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Note

Facile synthesis of a D-galactono-1,6-lactone derivative, a precursor of a copolyester

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Abstract—2,3,4,6-Tetra-*O*-methyl-D-galactonic acid (**5**) was readily prepared from D-galactono-1,4-lactone (**1**) in 47% yield. The sequence involves tritylation of HO-6 of **1**, followed by O-permethylation and deprotection. Lactonization of **5** led to the per-*O*-methyl-D-galactono-1,6-lactone, which was copolymerized with ε-caprolactone by ring-opening polymerization catalyzed by scandium triflate. The incorporation of the sugar comonomer into the polyester chain was about 10%.

Keywords: D-Galactono-1,4-lactone; Aldono-1,6-lactone; ε-Caprolactone; Copolyester

Polyesters and copolyesters of α-, β-, and ω-hydroxy acids are presently under investigation as matrices for controlled drug delivery and scaffolds for tissue engineering.[1–3] One commonly used synthetic strategy for preparing these polymers is the ring-opening polymerization of ε-caprolactone, lactide, and other cyclic esters. This reaction has been efficiently conducted using transition metal-initiating compounds[4] as well as enzymatic catalysis.[5,6]

The introduction of functional groups into the monomers is an important tool to tail and modulate the properties of the resulting polymers. Thus, ε-caprolactone, lactide, or glycolide have been polymerized with more hydrophilic lactones.[7] Also, dilactones with protected functionalities yield, after polymerization, polymers with hydrophilic pendant groups.[8] A higher biodegradability for these materials is expected as a result of the enhanced hydration. Due to the large number of hydroxyl functions in their structures, carbohydrates are employed as precursors of hydrophilic polymers.[2] Thus, carbohydrate-functionalized polyesters have been prepared using enzymes as catalysts,[9] and terminally carbohydrate-modified poly(ε-caprolactones) have been synthesized by lactic acid-promoted ring-opening polymerization of ε-caprolactone with methyl β-D-glucopyranoside or sucrose as initiators.[10] Additionally, derivatives of sugars seem to be suitable for the preparation of polyhydroxypolyalkanoates. For example, aldono-1,6-lactones are analogues of ε-caprolactone carrying several hydroxyl groups. However, as far as we know, just one preparation of a D-glucono-1,6-lactone derivative has been reported. Such a derivative was synthesized by Galbis and coworkers[11] by two alternative routes, both involving the oxidation of C-1 of glucose. Furthermore, the homopolymerization of the monomeric 1,6-lactone derivative and its copolymerization with L-lactide were attempted.

In our recent work on the synthesis of polyamides derived from D- and L-galactono-1,4-lactones,[12,13] we have succeeded in the preparation of selectively protected aldonic acid derivatives having free the hydroxyl group at C-6. These compounds are suitable for 1,6-lactone formation. We report here the synthesis of 2,3,4,5-tetra-*O*-methyl-D-galactono-1,6-lactone (**6**), by a short route starting from D-galactono-1,4-lactone (**1**). The homopolymerization of **6** and its copolymerization with ε-caprolactone were studied.

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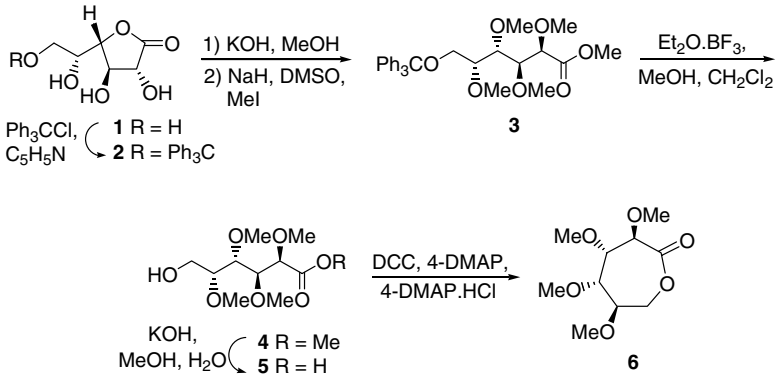


Scheme 1.

