Linear and three-arm star hydroxytelechelic poly(benzyl β-malolactonate)s: a straightforward one-step synthesis through ring-opening polymerization

Ghislaine Barouti, Cedric G. Jaffredo, Sophie M Guillaume

Linear and Three arm Hydroxytelechelic Poly(Benzyl β-Malolactonate)s: A Straightforward One-step Synthesis through Ring-Opening Polymerization

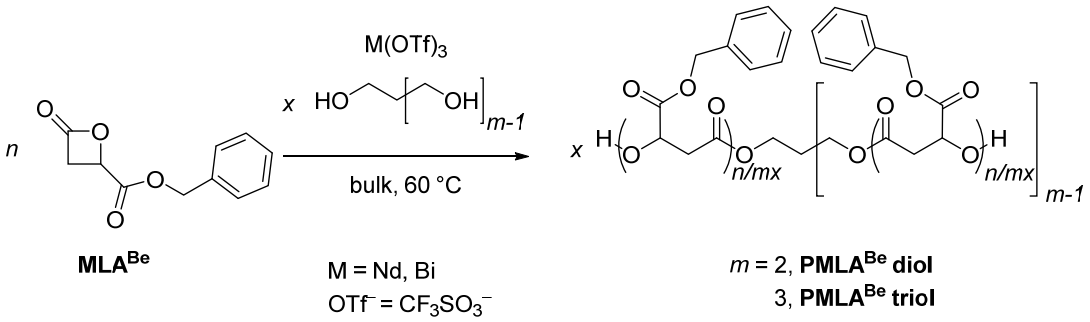
Ghislaine Barouti,[§] Cédric G. Jaffredo,[§] and Sophie M. Guillaume[*]

Institut des Sciences Chimiques de Rennes, UMR 6226 CNRS - Université de Rennes 1, Campus de Beaulieu, F-35042 Rennes Cedex, France

[§] Equally contributing first authors
[*] Corresponding author: sophie.guillaume@univ-rennes1.fr

Graphical abstract

PMLA^{Be}-*n*ol in one step!



MLA^{Be}

M = Nd, Bi
OTf$^-$ = $CF_3SO_3^-$

m = 2, **PMLA^{Be} diol**
3, **PMLA^{Be} triol**

Abstract

Ring-opening polymerization (ROP) of *racemic*-benzyl β-malolactonate (MLA^{Be}) initiated by an alcohol such as 1,3-propanediol (PPD) or 2-hydroxymethyl-1,3-propanediol (TMM), and catalyzed by a metal triflate $M(OTf)_3$ with M = Nd, Bi, proceeded under mild operating conditions (in bulk at 60 °C). The functionality of the alcohol dictates the topology of the resulting hydroxyl telechelic $PMLA^{Be}$. The ROP promoted by the neodymium-based catalytic system afforded a satisfactory activity and control in terms of molar mass and dispersity values ($M_{n,NMR}$ up to 7000 g.mol^{-1}, $Đ_M$ < 1.35). Mechanistic insights revealed that ring-opening of MLA^{Be} took place through the selective oxygen–acyl bond cleavage without undesirable side reactions such as transesterification or crotonisation, as evidenced by NMR and mass spectrometry analyses of the recovered polyesters. The structure of the corresponding α,ω-hydroxy telechelic $PMLA^{Be}$s was ascertained by ^1H and $^{13}C\{^1H\}$ NMR, SEC, and MALDI-ToF mass spectrometry analyses. In comparison, methane and trifluoromethane sulfonic acids did not allow the formation of well-defined $PMLA^{Be}$ diols. Differences in the behavior of MLA^{Be} and the related β-butyrolactone are highlighted. The present $Nd(OTf)_3$/PPD or TMM catalytic ROP of MLA^{Be} thus represents a valuable direct synthesis of $PMLA^{Be}$ diols and triols, respectively, without requiring chemical modification of a preformed $PMLA^{Be}$ precursor.

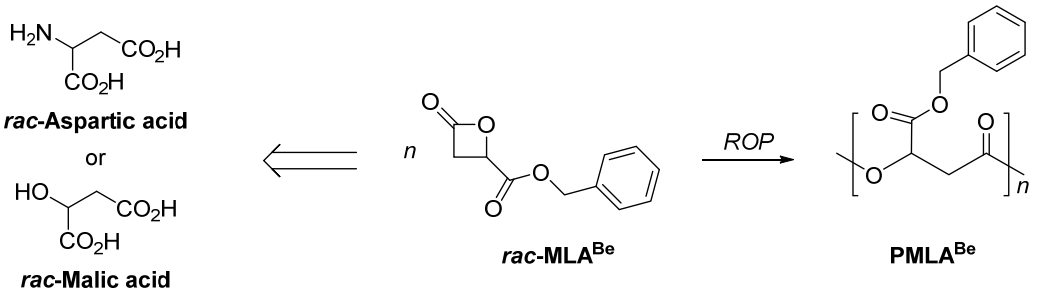
Keyword: hydroxy telechelic polymer, PHA, polyester, poly(hydroxyalkanoate), polymer diol, ring-opening polymerization (ROP), poly(benzyl β-malolactonate) ($PMLA^{Be}$)

Introduction

Hydroxy telechelic polymers are highly valuable building blocks for both academic and industrial applications. They are widely used as elementary constituents for the elaboration of copolymers combining other monomer(s) with various architectures (linear, star, branched, comb), by step-growth polymerization. In particular, one major valorization of polyols lies in the preparation of polyurethanes upon reaction of the reactive hydroxyl end-groups with poly(isocyanate)s, a major market in polymers manufacturing.[1,2,3,4]

Poly(hydroxyalkanoate)s (PHAs) are biocompatible and (bio)degradable aliphatic polyesters which are being developed for their applications as commodity plastics, as well as in the environment, and in the medical field.[5,6,7,8,9,10,11,12,13] One major drawback of natural PHAs, although quite extensively investigated, is their still unsatisfactorily productive preparation method from bacterial fermentation process, and their limited thermo-mechanical properties which somewhat restrain their extensive use. In this regard, the development of ring-opening polymerization (ROP) of four-membered ring cyclic β-lactones towards the formation of synthetic PHAs, enables to tackle both issues. Indeed, one can synthesize the monomers featuring the desired substituents on the β-position of the lactone. Next, provided the suitable efficient catalytic system is implemented, one can most conveniently access by ROP to finely tuned PHAs with adjusted chemical, macromolecular (in particular targeted molar mass values, low dispersity ($Đ_M = M_w/M_n$), evidence of limited undesirable side reactions (transesterification and transfer reactions), chain-end fidelity, microstructure – *i.e.* tacticity, hydrophilicity, degradation), and physical (especially thermal transition temperatures, crystallinity, elasticity) characteristics.[14,15,16] Whereas the most common and ubiquitous PHA is poly(3-hydroxybutyrate) (PHB; derived by ROP from β-butyrolactone (BL) which bears a methyl substituent),[14,15,16] the importance of poly(benzyl β-malolactonate) ($PMLA^{Be}$) and its parent benzyl-deprotected poly(malic acid) (PMLA), has significantly

grown over the past few years.[17,18,19,20,21,22] Indeed, these latter two PHA members are synthesized by ROP of benzyl β-malolactone (MLA^{Be}) followed by abstraction of the β-benzyloxycarbonyl substituents upon hydrogenolysis, respectively (Scheme 1).[14–21] The significant advantage of $PMLA^{Be}$/PMLA is that they are derived from aspartic or malic acids, two bio-renewable sugar-derived components listed in the top ten value-added chemicals established by the US Department Of Energy.[18–20,23,24] In this regard, MLA^{Be} and $PMLA^{Be}$ thus appear as potential valuable environmentally-friendly (bio)degradable alternatives to commodity plastics such as petrochemical polyolefins. Thanks to their biocompatibility, $PMLA^{Be}$ and PMLA are also used in the biomedical field.[21,22,25] The ease of the chemical modification of hydrophobic $PMLA^{Be}$ into its hydrophilic PMLA homologue upon hydrogenolysis under mild conditions (H_2, Pd/C, 23 °C) without backbone alteration,[18,20,21,25,26] and the availability of the thereby resulting $–CO_2H$ as anchoring sites for biologically active molecules,[27,28] is a rather unique characteristic among PHAs which is attracting much consideration, in particular for the design of amphiphilic self-assembling PMLA-based copolymers as drug delivery systems.[17–22,25,29]



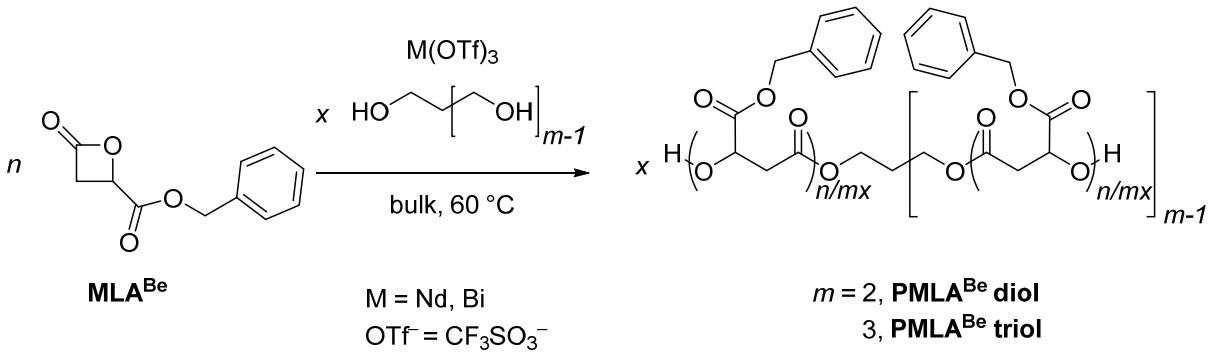
Scheme 1. Synthesis of poly(benzyl β-malolactonate) ($PMLA^{Be}$) by ROP of benzyl β-malolactonate (MLA^{Be}).

