), 128.45 (Ar-*ortho*, 2C), 69.48–68.74 ($CO_2CH(CH_3)CO_2$, 15C), 68.20 ($SiOCH(CH_3)CO_2$, 1C), 67.42 (CO_2CH_2Ph, 1C), 25.89 ($(CH_3)_3CSi$, 3C), 21.42 ($SiOCH(CH_3)CO$, 1C), 18.47 ($(CH_3)_3CSi$, 1C), 16.84 ($CO_2CH(CH_3)CO_2$, 15C), −4.71 ($(CH_3)_2Si$, 1C), −5.12 ($(CH_3)_2Si$, 1C). Mass spec for $C_{61}H_{86}O_{33}Si$ calculated: 1397.47; Found $(M+Na)^+$: 1397.45.

16mer-CO_2H, 20

The monoprotected, acid-functionalized 16mer-CO_2H, **20**, was prepared using the general procedure described above for deprotection of benzyl esters (hydrogenation), starting from the 16mer, **19**. The crude product was purified via gradient flash column chromatography (eluting with 1:1 hexane:ethyl acetate gradually increasing to 2:1

ethyl acetate:MeOH) to give **20** as a colorless solid (98% yield).

^{1}H NMR ($CDCl_3$): δ 5.14 (m, $CH(CH_3)CO_2[CH(CH_3)CO_2]_{15}H$, 15H), 4.92 (b, CO_2H, 1H), 4.38 (q, J = 6.8 Hz, $SiOCH(CH_3)CO$, 1H), 1.52 (m, $SiO[CH(CH_3)CO_2]_{16}H$, 48H), 0.89 (s, $(CH_3)_3CSi$, 9H), 0.09 (s, $(CH_3)_2Si$, 3H), 0.07 (s, $(CH_3)_2Si$, 3H). ^{13}C NMR ($CDCl_3$): δ 173.71–169.79 (CO_2, 16C), 69.69–68.71 ($CO_2CH(CH_3)CO_2$, 15C), 68.17 ($SiOCH(CH_3)CO_2$, 1C), 25.86 ($(CH_3)_3CSi$, 3C), 21.38 ($SiOCH(CH_3)CO$, 1C), 18.44 ($(CH_3)_3CSi$, 1C), 16.91–16.81 ($CO_2CH(CH_3)CO_2$, 15C), −4.75 ($(CH_3)_2Si$, 1C), −5.13 ($(CH_3)_2Si$, 1C). Mass spec for $C_{54}H_{80}O_{33}Si$ calculated: 1307.43; Found $(M+Na)^+$: 1307.43.

16mer-OH, 21

The monoprotected, hydroxyl-functionalized 16mer-OH, **21**, was prepared using the general procedure described above for deprotection of TBDMS groups (desilylation), starting from 16mer, **19**. The crude product was purified via flash column chromatography using 1:1 hexane:ethyl acetate as eluent yielding **21** as a colorless sticky oil (87% yield).

^{1}H NMR ($CDCl_3$): δ 7.33 (m, Ar, 5H), 5.17 (m, $CH(CH_3)CO_2[CH(CH_3)CO_2]_{15}CH_2Ph$, 17H), 4.34 (m, $SiOCH(CH_3)CO$, 1H), 2.74 (b, OH, 1H), 1.55 (m, $CH(CH_3)CO_2$, 48H). ^{13}C NMR ($CDCl_3$): δ 175.28–169.70 (CO_2, 16C), 135.25 (Ar, CH_2AC, 1C), 128.80 (Ar-*meta*, 2C), 128.70 (Ar-*para*, 1C), 128.42 (Ar-*ortho*, 2C), 69.46–69.19 ($CO_2CH(CH_3)CO_2$, 15C), 67.39 (CO_2CH_2Ph, 1C), 66.87 ($HOCH(CH_3)CO_2$, 1C), 20.68 ($HOCH(CH_3)CO$, 1C), 16.91–16.81 ($CO_2CH(CH_3)CO_2$, 15C). Mass spec for $C_{55}H_{72}O_{33}$ calculated: 1283.42; found $(M+Na)^+$: 1283.41.

32mer, 22

The doubly protected 32mer, **22**, was prepared using the general procedure described above for coupling, from the 16mers, **20** and **21**, with the modification that instead of DCC, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) was used (1.3 eq. to **21**). The crude product was purified via gradient flash column chromatography (eluting with 10:1 CH_2Cl_2:ethyl acetate gradually increasing to 5:1 CH_2Cl_2:ethyl acetate) to give **22** as a white solid (74% yield).

