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Access to new carbohydrate-functionalized polylactides via organocatalyzed ring-opening polymerization

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ABSTRACT

The 4-dimethylaminopyridine (DMAP) catalyzed ring-opening polymerization of lactide using various carbohydrate initiators has been assessed for the functionalization of polylactide. Selectively protected glucose derivatives bearing a free primary alcohol (**Glc-1r**) and a free secondary alcohol (**Glc-2r**), glucose and cyclodextrin diol derivatives (**Glc-diol** and **CD-diol**), methyl-α-D-glucopyranoside (**Glc-Me**) and native β-cyclodextrin (**CD**) were used as initiators. According to the solubility of the carbohydrate derivative, the polymerizations were conducted in chlorinated solvents and in the bulk. Relatively narrow distributions are obtained in high yields in the absence of side reactions, affording a 100% functionalization efficiency. The catalytic synthesis of new carbohydrate link-functionalized polylactides and carbohydrate core star polylactides is reported.

1. Introduction

Biodegradable polyesters based on renewable resources such as polylactide are used for packaging and biomedical applications including for instance drug delivery and temporary implants. Polylactide is mostly synthesized by ring-opening polymerization of the corresponding cyclic ester, lactide, although it can also be obtained by polycondensation of lactic acid. The hydrophobic nature of this polyester can hamper its use for specific applications. This can be circumvented by introducing hydrophilic functional groups into the polymer. The use of carbohydrates derivatives seems pertinent toward this issue, as carbohydrates are not only renewable resources, but also biocompatible and biodegradable compounds. The introduction of cyclodextrins into polylactide is also of interest in the frame of drug delivery applications, as cyclodextrins are able to host molecules of pharmaceutical interest [1]. The use of carbohydrates as ring-opening polymerization initiators has further some interest for macromolecular engineering, for the synthesis of star or link-functionalized polymers (polymers containing a central backbone functionality).

Various strategies have been reported for introducing carbohydrates into aliphatic polyesters [2,3]. Most of these strategies are based on metal catalysts and/or initiators [4–11]. Residual metal contaminants can hamper the use of the polymer for biomedical and pharmaceuticals applications [12]. The use of organic molecules or enzymes as catalysts is thus considered as an interesting alternative in this context.

Enzymatic catalysis was reported as a straightforward way for the synthesis of carbohydrate end-functionalized poly(ε-caprolactone) [13,14]. However, if enzymes are rather good catalysts for the ring-opening polymerization of ε-caprolactone, their performances for the ring-opening polymerization of lactides remain modest, yielding rather low yields and high dispersities in harsh experimental conditions [15–20]. The synthesis of carbohydrate end-capped poly(ε-caprolactone) was also reported using lactic acid as the catalyst, but lead to the simultaneous formation of lactic acid end-capped poly(ε-caprolactone) [21]. Cyclodextrins were also used as organo-initiators for the ring-opening polymerization of various lactones [22,23] and the ring-opening oligomerization of lactide [24] without additional co-catalyst. The latter polymerization yielded oligolactides on the C6 carbon with a number-average degree of polymerization of 3.5. Sparteine was also reported to catalyze the β-cyclodextrin initiated ring-opening polymerization of β-butyrolactone, leading to the side formation of unfunctionalized poly(-β-butyrolactone) [25]. The functionalization of polylactide with

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various carbohydrates using an organic catalyst has never been systematically studied as far as we know. It is thus of interest to assess an organic catalyst for this purpose. Organocatalysis has gained much interest these last years, and numerous catalysts such as organic acids, pyridines, nitrogen bases, phosphines, carbenes, and phosphazenes have been assessed for the ring-opening polymerization of cyclic esters [26,27]. We choose 4-dimethylaminopyridine (DMAP) as a catalyst. Mild polymerization conditions produce polylactides with predictable molecular weights and narrow dispersity using this catalyst combined to an alcohol as co-initiator [28]. We report herein the synthesis of various carbohydrate-functionalized polylactides using DMAP as a catalyst for the ring-opening polymerization of lactide. To the best of our knowledge, several polymers synthesized in this study have never been reported in the literature.

2. Experimental section

2.1. Materials

L-lactide and D,L-lactide (Aldrich) were recrystallized three times from toluene followed by sublimation under vacuum at 85 °C. 4-dimethylaminopyridine (DMAP - Aldrich) was co-evaporated three times with toluene followed by sublimation under vacuum at 85 °C before use. Chloroform (Aldrich) was washed with water, dried with $CaCl_2$, put under reflux with P_2O_5 and distilled. Dichloromethane was taken from a solvent purification system (MBraun MB SPS 800). All reagents and anhydrous solvents used for the synthesis of the carbohydrates initiators were purchased from Sigma–Aldrich and used directly without any further purification.

2.2. Carbohydrates synthesis

The different carbohydrates synthesized for this study are presented in Fig. 1. Classical carbohydrates protection and deprotection strategies were used for this purpose. The Methyl-α-D-glucopyranoside is a commercially available compound used as received for carbohydrate synthesis and purified by toluene distillation.

The compound **3** (referred to as **Glc-1r** hereafter) is easily obtained in 3 steps from the Methyl-α-D-glucopyranoside after selective tritylation of the O-6 position and benzylation of the position O-2, O-3 and O-4 in well established conditions in a 66% and 78% yield respectively (Scheme 1). The trityl group is selectively removed by refluxing in a mixture of acetic acid and water to give the compound **3** in a 60% yield.

2.2.1. Methyl-6-O-trityl-α-D-glucopyranoside - (*1*)

A solution of methyl-α-D-glucopyranoside (6.0 g, 0.03 mol), tritylchloride (11 g, 1.2 eq.), triethylamine (8 mL), and DMAP (290 mg, 0.5 eq.) in DMF (50 ml) was stirred overnight at room temperature under nitrogen. After 12 h stirring, the reaction mixture was poured into ice-water and extracted with dichloromethane. The organic extracts were washed with water, and dried with magnesium sulfate. After removal of the solvents, the solid was recrystallized from ethanol to give 8.9 g, (66%) of compound **1** as a white solid.