The past decade has witnessed a resurgence of interest in the ROP of MLA^{Be} to synthesize $PMLA^{(Be)}$ (co)polymers.[17–21] Besides the purely cationic and anionic

catalysts/initiators used in earlier investigations, recent catalytic systems based on either organic components such as guanidines, amidines, or phosphazenes, or discrete metal derivatives, have been demonstrated as effective for the preparation of $PMLA^{Be}$ (co)polymers.[20,30] To our knowledge, only a few metal-catalyzed ROPs of MLA^{Be} have been reported. Apart from the first established *O*–methoxy tetraphenylporphyrin aluminium ((TPP)Al(OCH_3)),[31] methylaluminoxane (MAO), ethylaluminoxane (EAO),[32,33] and tin(II) bis(2-ethylhexanoate) (Sn(octoate)$_2$ = $SnOct_2$)[34] ones, the more recently unveiled zinc β-diketiminate compound [(BDI)Zn($N(SiMe_3)_2$)] (BDI = $CH(CMeNC_6H_3$-2,6-$^iPr_2)_2$) or $M(OTf)_3$ (with M = Al, Nd, $OTf^- = CF_3SO_3^-$) associated to an alcohol (typically isopropanol (*i*PrOH) or benzyl alcohol (BnOH)), or the *in situ* generated yttrium isopropoxide complex supported by a tetradentate dichloro-substituted bis(phenolate) ligand, promoted the ROP of MLA^{Be} at 20–60 °C in bulk monomer, affording well-defined linear α-hydroxy, ω-alkoxycarbonyl telechelic $PMLA^{Be}$s.[26,35,36]

Polymer diols are often prepared upon post-polymerization chemical modification of a mono-hydroxyl end-capped polymer. The main reason is that direct synthetic routes to α,ω-dihydroxy telechelic polymers are less often encountered.[4] The first example of $PMLA^{Be}$ diol has thus been obtained by chemical transformation of a preformed α-hydroxy, ω-carboxylic acid $PMLA^{Be}$ sample.[37] More recently, we evidenced the straightforward one-step synthesis of $PMLA^{Be}$ diol by ROP of MLA^{Be} using rare earth borohydride initiators, $Ln(BH_4)_3(THF)_3$ (Ln = La, Nd, Sm), a strategy similarly implemented to access PHB diols.[38,39,40,41,42] The one drawback of this approach is the sensitivity of these rare earth borohydride complexes to air and moisture. Therefore, a more convenient (easy to handle) initiator and a more straightforward strategy are desirable for the synthesis of hydroxy telechelic $PMLA^{Be}$.

To that end, given the successful synthesis of BnO–PMLA^{Be}–OH by ROP of MLA^{Be} with Al(OTf)$_3$/BnOH,[35] and the efficiency of catalyst systems derived from metal triflates M(OTf)$_3$/^{i}PrOH (M = Nd, Bi) to promote the copolymerization of MLA^{Be} and BL,[36] metal triflates combined to several higher alcohols such as 1,3-propanediol (PPD), and 2-hydroxymethyl-1,3-propanediol (tris(hydroxymethyl)methane (trimethylolmethane, TMM), were thus investigated in the present study towards the synthesis of PMLA^{Be}-*n*-ols (Scheme 2). Also, the reported synthesis of the related PHB and PHB diol from the ROP of BL catalyzed by trifluoromethane[43,44,45] and methane sulfonic[45] acids (HOTf and MSA, respectively) in combination to an alcohol or diol initiator, prompted the similar investigation of these related organic sulfonic acids in the preparation of PMLA^{Be}-*n*-ols. The α,ω-hydroxy telechelic PMLA^{Be}s were characterized by ^{1}H, ^{13}C{^{1}H} NMR, SEC, and MALDI-ToF mass spectrometry analyses.



Scheme 2. Synthesis of PMLA^{Be}-*n*-ols by ROP of MLA^{Be} from metal triflate/alcohol systems.

Experimental section

Methods and Materials

All polymerizations were performed under inert atmosphere (argon) using standard Schlenk, vacuum line, and glove box techniques. *Racemic* benzyl β-malolactone (MLA^{Be}) was synthesized from (*R,S*)-aspartic acid according to the reported procedure.[29] Metal triflates M(OTf)$_3$ with M = Nd, Bi, trifluoromethanesulfonic acid (triflic acid, HOTf, ≥ 99%),

methanesulfonic acid (MSA, > 98%, Alfa Aesar), 1,3 propanediol (PPD, 98%), 2-hydroxymethyl-1,3-propanediol (tris(hydroxymethyl)methane, or trimethylolmethane, TMM, 97%), and all other reagents were used as received (Aldrich unless otherwise mentioned).

Instrumentation and measurements

^{1}H (500 and 400 MHz) and ^{13}C{^{1}H} (125 and 100 MHz) NMR spectra were recorded on Bruker Avance AM 500 and Ascend 400 spectrometers at 25 °C. Chemical shifts (δ) are reported in ppm and were referenced internally relative to tetramethylsilane (δ 0 ppm) using the residual ^{1}H and ^{13}C solvent resonances. Note that the ^{1}H NMR spectra of PMLA^{Be} systematically featured broadened signals (typically $\nu_{1/2}$ = *ca.* 26 Hz), as commonly encountered in the literature.[30,35-38]

Size-exclusion chromatography (SEC) giving number-average molar mass ($M_{n,SEC}$) and dispersity ($Đ_M = M_w/M_n$) values of the PMLA^{Be}s was carried out in THF at 30 °C (flow rate 1.0 mL.min^{-1}) on a Polymer Laboratories PL50 apparatus equipped with a refractive index detector and a set of two ResiPore PLgel 3µm MIXED-D 300 × 7.5 mm columns. The polymer samples were dissolved in THF (2 mg.mL^{-1}). All elution curves were calibrated with 11 monodisperse polystyrene standards (M_n range = 580 – 380,000 g·mol^{-1}); all $M_{n,SEC}$ values of the PMLA^{Be}s were uncorrected for their potential difference in hydrodynamic radius *vs.* polystyrene. The SEC traces of the polymers all exhibited a non-Gaussian shaped peak tailing at longer elution times, inducing relatively large dispersities which yet remained below 1.58. The $M_{n,SEC}$ values thus obtained often remained lower than the calculated values or the values determined by NMR ($M_{n,NMR}$, *vide infra*).

Monomer conversions were determined from ^{1}H NMR spectra of the crude polymer samples, from the integration (Int.) ratio Int.$_{PMLABe}$/[Int.$_{PMLABe}$ + Int.$_{MLABe}$], using the methine hydrogens –CH$_2$C*H*(CO$_2$Be)O (δ_{PMLABe} = 5.50–5.55 ppm, δ_{MLABe} = 4.88 ppm).

The molar mass values of $PMLA^{Be}$ samples were determined by ^1H NMR analysis in $CDCl_3$ from the relative intensities of the signals of the main-chain methylene hydrogens ($\delta_{CH2CH(CO2Be)}$ = 2.92 ppm), relative to the methylene hydrogens ($\delta_{CH(CH2O)x}$ = *ca.* 4.00–4.20, 1.80–2.10 ppm) of the PPD (x = 2), or TMM (x = 3) initiator (Table 1). The good resolution of the signals of the chain-end groups allowed their fairly reliable integration (Figures 2, 4, S1–S2). The number-average molar mass values thus obtained by ^1H NMR ($M_{n,NMR}$) were in close agreement with the ones calculated ($M_{n,theo}$), as reported in Table 1.

MALDI-ToF mass spectra were recorded at the CESAMO (Bordeaux, France) on a Voyager mass spectrometer (Applied Biosystems) equipped with a pulsed N_2 laser source (337 nm) and a time-delayed extracted ion source. Spectra were recorded in the positive-ion mode using the reflectron mode and with an accelerating voltage of 20 kV. A THF solution (1 mL) of the matrix (ditranol, Aldrich, 99 %) and a MeOH solution of the cationisation agent (NaI, (10 $mg.mL^{-1}$)) were prepared. A fresh solution of the polymer sample in THF (10 $mg.mL^{-1}$) was then prepared. The three solutions were next rapidly combined in a 1:1:10 volume ratio of matrix-to-sample-to-cationisation agent. One to two microliters of the resulting solution were deposited onto the sample target and vacuum-dried.

Typical MLA^{Be} homopolymerization. In a typical experiment (Table 1, entry 5), $Nd(OTf)_3$ (10 mg, 16.9 μmol) and a solution of 1,3 propanediol (PPD, 6.1 μL, 84.5 μmol, 5 equiv *vs.* $Nd(OTf)_3$) in toluene (0.1 mL; in light of this small volume, the polymerization can be considered as a bulk procedure) were charged in a Schlenk flask in the glove box, prior to the addition of MLA^{Be} (0.35 g, 1.69 mmol, 100 equiv). The mixture was then stirred at 60 °C for the appropriate reaction time (reaction times were not systematically optimized). The polymerization was quenched by addition of acetic acid (*ca.* 10 μL of a 1.6 $mol{\cdot}L^{-1}$ solution in toluene). The resulting mixture was concentrated to dryness under vacuum and the conversion was determined by ^1H NMR analysis of the residue in $CDCl_3$. The crude polymer

was then dissolved in CH_2Cl_2 (2 mL) and precipitated in cold pentane (10 mL), filtered and dried under vacuum at 45 °C overnight (typical isolated yield 90–95%). The final polymer was then analyzed by NMR, SEC and MALDI-ToF analyses (Table 1).