^{1}H NMR ($CDCl_3$): δ 7.34 (b, Ar, 5H), 5.15 (m, $CH(CH_3)CO_2[CH(CH_3)CO_2]_{31}CH_2Ph$, 33H), 4.39 (q, J = 6.8 Hz, $SiOCH(CH_3)CO$, 1H), 1.57 (m, $CH(CH_3)CO_2$, 96H), 0.90 (s, $(CH_3)_3CSi$, 9H), 0.10 (s, $(CH_3)_2Si$, 3H), 0.08 (s, $(CH_3)_2Si$, 3H). ^{13}C NMR ($CDCl_3$): δ 173.72–169.79 (CO_2, 32C), 135.26 (Ar, CH_2-C, 1C), 128.81 (Ar-*meta*, 2C), 128.72 (Ar-*para*, 1C), 128.44 (Ar-*ortho*, 2C), 69.47–68.72 ($CO_2CH(CH_3)CO_2$, 31C), 68.19 ($SiOCH(CH_3)CO_2$, 1C), 67.41 (CO_2CH_2Ph, 1C), 25.88 ($(CH_3)_3CSi$, 3C), 21.40 ($SiOCH(CH_3)CO$, 1C), 18.46 ($(CH_3)_3CSi$, 1C), 16.93–16.83 ($CO_2CH(CH_3)CO_2$, 31C), −4.71 ($(CH_3)_2Si$, 1C), −5.12 ($(CH_3)_2Si$, 1C). Mass spec for $C_{109}H_{150}O_{65}Si$ calculated: 2572.80; Found $(M + 2Na)^{+2}$: 1286.89. $[\alpha]^{23}_D = -140^\circ$ (c = 1.09 cg/mL $CHCl_3$).

32mer-CO_2H, 23

The monoprotected, acid-functionalized 32mer-CO_2H, **23**, was prepared using the general procedure described earlier for deprotection of benzyl esters (hydrogenation), starting from 32mer, **22**, and gave **23** as a white solid without any further purification (96% yield).

^{1}H NMR ($CDCl_3$): δ 5.50 (b, CO_2H, 1H), 5.14 (q, J = 7.0 Hz, $CH(CH_3)CO_2[CH(CH_3)CO_2]_{31}H$, 31H), 4.38 (q, J = 6.8 Hz, $SiOCH(CH_3)CO$, 1H), 1.52 (m, $SiO[CH(CH_3)CO_2]_{32}H$, 96H), 0.89 (s, $(CH_3)_3CSi$, 9H), 0.09 (s, $(CH_3)_2Si$, 3H), 0.07 (s, $(CH_3)_2Si$, 3H). ^{13}C NMR ($CDCl_3$): δ 174.10–169.68 (CO_2, 32C), 69.19–68.73 ($CO_2CH(CH_3)CO_2$, 31C), 68.18 ($SiOCH(CH_3)CO_2$, 1C), 25.87 ($(CH_3)_3CSi$, 3C), 21.38 ($SiOCH(CH_3)CO$, 1C), 18.44 ($(CH_3)_3CSi$, 1C), 16.81 ($CO_2CH(CH_3)CO_2$, 15C), −4.74 ($(CH_3)_2Si$, 1C), −5.13 ($(CH_3)_2Si$, 1C). Mass spec for $C_{102}H_{144}O_{65}Si$ calculated: 2459.76; Found $(M+Na)^+$: 2459.65.

32mer-OH, 24

The monoprotected, hydroxyl-functionalized 32mer-OH, **24**, was prepared using the general procedure described earlier for deprotection of TBDMS groups (desilylation), starting from 32mer, **22**. The crude product was purified via gradient flash column chromatography eluting with 5:1 CH_2Cl_2:ethyl acetate gradually increasing to 2:1 CH_2Cl_2:ethyl acetate) to give **24** as a white solid (75% yield).

^{1}H NMR ($CDCl_3$): δ 7.33 (m, Ar, 5H), 5.18 (m, $CH(CH_3)CO_2[CH(CH_3)CO_2]_{31}CH_2Ph$, 17H), 4.34 (m, $SiOCH(CH_3)CO$, 1H), 2.71 (b, OH, 1H), 1.56 (m, $CH(CH_3)CO_2$, 96H). ^{13}C NMR ($CDCl_3$): δ 175.29–169.71 (CO_2, 32C), 135.25 (Ar, CH_2AC,

1C), 128.80 (Ar-*meta*, 2C), 128.71 (Ar-*para*, 1C), 128.43 (Ar-*ortho*, 2C), 69.45–69.19 (CO_2**C**H(CH_3)CO_2, 31C), 67.39 (CO_2**C**H_2Ph, 1C), 66.87 (HO**C**H(CH_3)CO_2, 1C), 20.69 (HOCH(**C**H_3)CO, 1C), 16.92–16.82 (CO_2CH(**C**H_3)CO_2, 31C). Mass spec for $C_{103}H_{136}O_{65}$ calculated: 2413.72; Found $(M+H)^+$: 2413.63.

64mer, 25

The doubly protected 64mer, **25**, was prepared using the general procedure described above for coupling, from the 32mers, **23** and **24**, with the modification that instead of DCC, EDCI was used (1.3 eq. to **24**). The crude product was purified via flash column chromatography eluting with 5:1 CH_2Cl_2:ethyl acetate to give **25** as a white solid (70% yield).

