Selective Organocatalytic Ring-Opening Polymerization: A Versatile Route to Carbohydrate-Functionalized Poly(ϵ-caprolactones)

Per Valdemar Persson,[†] Jessica Schröder,[‡] Kristina Wickholm,[†] Erik Hedenström,[‡] and Tommy Iversen*,[†]

STFI, Swedish Pulp and Paper Research Institute, Box 5604, SE-114 86 Stockholm, Sweden, and Chemistry, Department of Natural and Environmental Sciences, Mid Sweden University, SE-851 70 Sundsvall, Sweden

Received March 4, 2004; Revised Manuscript Received May 27, 2004

ABSTRACT: Cationic catalysis using simple carboxylic acids to combine the ring-opening polymerization of ϵ-caprolactone and the regioselective acylation of carbohydrates has been investigated. L-Lactic acid catalyzed the acylation of methyl β-D-glucopyranoside and sucrose with ϵ-caprolactone in high yield by bulk polymerization at 120 °C. The main products were regioselectively acylated on the primary hydroxyl groups of the carbohydrate end groups. The overall conversion to methyl β-D-glucopyranoside-functionalized poly(ϵ-caprolactone) was more than 90%, M_w 2000 and polydispersity index 1.5, with one major product methyl 6-*O*-poly(ϵ-caprolactone)-β-D-glucopyranoside, in agreement with the corresponding *Candida antarctica* lipase B-catalyzed acylation.

Introduction

Aliphatic polyesters are gaining interest for both biomedical and commodity applications. One such biodegradable polyester, poly(ϵ-caprolactone), is degraded hydrolytically or enzymatically to 6-hydroxyhexanoic acid, a metabolite in the citric acid cycle.[1] Ring-opening polymerization[2−4] of ϵ-caprolactone has been achieved using initiators/catalysts based on aluminum,[5−8] tin,[9−12] titanium,[13] zinc,[14] and rare-earth metals.[15−17] The polymer, whether produced in an organic solvent or in bulk, is generally of high molecular weight and narrow polydispersity. However, metal initiator remnants are often found as end groups of the formed polyester. These traces usually have to be removed before the polymer can be utilized in biomedical or pharmaceutical applications. This limitation has inspired research on ring-opening polymerizations that do not use organometallic promoters or catalysts. In an effort to apply organic catalysis to controlled ring-opening polymerization, Hedrick and co-workers managed to synthesize end group functionalized polyesters using either N-heterocyclic carbenes or phosphines as catalysts.[18,19] Several groups have conducted studies on ϵ-caprolactone polymerization catalyzed by lipases.[20−27] The enzymatic method has several advantages: mild reaction conditions, nontoxic catalysts that can be recycled, and the possibility of controlling end group functionalization with high precision.[21] Cationic polymerization of cyclic esters has been accomplished with protonic acids or Lewis acids.[28] Less research effort has however been expended on cationic ring-opening polymerization in recent years, since high molecular weight polymers have mainly been obtained using anionic and coordination−insertion polymerization.

The synthesis of methyl or ethyl glycopyranoside-functionalized polyesters catalyzed by *Candida antarctica* lipase B (Novozym 435) has previously been reported.[29,30] To highlight the use of small molecule organocatalysts in cationic ring-opening polymerizations, we report the synthesis of terminally carbohydrate-modified poly(ϵ-caprolactones) using L-lactic acid as catalyst. The polymerizations were performed with methyl β-D-glucopyranoside, sucrose, or raffinose as initiator.

Experimental Section

Materials. Acetic anhydride (99.5%), ϵ-caprolactone (98%), dichloromethane (99.6%), L-lactic acid (98%), methyl β-D-glucopyranoside (98%), pyridine (99.8%) (Sigma-Aldrich Sweden AB), raffinose (98%) (Merck AG), and sucrose (99%) (Danisco Sugar AB) were dried either over P_2O_5 in a desiccator or over activated molecular sieves prior to use. Acetonitrile-d_3 (99.8%), 2,6-di-*tert*-butylpyridine (97%), hexanoic acid (99%), methyl trifluoromethanesulfonate (99%), potassium borohydride (98%), propanoic acid (99.5%), trifluoroacetic acid (99%) (Sigma-Aldrich Sweden AB), 6-hydroxyhexanoic acid (95%) (Acros Organics, Belgium), and other solvents (HPLC grade) were used as received.