PMLA^{Be} diol : ^{1}H NMR (500 MHz; $CDCl_3$, 25 °C): δ 7.30 (br m, 5n, C_6H_5), 5.50 (br m, 1nH, $CH_2CH(CO_2Be)O$), 5.12 (br s, 2nH, $OCH_2C_6H_5$), 4.18 (br m, 4H, $CH_2(CH_2OPMLA^{Be})_2$), 3.63 (br s, 2H, OH), 2.92 (br m, 2nH, $CHCH_2C(O)O$), 1.80 (br m, 2H, $CH_2(CH_2OPMLA^{Be})_2$) (Figure 2). $^{13}C\{^1H\}$ NMR (125 MHz; $CDCl_3$, 25 °C): δ 168.1 (*C*=O), 134.9 (*C*8), 126.6-127.0 (*C*9-11), 68.5 ($OCH(CO_2Be)CH_2C(O)$), 67.7 ($OCH_2C_6H_5$), 65.4 ($CH_2(CH_2OPMLA^{Be})_2$), 38.6 ($CH_2(CH_2OPMLA^{Be})_2$), 35.5 ($OC(O)CH_2CH$), (Figure 3). MALDI-ToF MS (Figure 6).

PMLA^{Be} triol : ^{1}H NMR (500 MHz; $CDCl_3$, 25 °C): δ 7.30 (br m, 5n, C_6H_5), 5.50 (br m, 1nH, $CH_2CH(CO_2Be)O$), 5.12 (br m, 2nH,$OCH_2C_6H_5$), 4.52 (br s, 3H, OH), 4.06 (br m, 4H, $CH(CH_2OPMLA^{Be})_3$), 2.92 (br m, 2nH, $CHCH_2C(O)O$), 2.05 (br m, 2H, $CH(CH_2OPMLA^{Be})_2$) (Figure 4). $^{13}C\{^1H\}$ NMR (125 MHz; $CDCl_3$, 25 °C): δ 172.8−168.2 (*C*=O), 135.1 (*C*8), 128.7−128.3 (*C*9-11), 68.8 ($OCH(CO_2Be)CH_2C(O)$), 67.7 ($OCH_2C_6H_5$), 67.4 ($CH(CH_2OPMLA^{Be})_3$), 38.7 ($CH(CH_2OPMLA^{Be})_3$), 35.4 ($OC(O)CH_2CH$), (Figure 5). MALDI-TOF MS (Figure 7).

Results and Discussion

ROP of MLA^{Be} promoted by metal triflates, trifluoromethane and methane sulfonic acids. The ring-opening polymerization (ROP) of *racemic*-MLA^{Be} (MLA^{Be}) was investigated using $M(OTf)_3$ with M = Nd, Bi, or trifluoromethane and methane sulfonic acids (HOTf and MSA, respectively) as catalyst, in association with 1,3 propanediol (PPD), or 2-hydroxymethyl-1,3-propanediol (tris(hydroxymethyl)methane or trimethylolmethane (TMM)), under a standard set of conditions *viz.* in bulk at 60 °C (refer to the Experimental

Section). The most significant data are gathered in Table 1. In order to get low molar mass samples suitable for NMR spectroscopy and MALDI-ToF mass spectrometry analyses (*vide infra*), the alcohol was used in excess (5 equiv.) under *immortal* ROP conditions.[46,47]

Table 1. ROP of MLA^{Be} catalyzed by $M(OTf)_3$ with M = Nd, Bi, or MSA, in presence of PPD or TMM initiator.[a]

Entry	Catalyst	Initiator	$[MLA^{Be}]_0$: $[Catalyst]_0$: $[Initiator]_0$ [a]	Reaction Time[b] (h)	MLA^{Be} Conv.[c] (%)	$M_{n,theo}$[d] (g·mol^{-1})	$M_{n,NMR}$[e] (g·mol^{-1})	$M_{n,SEC}$[f] (g·mol^{-1})	$Đ_M$[g]
1	$Bi(OTf)_3$	PPD	50:1:5	1	100	2100	1200	1000	1.34
2	$Bi(OTf)_3$	PPD	100:1:5	2	100	4200	1400	1200	1.43
3	$Bi(OTf)_3$	PPD	200:1:5	4	91	7600	1900	1100	1.39
4	$Nd(OTf)_3$	PPD	10:1:2	12	100	1100	1000	800	1.18
5	$Nd(OTf)_3$	PPD	20:1:2	16	83	1700	1800	1000	1.36
6	$Nd(OTf)_3$	PPD	50:1:5	16	93	2000	2300	2300	1.19
7	$Nd(OTf)_3$	PPD	100:1:5	26	89	3700	4200	3200	1.19
8	$Nd(OTf)_3$	PPD	200:1:5	96	81	6800	7000	3700	1.35
9	$Nd(OTf)_3$	TMM	60:1:5	18	91	2400	2300	1600	1.34
10	$Nd(OTf)_3$	TMM	120:1:5	48	66	3400	2600	1900	1.34
11	$Nd(OTf)_3$	TMM	240:1:5	96	60	6000	5700	3800	1.36
12	MSA	PPD	20:1:5	20	81	750	800	1300	1.58
13	MSA	PPD	30:1:5	20	91	1200	1000	1000	1.57
14	MSA	PPD	100:1:5	50	94	3900	2100	1700	1.30
15	MSA	PPD	200:1:5	50	42	3500	2300	500	1.38

[a] All reactions were performed in bulk at 60 °C (refer to the Experimental Section). [b] The reaction time was not necessarily optimized. [c] Monomer conversion determined by ^{1}H NMR analysis of the crude reaction mixture (refer to the Experimental Section). [d] Theoretical molar mass value calculated from the relation: $[MLA^{Be}]_0/[Initiator]_0 \times conv._{MLABe} \times M_{MLABe} + M_{Initiator}$, with M_{MLABe} = 206 g·mol^{-1}, M_{PPD} = 76 g·mol^{-1}, and M_{TMM} = 106 g·mol^{-1}. [e] Experimental molar mass value determined by ^{1}H NMR analysis of the isolated polymer, from the relative intensities of the resonances of the main chain methane or methylene hydrogens to the methylene hydrogens of the initiator (refer to the Experimental Section). [f] Number average molar mass value determined by SEC in THF at 30 °C *vs.* polystyrene standards (uncorrected values, refer to the Experimental Section). [g] Dispersity value (Mw/Mn) determined by SEC in THF at 30 °C.

The metallic triflates $Nd(OTf)_3$ and $Bi(OTf)_3$ were both found active catalysts in the ROP of MLA^{Be} initiated by 1,3-propane diol (Table 1, entries 1–8). Under the same conditions, the bismuth catalyst was more active than the neodymium, converting 100 equiv. of the lactone within 2 h as opposed to more than 26 h required with the rare earth metal

system (Table 1, entries 2 *vs.* 7). However, the control of the polymerization was significantly better using the $Nd(OTf)_3$/PPD catalytic system, as evidenced by the close match of the anticipated molar mass values ($M_{n,theo}$) with the molar mass values determined from ^1H NMR analysis of the precipitated polymer ($M_{n,NMR}$, refer to the Experimental Section; Figure S1), and by the slightly narrower dispersities measured by SEC analysis ($Đ_{M,Nd(OTf)3}$ = 1.2−1.3 *vs.* $Đ_{M,Bi(OTf)3}$ = 1.3−1.4).[48] These dispersity values remained in the range of those obtained from the related ROP of MLA^{Be} promoted by $Al(OTf)_3$/BnOH ($Đ_M$ = 1.2)[35] or organic bases ($Đ_M$ = 1.1−1.4).[30] Furthermore, these values indicated the occurrence of few undesirable transesterification side reactions (reshuffling (intermolecular) and backbiting (intramolecular), and chain transfer reactions) often observed in ROP of cyclic esters,[49] and/or a faster rate of initiation with respect to propagation. Furthermore, the molar mass value of the thus formed $PMLA^{Be}$ increased linearly with ($[MLA^{Be}]_0$ x $conv._{MLABe}$)/$[PPD]_0$ ratio, as depicted Figure 1. All these data are indicative of a living polymerization. The similar ROP of MLA^{Be} catalyzed by $Nd(OTf)_3$ in presence of a triol (TMM) afforded the corresponding $PMLA^{Be}$ triol, with a similar control of the polymerization in terms of $M_{n,theo}/M_{n,NMR}$ agreement and narrow dispersity (Table 1, entries 9–11). All these results allowed establishing the proof of this concept towards the synthesis of α,ω-hydroxy telechelic $PMLA^{Be}$s from metallic triflates and hydroxylated initiators.

