Preliminary communication/Communication

Polylactides with aldaric ester end groups or chain extending groups

Anita Haider, Charlotte K. Williams *

Department of Chemistry, Imperial College London, London SW7 2AZ, United Kingdom

ARTICLE INFO

ABSTRACT

The synthesis and characterisation of a series of poly(S,S-lactides) and poly(RR/SS-lactides) end capped or chain extended with aldaric ester groups are described. The aldaric esters are prepared from acetyl protected D-gluconolactone, D-galactonolactone and D-mannonolactone by ring opening with butanol or 1,4-butanediol, under acidic conditions. The aldaric esters are fully characterised, including by NMR spectroscopy and mass spectrometry. They are used as co-initiators, with an ethylzinc complex, to enable the controlled ring opening polymerisation of S,S- and rac-lactide. Thus, a series of polylactides are produced with various carbohydrate chain end or extending groups and are fully characterised, including by NMR spectroscopy and gel permeation chromatography (GPC). The polymerisation kinetics are examined, under pseudo first order conditions, and indicate that chain transfer reactions are occurring more rapidly than propagation reactions. The degradation kinetics of the polylactides are examined under acidic conditions; the aldaric esters increase the degradation rates compared to unfunctionalised end groups.

© 2010 Académie des sciences. Published by Elsevier Masson SAS. All rights reserved.

1. Introduction

The preparation of polymers from renewable resources is attracting increasing attention due to problems associated with the cost, security of supply, sustainability and environmental impact of petrochemicals [1]. The use of biomass (plant derived material such as cellulose, hemicelluloses or lignin) as a feedstock is particularly promising and biomass derived polyesters are already commercially available, e.g. Natureworks[TM] polylactide, Dupont Sorona[TM] and Metabolix Mirel[TM] polymers [2]. Polylactide (PLA) has attracted much attention as it derives entirely from renewable resources, has properties suitable for range of applications and can be degraded by hydrolysis reactions [3,4]. PLA is prepared from lactic acid, which is harvested from corn or sugar beet; the process involves formation of an oligo(lactic acid), its degradation to lactide (the cyclic dimer of lactic acid) and lactide ring opening polymerisation [5–9]. PLA has been applied for some time

in specialised medical applications, such as degradable sutures, pins, matrices for tissue engineering and drug delivery excipients [10]. Furthermore, recent manufacturing improvements have enabled it to be produced on sufficient scale and at a competitive price for some commodity applications, such as packaging [11]. However, there are still a number of limitations associated with polylactide, for example it is relatively slow to degrade and this relates to its hydrophobicity [3–5,10,11]. One strategy to increase degradation rates involves the preparation of polylactide with hydrophilic end groups. In keeping with the sustainability of polylactide, the end group should also derive from renewable resources. Carbohydrate end groups are attractive as they display a multitude of functional groups, are relatively inexpensive and are naturally occurring in large quantities [12]. A number of groups have investigated the preparation of polylactide end-capped with various hexoses and pentoses [13–23]. The majority of these studies have focussed on D-glucose and its derivatives and have lead to the production of branched and multi-arm polylactides, some of which are of interest for medical applications. We recently reported a method to prepare end-functionalised polylactide from a

* Corresponding author.
E-mail address: c.k.williams@imperial.ac.uk (C.K. Williams).

series of hexoses, pentoses and aldaric esters and established that acetyl-protecting groups were useful for increasing the hydrophilicity of the PLA [23]. Herein, we present the preparation of a series of six new aldaric esters and their use as co-initiators in the ring opening polymerisation of lactide.

2. Results and discussion

2.1. Carbohydrate co-initiator synthesis

2,3,4,6-Tetra-O-acetyl-D-gluconolactone was prepared in quantitative yield from D-gluconolactone, according to the literature method [24]. However, the isomeric lactones, D-mannonolactone and D-galactarolactone, were not commercially available. Therefore a four-step synthesis was devised which enabled good conversion to 2,3,4,6-tetra-O-acetyl-D-galactono/mannonolactone, in overall yields of 55 and 72 %, respectively. The syntheses involved preparation of penta-O-acetyl-D-galacto/mannopyranose, in quantitative yield, by treatment of D-galacto/manno-pyranose with acetic anhydride and trifluoroacetic acid for 20 hours [25]. The glycosyl bromides were prepared by reaction with hydrobromic acid, initially at low temperature but warming to room temperature and stirring for 20 h, and were isolated in 76 and 95 % yield, respectively. The glycosyl bromides were hydrolysed, using aqueous silver carbonate, to yield the tetra-O-acetyl-D-galacto/mannopyranose, in quantitative yield. The pyranoses were oxidised under Swern oxidation conditions, which enabled clean conversion to the target lactones in 83 and 76 % yield, respectively. The lactones and all intermediate compounds were fully characterised, details of which are provided in the experimental section (Scheme 1).
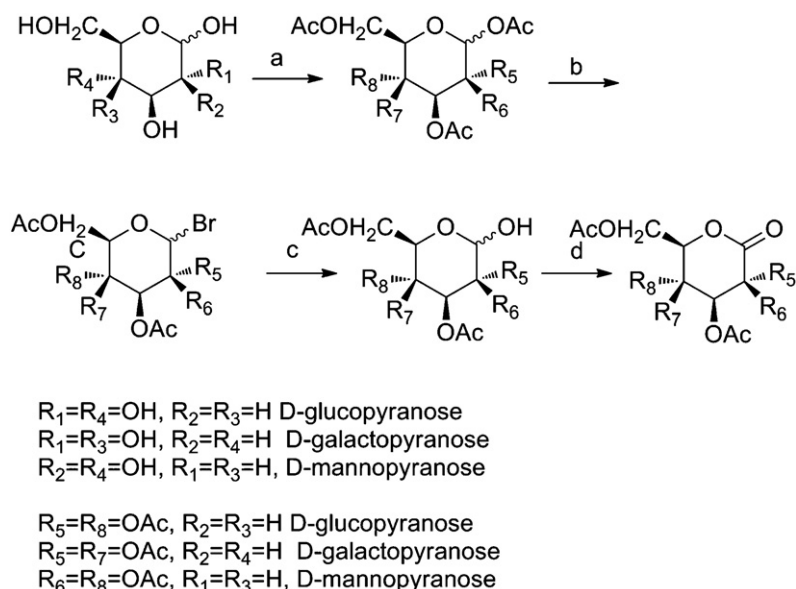
The acid catalysed ring opening of the acetyl-protected 1,5-lactones, in the presence of butan-1-ol or 1,4-butanediol, yielded aldaric esters with one or two free hydroxyl groups. These alcohol groups (a single one for butoxyesters and two hydroxyl groups for hydroxybutoxy-esters) were suitable as co-initiators for lactide ring opening polymerisation and enabled the preparation of polylactides with carbohydrate end groups/chain extender groups (Scheme 2).

The rate of lactone ring opening depended on the stereochemistry, decreasing in the order: per acetylated D-galactonolactone > per acetylated D-mannonlactone > per acetylated D-gluconolactone. This could relate to the relative stability of the aldaric esters and in particular for the D-glucose derivatives there is a 1,3-steric interaction between the acetate substituents. The reaction was also reversible, although the equilibrium lay far towards the aldaric esters, however, prolonged exposure to acid led to formation of the thermodynamic product, the per acetylated 1,4-lactone. Nonetheless, by controlling the reaction time, six aldaric esters were isolated in yields from 20–95 %. These aldaric esters were grouped according to the number of free hydroxyl groups and the stereochemistry of the starting lactone, thus compounds 1–3 were all prepared using 1,4-butanediol and had two hydroxyl groups, one a primary hydroxyl and the other a secondary group, whilst compounds 4–6 had a single, secondary hydroxyl group.