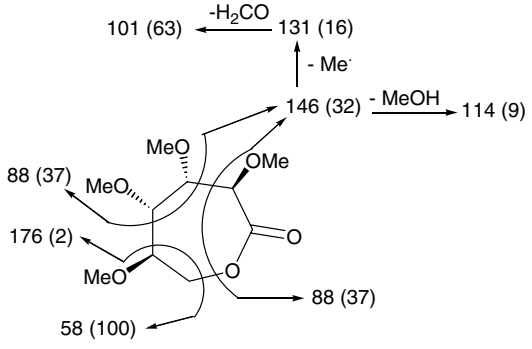
The ω-hydroxy acid **5** was readily prepared from **1** as depicted in Scheme 1 (47% overall yield). D-Galactono-1,4-lactone (**1**) was converted into the 6-*O*-trityl derivative **2**, as described for the analogue in the L-series.[12] Treatment of **2** with methanolic solution of KOH afforded the potassium salt of the aldonic acid, that was dried and O-permethylated with methyl iodide in Me_2SO, in the presence of sodium hydride. The opening of the lactone by formation of the potassium salt prevents side reactions during O-alkylation, such as eliminations and isomerizations.[14] Removal of the trityl group with $F_3B{\cdot}OEt_2$, followed by hydrolysis of the methyl ester with alkali, led to crystalline 2,3,4,5-tetra-*O*-methyl-D-galactonic acid (**5**), a direct precursor of the target 1,6-lactone **6**.

A number of procedures for lactonization and macrolactonization of hydroxy acids have been described, and recently reviewed.[15] We have followed the Keck–Boden modification of the original Steglich procedure,[16] which employs dicyclohexylcarbodiimide-4-*N*,*N*-dimethylaminopyridine (DMAP) for the lactonization. Keck and Boden have shown the crucial role of DMAP hydrochloride as a proton-transfer reagent that prevents the formation of *N*-acyl urea as an undesired byproduct.[16] This reaction when applied to **5** afforded **6** in 56% yield.

The structure of **6** was confirmed by comparison of the NMR spectra with those of **5**. Thus, the methylene protons (H-6,6′) appeared shifted downfield as expected for the deshielding effect of the esterification of HO-6. The remarkable changes in coupling constant values from **5** to **6** were also indicative of ring formation. For the hydroxy acid **5**, the small values for $J_{2,3}$ and $J_{4,5}$ (2.5 and 2.8 Hz, respectively) and the large one for $J_{3,4}$ (8.6 Hz), agree with a planar zigzag conformation for the sugar backbone. It has been established that open-chain derivatives of galactose adopt preferentially such a conformation.[13,17] In contrast, the lactone **6** showed relatively large values for $J_{2,3}$ and $J_{4,5}$ (6.8 and 7.0 Hz, respectively) and a small one for $J_{3,4}$ (~1 Hz), as a result of the cyclization to a seven-membered lactone ring.

Furthermore, the Fourier-transform IR spectrum of **6** showed the stretching of the carbonyl group at 1749 cm^{-1}, similar to that observed for the ε-caprolactone (1740 cm^{-1}). The structure of **6** was further confirmed by mass spectrometry. The MALDI-TOF spectrum of **6** presented a single peak at *m*/*z* 256.5 (theoretical for $M+Na^+$: 257.2). This result excludes the formation of dimeric or oligomeric rings, as observed for cyclizations of related compounds.[18] Lactone **6**, when subjected to GC–MS gave a chromatogram that showed a single signal (retention time 10 min). The corresponding electron impact-mass spectrum (EIMS) exhibited the peak at highest mass of *m*/*z* 203, which was attributed to the loss of a methoxy group from the molecular ion, and other diagnostic fragmentations are illustrated in Scheme 2.

The homopolymerization of lactone **6** promoted by aluminum isopropoxide ($Al(O^iPr)_3$) or scandium triflate ($Sc(OTf)_3$) was attempted. However, the polymerization failed with both catalysts. In the case of $Al(O^iPr)_3$, the formation of decomposition products was detected. This fact was attributed to the instability of aldonolactone derivatives towards strong bases, which usually induce eliminations and isomerizations.[14] However, using $Sc(OTf)_3$, the monomer **6** was recovered unaltered from

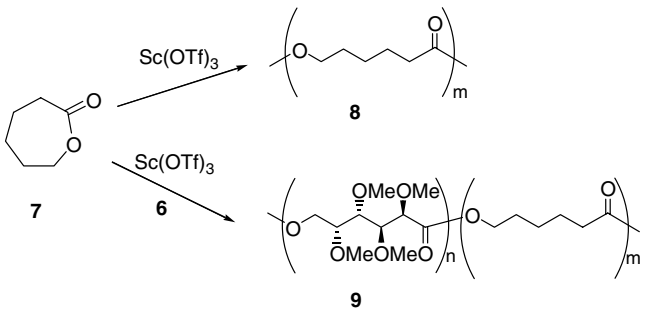


Scheme 2. EIMS of compound **6**. Relative intensities (%) are given in brackets.