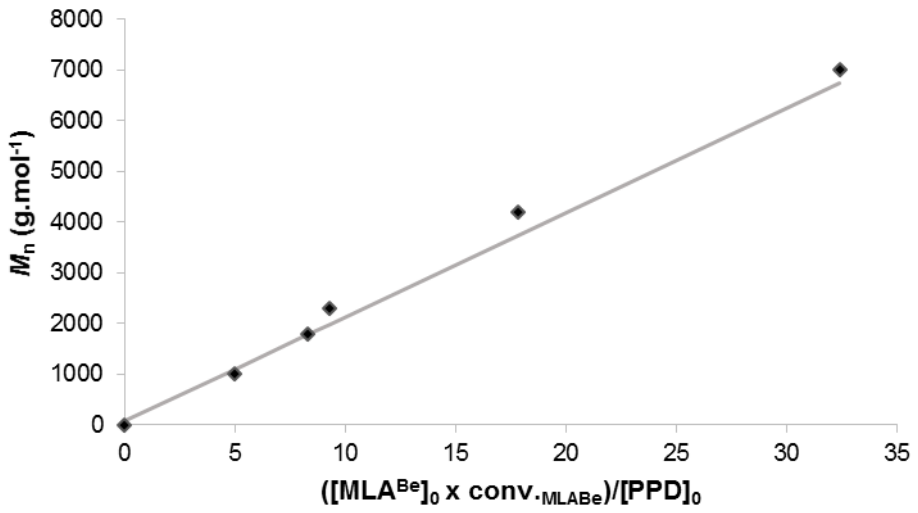


Figure 1. Variation of $M_{n,NMR}$ (◆) and $M_{n,theo}$ (solid line) values of PMLA^{Be}, produced in the presence of Nd(OTf)$_3$/PPD, as a function of ([MLA^{Be}]$_0$ x conv.$_{MLABe}$)/[PPD]$_0$ (Table 1, entries 4–8).

As initially investigated by Pohl and co-workers,[43] the protic acid catalyzed ROP of β-butyrolactone (BL) mediated by triflic acid (HOTf)[43–45] or methane sulfonic acid (MSA)[45] in presence of an alcohol (ROH), afforded α-hydroxy,ω-alkoxy telechelic PHBs. The polymerizations of BL proceeded at 30–35 °C in an aprotic solvent (C_6D_6-NMR tube experiments, or toluene) with methanol or *n*-pentanol, *via* selective oxygen–acyl bond cleavage, along with formation of a minor amount of macrocycles while crotonate chain-ends were observed at higher temperatures. In these ROPs of BL, HOTf showed a better activity and selectivity compared to MSA which led to some cyclisation and crotonisation reactions. Also, the use of a dihydroxylated initiator (1,4-butane diol) with HOTf catalyst gave the corresponding PHB diol.[45] In comparison to these acid catalyzed ROPs of BL, ROP of the related MLA^{Be} β-lactone mediated by HOTf/PPD at 60 °C did not enable the synthesis of PMLA^{Be} diol. Indeed, a white precipitate, possibly arising from some transesterification reactions, was then recovered from which no product besides some fumaric acid could be

identified. On the other hand, PPD effectively initiated the ROP of MLA^{Be} catalyzed by MSA under the same operating conditions (Table 1, entries 12–15). The polymerization proceeded also with oxygen–acyl bond cleavage leading to $PMLA^{Be}$ diol as characterized by ^{1}H NMR analysis (*vide infra*, Figure S2). However, the polymers failed to show a good correlation for their molar mass between the theoretical values ($M_{n,theo}$) and the experimental ones as determined by ^{1}H NMR ($M_{n,NMR}$, Table 1; *vide infra*). Thus, as opposed to the ROP of BL, neither HOTf nor MSA efficiently promoted the ROP of MLA^{Be} initiated by PPD at 60 °C. The benzylester substituent of MLA^{Be} thus altered the reactivity of the β-lactone as compared to the methyl group of BL, most likely as the result of its electronic contribution. Thus, $Nd(OTF)_3$/PPD and $Nd(OTF)_3$/TMM revealed as the most effective catalytic systems for the controlled ROP of MLA^{Be} towards hydroxyl end-capped $PMLA^{Be}$s, as further evidenced by spectroscopic characterizations (*vide infra*). This direct strategy towards the synthesis of $PMLA^{Be}$ diol and triol compares favorably well with the previously reported formation of $PMLA^{Be}$ diol through the chemical modification of a pre-isolated α-hydroxy, ω-carboxylic acid $PMLA^{Be}$ sample. Indeed, this prior experiment reported that in presence of an excess of borane-tetrahydrofuran adduct (BH_3.THF; 3.5 equiv.) at 0 °C in anhydrous THF over 5 h, the reduction of the carboxylic acid end-group into a hydroxyl one proceeded to afford the $PMLA^{Be}$ diol (92% yield; $M_{n,NMR}$ = 7900 g.mol^{-1}; $Đ_M$ = 1.5).[37]

Characterization of the $PMLA^{Be}$s. ^{1}H NMR analysis of the precipitated $PMLA^{Be}$-*n*-ols enabled to verify the presence of MLA^{Be} repeating units as well as to confirm the nature of the chain-end groups. The typical spectrum of a low molar mass $PMLA^{Be}$ diol is illustrated Figure 2 with the sample isolated from the ROP of MLA^{Be} promoted by $Nd(OTf)_3$ in the presence of 1,3 propanediol as initiator (Table 1, entry 1). Besides the expected ester backbone signals of the methine and methylene hydrogens observed in a 1:2 ratio (δ = 5.50 ppm ($CH_2CH(CO_2Be)O$), 2.92 ppm ($CHCH_2C(O)O$), as well as the signals of the benzyloxy

pending substituent (δ = 7.30, 5.12 ppm (OCH($CO_2CH_2C_6H_5$)CH_2C(O)), the central trimethylene moiety (δ = 4.18, 1.80 ppm (O$CH_2CH_2CH_2$O)), and the terminal hydroxyl (δ = 3.63 ppm) resonances were also observed (Figure 2). The signals of the chain-end groups and especially of the trimethylene central sequence being well resolved, this allowed a fairly reliable integration of the resonances as illustrated in Figure 2. Consequently, evaluation of the PMLA^{Be}s molar mass ($M_{n,NMR}$) from the relative intensity of the chain-end and of the alcohol segment *vs.* the main chain signals, gave values in good agreement with the ones calculated from the monomer conversion and the initial amount of MLA^{Be} and initiator ($M_{n,theo}$), as reported Table 1. The corresponding $^{13}C\{^1H\}$ NMR spectrum also evidenced MLA^{Be} units[30] along with the alcohol segment (δ = 65.4, 38.6 ppm (O$CH_2CH_2CH_2$O)) (Figure 3). The same ^1H and $^{13}C\{^1H\}$ patterns were obtained in the spectra of PMLA^{Be} diol and PMLA^{Be} triol, similarly synthesized from $Bi(OTf)_3$,MSA/PPD and $Nd(OTf)_3$/TMM, respectively. The only distinctive feature was the relative intensity of the ^1H NMR signals corresponding to the hydrogens of the central alcohol moiety which differed from PPD (*vide supra*) to TMM (δ = 4.06 ppm, 6H, (OCH_2CH($CH_2O)_2$)), 2.05 ppm, 1H, ($OCH_2CH(CH_2O)_2$)) (Figures 4, 5). Also, the ^1H NMR spectra of PMLA^{Be} diols synthesized using either $Bi(OTf)_3$ or MSA catalyst with PPD, showed the expected integral value for the methylene signal of the main chain ((CHCH_2C(O)O), δ = 2.92 ppm), whereas the methine and methylene signals ((CH(CO_2CH_2Ph)CH_2C(O)O), δ = 5.50, 5.12 ppm, respectively) failed to provide the corresponding expected integral values (2:1:2 ratio, respectively; Figures S1–S2). This incoherence suggested the presence of (an) unidentified side species and further highlighted the poor control in the case of the ROP mediated by these two catalyst systems.

NMR analyses also provided valuable information about the mechanism taking place during the polymerization of MLA^{Be} promoted by $Nd(OTf)_3$. First, the alcohol used as initiator was found to be quantitatively incorporated into the PMLA^{Be} chains as a central

linkage. Also, the relative intensity ratio between the PPD or TMM (signals *a*,*b*) and the terminal hydroxyl (signal *g*) signals supported an efficient initiation with all the polymer chains being initiated by the alcohol. Furthermore, these observations evidenced the selective ring-opening of MLA^{Be} occurring with oxygen–acyl bond cleavage, thereby generating a propagating hydroxyl chain-end, and ultimately affording a hydroxyl end-capping group. Indeed, as a four membered-ring β-lactone, MLA^{Be} may also be ring-opened with oxygen–alkyl bond rupture to give propagating carboxylic acid chain resulting in –COOH (δ= *ca.* 10.8 ppm) end-functionalized $PMLA^{Be}$,[18–20] a chain-end yet not observed in the present study. Finally, MLA^{Be} is also prone to undergo crotonisation reactions upon elimination of H_2O, leading to an acrylic non-propagating chain end.[18–20] Such –C(O)CH=CH(CO_2CH_2Ph) moieties ($\delta_{CH=CH}$ = *ca.* 5.70–5.80, 6.80–7.00 ppm) were not observed in the NMR nor in mass (*vide infra*) spectra of the recovered polyester samples. These observations are in agreement with the narrow dispersities measured by SEC (*vide supra*). Based on these findings, the ROPs of MLA^{Be} promoted by $Nd(OTf)_3$/PPD,TMM were thus further demonstrated to proceed with a good control and high selectivity, whereas in the case of $Bi(OTf)_3$ and MSA catalyzed ROPs in presence of PPD as initiator, the overall control was poorer.

