

Supporting Information

RSC Advances

A new and Efficient Lactic Acid Polymerization by Multimetallic Cerium Complexes: a Poly(lactic acid) suitable for Biomedical Applications

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Table of Contents

General methods.....	3
Optimization step for pre-polymer synthesis: test for commercially available catalysts	4
Ring opening polymerization batch process: screening of several reaction times.....	5
General experimental procedure for the two-step polycondensation (PC), Solid State polymerization (SSP) process.....	6
General experimental procedure for the solvent free ring-opening polymerization (ROP) of LA under microwaves	7
The XPS depiction of the method.....	8
Figure S1. ¹ H-NMR of OLLA (Table S1, entry 1g), with CeCl ₃ ·7H ₂ O-NaI system.....	8
Figure S2. TG result comparison between three different samples: prepolymer Mw = 3600; OLLA 2 Mw = 48300; PLLA 4 Mw = 146000.....	9
Figure S3. Molecular weight vs CeCl ₃ ·7H ₂ O-NaI molar ratio.....	10

Figure S4. Dependence of molecular weight vs reaction time.....	10
Figure S5. Dependence of molecular weight vs reaction time under mW irradiation...	11
Figure S6. FTIR-ATR spectra of L-lactic acid purchased from Sigma Aldrich.....	12
Figure S7. FTIR-ATR spectra of PLLA Mw=146000 (Table 2, entry 2m)	13
Figure S8. ¹ H-NMR of Poly(L-lactic acid) (PLLA); ¹ H-NMR (400MHz, CDCl ₃) δ _H = 1.6 (CH ₃), 5.1(-OOCCH(CH ₃)O-)	14
Figure S9. ¹³ C-NMR of Poly(L-lactic acid) (PLLA); ¹³ C-NMR (100MHz, CDCl ₃) δ _C = 16.8 (CH ₃), 69.2 (-OOCCH(CH ₃)O-), 169.8 (-OOCCH(CH ₃)O-)	15
Figure S10. GPC graph of PLLA 4 generated in presence of CeCl ₃ ·7H ₂ O:NaI (1:1) at 180°C for 7 hours. (Table 2, entry 2c)	16
Figure S11. GPC graph of PLLA 4 generated starting from entry 2c (Mw = 48300 Da) at 150°C under reduced pressure (0.5Torr) for 16 hours. (Table 2, entry 2l)	17
Figure S12. GPC graph of PLLA 4 generated starting from entry 2c (Mw = 48300 Da) at 150°C under reduced pressure (0.5Torr) for 29 hours. (Table 2, entry 2m)	17
Figure S13. GPC graph of PLLA 4 starting from L-Lactide and CeCl ₃ ·7H ₂ O:NaI (1:1) with 3 mol% of BnOH at 165°C for 12 hours. (Table 4, entry 4b)	18
Figure S14. GPC graph of PLLA 4 starting from L-Lactide and CeCl ₃ ·7H ₂ O:NaI (1:1) with 3 mol% of BnOH at 165°C for 1 hour (mW). (Table 5, entry 5b)	18
Figure S15. GPC graph of PLLA 4 starting from L-Lactide and CeCl ₃ ·7H ₂ O:NaI (1:1) with 1.5 mol% of BnOH at 165°C for 1 hour (mW). (Table 6, entry 6f)	19
Figure S16. Mark-Houwink plot of PLLA 4 generated starting from entry 2c (Mw = 48300 Da) at 150°C under reduced pressure (0.5Torr) for 16 hours. (Table 2, entry 2l)	20
Figure S17. Mark-Houwink plot of PLLA 4 generated starting from entry 2c (Mw = 48300 Da) at 150°C under reduced pressure (0.5Torr) for 29 hours. (Table 2, entry 2m)	20
References	21

General Methods

Cerium(III) chloride heptahydrate, sodium iodide are commercially available and used without further purification. L-Lactic acid (80%), catalysts and solvents were purchased from Sigma Aldrich, 80% L-Lactic Acid from Sigma Aldrich (LLA) was treated to remove water first. All solvents were dried and freshly distilled prior to use, in particular THF, Tetrahydrofuran anhydrous, $\geq 99.9\%$ with 250 ppm BHT as inhibitor. Concerning the products, characterization data for polyester compounds are reported because these data were used to demonstrate the goodness of our new methodology. Infrared spectra were recorded with a Perkin-Elmer FT-IR spectrometer Spectrum Two UATR, equipped with a ZnSe crystal. The FTIR spectroscopy measurements were performed in a $400\text{-}4000\text{ cm}^{-1}$ range at a 2 cm^{-1} resolution, 4 scans and processed by a Perkin-Elmer data manager (Spectrum). $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra were recorded on a Varian Mercury 400 (400 MHz). Chemical shifts are quoted in ppm and are referenced to residual protons in the deuterated solvent as the internal standard such as CDCl_3 (7.26ppm). Thermogravimetric analysis was carried out using a Perkin-Elmer STA 6000 thermal analyser. The thermal analysis was performed in a nitrogen atmosphere with a flow rate of 50 mL/min using an alumina (Al_2O_3) crucible. A constant heating rate of $10^\circ\text{C}/\text{min}$ was maintained until the maximum temperature of 900°C was reached. Molecular weight distributions (MWDs) were assessed by GPC using THF eluent. The Gel Permeation Chromatography measurements were carried out with an Agilent 1260 Infinity II Multi Detector Suite (MDS) device. In this device, there was an Agilent 1260 Infinity Quaternary Pump (G7111B), containing a 4-channel vacuum degasser to pump the eluent into the system. The auto sampler was G7129A and the thermostat column compartment G7116A. The used device consisted of three different detectors (G7800A): a dual light scattering detector (measuring in the angles of 15° and 90°), a refractive index detector RI operating at 658 nm, and a viscosimeter VS-detector. The THF mobile phase contained 250ppm of butylhydroxytoluene (BHT) and the flow rate was fixed at 1.0 mL/min. The THF GPC system was equipped with two $5\text{ }\mu\text{m}$ columns (30 cm) in series, a mixed C and a mixed D column. A guard column (Agilent GPC/SEC Guard Column, a HPLC Guard Column PLgel $5\text{ }\mu\text{m}$, $7,5 \times 50\text{ mm}$) was settled. A series of ten narrow-monodisperse polystyrene (PS) standards (M_p values ranging from 580 to 283800 g mol^{-1}) were used for column calibration. Microwave irradiations were performed by means of a Biotage® Initiator⁺.

Optimization step for pre-polymer synthesis: test for commercially available catalysts

Table S1. Screening of catalysts and properties of the prepolymer.

L-lactic acid **1** $\xrightarrow[3\text{h, } 180^\circ\text{C}]{\text{Catalyst (0.1 mol\%)}}$ Oligo(L-lactic acid) **2**
OLLA

Entry	Catalyst	Mn ^a (g mol ⁻¹)	Mn ^b (g mol ⁻¹)	Mw ^b (g mol ⁻¹)	T _{on} ^c (°C)	Yield ^d (%)
S1a	/	220	340	450	239	55
S1b	CuCl ₂	780	650	900	250	40
S1c	InCl ₃	750	500	600	250	45
S1d	FeCl ₃	560	570	899	250	38
S1e	SnCl ₂ ·2H ₂ O	1690	2000	2200	269	47
S1f	CeCl ₃ ·7H ₂ O	630	500	640	260	42
S1g	CeCl ₃ ·7H ₂ O-NaI	1270	2000	3600	270	55
S1h	ZnO	690	530	700	270	38
S1i	Fe ₂ O ₃	530	540	750	234	46
S1l	TiO ₂	430	400	500	230	48
S1m	Al ₂ O ₃	300	490	700	255	41
S1n	LaCl ₃	290	390	590	242	50

^a ¹H-NMR analysis. ^b GPC analysis (detector RI, refractive index). ^c TGA analysis. ^dyield (%) calculated by the equation $Y = [\text{g PLLA} / \text{g LLA}] * 100$.