Characterization. For gel permeation chromatography (GPC) weighed samples (5−10 mg) of the crude reaction mixtures were diluted in tetrahydrofuran to a concentration of 10 mg/mL and filtered through a 0.45 μm PTFE membrane prior to injection into the GPC system (Rheodyne 7125 injector, 20 μL sample loop, a Waters HPLC pump 510, and a Waters 410 differential refractometer). The separation was accomplished at 25 °C in three columns connected in series (50, 100, and 500 Å, bead size 5 μm, Ultrastyragel, Waters). Tetrahydrofuran was used as eluent at a flow rate of 1 mL/min. The GPC system was calibrated using polystyrene standards, 266−34 500 Da (Machery Nagel). For analysis by matrix-assisted laser desorption/ionization time-off-flight mass spectroscopy (MALDI−TOF MS), the diluted GPC sample (10 μL) was mixed with a matrix solution (40 μL, gentisic acid dissolved in equal volumes of methanol and water to 50 mg/mL). This solution (0.5 μL) was applied to the sample probe and inserted in the spectrometer after removal of the solvent under reduced pressure. The analyses were performed employing a Hewlett-Packard G2025A LD-TOF instrument with a linear detector and using 1−5 μJ energy pulses of a UV (337 nm) laser beam. Positive ion spectra representing the sums of 20−50 laser shots were gathered utilizing an extraction voltage of 30 kV and laser power slightly greater than the minimum required for

[†] STFI, Swedish Pulp and Paper Research Institute.
[‡] Mid Sweden University.
* Corresponding author: Tel +46-8-6767000; Fax +46-8-108340; e-mail tommy.iversen@stfi.se.

10.1021/ma049562j CCC: $27.50
Published on Web 07/17/2004

generation of analyte ions. ^{1}H and ^{13}C NMR spectra were obtained with a Bruker Avance DPX 250 spectrometer at 25 °C using acetonitrile-d_3 as solvent and tetramethylsilane as internal reference. Gas chromatography−mass spectroscopy (GC-MS) was performed on a VG 70-250-SE instrument. The GC column was a Varian VF-5MS, 30 m × 0.25 mm, and initial oven temperature 100 °C programmed at 5 °C/min to 300 °C. Peaks were identified on the basis of relative retention time and fragmentation pattern.[32]

Polymerizations. The reactions were performed in dried glass tubes sealed with plugs containing activated silica. Representative procedure: Methyl β-D-glucopyranoside (166 mg, 0.82 mmol) was preheated with ϵ-caprolactone (809 mg, 7.1 mmol) at 120 °C for 30 min under stirring to remove residual water. The polymerization was started by the addition of L-lactic acid (74 mg, 0.82 mmol) dissolved in ϵ-caprolactone (125 mg, 1.1 mmol). To prepare samples for characterization by NMR and methylation analysis, the temperature was maintained at 120 °C for 1.5 h. The conversion of ϵ-caprolactone after 1.5 h was 30%, M_w 700 and PDI 1.2 (from GPC), and the yield, expressed as carbohydrate-functionalized polyester in relation to the total polymer product, was about 90% (from MALDI−TOF MS). Before NMR and methylation analysis the crude methyl 6-*O*-poly(ϵ-caprolactone)-β-D-glucopyranoside was purified from unreacted methyl β-D-glucopyranoside by silica gel chromatography using gradients from 20% hexane in ethyl acetate to 20% methanol in ethyl acetate in a pressurized system (Bäckström Separo). Fractions were screened by MALDI−TOF MS, and those containing methyl β-D-glucopyranoside-functionalized poly(ϵ-caprolactone) were pooled together. The major product, about 95% as determined by integration of the C1 region in the ^{13}C NMR spectrum, was methyl 6-*O*-poly(ϵ-caprolactone)-β-D-glucopyranoside.[30]