^{1}H NMR ($CDCl_3$): δ 7.34 (b, Ar, 5H), 5.15 (m, CH(CH_3)CO_2[C**H**(CH_3)CO_2]$_{63}$C**H**$_2$Ph, 65H), 4.39 (q, J = 6.8 Hz, SiOC**H**(CH_3)CO, 1H), 1.55 (m, CH(C**H**$_3$)CO_2, 192H), 0.89 (s, (C**H**$_3$)$_3$CSi, 9H), 0.10 (s, (C**H**$_3$)$_2$Si, 3H), 0.08 (s, (C**H**$_3$)$_2$Si, 3H). ^{13}C NMR ($CDCl_3$): δ 173.74–169.79 (**C**O_2, 64C), 135.26 (Ar, CH_2*A***C**, 1C), 128.81 (Ar-*meta*, 2C), 128.73 (Ar-*para*, 1C), 128.44 (Ar-*ortho*, 2C), 69.47-68.73 (CO_2**C**H(CH_3)CO_2, 63C), 68.19 (SiO**C**H(CH_3)CO_2, 1C), 67.41 (CO_2**C**H_2Ph, 1C), 25.88 ((**C**H_3)$_3$CSi, 3C), 21.40 (SiOCH(**C**H_3)CO, 1C), 18.46 ((CH_3)$_3$**C**Si, 1C), 16.83 (CO_2CH(**C**H_3)CO_2, 63C), −4.72 ((**C**H_3)$_2$Si, 1C), −5.12 ((**C**H_3)$_2$Si, 1C). Mass spec for $C_{205}H_{278}O_{129}Si$ calculated: 4877.48; Found $(M + 2Na)^{+2}$: 2438.68.

16mer-OH-CO_2H, 26

The doubly deprotected, acid-hydroxyl-functionalized 16mer-OH-CO_2H, **26**, was prepared using the general procedure described above for deprotection of benzyl esters (hydrogenation), starting from 16mer-OH, **21**. 16mer-OH-CO_2H, **26**, was obtained as a colorless solid without any further purification (99% yield).

^{1}H NMR ($CDCl_3$): δ 5.15 (m, CH(CH_3)CO_2[C**H**(CH_3)CO_2]$_{15}$H, 15H), 4.41 (b, O**H**, 2H), 4.37 (q, J = 6.9 Hz, HOC**H**(CH_3)CO, 1H), 1.54 (m, HO[CH(C**H**$_3$)CO_2]$_{16}$H, 48H). ^{13}C NMR ($CDCl_3$): δ 175.34–169.73 (**C**O_2, 16C), 69.22–68.98 (CO_2**C**H(CH_3)CO_2, 15C), 66.92 (HO**C**H(CH_3)CO_2, 1C), 20.66 (HOCH(**C**H_3)CO, 1C), 16.83 (CO_2CH(**C**H_3)CO_2, 15C). Mass spec for $C_{48}H_{66}O_{33}$ calculated: 1193.34; Found $(M+Na)^+$: 1193.33.

32mer-OH-CO_2H, 27

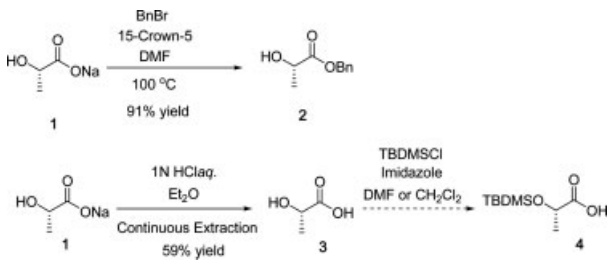
The doubly deprotected, acid-hydroxyl-functionalized 32mer-OH-CO_2H, **27**, was prepared using the general procedure described above for deprotection of benzyl esters (hydrogenation), starting from 32mer-OH, **24**. 32mer-OH-CO_2H, **27**, was obtained as a white solid without any further purification (100% yield).

^{1}H NMR ($CDCl_3$): δ 5.15 (m, CH(CH_3)CO_2[C**H**(CH_3)CO_2]$_{31}$H, 31H), 4.70 (b, O**H**, 2H), 4.37 (q, J = 7.0 Hz, HOC**H**(CH_3)CO, 1H), 1.56 (m, HO[CH(C**H**$_3$)CO_2]$_{32}$H, 96H). ^{13}C NMR ($CDCl_3$): δ 175.26–169.69 (**C**O_2, 32C), 69.17 (CO_2**C**H(CH_3)CO_2, 31C), 66.86 (HO**C**H(CH_3)CO_2, 1C), 20.61 (HOCH(**C**H_3)CO, 1C), 16.78 (CO_2CH(**C**H_3)CO_2, 31C). Mass spec for $C_{96}H_{130}O_{65}$ calculated: 2368.67; Found $(M + 2Na)^{+2}$: 1184.35.

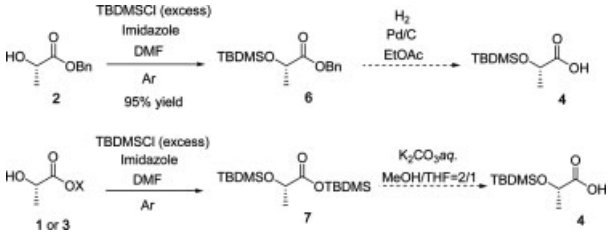
RESULTS AND DISCUSSION

The key intermediate in the synthesis of poly(lactide) oligomers is a double protected dimer which allows orthogonal deprotection to give monofunctional dimers that can be coupled to afford the tetramer. In selecting protecting groups for the hydroxyl and carboxy groups the proven orthogonality of *t*-butyldimethylsilyl (TBDMS) ethers as the protecting group for the hydroxyl group and benzyl (Bn) esters for the carboxylic acid group strongly suggest the dimer, **5**, as target material. Starting from the commercially available sodium lactate, initial attempts to synthesize the dimer, **5**, entailed preparation of the monofunctional monomers, **2** and **4**, followed by coupling (Scheme 1).

