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Note

Synthesis of 2,3,4,5-tetra-*O*-methyl-D-glucono-1,6-lactone as a monomer for the preparation of copolyesters

Inmaculada Molina Pinilla, Manuel Bueno Martínez, Juan A. Galbis*

Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia Química Orgánica y Farmacéutica, Universidad de Sevilla, 41071 Sevilla, Spain

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Abstract

2,3,4,5-Tetra-*O*-methyl-D-glucono-1,6-lactone has been prepared as a crystalline compound in acceptable yield by two different routes. An initial assay of copolymerization with L-lactide by ring-opening polymerization was carried out. The incorporation of the carbohydrate monomer into the polymer chain was about 2%.

Keywords: D-Gluconic acid, protected; D-Glucono-1,6-lactone, protected; L-Lactide; Ring-opening polymerization; Copolyesters

1. Introduction

We have previously described several carbohydrate-based-monomers which have been used for the synthesis of various polyamides[1] and poly(ester amide)s[2] derived from sugars such as L-arabinose, D-xylose or D-glucose. In this paper we prepared, by two different routes, the 2,3,4,5-tetra-*O*-methyl-D-glucono-1,6-lactone (**11**), which can be used as a monomer in the preparation of copolyesters.

Ring-opening polymerization (ROP) of lactones, using different types of catalyst, has been used for the preparation of aliphatic polyesters,[3] a type of degradable polymers most widely used in the biomedical field,[4] as drug delivery systems, biodegradable sutures, resorbable prostheses, etc. Homopolymerization and copolymerization of ε-caprolactone,[5] some functionalized ε-caprolactone,[6] and other cyclic ester[7]—functionalized or not—are well known. However, as substitution of the lactone ring increases, homopolymerization of the monomer becomes more difficult. In our hands, attempts at homopolymerization of the tetra-substituted ε-caprolactone **11** failed, but its copolymerization with L-lactide seemed promising. A preliminary copolymerization experiment is reported in this paper.

2. Results and discussion

First, the synthesis of **10** was achieved (Scheme 1) by protection of the primary alcohol group of methyl α-D-glucopyranoside as its triphenylmethyl derivative **2** followed by treatment with methyl iodide–potassium hydroxide in dimethyl sulfoxide to give the tetra-*O*-methyl derivative **3**. Removal of the 6-*O*-triphenylmethyl group in **3** by acid hydrolysis led to **4** which was then treated with sodium hydride and benzyl bromide in THF, giving **5** in good yield (about 70% from **3**). Acid hydrolysis of **5** followed by oxidation[8] with acetic anhydride and dimethyl sulfoxide gave 6-*O*-benzyl-2,3,4-tri-*O*-methyl-D-glucono-1,5-lactone (**7**). Opening of the lactone ring in **7** and methylation of HO-5 was performed with methyl iodide and potassium hydroxide in THF to give 6-*O*-benzyl-2,3,4,5-tetra-*O*-methyl-D-gluconic acid (**8**, 75%), the methyl ester of which **9** can be isolated from the reaction mixture (see Section 3) or converted into **8** by hydrolysis. Removal of the 6-*O*-benzyl group was achieved by acid hydrolysis or by hydrogenation with Pd–10% C in ethyl acetate to give **10** in about 90% yield.

Compound **10** was also prepared by a different route (Scheme 2) starting with D-glucose diethylmercaptal

* Corresponding author. Tel.: +34-954556736; fax: +34-954556737
E-mail address: jgalbis@us.es (J.A. Galbis).

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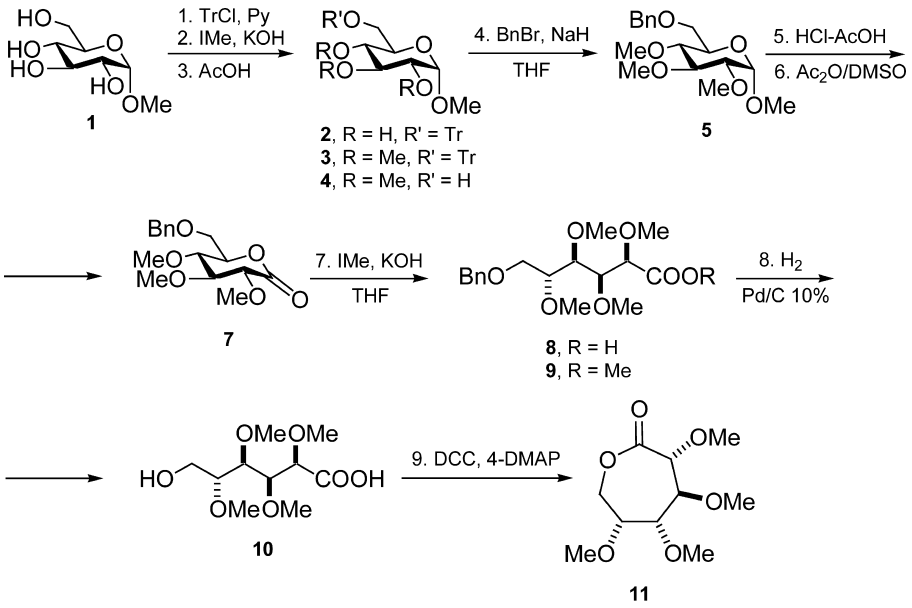
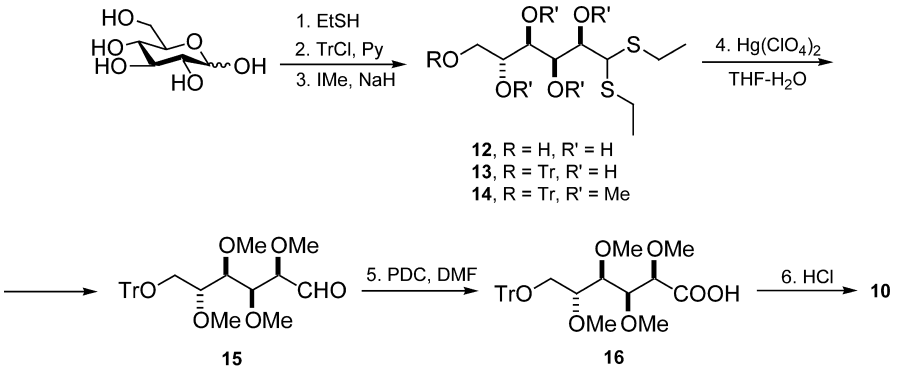