2.2. Lactide ring opening polymerisations

The new aldaric esters were used as co-initiators for (S,S) and rac-lactide ring opening polymerisations (Scheme 3).

The polymerisations were all carried out at room temperature with an initiator to lactide ratio of 1:50 and

$R_1 = R_4 = OH, R_2 = R_3 = H$ D-glucopyranose
$R_1 = R_3 = OH, R_2 = R_4 = H$ D-galactopyranose
$R_2 = R_4 = OH, R_1 = R_3 = H,$ D-mannopyranose

$R_5 = R_8 = OAc, R_2 = R_3 = H$ D-glucopyranose
$R_5 = R_7 = OAc, R_2 = R_4 = H$ D-galactopyranose
$R_6 = R_8 = OAc, R_1 = R_3 = H,$ D-mannopyranose

Scheme 1. Synthesis of the acetyl protected 1,5-lactones derived from D-galactose and D-mannose. Reagents and Conditions: (a) TFA, Ac_2O, 25 °C, 20 h; quantitative b) HBr (AcOH), DCM, 0 °C-25 °C, 20 h; 76 % (2,3,4,6-tetra-O-acetyl-D-galactopyranosyl bromide), 95 % (2,3,4,6-tetra-O-acetyl-D-mannopyranosyl bromide) c) Ag_2CO_3, acetone, water, 0 °C-25 °C, 20 h; quantitative d) i) 7 eq. (COCl)$_2$, 13 eq. DMSO, −78 °C, 2 h ii) 5 eq. NEt$_3$, −78 °C, 30 min, 83 % (2,3,4,6-tetra-O-acetyl-D-galactonolactone), 76 % (2,3,4,6-tetra-O-acetyl-D-mannonolactone).
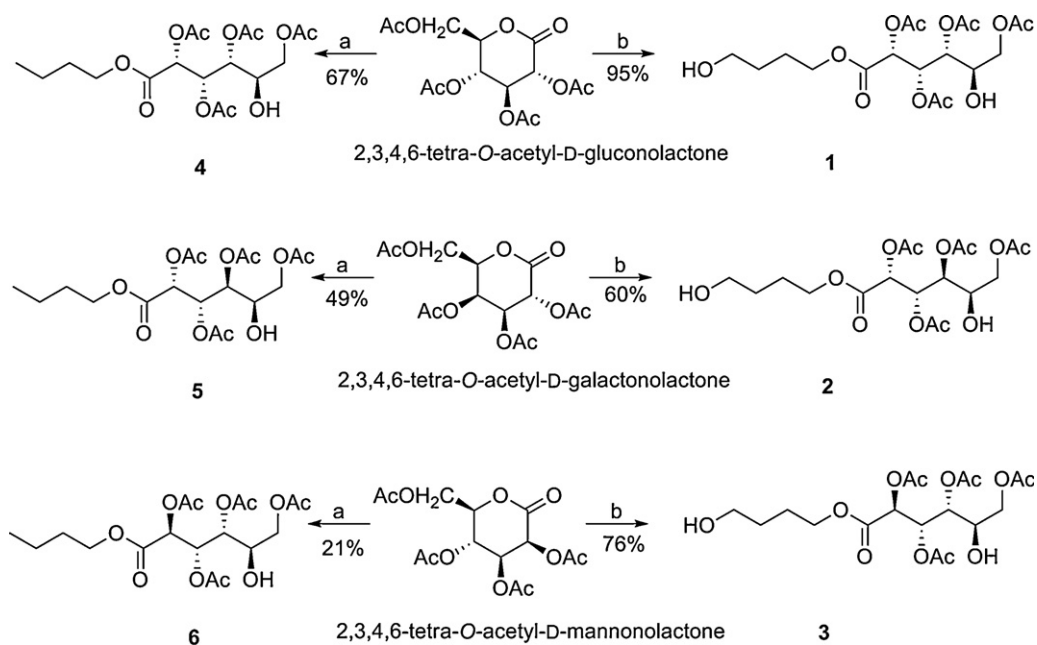
Scheme 2. Synthesis of aldaric esters **1-6** by reaction of the per-acetylated 1,5-lactones with butan-1-ol and 1,4-butanediol. Reagents and Conditions: a) 0.1 eq. p-TSA, 1.0 eq. butan-1-ol, CHCl₃, 0 °C or 25 °C b) 0.1 eq. p-TSA, 1.0 eq. 1,4-butandiol, CH₂Cl₂, 0 °C or 25 °C.

at a 0.7 M lactide concentration. The true initiator was generated in situ by a stoichiometric reaction between the hydroxyl group(s) on **1-6** and a well-defined zinc complex, LZnEt (Fig. S1) [22]. The zinc complex was chosen because it had previously shown very good activity and control for lactide polymerisation using aliphatic alcohols and carbohydrate alcohols [22,23,26]. The initiating groups **1-3** gave polylactides where the carbohydrate group was a chain extender (Scheme 3), whilst the initiators **4–6** gave polylactide end-capped with the carbohydrate group (Scheme 3). The polymerisation was well controlled and by using a co-initiator:lactide loading of 1:50 it was possible to prepare polylactide with degree of polymerisation 30–50. The properties of the polylactide produced using the different initiators are compared in Table 1. The M_n was determined by SEC, using THF and with a correction factor as noted in the

literature [27]. ¹H NMR spectroscopy could also be used to deduce the molecular weight, by integration of the signals due to the methyne protons on the lactide repeat unit against the acetyl signals on the co-initiator. The molecular weights determined from NMR, SEC and the M_n calculated from the degree of polymerisation were all in excellent agreement. Thus, using co-initiator **1** at a conversion of 95 % (DP = 47) gave the calculated M_n of 7200, which was in close agreement with the M_n determined by SEC (6300) and that determined by ¹H NMR (6700).