2.2.2. Methyl 2,3,4 tri-O-benzyl-6-O-trityl-α-D-glucopyranoside (*2*)

A solution of **1** (8.9 g, 0.03 mol) in DMF was added at 0 °C to NaH (60% in mineral oil, 3.6 g, 4.5 eq.). After 30 min BnBr (10.5 ml, 4.5 eq) was added and the reaction mixture was stirred overnight at room temperature. The reaction was then quenched with water (40 mL) and the aqueous layer was washed with ethyl acetate (4 × 50 mL). The organic extracts were dried with magnesium sulfate. After removal of the solvents, the residue was purified by chromatography (eluent gradient, EtOAc/Petroleum ether 1/5 to 1/3), to afford the compound **2** as a white solid (11 g, 78%).

2.2.3. Methyl 2,3,4 tri-O-benzyl-α-D-glucopyranoside (*3* or *Glc-1r*)

A solution of **2** (11 g, 0.015 mol), in a mixture acetic acid/water (9/1) was stirred at reflux during 5 h. The solvent was co-evaporated with toluene and the residue was purified by chromatography (eluent gradient, EtOAc/Petroleum ether 1/3 to 1/1), to afford the compound **3** as a white solid (4.2 g, 60%).

The diol **6** (referred to as **Glc-diol** hereafter) was obtained in a 3 steps synthesis from the Methyl-α-D-glucopyranoside (Scheme 2). The 4–6 benzylidene **4** was obtained in acidic condition by the reaction with benzaldehyde dimethyl acetal, and then the position O-2 and O-3 were methylated to give the fully protected compound **5**. Selective cleavage of the benzylidene in aqueous acidic conditions allowed us to obtain the diol **6**.

2.2.4. Methyl 4,6-O-benzylidene-α-D-glucopyranoside (*4*)

To a solution of methyl α-D-glucopyranoside (2.11 g, 10.87 mmol) in dry acetonitrile (60 mL) was added benzaldehyde dimethyl acetal (2.80 g, 18.40 mmol) and the solution acidified with camphorsulfonic acid (catalytic amount). After stirring at room temperature overnight the mixture was neutralized with triethylamine and concentrated in vacuo to dryness using toluene as a cosolvent. The resulting residue was recrystallized from ethyl acetate – hexane to afford compound **4** as a white crystalline solid (2.22 g, 76%).

2.2.5. Methyl 4,6-O-benzylidene-2,3-di-O-methyl-α-D-glucopyranoside (*5*)

Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (500 mg, 1.77 mmol) was dissolved in dry DMF (20 mL) under a nitrogen atmosphere. To this was added 60% NaH suspended in oil (260 mg, 6.50 mmol) followed by the dropwise addition of methyl iodide (340 μL, 5.46 mmol) and the reaction was left to stir for 16 h under a nitrogen atmosphere at room temperature. After this time, the reaction was quenched with water (40 mL) and the aqueous layer was washed with ethyl acetate (3 × 50 mL). The combined organic layers were then washed with saturated $NaHCO_3$ (3 × 50 mL) and water (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent removed in vacuo and the residue recrystallized from ethanol to furnish **5** as a white solid (270 mg, 49%).

2.2.6. Methyl 2,3-di-O-methyl-α-D-glucopyranoside (*6* or *Glc-diol*)

To methyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-α-D-glucopyranoside (250 mg, 0.81 mmol) was added a solution of 80% acetic acid in water (15 mL) and the mixture was heated to 50 °C. After a period of 4 h, the reaction mixture was cooled, concentrated in vacuo, and then co-evaporated with toluene (3 × 20 mL). The residue was recrystallized from ethyl acetate – Petroleum ether to give the desired compound **6** as a white solid (73 mg, 41%).

The required compound **10** (referred to as **Glc-2r**), partially protected benzyl-β-D-glucopyranoside, was prepared in 6 steps synthesis from commercial glucose pentaacetate by the orthoester procedure (Scheme 3). The *O*-benzyl orthoester **7** was obtained under Lemieux–Morgan conditions, the acetyl groups of **7** were replaced by benzyl groups, and the orthoester **8** was rearranged into the corresponding benzyl-β-glycoside **10** by treatment with trimethylsilyl triflate followed by de-*O*-acetylation at O-2.

2.2.7. 3,4,6-Tri-O-acetyl-α-D-glucopyranose 1,2-(benzyl orthoacetate) (*7*)

Glucose pentaacetate (5 g, 0.013 mol) was dissolved in a solution of HBr (33%) in acetic acid (15 mL), after 3 h at room

