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Cyclic oligomers (macroaldonolactones) from a protected D-galactonic acid monomer

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ABSTRACT

Dicyclohexylcarbodiimide-promoted self-condensation of 2,3:4,5-di-*O*-isopropylidene-D-galactonic acid (**3**) led to the macrocyclic oligomeric cyclo[(2,3:4,5-di-*O*-isopropylidene-(1→6)-D-galactonate)$_2$] (**4**) and cyclo[(2,3:4,5-di-*O*-isopropylidene-(1→6)-D-galactonate)$_3$] (**5**), having, respectively, 14- and 21-membered rings. The macrocycles **4** and **5** were also synthesized by cyclization of the respective linear dimer **11** and trimer **14** ω-hydroxy acids precursors prepared by stepwise additions of **3**. Compounds **4** and **5** are biomaterials that may be described as macrolactone-cyclodextrins.

Cyclodextrins have attracted considerable attention in recent years due to their wide range of industrial uses as complexing systems for environmental remediation,[1] fragrance anchoring to fabrics,[2] or even drug and gene-controlled release systems for the pharmaceutical industry.[3–5] The chirality of cyclodextrins is applied in asymmetric organic synthesis[6,7] and chromatography separations.[8–10]

The versatility of carbohydrate macrocycles relies on the size of the ring and the chirality that allow the formation of inclusion complexes with different organic and inorganic molecules. A wide range of carbohydrate macrocycles have been reported,[11] mostly constituted by monosaccharides linked through glycosidic bonds. However, there are limited examples of macrocyclic lactones derived from sugars. Monosaccharides conjugated with hydroxy acids have been employed as precursors of sugar-fatty acid macrolactones such as macroviracins, cycloviracins, and others.[12] Cyclic and linear polyesters have been obtained by polycondensation of isosorbide and suberoyl chloride or other aliphatic dicarboxylic acid chlorides.[13] The ring-opening polymerization of lactones, successfully applied for the preparation of cyclic poly(lactide) from lactide,[14] has recently been employed to a racemic derivative of D-gluconolactone to yield a functionalized cyclic polyester.[15]

As continuation of our studies on biodegradable polymers based on the galactose structure,[16–19] we describe herein the synthesis of two macrocyclic oligomers obtained by direct cyclization of a linear aldonic acid monomer derived from D-galactono-1,4-lactone (**1**). Alternatively, each macrocycle has been selectively prepared by cyclization of the respective linear dimer or trimer, synthesized by consecutive addition of the monomer. The resulting oligomeric cyclo[(2,3:4,5-di-*O*-isopropylidene-(1→6)-D-galactonate)$_2$] (**4**) and cyclo[(2,3:4,5-di-*O*-isopropylidene-(1→6)-D-galactonate)$_3$] (**5**) may be described as cyclodextrin-macroaldonolactones.

The precursor of the cyclic oligomers, the 2,3:4,5-di-*O*-isopropylidene-D-galactonic acid (**3**) was prepared from **1** in two steps (Scheme 1). Treatment of **1** with 2,2-dimethoxypropane, under catalysis with *p*-toluenesulfonic acid (*p*-TsOH), afforded the diacetonide **2** as major product.[20] Alkaline hydrolysis of the ester function gave, upon acidification, the hydroxy acid **3**. The *galacto* configuration was selected for the synthesis of the macrocycles as the precursor aldonic acid **3** may be obtained in a reasonable scale and also because the *trans–trans*-acetonides[21] would preclude the formation of the polyhydroxy caprolactone derivative during the cyclization reaction.

Attempts were made to generate cyclic oligomers from **3**. We have previously observed the formation of a cyclic trimer during the polymerization of an activated analogue of **3**, the 6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonic acid.[19] Moreover, Fleet and co-workers[21] reported the formation of cyclic oligomers (being the trimer the main product) during the cyclization reaction of such a sugar amino acid. It seems reasonable that the formation of bigger and more flexible cycles would allow liberation of ring tension compared with the seven-membered lactone having two dioxolane rings fused.