Methyl β-D-glucopyranoside end group: ^{1}H NMR (CD_3CN): δ 3.07 (1H, dd, J = 8.6, 7.7 Hz, H2), 3.29 (1H, H3), 3.32 (1H, H4), 3.40 (1H, H5), 3.42 (3H, s, OCH_3), 4.13 (1H, d, J = 7.7 Hz, H1), 4.19 (1H, dd, J = 11.9, 5.8 Hz, H6), 4.30 (1H, dd, J = 11.9, 2.2 Hz, H6). ^{13}C NMR (CD_3CN): δ 103.7 (C1), 76.3, 73.6, 73.4, 70.0, 56.1 (OCH_3). The carbohydrate C6 could not be assigned due to overlap with end groups of the poly(ϵ-caprolactone) chains.

The same protocol was used for polymerizations initiated with sucrose and raffinose, catalyzed by other acids, and to study the influence of L-lactic acid concentration on the polymerization rate. In control experiments with sucrose and ϵ-caprolactone alone, no polymeric product was detected. Samples were collected at different reaction times for characterization using GPC and MALDI−TOF MS.

Methylation Analysis. To confirm acyl positions and determine the degree of substitution, hydroxyl groups were methylated according to Arnarp et al.[31,32] A representative procedure for methylation analysis is as follows. In an oven-dried flask with a rubber septum purified methyl 6-*O*-poly(ϵ-caprolactone)-β-D-glucopyranoside (90 mg, estimated amount of methyl β-D-glucopyranoside end group 0.1 mmol) and 2,6-di-*tert*-butylpyridine (355 μL, 1.6 mmol) were dissolved in dry dichloromethane (2 mL) under an argon atmosphere. After cooling to 0 °C methyl trifluoromethanesulfonate (100 μL, 0.88 mmol) was added by syringe. The reaction mixture was kept at 0 °C for 2 h and at room temperature overnight. After solvent removal the crude methylated polymer was purified by flash chromatography on silica gel using ethyl acetate as solvent. The methylated polymer (30 mg) was dissolved in trifluoroacetic acid (0.5 mL), and water (2.5 mL) was added dropwise to avoid precipitation of the polymer. After heating at 95 °C for 1 h aqueous trifluoroacetic acid (2 M, 20 mL) was added, and the hydrolysis was allowed to proceed at 95 °C overnight. The solution was concentrated and coevaporated with ethanol to remove traces of trifluoroacetic acid. The residue was dissolved in ammonium hydroxide (100 μL, 12 M), an aqueous solution of potassium borohydride (100 μL, 600 mg/mL) was added, and the solution was heated at 40 °C. After 1 h the solution was concentrated and coevaporated with three portions (5 mL) of methanol acidified with a few drops of acetic acid. The resulting alditols were acetylated with acetic anhydride and pyridine (1:1, 1 mL) at 95 °C for 1 h, and the excess reagents were removed by evaporation. The partially methylated alditol acetates were dissolved in dichloromethane (0.2 mL) and analyzed by GC-MS (Table 3).

Table 1. Conversion of ϵ-Caprolactone at 120 °C Catalyzed by Low Molecular Weight Carboxylic Acids

	ϵ-caprolactone conversion[a] (%)	
catalyst	neat (1.5 h)	with initiator present (3 h)
L-lactic acid	20	95
propanoic acid		15
hexanoic acid		20
6-hydroxyhexanoic acid	*b*	30

[a] According to GPC. Molar ratio of lactone to acid 10:1. Acid and initiator (methyl β-D-glucopyranoside) in equimolar amounts. [b] Small amounts of oligomeric product according to MALDI−TOF MS.

Table 2. Influence of Molar Ratio on Molecular Weight (M_w) and Polydispersity Index (PDI) at Complete Conversion of ϵ-Caprolactone[a]

molar ratio Me Glc*p*:LA:ϵ-CL	M_w (kDa)	PDI	reaction time (h)
1:1:40	6.5	1.5	21
1:4:40	3.2	1.3	5
1:1:10	1.6	1.3	4

[a] Me Glc*p* = methyl β-D-glucopyranoside; LA = L-lactic acid; ϵ-CL = ϵ-caprolactone.