All reported inorganic salts were used conducting the oligomerization in a batch reaction system of 8 mL, for 3 hours at 180°C.

Ring opening polymerization batch process: screening of several reaction times

Table S2. ROP kinetic study

Entry	Time	Mn (g/mol) ^a	M _w (g/mol) ^a	PD ^a	T _{onset} (°C) ^b	Conv. (%) ^a
S2a	2	11500	14200	1.20	243	65
S2b	4	9200	14200	1.50	282	89
S2c	6	12400	16100	1.30	268	94
S2d	8	13200	16600	1.20	284	96
S2e	10	13700	16700	1.22	284	96
S2f	12	16700	18100	1.08	291	96
S2g	14	16100	16900	1.05	273	92

^a GPC analysis (triple detector). ^b TGA analysis.

General experimental procedure for the two-step polycondensation (PC), Solid State polymerization (SSP) process

FIRST CATALYST SCREENING - *Direct Polycondensation of L-lactic acid 1 to OLLA 2*. In a 25 mL two-necked round bottom flask, 8mL of L-lactic acid **1** (80%) was treated and heated at 180°C for 3 hours under magnetic stirring in the presence of an equimolar ratio (0.1mol%) of catalyst (see Table 1). After the set time, the product was dissolved in chloroform (CHCl₃) and subsequently precipitated into diethyl ether (Et₂O).

FIRST POLYCONDANSATION STEP - *Melt-Solid polycondensation of L-Lactic Acid 1 to OLLA 2: I° STEP*. In a 25 mL two-necked round bottom flask, 4mL of L-lactic acid **1** (80 wt%) was dehydrated at 150°C. The dehydration step was performed for 2 hours under atmospheric pressure, then at a reduced pressure of 100 Torr for further 2 hours, and finally at 30 Torr for other 4 hours, keeping the temperature at 150°C all the time. The obtained Oligo(L-lactic acid) (OLLA) **2** resulted in a glassy solid at room temperature with a number average molecular weight of Mn = 2300 g mol⁻¹ determined by ¹H-NMR. This Mn was confirmed with a GPC analysis of Mn = 2000 g mol⁻¹.

TWO STEP SYNTHESIS - *Melt-Solid polycondensation-SSP from OLLA 2 to PLLA 4: II° STEP*. In a 25 mL two-necked round bottom flask, 5g of Oligo(L-lactic acid) (OLLA) **2** were mixed with a predetermined amount of catalyst (see Table 2). Then the mixture was heated under mechanical stirring and the pressure was reduced stepwise to 10 Torr, allowing the reaction to stir for an appropriate time (see Table 2). The Solid State polymerization (SSP) was performed at 105°C for 1 hour under reduced pressure (0.5 Torr). The product **4** was dissolved in chloroform (CHCl₃) and subsequently recrystallized into diethyl ether (Et₂O). Poly(lactic acid) (PLLA) **4** obtained with this polymerization procedure was subjected to chemical characterization by infrared spectroscopy (FTIR-ATR), nuclear magnetic resonance (NMR), Thermogravimetric analysis (TGA) and gel permeation chromatography (GPC) analysis.

General experimental procedure for the solvent free ring-opening polymerization (ROP) of LA.

ROP POLYMERIZATION in batch – *Ring Opening Polymerization from L-Lactide 3 to PLLA 4*: In a 25 mL two-necked round bottom flask, 3g of L-lactide **3** were mixed with a predetermined amount of catalyst (see Table 3) and co-initiators (see Table 4). Then, the mixture was heated at 165°C under mechanical stirring for an appropriate time (see Figure S4). The product **4** was dissolved in chloroform (CHCl₃) and subsequently recrystallized into diethyl ether (Et₂O). Poly(lactic acid) (PLLA) **4** obtained with this polymerization procedure was subjected to chemical characterization by infrared spectroscopy (FTIR-ATR), nuclear magnetic resonance (NMR), thermogravimetric analysis (TGA) and gel permeation chromatography (GPC) analysis.

ROP POLYMERIZATION under microwaves irradiation – *Ring Opening Polymerization from L-Lactide 3 to PLLA 4*: 3g of L-lactide **3** were irradiated by Biotage® Initiator⁺ at appropriate temperature (see Table 5) and time (see Figure S5), with a predetermined amount of catalyst and co-initiators (see Table 6). The product **4** was dissolved in chloroform (CHCl₃) and subsequently recrystallized into diethyl ether (Et₂O).

Poly(lactic acid) (PLLA) **4** obtained with this polymerization procedure was subjected to chemical characterization by infrared spectroscopy (FTIR-ATR), nuclear magnetic resonance (NMR), thermogravimetric analysis (TGA) and gel permeation chromatography (GPC) analysis.

XPS depiction of the method

All the XPS spectra were taken after deposition of a homogeneous layer of the fine powdered samples of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O-NaI}$, respectively, transferred onto a sample holder by means of a scotch tape. The photon source was the unmonochromatized Al $K\alpha$ ($h\nu = 1486.7$ eV) line. The analyser is a VG-Clam 4 hemispherical analyser providing an overall resolution of 0.7 eV for a constant pass energy of 22 eV. All spectra have been aligned to the silica Si 2p core level (103.4 eV) in order to compensate charging of the samples. All measurements have been performed below 10^{-9} Torr.

From the present study we cannot observe a variation within few percent in the intensity of the f^2 satellite, signifying that the introduction of the NaI in the system does not vary the degree of the hybridization of the f states with conduction states. Such a hybridization is certainly enhanced for both samples with respect to the only CeCl_3 molecular structure, but this characteristic is conserved after the insertion of NaI. Furthermore, it can be excluded the presence of an initial f^0 (metallic) state due to the promotion of the “f” electron in the valence bond. Such a peak is in general observed at 10 eV higher binding energies.

Figure S1

OLLA 2 $^1\text{H-NMR}$ Spectrum

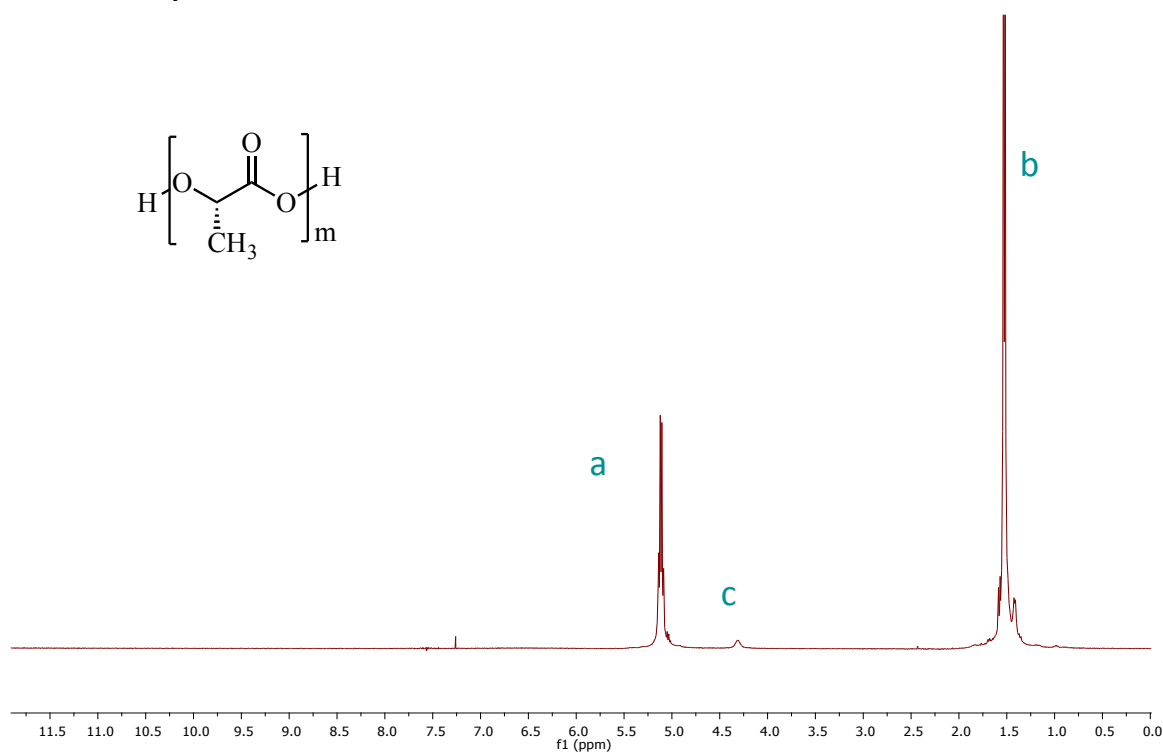


Figure S1. $^1\text{H-NMR}$ of OLLA (Table S1, entry 1g), with $\text{CeCl}_3 \cdot 7\text{H}_2\text{O-NaI}$ system.