The polymerisation control is further supported by the linear fit of the semi-logarithmic plots, $\ln\{[LA]_0/[LA]_t\}$ against time, for the various co-initiators (Fig. 1).
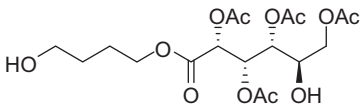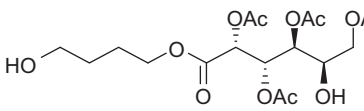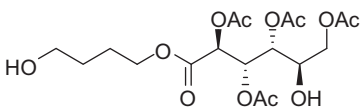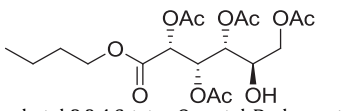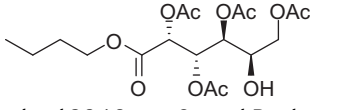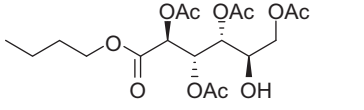
The gradients in Fig. 1 are the pseudo-first order rate constants, k_{obs} for the co-initiators; the bifunctional co-initiators, **1-3**, have values between 0.60 and
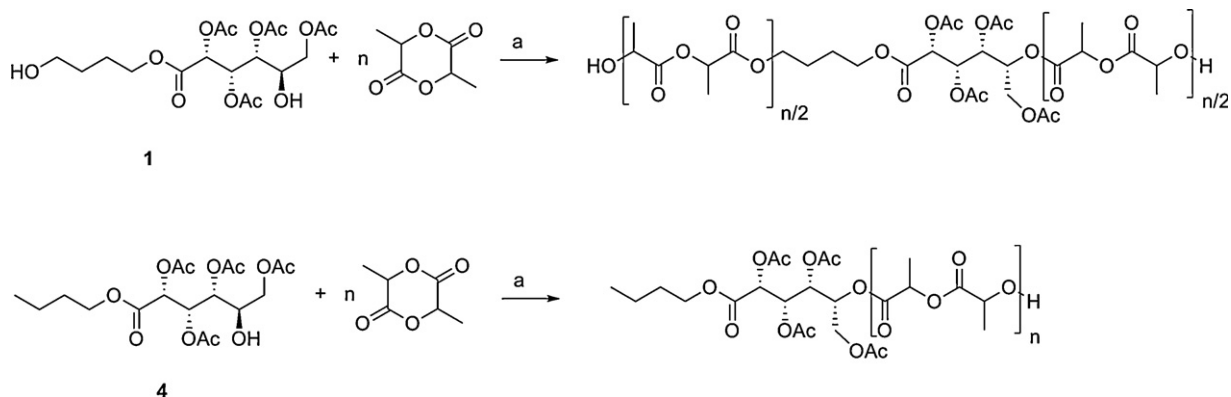
Scheme 3. Polylactide synthesised using mono- and bi-functional carbohydrate co-initiators. Reagents and conditions: a [LA]₀ = 0.7 M, **[1–6]₀** = 0.014 M, [LZnEt]₀ = 0.014 M, CHCl₃, 25 °C (n = 50). Note that although the values n/2 are used to represent the chain extended polymers formed from co-initiators 1-3, the differences in relative initiation rates between the hydroxyl groups could mean that slight differing values are obtained.

Table 1

Polylactide prepared using co-initiators 1–6. Polymerisation conditions: $[(S,S)\text{-LA}]_0 = 0.7$ M, $[\mathbf{1–6}]_0 = 0.014$ M, $[\text{LZnEt}]_0 = 0.014$ M, $CDCl_3$, room temperature.

Co-initiator #	Co-initiator Chemical structure	% conv[a]	M_n Calc.[b]	M_n NMR[c]	M_n SEC[d] (PDI)
1	4-hydroxybutyl 2,3,4,6-tetra-O-acetyl-D-gluconate	95	7300	8300	7400 (1.52)
2	4-hydroxybutyl 2,3,4,6-tetra-O-acetyl-D-galactonate	94	7200	6700	6300 (1.24)
3	4-hydroxybutyl 2,3,4,6-tetra-O-acetyl-D-mannonate	98	7500	6600	8300 (1.66)
4	n-butyl 2,3,4,6-tetra-O-acetyl-D-gluconate	98	7500	5500	5900 (1.32)
5	n-butyl 2,3,4,6-tetra-O-acetyl-D-galactonate	62[e]	4900	4900	5300 (1.31)
6	n-butyl 2,3,4,6-tetra-O-acetyl-D-mannonate	82	6300	6500	5900 (1.33)

[a] Determined by normalization of the integrals for the CH resonances in lactide (5.00 ppm) and polylactide (5.20 ppm).

[b] M_n calc = $(144 \times \%$ conv. $\times 50) + $ RMM (co-initiator **1-6**).

[c] Determined by integration of the CH signal in polylactide (5.20 ppm) versus the acetyl signal in the initiator (2.10 ppm).

[d] Determined by GPC, using polystyrene standards to calibrate the instrument and with a correction factor of 0.58 [27].

[e] Reaction was quenched before complete conversion could be attained.

$0.95 \, h^{-1}$ whilst the monofunctional co-initiators, **4–6**, have values between 0.27 and $0.37 \, h^{-1}$. This difference can be rationalised by the active species present in the polymerisation reaction. The mechanism involves in situ generation of the initiator by reaction between LZnEt and the alcohol moieties to form a zinc alkoxide. This is followed by initiation and propagation and in order for the polymerisation to be controlled the rate of propagation should exceed the rate of initiation. Free alcohol groups are significant as they can act as chain transfer agents. Chisholm et al. have established that chain transfer occurs significantly faster than propagation in lactide polymerisation [28]. This dictates that k_{obs} is a function of the initial hydroxyl group concentration, therefore the rate is doubled for co-initiators **1–3** because the initial hydroxyl concentration is twice that for co-initiators **4–6**. This also rationalises the chain extended structure of the PLA derived from bifunctional co-initiators: chain transfer allows the polymer chain to grow from both ends of the molecule. Thus the carbohy-

drate unit is no longer an end group but is a chain extender, as shown in Scheme 3.

Another characteristic of these polymerisation reactions is the induction period which is manifested by a non-zero x-intercept in the semi-logarithmic plot, $\ln\{[\text{LA}]_0/[\text{LA}]_t\}$ against time (Fig. 1). The induction period ranges between 1 and 3 h and reflects the time taken for the alcohol groups to react with the alkyl zinc co-initiator. The PLA produced from rac-lactide was atactic.

2.3. Degradation studies

There are a multitude of methods used to analyse the degradation of polylactide including in vitro and bulk degradation studies [29–36]. Acid catalysed degradation is useful as it is much accelerated compared to standard aqueous conditions. The polymers were dissolved in TFA(aq.)/$CHCl_3$ (2 % v/v) and were analysed by SEC (polystyrene standards, $CHCl_3$) until complete degradation had occurred. Analysis of the degradation was based on the
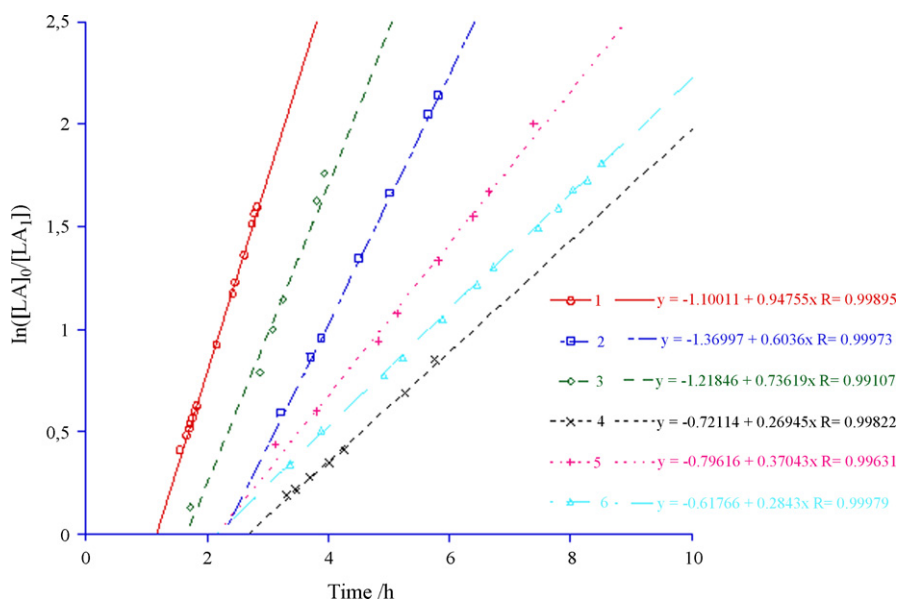
Fig. 1. Polymerisation of S,S-lactide using co-initiators **1-6**. The polymerisation conditions: $[(S,S)\text{-LA}]_0 = 0.7$ M, **[1–6]$_0$ =** 0.014 M, $[\text{LZnEt}]_0 = 0.014$ M, CDCl$_3$, 25 °C. The gradients give the pseudo first order rate constants (k_{obs}) and the x axis intercept gives the initiation time (t_i). **1**, $k_{obs} = 0.95$ h^{-1}, $t_i = 1$ h; **2**, $k_{obs} = 0.60$ h^{-1}, $t_i = 2.3$ h; **3**, $k_{obs} = 0.74$ h^{-1}, $t_i = 1.6$ h; **4**, $k_{obs} = 0.27$ h^{-1}, $t_i = 2.7$ h; **5**, $k_{obs} = 0.37$ h^{-1}, $t_i = 2.2$ h; **6**, $k_{obs} = 0.28$ h^{-1}, $t_i = 2.2$ h.