Table 3. Results from the Methylation Analysis of Carbohydrate-Functionalized Poly(ϵ-caprolactones)

	carbohydrate end-function of polyester[a]	
	methyl β-D-glucopyranoside (mol %)	sucrose (mol %)
1,3,4,6-tetra-*O*Me−		4
2,3,4,6-tetra-*O*Me−		10
2,3,6-tri-*O*Me−		6
2,3,4-tri-*O*Me−	95	45
3,4,6-tri-*O*Me−		10
di-*O*Me−	5	21
mono-*O*Me−		4
av degree of substitution	1.1	2.4

[a] Reaction time 1.5 h, 120 °C. The molar ratio of lactone to acid to carbohydrate was 10:1:1.

Results and Discussion

Selection of L-Lactic Acid as Organocatalyst. The criteria for the choice of organocatalyst were that the catalyst should be easily handled without the need for extraordinary precautions with regard to atmosphere, humidity, or equipment and that the catalyst should be nontoxic and preferably a natural product with no necessity to remove catalyst remnants after the completed reaction. These criteria can be fulfilled by several low molecular weight carboxylic acids. 6-Hydroxyhexanoic acid generated in situ by the addition of water to ϵ-caprolactone catalyzes the ring-opening polymerization of the lactone.[34] Accordingly, propanoic, L-lactic, hexanoic, and 6-hydroxyhexanoic acid were compared for their ability to polymerize neat ϵ-caprolactone at 120 °C. Analysis of the reaction mixtures by MALDI−TOF MS after 1.5 h showed that, in the L-lactic acid-catalyzed reaction, 20% of the monomer had been converted to oligomeric products (M_w = 1200, PDI 1.1 according to GPC). In the 6-hydroxyhexanoic acid-catalyzed reaction, only diminutive amounts of oligomers could be detected by MALDI−TOF MS, and in the two other reactions no polymerization products were formed during the first 1.5 h (Table 1).

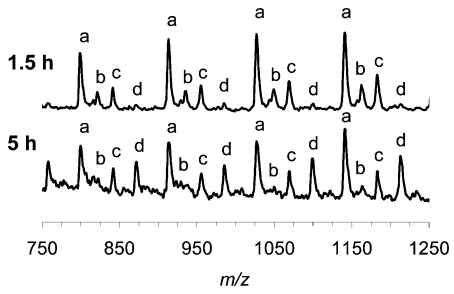


Figure 1. MALDI−TOF mass spectra of the bulk polymerization of ϵ-caprolactone catalyzed by L-lactic acid (molar ratio of lactone to acid 10:2, 120 °C, 1.5 and 5 h). The marked peaks *a*−*d* are adducts of poly(ϵ-caprolactone) carrying different end groups: *a* and *b*, L-lactic acid-functionalized poly(ϵ-caprolactone);[36] *c*, poly(ϵ-caprolactone) from water-initiated polymerization; *d*, poly(ϵ-caprolactone) difunctionalized with L-lactic acid.

Figure 1 shows an expanded view of the 750−1250 Da region of the MALDI−TOF MS spectra of the L-lactic acid-catalyzed reaction. The main product was L-lactic acid-functionalized poly(ϵ-caprolactone) together with small amounts of poly(ϵ-caprolactone) from water-initiated polymerization. Poly(ϵ-caprolactone) difunctionalized with L-lactic acid, from initiation and termination, was also detected, and the relative amount of this product increased with increasing reaction time. The overall pattern resembled that observed in the *Candida antarctica* lipase B-catalyzed formation of hydroxy acid-functionalized poly(ϵ-caprolactone)[21] and agrees with an activated monomer mechanism.[35]

Various carboxylic acids were also screened with an initiating agent (methyl β-D-glucopyranoside) present in the reaction mixture. The conversion of monomer by the different acids after 3 h reaction is shown in Table 1. L-Lactic acid-containing reactions exhibited the highest conversion, both with and without methyl β-D-glucopyranoside present. The greater catalytic efficiency of L-lactic acid could be due to its higher acid strength, pK_a 3.8, compared to about 4.9 for the carboxylic acids lacking an α-hydroxy group.