Thermogravimetric analysis (TGA)

Figure S2 shows the TG/DTA results for three different samples, the prepolymer after the dehydration $M_w = 3518$ ($T_{\text{onset}} = 270^\circ\text{C}$), $M_w = 48240$ ($T_{\text{onset}} = 300^\circ\text{C}$) and $M_w = 146006$ ($T_{\text{onset}} = 310^\circ\text{C}$) at the same heating rates. The TG results confirm differences in thermal decomposition, increasing the molecular weight there is a significant increment of the T_{onset} . The presence of one stereoisomer is also confirmed by TGA analysis, showing the complete degradation in one single stage.

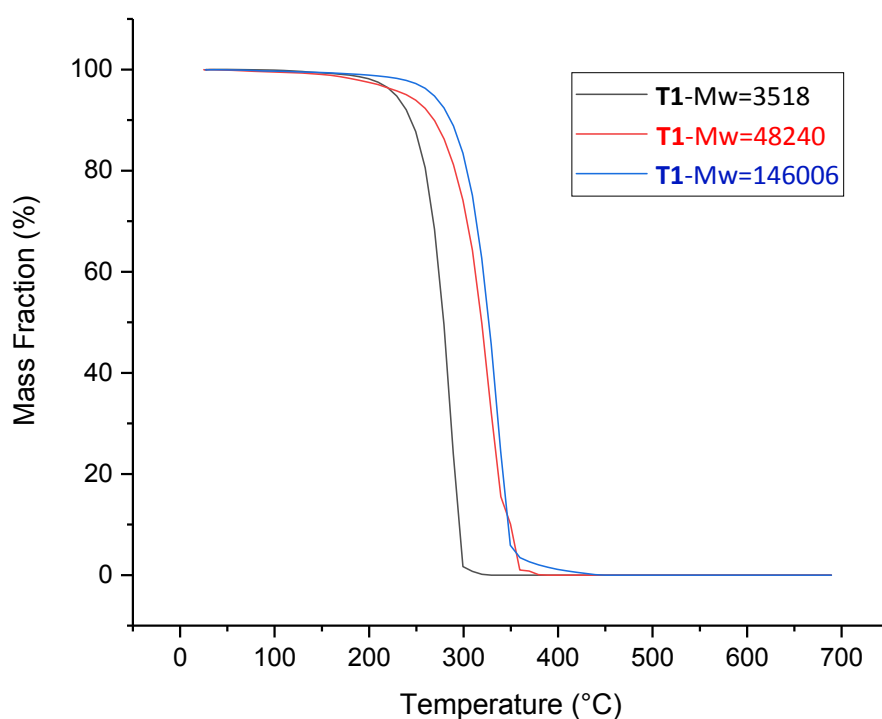


Figure S2. TG result comparison between three different samples: prepolymer $M_w = 3600$; OLLA **2** $M_w = 48300$; PLLA **4** $M_w = 146000$.

Figure S3

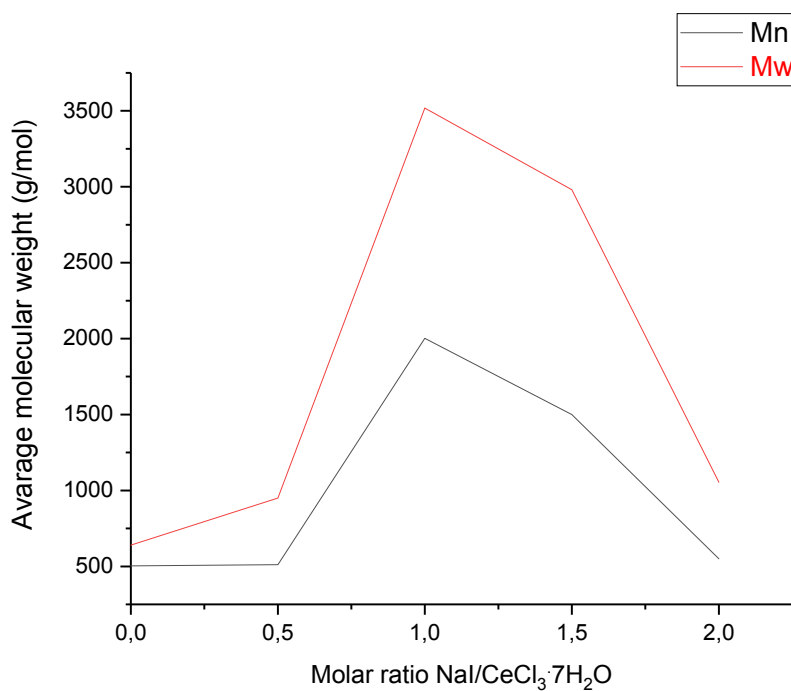


Figure S3. Molecular weight vs CeCl₃·7H₂O-NaI molar ratio.

