Synthesis and polymerization of conveniently substituted 6-amino-6-deoxy-D-galactonic acid derivatives

Carmen L. Romero Zaliz[a], Rosa Erra-Balsells[a], Hiroshi Nonami[b], Yasuto Sato[b], and Oscar Varela*[a]

[a] CIHIDECAR-CONICET. Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Pabellón II, Ciudad Universitaria, 1428-Buenos Aires, Argentina; [b] Plant Biophysics/Biochemistry Research Laboratory, College of Agriculture, Ehime University, 3-5-7 Tarumi, Matsuyama 790-8566, Japan
E-mail: varela@qo.fcen.uba.ar

Dedicated to Prof. Rosa Muchnik de Lederkremer on the occasion of her 70th birthday

Abstract

Methyl 6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonate (**1**), prepared in two steps from D-galactono-1,4-lactone, was hydrolyzed to the corresponding acid **2**, which was esterified with phenol (PhOH) in the presence of dicyclohexylcarbodiimide (DCC) to give the phenyl ester **3**. Hydrogenolysis of the azide function of **3** yielded the hydrochloride derivative of the amino acid **4**. Compound **4** is conveniently substituted for the polycondensation; therefore, this reaction was conducted using DMF as solvent and *N*,*N*-diisopropylethylamine as a basic catalyst. The MALDI-TOF mass spectrum of the isolated product (**5**) indicated that this was a mixture of the cyclic trimer (M + Na^+, 793.7) and linear oligomers (from the tetramer to the tetradecamer). To favor the linear polymerization the dimeric amino acid **10** was prepared starting from **2**. Thus, hydrogenation of **2** gave the amino acid **6**, and treatment of **2** with pentachlorophenol-DCC gave the pentachlorophenyl ester **7**. Coupling of **6** with **7** in the presence of DCC gave the dimer **8**, which was converted (PhOH, DCC) into **9**. Hydrogenolysis of **9** afforded the dimeric amino acid **10**, which was polymerized under the conditions employed for **4**. The resulting polyamide **11** was highly soluble in common organic solvents, and its molecular weight was established by MALDI-TOF MS and size exclusion chromatography (M_w = 2700).

Keywords: Sugar amino acids, acetal, D-galactonic acid, polymerization, polyamide

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Introduction

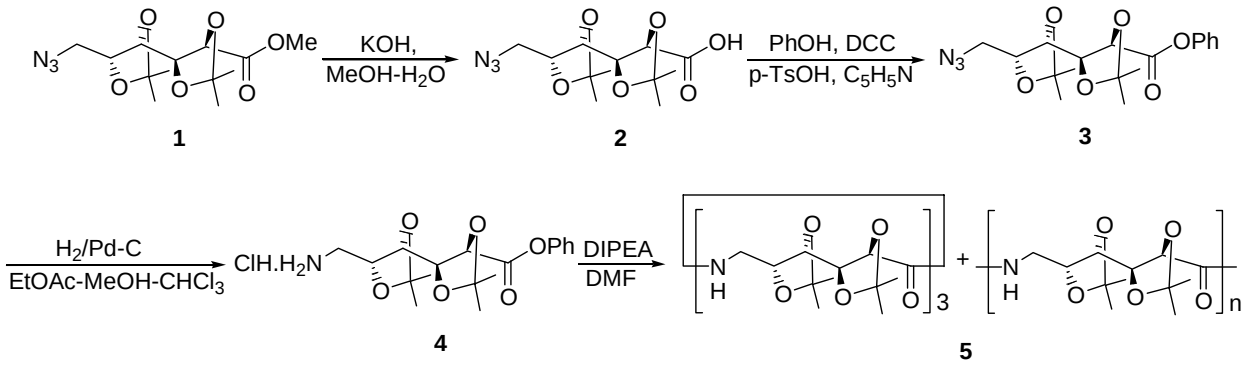
The synthesis of biodegradable polymers is a topic of current intensive research.[1] Biodegradable polymers are environmentally friendly[2] and have found a wide range of practical uses, mainly as biomedical materials.[3] For example, polyhydroxyalkanoates are employed as biodegradable suture strings[4] and as scaffolds for the controlled delivery of drugs.[5] Similarly, the synthesis of polyamides more hydrophylic and degradable than industrial nylons has attracted considerable attention.[1,6,7] Readily available, renewable natural products are the preferred substrates for the preparation of biodegradable polyamides. Amongst the natural regrowing resources, carbohydrates constitute particularly convenient starting materials, due to their abundance and configurational diversity.[6,8] Thus, aldaric acids have been frequently employed for the synthesis of polyhydroxylated nylon 6,6 and related polyhydroxypolyamides. These investigations have been pioneered by Ogata et al.,[9] who studied the polycondensation of ethyl galactarate with alkylenediamines. More recently it has been reported the synthesis and properties of polyhydroxypolyamides derived from D-glucaric,[10] *meso*-xylaric,[10,11] *meso*-galactaric[10,11] and D-mannaric acids.[10,12] Also activated glucaric and galactaric acid derivatives were condensed with α,ω-diaminoalkyl polydimethylsiloxanes to give carbohydrate-segmented silicone polyamides,[13] and aminosaccharide-derived polymers having urea, urethane and amide linkages have been synthesized from glycosylamines.[14] Stereoregular AABB type polyamides have been also prepared from 1,6-diaminoalditols and mannaric acid [15] or dioic acids.[16]