Poly(ϵ-caprolactone) End-Functionalized with Carbohydrates. The resemblance of the L-lactic acid-catalyzed and lipase-catalyzed reactions tempted us to scrutinize possible ways of preparing poly(ϵ-caprolactone) end-functionalized with carbohydrates.[29,30,37] The low solubility of sugars in most nonaqueous solvents at reasonable temperatures often restricts the yield in the enzyme-catalyzed acylation of underivatized mono- and disaccharides. Compared with the enzymatic reactions reported so far, the L-lactic acid-catalyzed polymerization of ϵ-caprolactone can be performed at relatively higher temperatures at which ϵ-caprolactone starts to be a good solvent for many sugars. Thus, to study sugar initiation in combination with L-lactic acid catalysis, polymerizations were performed at 120 °C with methyl β-D-glucopyranoside, sucrose, or raffinose present as initiator (Scheme 1).

Figure 2 shows the consumption of ϵ-caprolactone in the presence of the different carbohydrates compared with the corresponding neat ϵ-caprolactone polymerization. The higher conversion rates with carbohydrate initiators present could be related to a higher reactivity of their primary hydroxyl groups as compared to the secondary hydroxyl group of L-lactic acid.

The polymer molecular weights were similar to those reported for enzyme-catalyzed polymerizations.[29,30] Figure 3 shows the molecular weight and polydispersity index as a function of reaction time for the carbohydrate-initiated polymerizations. The sucrose-functionalized polyester reached a M_w of about 4000 after 5 h reaction, whereas the polymerizations initiated with methyl glucoside or raffinose leveled off at molecular weights slightly below 2000.

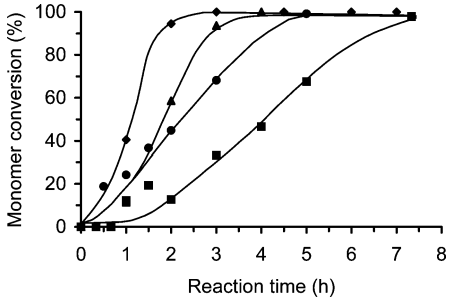


Figure 2. L-Lactic acid-catalyzed conversion (from GPC) of ϵ-caprolactone at 120 °C in the presence of methyl β-D-glucopyranoside (▲), sucrose (●), or raffinose (◆). The molar ratio of ϵ-caprolactone to L-lactic acid to carbohydrate was 10:1:1. The corresponding reference reaction with only monomer and catalyst exhibits a lower conversion rate (■).

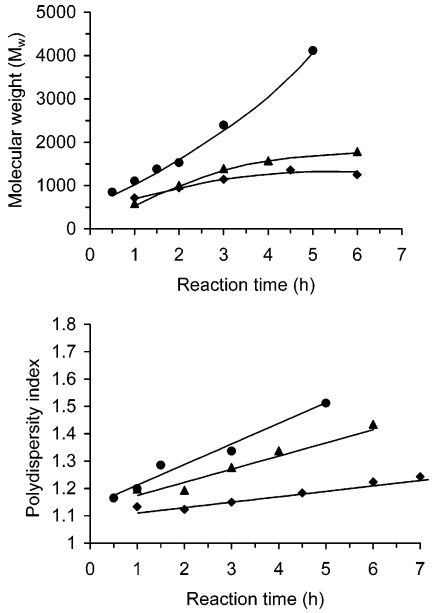
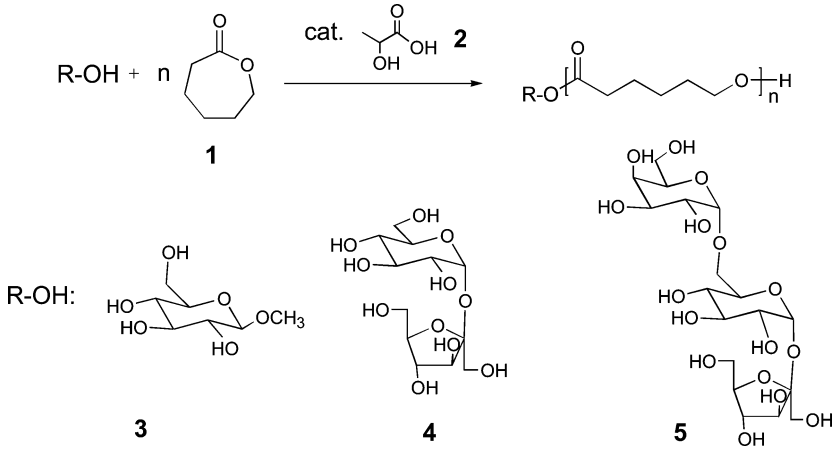