Although the synthesis of **2** proved facile, all attempts to prepare the TBDMS protected acid, **4**, were complicated by either low yields or inefficient purification strategies. For example, direct etherification of **3** gave low yields of **4** (Scheme 1)



Scheme 1. Synthesis of benzyl ester, **2**, and attempted synthesis of acid, **4**.



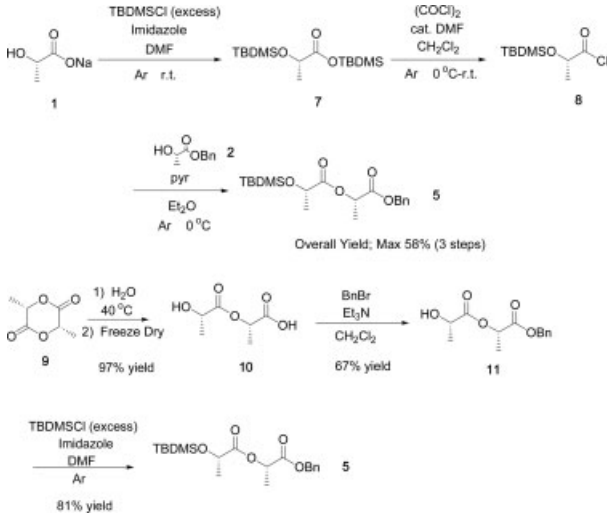
Scheme 2. Alternate unsuccessful strategies to **4**.

while debenzylation of the doubly protected monomer, **6**, or hydrolysis of the bis(TBDMS) derivative, **7**, resulted in decomposition and complex reaction mixtures (Scheme 2).

Alternatively the silyl ester, **7**, could be converted to the acyl halide followed by coupling with the hydroxy benzyl ester, **2**, to afford **5**, however the difficulty in preparing **8** and purifying **5** via this strategy were still problematic. Realizing the potential difficulty in preparing the desired TBDMS-protected lactic acid derivative, **4**, alternate strategies were developed starting from the cyclic lactide, **9**.[12] Initial hydrolysis of **9** was found to be selective[12] giving rise to the dimeric acid-alcohol, **10**, which could then be esterified with benzyl bromide followed by reaction with TBDMSCl to give **5** in high overall yields (Scheme 3).

From the dimer, **5**, orthogonal deprotection of the benzyl ester group to give the carboxylic acid, **12**, proved to be a quantitative reaction while the reaction of **5** with tetra-*n*-butyl ammonium fluoride resulted in a high yield of the desired ester-alcohol, **11**. Coupling of the orthogonally protected dimers, **11** and **12** in the presence of DCC and DPTS proved to be a high yielding procedure affording the tetramer, **13,** with minimal side products (Scheme 4).

From the tetramer, **13**, the coupling and respective deprotection reactions were reproducible

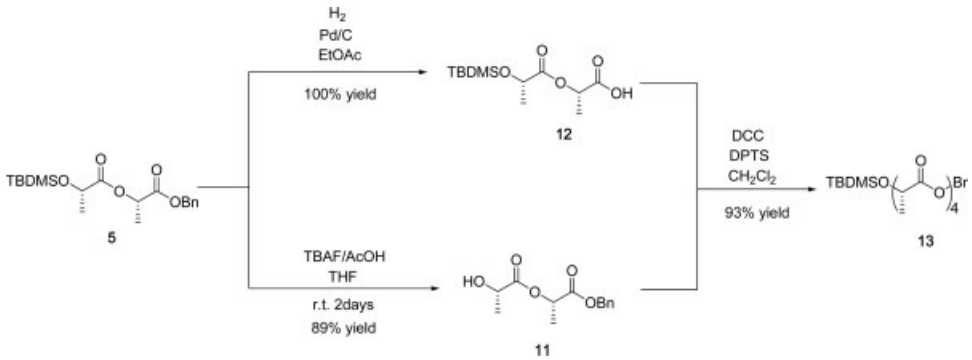


Scheme 3. Synthetic routes to the doubly protected dimer, **5**.