the reaction mixture. From the variety of transition or rare-earth metal initiators for the ring-opening polymerization,[4] $Sc(OTf)_3$ presents some advantages, as being a commercially available compound that catalyzes polymerizations at rt, for short times, and that contamination by protic compounds (such as water) does not suppress its catalytic activity.[19] In order to verify that the catalyst was active, the $Sc(OTf)_3$-induced homopolymerization of ε-caprolactone (**7**) in dry toluene was conducted at rt for 16 h. As expected poly(ε-caprolactone) (**8**) was obtained. Polyester **8** showed NMR spectra that were in accordance to those already reported.[4] From the integral of the triplet that appeared at 4.06 ppm (methylene group bonded to oxygen) and that at 3.65 ppm (terminal hydroxymethyl group) the molecular weight of the polyester was estimated (M_w 4000). Also the M_w value (4900) was determined by size exclusion chromatography (SEC) of the polymer.

As homopolymerization of lactones becomes more difficult when the substitution of the lactone ring increases,[11] the copolymerization of **6** and **7** initiated by $Sc(OTf)_3$ was studied under different conditions (Scheme 3). Thus, the aldono-1,6-lactone **6** was stirred in a toluene soln with the catalyst at rt for 24 h, and then ε-caprolactone **7** (identical number of molar equivalents as **6**) was injected to the mixture. The stirring was continued for 48 h. The same experiment was conducted but starting with ε-caprolactone and injecting **6** after 24 h. In both cases, the NMR spectra of the polyesters that were isolated and purified were very similar, and they revealed that about 10% of **6** had been incorporated to the polymeric chain. Also, the molecular weight of the material obtained in the first polymerization was similar to that obtained in the second one (~3000, estimated from the ^1H NMR spectra). The ^{13}C NMR spectra of the copolymer showed the signal of the carbons bonded to oxygen of the sugar comonomer between 77.1 and 81.0 ppm, and those of the methyl groups in the range of 62.1–58.0 ppm. In these regions, more signals appeared than those expected for a regular repeating unit of the copolyester, which suggests different chemical environments (acid or hydroxy end or incorporation into the chain) for the aldonic acid derivative in the polymer.

The copolymer **9** was also synthesized adding successively equimolar amounts of comonomers **6** and **7** to a suspension of $Sc(OTf)_3$ in toluene. The resulting copolyester **9** gave NMR and IR spectra identical to those shown by the polymers prepared previously under different reaction conditions. We have also found that the incorporation of aldonic acid to the polymer could not be increased using higher concentrations of **7** during the polymerization. Polyester **9** displayed unimodal chromatograms by SEC, using THF as solvent, from which the molecular weight (M_w 3500) was estimated.



Scheme 3.

These results show that the copolymerization of aldono-1,6-lactone derivatives with ε-caprolactone can be successfully conducted. Further efforts are needed to achieve higher incorporation of the sugar into the copolymer chain. Other lactones, such as L-lactide, may be employed in order to obtain hydrophilic and potentially biodegradable polyhydroxypolyalkanoates. The lactone **6**, similar to its D-gluco analogue, seems to be less reactive than ε-caprolactone for the ring-opening polymerization. The lower reactivity of **6** can be explained taking into account the mechanism proposed for the $Sc(OTf)_3$-catalyzed polymerization.[19] The first step is the coordination of the metal to the lactone carbonyl, which is activated (the 'activated monomer mechanism'[20]) for the attack of traces of water contained in the $Sc(OTf)_3$ (lanthanide salts are extremely difficult to obtain in anhydrous state[21]) In the case of **6**, the methoxy groups can compete with the carbonyl for the coordination with $Sc(OTf)_3$, thus diminishing its catalytic activity. On the other hand, as one molecule of reactive catalyst produces a large number of polymer molecules,[19] an increment in the lanthanide will generate a larger number of polymeric chains, resulting in the lowering of the molecular weight of the polyester.

1. Experimental

1.1. General methods

Melting points were determined with a Fisher–Johns apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was performed on Silica Gel 60 F_{254} (E. Merck) aluminum-supported plates (layer thickness 0.2 mm). Visualization of the spots was effected by exposure to UV light or by charring with a soln of 5% (v/v) sulfuric acid in EtOH, containing 0.5% *p*-anisaldehyde. Column chromatography was carried out with Silica Gel 60 (230–400 mesh, E. Merck). Optical rotations were measured with a Perkin–Elmer 343 digital polarimeter at 25 °C. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AC-200 or Bruker AMX-500 spectrometers. Size exclusion