Figure 3. Molecular weight and polydispersity index (from GPC) of poly(ϵ-caprolactone) functionalized with methyl β-D-glucopyranoside (▲), sucrose (●), or raffinose (◆) in bulk polymerization at 120 °C catalyzed by L-lactic acid. The molar ratio of ϵ-caprolactone to L-lactic acid to carbohydrate was 10:1:1.

The yield of carbohydrate-functionalized polyester in relation to the total polymer product, calculated from the areas of discernible peaks in MALDI−TOF MS spectra between 1000 and 2000 Da, was 90, 80, and 60% respectively for methyl β-D-glucopyranoside, sucrose, and raffinose (1.5 h; spectra not shown). The lower yield of the raffinose-functionalized polyester is probably due to the lower solubility of raffinose in ϵ-caprolactone, which allows stronger competition from initiation by water and L-lactic acid.

Figure 4 shows MALDI−TOF MS spectra of carbohydrate-functionalized poly(ϵ-caprolactone). In the raffinose-initiated sample a smaller product distribution corresponding to disaccharide-initiated polymers is discernible, indicating that acid hydrolysis is a compet-

Scheme 1. Polymerization of ϵ-Caprolactone (1) Catalyzed by L-Lactic Acid (2) and Initiated with Methyl β-D-Glucopyranoside (3), Sucrose (4), or Raffinose (5)



ing reaction. It should be noted, although it is not visible in Figure 4, that L-lactic acid act as a terminator at longer reaction times in a manner similar to that in the neat ϵ-caprolactone polymerizations (Figure 1). The presence of both an initiation and a termination reaction gives possibilities to partly control the resulting molecular weight of the polymer by adjusting the molar ratio of initiator to L-lactic acid (catalyst and terminator) to ϵ-caprolactone as shown in Table 2.

Determination of Acylation Position. NMR analysis and methylation analyses were performed on fractions purified to remove unreacted sugars. Because of the relatively high average M_w of the carbohydrate-functionalized poly(ϵ-caprolactones), the ^{1}H and ^{13}C NMR spectra were all characterized by low signal intensities for the carbohydrate end groups. Only the major product (95%, 1.5 h reaction time) in the methyl β-D-glucopyranoside-functionalized poly(ϵ-caprolactone) NMR spectrum could be assigned to methyl 6-*O*-poly(ϵ-caprolactone)-β-D-glucopyranoside.[30]

Carbohydrates that contain alkali-labile *O*-acyl groups cannot be methylated under the conventional strongly alkaline conditions without the loss of some of those groups.[31] Instead, the methylation was performed using methyl trifluoromethanesulfonate together with 2,6-di-*tert*-butylpyridine as proton scavanger.[31] The results of the methylation analyses in Table 3 show that the main products are acylated on the primary hydroxyl groups of the carbohydrate end groups, for both methyl β-D-glucopyranoside-initiated and sucrose-initiated polymerizations with a regioselectivity well in agreement with the corresponding lipase-catalyzed acylations of mono- and disaccharides.[29,30,38−41] No methylation analysis of the raffinose-functionalized polyester was performed because of the complexity of the resulting products as a result of competing hydrolysis during polymerization. The difference in the average degree of substitution, 1.1 and 2.4 for methyl β-D-glucopyranoside-functionalized and sucrose-functionalized poly(ϵ-caprolactone), respectively, could explain the higher molecular weight of the sucrose-functionalized polymer, M_w of about 4000 compared to slightly less than 2000 for the methyl β-D-glucopyranoside-functionalized product (Figure 3).