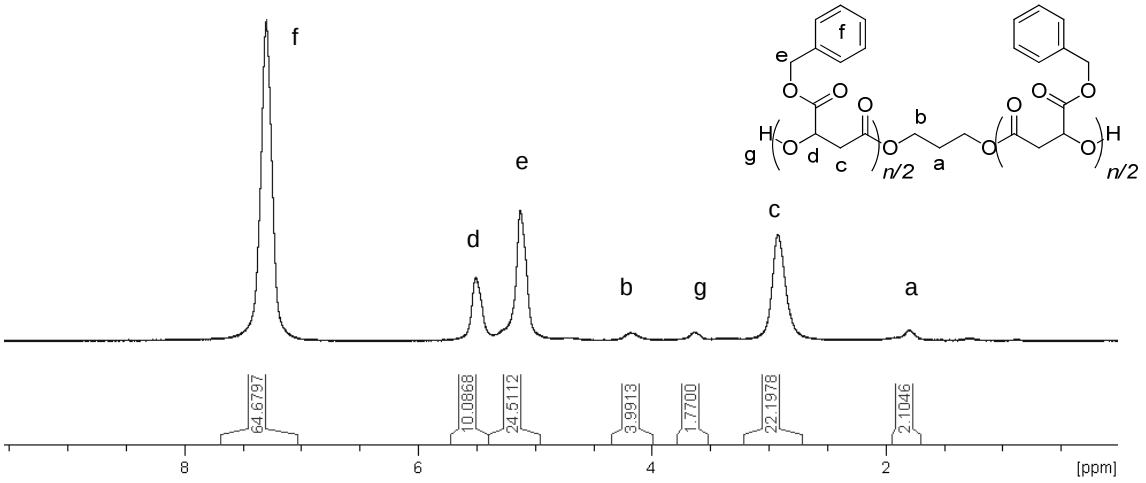


Figure 2. ^{1}H NMR spectrum ($CDCl_3$, 500 MHz, 25 °C) of a $PMLA^{Be}$ diol synthesized by ROP of MLA^{Be} catalyzed by $Nd(OTf)_3$ in the presence of 5 equiv. of 1,3 propanediol as initiator (Table 1, entry 6).

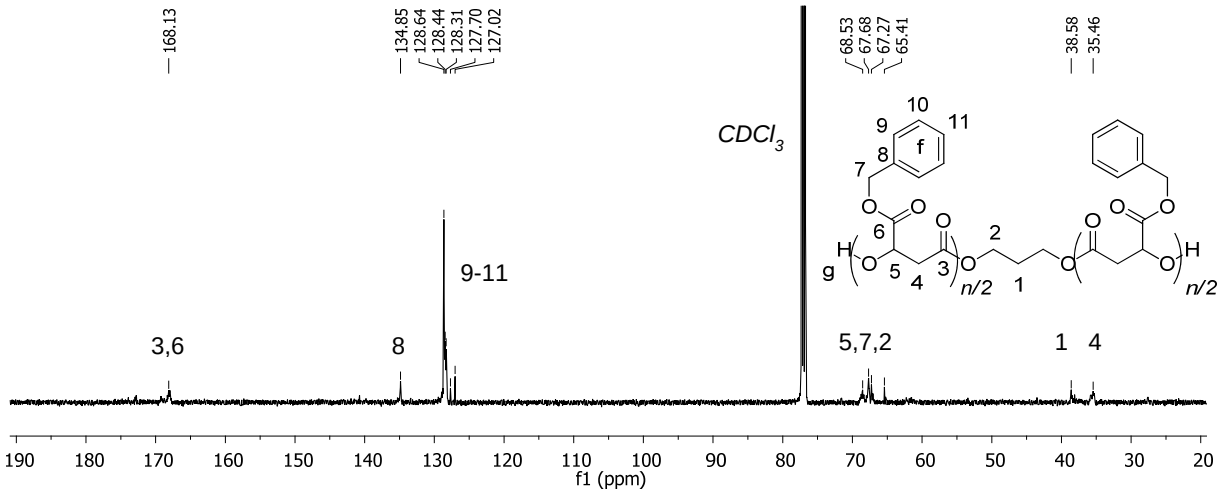


Figure 3. $^{13}C\{^{1}H\}$ NMR spectrum ($CDCl_3$, 125 MHz, 25 °C) of a $PMLA^{Be}$ diol synthesized by ROP of MLA^{Be} catalyzed by $Nd(OTf)_3$ in presence of 5 equiv. of 1,3 propanediol as initiator (Table 1, entry 6).

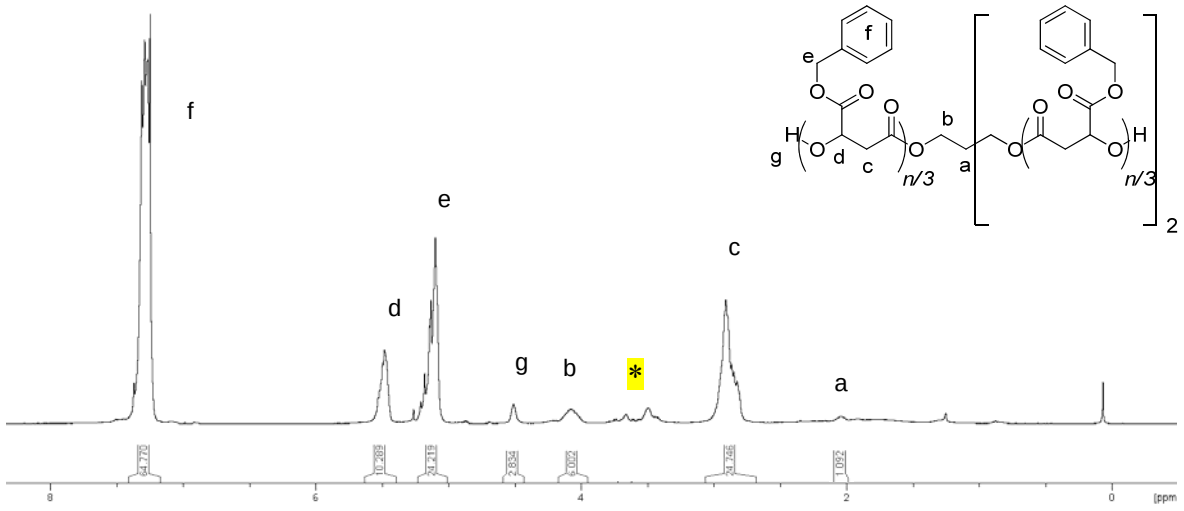


Figure 4. ^{1}H NMR spectrum ($CDCl_3$, 500 MHz, 25 °C) of a $PMLA^{Be}$ triol synthesized by ROP of *rac*-MLA^{Be} catalyzed by $Nd(OTf)_3$ in presence of 5 equiv. of 2-hydroxymethyl-1,3-propanediol as initiator (* marker stands for residual MLA^{Be}; Table 1, entry 10).

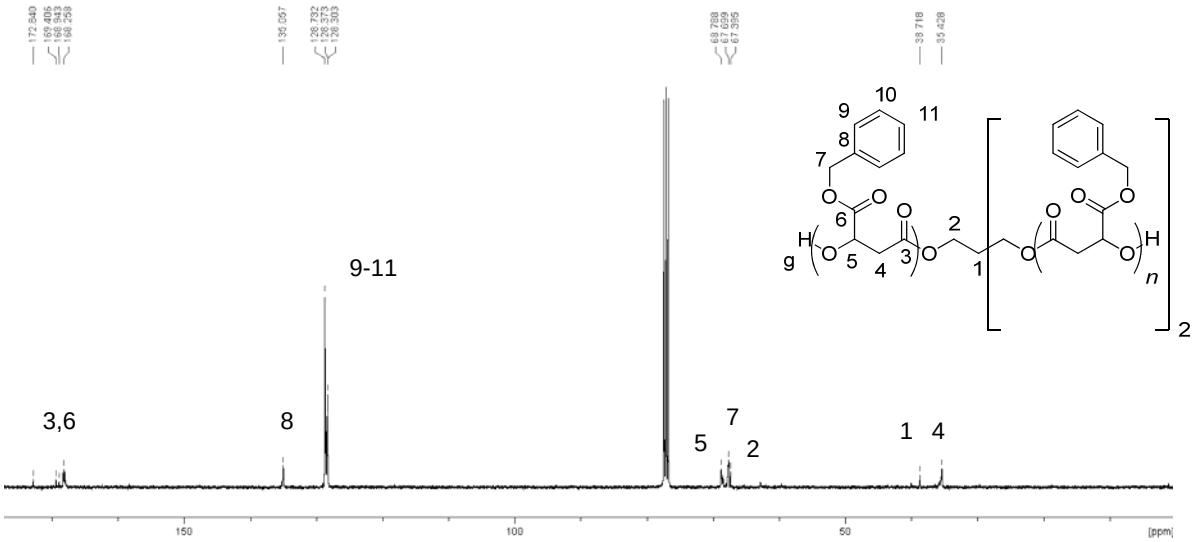


Figure 5. $^{13}C\{^{1}H\}$ NMR spectrum ($CDCl_3$, 125 MHz, 25 °C) of a $PMLA^{Be}$ triol synthesized by ROP of *rac*-MLA^{Be} catalyzed by $Nd(OTf)_3$ in presence of 5 equiv. of 2-hydroxymethyl-1,3-propanediol as initiator (Table 1, entry 10).