Figure S4

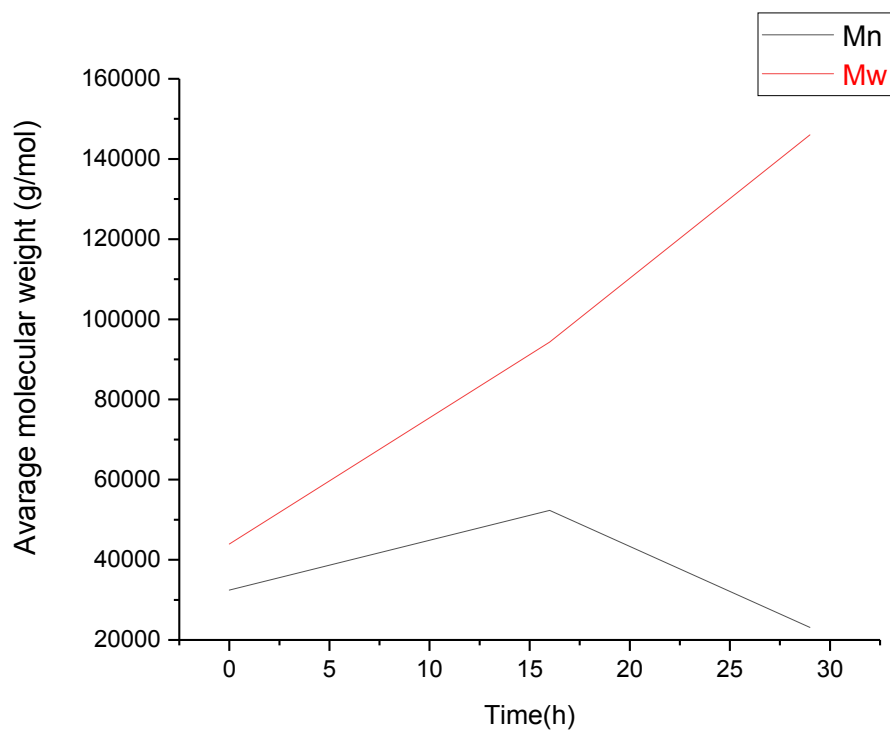


Figure S4. Dependence of molecular weight vs reaction time

Figure S5

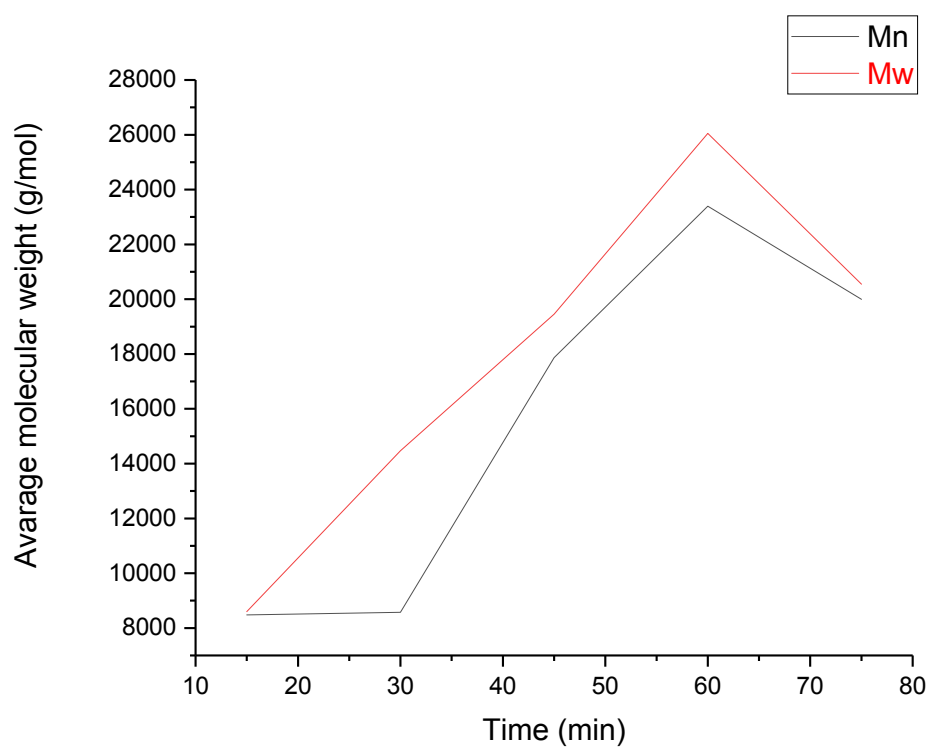


Figure S5. Dependence of molecular weight vs reaction time under mW irradiation

Infrared spectroscopy (FTIR-ATR) analysis²

L-Lactic acid was first treated to remove the excess of water and then an FTIR-ATR analysis was performed, and in Figure 4 is reported the spectrum. After polymerization the PLLA was subjected to the same analysis comparing the results with those reported in literature, in Figure S6 the PLLA spectrum is shown, in which is evident the absence of a peak at 3386 cm^{-1} , due to the -OH stretching, demonstrating the goodness of this new catalyst for the polymerization of LA. Furthermore, FTIR spectra of PLLA revealed characteristic absorption peaks of the ester functionality at 1746 (stretching of C=O) and 1081 cm^{-1} (stretching of C-O), and other peaks at $2944\text{-}2994\text{ cm}^{-1}$ for CH_2 and CH_3 stretching, as reported in literature by Choubisa *et al.*³

Figure S6

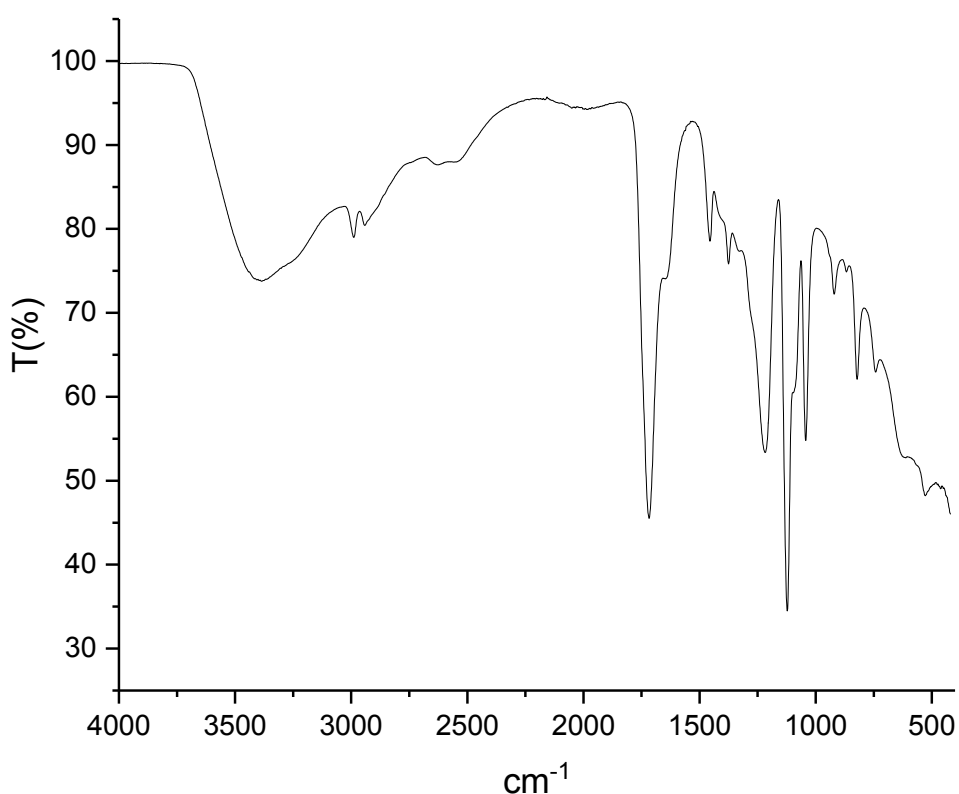


Figure S6. FTIR-ATR spectra of L-lactic acid purchased from Sigma Aldrich.

Figure S7

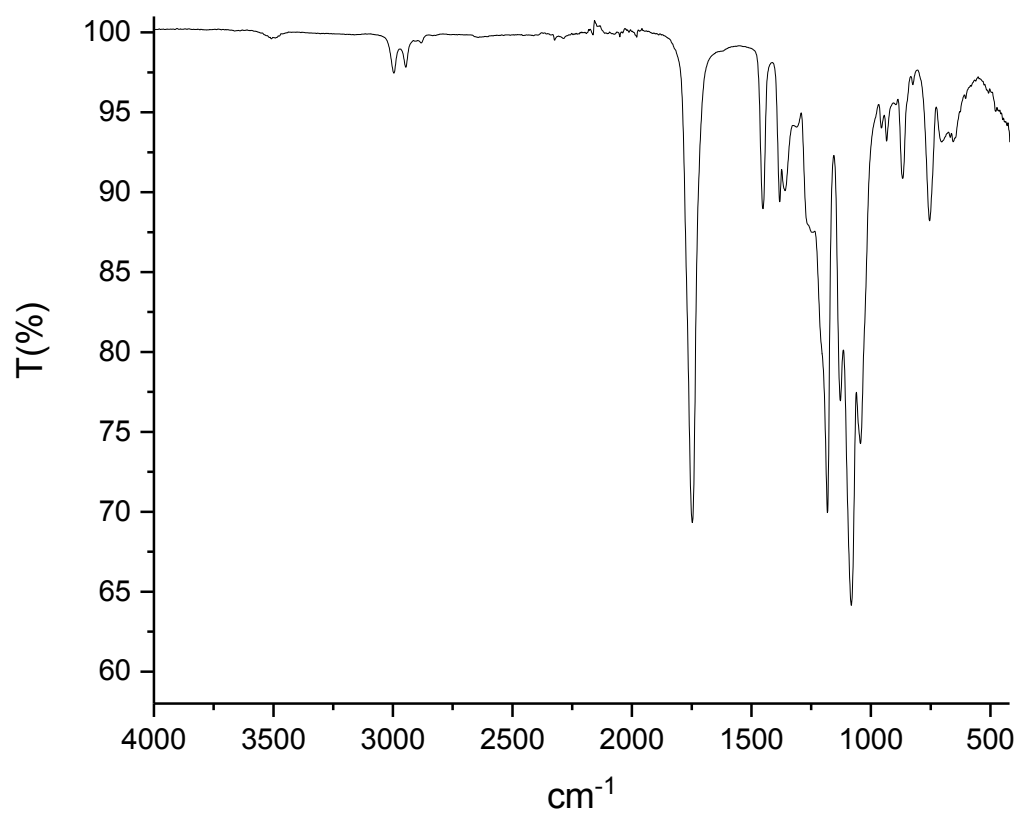


Figure S7. FTIR-ATR spectra of PLLA Mw=146000 (Table 2, entry 2m).