A number of activating agents have been employed for macrolactonizations of hydroxy acids.[22] The use of *N*,*N*′-dicyclohexylcarbodiimide (DCC) in the presence of 4-(dimethylamino)pyridine

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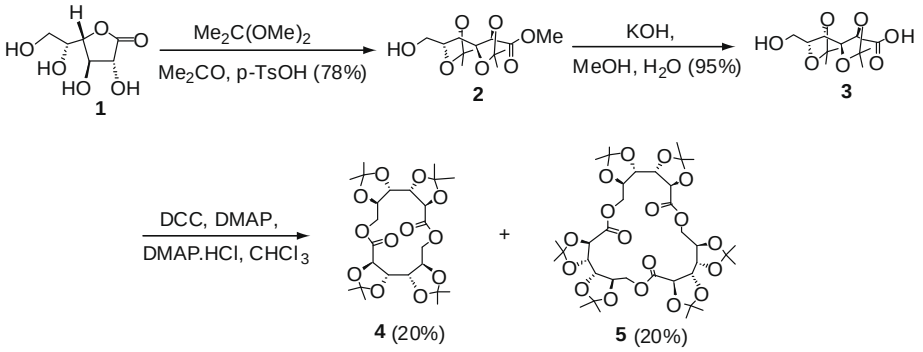


Scheme 1.

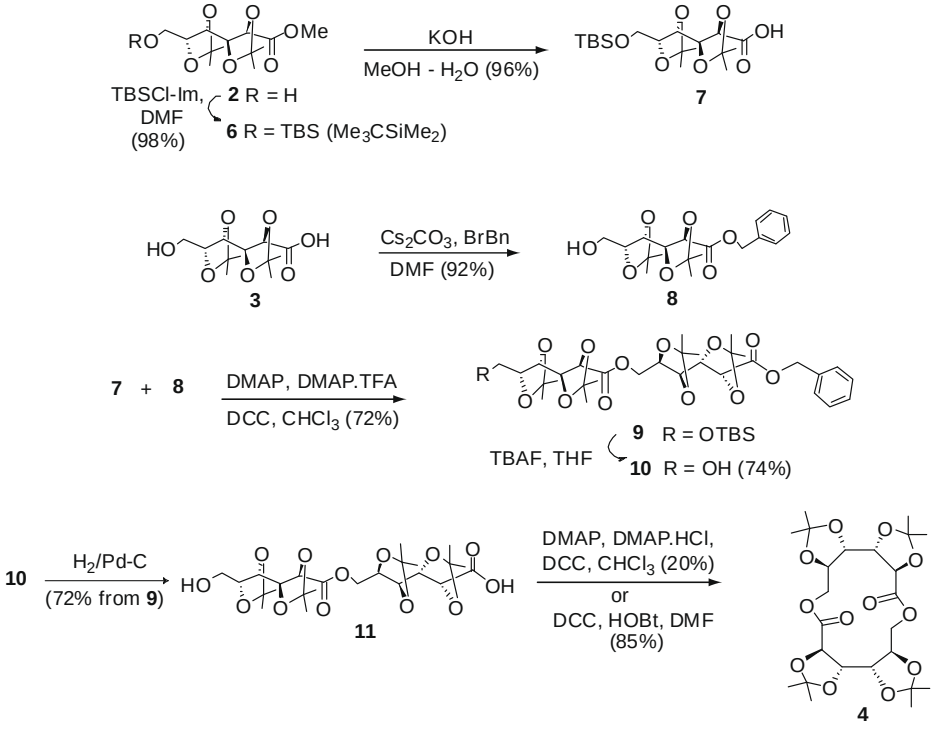
(DMAP)–DMAP hydrochloride led to satisfactory results in the cyclization of **3**. Under these conditions two main products were obtained together with mixture of oligomers of lower mobility by TLC. The faster moving components of the mixture (R_f = 0.31 and 0.28, hexane/EtOAc 1.5:1) were isolated by column chromatography, and their structures were established by MS and NMR spectroscopy as the 14- and 21-membered ring cyclic dilactone **4** and trilactone **5**, respectively.[23]

Analysis of coupling constant values from the ^{1}H NMR spectra of compounds **3**, **4,** and **5** showed variations that were attributed to conformational changes. While $J_{2,3}$ and $J_{4,5}$ show values characteristic of coupled protons in a 1,3-dioxolane ring, the $J_{3,4}$ value was very sensitive toward conformational changes (Table 1). Thus, the open-chain aldonic acid **3** exhibited a large $J_{3,4}$ value (8.5 Hz) which indicates an *anti* disposition for H-3 and H-4, as expected for the extended zigzag conformation typical of galactose derivatives. Interestingly, the $J_{3,4}$ value is smaller (1.6 Hz) in the cyclic dimer **4**, in agreement with a *gauche* disposition of such protons. In the case of the trimer **5**, as some degree of flexibility may be possible, $J_{3,4}$ appears as an average value (3.5 Hz) between the linear monomer and the cyclic dimer.