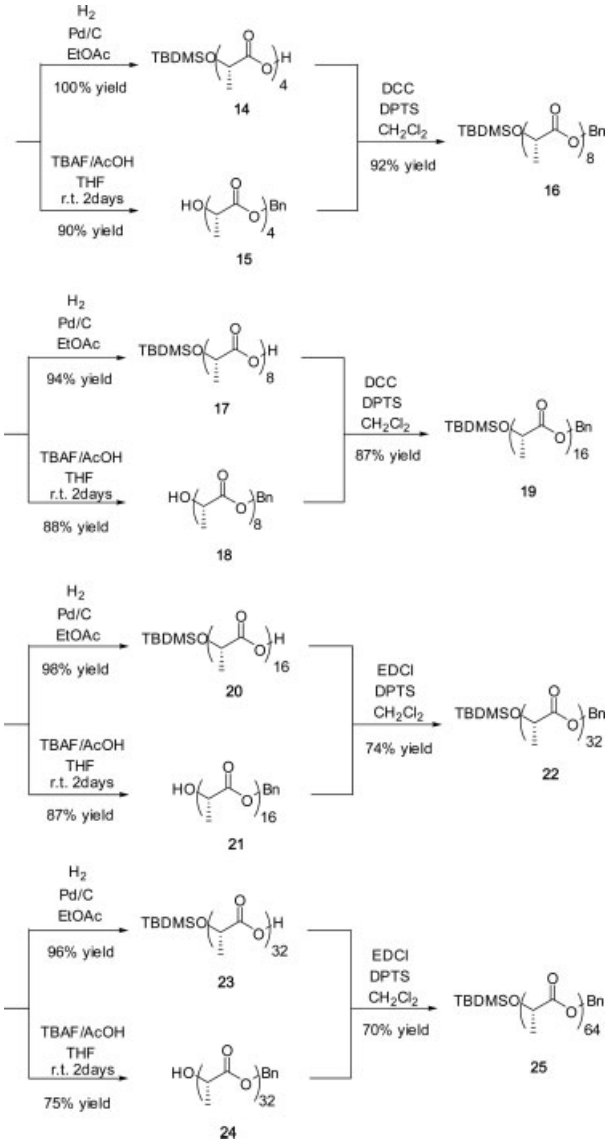
and resulted in high yields (over 90% yields for deprotection and 70–95% yields for coupling reactions) with DCC being used as the coupling reagent up to 16mer and EDCI for the higher molecular weight oligomers, 32mer, **22**, and 64mer, **25**, because of the difficulty in removing small amounts of the DCC adducts formed during the coupling procedure (Scheme 5). Significantly, the efficient nature of this synthetic strategy coupled with the orthogonality of the protecting groups allowed gram quantities of **22** and **25** to be prepared with Figure 1 showing the 64mer, **25**, which has a molecular weight of 4834 and molecular formulae of $C_{205}H_{278}O_{129}Si$.

Characterization

Given the wide applicability of these materials in fundamental structure/property studies in both biomaterial engineering and polymer physics, it



Scheme 4. Formation of the tetramer, **13**, from the orthogonally protected dimer, **5**.



Scheme 5. Synthetic strategy for well-defined oligomers of (L)-lactic acid up to the 64mer, **25**.

was critical to fully characterize and determine the purity of these materials. On the basis of the synthetic approach described above for the preparation of well-defined lactide oligomers, the purity and molecular weight profile of all the oligomers were examined using a combination of ^{1}H, ^{13}C NMR, mass spectroscopy (ESI^{+}/TOF) combined with matrix assisted laser desorption/ionization (MALDI) and SEC. As shown in Figure 2, SEC results for the doubly protected monomer, **6**, through 64mer, **25**, reveal low polydispersity, monomodal peaks for all of the oligomers prepared with the polystyrene equivalent molecular weight for the 64mer (9100 a.m.u.) being significantly higher than the actual molecular weight (4834 a.m.u.) which is fully consistent with poly (lactide) systems. The absence of lower molecular weight impurities, unreacted starting materials, side products, and so forth, also demonstrated the efficiency of the synthetic strategy.

Confirmation of the molecular weights and associated purity of the lactide oligomers was investigated by both electrospray as well as MALDI mass spectrometry. In all cases, molecular ions for the desired oligomeric species were observed with only minor amounts of contamination from failure sequences or chain end impurities. For example, the MALDI mass spectra for the series of lactide oligomers from the tetramer, **13**, to 64mer, **25**, is shown in Figure 3 and reveals prominent molecular ions corresponding to the desired oligomers with minor amounts of failure sequences being observed for the 16mer, 32mer, and 64mer. In the latter case, molecular ions for oligomers corresponding to the 63mer, 62mer, and 61mer, and so forth, were observed with intensity levels similar to that obtained for the convergent synthesis of dendritic macromolecules.[13]

Further, structural characterization was provided by ^{1}H and ^{13}C NMR spectroscopy which allowed the stepwise growth of the oligomeric series to be accurately followed because of unique resonances for both chain ends and backbone repeat units. ^{1}H NMR spectra of the doubly protected oligomers showed unique resonances for the single benzyl ester chain end at 7.3 ppm and the single TBDMS group at the other chain end is similarly clearly distinguishable at 0.0 and 0.85 ppm. Integration of these resonances and comparison with the integration values for the lactide backbone allowed the number of repeat units to be determined and all cases was shown to agree with that expected from the synthetic strategy. The orthogonality of the deprotection reactions could also be easily followed because of the loss of these respective peaks after removal. Similar trends were observed in the ^{13}C NMR spectra and further aided structural identification of these materials.