Formation of hydroxy telechelic $PMLA^{Be}$s was further supported by MALDI-ToF mass spectrometry (MS) analyses. The spectrum recorded from a low molar mass sample prepared from the $Nd(OTf)_3$/PPD catalytic system and using ditranol as a matrix, revealed a very major population of α,ω-dihydroxy telechelic $PMLA^{Be}$ featuring a repeating unit of 206 $g.mol^{-1}$ (M_{MLABe}) (Figure 6). This was unequivocally confirmed by the close match with the isotopic simulation of a $PMLA^{Be}$ ionized by Na^+ and end-capped by hydroxyl groups, that is $[CH_2\{CH_2O(C(O)CH_2CH(C(O)OCH_2Ph)O)_nH\}_2].Na^+$ with *e.g.* m/z = 2160.6 $g.mol^{-1}$ (*vs.* $m/z_{(experimental)}$ = 2160.2 $g.mol^{-1}$) for $2n$ = 10 (zoom of Figure 6). Similarly, the MALDI-ToF MS of a low molar mass $PMLA^{Be}$ sample synthesized from the $Nd(OTf)_3$/TMM catalytic system also using ditranol as a matrix, displayed a major population with a repeating unit of 206 $g.mol^{-1}$ corresponding to α,ω-trihydroxy telechelic $PMLA^{Be}$ ionized by Na^+, that is $[CH\{CH_2O(C(O)CH_2CH(C(O)OCH_2Ph)O)_nH\}_3].Na^+$ with *e.g.* m/z = 2602.8 $g.mol^{-1}$ (*vs.* $m/z_{(experimental)}$ = 2601.9 $g.mol^{-1}$) for $3n$ = 12, as confirmed by the isotopic simulation (Figure 7).

The minor envelope observed in this latter MS spectrum was assigned to the same macromolecules ionized by K^+. Noteworthy, these MALDI-ToF MS analyses showed no indication of carboxylic acid or crotonate chain-end groups, or any other species, in agreement with NMR analyses (*vide supra*).

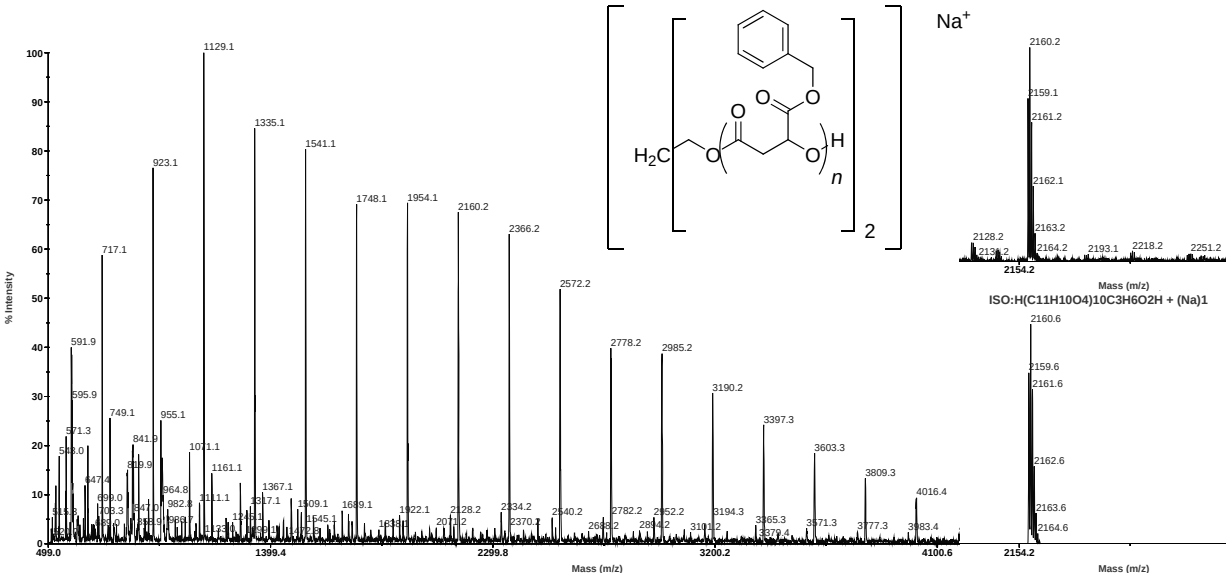


Figure 6. MALDI-ToF MS spectrum of a $PMLA^{Be}$ diol synthesized by ROP of MLA^{Be} catalyzed by $Nd(OTf)_3$ in presence of 5 equiv. of 1,3 propanediol as initiator, using ditranol as a matrix (Table 1, entry 4). The left zooms correspond to the recorded (top) and the simulated (bottom) alike region.

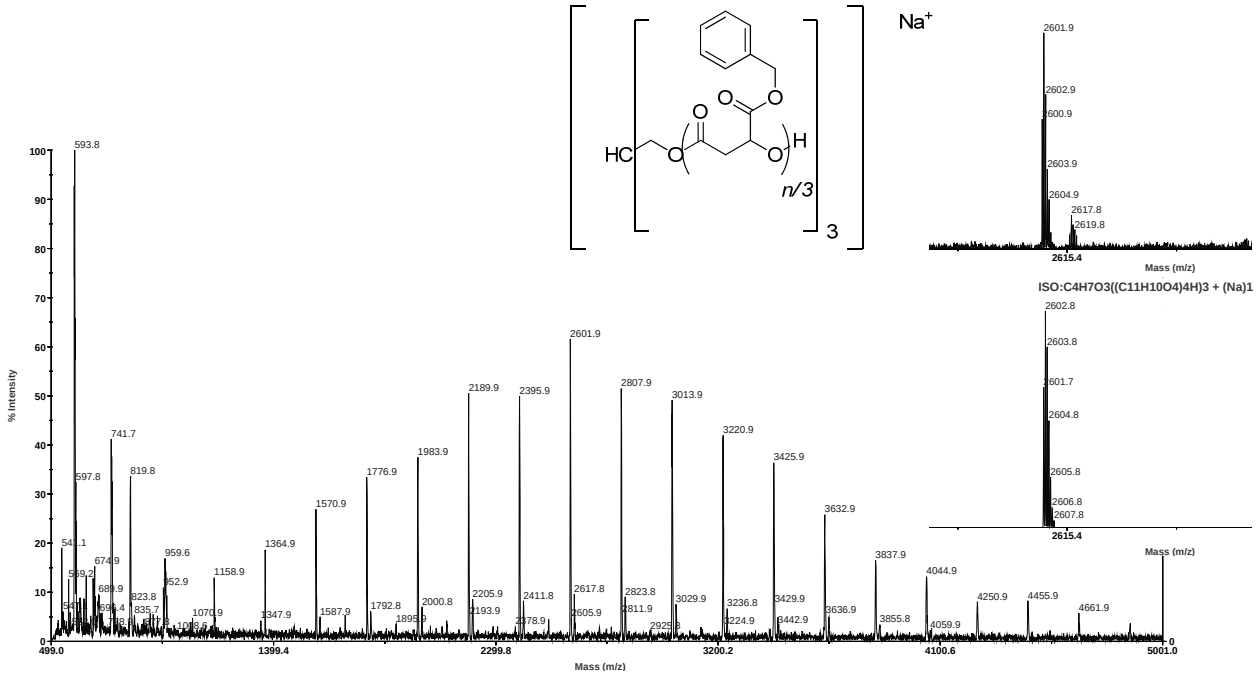


Figure 7. MALDI-ToF MS spectrum of a $PMLA^{Be}$ triol synthesized by the ROP of MLA^{Be} catalyzed by $Nd(OTf)_3$ in presence of 5 equiv. of 2-hydroxymethyl-1,3-propanediol as initiator, using ditranol as a matrix (Table 1, entry 8). The left zooms correspond to the recorded (top) and the simulated (bottom) alike region.

Conclusion

Catalytic systems composed of $Nd(OTf)_3$ catalyst in the presence of hydroxyl-group containing compounds such as PPD or TMP as initiator, were found to promote the controlled ROP of benzyl β-malolactonate under mild conditions (*i.e.* in the absence of a solvent at 60 °C). The ring-opening of MLA^{Be} proceeds through the selective oxygen–acyl bond cleavage without undesirable side reactions such as inter- or intra-molecular transesterification reactions or crotonisation, as evidenced by ^{1}H and $^{13}C\{^{1}H\}$NMR and MALDI-ToF mass spectrometry analyses of the recovered polyesters. Both $Bi(OTf)_3$ and methane sulfonic acid organo-catalyst also enabled the ROP of MLA^{Be} in the presence of PPD, yet with a poor control. However, the alike triflic acid mediated ROP of MLA^{Be} failed

to afford the expected polymer, whereas HOTf was found active in the ROP of the related β-butyrolactone.[45] This again highlights the significant differences previously reported[38,39] between these two four membered-ring β-lactones – differing by the nature of the substituent in β-position of the lactone– both of which are yet challenging to ring-open polymerize. Direct synthesis (*i.e.* not by chemical modification of a preformed polymer) of $PMLA^{Be}$ diols and triols from a simple metal triflate and alcohol (both reactants being commercially available) further strengthens the growing interest in this monomer and its resulting polymer.

Acknowledgements

The authors gratefully thank the CNRS, the Region Bretagne (Ph.D. grant to C. G. J.) and the Fondation pour la Recherche Médicale (FRM "Chimie pour la Médecine") (Ph.D. grant to G. B.) for supporting this research.

Electronic supplementary information (ESI) available: ^{1}H NMR spectra of $PMLA^{Be}$ diol synthesized from $Bi(OTf)_3$/PPD and MSA/PPD catalytic systems.