Scheme 1.

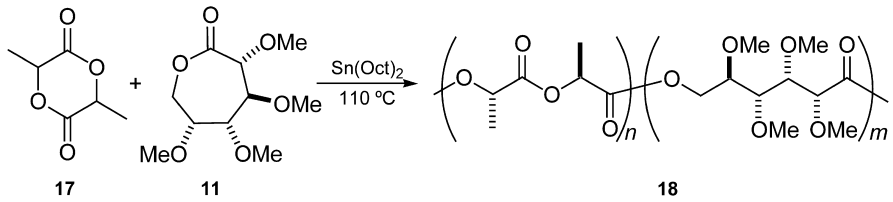
(**12**).[9] Thus, protection of the primary hydroxyl group as the triphenylmethyl derivative **13**, followed by methylation of the secondary hydroxyl groups by treatment with methyl iodide and sodium hydride in dry DMF, gave **14** in good yield. Removal of the diethylmercaptal protecting group[10] and oxidation[11] of the resulting aldehyde led to 6-*O*-triphenylmethyl-2,3,4,5-tetra-*O*-methyl-D-gluconic acid (**16**), which was easily transformed into **10** by deprotection of the triphenylmethyl group under acid conditions. This route is shorter, and enabled us to obtain the ω-hydroxyacid **10** in a higher yield. We could not obtain elemental analyses within the accepted limits for some of these oily and highly hygroscopic compounds. However, the obtained analyses could be adjusted by addition to the formulae of small proportions of water. These compounds were characterized by NMR and HRMS.

Both routes include a final lactonization step of the ω-hydroxyacid into the 1,6-D-gluconolactone **11**. There are various methods to achieve this purpose, such as those of Corey,[12] Mukaiyamam,[13] Masamune,[14] or Mitsunobu.[15] In our case, **10** was converted to the corresponding 1,6-lactone by treatment[16] of the ω-hydroxyacid with DCC and DMAP in the presence of 4-(dimethylamino)pyridine hydrochloride. By this procedure, **11** was obtained in good yield as a crystalline compound whose analytical and spectroscopic data were in agreement with the assigned structure.

Copolymerization of L-lactide **17** with hydrophilic cyclic monomers offers the possibility of modulating the crystallinity of the copolymer and thereby controlling its degradability. We have carried out a preliminary experiment of copolymerization by bulk ROP of a mixture of L-lactide and **11**, in a ratio of 5:1, using tin (II) 2-ethylhexanoate ($SnOct_2$) as initiator (Scheme 3). From the copolymerization reaction mixture, we obtained two copolymers containing different amounts of the carbohydrate monomer, as was determined by



Scheme 2.



Scheme 3.

Table 1
Some physical characteristics of copolymers **18a** and **18b**

Copolymer	Yield (%)	Sugar [a] monomer (%)	M_w [b]	M_n [b]	M_w/M_n [b]	T_g [c] (°C)	Tm [c] (°C)	ΔH [c] (J g^{-1})
18a	12	1.3	23,700	20,100	1.2	57.4	155.3 149.8	33.1
18b	29	2.2	18,500	14,900	1.2	55.9	144.4 136.0	12.5

[a] Determined by ^{1}H NMR.
[b] Determined by GPC, using THF as solvent.
[c] Measured by DSC, second heating.