Nuclear Magnetic Resonance (NMR) analysis

In the ^1H -NMR spectrum (Figure S8) the signal of methine proton at 5.1 ppm and the signal of methyl proton at 1.6 ppm were observed. Two very weak signal was also observed around 4.5 ppm and 1.4 ppm and were assigned to methine and methyl protons next to terminal hydroxyl and carboxyl groups, respectively.

Figure S8

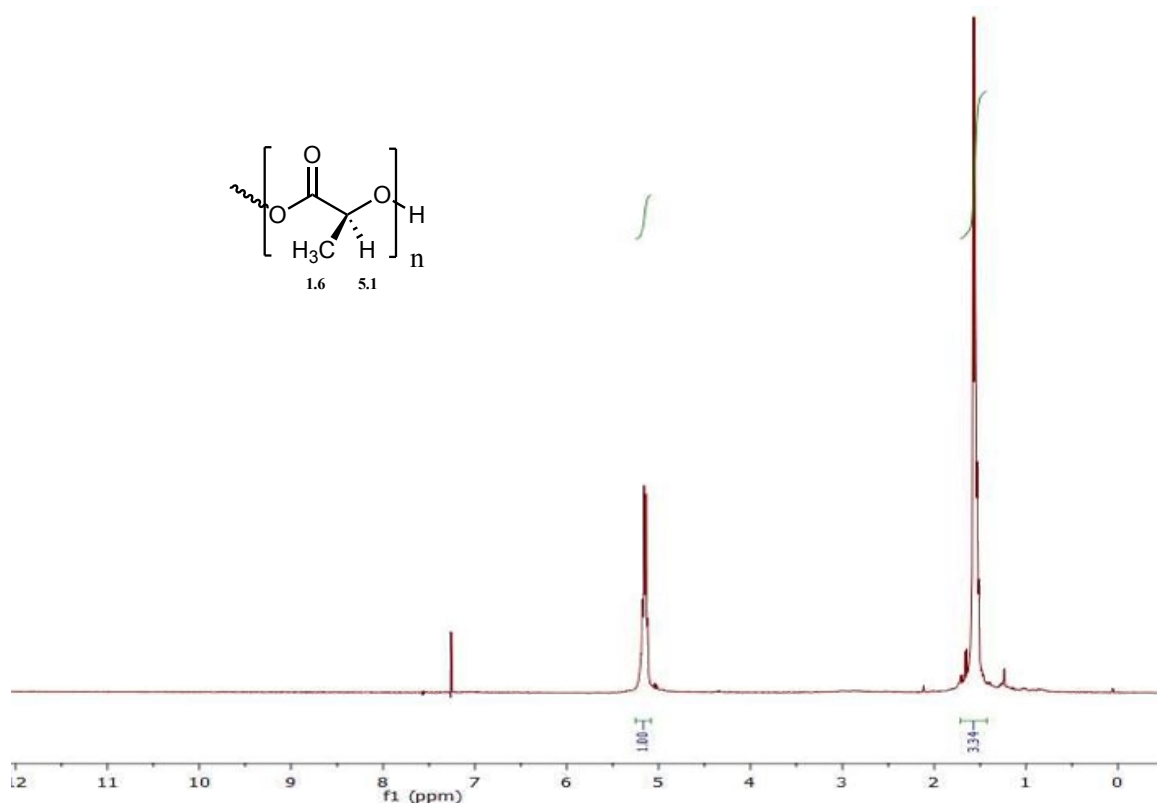


Figure S8. ^1H -NMR of Poly(L-lactic acid) (PLLA); ^1H -NMR (400MHz, CDCl_3) $\delta_{\text{H}} = 1.6$ (CH_3), 5.1(- $\text{OOCCH}(\text{CH}_3)\text{O}$ -).

In the ^{13}C -NMR spectrum (Figure S9) were observed the signals related to the novel formed ester group at 169.8 ppm, the signal of the α -carbon at 69.2 ppm and the methine group at 16.8 ppm.

Figure S9

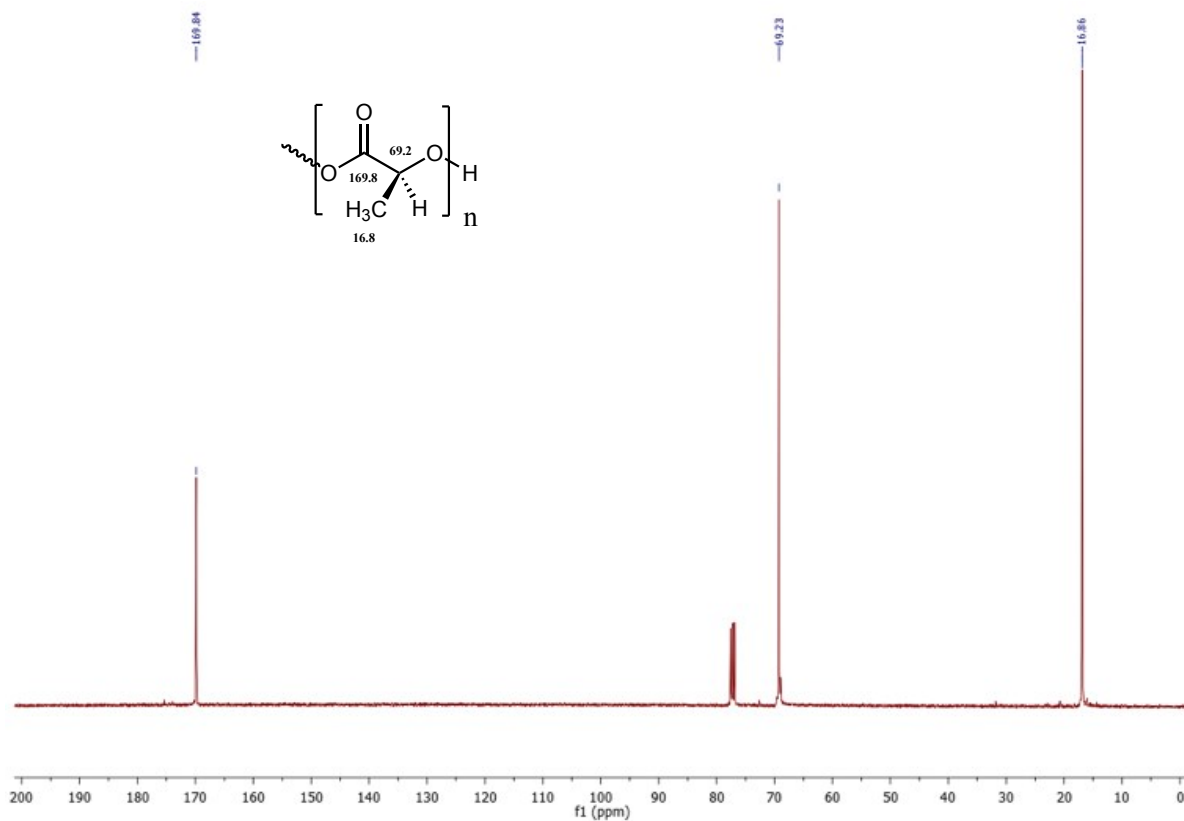


Figure S9. ^{13}C -NMR of Poly(L-lactic acid) (PLLA); ^{13}C -NMR (100MHz, CDCl_3) $\delta_{\text{C}} = 16.8$ (CH_3), 69.2 ($-\text{OOC}\underline{\text{C}}\text{H}(\text{CH}_3)\text{O}-$), 169.8 ($-\text{OOC}\underline{\text{C}}\text{H}(\text{CH}_3)\text{O}-$).