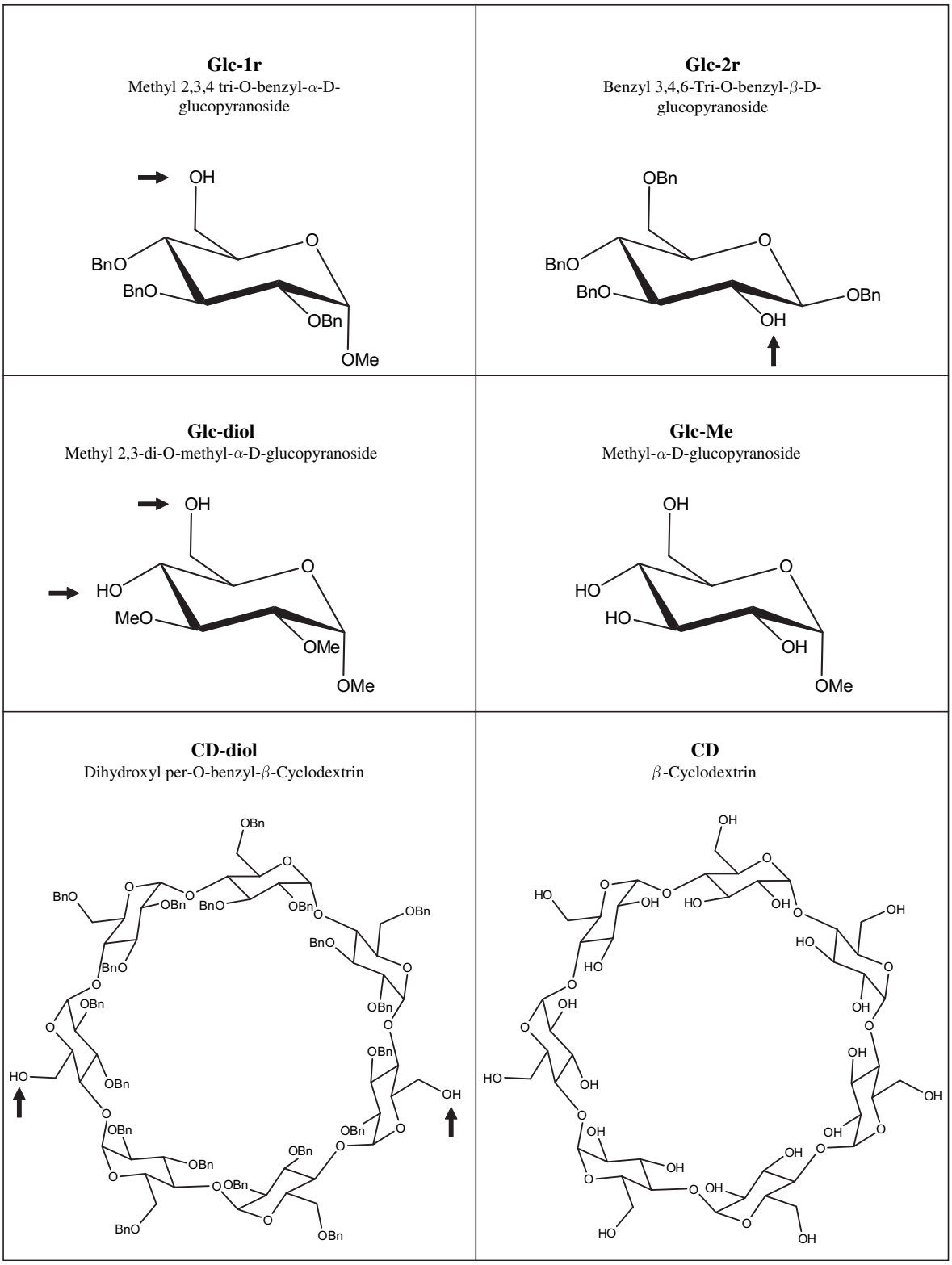
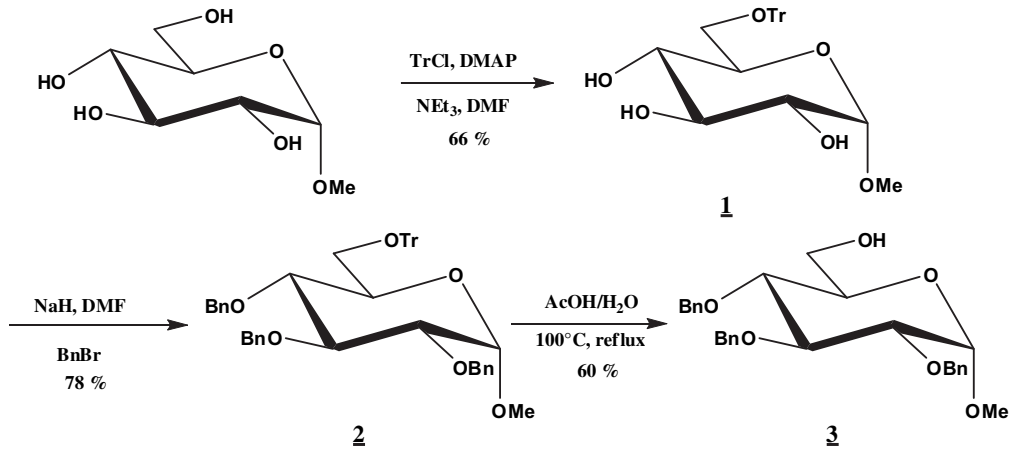


Fig. 1. Carbohydrates initiators used for the ring-opening polymerization of lactide.

temperature, CH_2Cl_2 (100 mL) was added. The organic layer was washed with cold water (3 × 50 mL), and a saturated solution of $NaHCO_3$ (3 × 50 mL) then dried with magnesium sulfate. After removal of the solvents, the residue was dissolved in lutidine (15 mL) and tetrabutylammonium bromide (1.5 g; 0.3 eq) and benzyl alcohol (4 mL, 3eq.) were added. After 1 night at 50 °C, CH_2Cl_2 (100 mL) was added and the organic layer was washed with a 0.5 M solution of HCl and with a saturated solution of $NaHCO_3$ (3 x 50 mL) then dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography (eluent gradient, EtOAc/pentane 1/4 to 1/2), to afford the orthoester **7** (3.4 g, 70%).



Scheme 1. Glc-1r synthesis.

*2.2.8. 3,4,6-Tri-O-benzyl-α-D-glucopyranose 1,2-(benzyl orthoacetate) (**8**)*

To a solution of **7** (3.4 g; 0.008 mol) in THF (50 mL) was added BnCl (5.3 mL, 5 eq.) and KOH (4.9 g, 10 eq.). After 3 h refluxing, the reaction was diluted with CH_2Cl_2 (50 ml) and the organic layer was washed with water (3 × 50 mL) and with a saturated solution of $NaHCO_3$ (3 × 50 mL) then dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography (eluent gradient, EtOAc/pentane 1/5 to 1/3), to afford the orthoester **8** (3.35 g, 71%).

*2.2.9. Benzyl 3,4,6-tri-O-benzyl-4-O-acetyl-β-D-glucopyranoside (**9**)*

To a solution of compound **8** (2.0 g, 3.4 mmol) in CH_2Cl_2 (30 ml) in presence of molecular sieves was added at 0 °C TMSOTf (80 μL, 0.8 mmol catalytic). After 2 h, the reaction mixture was washed with a saturated solution of $NaHCO_3$ (3 × 50 mL) and with water (3 × 50 mL) then dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography (eluent gradient, EtOAc/pentane 1/5 to 1/3), to afford the compound **9** (1.4 g, 70%).