The presence of the optically active, CH-unit along the backbone of the oligomers also gives rise to unique resonances which provide insight into possible racemization of the oligomers during synthesis, a side reaction that has been observed with DCC during peptide synthesis.[14] Examination of a series of homonuclear decoupled ^{1}H NMR spectra for each oligomer and comparison with previous reports,[15] showed that all

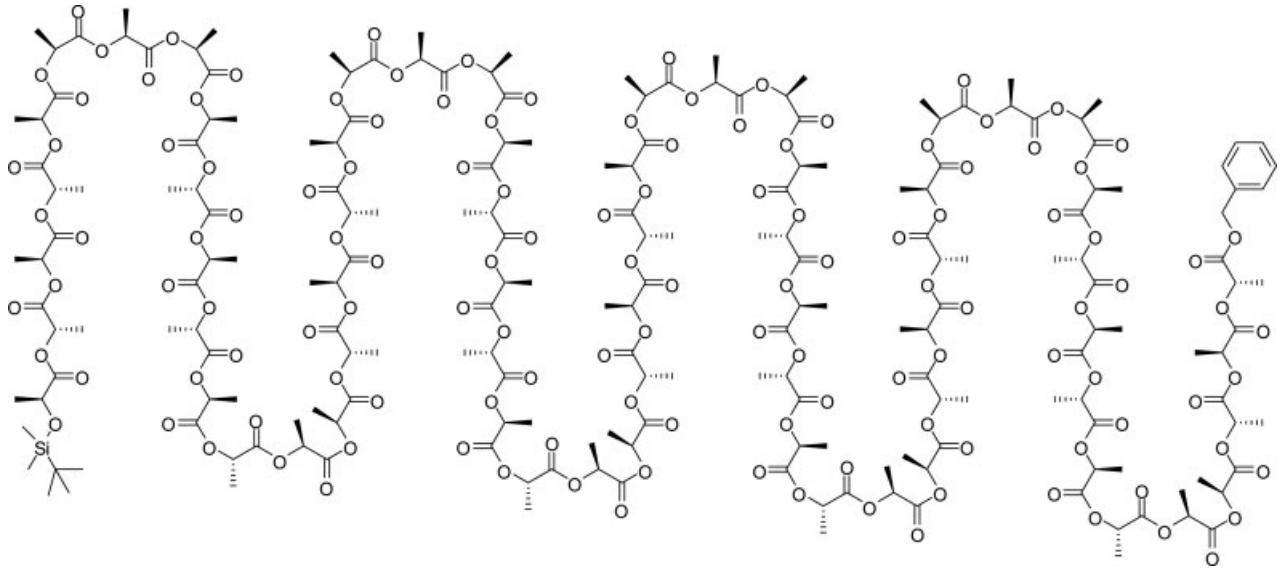


Figure 1. Chemical structure of (L)-lactic acid 64mer, **25**, (Molecular Formula: $C_{205}H_{278}O_{129}Si$, $M_w = 4834.41$).

stereoconfigurations were retained during the coupling reactions. For example, the higher molecular oligomer 32mer-CO_2H, **23**, showed only a sharp singlet for the nonchain end repeat units confirming the stereogenic sequence of -*SSSS*- derived from the starting (L)-lactide monomer. This retention of stereochemistry was confirmed by single crystal diffraction and associated structural determination of the tetramer, **13**, which clearly shows that no racemization has occurred and all *S* configurations were retained during the multistep synthetic pathway (Figure 4). This result is further supported by circular dichroism measurements and optical rotation values which showed a value of -140° for the 32mer, **22**, compared to -28° for the monomer.

The availability of molecularly discrete oligomers of poly(lactide) permits a systematic study of the influence of molecular weight and chain end structure on the physical properties of this scientifically and commercially important semicrystalline polymer. Such a study would complement our recently reported examination of poly(caprolactone)[5] and further add to the knowledge of molecular weight effects for other semicrystalline polymers such as polyethylene.[16] To investigate these unique series of materials, SAXS measurements were conducted on a library of well-defined oligomers at room temperature. As can be seen in Figure 5, the effect of oligomer size leads to significant differences in the intermediate-SAXS profile which were mirrored in corresponding ultra-

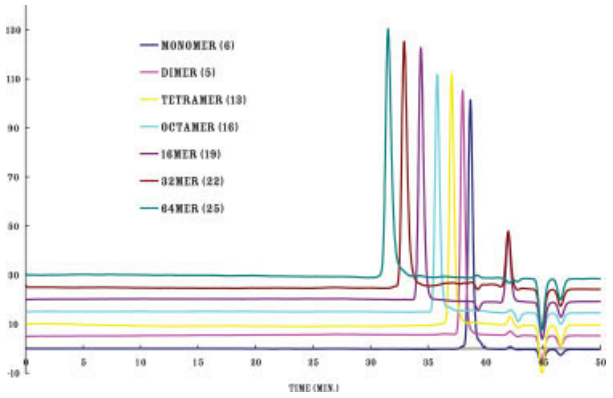


Figure 2. Composite SEC traces for (L)-lactide oligomers from the monomer, **6**, to the 64mer, **25**.

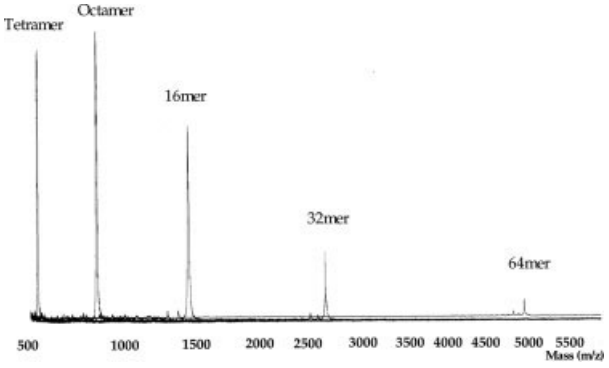


Figure 3. MALDI mass spectra for (L)-lactide oligomers from tetramer, **13**, to 64mer, **25** (Matrix; Dithranol, Cation reagent; Sodium trifluoroacetate).