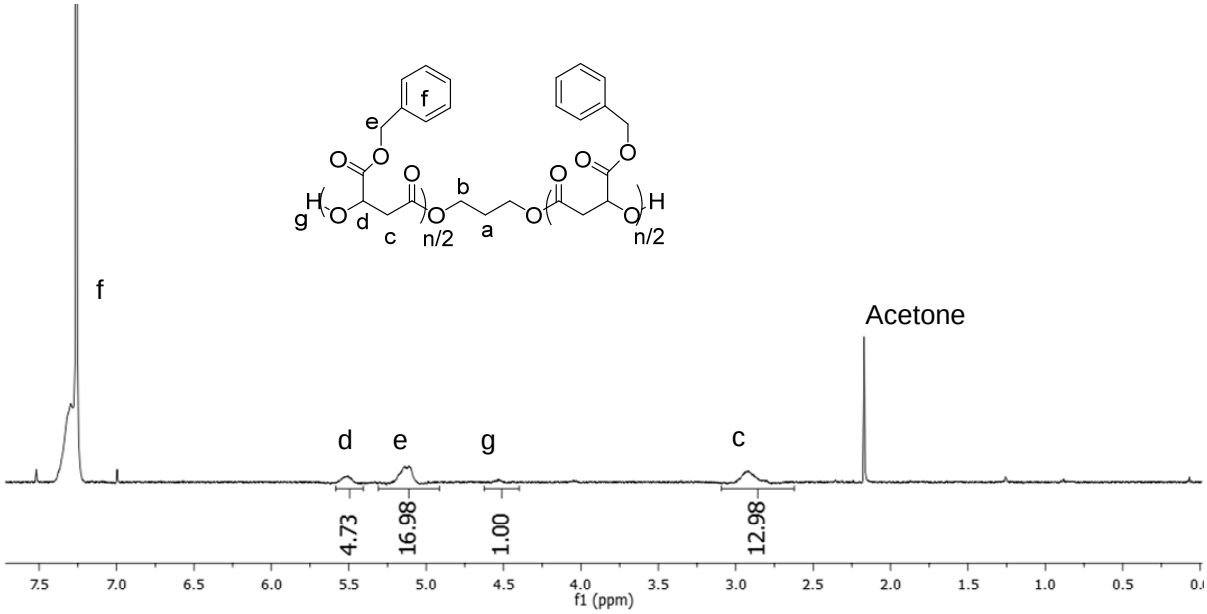


Figure S1. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz, 25 °C) of a $PMLA^{Be}$ diol synthesized by ROP of MLA^{Be} catalyzed by $Bi(OTf)_3$ in presence of 5 equiv. of 1,3-propane diol as initiator (Table 1, entry 2).

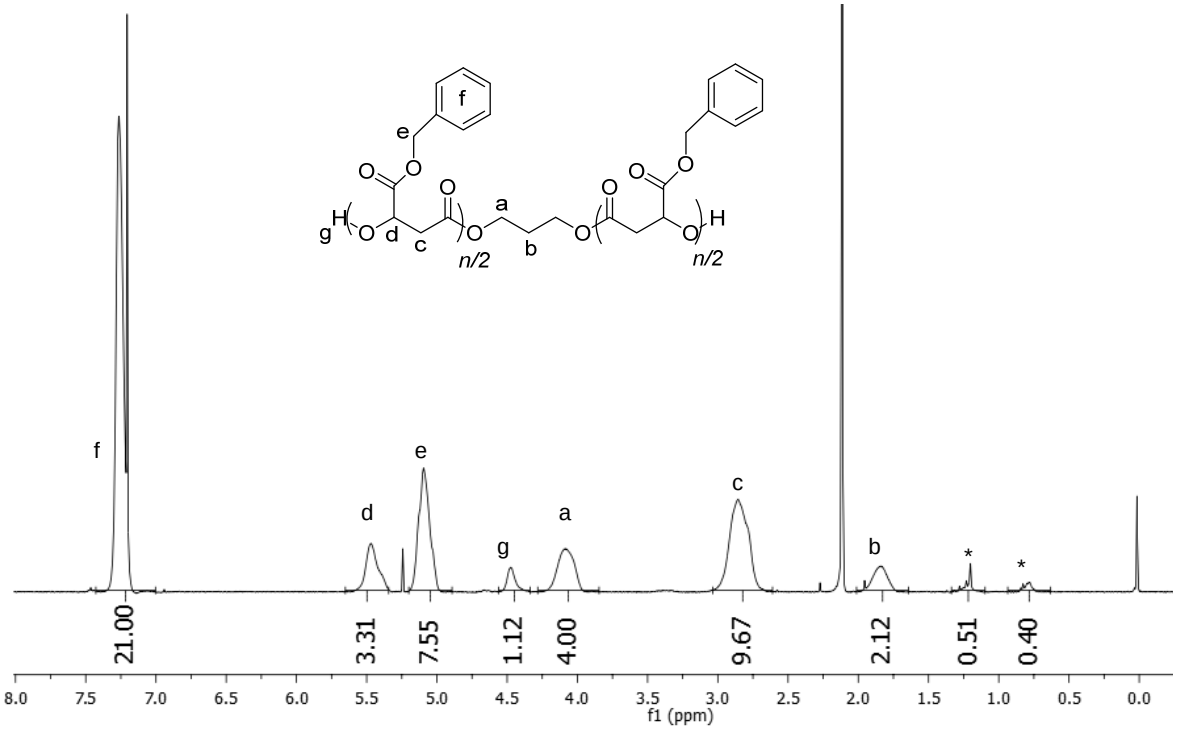


Figure S2. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz, 25 °C) of a $PMLA^{Be}$ diol synthesized by ROP of MLA^{Be} catalyzed by MSA in presence of 5 equiv. of 1,3-propane diol as initiator (Table 1, entry 13).

References

[1] E. J. Goethals in *Telechelic polymers: Synthesis and applications*, ed. E. J. Goethals, CRC Press, Inc., Boca Raton, Florida, 1989.

[2] M. A. Tasdelen, M. U. Kahveci, Y. Yagci *Prog. Polym. Sci.*, 2011, **36**, 455–567.

[3] F. Lo Verso, C. N. Likos *Polymer*, 2008, **49**, 1425–1434.

[4] S. M. Guillaume *Eur. Polym. J.,* 2013, **49**, 769–779.

[5] B. Laycock, P. Halley, S. Pratt, A. Werker and P. Lant, *Prog. Polym. Sci.,* 2013, **38**, 536–583.

[6] Taguchi, S.; Iwata, T.; Abe, H.; Doi, Y. *Polym. Sci.: A Comprehensive Ref.*, 2012, **9**, 157–182.

[7] X. Gao, J.-C. Chen, Q. Wu, G.-Q. Chen, *Current Opinion in Biotechnology*, 2011, **22**, 768–774.

[8] Lu, J.; Tappel, R. C.; Nomura, C. T. *J. Macromol. Sci. C: Polym. Rev.*, 2009, **49**, 226–248.

[9] Lenz, R. W.; Marchessault, R. H. *Biomacromolecules*, 2005, **6**, 1–8.

[10] Chen, G.-Q. *Chem. Soc. Rev.*, 2009, **38**, 2434–2446.

[11] Zinn, M.; Witholt, B.; Egli, T. *Adv. Drug Deliv. Rev.*, 2001, **53**, 5–21

[12] Hazer, D. B.; Kilicay, E.; Hazer, B. *Mater. Sci. and Eng. C*, 2012, **32**, 637–647.

[13] Hazer, B. *Energy and Power Engineering*, 2010, **1**, 31–38.

[14] Coulembier, O.; Dubois, P. in *Handbook of Ring-Opening Polymerization;* Dubois, P., Coulembier, O., Raquez, J.-M. Eds.; Wiley-VCH, 2009; p 227–254.

[15] Thomas, C. M. *Chem. Soc. Rev.* 2010, **39**, 165–173.

[16] J.-F. Carpentier, *Macromol. Rapid Commun.* 2010, **31**, 1696–1705.

[17] M. Vert *Polym. Degrad. Stab.*, 1998, **59**, 169v175.

[18] O. Coulembier, P. Degée, J. L. Hedrick, P. Dubois *Prog. Polym. Sci.*, 2006, **31**, 723–747.

[19] R. J. Pounder, A. P. Dove *Polym. Chem.*, 2010, **1**, 260–271

[20] C. G. Jaffredo, S. M. Guillaume *Polym. Chem.* 2014, **5**, 4168–4194.

[21] S. L. King, V. X. Truong, C. Kirchhoefer, A.Pitto-Barry, A. P. Dove *Green Mat.,* 2014, **3**, 107–122.

[22] J. Y. Ljubimova, M. Fujita, A. V. Ljubimov, V. P. Torchilin, K. L. Black, E. Holler *Nanomedicine*, 2008, **3**, 247–265.

[23] A. Aden, J. Bozell, J. Holladay, J. White, A. Manheim, in *Top Value Added Chemicals From Biomass, Volume 1: Results of Screening for Potential Candidates from Sugars and Synthesis Gas*, eds. T. Werpy, G. Petersen, Washington DC, 2004.

[24] J. J. Bozell, G. R. Petersen *Green Chem.*, 2010, **12**, 539–554.

[25] P. Loyer, S. Cammas-Marion, *J. Drug Target.*, 2014, **22**, 556–575.

[26] C. G. Jaffredo, J.-F. Carpentier, S. M. Guillaume, *Angew. Chem. Int. Ed.* 2014, **53**, 1–6.

[27] S. Osanai, K. Nakamura *Biomaterials*, 2000, **21***,* 867–876.

[28] S. Cammas-Marion, P. Guérin *Macromol. Symp.*, 2000, **153**, 167–186.

[29] S. Cammas, I. Renard, V. Langlois, P. Guérin *Polymer*, 1996, **18**, 4215–4220.

[30] C. G. Jaffredo, J.-F. Carpentier, S. M. Guillaume *Polym. Chem.*, 2013, **4**, 3837–3850.

[31] P. Guerin, J. Francillette, C. Braud, M. Vert *Makromol. Chem., Macromol. Symp.*, 1986, **6**, 305–314.