*2.2.10. Benzyl 3,4,6-tri-O-benzyl-β-D-glucopyranoside (**10** or **Glc-2r**)*

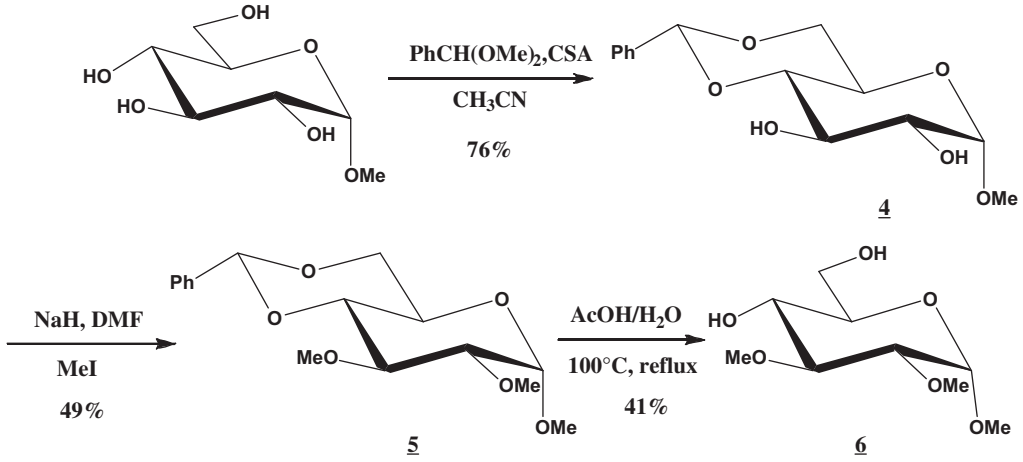
To a solution of compound **9** (1.4 g, 2.4 mmol) in MeOH (5 ml) was added MeONa. After 1 night, the reaction mixture was neutralized with H^+-resin (Amberlire IR-120). After filtration, the organic layer was concentrated in vacuo. The residue was purified by chromatography (eluent gradient, EtOAc/pentane 1/5 to 1/3), to afford the compound **10** (0.78 g, 62%).

2.2.11. De-O-benzylation of perbenzylated cyclodextrins

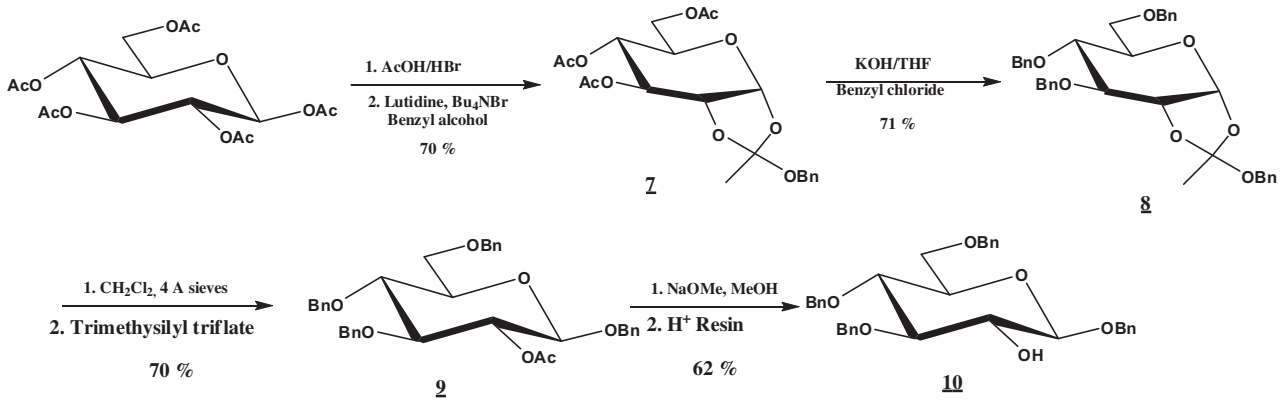
The cyclodextrins diols were obtained from perbenzylated cyclodextrins in presence of DIBAL-H with a procedure developed by Sinaÿ [29] and modified by Bols [30]. Molecular sieves (4 Å, 1 g) were added at room temperature under nitrogen to a solution of per-*O*-benzyl-*β*-cyclodextrin (5 g, 1.65 mmol) in anhydrous toluene (270 mL), and the system was stirred for 1 h. After that, DIBAL (66 mL, 66.4 mmol, 1.0 M in toluene) was added dropwise. The reaction mixture was stirred for 6 h at room temperature and was then cooled to 0 °C, water (30 mL) was carefully added dropwise, and the mixture was stirred vigorously at room temperature for 15 min. The mixture was diluted with EtOAc (50 mL) and filtered, with washing with EtOAc (3 times 100 mL). The organic layer was washed with brine (2x75 mL), dried ($MgSO_4$) and filtered, and the organic solvent was removed in vacuo. The residue was purified by chromatography (eluent gradient, EtOAc/pentane 1/5 to 1/2), to afford the expected diol (3.79 g, 81%) as a white foam. The NMR assignments are in agreement with those reported in ref. [29].

2.3. Polymerization

In a typical polymerization run, lactide (*ca.* 300 mg), the carbohydrate initiator (*ca.* 10–100 mg according to the nature of the initiator and the ratio) and the catalyst (*ca.* 20–40 mg according to the ratio) were weighted into a flask in a glove box. After an eventual introduction of the solvent (*ca.* 1.5 to 0.75 ml), the mixture



Scheme 2. Glc-diol synthesis.



Scheme 3. Glc-2r synthesis.

was magnetically stirred at the reaction temperature for a given time, quenched with a methanol/water mixture and the resulting solution was poured into methanol, leading to the precipitation of an off-white polymer. The solvents were evaporated under partial vacuum, and the product was dried under vacuum for 48 h.

2.4. Measurements

NMR spectra were recorded on a AC 300 Bruker spectrometer at room temperature in DMSO-*d6*. Approximately 5 and 40 mg of sample were directly dissolved into the NMR tube in 0.6 mL of solvent for ^{1}H and ^{13}C NMR, respectively. The chemical shifts were calibrated using the residual resonances of the solvent. The conversion and degree of polymerization were calculated by the integration of the proton of C*H* groups of D,L-lactide or L-lactide, the proton of C*H* groups of polylactide (PLA) and the proton of C*H*-OH end groups which are at $\delta = 5.46$ ppm, $\delta = 5.21$ ppm and $\delta = 4.22$ ppm respectively. The conversion was calculated from the ratio C*H* PLA/(C*H* PLA + C*H* lactide). The degree of polymerization equals the ratio C*H* PLA/C*H*—OH end group. For **Glc-1r** end-capped PLA, overlapping of the —CH—OH end group signal with the two protons of the C6 carbon of the carbohydrate end-goup (4.29 ppm) is observed. Both signals were simultaneously integrated. A deconvolution was performed for **CD-diol** and **CD-**end-capped PLA due to overlapping signals. The calculated degree of polymerization is equal to the ratio of monomer/hydroxyl multiplied by the conversion.