widely accepted random chain scission mechanism for acid catalysed degradation [30–39]. Liu et al. [34] have shown the relationship between the molecular number and the degradation rate constant, k_d, can be simplified:

$$M_0/M_t - 1 = -M_0 k_d t$$

where M_0 and M_t are the molecular number at time 0 and t, respectively. The plots of $[M_0/M_t - 1]/M_0$ versus time were

linear, supporting a random chain scission degradation pathway, the gradients correspond to the degradation rate constant, k_d. The polylactide prepared from rac-lactide underwent significantly more rapid degradation than the isotactic polylactide derived from S,S-lactide (Fig. 2) [29]. Fig. 3 compares the degradation of PLA initiated using compounds **1**, **4** and ^{i}PrOH. The carbohydrate moieties
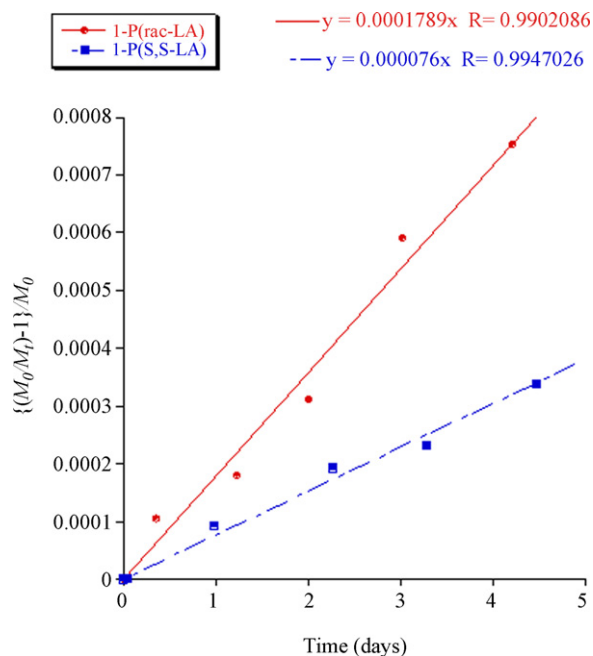
Fig. 2. Polylactide degradation assessed by plotting $(M_0/M_t-1)/M_0$ versus time for polymer prepared from initiator **1** and rac-lactide ($M_0 = 7300$; $k_d = 1.79 \times 10^{-4}$ day^{-1}) or S,S-lactide ($M_0 = 7400$; $k_d = 0.76 \times 10^{-4}$ day^{-1}).
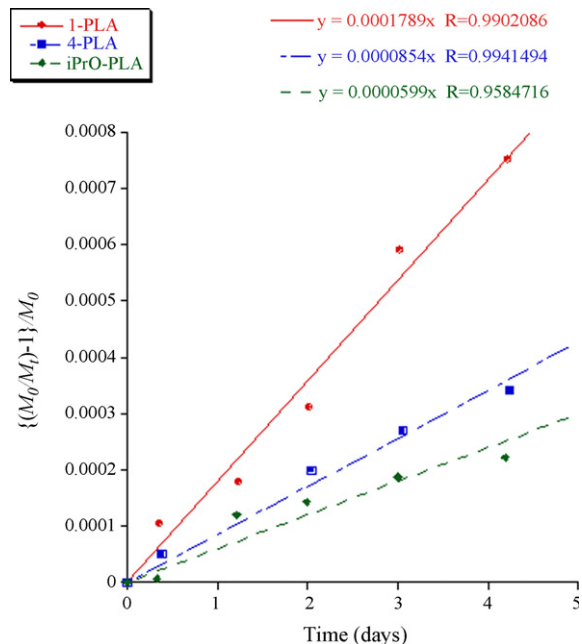
Fig. 3. Plot of $(M_0/M_t-1)/M_0$ versus time for the degradation of polylactide prepared from rac-lactide and initiators **1** ($M_0 = 7300$; $k_d = 1.79 \times 10^{-4}$ day^{-1}), **4** ($M_0 = 7500$; $k_d = 0.85 \times 10^{-4}$ day^{-1}), and ^{i}PrOH ($M_0 = 2500$; $k_d = 0.60 \times 10^{-4}$ day^{-1}).

clearly increase the degradation rate compared to the *i*-propoxyester terminated polylactide. The carbohydrates **1** and **4** both derive from D-glucose, and differ only in the polymer structure (Scheme 3). The polylactide initiated using compound **1** degrades more rapidly; this could be because the hydrophilic carbohydrate group is in the centre of the PLA chain, which facilitates breakdown of the chain into smaller and more rapidly degradable units. There is no particular influence of the carbohydrate stereochemistry on the degradation kinetics with similar results being obtained for polylactide prepared from **2**, **3**, **5** and **6** (data not shown). However, it is clear that the carbohydrate groups increase the degradation rate of polylactide compared to unfunctionalised alcohol end groups. This is probably due to the hydrophilicity of the acetyl-protected carbohydrate moieties, which are expected to increase the rate of hydrolysis of the polylactide chain and thereby increase the degradation rate.

3. Conclusions

In conclusion, a series of six aldaric esters were prepared in good yields, from the hexoses D-gluconolactone, D-galactose and D-mannose. The synthesis involved preparation of per-acetyl protected lactones and ring opening of the lactones, with either butanol or 1,4-butanediol, to yield aldaric esters with one or two free hydroxyl groups, respectively. The aldaric esters were used as co-initiators, with a zinc complex, for the ring opening polymerisation of lactide. The polymerisations were all well controlled, as shown by the good agreements between theoretical and experimental molecular weights and the linear reaction kinetics. The aldaric esters with a single hydroxyl group formed polylactide with a carbohydrate end group, whilst the aldaric esters with two hydroxyl groups formed polylactides chain extended by the carbohydrate moiety. The polymerisation kinetics were analysed, under pseudo first order conditions, and showed that the rates of polymerisation depended on the concentration of free hydroxyl groups, consistent with chain transfer occuring more rapidly than propagation. The acid catalysed degradation of the polyesters was examined by GPC and showed that the carbohydrate groups increased the degradation compared to polymers with unfunctionalised end groups. This is because the acetyl protected aldaric ester groups are hydrophilic and thus improve water uptake by the polyester and thereby increase the degradation rate. The strategy of introducing carbohydrate functionality into polylactide is therefore valid as it maintains the renewability of the material whilst increasing the degradation rate.