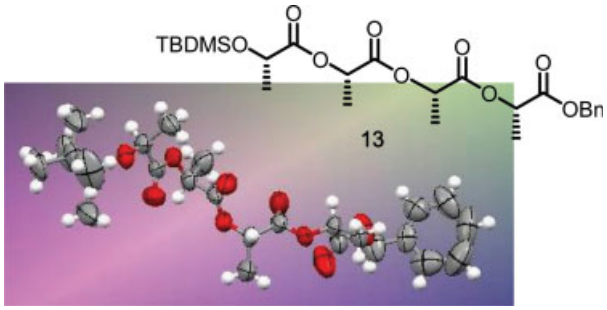


Figure 4. Structure of tetramer, **13**, as determined by single crystal diffraction.

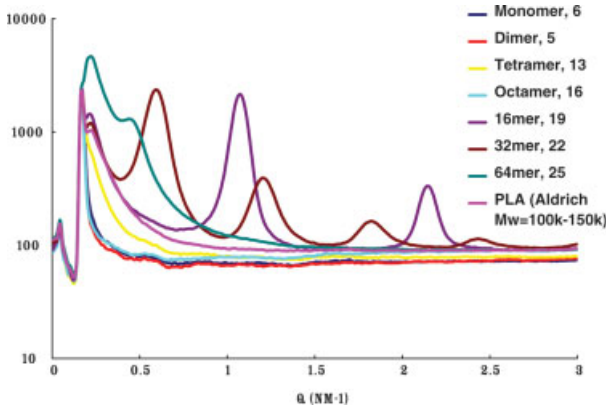


Figure 5. Intermediate-SAXS data for well-defined (L)-lactide oligomers from the monomer, **6**, to the 64mer, **25**. Commercially available and polydisperse poly(L)-lactide is shown for comparison.

SAXS and WAXS measurement results. Analysis of this data confirms a lamellae structure is observed for the 16mer, **19**, through 64mer, **25**, with the lamellae thickness (D) being very close to the theoretical molecular lengths in the case of the 16mer, **19**, and 32mer, **22**. This indicates that the molecules are extended in the lamellae structures which correlate with the observation of oligomer length corresponding with lamellae thickness for the octamer and 16mer caprolactone derivatives. Significantly, the 64mer, **25**, showed a lamellae thickness (14 nm) approximately half that expected for the molecular length (23 nm) which suggests that the chains are folded in the crystal structure. Interestingly, no significant change in lamellae thickness was observed when the protecting groups at the chain ends of the oligomers were removed, though the percent crystallinity decreased for the hydroxyl and acid-terminated materials.

The crystalline nature and thermal properties of the lactide oligomers was also studied by DSC and TGA. Figure 6 shows the DSC traces for the 16mer, **19**, 32mer, **22**, and 64mer, **25**, compared to a high molecular weight PLA sample. As expected, the oligomers show well-defined melting transitions that increase from 92 °C to 164 °C on going from the 16mer to the 64mer and have a degree of fine structure which correlates with the previously reported higher order results for polydisperse lactic acid oligomers and polymers.[17] Interestingly, the effect of the chain end groups

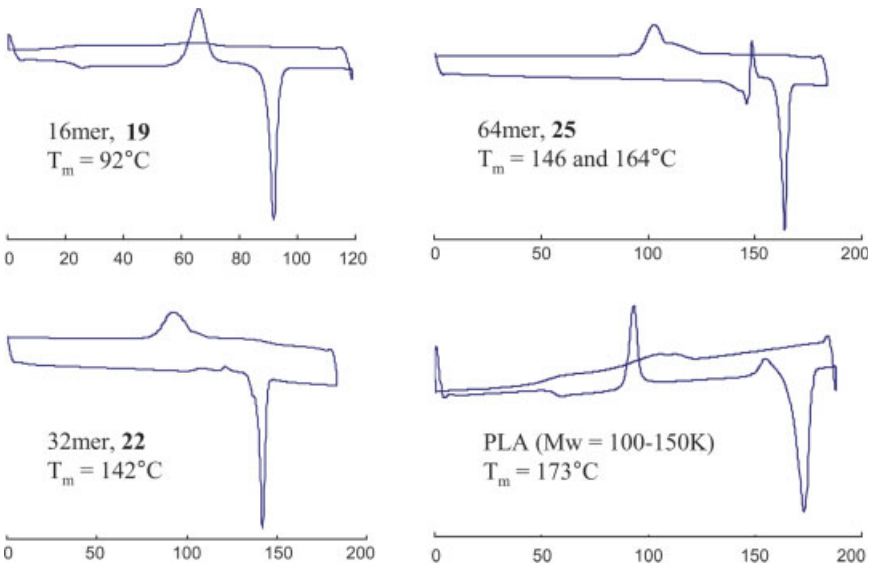


Figure 6. DSC traces for the well-defined (L)-lactide oligomers, 16mer, **19**, 32mer, **22**, and 64mer, **25**, compared with a commercially available high molecular weight PLA sample.

was minimal with little, if any, difference in melting temperature observed with variation in the chain ends. For example, the doubly protected 32mer, **22**, was observed to have a T_m of 142 °C, while the 32mer-CO_2H, **23**, 32mer-OH, **24**, and fully deprotected 32mer-OH-CO_2H, **27**, possessed T_ms of 138 °C, 139 °C, and 140 °C, respectively.