NMR studies. The first fraction (copolymer **18a**) was insoluble in acetone and had the higher molecular weight and the lower content in sugar monomer (Table 1). The second fraction (copolymer **18b**) was soluble in acetone. Both copolymers had similar infrared and ^{1}H NMR spectra. IR spectra contained the typical ester absorption band at 1753 cm^{-1}. In the ^{1}H NMR spectra, the characteristic signals of the lactic monomer were detected at 5.14 (CH, quartet) and 1.55 (CH_3, doublet). Besides these signals, those corresponding to the carbohydrate monomer appeared between 4.5 and 3.3 ppm (see Section 3 for a more detailed assignment). Thermal properties of the two copolymers were similar, as determined by differential scanning calorimetry (DSC). In both cases, thermograms corresponding to the second heating run displayed an exothermic crystallization peak at 117 °C and two close endothermic melting peaks. Copolymer **18b** showed lower Tg and Tm values than **18a** (Table 1), which can be related with its higher carbohydrate monomer content. Gel permeation chromatography (GPC) of the copolymers displayed unimodal chromatograms. The results of the GPC study are also presented in Table 1.

3. Experimental

3.1. General methods

Thin layer chromatography (TLC) was performed on Silica Gel 60 F254 (E. Merck) with detection by UV light or charring with H_2SO_4. Flash column chromatography was performed using E. Merck Silica Gel 60 (230–400 mesh). IR spectra (films or KBr discs) were recorded with a JASCO FT/IR-410 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AMX-500 or a Bruker 200 AC-P spectrometers. Chemical shifts are reported as parts per million downfield from Me_4Si. Two-dimensional ^{1}H–^{1}H homonuclear and ^{13}C–^{1}H heteronuclear shift correlation spectra were recorded with COSY, HETCOR pulse sequences. The assignments showing an asterisk may be reversed. Elemental analyses were determined in the Microanalysis Laboratories at the Universidad Complutense (Madrid) and in the CSIC, Isla de la Cartuja (Sevilla). Optical rotations were measured at 20 ± 5 °C with a Bellingham and Standley Inc., P20 polarimeter. FABMS analyses were performed on a double-focusing Kratos MS 80RFA mass spectrometer equipped with the standard FAB source. Argon was used as the bombarding gas. Spectra were obtained using nitrobenzene–NaI as a matrix. Melting points were determined by DSC using a Perkin–Elmer DSC series 6, calibrated with indium. Samples of about 2–3 mg were heated at a rate of 10 °C min^{-1} and cooled to room temperature (rt). The peak temperatures were taken as melting points. GPC was performed at rt with a Waters apparatus equipped with a Waters 410 differential refractometer and a 60 cm PL gel 5 μm MIXED-C column, using THF as solvent. The flow rate was 1 mL min^{-1}. Calibration was based on polystyrene standards.

3.2. Methyl 2,3,4-tri-*O*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (3)

To a solution of **2** (10 g, 223 mmol) in dry Me_2SO (40 mL) was added KOH (15.4 g, 0.274 mmol) and IMe

(6.0 mL, 91.5 mmol). The reaction mixture was stirred at rt for 4 h, poured into an ice-water mixture and extracted with CH_2Cl_2 (4 × 30 mL). The organic phase was concentrated under diminished pressure to a residue that was dissolved in EtOH to give **3** as a solid (8 g, 73%): mp 104–106 °C; $[\alpha]_D$ +84° (*c* 0.9, $CHCl_3$); IR (KBr): *v* 3061, 3032, 1597 cm^{-1} (Arom.); NMR data ($CDCl_3$): ^1H δ 7.55–7.20 (m, 15H, Arom.), 4.90 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 3.66–3.05 (m, 6H, H-2,3,4,5,6a,6b), 3.61, 3.55, 3.44, 3.27 (4s, 12H, OMe); ^{13}C δ 143.99, 128.71, 127.67, 126.88 (Arom.), 97.26 (C-1), 86.19 (*C*Ph_3), 83.67, 81.84, 79.92, 70.04 (C-2,3,4,5), 62.37 (C-6), 60.89, 60.31, 58.96, 54.88 (OMe). Anal. Calcd for $C_{29}H_{34}O_6$: C, 72.78; H, 7.16. Found: C, 72.79; H, 7.02.

3.3. Methyl 2,3,4-tri-*O*-methyl-α-D-glucopyranoside (4)

A solution of **3** (10 g, 21 mmol) in AcOH–water (4:1, 80 mL) was heated at 70 °C for 2 h. After this time, the solid precipitate was filtered out, and the filtrate concentrated under diminished pressure to give an oil that was chromatographed on a silica gel column (eluent 1:0–40:1 CH_2Cl_2–MeOH) to give **4** as an oil (4.34 g, 88%); $[\alpha]_D$ +162° (*c* 1.4, $CHCl_3$); IR: *v* 3480 cm^{-1} (OH); NMR data ($CDCl_3$): ^1H δ 4.75 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 3.76 (dd, 1H, $J_{5,6a}$ 2.7, $J_{6a,6b}$ 11.8 Hz, H-6a), 3.67 (dd, 1H, $J_{5,6b}$ 4.2 Hz, H-6b), 3.52–3.43 (m, 2H, H-3*,5), 3.12 (dd, 1H, $J_{2,3}$ 9.5 Hz, H-2), 3.11 (t, 1H, $J_{3,4}$ 9.5 Hz, H-4*), 3.57, 3.51, 3.47, 3.35 (4s, 12H, OMe), 2.22 (bs, 1H, OH); ^{13}C δ 97.40 (C-1), 83.29 (C-3*), 81.73 (C-2), 79.48 (C-4*), 70.56 (C-5), 61.70 (C-6), 60.71, 60.40, 58.89, 55.01 (OMe). Anal. Calcd for $C_{10}H_{20}O_6$: C, 50.83; H, 8.53. Found: C, 50.85; H, 8.53.