In contrast to the numerous reports (cited above) on the synthesis of polyhydroxylated nylon 6,6, only a few preparations of polyhydroxy derivatives of nylon 6 have been described. For the synthesis of such nylon 6 analogs, sugar amino acids have been employed as precursors. Sugar amino acids are currently exploited as peptidomimetics and as building blocks for the construction of new biomaterials.[17] Thus, sugar-based polyamides have been synthesized from amino acids derived from pentoses[18] or from D-glucose or D-glucosamine,[19] and linear oligomers were obtained on polymerization of protected 6-amino-6-deoxy-D-allonate.[20] We have also described the synthesis of sugar amino acids[21,22] and amino acids from other natural products[23,24] and their polymerization reactions were studied. For example, polycondensation of 6-amino-6-deoxy-2,3,4,5-tetra-*O*-methyl-D- and L-galactonic acids[22] led to stereoregular polyamides having a relatively high molecular weight.[25] We report here the attempted polymerization of 2,3:4,5-di-*O*-isopropylidene derivatives of 6-amino-6-deoxy-D-galactonic acid. The resulting products possess removable protecting groups that could facilitate the preparation of free polyhydroxylated analogs of nylon 6.

Results and Discussion

Methyl 6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonate (**1**) was synthesized from commercially available D-galactono-1,4-lactone in two steps, in about 80% overall yield.[22]

Hydrolysis of the ester group of **1** with KOH in MeOH-water gave the crystalline acid **2**, isolated in 97% yield (Scheme 1). The carboxylic acid group of **2** was converted into the phenyl ester by reaction with phenol in the presence of dicyclohexylcarbodiimide (DCC) and *p*-toluenesulfonic acid.[26] Replacement of the original methyl group in **1** by phenyl was effected to increase the reactivity of the ester function in the nucleophylic attack of the amine, during the polycondensation.



Scheme 1

The hydrogenolysis of the azide group of **3** was conducted using a mixture of EtOAc-MeOH-$CHCl_3$ as solvent. The hydrogen chloride released by hydrogenation of chloroform led to the hydrochloride derivative **4**, without affecting the acid labile isopropylidene groups.[27] Compound **4** constitutes a suitable monomer for the polycondensation as it contains in the same molecule an amino and an activated carboxylic acid. However, it should be taken into account that in ω-amino acids intramolecular condensation with formation of the lactam competes with the growing chain to give a linear polymer.[28] Thus, attempted polymerization of active esters of tetra-*O*-methyl-6-amino-6-deoxy-D-gluconic[19] and D-galactonic[25] acids led to lactam formation. These monomers, compared to **4** should have a higher degree of flexibility, facilitating the lactamization, whereas the formation of the seven-member lactone ring from **4** should be more difficult because of the constrain of two dioxolane rings fused to the sugar chain. Thereore, the polymerization of **4** was attempted, using *N*,*N*-dimethylformamide (DMF) as solvent and *N*,*N*'-diisopropylethylamine (DIPEA) to release the amine from its hydrochloride derivative. Analysis of the product isolated from the polycondensation reaction by MALDI-TOF mass spectrometry revealed formation of polymeric species. However, this spectrum exhibited a rather particular pattern of signals (Fig. 1), showing a strong peak at *m/z* = 793.7 and a distribution of less intense signals at higher *m/z* values. These signals were separated, as expected, by 257 mass units, which corresponds to the mass of the repeating unit of an open-chain polyamide. The MS data suggests that **5** is a mixture of oligomers having as major component (~50%) the cyclic trimer ($M + Na^+$, calculated 794.4), and that the minor products are mainly open chain oligomers having *m/z* values from 1100 ($M + Na^+$ + MeOH, tetramer) to 3670 (tetradecamer). In agreement with the MS, the NMR spectra of the mixture **5** showed clearly that the highest signals maintained a good

correlation with the NMR spectra reported for the cyclic trimer of the amino acid **4**, which had been synthesized and isolated by Fleet et al.[29,30] Also, in agreement with our results, they have shown that polycondensation of the free amino acid **6**, under conditions that favored the cyclooligomerization led to the formation of cyclooligomers, being the cyclic trimer the main product. The molecular weight for the linear polymer constituent of **5** was estimated from its MALDI-TOF MS taking into account the *m/z* value of each peak and its relative intensity (M_w = 2028, M_n = 1830, and polydispersity = 1.11).