The strong correlation between oligomer length and melting transitions prompted an examination of the effect of structure on thermal decomposition profiles. As previously observed for well-defined caprolactone derivatives,[5] the thermal stability of the lactide series was very dependent on both chain length as well as chain end functionality with dramatic differences also being observed when the oligomers were compared to commercially available poly(lactide) samples. Analysis of the decomposition of the lactide oligomers with increasing molecular weight showed a systematic increase in thermal stability from Monomer, **6**, and Dimer, **5**, which begin to decompose at ~ 100 °C through to Octamer, **16**, having a decomposition profile very similar to that of the commercial, high molecular PLA material (250 °C). Interestingly, the 16mer, 32mer, and 64mer all showed similar decomposition profiles and were significantly more stable than the commercial sample with decomposition occurring above 300 °C (Fig. 7).

The effect of chain end functionality on thermal decomposition was then studied for the 32mer series with all of the 32mer samples, irrespective of the end groups, showing increased stability when compared with the commercial Poly(lactide) (Fig. 8). Interestingly, the 32mer with the lowest thermal stability was the monohydroxyl, benzyl ester terminated derivative, **24**, followed by the doubly deprotected, hydroxyl-carboxylic acid 32mer, **27**. From these results, it is apparent that the presence of a hydroxyl chain end leads to decreased thermal stability, presumably because of the occurrence of chain backbiting and associated depolymerization which is similar to that observed for the well-defined caprolactone oligomers. The derivative with the highest thermal stability was the doubly protected 32mer, **22**.

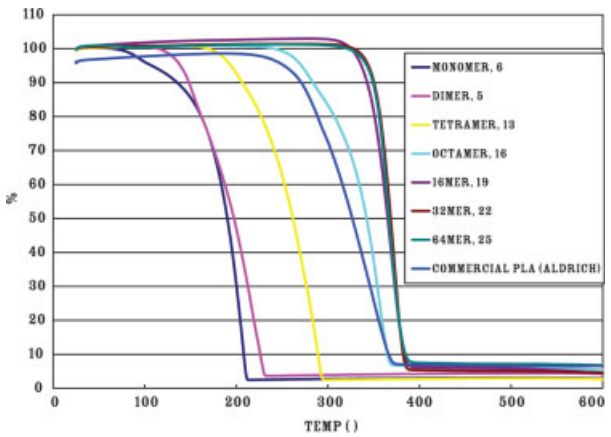


Figure 7. TGA profiles for (L)-lactide oligomers from monomer, **6**, through 64mer, **25**, compared to a commercial PLA sample (M_w = 100,000–150,000 a.m.u.).

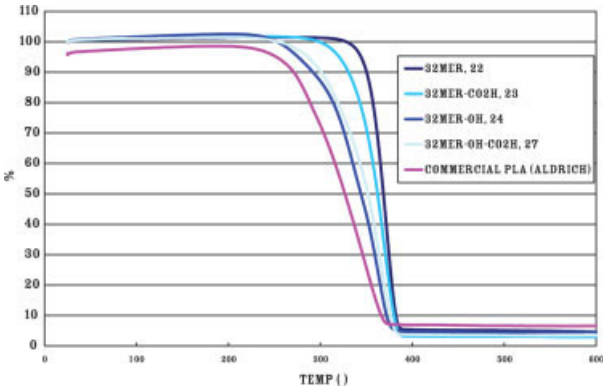


Figure 8. TGA profiles for the series of 32mer oligomers with different end groups, TBDMS and Bn **22**, TBDMS and CO_2H **23**, HO and Bn **24**, and HO and CO_2H **27**, compared to commercial PLA (M_w = 100,000–150,000 a.m.u.).

CONCLUSIONS

A synthetic strategy for the preparation of well-defined (L)-lactic acid oligomers up through 64mer was developed using an iterative divergent-convergent approach. By the selection of orthogonal protective groups, *t*-butyldimethylsilyl ether and benzyl ester, high yields of a library of oligomers were obtained with full retention of stereochemistry. Characterization by a combination of spectroscopic and chromatographic techniques revealed high purity for each oligomer and the absence of significant defect structures. A direct correlation between oligomer length and thermal properties was observed with novel semicrystalline behavior being observed for oligomers above the 16mer. A similar relationship between oligomer length and crystallinity was observed by SAXS measurements with lamellae crystals that increased in thickness with oligomer length in cases of the 16mer and 32mer. Interestingly, for the 64mer, chain folding was observed with a unit thickness of approximately half the extended molecular length. Similar structural effects were also found for DSC and TGA results with higher thermal

stability being observed for the well-defined oligomers when compared to commercial PLA materials. The availability of well-defined oligomers of (L)-lactic acid is expected to allow new insights into the fundamental physical and biomaterial properties of this widely studied and commercially important polymer.

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