Size exclusion chromatography was performed in THF as eluent at 40 °C using a Waters SIS HPLC-pump, a Waters 2414 refractometer and Waters styragel column HR3 and HR4. The calibration was done using polystyrene standards. MALDI-TOF-MS was performed on an Ultraflex II spectrometer (Bruker). The instrument was operated in either the reflector or linear mode. The spectra were recorded in the positive-ion mode. The samples were prepared by taking 2 μL of a THF solution of the polymer (10 mg/mL) and adding this to 16 μL of 1,8-dihydroxy-9(10H)-anthracenone (dithranol, 10 mg/mL in THF) to which 2 μL of CF_3SO_3Ag (2 mg/mL in THF) had been added. A 1 μL portion of this mixture was applied to the target and 50–100 single shot spectra were accumulated. The given masses represent the average masses of the Ag^+ adducts. The spectrometer was calibrated with an external mixture of angiotensin I, ACTH 18-39 and bovine insulin or PEG 1500.

3. Results and discussion

The carbohydrates used as initiators for the DMAP catalyzed ring-opening polymerization of lactide are presented in Fig. 1. Synthesis details are given in the experimental part. Protected glucose derivatives bearing a primary and a secondary alcohol were synthesized and referred to as **Glc-1r** and **Glc-2r**, respectively. Two di-functional initiators were also synthesized in order to achieve link-functionalized polymers. The glucose di-functional initiator is referred to as **Glc-diol**, while the cyclodextrin di-functional initiator is referred to as **CD-diol**. Methyl-α-D-glucopyranoside, a tetra-functional initiator referred to as **Glc-Me** and native β-cyclodextrin containing 21 initiating hydroxyl groups referred to as **CD** were also selected for the synthesis of star PLA.

Representative results of the ring-opening polymerization of lactide initiated by **Glc-1r**, **Glc-2r**, **Glc-diol** and **CD-diol** in chlorinated solvents are presented in Table 1. **Glc-Me** and **CD** are not soluble in these solvents, and were used as initiators in bulk polymerization as discussed hereafter. Blank experiments showed that the lactide ring could not be opened by DMAP alone or carbohydrates alone. From Table 1, narrow distributions are obtained, and the number-average polymerization degree measured by NMR corresponds well with that calculated considering the growth of one polymeric chain per initiating hydroxyl group. The reaction is quantitative using **Glc-1r** under the experimental conditions of ref. [28] for small values of monomer/ROH ratio (entries 1–2), but the yield drops for higher values (entry 3). This can be circumvented by increasing the amount of catalyst and the concentration of the reaction (entries 4–5). Similar trends are observed using **Glc-2r** as initiator (entry 8 *vs.* 7). It can be seen that primary alcohols are more reactive toward the initiation step than secondary alcohols (entries 3 *vs.* 7), which may be attributed to steric considerations. The di-functional **Glc-diol** containing both a primary and a secondary alcohol leads to values of the yield intermediates between **Glc-1r** and **Glc-2r** (entry 10 *vs.* 3 and 7). We observed also that the ring-opening-polymerization of L-lactide occurs faster than that of D,L-lactide under similar experimental conditions (entries 6 *vs.* 3 for **Glc-1r** and 9 *vs.* 7 for **Glc-2r**).

Among the different initiators used in dichloromethane, **CD-diol** leads to the highest yield (entry 11 *vs.* 3,7 and 10). This accelerating effect on the initiating step may be attributed to supramolecular interactions between the cyclodextrin and the lactide molecule. Harada et al. [22,23] showed in the case of lactones that the reaction takes place via inclusion of the monomer in the cavity of the cyclodextrin. The included lactone is activated by the formation of hydrogen bonds between the hydroxyl group of the cyclodextrin and its carbonyl oxygen in the initiation step. Note that the reaction was conducted without additional catalyst in this case. The formation of an inclusion complex between the cyclodextrin and the lactide monomer may accelerate the reaction initiated by **CD-diol** *vs.* other carbohydrates by increasing the

Table 1
DMAP catalyzed ring-opening polymerization of D,L-lactide in dichloromethane using carbohydrate initiators.

	Initiator	Cata/ROH	Lact/ROH	Conc.[a] mg/ml	Time (h)	Conv. (%)	DP/OH[b] calc.	DP/OH[c] RMN	DP tot.[d] NMR	$Đ_M$[e]
1	**Glc-1r**	2	2	200	39	98	2	2	2	nd
2	**Glc-1r**	2	5	200	24	97	5	5	5	nd
3	**Glc-1r**	2	30	200	39	46	14	14	14	1.14
4	**Glc-1r**	4	30	200	39	68	21	21	21	1.16
5	**Glc-1r**	4	30	400	39	91	27	25	25	1.16
6[f]	**Glc-1r**	2	30	200	39	65	20	18	18	1.07
7	**Glc-2r**	2	30	200	39	19	6	6	6	nd
8	**Glc-2r**	4	30	400	39	37	11	10	10	1.20
9[f]	**Glc-2r**	2	30	200	39	32	9	9	9	1.20
10	**Glc-diol**	2	30	200	39	34	20	20	40	1.17
11	**CD-diol**	2	30	200	39	82	25	25	50	1.10
12[g]	**Glc-1r**	4	30	200	39	89	27	27	27	1.32
13[g,h]	**Glc-1r**	4	30	400	24	95	29	29	29	1.19
14[g,h]	**Glc-diol**	4	30	400	24	97	29	28	56	1.32

[a] Lactide concentration in mg/ml.
[b] Number-average degree of polymerization per initiating hydroxyl group calculated considering the growth of one macromolecular chain per hydroxyl group.
[c] Number-average degree of polymerization per initiating hydroxyl group measured by ^{1}H NMR.
[d] Total number-average degree of polymerization measured by ^{1}H NMR.
[e] Dispersity measured by size exclusion chromatography.
[f] L-lactide as monomer.
[g] $CHCl_3$ as solvent.
[h] Temperature 50 °C.

probability of meeting between the initiating primary alcohol and the lactide molecule.[1] The use of chloroform as solvent leads to higher yields, at the detriment of the dispersity however (entry 12 *vs.* 4). The reaction can further be performed at 50 °C in this solvent, affording nearly quantitative reactions in 24 h.