The above results confirmed the formation of PLA.⁴⁻⁶ from the ^1H -NMR and ^{13}C -NMR spectrums can be clearly seen the absence of other stereoisomers, confirming the presence of just one stereoisomer of the polymer.

Gel permeation chromatography (GPC)

The absolute molecular mass for PLLA were measured using size exclusion or gel permeation chromatography (SEC or GPC), with a GPC-Infinity II 1260, using a Universal calibration curve. The analysis of the data was performed using the Precision Detectors software and Agilent GPC/SEC software. The GPC-Infinity II 1260 was equipped with two columns in series, a PLgel 5 μm MIXED-C and a PLgel 5 μm MIXED-D, running THF as solvent at a flow rate of 1 mL min^{-1} at 308 K. Two injections of PLLA samples were carried out. The sample was injected using an auto sampler G7129A, and 100 μL were injected into the columns in 30 minutes run. We carried out several runs as all the examples present in Table 2, and herein are reported all the GPC graphs.

Figure S10

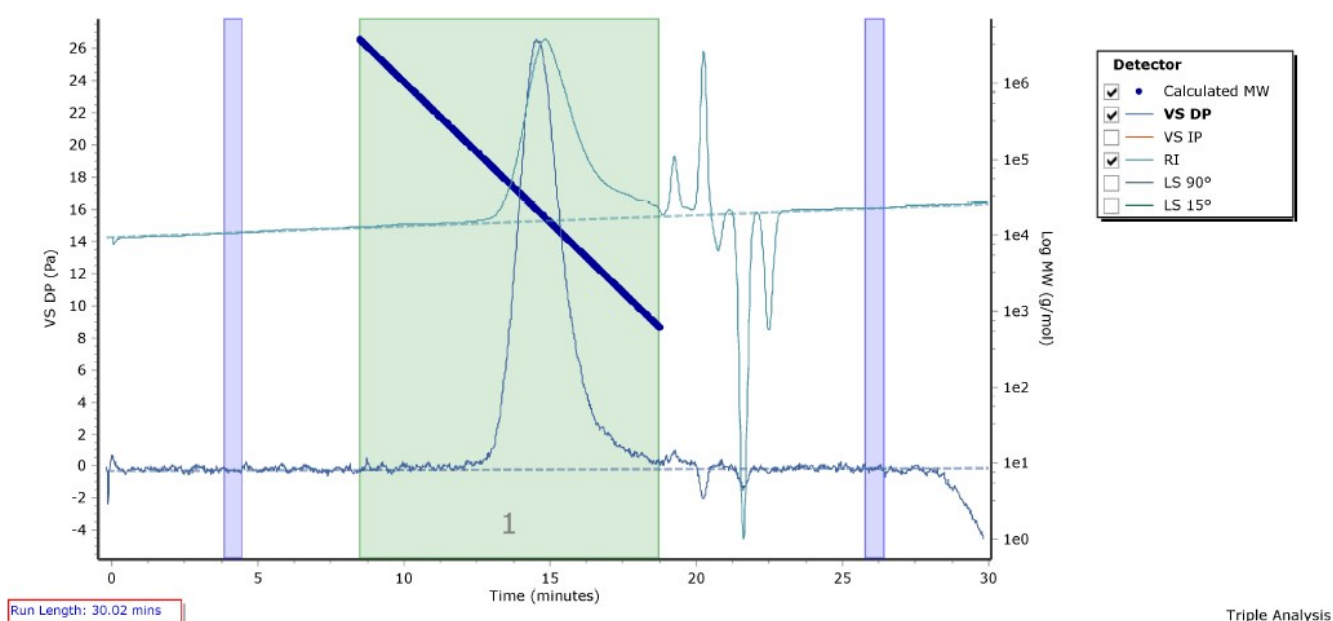


Figure S10. GPC graph of PLLA 4 generated in presence of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}:\text{NaI}$ (1:1) at 180°C for 7 hours. (Table 2, entry 2c).

Figure S11

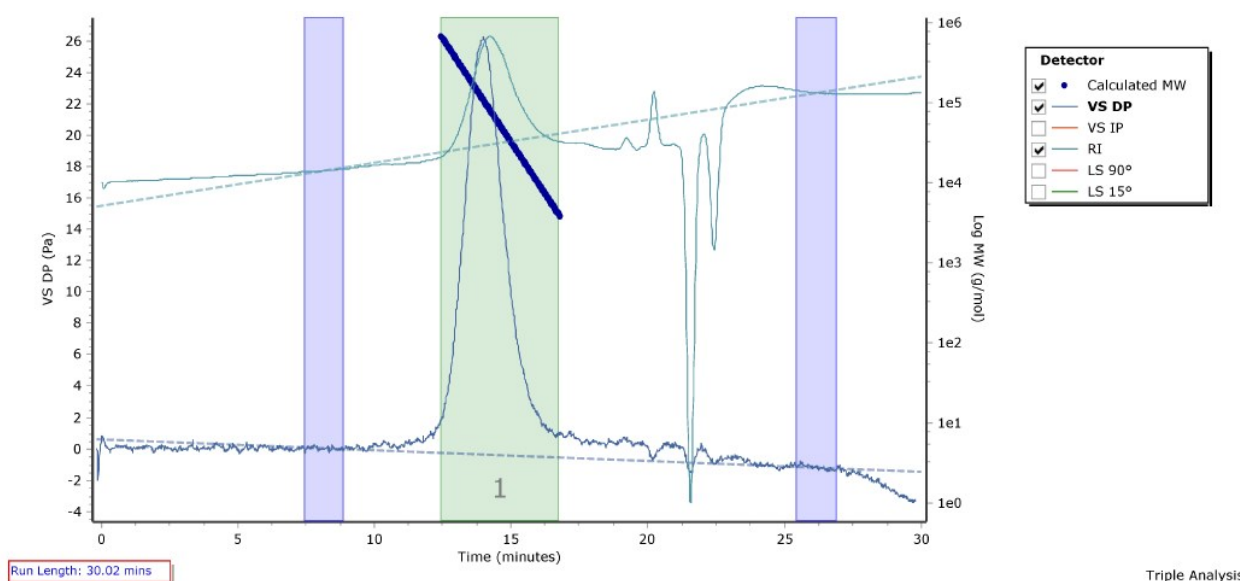


Figure S11. GPC graph of PLLA 4 generated starting from entry 2c ($M_w = 48300$ Da) at 150°C under reduced pressure (0.5Torr) for 16 hours. (Table 2, entry 2l).