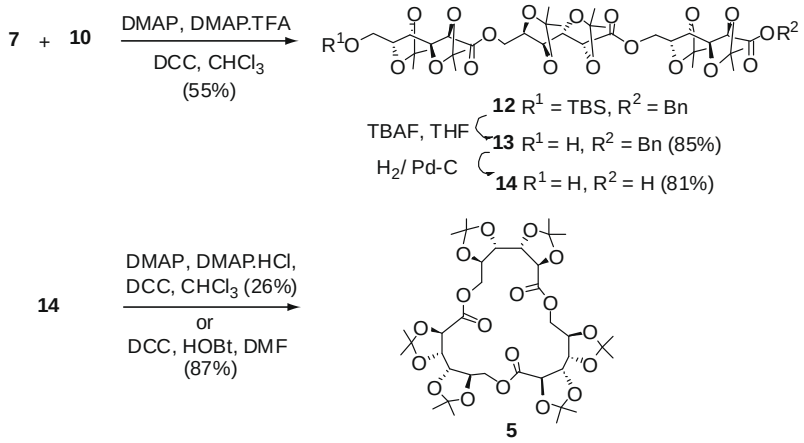
Table 1
^{1}H NMR Coupling constant values for compounds **3**, **4,** and **5**

Compound	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
3	5.8	8.5	7.7	3.7	4.3	12.0
4	7.6	1.6	7.2	2.8	8.9	10.5
5	6.6	3.5	7.4	5.3	5.0	11.6

In order to confirm the structure of **4** and **5** and to explore the feasibility to synthesize cyclic oligomers with different sizes, we designed a route based in the stepwise addition of the monomer **3** to yield a linear dimer (**11**) and trimer (**14**). The cyclization of these two compounds to the respective macrocycles **4** and **5** was conducted. Protection of the free hydroxyl group at C-6 of methyl 2,3:4,5-di-*O*-isopropylidene-D-galactonate (**2**) as *tert*-butyldimethylsilyl (TBS) ether gave **6**, which upon hydrolysis of the ester gave **7** (Scheme 2). In addition, esterification of the carboxylic acid **3** with benzyl bromide gave the hydroxyester **8**, having the hydroxyl



Scheme 2.



Scheme 3.

group at C-6 free for the dimerization. The condensation reaction between **7** and **8** took place using DCC as condensing agent in the presence of DMAP–DMAP·TFA to give the protected linear dimer **9** (72% yield). This compound was treated with tetrabutylammonium fluoride (TBAF) in THF to release the terminal hydroxyl group. The resulting product **10** reacted with hydrogen in the presence of 10% Pd/C with removal of the benzyl ester to produce the dimeric hydroxy acid **11** (72% yield from **9**).[24]

Cyclization of **11** (0.5 mmol) promoted by DCC (1.0 mmol) in the presence of DMAP (1.5 mmol) and DMAP·HCl (1.0 mmol) afforded crystalline cyclo [(2,3:4,5-di-*O*-isopropylidene-(1→6)-D-galactonate)$_2$] (**4**) in 20% yield. However, the analogous reaction of **11** (0.2 mmol) with 1-hydroxybenzotriazole (HOBt, 0.4 mmol) and DCC (0.4 mmol) in DMF afforded the macrocycle **4** in 85% yield.

The cyclic trimer **5** was prepared following a procedure similar to the one employed for the synthesis of **4**. Condensation of the aldonic acid derivative **7** with the dimer alcohol **10** gave the trimer **12** (Scheme 3). Deprotection of the silyl ether of **12** with TBAF led to **13**, which was subjected to hydrogenolysis to afford the linear ω-hydroxy acid **14** (69% from **12**).[24] Cyclization of **14** in the presence of DCC, DMAP–DMAP·HCl gave crystalline cyclo [(2,3:4,5-di-*O*-isopropylidene-(1→6)-D-galactonate)$_3$] (**5**) in 26% yield; whereas the use of HOBt and DCC resulted, as observed in the cyclization of **11**, in a considerable increment in the yield of **5** (87%). In the DCC–DMAP protocol the formation of unreactive *N*-acyl urea byproducts decreases the yield of macrolactones.