3.4. Methyl 6-*O*-benzyl-2,3,4-tri-*O*-methyl-α-D-glucopyranoside (5)

To a solution of **4** (1 g, 4.23 mmol) in dry THF (40 mL) was added NaH (oil suspension 60%, 0.22 g, 5 mmol) at 0 °C. After stirring at rt for 30 min, the mixture was cooled to 0 °C and benzyl bromide (0.6 mL) was added. The reaction mixture was allowed to warm to rt and the stirring was kept until the reaction finished (TLC 20:1 CH_2Cl_2–MeOH). At this point, the mixture was again cooled to 0 °C and EtOH (10 mL) was added. After stirring at rt for 30 min, the reaction mixture was diluted with EtOAc (40 mL) and washed with brine. The organic phase was dried ($MgSO_4$) and concentrated to dryness giving an oil that was chromatographed on a silica gel column (eluent 2:1–1:1 C_6H_{14}–EtOAc) to give **5** as an oil (1.2 g, 86%); $[\alpha]_D$ +124° (*c* 1.6, $CHCl_3$); IR: *v* 3030 cm^{-1} (Arom.); NMR data ($CDCl_3$): ^1H δ 7.40–7.20 (m, 5H, Arom.), 4.83 (d, 1H, $J_{1,2}$ 3.0 Hz, H-1), 4.65 (d, 1H, *J* 12.1 Hz, CH_2Ph), 4.53 (d, 1H, *J* 12.1 Hz, CH_2Ph), 3.80–3.40 (m, 4H, H-3,5,6a,6b), 3.30–3.20 (m, 2H, H-2,4), 3.61, 3.50, 3.47, 3.40 (4s, 12H, OMe); ^{13}C δ 137.48, 127.65, 127.04, 126.94 (Arom.), 96.83 (C-1), 83.0, 81.10, 78.72, 69.43 (C-2,3,4,5), 72.74 (*C*H_2Ph), 67.97 (C-6), 60.11, 59.69, 58.20, 54.39 (OMe). Anal. Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.59; H, 8.10.

3.5. 6-*O*-Benzyl-2,3,4-tri-*O*-methyl-D-glucopyranose (6)

A solution of **5** (2 g, 6.13 mmol) in a mixture of AcOH (50.73 mL) and 4 N H_2SO_4 (28.44 mL) was heated at 80 °C for 1 day. After this time, the acids were neutralized with $NaHCO_3$ and the solution extracted with CH_2Cl_2 (6 × 40 mL). The organic phase was concentrated and the residue chromatographed on a silica gel column (eluent 2:1–1:1 C_6H_{14}–EtOAc) to give **6** (mixture of anomers) as an oil (1.8 g, 94%); IR: *v* 3414 (OH), 3088, 3030 cm^{-1} (Arom.); NMR data ($CDCl_3$): ^1H δ 7.35–7.15 (m, 5H, Arom.), 5.28 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1α), 4.61 (d, 1H, *J* 12.2 Hz, CH_2Phα), 4.59 (d, 1H, *J* 12.1 Hz, CH_2Phβ), 4.54 (d, 1H, $J_{1,2}$ 7.7 Hz, H-1β), 4.49 (d, 1H, *J* 12.2 Hz, CH_2Phα), 4.50 (d, 1H, *J* 12.1 Hz, CH_2Phβ), 4.00–2.90 (m, 6H, H-2,3,4,5,6), 3.60, 3.47, 3.45 (3s, 9H, 3 OMeβ), 3.59, 3.58, 3.44 (3s, 9H, OMeα); ^{13}C δ 137.69, 128.14, 127.66, 127.46 (Arom.), 96.80 (C-1β), 90.21 (C-1α), 86.24, 84.44, 79.46, 74.13, (C-2,3,4,5β), 82.99, 81.72, 79.46, 69.60 (C-2,3,4,5α), 73.18 (*C*H_2Phα,β), 68.84 (C-6β), 68.58 (C-6α), 60.63, 60.54, 60.27, 60.17, 58.53 (OMeα,β). HRMS: *m*/*z* 294.146154 (calcd for $[M-H_2O]^+$: 294.146724).