Figure S12

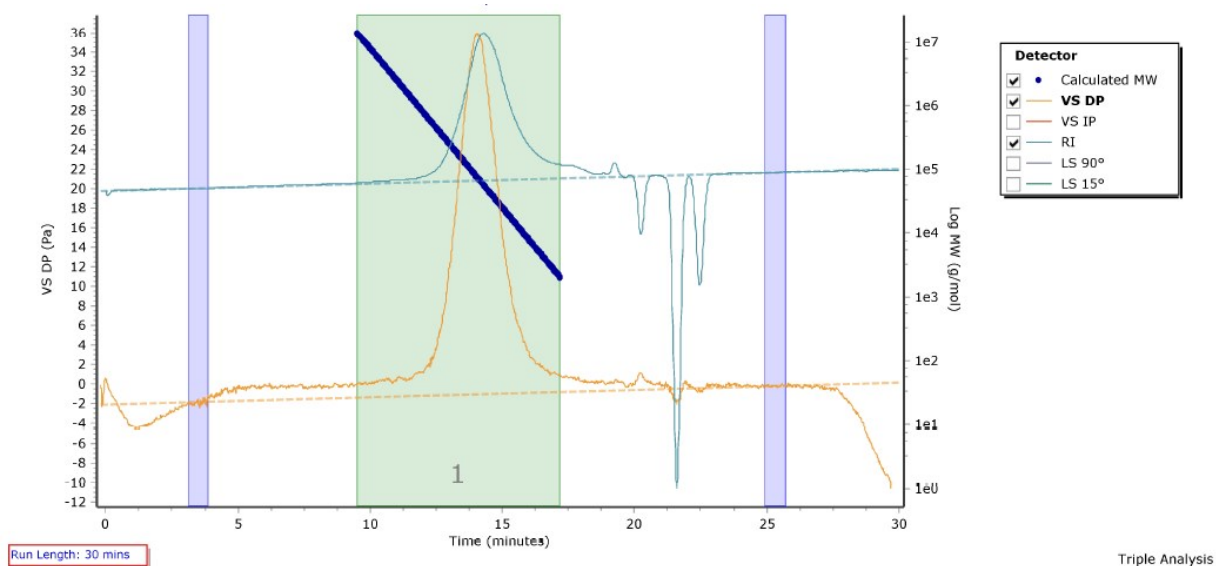


Figure S12. GPC graph of PLLA 4 generated starting from entry 2c ($M_w = 48300$ Da) at 150°C under reduced pressure (0.5Torr) for 29 hours. (Table 2, entry 2m).

Figure S13

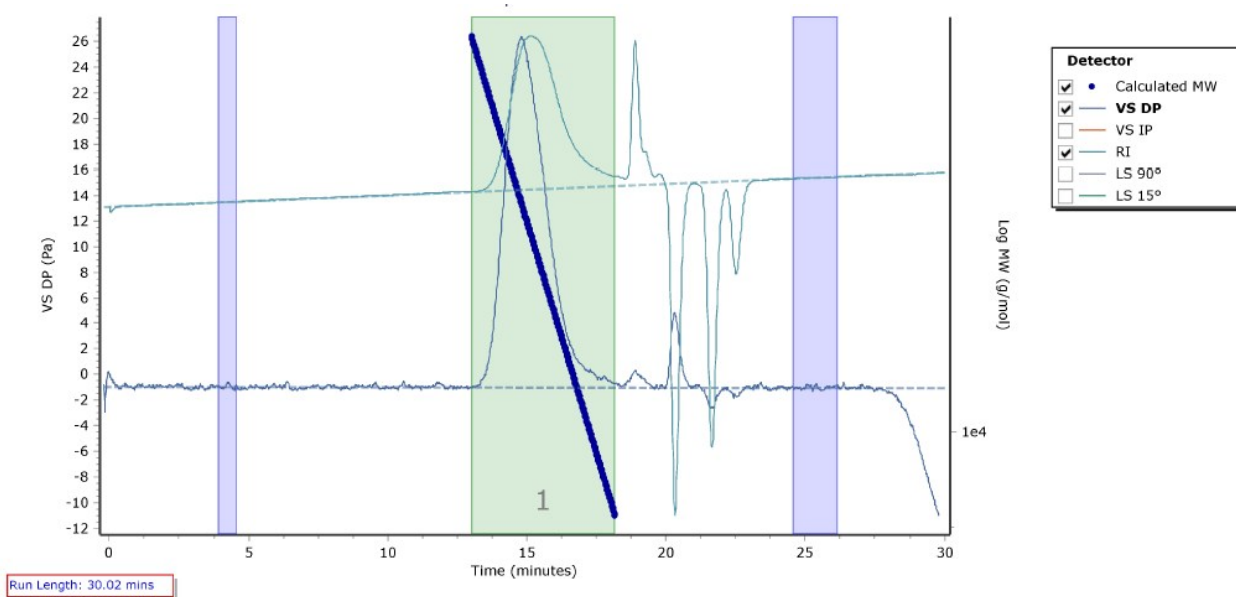


Figure S13. GPC graph of PLLA 4 starting from L-Lactide and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}:\text{NaI}$ (1:1) with 3 mol% of BnOH at 165°C for 12 hours. (Table 4, entry 4b).

Figure S14

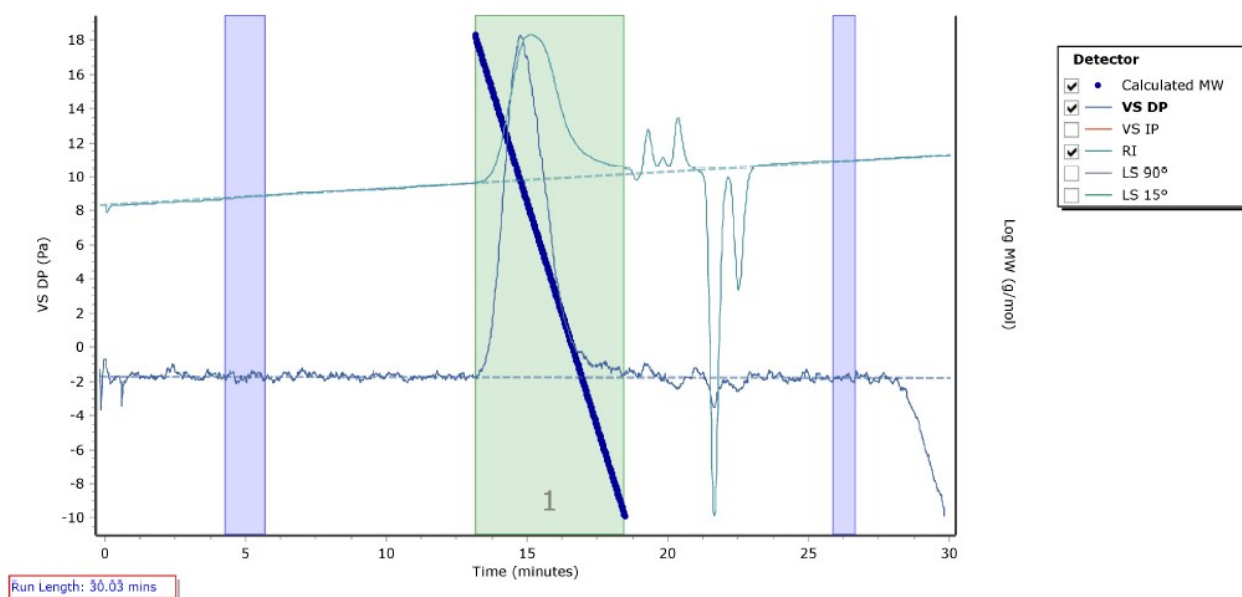


Figure S14. GPC graph of PLLA 4 starting from L-Lactide and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}:\text{NaI}$ (1:1) with 3 mol% of BnOH at 165°C for 1 hour (mW). (Table 5, entry 5b).