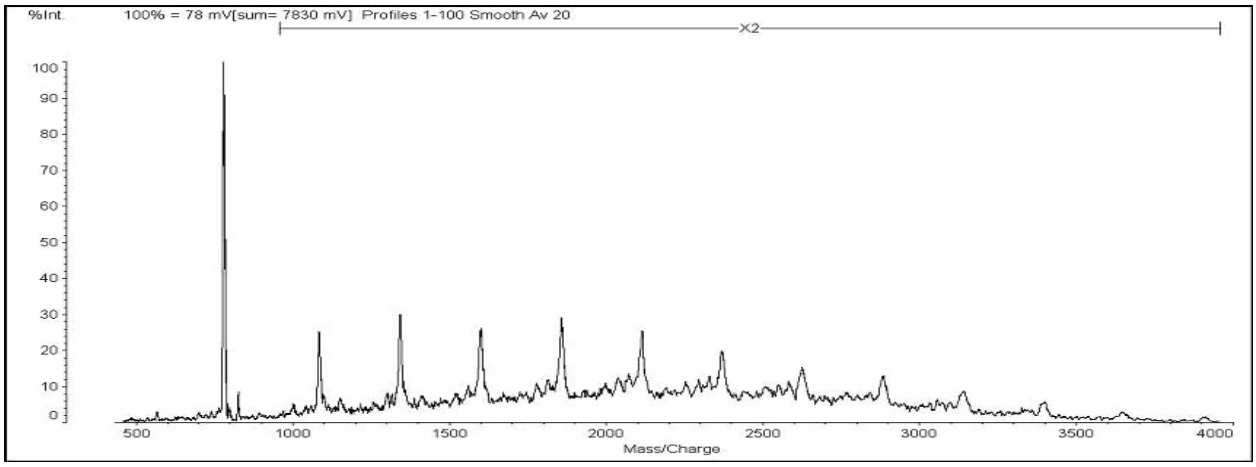
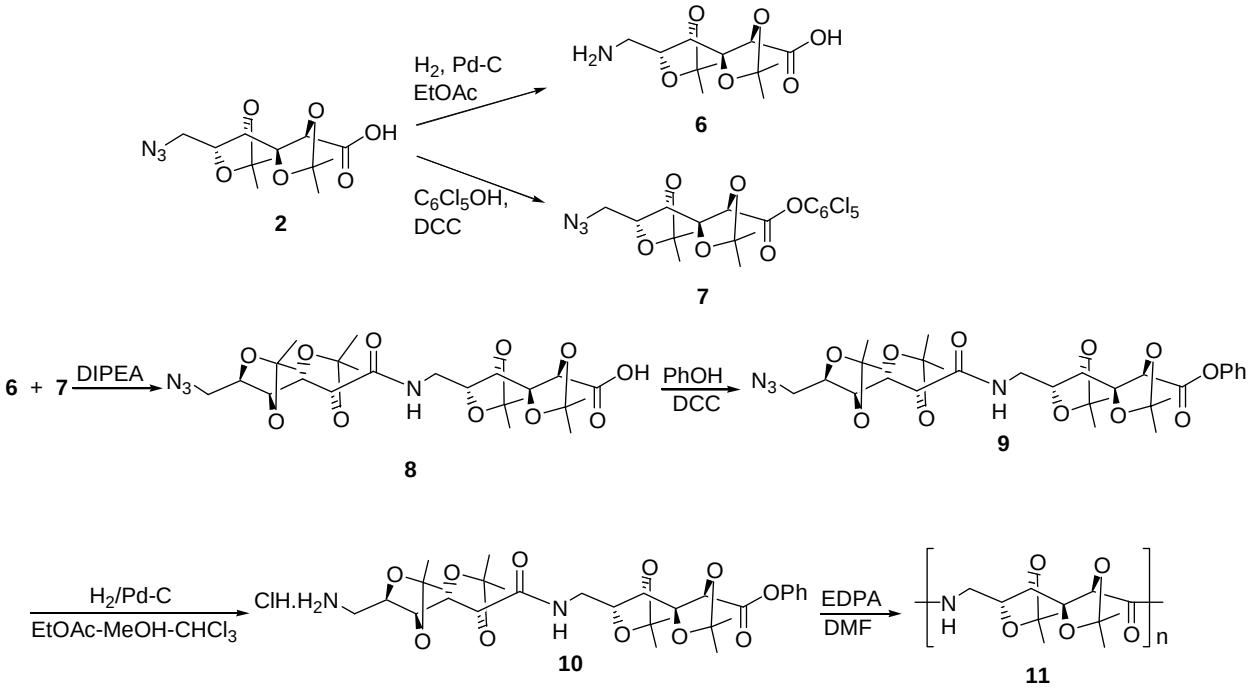


Figure 1. MALDI-TOF Mass Spectrum of 5.

In view of the previous results, we considered that the dimeric amino acid would provide a better opportunity for the preparation of a linear polyamide, as the formation of the cyclic trimer, obtained from the monomer **4**, will be prevented. For the synthesis of the dimer **8**, the hydrochloride derivative of the amino acid **6** was obtained by hydrogenolysis of **2**. The other precursor of the dimmer, the pentachlorophenyl ester **7**, was prepared by treatment of **2** with pentachlorophenol in the presence of DCC. Reaction of the amino group of **6**, using DIPEA as catalyst, with the active ester of **7** gave the expected dimer **8**, which was employed crude for the esterification with phenol. The phenyl ester **9** was obtained as a crystalline product in 51% yield for the two steps.