3.6. 6-*O*-Benzyl-2,3,4-tri-*O*-methyl-D-glucono-1,5-lactone (7)

Acetic anhydride (7.9 mL) was added to a solution of **6** (1.2 g, 3.84 mmol) in dry Me_2SO (11.8 mL). After standing at rt for 24 h, the reaction mixture was poured into ice-water (40 mL), the oil formed was separated and the aqueous phase extracted with CH_2Cl_2 (4 × 50 mL). The oil and the organic phase were combined, concentrated under diminished pressure and finally, Me_2SO was evaporated under high vacuum. The residue was chromatographed on a silica gel column (eluent 4:1 C_6H_{14}–EtOAc) to give **7** as an oil (1.0 g, 84%); $[\alpha]_D$ +42° (*c* 1.1, $CHCl_3$); IR: *v* 1757 cm^{-1} (ester); NMR data ($CDCl_3$): ^1H δ 7.40–7.25 (m, 5H, Arom.), 4.62 (d, 1H, *J* 12.1 Hz, CH_2Ph), 4.55 (d, 1H, *J* 12.1 Hz, CH_2Ph), 4.40 (m, 1H, H-5), 3.82 (d, 1H, $J_{2,3}$ 5.9 Hz, H-2), 3.74 (dd, 1H, $J_{5,6}$ 1.8, $J_{6,6'}$ 11.0 Hz, H-6), 3.70 (dd, 1H, $J_{5,6'}$ 3.2 Hz, H-6′), 3.60–3.50 (m, 2H, H-3,4), 3.56, 3.52, 3.46 (3s, 12H, OMe); ^{13}C δ 168.91 (CO), 137.67, 128.34, 127.72, 127.67 (Arom.), 82.51 (C-3), 79.51 (C-2), 77.85, 77.82 (C-4,5), 73.55 (*C*H_2Ph), 68.53 (C-6), 59.33, 58.98, 58.77 (OMe). HRMS: *m*/*z* 310.142849 (calcd for $[M]^+$: 310.141639).

3.7. 6-*O*-Benzyl-2,3,4,5-tetra-*O*-methyl-D-gluconic acid (8)

Freshly crushed KOH (1.96 g, 35.09 mmol) and MeI (1.4 mL, 21.83 mmol) were added to a solution of **7** (2.0 g, 6.4 mmol) in dry THF (8.0 mL). After stirring, protected from the light, at rt for 24 h, the reaction mixture was poured into water (20 mL) and the stirring was kept for 5 h more. The aqueous solution was washed with CH_2Cl_2 (4 × 20 mL), acidified (pH 4–5, HCl), and extracted with CH_2Cl_2 (4 × 20 mL). The organic phases were combined and concentrated under diminished pressure to give **8** as an oil (0.6 g, 75%); $[\alpha]_D$ +1° (*c* 1.3, $CHCl_3$); IR: *v* 3430–2600 (COOH), 1744 cm^{-1} (CO); NMR data ($CDCl_3$): ^1H δ 9.18 (bs, 1H, COOH), 7.40–7.15 (m, 5H, Arom.), 4.58 (d, 1H, *J* 12.1 Hz, C*H*$_2$Ph), 4.55 (d, 1H, *J* 12.1 Hz, C*H*$_2$Ph), 3.98 (d, 1H, $J_{2,3}$ 5.0 Hz, H-2), 3.78 (t, 1H, H-3), 3.77 (dd, 1H, $J_{5,6a}$ 3.9 Hz, H-6a), 3.66 (dd, 1H, $J_{3,4}$ 4.7 Hz, $J_{4,5}$ 6.5 Hz, H-4), 3.56 (dd, 1H, $J_{5,6b}$ 4.1, $J_{6a,6b}$ 10.6 Hz, H-6b), 3.43–3.39 (m, 1H, H-5), 3.53, 3.49, 3.42, 3.41 (4s, 12H, OMe); ^{13}C δ 173.39 (C-1), 137.98, 128.31, 127.73, 127.60 (Arom.), 81.59 (C-3), 80.00 (C-5), 79.27 (C-2*), 79.17 (C-4*), 73.37 (*C*H$_2$Ph), 67.59 (C-6), 60.72, 60.60, 59.28, 57.36 (OMe). Mass spectrum: *m*/*z* 294.146845 (calcd for $[M-H_2O-CH_2O]^+$: 294.146724); 235.118279 (calcd for $[M-OCH_2Ph]^+$: 235.118164).

The methyl ester **9** could be isolated as an oil (30%) from the reaction mixture, by pouring it into water, and immediate extraction of the resulting solution with CH_2Cl_2. NMR data ($CDCl_3$): ^1H δ 7.20–7.10 (m, 5H, Arom.), 4.30 (s, 2H, C*H*$_2$Ph), 3.78 (d, 1H, $J_{2,3}$ 4.7 Hz, H-2), 3.65–3.07 (m, 5H, H-3,4,5,6), 3.53, 3.28, 3.24, 3.21, 3.20 (5s, 15H, OMe); ^{13}C δ 169.92 (C-1), 137.31, 127.37, 126.74, 126.63 (Arom.), 81.17, 79.68, 79.47, 79.10 (C-2,3,4,5), 72.40 (*C*H$_2$Ph), 67.30 (C-6), 59.74, 59.62, 57.82, 56.62, 50.79 (OMe). HRMS: *m*/*z* 356.184486 (calcd for $[M]^+$: 356.183504); 249.134113 (calcd for $[M-OCH_2Ph]^+$: 249.133814).