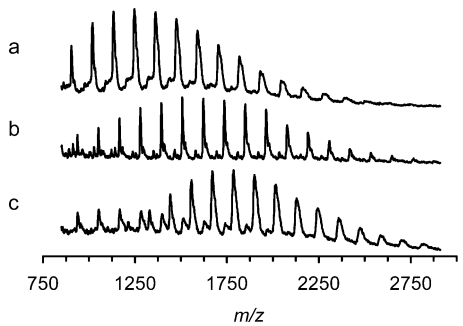


Figure 4. MALDI−TOF MS spectra of purified fractions from the L-lactic acid-catalyzed synthesis of poly(ϵ-caprolactone) functionalized with (a) methyl β-D-glucopyranoside, (b) sucrose, or (c) raffinose.

Conclusions

L-Lactic acid was efficient in catalyzing the ring-opening polymerization of ϵ-caprolactone. L-Lactic acid catalyzed the acylation of methyl β-D-glucopyranoside and sucrose with ϵ-caprolactone in high yield by bulk polymerization. The main products were regioselectively acylated on the primary hydroxyl groups of the carbohydrate end groups. Furthermore, the L-lactic acid-catalyzed ring-opening polymerization was similar to the corresponding *Candida antarctica* lipase B catalyzed reaction with respect to both efficiency and regioselectivity.

Acknowledgment. IRECO Holding AB is gratefully acknowledged for financial support. Anders Uhlin is thanked for technical assistance.

References and Notes

(1) Goldberg, D. *J. Environ. Polym. Degrad.* **1995**, *3*, 61.
(2) Albertsson, A.-C.; Varma, I. K. *Biomacromolecules* **2003**, *4*, 1466.
(3) Gross, R. A.; Kumar, A.; Kalra, B. *Chem. Rev.* **2001**, *101*, 2097.
(4) Kobayashi, S.; Uyama, H.; Kimura, S. *Chem. Rev.* **2001**, *101*, 3793.
(5) Ouhadi, T.; Stevens, C.; Teyssié, P. *Macromol. Chem., Suppl.* **1975**, *1*, 191.
(6) Vion, J.-M.; Jerome, R.; Teyssié, P.; Aubin, M.; Prud'homme, R. E. *Macromolecules* **1986**, *19*, 1828.
(7) Duda, A.; Penczek, S. *Macromolecules* **1995**, *28*, 5981.
(8) Dubois, P.; Ropson, N.; Jerome, R.; Teyssié, P. *Macromolecules* **1996**, *29*, 1965.
(9) Kricheldorf, H. R.; Eggerstedt, S. *Macromol. Chem. Phys.* **1998**, *199*, 283.
(10) Kricheldorf, H. R.; Sumbel, M. V.; Kreiser-Saunders, I. *Macromolecules* **1991**, *24*, 1944.
(11) Storey, R. F.; Sherman, J. W. *Macromolecules* **2002**, *35*, 1504.