Scheme 2

Catalytic hydrogenation of **9** in the presence of chloroform afforded the crystalline hydrochloride derivative **10**, the desired amino acid dimer suitable for the homopolycondensation. This reaction was conducted in solution of DMF containing DIPEA for the activation of the amine. The mixture was purified by dilution with CH_2Cl_2 and washing with water. The syrup obtained became solid upon standing, and this product (**11**) was analyzed by MALDI-TOF MS. The mass spectrum showed a distribution of open-chain oligomers having *m/z* values from 1069 (M + Na^+, tetramer) to 4153 (M + Na^+, hexadecamer). As expected, the *m/z* difference between vicinal peaks was 514, which corresponded to the mass of the dimer **10**, once incorporated into the polyamide chain. On the basis of *m/z* values of each peak and its respective intensity the molecular weight of **11** was calculated (M_w = 2288, M_n = 2067, and polydispersity = 1.11). The ^{1}H-NMR spectrum of **11** showed a pattern of signals similar to that of **5**. However, the ^{13}C-NMR spectrum of **5** showed a resonance at 74.9 ppm, signal which was absent in the spectrum of **11**. Interestingly, similar high field resonances (assigned to C-2) were observed for the cyclic trimer[29] (74.95 ppm) and cyclic tetramer[30] (74.4 ppm) derivatives of **6**; whereas in the respective spectra of the linear oligomers, the highest field resonances for carbons bonded to oxygen appeared at 76.5-77.0 ppm.[30] This result seems to bring additional support to the structure assigned for the polycondensation products **5** and **11**.

Finally, the molecular weight of **5** and **11** was determined using size exclusion chromatography (SEC). Interestingly, compound **5** showed a main peak corresponding to M_w = 2546 and a shoulder of lower M_w, in agreement with the composition of the open chain and

cyclic oligomers detected by MS. As expected, SEC of polyamide **11** gave a single peak, from which a M_w = 2700 was calculated, this value was coincident with that determined by MS.

In contrast to regular nylons, polyamide **11** was highly soluble in practically all organic solvents, including chloroform. The enhanced solubility in this solvent is a rather common phenomenon for polyamides derived from carbohydrates.[18,19,25]

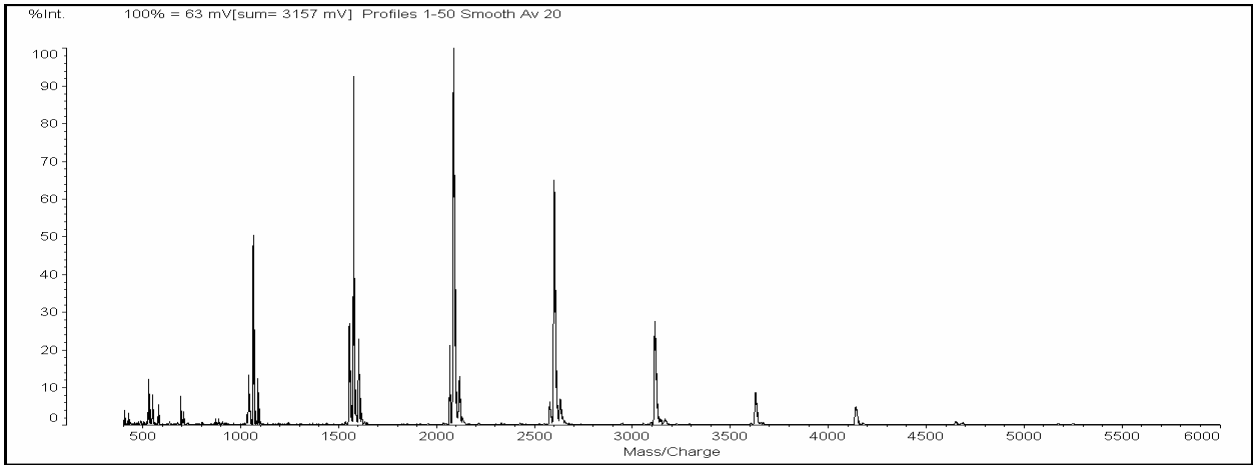


Figure 2. MALDI-TOF Mass Spectrum of **11**.

In summary, we described here convenient procedures for the synthesis of monomeric (**4**) and dimeric (**10**) sugar amino acids as precursors of polyamides. Polymerization of **4** led to a cyclic trimer and linear oligomers, whereas, polymerization of **10** led to the linear polyamide **11**. In both cases the linear polymer constituent of **5** and **11** showed relatively low molecular weights. We can conclude that the substitution pattern in the precursors exerts a strong influence in the molecular weight of the polymer obtained as, under the same conditions, polycondensation of the per-*O*-methyl analog of **10** led to a linear polyamide having a high M_w.[25] Polyamides of the type of **11** possessing readily removable *O*-protecting groups are convenient precursors of analogs of nylon 6 having free hydroxyl groups in their chains.

Experimental Section

General Procedures. Melting points (mp) were determined with a Fisher-Johns apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was performed on 0.2 mm silica gel 60 F_{254} (Merck) aluminum supported plates. Visualization of the spots was effected by charring with a solution of 5% sulfuric acid in EtOH, containing 0.5% *p*-anisaldehyde. Column chromatography was performed with silica gel 60 (230-400 mesh, Merck). Optical rotations were measured with a Perkin-Elmer Model 343 digital polarimeter at 25 ^{o}C in the solvent indicated in each individual case. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AC

200 or Bruker AMX-500 spectrometers. TMS was employed as an internal standard for solutions in $CDCl_3$. Size exclusion chromatography (SEC) was performed at room temperature with a Waters apparatus equipped with a Waters 2414 refractive index detector and Styragel HR (7.8 x 300 mm) Waters columns, using THF as mobile phase. The flow rate was 1mL min^{-1}. Calibration was based on polystyrene standards.