3.8. 6-*O*-Triphenylmethyl-D-glucose diethyl dithioacetal (13)

To a solution of D-glucose diethyl dithioacetal (**12**, 2.25 g, 7.85 mmol) in dry DMF (10 mL) were added Et_3N (1.96 mL, 14 mmol) and 4-DMAP (cat.). After 10 min, chlorotriphenylmethane (2.4 g, 8.6 mmol) was added and the reaction mixture was stirred at rt overnight. The reaction mixture was quenched by adding ice-water, and the aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under diminished pressure. The residue was chromatographed on a silica gel column (eluent 2:1 C_6H_{14}–EtOAc) to give **21** as a solid (3.5 g, 95%): mp 65–66 °C; $[\alpha]_D$ +25° (*c* 1.2, $CHCl_3$); IR: *v* 3441 (OH), 3057, 3031, 1597 cm^{-1} (Arom.); NMR data ($CDCl_3$): ^1H δ 7.60–7.20 (m, 15H, Arom.), 4.27 (bs, 1H, H-3), 4.06 (d, 1H, $J_{1,2}$ 8.6 Hz, H-1), 3.89 (m, 1H, H-5), 3.80 (dd, 1H, $J_{4,5}$ 7.0, $J_{3,4}$ 1.4 Hz, H-4), 3.65 (dd, 1H, $J_{2,3}$ 1.9 Hz, H-2), 3.36 (m, 2H, H-6a,6b), 2.68 (m, 4H, SC*H*$_2$CH$_3$), 1.27 (t, 6H, SCH$_2$C*H*$_3$); ^{13}C δ 143.70, 128.60, 127.89, 127.12 (Arom.), 86.97 (*C*Ph$_3$), 75.09 (C-2), 74.11 (C-4), 70.99 (C-5), 68.26 (C-3), 64.71 (C-6), 55.26 (C-1), 25.87, 23.71 (S*C*H$_2$CH$_3$), 14.58, 14.41 (SCH$_2$*C*H$_3$). Anal. Calcd for $C_{28}H_{36}O_5S_2$: C, 65.09; H, 7.02. Found: C, 65.31; H, 6.74.

3.9. 2,3,4,5-Tetra-*O*-methyl-6-*O*-triphenylmethyl-D-glucose diethyl dithioacetal (14)

To NaH (60% oil suspension, 0.32 g, 8.08 mmol) washed with C_6H_{14}, was added dropwise, under stirring, a solution of **13** (1.0 g, 1.9 mmol) in anhyd DMF (25 mL). The stirring was continued for 1 h at rt, and then cooled at 0 °C. Methyl iodide (1.1 mL, 17.67 mmol) was added, and the reaction mixture stirred at 0 °C until the reaction was almost completed (about 2 h, TLC eluent 2:1 C_6H_{14}–EtOAc). The reaction was quenched by adding an excess of MeOH at 0 °C, diluted with water (50 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extract was washed with water (30 mL), dried ($MgSO_4$), and evaporated under diminished pressure. The residue was chromatographed on a silica gel column (eluent 6:1 C_6H_{14}–EtOAc) to give **14** as an oil (0.8 g, 80%); $[\alpha]_D$ −7° (*c* 1.2, $CHCl_3$); IR: *v* 3058, 3023, 1597 cm^{-1} (Arom.); NMR data ($CDCl_3$): ^1H δ 7.50–7.15 (m, 15H, Arom.), 3.93 (d, 1H, $J_{1,2}$ 1.6 Hz, H-1), 3.79 (dd, 1H, $J_{2,3}$ 7.0, $J_{3,4}$ 3.1 Hz, H-3), 3.69 (dd, 1H, H-2), 3.61, 3.52, 3.46, 3.22 (s, 3H, OMe), 3.53 (dd, 1H, $J_{4,5}$ 3.6 Hz, H-4), 3.47 (m, 1H, H-6), 3.45–3.35 (m, 1H, H-5), 3.08 (dd, 1H, $J_{5,6'}$ 4.1, $J_{6,6'}$ 10.2 Hz, H-6′), 2.90–2.55 (m, 4H, SC*H*$_2$CH$_3$), 1.30, 1.26 (t, 6H, SCH$_2$C*H*$_3$); ^{13}C δ 143.99, 128.72, 127.70, 126.90 (Arom.), 86.38 (*C*Ph$_3$), 85.84 (C-2), 82.71 (C-3), 80.77 (C-5), 79.66 (C-4), 61.57 (C-6), 61.51, 61.10, 60.20, 58.08 (4 OMe), 53.17 (C-1), 25.44, 25.07 (S*C*H$_2$CH$_3$), 14.54 (SCH$_2$*C*H$_3$). Anal. Calcd for $C_{33}H_{44}O_5S_2$: C, 67.81; H, 7.53; S, 10.97. Found: C, 67.92; H, 7.75; S, 10.91.