(12) Penczek, S.; Duda, A.; Kowalski, A.; Libiszowski, J.; Majerska, K.; Biela, T. *Macromol. Symp.* **2000**, *157*, 61.
(13) Okuda, J.; Rushkin, I. L. *Macromolecules* **1993**, *26*, 5530.
(14) Barakat, I.; Dubois, P.; Jerome, R.; Teyssié, P. *Macromolecules* **1991**, *24*, 6542.
(15) Shen, Y.; Shen, Z.; Zhang, Y.; Yao, K. *Macromolecules* **1996**, *29*, 8289.
(16) Stevels, W. M.; Ankoné, M. J. K.; Dijkstra, P. J.; Feijen, J. *Macromolecules* **1996**, *29*, 8296.
(17) Deng, X.; Zhu, Z.; Xiong, C.; Zhang, L. *J. Appl. Polym. Sci.* **1997**, *64*, 1295.
(18) Connor, E. F.; Nyce, G. W.; Myers, M.; Möck, A.; Hedrick, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 914.
(19) Myers, M.; Connor, E. F.; Glauser, T.; Möck, A.; Nyce, G.; Hedrick, J. L. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 844.
(20) Kumar, A.; Gross, R. A. *Biomacromolecules* **2000**, *1*, 133.
(21) Córdova, A.; Iversen, T.; Hult, K. *Polymer* **1999**, *40*, 6709.
(22) MacDonald, R. T.; Pulapura, S. K.; Svirkin, Y. Y.; Gross, R. A.; Kaplan, D. L.; Akkara, J.; Swift, G.; Wolk, S. *Macromolecules* **1995**, *28*, 73.
(23) Namekawa, S.; Suda, S.; Uyama, H.; Kobayashi, S. *Int. J. Biol. Macromol.* **1999**, *25*, 145.
(24) Uyama, H.; Kobayashi, S. *Chem. Lett.* **1993**, 1149.
(25) Henderson, L. A.; Svirkin, Y. Y.; Gross, R. A.; Kaplan, D. L.; Swift, G. *Macromolecules* **1996**, *29*, 7759.
(26) Knani, D.; Gutman, A. L.; Kohn, D. H. *J. Polym. Sci., Part A: Polym. Chem.* **1993**, *31*, 1221.
(27) Wahlberg, J.; Persson, P. V.; Olsson, T.; Hedenström, E.; Iversen, T. *Biomacromolecules* **2003**, *4*, 1068.
(28) Uyama, H.; Kobayashi, S. In *Catalysis in Precision Polymerization*; Kobayashi, S., Ed.; John Wiley & Sons: Chichester, 1997; pp 399−403.
(29) Bisht, K. S.; Deng, F.; Gross, R. A.; Kaplan, D. L.; Swift, G. *J. Am. Chem. Soc.* **1998**, *120*, 1363.
(30) Córdova, A.; Iversen, T.; Hult, K. *Macromolecules* **1998**, *31*, 1040.
(31) Arnarp, J.; Kenne, L.; Lindberg, B.; Lönngren, J. *Carbohydr. Res.* **1975**, *44*, C5.
(32) For a practical guide to methylation analysis of carbohydrates, see: Jansson, P. E.; Kenne, L.; Liedgren, H.; Lindberg, B.; Lönngren, J. *Chem. Commun. (Stockholm Univ.)* **1976**, 75.
(33) Fox, A.; Morgan, S. L.; Gilbart, J. In *Analysis of Carbohydrates by GLC and MS*; Biermann, C. J., McGinnis, G. D., Eds.; CRC Press: Boca Raton, FL, 1989; pp 87−117.
(34) Rozenberg, B. A. *Makromol. Chem., Macromol. Symp.* **1992**, *60*, 177.
(35) Kubisa, P.; Penczek, S. *Prog. Polym. Sci.* **1999**, *24*, 1409.
(36) The signals *a* and *b* are both L-lactic acid-initiated polyester; *a* is the sodium adduct whereas *b* is a mix of adducts carrying either one potassium or two sodium ions. This was determined from MALDI−TOF MS spectra of samples treated with excessive amounts of sodium or potassium salts.
(37) Kumar, A.; Gross, R. A. *J. Am. Chem. Soc.* **2002**, *124*, 1850.
(38) Therisod, M.; Klibanov, A. M. *J. Am. Chem. Soc.* **1986**, *108*, 5638.
(39) Adelhorst, K.; Björkling, F.; Godtfredsen, S. E.; Kirk, O. *Synthesis* **1990**, 112.
(40) Woudenberg-van Oosterom, M.; van Rantwijk, F.; Sheldon, R. A. *Biotechnol. Bioeng.* **1996**, *49*, 328.
(41) Ferrer, M.; Cruces, M. A.; Bernabé, M.; Ballesteros, A.; Plou, F. J. *Biotechnol. Bioeng.* **1999**, *65*, 10.

MA049562J