MALDI-ToF analyses of the so-formed polylactide were further conducted. A typical example is presented in Fig. 2. The major distribution (•) corresponds to n times 72 g/mol plus the molecular weight of the initiator and a silver ion ($M_{lactide}$ = 144 g/mol). The minor distribution (•) can be assigned to *n* times 72 g/mol plus the molecular weight of the initiator and 2 silver ions. All macromolecular chains are thus **Glc-1r** end-capped. The presence of both odd and even multiple of 72 indicates that transesterification is occurring. The MALDI-ToF analyses of the polylactides obtained using **Glc-2r**, **Glc-diol** and **CD-diol** as initiators show similarly that all polymer chains are end-capped with the carbohydrate initiator, indicating that the polymerization was not initiated by any other molecule. Odd and even multiples of 72 were also found on the spectra of the PLA obtained using **Glc-diol** and **CD-diol**, while only even multiple of 72 g/mol are observed using **Glc-2r**. This indicates that transesterification does not occur starting from this latter secondary alcohol. Following Peruch and coworkers [32], this can be related to DMAP catalyzed-depolymerization experiments of polylactide [33] where it was shown that secondary alcohols are not able to depolymerize poly(L-lactide) while primary alcohol did depolymerize the polymer. From these findings, it was advanced that for primary alcohols, transesterification occurs during the initiation of the polymerization since the growing hydroxyl-terminated polylactides is a secondary alcohol that may not be able to lead to transesterification. Secondary alcohols are thus less reactive than primary alcohols for both transesterification and initiation, as the polymerization activity is higher using primary alcohols as initiators.

NMR analyses were further performed in order to confirm the structure of the end-capped polylactide. A typical example is given in Fig. 3. The spectra of the **Glc-1r** initiator and the corresponding functionalized PLA show the shift of the resonance peaks after the polymerization. In particular, the resonance peaks at δ = 3.42 ppm which are assigned to the protons 6 of the methylene group of **Glc-1r** disappeared and we found the new resonance peaks in the 4.26–4.36 ppm range which are assigned to the protons 6 of the **Glc-1r**-end-cappedd-PLA. Unambiguous assignments of the signal were done by ^{1}H–^{1}H COSY analysis (Fig. 4). Similar analyses were performed for **Glc-2r** and **Glc-diol** and the corresponding end-capped polylactides, leading to similar findings. The spectra of **CD-diol** and the corresponding end-capped polymer did not enable to perform this kind of analysis due the signal overlapping. The formation of **CD-diol** link-functionalized PLA was thus assumed from the MALDI-ToF analysis and the good agreement between calculated and measured number-average degree of polymerization.

The polymerization was further assessed in bulk at a temperature of 120 °C. The results are presented in Table 2. The reactions are

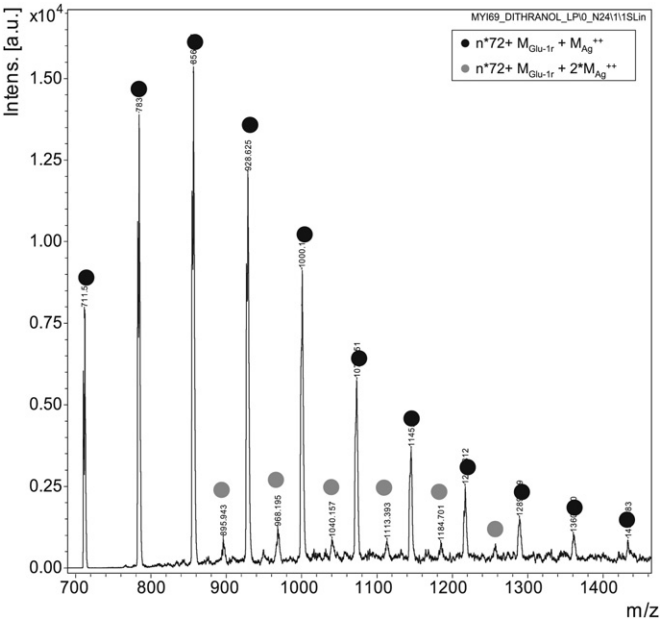


Fig. 2. MALDI-ToF spectra of entry 2.

[1] There is still some debate between a nucleophilic [28] and a general base [31] mechanism for the DMAP catalyzed ring-opening polymerization of lactide, and the supramolecular interaction advanced here may be suitable for both mechanisms.