4. Experimental section

^{1}H NMR spectra were collected on a Bruker AV400 instrument. ^{13}C{^{1}H} NMR spectra were collected on a Bruker AV500 instrument. CDCl$_3$ was used as the NMR solvent and reference compound. The GPC measurements were performed on a Polymer labs GPC 60 instrument with two Polymer labs mixed D columns and THF at a flow rate of 1 mLmin^{-1} as the eluent. Narrow molecular weight polystyrene standards were used to calibrate the instrument and a correction factor of 0.58 was applied to the M_n obtained as outlined in the literature [27]. [*S,S*]-Lactide and *rac*-lactide were donated by Purac Plc, they were purified by recrystallization from hot toluene followed by repeated sublimations in vacuo (3 times). 2,3,4,6-Tetra-*O*-acetyl-D-glucono-1,5-lactone was prepared according to the literature in a single step from D-gluconolactone [24]. The other two lactones were prepared according to a four stage procedure involving per actylation, bromination, hydrolysis and oxidation. The starting materails: 1,2,3,4,6-penta-*O*-acetyl-α-D-galactopyranose and 1,2,3,4,6-penta-*O*-acetyl-α-D-mannopyranose were prepared according to the literature [25].

4.1. General procedure for the synthesis of glycosyl bromides

The procedure for the synthesis of glycoside bromides from their corresponding peracetylated pyranosides was adapted from the one reported by Mitchell et al. [40]. The reactions were allowed to proceed for 20 h instead of 1 h at r.t. as reported in the literature. Reactions were monitored by TLC. The resulting products were in the form of syrups.

4.1.1. 2,3,4,6-Tetra-O-acetyl-α-D-galactopyranosyl bromide

76 % yield. TLC R_f 0.50 (EtOAc:Hexane; 1:1). ^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 6.68 (1 H, d, J = 3.9 Hz, H-1), 5.50 (1 H, m, H-4), 5.39 (1 H, m, H-3), 5.03 (1 H, dd, J = 10.5, 3.9 Hz, H-2), 4.47 (1 H, m, H-5), 4.17 (1 H, dd, J = 11.4, 6.3 Hz, H-6), 4.10 (1 H, dd, J = 11.4, 6.8 Hz, H-6'), 2.14, 2.10, 2.05, 2.00 (4 x 3 H, 4 x s, 4 x (COC*H*$_3$)). ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 170-169 (*C*OCH$_3$), 88.07 (C-1), 71.01 (C-5), 67.95 (C-3), 67.72 (C-2), 66.93 (C-4), 60.81 (C-6), 20.72, 20.62, 20.56, 20.54 (COC*H*$_3$) ppm. MS (CI, ammonia): m/z (%) 428 (100 %, M + NH$_4$, Br-79), 430 (100 %, M + NH$_4$, Br-81).

4.1.2. 2,3,4,6-Tetra-O-acetyl-α-D-mannopyranosyl bromide [41]

95 % yield. TLC R_f 0.38 (EtOAc:Hexane 1:1). ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.32 (1 H, br s, H-1), 5.74 (1 H, dd, J = 10.1, 3.4 Hz, H-3), 5.47 (1 H, dd, J = 3.4, 1.6 Hz, H-2), 5.39 (1 H, apt, J = 10.2 Hz, H-4), 4.36 (1 H, dd, J = 12.4, 4.9 Hz, H-6), 4.25 (1 H, ddd, J = 10.2, 4.9, 2.0 Hz, H-5), 4.16 (1 H, dd, J = 12.5, 2.1 Hz, H-6'), 2.20, 2.13, 2.10 (3 H, s, (COC*H*$_3$)), 2.03 (3 H, s, (COC*H*$_3$)) ppm. NMR data in agreement with literature data [41].

4.2. General procedure for the hydrolysis of glycoside bromides

The procedure for the hydrolysis of glycoside bromides to their corresponding pyranoses was adapted from one reported by Grummitt et al. [42] using Ag$_2$CO$_3$. The reactions were allowed to proceed for 20 h, instead of 4 h 0 as reported in the literature. Reactions were monitored by TLC.

4.2.1. 2,3,4,6-Tetra-O-acetyl-α-D-galactopyranose

88 % yield. TLC R_f 0.20 (EtOAc:Hexane 1:1). ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.50 (1 H, d, J = 3.4 Hz, H-1), 5.46 (1 H,

m, H-2), 5.39 (1 H, m, H-3), 5.13 (1 H, dd, J = 10.8, 3.6 Hz, H-4), 4.46 (1 H, m, H-5), 4.15 (2 H, m, H-6, H-6'), 2.14, 2.13, 2.09, 2.08 (4 x 3 H, s, (COCH$_3$)) ppm. ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 170-169 (COCH$_3$), 90.67 (C-1), 68.24 (C-4), 68.15 (C-2), 67.18 (C-3), 62.54 (C-5), 61.81 (C-6), 20.82-20.55 (4 x (COCH$_3$)) ppm. MS (CI, ammonia): m/z (%) 366 (M + NH$_4$, 100 %).

4.2.2. 2,3,4,6-Tetra-O-acetyl-α-D-mannopyranose [42]

Quantitative yield. TLC R_f 0.22 (EtOAc:Hexane 1:1). ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.39 (1 H, dd, J = 10.1, 3.3 Hz, H-3), 5.28 (1 H, d, J = 9.88, H-4), 5.26 (1H, dd, J = 3.3, 2.0 Hz, H-2), 5.25 (1H, br, H-1), 4.28 - 4.16 (2 H, m, H-5, H-6), 4.15–4.08 (1 H, m, H-6'), 2.14, 2.08, 2.03, 1.98 (4 x 3 H, 4 x s, 4 x (COCH$_3$)) ppm. ^{13}C{^{1}H} NMR (400 MHz, CDCl$_3$) δ 170.8, 170.1, 170.0, 169.8 (4 x COCH$_3$), 91.9 (C-1), 70.1, 68.8, 68.1, 66.1, (C-2 to C-5), 62.5 (C-6), 20.9, 20.8, 20.6, (COCH$_3$) ppm. MS (CI, ammonia): m/z (%) 366 (M + NH$_4$, 100 %). ^{1}H NMR data in agreement with the literature [42].

4.3. General procedure for the Swern oxidation of pyranoses

Oxalyl chloride (3.4 mL, 39 mmol, 7 eq.) was dissolved in dry DCM (100 mL) and cooled to -78 °C. A solution of DMSO (5.4 mL, 76 mmol, 13 eq.) in DCM (15 mL) at −78 °C was added dropwise to the oxalyl chloride solution under N$_2$. After 15 min a solution of the funcitonalised pyranose (5.7 mmol, 1 eq.) in DCM (50 mL) at −78 °C was added dropwise. After 30 min NEt$_3$ (4.0 mL 29 mmol, 5 eq) was slowly introduced and the reaction mixture was stirred at 78 °C for a further 30 min (until this point, the reaction temperature was not allowed to rise beyond −60 °C). The reaction mixture was then allowed to warm to −30 °C and washed with ice-water (200 mL), 1 M HCl (200 mL), saturated NaHCO$_{3(aq)}$ (200 mL), water (200 mL) and brine (200 mL). The organic layer was dried (MgSO$_4$) and concentrated in vacuo to yield the product as a syrup.

4.3.1. 2,3,4,6-Tetra-O-acetyl-D-galactono-1,5-lactone

(1.66 g, 4.79 mmol, 83 %). TLC R_f 0.33 (EtOAc:Hexane 1:1). [α]$_D^{25}$ = +43.2° (c, 1.25, CHCl$_3$) ν_{max}(neat) 1766 cm^{-1} (C = O).^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 5.70 (1 H, dd, J = 2.76, 1.5 Hz, H-4), 5.47 (1 H, dd, J = 10.28, 2.9 Hz, H-3), 5.28 (1 H, d, J = 10.3 Hz, H-2), 4.82 (1 H, m, H-5), 4.25 (2 H, m, H-6, H-6'), 2.20 (3 H, s, COCH$_3$), 2.19 (3 H, s, COCH$_3$), 2.10 (3 H, s, COCH$_3$), 2.08 (3 H, s, COCH$_3$) ppm. ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 170.18, 170.12, 169.75, 169.46 (COCH$_3$); 164.95 (C-1); 74.71 (C-5); 69.16 (C-3); 68.44 (C-2); 66.22 (C-4); 60.98 (C-6); 20.56, 20.52, 20.44, 20.41 (COCH$_3$) ppm. MS (CI, ammonia): m/z (%) 364 (100 %, M + NH$_4$). Anal Calcd for C$_{14}$H$_{18}$O$_{10}$: C, 48.56 %; H, 5.24 %. Anal Found: C, 48.65 %; H 5.37 %.