chromatography (SEC) was performed at rt with a Waters apparatus equipped with a Waters 2414 refractive index detector and Styragel HR (7.8×300 mm) Waters columns, using THF as mobile phase. The flow rate was 1 mL min^{-1}. Calibration was based on polystyrene standards. IR spectra (films) were recorded with a Nicolet 510P FTIR spectrometer. MALDIMS measurements were performed using a Shimadzu Kratos, Kompact MALDI 4 (pulsed extraction) laser desorption time-of-flight mass spectrometer (Shimadzu, Kyoto, Japan) equipped with a pulsed nitrogen laser (337 nm; pulse width 3 ns), tunable PDE and PSD (MS/MS device) modes. GC–EIMS analyses were made in a GC–MS QP5050A (Shimadzu), using a ionization potential of 70 eV. Conditions: injector temperature 240 °C, interface temperature 270 °C, oven temperature from 150 °C at 10 °C/min to 250 °C (20 min), split 90:1, total flow 20 mL min^{-1}, column flow 0.2 mL min^{-1}. The mass spectrometer was used in scan mode (40–500 amu).

1.2. 6-*O*-Trityl-D-galactono-1,4-lactone (2)

It was prepared by reaction of triphenylmethyl chloride (trityl chloride, 1.87 g, 6.72 mmol) with D-galactono-1,4-lactone (**1**, 1.0 g, 5.61 mmol) in anhyd pyridine (8.4 mL), as previously described.[12] Crystalline **2** (2.25 g, 95%) gave mp 77–78 °C, $[\alpha]_D$ +20.0 (*c* 1.0, $CHCl_3$). Lit.[12] mp 77–78 °C, $[\alpha]_D$ −22.4 for the enantiomer.

1.3. Methyl 2,3,4,5-tetra-*O*-methyl-6-*O*-trityl-D-galactonate (3)

To a soln of **2** (1.00 g, 2.38 mmol) was slowly added 30% KOH in MeOH with stirring. When the alkalinity of the soln (pH ~7.5) persisted for about 30 min, the solvent was evaporated to afford the solid potassium salt. The dried solid was dissolved in anhyd Me_2SO (6.5 mL), and a suspension of NaH (1.15 g) in Me_2SO (10 mL) was added to the cooled soln (ice bath). The mixture was stirred at rt for 30 min, cooled to 0 °C, and methyl iodide (1.75 mL) was injected. After 2 h at rt, MeOH was added carefully to the suspension, which was then neutralized with acetic acid, diluted with water and extracted with CH_2Cl_2 (3×80 mL). The extract was dried ($MgSO_4$) and concentrated to afford a syrup that was subjected to column chromatography with 5:1 hexane–EtOAc. Compound **3** was isolated as a colorless oil (0.94 g, 78%); $[\alpha]_D$ +8.0 (*c* 1.0, $CHCl_3$). Lit.[12] $[\alpha]_D$ −5.1 for the enantiomer.

1.4. Methyl 2,3,4,5-tetra-*O*-methyl-D-galactonate (4)

Trityl removal[12] from **3** (0.75 g, 1.48 mmol) with $F_3B{\cdot}OEt_2$ (0.2 mL) in MeOH (0.6 mL) and CH_2Cl_2 (40 mL) afforded oily **4** (0.28 g, 72%); $[\alpha]_D$ +10.0 (*c* 0.9, $CHCl_3$). Lit.[12] $[\alpha]_D$ −10.5 for the enantiomer.

1.5. 2,3,4,5-Tetra-*O*-methyl-D-galactonic acid (5)

To a soln of **4** (0.72 g, 1.46 mmol) in MeOH–water (3:1, 15 mL) was added a soln of KOH (0.2 g, 3.57 mmol) in the same solvent (1 mL). The mixture was stirred at rt for 3 h and the MeOH evaporated. The residue was diluted with water (80 mL), acidified with HCl (5%) to pH 3 and extracted with CH_2Cl_2 (3×50 mL). The organic extract was dried ($MgSO_4$) and concentrated to give **5** (0.33 g, 90%) as a crystalline solid. Recrystallized from hexane–EtOAc, **5** gave mp 143 °C; $[\alpha]_D$ −10.4 (*c* 0.8, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ: 4.06 (d, 1H, $J_{2,3}$ 2.5 Hz, H-2), 3.91 (dd, 1H, $J_{5,6}$ 5.5, $J_{6,6'}$ 11.6 Hz, H-6), 3.88 (dd, 1H, $J_{3,4}$ 8.5 Hz, H-3), 3.86 (dd, 1H, $J_{5,6'}$ 4.8 Hz, H-6′), 3.55 (dd, 1H, $J_{4,5}$ 2.8 Hz, H-4), 3.51 (m, 1H, H-5), 3.53, 3.51, 3.50, 3.45 (4s, 12H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 174.2 (C-1), 81.0, 80.0, 79.7, 79.4 (C-2,3,4,5), 61.2 (C-6), 60.4, 60.0, 58.9, 58.0 (OCH_3). Anal. Calcd for $C_{10}H_{20}O_7$: C, 47.61; H, 7.99. Found: C, 47.81; H, 7.97.