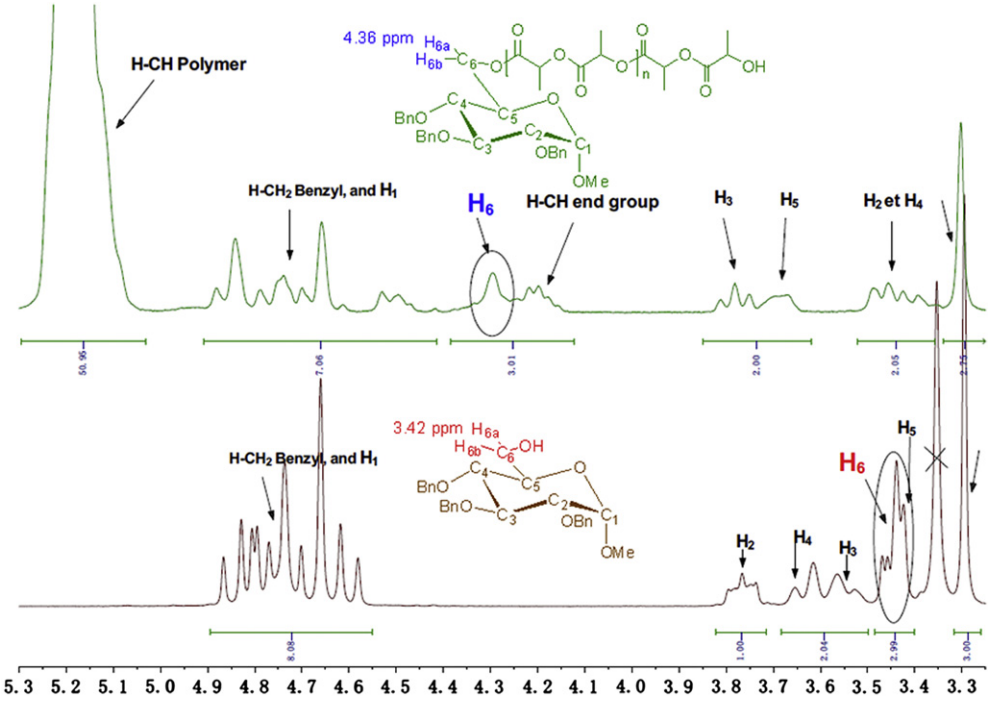


Fig. 3. ^{1}H NMR spectra in DMSO-d6 of **Glc-1r** (bottom) **Glc-1r** end-capped polylactide (top).

almost quantitative in 30 min, with measured degrees of polymerization corresponding to calculated ones considering one growing chain per hydroxyl group. The dispersity is slightly higher than that obtained in chlorinated solvents. Higher degrees of polymerization per OH group can be obtained in bulk in 1 h at 120 °C (entry 16). The MALDI-ToF analyses show that in the bulk, transesterification occurs in the presence of all initiators, including secondary alcohols. This may be attributed to a higher reaction temperature (120 *vs.* 35 °C in chlorinated solvents). All PLA chains formed are end-capped by a carbohydrate derivative, highlighting a 100% functionalization efficiency in the bulk. The structure was confirmed by NMR analysis using the same procedure as above for **Glc-1r**, **Glc-2r** and **Glc-diol**. The analysis could not be performed for **CD-diol,** due to overlapping signals. The **Glc-Me** initiator is not soluble in DMSO, making any comparison with **Glc-Me** end-capped PLA impossible. The formation of **CD-diol** link-functionalized PLA and **Glc-Me** core star PLA were thus assumed from the MALDI-ToF analyses and the good agreement between calculated and measured number-average degree of polymerization. The native **CD** is in turn soluble in DMSO. The 6-O*H*, 3-O*H* and 2-O*H* signals on the spectra of the **CD** initiator (4.48, 5.69 and 5.74–5.76 ppm respectively) were not observed on the spectra of **CD** end-capped PLA, confirming that all hydroxyl groups did initiate the ring-opening polymerization of lactide. The bulk polymerization enables thus the carbohydrate functionalization of PLA in shorter reactions times, and the synthesis of star polymers starting from methyl-α-D-glucopyranoside and native β-cyclodextrin which are not soluble in common solvents.

Carbohydrates end-capped PLA can easily be obtained via DMAP catalyzed ring-opening polymerization of lactide, as well as carbohydrate link-functionalized PLA and carbohydrate core star PLA (Scheme 4). The reaction is adapted for the synthesis of small molecular objects, where two lactide units are linked to a glucose derivative, to the synthesis of polymer with higher number-average

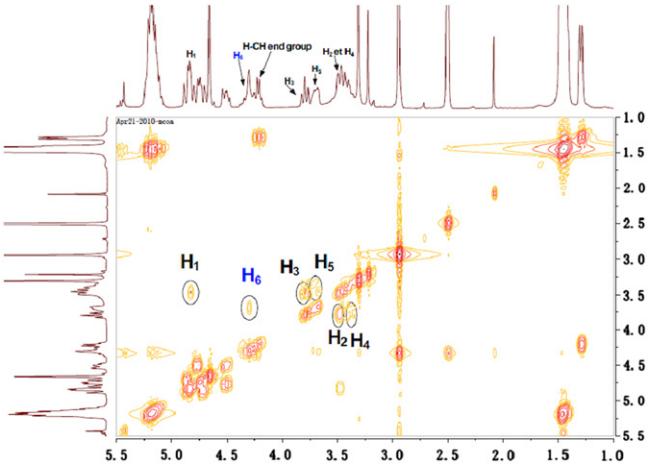
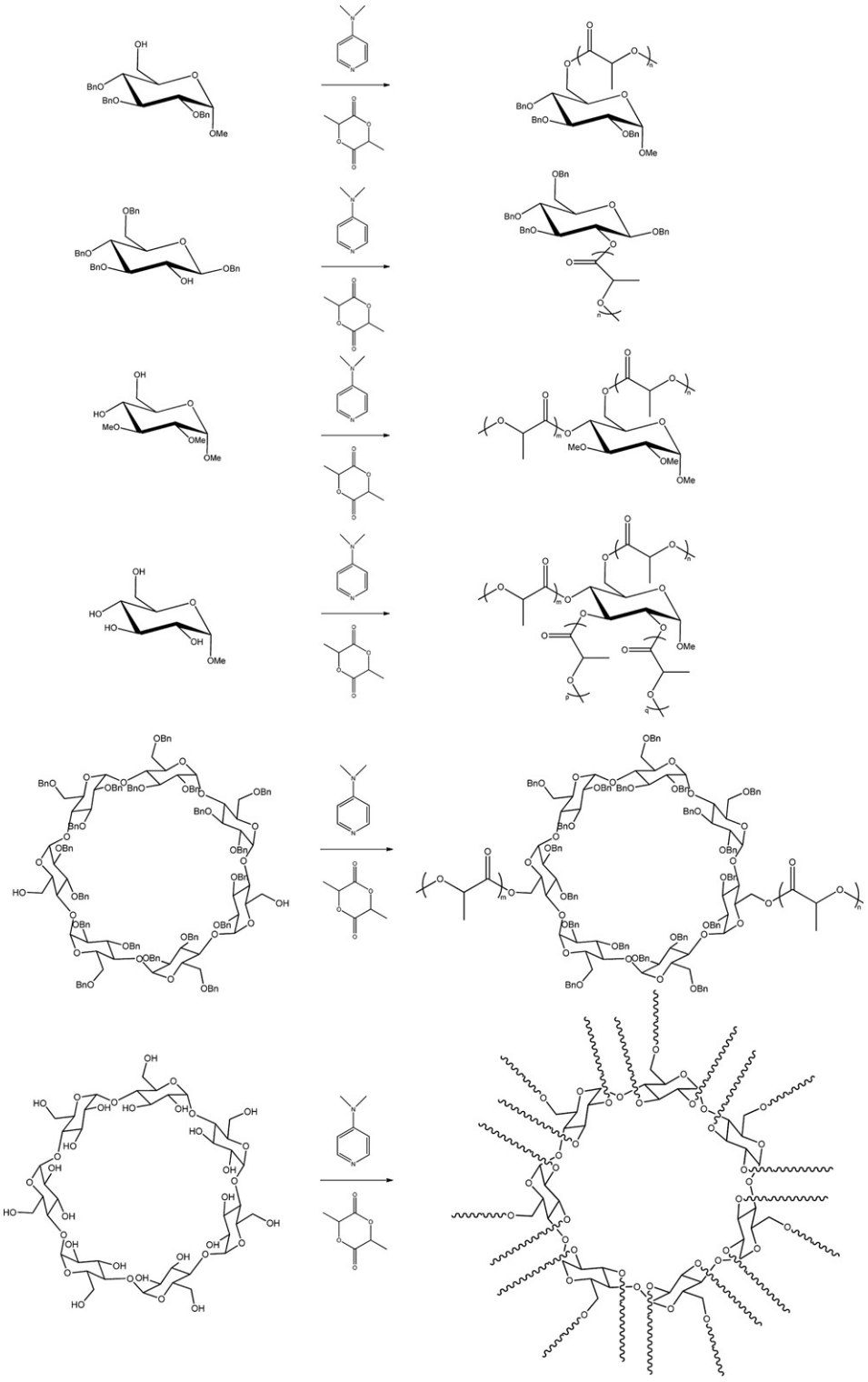