4.3.2. 2,3,4,6-Tetra-O-acetyl-D-mannono-1,5-lactone [43]

(1.50 g, 4.34 mmol, 76 %). TLC R_f 0.25 (EtOAc:Hexane 1:1). [α]$_D^{25}$ = 30.4°(c, 1.25, CHCl$_3$). ν_{max}(neat) 1748 cm^{-1} (C = O). ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.75 (1 H, d, J = 3.9 Hz, H-2), 5.52-5.46 (1 H, m, H-3), 5.07–5.03 (1 H, m, H-4), 4.62 (1 H, ddd, J = 8.6, 5.8, 3.2 Hz, H-5), 4.37 (1 H, dd, J = 12.4, 3.1 Hz, H-6), 4.27 (1 H, dd, J = 12.5, 5.8 Hz, H-6'), 2.15 (3 H, s, COCH$_3$), 2.16 (3 H, s, COCH$_3$), 2.18 (3 H, s, COCH$_3$), 2.12 (3 H,

s, COCH$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 170.39, 169.41, 169.04, 168.97 (COCH$_3$), 164.81 (C-1), 75.37 (C-5), 70.38 (C-3), 69.10 (C-4), 66.53 (C-2), 62.26 (C-6), 20.63 - 20.38 (COCH$_3$) ppm. MS:(CI - NH$_3$) m/z: 364 (M + NH$_4$, 60 %). Anal Calcd. for C$_{14}$H$_{18}$O$_{10}$: C, 48.56 %; H, 5.24 %. Found: C, 48.70 %; H, 5.12 %.

4.4. General procedure for preparation of initiators 1-6

The 1,5-lactone (300 mg) was dissolved in CHCl$_3$ (15 mL) and to it was added a 1.0 M solution of the alcohol (1 eq.) containing p-TSA (0.1 eq.) After the appropriate time (15 mins -2 h), the reaction was quenched with NaHCO$_{3(aq)}$ (50 mL), washed with water (2 × 50 mL) and dried (MgSO$_4$). The organic layer was concentrated in vacuo to yield the aldaric ester as a syrup. n-Butyl aldaric esters were prepared using butan-1-ol and 4-hydroxybutyl aldaric ester were prepared using 1,4-butanediol.

4.4.1. 4-Hydroxybutyl 2,3,4,6-tetra-O-acetyl-D-gluconate 1

Reaction time: 2 h. (0.37 g, 0.89 mmol, 95 %). TLC R_f 0.43 – some decomposes to lactone on TLC plate (EtOAc:Hexane 1:1). [α]$_D^{25}$ = +45.2° (c, 1.15, CHCl$_3$). ν_{max}(neat) 3485 cm^{-1} (OH), 1738 cm^{-1} (C = O). ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.74 (1 H, m, H-2), 5.29 (1 H, m, H-3), 5.20 (1 H, dd, J = 8.3, 3.6 Hz, H-4), 4.22–4.12 (6 H, m, J = 14.3, 7.2 Hz, C(O)OCH$_2$CH$_2$CH$_2$-CH$_2$OH, H-6), 3.84(1 H, m, H-5), 3.01 (1 H, d, J = 5 Hz, OH), 2.16 (3 H, s, COCH$_3$), 2.14 (3 H, s, COCH$_3$), 2.10 (6 H, s, 2 x COCH$_3$), 1.27 (4 H, m, C(O)OCH$_2$CH$_2$CH$_2$CH$_2$OH) ppm. ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 171.15, 170.58, 169.76, 166.76 (COCH$_3$, C-1), 71.81 (C-3), 70.56 (C-4), 69.50 (C-2), 68.41 (C-5), 64.65, 62.16 (C(O)OCH$_2$CH$_2$CH$_2$CH$_2$OH, C-6), 20.78, 20.58, 20.47 (COCH$_3$), 14.00 (C(O)OCH$_2$CH$_2$CH$_2$-CH$_2$OH) ppm. MS: (CI - NH$_3$) m/z: 454 (M + NH$_4$, 25 %). Anal Calcd. for C$_{18}$H$_{28}$O$_{12}$: C, 49.54 %; H, 6.47 %. Anal Found: C, 49.62 %; H, 6.38 %.

4.4.2. 4-Hydroxybutyl 2,3,4,6-tetra-O-acetyl-D-galactonate 2

(0.76 g, 1.11 mmol, 60 % yield). TLC: decomposes on silica. [α]$_D^{25}$ = +8.00°(c, 0.5, CHCl$_3$). ν_{max}(neat) 3519 cm^{-1} (OH), 1749 cm^{-1} (C = O). ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.78 (1 H, dd, J = 9.8, 2.0 Hz, H-2), 5.21-5.16 (1 H, m, H-3), 4.22–4.06 (4 H, m, H-4, H-5, H-6, H-6'), 4.03-3.82 (2 H, m, C(O)OCH$_2$CH$_2$CH$_2$OH), 3.72–3.63 (2 H, m, C(O)OCH$_2$CH$_2$-CH$_2$OH), 2.18 (3 H, s, COCH$_3$), 2.14 (3 H, s, COCH$_3$), 2.13 (3 H, s, COCH$_3$), 2.09 (3 H, s, COCH$_3$), 1.81–1.68 (2 H, m, C(O)OCH$_2$CH$_2$CH$_2$CH$_2$OH), 1.32–1.23 (2 H, m, C(O)OCH$_2$CH$_2$CH$_2$CH$_2$OH) ppm. ^{13}C{^{1}H} NMR (126 MHz, CDCl3) δ 170.98–169.35 (COCH$_3$), 168.03 (C-1), 69.709 (C-2), 68.531 (C-3), 68.21, 68.29, 68.21, 63.51 (C-4, C-5, C-6, C-6'), 68.27 (C(O)OCH$_2$CH$_2$CH$_2$CH$_2$OH), 25.38 (C(O)OCH$_2$CH$_2$CH$_2$CH$_2$OH), 21.08–19.66 (COCH$_3$), 12.97 (C(O)OCH$_2$CH$_2$CH$_2$CH$_2$OH) ppm. MS: (CI - NH$_3$) m/z: 454 (M + NH$_4$, 100 %). Anal. Calcd. for C$_{18}$H$_{28}$O$_{12}$ C, 49.54 %; H, 6.47 %. Anal. Found: C, 49.50 %; H, 6.57 %.