1.6. 2,3,4,5-Tetra-*O*-methyl-1,6-D-galactonolactone (6)

A soln of **5** (0.25 g, 0.99 mmol) in anhyd $CHCl_3$ (7 mL) was added dropwise to a soln of DCC (0.47 g, 2.20 mmol), 4-DMAP (0.44 g, 3.60 mmol), and 4-DMAP hydrochloride (0.37 g, 2.30 mmol) in anhyd $CHCl_3$ (30 mL). The reaction mixture was stirred at rt for 18 h, when TLC (1:1 hexane–EtOAc) showed a major spot having R_f 0.27. The suspension was filtered and the solvent evaporated. The residue was purified by column chromatography (1:1 hexane–EtOAc) to give **6** (0.13 g, 56%) as a colorless syrup that crystallized on standing; mp 67–68 °C; $[\alpha]_D$ +10.5 (*c* 0.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 4.44 (dd, 1H, $J_{5,6}$ 6.8, $J_{6,6'}$ 12.9 Hz, H-6), 4.28 (d, 1H, $J_{2,3}$ 6.0 Hz, H-2), 4.23 (dd, 1H, $J_{5,6'}$ 2.4 Hz, H-6′), 3.79 (br s, 1H, H-3), 3.58 (ddd, 1H, $J_{4,5}$ 8.0 Hz, H-5), 3.50 (br s, 1H, H-4), 3.53, 3.52, 3.48, 3.47 (4s, 12H, OCH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 176.3 (C-1), 80.9, 80.0, 79.6, 79.3 (C-2,3,4,5), 61.2, 60.5, 58.9, 58.0 (OCH_3). Anal. Calcd for $C_{10}H_{18}O_6$: C, 51.27; H, 7.75. Found: C, 50.92; H, 8.02.

1.7. General procedure for lactone polymerization or copolymerization initiated with $Sc(OTf)_3$

1.7.1. Poly(ε-caprolactone) (8). A suspension of $Sc(OTf)_3$ (10 mg, 20 μmol) in dry toluene (1 mL) was placed in a sealed vial, under an argon atmosphere, and freshly distilled caprolactone (**7**, 0.11 mL, 0.99 mmol) was injected slowly with a syringe. The reaction mixture was stirred at rt for 16 h, when TLC (EtOAc) showed no remaining caprolactone (R_f 0.51). The mixture was diluted with toluene (30 mL) and washed with water (2×10 mL). The organic extract was dried ($MgSO_4$), filtered, and concentrated, to afford

poly(ε-caprolactone) **8** (0.10 g, 85%) as a white solid; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.06 (t, 2H, J 6.6 Hz, CH_2-α), 2.31 (t, 2H, J 7.4 Hz, CH_2-ε), 1.63 (m, 4H, CH_2-β, δ), 1.38 (m, 2H, CH_2-γ); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 173.5 (CO), 64.1 (OCH_2), 34.1 ($COCH_2$), 28.3, 25.5, 24.5 ($3CH_2$). These spectra were similar to those already described for poly(ε-caprolactone).[4]

1.7.2. Poly(ε-caprolactone)-co-poly(2,3,4,5-tetra-*O*-methyl-1,6-D-galactonolactone) (9). The procedure described above was applied for the copolymerization of **6** with **7**. Compound **6** (0.034 mL, 0.31 mmol) and **7** (0.07 g, 0.31 mmol) were successively injected to a suspension of $Sc(OTf)_3$ (3.1 mg, 6.2 μmol) in dry toluene (0.7 mL). After the work-up and washing of the residue with hexane (2 × 2 mL), the polyester **9** (70 mg, 66%) was obtained as a white solid; $[\alpha]_D$ −3.4 (c 1.1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.50–3.80 (m, 6H, H-galactonic acid), 4.06 (t, 2H, J 6.6 Hz, OCH_2), 3.55–3.30 (m, 12H, OCH_3), 2.31 (t, 2H, J 7.5 Hz, $COCH_2$), 1.75–1.25 (m, 6H, $3CH_2$); IR: 1735 cm^{-1} (CO), 1100 cm^{-1} (OCH_3); M_w 3500 (SEC).

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