MALDI-TOF-MS Analysis. 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 (λ_{em} = 337 nm; pulse width = 3 ns), tunable PDE and PSD (MS/MS device) modes. Experiments were performed using firstly the full range setting for laser firing position in order to select the optimal position for data collection, and secondly fixing the laser firing position in the sample sweet spots. The samples were irradiated just above the threshold laser power for obtaining molecular ions and with higher laser power for studying cluster formation. Thus, the irradiation used for producing a mass spectrum was analyte-dependent. Usually 100 spectra were accumulated. All samples were measured in the linear and the reflectron modes, and as routine in both the positive- and the negative-ion mode were detected, although no signals corresponding to the oligomers in the negative-ion mode were detected. As the signals of oligomer ions were not enough intense in the reflectron positive-ion mode, PSD experiments were not performed. 2,5-Dihydroxybenzoic acid (DHB, gentisic acid) and 9H-pyrido[3,4-*b*]indole (*nor*-harmane) were employed as matrices. Matrix stock solutions were made by dissolving 2 mg of the selected compound in 0.2 mL of 1:1 (v/v) MeOH-H_2O or in 0.2 mL of 2:3 (v/v) MeCN-H_2O. Analyte solutions were freshly prepared by dissolving the samples (1 mg) in MeOH (0.5 mL). To prepare the analyte-matrix deposit the two methods reported by us were used: method A (thin layer deposit) and method B (mixture method).[31,32] The resulting solid partially crystalline layers were found to be relative homogeneous in both cases. *Nor*-harmane and gentisic acid as matrices showed signals of higher quality by using Method A. The spectra were calibrated by using as external calibration reagents: (a) commercial proteins (neurotensin; insulin) with SA as matrix in positive- or negative-ion mode and (b) α-, β- and γ-cyclodextrins with *nor*-harmane as matrix in positive- or in negative-ion mode. The Kratos Kompact calibration program was used.

6-Azido-6-deoxy-2,3:4,5-di-*O*-isopropyilidene-D-galactonic acid (2). Methyl 6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonate[22] (**1**, 0.50 g, 1.59 mmol) was dissolved in MeOH-water (3:1) and a solution of KOH (0.2 g, 3.57 mmol) in MeOH-water (3:1, 1 mL) was added. The reaction mixture was stirred at room temperature for 3 h, and the solvent was evaporated. The residue was diluted with water (80 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The aqueous phase was acidified with aqueous 5 % HCl to pH 3 and extracted again with CH_2Cl_2 (3 x 50 mL). The organic phase was dried ($MgSO_4$) and concentrated to afford a solid, which was recrystallized from EtOAc-hexane to give **2** (0.47 g, 97%); mp 76 ºC; $[\alpha]_D$ +40.7 (*c* 1.1, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 8.75 (bs, 1H, COO*H*), 4.62 (d, 1H, $J_{2,3}$= 5.5 Hz, H-2), 4.33 (dd,

1H, $J_{3,4}$= 7.2 Hz, H-3), 4.20 (ddd, 1H, $J_{4,5}$= 7.6, $J_{5,6}$= 3.1, $J_{5,6'}$= 4.8 Hz, H-5), 3.99 (t, 1H, H-4), 3.66 (dd, 1H, $J_{6,6'}$= 13.2 Hz, H-6), 3.33 (dd, 1H, H-6'), 1.49, 1.47, 1.44, 1.43 (4s, 12H, C(CH_3)$_2$); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 174.4 (C-1), 112.7, 110.8 (*C*(CH$_3$)$_2$), 79.5, 78.7, 77.8, 77.0 (C-2–5), 51.7 (C-6), 27.1, 26.9, 26.8, 25.9 (C(*C*H$_3$)$_2$). Anal. calcd. for $C_{18}H_{19}N_3O_6$: C, 47.84; H, 6.36; N, 13.95. Found: C, 47.72; H, 6.35; N, 14.07.

Phenyl 6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonate (3). To a solution of **2** (0.50 g, 1.66 mmol) and phenol (0.18 g, 1.90 mmol) in pyridine (5 mL), *p*-toluenesulfonic acid monohydrate (*p*-TSA, 0.017 g, 0.09 mmol) was added[26] and the mixture was stirred at room temperature for 15 min. Upon addition of dicyclohexylcarbodiimide (DCC, 0.48 g, 2.30 mmol) the stirring was continued for additional 24 h, when TLC (hexane-EtOAc 4:1) showed the complete conversion of the starting material (R_f 0.12) into a main spot having R_f 0.57. The mixture was diluted with ethyl ether (80 mL) and filtered. The filtrate was extracted with water (3 x 50 mL) and the organic phase was dried ($MgSO_4$), filtered and concentrated. The residue crystallized from EtOAc-hexane to give pure **3** (0.46 g, 74%); mp 60 ºC; $[\alpha]_D$ +8.9 (*c* 1.3, $CHCl_3$); ^{1}H -NMR (200 MHz, $CDCl_3$) δ: 7.46-7.07 (m, 5H, H-aromatic), 4.77 (d, 1H, $J_{2,3}$= 5.3 Hz, H-2), 4.44 (dd, 1H, $J_{3,4}$= 7.7 Hz, H-3), 4.22 (ddd, 1H, $J_{4,5}$= 7.5, $J_{5,6}$= 3.1, $J_{5,6'}$= 4.9 Hz, H-5), 4.01 (t, 1H, H-4), 3.68 (dd, 1H, $J_{6,6'}$= 13.2 Hz, H-6), 3.35 (dd, 1H, H-6'), 1.50 (x3), 1.43 (2s, 12H, C(CH_3)$_2$); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 169.4 (C-1), 150.4, 129.5, 126.2, 121.1 (C-aromatic), 112.7, 110.6 (*C*(CH$_3$)$_2$), 80.3, 79.1, 77.9, 77.8 (C-2–5), 51.9 (C-6), 27.3, 27.0 (x2), 26.1 (C(*C*H$_3$)$_2$). Anal. calcd. for $C_{18}H_{23}N_3O_6$: C, 57.29; H, 6.14; N, 11.13. Found: C, 57.36; H, 6.17; N, 11.09.