3.10. 2,3,4,5-Tetra-*O*-methyl-6-*O*-triphenylmethyl-D-glucose (15)

To a solution of **14** (2.35 g, 4 mmol) and $CaCO_3$ (7.21 g, 72.1 mmol) in THF (150 mL) and water (35 mL) was added dropwise a 2 M aq soln of $Hg(ClO_4)_2$ (4.06 mL, 8.1 mmol). After 5 h of stirring at rt, the reaction mixture was diluted with ether (60 mL) and filtered through a plug of neutral alumina. The filtrate was washed with water (100 mL) and extracted with EtOAc (3 × 90 mL). The combined organic extract was dried,

filtered and evaporated. Flash chromatography (eluent 6:1–2:1 C_6H_{14}–EtOAc) gave **15** as an oil (1.7 g, 89%); $[\alpha]_D$ −24° (*c* 1.2, $CHCl_3$); IR: *v* 3058, 3024, 1597 (Arom.), 1730 cm^{-1} (CO); NMR data ($CDCl_3$): ^1H δ 9.67 (s, 1H, H-1), 7.55–7.15 (m, 15H, Arom.), 3.91 (dd, 1H, $J_{2,3}$ 5.7, $J_{3,4}$ 2.1 Hz, H-3), 3.82 (d, 1H, H-2), 3.60–3.35 (m, 3H, H-4,5,6), 3.53, 3.52, 3.45, 2.96 (s, 12H, OMe), 3.03 (dd, 1H, $J_{5,6'}$ 3.7, $J_{6,6'}$ 10.3 Hz, H-6′); ^{13}C δ 199.46 (C-1), 143.83, 128.71, 127.71, 126.94 (Arom.), 86.51 (CPh_3), 82.29, 81.46, 79.51, 77.89 (C-2,3,4,5), 61.40 (C-6), 59.50, 59.43, 59.24, 58.16 (OMe). Anal. Calcd for $C_{29}H_{34}O_6$: C, 72.78; H, 7.16. Found: C, 72.54; H, 6.83.

3.11. 2,3,4,5-Tetra-*O*-methyl-6-*O*-triphenylmethyl-D-gluconic acid (16)

A mixture of **15** (0.524 g, 1.09 mmol) and pyridinium dichromate (3 equiv 1.236 g, 3.28 mmol) in dry DMF (2 mg mL^{-1} DMF, 1.04 mL) was stirred at rt for 20 h. After this time, the reaction mixture was diluted with water (7 mL), extracted with ether (3 × 25 mL), and the combined organic extract dried ($MgSO_4$). Removal of the solvent under diminished pressure gave **16** as a syrup (0.42 g, 77%); $[\alpha]_D$ −2° (*c* 1.2, $CHCl_3$); IR: *v* 3500–2500 (acid), 3058, 3030, 1597 (Arom.), 1753 cm^{-1} (CO); NMR data ($CDCl_3$): ^1H δ 7.60–7.10 (m, 15H, Arom.), 3.99 (d, 1H, $J_{2,3}$ 4.6 Hz, H-2), 3.83 (t, 1H, $J_{3,4}$ 4.6 Hz, H-3), 3.73 (dd, 1H, $J_{4,5}$ 6.9 Hz, H-4), 3.52, 3.48, 3.43, 3.23 (s, 12H, OMe), 3.60–3.50 (m, 1H, H-6a), 3.39 (m, 1H, H-5), 3.14 (dd, 1H, $J_{5,6'}$ 3.9, $J_{6,6'}$ 10.3 Hz, H-6b); ^{13}C δ 173.38 (C-1), 143.86, 128.69, 127.69, 126.92 (Arom.), 86.63 (CPh_3), 81.51 (C-3), 80.61 (C-5), 79.27 (C-2), 79.13 (C-4), 61.63 (C-6), 60.61, 60.45, 59.28, 58.01 (OMe). HRMS: *m*/*z* 517.222041 (calcd for $[M + Na]^+$: 517.220224).

3.12. 2,3,4,5-Tetra-*O*-methyl-D-gluconic acid (10)

3.12.1. From 16. A solution of **16** (0.417 g, 0.843 mmol) in a mixture of AcOH–water (4/1, 2.5 mL) was stirred at 70 °C for 7 h. The reaction mixture was diluted with water (3 mL) and the resulting yellow precipitate filtered out. The resulting solution was concentrated under diminished pressure affording **10** (0.19 g, 90%).