[32] R. A. Gross, Y. Zhang, G. Konrad, R. W. Lenz, *Macromolecules*, 1988, **21**, 2657–2668.

[33] R. A. Gross, G. Konrad, Y. Zhang, R. W. Lenz, *ACS Polym. Prepr.*, 1987, **28**, 373–374.

[34] O. Coulembier, P. Degée, C. Barbaud, P. Guérin, P. Dubois, *Polym. Bull.*, 2004, **51**, 365–372.

[35] M. Helou, G. Moriceau, Z. W. Huang, S. Cammas-Marion, S. M. Guillaume, *Polym. Chem.*, 2011, **2**, 840–850.

[36] C. G. Jaffredo, J.-F. Carpentier, S. M. Guillaume, *Macromolecules* 2013, **46**, 6765–6776.

[37] O. Coulembier, P. Degée, P. Dubois, *Macromol. Chem. Phys.* 2006, **207**, 484v491.

[38] C. G. Jaffredo, M. Schmid, I. del Rosal, T. Mevel, P. W. Roesky, L. Maron, S. M. Guillaume, *Chem. Eur. J.* , 2014, **44**, 14387–14402.

[39] S. M. Guillaume, L. Annunziata, L. Maron, C. Iftner, I. del Rosal, P. W. Roesky, M. Schmid, *Polym. Chem.* 2013, **4**, 3077–3087.

[40] S. M. Guillaume, L. Maron, P. W. Roesky in *Catalytic behavior of rare-earth borohydride complexes in polymerization of polar monomers*, *Vol. 244* Eds.: J.-C. G. Bünzli, V. K. Pecharsky), Elsevier, Amsterdam, 2014, pp. 1–86.

[41] S. M. Guillaume, M. Schappacher, A. Soum, *Macromolecules*, 2003, **36**, 54–60.

[42] N. Barros, P. Mountford, S. M. Guillaume, L. Maron *Chem. Eur. J.*, 2008, **14**, 5507–5518.

[43] F. A. Jaipuri, B. D. Bower, N. L. Pohl, *Tetrahedron Asymmetry*, 2003, **14**, 3249–3252.

[44] M. Basko, A. Duda, S. Kazmierski, P. Kubisa, *J. Polym. Sci., Polym. Chem.*, 2013, **51**, 4873–4884.

[45] A. Couffin, B. Martín-Vaca, D. Bourissou, C. Navarro, *Polym. Chem.*, 2014, **5**, 161–168.

[46] S. M. Guillaume, J.-F. Carpentier, *Catal. Sci. Techn.* 2012, **2**, 898–906.

[47] N. Ajellal, J.-F. Carpentier, C. Guillaume, S. M. Guillaume, M. Helou, V. Poirier, Y. Sarazin, A. Trifonov, *Dalton Trans.*, 2010, **39**, 8363–8376.

[48] The ROP mediated by $Bi(OTf)_3$/PPD gave $M_{n,NMR}$ values for the precipitated polymer lower than $M_{n,theo}$ along with slightly larger dispersity values, indicative of the slightly greater occurrence of undesirable transfer reactions,[49] as compared to the neodymium-based catalytic system.

[49] Buchard, A.; Bakewell, C. M.; Weiner, J.; Williams, C. K. *Top. Organomet. Chem.*, **2012**, *39*, 175–224.

Electronic Supplementary Information

Linear and Three-arm Star Hydroxytelechelic Poly(Benzyl β-Malolactonate)s: A Straightforward One-step Synthesis through Ring-Opening Polymerization

Ghislaine Barouti,[§] Cédric G. Jaffredo,[§] and Sophie M. Guillaume[49]

Institut des Sciences Chimiques de Rennes, UMR 6226 CNRS - Université de Rennes 1, Campus de Beaulieu, F-35042 Rennes Cedex, France

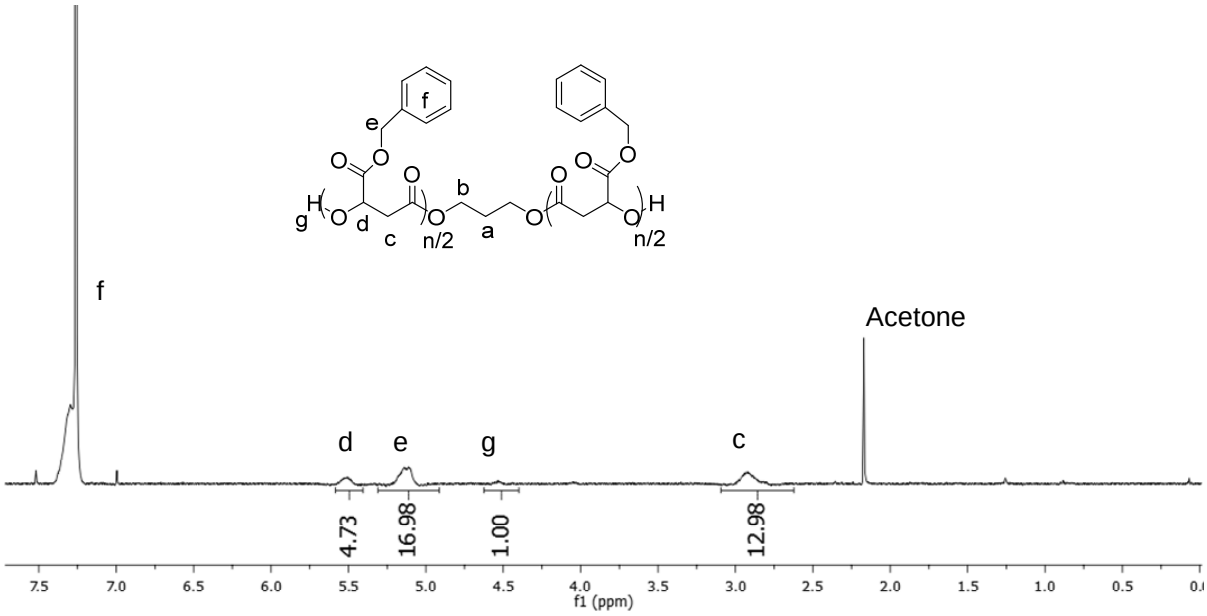


Figure S1. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz, 25 °C) of a $PMLA^{Be}$ diol synthesized by ROP of MLA^{Be} catalyzed by $Bi(OTf)_3$ in presence of 5 equiv. of 1,3-propane diol as initiator (Table 1, entry 2).

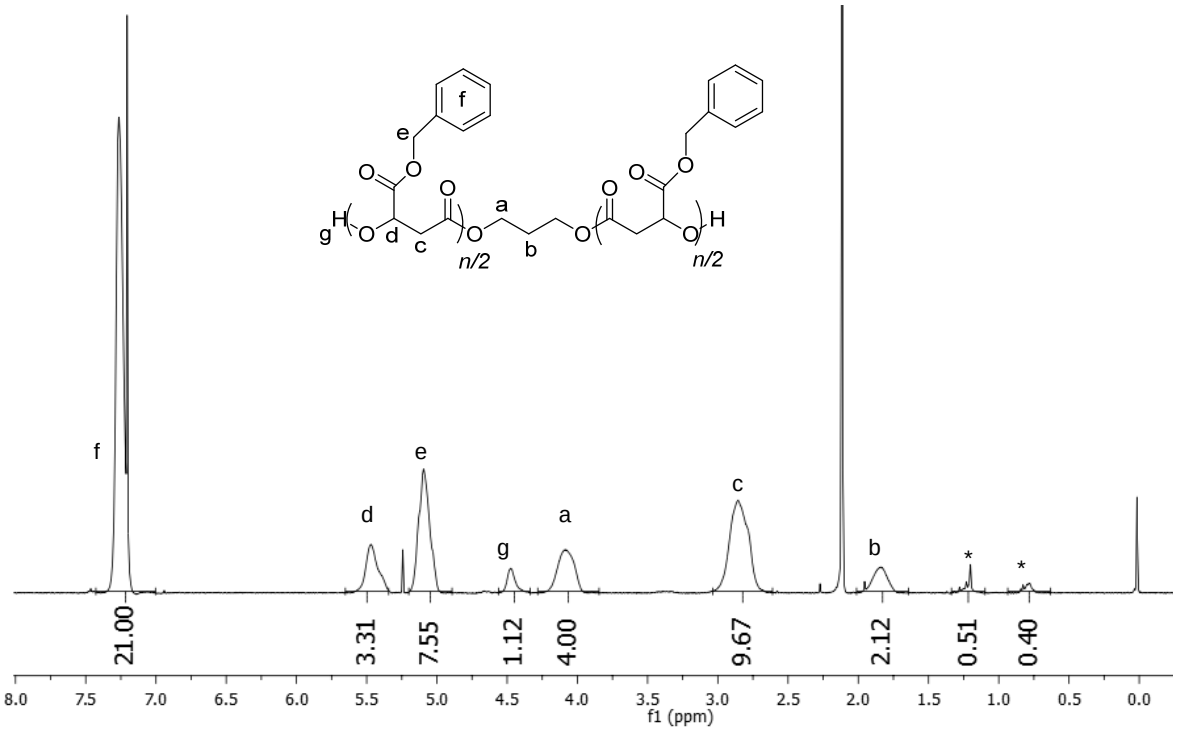


Figure S2. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz, 25 °C) of a $PMLA^{Be}$ diol synthesized by ROP of MLA^{Be} catalyzed by MSA in presence of 5 equiv. of 1,3-propane diol as initiator (Table 1, entry 13).