Phenyl 6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonate hydrochloride (4). Compound **3** (0.10 g, 0.19 mmol) in a solution of EtOAc-MeOH-$CHCl_3$ (1.0:0.1:0.2; 4 mL) was hydrogenated at 30 psi in the presence of 10% Pd-C. After 4 h the catalyst was filtered and the mixture was concentrated to give **4** as a crystalline, hygroscopic product. Recrystallization from EtOAc afforded pure **4** (0.95 g, 93%), mp 172 ºC (dec.); $[\alpha]_D$ –24.6 (*c* 1.0, DMSO); ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 8.32 (bs, 2H, NH_2), 7.45 (dd, 2H, *J* = 7.8, *J* = 7.5 Hz, H-aromatic), 7.30 (t, 1H, *J* = 7.5 Hz, H-aromatic), 7.19 (d, 2H, *J* = 7.8 Hz, H-aromatic), 4.84 (d, 1H, $J_{2,3}$= 5.4 Hz, H-2), 4.57 (dd, 1H, $J_{3,4}$= 6.7 Hz, H-3), 4.29 (m, 1H, H-5), 4.08 (t, 1H, $J_{4,5}$= 6.9 Hz, H-4), 3.10 (m, 1H, H-6), 3.04 (m, 1H, H-6'), 1.48, 1.44, 1.43, 1.40 (4s, 12H, C(CH_3)$_2$); ^{13}C-NMR (50.3 MHz, DMSO-d_6) δ: 169.2 (C-1), 150.0, 129.6, 126.2, 121.4 (C-aromatic), 111.9, 110.2 (*C*(CH$_3$)$_2$), 79.0, 78.0, 76.5, 75.5 (C-2–5), 41.0 (C-6), 27.0 (x2), 26.8, 26.0 (C(*C*H$_3$)$_2$). Anal. calcd. for $C_{18}H_{26}NO_6Cl$: C, 55.75; H, 6.76; N, 3.61. Found: C, 55.57; H, 6.70; N, 3.54.

Polycondensation of 4. To a solution of **3** (0.16 g, 0.40 mmol) in DMF (0.2 mL), *N*,*N*-diisopropylethylamine (DIPEA, 0.1 mL, 0.60 mmol) was added. The reaction mixture was stirred at room temperature for 7 days under Ar atmosphere, and then concentrated. The residue was diluted with CH_2Cl_2 (30 mL) and the solution washed with water (2 x 30 mL). The organic layer was dried ($MgSO_4$) and concentrated to afford **5** (0.086 g, 64%), as a syrup that became solid upon standing; ^{1}H-NMR (500 MHz, CD_3CN) δ: 7.01 (bs, N*H*), 4.52-4.38 (H-2), 4.32-4.21 (H-3,5), 4.15 and 3.98-3.92 (H-4), 3.60-3.39 (H-6,6'); ^{13}C-NMR (125.7 MHz, CD_3CN) highest

peaks: δ: 171.1 (C-1), 111.3, 109.7 (Me_2CO), 79.3-78.5, 77.0-76.2, 75.5, 74.9, 42.1, 40.6, 27.1-25.5; MALDI-TOF MS: see Fig. 1.

6-Amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonic acid (6). Compound **2** (1.00 g, 3.32 mmol) was dissolved in EtOAc (15 mL) and hydrogenated at 42 psi for 8 h in the presence of 10% Pd-C. The catalyst was filtered off and the filtrate was concentrated to a solid, which was recrystallized from MeOH to give pure **6** (0.74 g, 81%); mp 223 ºC (dec.); $[\alpha]_D$ –3.6 (*c* 0.9, H_2O); ^{1}H-NMR (500 MHz, D_2O) δ: 4.36 (dd, 1H, $J_{2,3}$= 6.4, $J_{3,4}$= 4.4 Hz, H-3), 4.35 (ddd, 1H, $J_{4,5}$= 7.8, $J_{5,6}$= 3.1, $J_{5,6'}$= 8.8 Hz, H-5), 4.26 (d, 1H, H-2), 4.11 (dd, 1H, H-4), 3.30 (dd, 1H, $J_{6,6'}$= 13.5 Hz, H-6), 3.18 (dd, 1H, H-6'), 1.34 (x3), 1.27 (2s, 12H, $C(CH_3)_2$); ^{13}C-NMR (125.7 MHz, D_2O) δ: 177.8 (C-1), 112.2, 112.0 ($C(CH_3)_2$), 79.0, 78.9, 77.9, 74.8 (C-2–5), 42.5 (C-6), 26.9, 26.7 (x2), 25.6 ($C(CH_3)_2$). Anal. calcd. for $C_{12}H_{21}NO_6.0.5H_2O$: C, 50.67; H, 7.74; N, 4.93. Found: C, 51.34; H, 7.59; N, 5.05.