Fig. 4. ^{1}H-^{1}H COSY spectra of a **Glc-1r** end-capped polylactide.

Table 2
DMAP catalyzed ring-opening polymerization of D,L-lactide at 120 °C in bulk using carbohydrate initiators (DMAP/ROH = 2).

	Init.	Mon/ROH	Time (min)	Conv. (%)	DP/OH[a] calc.	DP/OH[b] NMR	DP tot.[c] NMR	$Đ_M$[d]
15	**Glc-1r**	30	25	95	29	27	27	1.43
16	**Glc-1r**	100	60	95	95	92	92	1.48
17	**Glc-2r**	30	30	93	28	28	28	1.43
18	**Glc-diol**	30	30	61	18	16	32	1.25
19	**Glc-Me**	5	30	100	5	5	20	1.25
20	**Glc-Me**	30	120	96	29	27	92	1.40
21	**CD-diol**	30	60	92	28	26	52	1.30
22	**CD**	10	30	97	10	10	210	1.09

[a] Number-average degree of polymerization per initiating hydroxyl group calculated considering the growth of one macromolecular chain per hydroxyl group.
[b] Number-average degree of polymerization per initiating hydroxyl group measured by ^{1}H NMR.
[c] Total number-average degree of polymerization measured by ^{1}H NMR.
[d] Dispersity measured by size exclusion chromatography.



Scheme 4. Carbohydrate functionalized polylactides synthesized via organocatalytic ring-opening poylmerization.

molecular weight. From the reactivity of primary alcohols *vs.* secondary alcohols, it is likely that the arm resulting from the primary alcohol is longer than that/those resulting from the secondary alcohols for these functionalized polymers.

Cyclodextrin based PLA materials are interesting materials for biomedical and pharmaceutical applications [1]. The synthesis of cyclodextrin end-capped PLA has been reported by coupling reactions between PDLA and amino-cyclodextrins [34–36]. Cyclodextrin core star oligolactides can be synthesized by the ring-opening polymerization of lactide without catalyst in dimethylformamide [24], leading to an average degree of polymerization of 3.5. The main initiators were reported to be the primary C6 alcohols, leading thus to a 7 arms compound. Reaction between β-cyclodextrin, lactide and glycolide were also reported in the

presence of $Sn(Oct)_2$ [37]. The highest monomer/β-CD ratio reported was 8, which did not enable to fully functionalize the β-CD. The ring-opening polymerization of L-lactide using potassium and partially protected α-cyclodextrin as initiator was also reported, but the resulting polymers were poorly characterized [38]. The synthesis of PLA–$(Tosyl)_7$-β-cyclodextrin was reported by the $Sn(Oct)_2$ catalyzed ring-opening polymerization of lactide starting from tosylated β-cyclodextrin [39]. The tosyl groups were further used as initiator for ring-opening polymerization of 2-ethyl-2-oxazoline leading to amphiphilic copolymers containing a cyclodextrin core and PLA and poly(2-ethyl-2-oxazoline) arms. Considering hexoses derivatives core star PLA, an ethyl-glucopyranoside core star poly(L-lactide-*co*-ε-caprolactone) has been synthesized in a multistep process involving enzymatic catalyzed ring-opening polymerization of ε-caprolactone and $Sn(oct)_2$ catalyzed ring-opening polymerization of lactide [40]. Carbohydrates including cyclodextrin core star PDLA such as those synthesized in this study have in turn never been reported in the literature as far as we know [41], as well as **Glc-diol** and **CD-diol** link-functionalized PDLA. Link-functionalized polymers are polymers containing a central backbone functionality [42,43]. Chemical alteration/derivatization of the incorporated groups can provide new routes into biodegradable functionalized materials, and star or network polymers. Link-functionalized polymers are also of interest as mechanoresponsive polymeric materials [44,45].

4. Conclusion

DMAP is a powerful catalyst for the carbohydrate functionalization of PLA via ring-opening polymerization. The reactions can be performed in mild conditions in chlorinated solvents, or at 120 °C in the bulk. In all cases, no side initiation occurs, leading to a 100% functionalization efficiency. Carbohydrate end-capped PLA, carbohydrate link-functionalized PLA and carbohydrate core star PLA were synthesized by an organocatalyzed reaction, and should reveal some interesting potentialities for various applications.

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