3.12.2. From 8. A solution of **8** (1.47 g, 4.29 mmol) in dry EtOAc (30 mL) was hydrogenated (35 psi) at rt in the presence of 10% Pd–C (30 wt.%, 0.441 g). The suspension was stirred for 24 h at rt, filtered and the filtrate evaporated under diminished pressure to give an oil which was dissolved in water (5 mL). The aqueous solution was washed once with CH_2Cl_2 (0.5 mL), and concentrated again to give the title compound as a colorless oil (0.89 g, 82%); $[\alpha]_D$ +25° (*c* 1.2, $CHCl_3$); IR: *v* 1734 cm^{-1} (CO); NMR data ($CDCl_3$): ^1H δ 3.96 (d, 1H, $J_{2,3}$ 5.3 Hz, H-2), 3.89 (dd, 1H, $J_{5,6a}$ 3.3, $J_{6a,6b}$ 12.1 Hz, H-6a), 3.69 (dd, 1H, $J_{5,6b}$ 3.3 Hz, H-6b), 3.68 (m, 1H, H-3), 3.58 (dd, 1H, $J_{3,4}$ 4.3, $J_{4,5}$ 6.3 Hz, H-4), 3.53, 3.48, 3.47, 3.41 (s, 12H, OMe), 3.34 (ddd, 1H, H-5); ^{13}C δ 173.28 (C-1), 81.64 (C-3), 80.91 (C-5), 79.97 (C-2), 79.93 (C-4), 59.37 (C-6), 60.72, 60.70, 59.10, 57.12 (OMe). HRMS: *m*/*z* 253.129554 (calcd for $[M]^+$: 253.128728).

3.13. 2,3,4,5-Tetra-*O*-methyl-D-glucono-1,6-lactone (11)

To a mixture of dicyclohexylcarbodiimide (0.327 g, 1.58 mmol), 4-(dimethylamino)pyridine (0.290 g, 2.38 mmol), and 4-(dimethylamino)pyridine hydrochloride[17] (0.250 g, 1.58 mmol) in EtOH-free $CHCl_3$ (20.0 mL) was added dropwise, under Ar atmosphere, a solution of **10** (0.2 g, 0.793 mmol) in EtOH-free $CHCl_3$ (5.0 mL). After the addition was complete, the reaction mixture was stirred for 24 h at rt. Methanol (0.95 mL) and AcOH (0.18 mL, 4.0 equiv) were added to the reaction flask and the stirring was continued for 30 min. The reaction mixture was concentrated to 5 mL, diluted with ether (25 mL), filtered, and concentrated to dryness. The residue was taken up in a minimal amount of ether and purified by flash column chromatography (eluent ether) to give **11** as a crystalline compound (0.148 g, 80%): mp 62–63 °C; $[\alpha]_D$ −12° (*c* 1.2, $CHCl_3$); IR: *v* 1750 cm^{-1} (CO); NMR data ($CDCl_3$): ^1H δ 4.61 (dd, 1H, $J_{5,6}$ 4.4, $J_{6,6}$ 13.5 Hz, H-6), 4.20 (dd, 1H, $J_{5,6'}$ 2.4 Hz, H-6′), 4.05 (d, 1H, $J_{2,3}$ 5.2 Hz, H-2), 3.69 (m, 2H, H-3,4), 3.60 (ddd, 1H, $J_{4,5}$ 3.3 Hz, H-5), 3.50, 3.48, 3.45, 3.40 (s, 12H, OMe); ^{13}C δ 169.25 (C-1), 82.71 (C-2), 80.24 (C-3*), 79.62 (C-4*), 76.57 (C-5), 65.00 (C-6), 59.58, 59.29, 58.75, 57.16 (OMe). Anal. Calcd for $C_{10}H_{18}O_6$: C, 51.27; H, 7.74. Found: C, 51.51; H, 7.77.

3.14. Copolymerization of 11 with L-lactide

An homogeneous mixture of L-lactide (**17**, 154 mg, 1.07 mmol) and 2,3,4,5-tetra-*O*-methyl-D-glucono-1,6-lactone (**11**, 100 mg, 0.43 mmol) was introduced into a round-bottomed flask with 1.5% $Sn(Oct)_2$ as initiator. After degassing, the flask was sealed under vacuum and allowed to rotate continuously at 110 °C for 15 days. The resulting crude polymer was treated with C_3H_6O and the insoluble solid was filtered and washed several times with more C_3H_6O giving copolymer **18a** (12%). The filtrate was concentrated to dryness, redissolved in the minimum amount of C_3H_6O and precipitated in EtOH. The process of dissolution/precipitation was repeated twice. Finally, the copolymer was filtrated and washed with EtOH (5 × 2 mL) to obtain copolymer **18b** (29%). IR: *v* 1753 cm^{-1} (CO); NMR data ($CDCl_3$): ^1H δ 5.14 (q, 1H, *J* 7.1 Hz, CH), 4.48 (dd, 1H, $J_{5,6}$ 2.6, $J_{6,6}$ 12.0 Hz, H-6), 4.17 (dd, 1H, $J_{5,6'}$ 5.8 Hz, H-6′), 4.07 (d,

1H, $J_{2,3}$ 5.0 Hz, H-2), 3.65 (bt, 1H, $J_{3,4}$ 4.9 Hz, H-3), 3.55 (bt, 1H, $J_{4,5}$ 5.1 Hz, H-4), 3.52–3.46 (m, 1H, H-5), 3.50, 3.42, 3.40, 3.37 (s, 12H, OMe), 1.56 (d, 3H, CH_3). Some other physical characteristics of these copolymers are collected in Table 1.

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