Pentaclorophenyl 6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonate (7). To a solution of **2** (0.60 g, 1.99 mmol) in dry EtOAc (11 mL), pentachlorophenol (0.70 g, 2.60 mmol) and DCC (0.55 g, 2.60 mmol) were added and the mixture was stirred overnight at room temperature. TLC (hexane) showed the complete conversion of the starting material (R_f 0.0) into a main UV-active spot (R_f 0.32). The suspension was filtered and the filtrate was concentrated to a syrup which was purified by column chromatography (hexane). Crystalline **7** (0.69 g, 92%) was obtained and recrystallized from MeOH; mp 95 ºC; $[\alpha]_D$ –5.2 (*c* 1.3, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.94 (d, 1H, $J_{2,3}$= 5.0 Hz, H-2), 4.60 (dd, 1H, $J_{3,4}$= 7.5 Hz, H-3), 4.23 (ddd, 1H, $J_{4,5}$= 7.5, $J_{5,6}$= 3.2, $J_{5,6'}$= 4.9 Hz, H-5), 4.04 (t, 1H, H-4), 3.69 (dd, 1H, $J_{6,6'}$= 13.2, H-6), 3.37 (dd, 1H, H-6'), 1.53, 1.51, 1.50, 1.42 (4s, 12H, $C(CH_3)_2$); ^{13}C-NMR (125.7 MHz, $CDCl_3$) δ: 166.9 (C-1), 143.5, 132.2, 132.1 (C-aromatic), 113.5, 110.8 ($C(CH_3)_2$), 80.1, 79.0, 78.0, 77.4 (C-2–5), 51.9 (C-6), 27.4, 27.0 (x2), 26.1 ($C(CH_3)_2$). Anal. calcd. for $C_{18}H_{18}O_6N_3Cl_5$: C, 39.34; H, 3.30; N, 7.65; Cl, 32.25. Found: C, 39.53; H, 3.24; N, 7.46; Cl, 31.99.

6-*N*-(6′-Azido-6′-deoxy-2′,3′:4′,5′-di-*O*-isopropylidene-D-galactonyl)-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonic acid (8) and conversión into the phenyl ester 9. To a solution of **7** (1.47 g, 2.69 mmol) in DMF (15 mL) a solution of **6** (0.74 g, 2.69 mmol) in DMF (15 mL) and DIPEA (0.70 mL, 4.20 mmol) were added. After stirring at room temperature for 16 h, TLC (EtOAc) showed the conversion of **7** (R_f 0.93) into the more polar product (R_f 0.19). The mixture was concentrated and the residue was dissolved in sat. aq. $NaHCO_3$ (100 mL). The solution was extracted with CH_2Cl_2 (3 x 100 mL) and the aqueous phase was acidified with HCl (10%) to pH 3, and extracted with CH_2Cl_2 (3 x 100 mL). The organic extract was dried ($MgSO_4$), filtered and concentrated to afford **8** as a colorless syrup. This product was used for the next step without further purification.

To a solution of crude **8** (0.56 g, 1.00 mmol) and phenol (0.14 g, 1.49 mmol) in anhydrous pyridine (7 mL) *p*-TSA monohydrate (0.01 g, 0.05 mmol) was added[26] and the solution was stirred at room temperature for 15 min. Upon addition of DCC (0.39 g, 1.80 mmol) the stirring was continued overnight. Monitoring of the reaction mixture by TLC (EtOAc) showed the conversion of **8** (R_f 0.10) into a main spot (R_f 0.80). The mixture was diluted with water

(100 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated. Purification of the residue by column chromatography (hexane-EtOAc 5:1) afforded phenyl 6-*N*-(6'-azido-6'-deoxy-2',3':4',5'-di-*O*-isopropylidene-D-galactonyl)-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonate (**9**, 0.37 g, 51%, 2 steps) as a colorless syrup which crystallized from EtOAc-hexane; mp 176ºC (dec.); $[\alpha]_D$ +4.1 (*c* 0.6, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.46-7.10 (m, 5H, H-aromatic), 6.97 (t, 1H, $J_{6a,NH} \cong J_{6b,NH}$= 5.5 Hz, N*H*), 4.77 (d, 1H, $J_{2,3}$= 5.5 Hz, H-2), 4.51 (d, 1H, $J_{2',3'}$= 6.1 Hz, H-2'), 4.47 (dd, 1H, $J_{3,4}$= 7.4 Hz, H-3), 4.32 (ddd, 1H, $J_{4',5'}$= 8.1, $J_{5',6'a}$= 3.3, $J_{5',6'b}$= 4.7 Hz, H-5'), 4.30 (dd, 1H, $J_{3',4'}$= 5.2 Hz, H-3'), 4.17 (ddd, 1H, $J_{4,5}$= 7.3, $J_{5,6a}$= 4.6, $J_{5,6b}$= 5.7 Hz, H-5), 4.12 (dd, 1H, H-4'), 3.82 (t, 1H, H-4), 3.67-3.56 (m, 3H, H-6_a, H-6'$_a$, H-6_b), 3.33 (dd, 1H, $J_{6'a,6'b}$= 13.2 Hz, H-6'$_b$), 1.53, 1.51, 1.49 (x2), 1.45 (x2), 1.42, 1.41 (6s, 24H, C(C*H*$_3$)$_2$); ^{13}C-NMR (125.7 MHz, $CDCl_3$) δ: 170.8, 169.4 (C-1,1'), 150.4, 129.5, 126.2, 121.1 (C-aromatic), 112.8, 111.4, 110.3, 110.1 (*C*(CH$_3$)$_2$), 80.0, 79.1 (x2), 78.3, 77.7, 77.6, 77.4, 76.9 (C-2,2',3,3',4,4',5,5'), 51.7 (C-6'), 40.8 (C-6), 27.3, 27.2, 27.0 (x2), 26.9, 26.8, 26.1, 26.0 (C(*C*H$_3$)$_2$). Anal. calcd. for $C_{30}H_{42}O_{11}N_4$: C, 56.77; H, 6.67. Found: C, 57.16; H, 6.88.