Figure S15

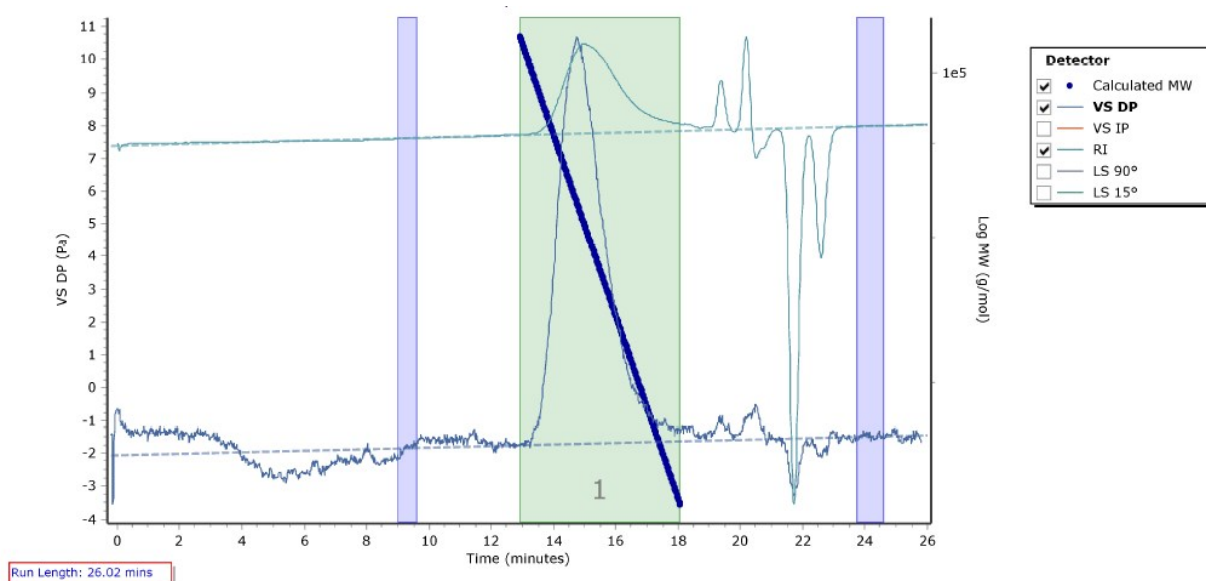


Figure S15. GPC graph of PLLA 4 starting from L-Lactide and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}:\text{NaI}$ (1:1) with 1.5 mol% of BnOH at 165°C for 1 hour (mW). (Table 6, entry 6f).

The GPC contains three detectors: a light scattering detector (LS), in order to determine absolute molar masses and the radius of gyration (R_g) of the sample polymers. The relationship between R_g and molar mass M can be expressed as in Equation 3:

$$R_g = K \cdot M^{\nu} \quad (1)$$

K and ν are constants for specific solvent-polymer combinations, in this case PLLA and THF as solvent; a viscometer detector (VS), for the measurement of intrinsic viscosity of the PLLA samples which determines the important Mark-Houwink parameters, useful for examining polymer structures in solution; a refractive index detector (RI), which is the base indicator of molecular weight determination. The RI detector analyses the concentration and the change of the refractive index as a function of the concentration (dn/dc). The results from the different detectors are combined to get more accurate molar masses for the polymers than what can be achieved with conventional calibration. Three samples were analysed, PLLA with $M_w = 48300$ ($\text{PDI}=1.08$), and PLLA both with $M_w = 94500$ ($\text{PD}=1.80$) and $M_w = 146000$ ($\text{PD}=6.30$) g mol^{-1} . The Mark-Houwink plot shown in Figure 9, demonstrate the linearity of the polymer chains, with a slight ramification.⁷

Figure S16

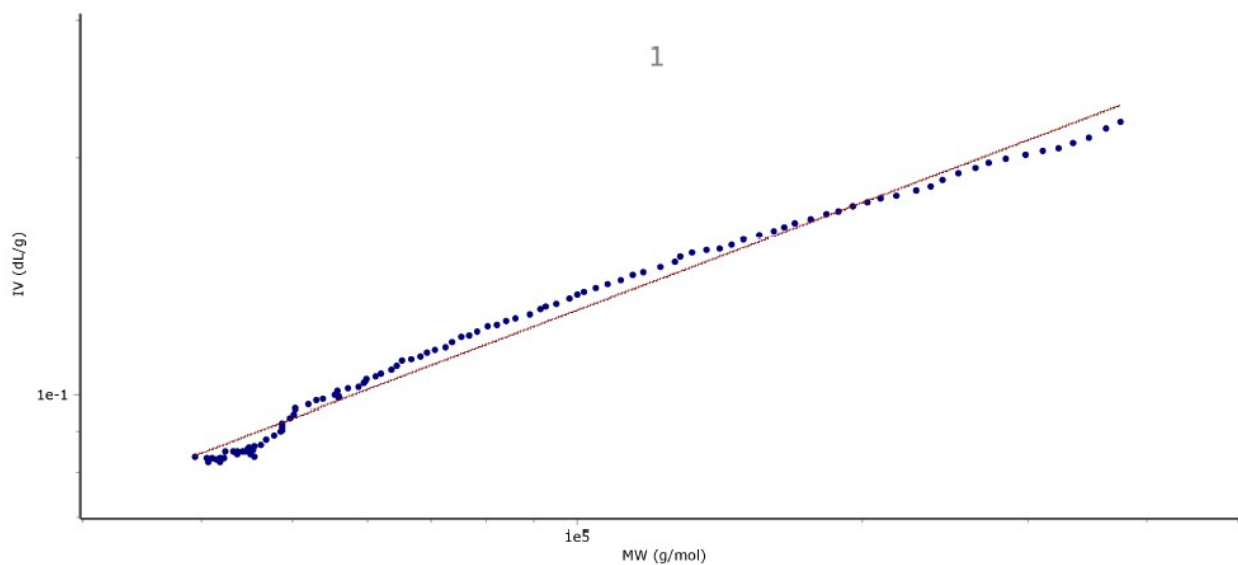


Figure S16. Mark-Houwink plot of PLLA 4 generated starting from entry 2c (Mw = 48300 Da) at 150°C under reduced pressure (0.5Torr) for 16 hours. (Table 2, entry 2l).

Figure S17

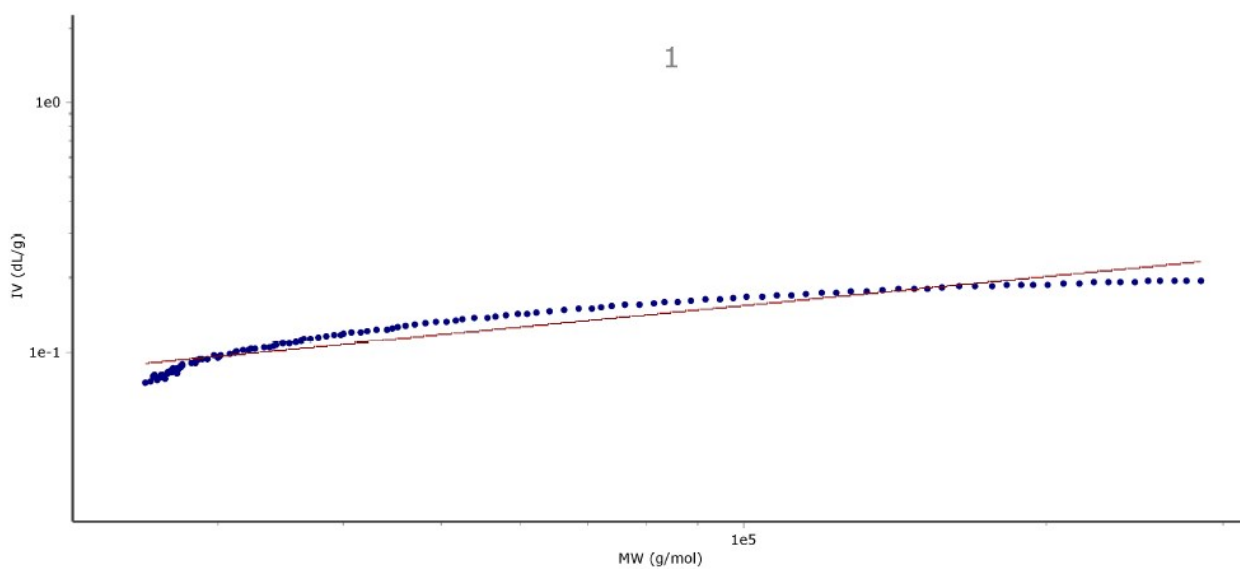


Figure S17. Mark-Houwink plot of PLLA 4 generated starting from entry 2c (Mw = 48300 Da) at 150°C under reduced pressure (0.5Torr) for 29 hours. (Table 2, entry 2m).

This kind of polymer structure suggests a specific chemical mechanism in which an intramolecular transesterification step is avoided, confirmed from the $^1\text{H-NMR}$ spectrum (Figure S8), in which all peaks associated to the lactide are absent. These results also confirm a stepwise polymerization without a transfer chain side reaction. Thus, an intermolecular transesterification has been activated by the catalyst, and the products from this latter reaction are linear polymer chains of different lengths.

References

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