This side reaction may be prevented by adding a proton source, such as DMAP·HCl[25] or DMAP·TFA,[26] to the reaction mixture. However, even with these additives, the formation of the *N*-acyl urea was detected in the cyclization of **11** and **14**. In contrast, the use of HOBt–DCC gave good yields of the expected macrolactones. These reagents have been employed for rather difficult macrolactonizations.[27]

In conclusion, two 14- and 21-membered ring macrocycles, having the *galacto* configuration for the constituent units, have been synthesized using a straightforward approach from a selectively acetonide-protected aldonic acid. This compound was also employed as key precursor of a linear dimer and trimer ω-hydroxy acids, which have been successfully converted into macrocycles. The macrolactonization promoted by DCC–HOBt gave a higher yield than that performed with DCC, DMAP–DMAP·HCl. The resulting carbohydrate-based macrocycles are biomaterials that may be described as macrolactone–cyclodextrins. They are soluble in organic solvents of varied polarity, and they are expected to be able to complex a variety of organic and inorganic species.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.123.

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23. *Compound* **3**: mp 121–122 °C; $[\alpha]_D$ −11.3 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{12}H_{20}O_7$: C, 52.17; H, 7.30. Found: C, 52.09; H, 7.14. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.14 (sa, 1H, COO*H*), 4.62 (d, 1H, $J_{2,3}$ = 5.8 Hz, H-2), 4.36 (dd, 1H, $J_{3,4}$ = 8.5 Hz, H-3), 4.14 (ddd, 1H, $J_{4,5}$ = 7.7, $J_{5,6}$ = 3.7, $J_{5,6'}$ = 4.3 Hz, H-5), 4.00 (dd, 1H, H-4), 3.88 (dd, 1H, $J_{6,6'}$ = 12.0, H-6), 3.74 (dd, 1H, H-6′), 1.49, 1.45 (×2), 1.43 (4s, 12H, C(*CH*$_3$)$_2$). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 173.1 (C-1), 112.6, 110.3 (*C*(CH$_3$)$_2$), 79.9, 79.3, 77.7, 76.9 (C-2–C-5), 62.2 (C-6), 27.0 (×2), 26.8, 25.9 (C(*C*H$_3$)$_2$). *Compound* **4**: mp 190–191 °C; $[\alpha]_D$ −15.7 (*c* 0.9, $CHCl_3$). Anal. Calcd for $C_{24}H_{36}O_{12}$: C, 55.81; H, 7.02. Found: C, 55.85; H, 7.26. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.60 (dd, 1H, $J_{5,6}$ = 2.8, $J_{6,6'}$ = 10.5 Hz, H-6), 4.48 (d, 1H, $J_{2,3}$ = 7.6 Hz, H-2), 4.38 (dd, 1H, $J_{3,4}$ = 1.6 Hz, H-3), 4.27 (dd, 1H, $J_{4,5}$ = 7.2 Hz, H-4), 4.16 (dd, 1H, $J_{5,6'}$ = 8.9 Hz, H-6′), 4.13 (ddd, 1H, H-5), 1.51, 1.48, 1.47, 1.44 (4s, 12H, C(*CH*$_3$)$_2$). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 169.6 (C-1), 112.1, 110.6 (*C*(CH$_3$)$_2$), 79.2, 78.2, 74.2, 72.9 (C-2–C-5), 65.1 (C-6), 27.3, 26.6 (×2), 25.8 (C(*C*H$_3$)$_2$). MALDI-MS: 539.2 (M+Na). *Compound* **5**: mp 74–75 °C; $[\alpha]_D$ −9.1 (*c* 0.5, $CHCl_3$). Anal. Calcd for $C_{36}H_{54}O_{18}$: C, 55.81; H, 7.02. Found: C, 56.43; H, 7.05. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.57 (d, 1H, $J_{2,3}$ = 6.6 Hz, H-2), 4.42 (dd, 1H, $J_{3,4}$ = 3.5 Hz, H-3), 4.38 (dd, 1H, $J_{5,6}$ = 5.3, $J_{6,6'}$ = 11.6 Hz, H-6), 4.33 (dd, 1H, $J_{5,6'}$ = 5.0 Hz, H-6′), 4.25 (ddd, 1H, $J_{4,5}$ = 7.4 Hz, H-5), 4.11 (dd, 1H, H-4), 1.48, 1.44, 1.43, 1.41 (4s, 12H, C(*CH*$_3$)$_2$). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 170.5 (C-1), 112.4, 110.5 (*C*(CH$_3$)$_2$), 79.1, 78.5, 75.4, 74.9 (C-2–C-5), 65.1 (C-6), 27.1, 26.7, 26.6, 25.8 (C(*C*H$_3$)$_2$). MALDI-MS: 797.3 (M+Na).
24. *Compound* **11:** ^{1}H NMR($CDCl_3$, 500 MHz): 4.61 (d, 1H, $J_{2',3'}$ = 5.5 Hz, H-2), 4.60 (d, 1H, $J_{2,3}$ = 6.0 Hz, H-2), 4.51 (m, 1H, $J_{5,6a}$ = 5.3, $J_{6a,6b}$ = 11.5 Hz, H-6a), 4.40 (dd, 1H, $J_{3',4'}$ = 6.7 Hz, H-3′), 4.36 (t, 1H, $J_{2,3} \sim J_{3,4}$ = 6.0 Hz, H-3), 4.32–4.26 (m, 2H, $J_{5,6b}$ = 5.5 Hz, H-5,6b), 4.10 (dt, 1H, $J_{4',5'}$ = 7.8, $J_{5',6'a}$ = 4.2, $J_{5',6'b}$ = 4.5 Hz, H-5′), 4.01 (dd, 1H, H-4), 3.98 (dd, 1H, H-4′), 3.85 (dd, 1H, $J_{6'a,6'b}$ = 11.9 Hz, H-6′a), 3.75 (dd, 1H, H-6′b), 1.48 (×2), 1.45, 1.45, 1.44, 1.43 (×2), 1.42 (6s, 24H, C(*CH*$_3$)$_2$). ^{13}C NMR ($CDCl_3$, 125.7 MHz): 170.6 (×2) (C-1,1′), 112.4, 112.3, 110.7, 110.0 (*C*(CH$_3$)$_2$), 79.7, 79.6, 79.2, 77.7, 77.6, 76.8, 76.6, 76.5 (C-2,2′,3,3′,4,4′,5,5′), 64.8, 62.5 (C-6,6′), 27.1, 27.0, 26.8, 26.0, 25.9 (C(*C*H$_3$)$_2$). *Compound* **14:** ^{1}H NMR ($CDCl_3$, 500 MHz): 4.60 (d, 1H, $J_{2'',3''}$ = 5.4 Hz, H-2″), 4.59 (d, 1H, $J_{2',3'}$ = 5.6 Hz, H-2′), 4.58 (d, 1H, $J_{2,3}$ = 5.2 Hz, H-2), 4.54–4.44 (m, 2H, H-6a,6′a), 4.40 (dd, 1H, $J_{3'',4''}$ = 6.9 Hz, H-3″), 4.37 (dd, 1H, $J_{3',4'}$ = 7.6 Hz, H-3′), 4.36 (dd, 1H, $J_{3,4}$ = 6.1 Hz, H-3), 4.30–4.21 (m, 4H, H-5,5′,6b,6′b), 4.08 (m, 1H, $J_{4'',5''}$ = 7.4, $J_{5'',6''a}$ = 4.2, = $J_{5'',6''b}$ = 4.3 Hz, H-5″), 4.00 (t, 1H, $J_{4,5}$ = 6.7 Hz, H-4), 3.97 (t, 1H, H-4″), 3.93 (t, 1H, $J_{4',5'}$ = 7.0 Hz, H-4′), 3.83 (dt, 1H, $J_{6''a,6''b}$ = 11.9 Hz, H-6″a), 3.74 (m, 1H, H-6″b), 1.48 (×2), 1.45, 1.44 (×2), 1.43, 1.42 (×4), 1.41, 1.40 (7s, 36H, C(*CH*$_3$)$_2$). ^{13}C NMR ($CDCl_3$, 125.7 MHz): 172.5 (C-1), 170.5, 170.4 (C-1′,1″), 112.5 (×2), 112.4, 110.8, 110.6, 109.9 (*C*(CH$_3$)$_2$), 79.8, 79.7 (×2), 79.1 (C-3,3′,3″,5″), 77.8, 77.7, 77.5, 77.4, 77.3, 77.1, 76.8, 76.3 (C-2,2′,2″,4,4′,4″,5,5′), 64.8, 64.7 (C-6,6′), 62.5 (C-6″), 27.3, 27.2, 27.1, 27.0 (×3), 26.9, 26.8, 26.7, 26.1, 26.0, 25.9 (C(*C*H$_3$)$_2$).
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