Phenyl 6-*N*-(6′-amino-6′-deoxy-2′,3′:4′,5′-di-*O*-isopropyilidene-D-galactonyl)-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonate hydrochloride (10). Compound **9** (0.27 g, 0.43 mmol) was dissolved in EtOAc/MeOH/$CHCl_3$ (10:1:2, 6.6 mL) and hydrogenated at 30 psi for 5 h in the presence of 10% Pd-C. The catalyst was filtered and the filtrate was concentrated to a solid that crystallized from MeOH-ethyl ether, to afford **10** (0.19 g, 69%); mp 176ºC (dec.); $[\alpha]_D$ −10.0 (*c* 0.6, $CHCl_3$); ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 8.18 (bs, 2H, N*H*$_2$), 8.09 (t, 1H, $J_{6a,NH}$= $J_{6b,NH}$= 5.8 Hz, CON*H*), 7.45 (dd, 2H, *J* = 7.7, *J* = 7.3 Hz, H-aromatic), 7.30 (t, 1H, *J* = 7.3 Hz, H-aromatic), 7.17 (d, 2H, *J* = 7.7 Hz, H-aromatic), 4.81 (d, 1H, $J_{2,3}$ = 5.5 Hz, H-2), 4.50 (dd, 1H, $J_{3,4}$= 6.5 Hz, H-3), 4.35 (d, 1H, $J_{2',3'}$= 6.3 Hz, H-2'), 4.28 (dd, 1H, $J_{3',4'}$= 5.3 Hz, H-3'), 4.26 (m, 1H, H-5'), 4.15 (m, 1H, H-5), 4.02 (dd, 1H, $J_{4',5'}$= 7.5 Hz, H-4'), 3.97 (t, 1H, $J_{4,5}$= 6.5 Hz, H-4), 3.44 (ddd, 1H, $J_{5,6a}$= 5.5, $J_{6a,6b}$= 13.7 Hz, H-6a), 3.38 (ddd, 1H, $J_{5,6b}$= 5.9 Hz, H-6b), 3.09 (dd, 1H, $J_{5',6'a}$= 2.7, $J_{6'a,6'b}$= 13.4 Hz, H-6'a), 2.98 (dd, 1H, $J_{5',6'b}$= 8.8 Hz, H-6'b), 1.44, 1.41(x2), 1.39, 1.37, 1.36, 1.34, 1.33 (7s, 24H, C(C*H*$_3$)$_2$); ^{13}C-NMR (125.7 MHz, DMSO-d_6) δ: 169.8, 169.4 (C-1,1'), 150.0, 129.6, 126.2, 121.4 (C-aromático), 111.7, 110.6, 109.9, 109.4 (*C*(CH$_3$)$_2$), 79.2, 78.5, 78.1, 77.8, 77.2, 76.6, 76.2, 74.6 (C-2, 2', 3, 3', 4, 4', 5, 5'), 41.1, 40.9, (C-6, 6'), 27.4, 27.0, 26.9 (x2), 26.8, 26.7, 25.9, 25.8 (C(*C*H$_3$)$_2$). Anal. calcd. for $C_{30}H_{45}O_{11}N_2Cl.H_2O$: C, 54.41; H, 7.15. Found: C, 54.34; H, 7.28.

Polycondensation of 10. Synthesis of Poly(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonic acid) (11). To a solution of **10** (0.19 g, 0.30 mmol) in dry DMF (0.2 mL) DIPEA (0.07 mL) was added under Ar, and the mixture stirred at room temperature for 7 days. The mixture was concentrated, then diluted with CH_2Cl_2 (50 mL) and the resulting solution was washed with water (20 mL, twice). The organic extract was dried ($MgSO_4$) and concentrated to a syrup, which solidified on standing at room temperature to aford **11** (0.09 g, 60%); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.01 (bs, N*H*CO), 4.51-4.45 (H-2), 4.32-4.24 (H-3, 5), 3.81-3.95 (H-4), 3.65-3.50 (H-6, 6'), 1.47-1.41 ((C*H*$_3$)$_2$CO); ^{13}C-NMR (125.7 MHz, $CDCl_3$) highest signals = δ:

170.7 (C-1), 111.3, 109.8 ($(CH_3)_2CO$), 78.9, 78.6, 76.8, 76.3, 40.4, 27.2, 26.9, 26.7, 26.0; MALDI-TOF MS: see Fig. 2.

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