4.4.3. 4-Hydroxybutyl 2,3,4,6-tetra-O-acetyl-D-mannonate 3

(0.96 g, 2.20 mmol, 76 % yield). TLC: decomposes to lactone on silica. [α]$_D^{25}$ = +13.09°(c, 2.75, CHCl$_3$). ν_{max} (neat) 1761 cm^{-1} (C = O). ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.66 (1 H, dd, J = 8.6, 2.2 Hz, H-3), 5.27 (1 H, dd, J = 9.1, 2.1 Hz,

H-4), 5.17 (1 H, d, J = 7.8 Hz, H-2), 4.29–4.07 (3 H, m, H-5, H-6, H-6'), 4.01 (2 H, m, C(O)OCH$_2$CH$_2$CH$_2$CH$_2$OH), 3.68 (2 H, m, C(O)OCH$_2$CH$_2$CH$_2$CH$_2$OH), 2.15 (3 H, s, COCH$_3$), 2.13 (3 H, s, COCH$_3$), 2.09 (6 H, 2 x s, COCH$_3$), 1.75 (2 H, m, C(O)OCH$_2$CH$_2$CH$_2$CH$_2$OH), 1.27 (2 H, m, C(O)OCH$_2$CH$_2$CH$_2$CH$_2$OH) ppm. ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 171-169 (COCH$_3$, C-1), 66.44 (C-3), 69.55 (C-4), 69.55 (C-2), 64.21, 62.87, 61.96 (C-5, C-6, C-6'), 64.65 (C(O)OCH$_2$CH$_2$CH$_2$CH$_2$OH), 61.96 (C(O)OCH$_2$CH$_2$CH$_2$CH$_2$OH), 25.42 (C(O)OCH$_2$CH$_2$CH$_2$CH$_2$OH), 20.02 (COCH$_3$), 20.02 (COCH$_3$), 20.48 (COCH$_3$), 20.48 (COCH$_3$), 13.78 (C(O)OCH$_2$CH$_2$CH$_2$CH$_2$OH), ppm. MS: (CI - NH$_3$) *m/z*: 454 (M + NH$_4$, 29 %). Anal Calcd for C$_{18}$H$_{28}$O$_{12}$ C, 49.54 %; H, 6.47 %. Anal Found C, 49.68 %; H, 6.39 %.

4.4.4. n-Butyl 2,3,4,6-tetra-O-acetyl-D-gluconate 4

(0.28 g, 0.66 mmol, 67 % yield). TLC: decomposes on silica. [α]$_D^{25}$ = +24.9° (c, 1.85, CHCl$_3$). ν_{max}(neat) 3523 cm^{-1} (OH), 1741 cm^{-1} (C = O). ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.73 (1 H, apt t, J = 3.7 Hz, H-3), 5.30 (1 H, d, J = 3.9 Hz, H-2), 5.20 (1 H, dd, J = 8.3, 3.6 Hz, H-4), 4.23–4.02 (4 H, m, H-6. H-6', C(O)OCH$_2$CH$_2$CH$_2$CH$_3$), 3.89–3.80 (1 H, m, H-5), 2.16 (3 H, s, COCH$_3$), 2.13 (3 H, s, COCH$_3$), 2.09 (6 H, s, 2 x COCH$_3$), 1.66–1.57 (2 H, m, C(O)OCH$_2$CH$_2$CH$_2$CH$_3$), 1.45–1.31 (2 H, m, C(O)OCH$_2$CH$_2$CH$_2$CH$_3$), 0.93 (3 H, apt t, J = 7.4 Hz, C(O)OCH$_2$CH$_2$CH$_2$CH$_3$) ppm. ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 171.13, 170.51, 169.73, 166.87 (COCH$_3$, C-1), 71.75 (C-2), 70.78 (C-4), 69.51 (C-3), 68.41 (C-5), 65.94, 64.66 (C-6, C(O)OCH$_2$CH$_2$CH$_2$CH$_3$) 30.39 (C(O)OCH$_2$CH$_2$CH$_2$CH$_3$), 20.74, 20.54, 20.44 (COCH$_3$), 18.93 (C(O)OCH$_2$CH$_2$CH$_2$CH$_3$), 13.61 (C(O)OCH$_2$CH$_2$CH$_2$CH$_3$) ppm. MS: (CI - NH$_3$) *m/z*: 438 (M + NH$_4$, 100 %). Anal. Calcd. for C$_{17}$H$_{26}$O$_{11}$: C, 51.42 %; H, 6.71 %. Anal. Found: C, 51.33 %; H, 6.78 %.

4.4.5. n-Butyl 2,3,4,6-tetra-O-acetyl-D-galactonate 5

(0.15 g, 0.35 mmol, 49 % yield). TLC: decomposes on silica. [α]$_D^{25}$ = +6.7° (c, 1.8, CHCl$_3$). ν_{max}(neat) 3430 cm^{-1} (OH), 1751 cm^{-1} (C = O). ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.76 (1 H, m, H-2), 5.30 (1 H, dd, J = 3.9, 2.0 Hz, H-4), 5.16 (1 H, m, H-3), 4.25–4.15 - 4.06 (4 H, m, C(O)OCH$_2$CH$_2$CH$_2$CH$_3$, H-6), 3.97 (1 H, dd, J = 11.5, 7.4 Hz, H-5), 2.15 (3 H, s, COCH$_3$), 2.11 (3 H, s, COCH$_3$), 2.07 (3 H, s, COCH$_3$), 2.06 (3 H, s, COCH$_3$), 1.72–1.52 (2 H, m, C(O)OCH$_2$CH$_2$CH$_2$CH$_3$), 1.45–1.20 (2 H, m, C(O)OCH$_2$CH$_2$CH$_2$CH3), 0.88 (3 H, m, C(O)OCH$_2$CH$_2$CH$_2$CH$_3$) ppm. ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 170.99, 170.51, 170.18, 169.36 (COCH$_3$), 167.76 (C-1), 69.62 (C-2, C-4), 68.65 (C-3), 67.71 (C-5), 66.01 (C(O)OCH$_2$CH$_2$CH$_2$CH$_3$), 65.86 (C-6), 30.3 (C(O)OCH$_2$CH$_2$CH$_2$CH$_3$), 20.74, 20.71, 20.55, 20.43 (COCH$_3$) 18.95 (C(O)OCH$_2$CH$_2$CH$_2$CH$_3$) 13.6 (C(O)OCH$_2$CH$_2$CH$_2$CH$_3$) ppm. MS: (CI - NH$_3$) *m/z*: 438 (M + NH$_4$, 100 %). Anal. Calcd. for C$_{18}$H$_{28}$O$_{11}$: C, 51.42 %; H, 6.71 %. Anal. Found: C, 51.33 %; H, 6.60 %.

4.4.6. n-Butyl 2,3,4,6-tetra-O-acetyl-D-mannonate 6

(0.13 g, 0.30 mmol, 21 % yield). TLC: decomposes on silica. ν_{max}(neat) 3406 cm^{-1} (OH), 1749 cm^{-1} (C = O). ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.67 (1 H, dd, J = 8.5, 2.2 Hz, H-3), 5.28 (1 H, dd, J = 9.1, 2.2 Hz, H-2), 5.09 (1 H, d, J = 8.5 Hz, H-4), 4.29 - 4.14 (2 H, m, C(O)OCH$_2$CH$_2$CH$_2$CH$_3$), 4.11 (2 H, td,

J = 11.0, 5.3 Hz, H-6/H-6'), 3.80 (1 H, ddd, J = 11.6, 8.1, 3.4 Hz, H-5), 2.15, 2.13, 2.09 (12 H, 4 x COCH$_3$), 1.69 - 1.52 (2 H, m, C(O)OCH$_2$CH$_2$CH$_2$CH$_3$), 1.38 (2 H, td, J = 15.0, 7.4, Hz, C(O)OCH$_2$CH$_2$CH$_2$CH$_3$), 0.94 (3 H, t, J = 7.4 Hz, C(O)OCH$_2$CH$_2$CH$_2$CH$_3$) ppm. ^{13}C{^{1}H} NMR (126 MHz, CDCl3) δ 171.14, 170.85, 169.64, 169.55 (COCH$_3$), 167.57 (C-1), 69.59 (C-4), 69.55 (C-2), 68.97 (C-3), 67.62 (C-5), 64.78 (C-6), 65.91 (C(O)OCH$_2$CH$_2$CH$_2$CH$_3$), 30.36 (C(O)OCH$_2$CH$_2$CH$_2$CH$_3$), 20.77, 20.62, 20.39 (COCH$_3$), 18.94 (30.36 (C(O)OCH$_2$CH$_2$CH$_2$CH$_3$)) 13.6 (30.36 (C(O)OCH$_2$CH$_2$CH$_2$CH$_3$)) ppm. MS: (CI - NH$_3$) *m/z*: 438 (M + NH$_4$, 100 %).

4.5. Lactide Polymerisation Protocol

To a solution of LZnEt (0.1 mL of 0.07 M solution in CDCl$_3$, 7.00 µmol, 1 eq.) and the aldaric ester (0.1 mL of 0.07 M solution in CDCl$_3$, 7.00 µmol, 1 eq.), in a Young's tap NMR tube, was added lactide (50.4 mg, 0.35 mmol, 50 eq.) and CDCl$_3$ (0.3 mL). Monomer conversion was monitored by ^{1}H NMR spectroscopy. Once complete conversion was achieved, the polymer was isolated by repeated precipitation into hexane (isolated yield = 90 % in all cases) and was analyzed by ^{1}H NMR spectroscopy and GPC.

4.6. Degradation Protocol

The polymer sample (20 mg), which had previously been dried in vacuo was dissolved in CHCl$_3$ to form a 3 mg/mL solution. To this was added TFA$_{(aq)}$/CHCl$_3$ (2 % v/v) (0.1 mL per mL of polymer solution). Aliquots were taken on a daily basis and analysed by GPC (CHCl$_3$, polystyrene standards).

References

[1] A.J. Ragauskas, C.K. Williams, B.H. Davison, G. Britovsek, J. Cairney, C.A. Eckert, W.J. Fredrick Jr., J.P. Hallett, D.J. Leak, C.L. Liotta, J.R. Mielenz, R. Murphy, R. Templer, T. Tschaplinski, Science 311 (2006) 484.
[2] http://www.natureworksllc.com/, http://www2.dupont.com/Sorona/en_US/, http://www.mirelplastics.com/.
[3] W. Amass, A. Amass, B. Tighe, Polymer Int. 47 (1998) 89.
[4] R.W. Drumwright, P.R. Gruber, D.E. Henton, Adv. Mater. 12 (2000) 1841.
[5] R.H. Platel, L.M. Hodgson, C.K. Williams, Polym. Rev. 48 (2008) 11.
[6] O. Dechy-Cabaret, B. Martin-Vaca, D. Bourissou, Chem. Rev. 104 (2004) 6147.
[7] A.P. Dove, Chem. Commun. (2008) 6446.
[8] B.J. O'Keefe, M.A. Hillmyer, W.B. Tolman, Dalton Trans. (2001) 2215.
[9] C.K. Williams, Chem. Soc. Rev. 36 (2007) 1573.
[10] A.C. Albertsson, I.K. Varma, Biomacromolecules 4 (2003) 1466.
[11] R. Auras, B. Harte, S. Selke, Macromol. Biosci. 4 (2004) 835.
[12] M. Tang, A.J.P. White, M.M. Stevens, C.K. Williams, Chem. Commun. (2009) 941.
[13] K. Bernard, P. Degeé, P. Dubois, Polymer Int. 52 (2003) 406.
[14] K.S. Bisht, F. Deng, R.A. Gross, D.L. Kaplan, G.J. Swift, Am. Chem. Soc. 120 (1998) 1363.
[15] A. Córdova, T. Iversen, K. Hult, Macromolecules 31 (1998) 1040.
[16] F. Deng, K.S. Bisht, R.A. Gross, D.L. Kaplan, Macromolecules 32 (1999) 5159.
[17] H.R. Kricheldorf, A. Stricker, Macromolecules 33 (2000) 696.
[18] Y. Nagasaki, K. Yasugi, Y. Yamamoto, A. Harada, K. Kataoka, Biomacromolecules 2 (2001) 1067.
[19] T. Ouchi, T. Uchida, Y. Ohya, Macromol. Biosci. 1 (2001) 371.
[20] P.V. Persson, J. Schröder, K. Wickholm, E. Hedenström, T. Iversen, Macromolecules 37 (2004) 5889.
[21] K. Yasugi, T. Nakamura, Y. Nagasaki, M. Kato, K. Kataoka, Macromolecules 32 (1999) 8024.
[22] A.F. Haider, C.K. Williams, J. Polym. Sci., Part A: Polym. Chem. 46 (2008) 2891.

[23] M. Tang, A.F. Haider, C. Minelli, M.M. Stevens, C.K. Williams, J. Polym. Sci. Part A: Polym. Chem. 46 (2008) 4352.
[24] C.C. Joseph, H. Regeling, B. Zwanenburg, G.J.F. Chittenden, Tetrahedron 58 (2002) 6907.
[25] D. Wahlera, O. Boujarda, F. Lefèvre, J.L. Reymond, Tetrahedron 60 (2004) 703.
[26] C.K. Williams, L.E. Breyfogle, S.K. Choi, W. Nam, V.G. Young Jr., M.A. Hillmyer, W.B. Tolman, J. Am. Chem. Soc. 125 (2003) 11350.
[27] A. Kowalski, A. Duda, S. Penczek, Macromolecules 31 (1998) 2114.
[28] M.H. Chisholm, E.E. Delbridge, J.C. Gallucci, New J. Chem. 28 (2004) 145.
[29] M. Vert, S. Li, H.J. Garreau, Controlled Release 16 (1991) 15.
[30] Y.X. Li, C. Volland, T. Kissel, Polymer 39 (1998) 3087.
[31] X.H. Zong, Z.G. Wang, B.S. Hsiao, B. Chu, J.J. Zhou, D.D. Jamiolkowski, E. Muse, E. Dormier, Macromolecules 32 (1999) 8107.
[32] P. Nugroho, H. Mitomo, F. Yoshii, T. Kume, Polym. Degrad. Stab. 72 (2001) 3373.

[33] G. Sivalingam, G. Madras, Polym. Degrad. Stab. 84 (2004) 393.
[34] X.B. Liu, Y.B. Zou, W.T. Li, G.P. Cao, W. Chen, J. Polym. Degrad. Stab. 91 (2006) 3259.
[35] A. Kulkarni, J. Reiche, A. Lendlein, Surf. Interface Anal. 39 (2007) 740.
[36] E. Vey, A.F. Miller, M. Claybourn, A. Saiani, Macromol. Symp. 251 (2007) 81.
[37] A. Belbella, C. Vauthier, H. Fessi, J.P. Devissaguet, F. Puisieux, Int. J. Pharm. 129 (1996) 95.
[38] C.J. Shih, Controlled Release 34 (1995) 9.
[39] C. Shih, Pharm. Res. 12 (1995) 2036.
[40] S.A. Mitchell, M.R. Pratt, V.J. Hruby, R. Polt, J. Org. Chem. 66 (2001) 2327.
[41] C. Nobrega, J.T. Vazquez, Tet. Asymm. 14 (2003) 2793.
[42] A.R. Grummitt, M.M. Harding, P.I. Anderberg, A. Rodger, Eur. J. Org. Chem. (2003) 63.
[43] D. Senni, J.P. Praly, Synth. Commun. 28 (1998) 433.