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Synthesis of stereoregular poly-*O*-methyl-D- and L-polygalactonamides as nylon 6 analogues

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Abstract—Conveniently activated dimers: (pentachlorophenyl 6-(6′-(*tert*-butoxycarbonylamino)-6′-deoxy-2′,3′,4′,5′-tetra-*O*-methyl-D-galactonamide)-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-galactonate) **7** and its analogue in the L-series **16**, were prepared, respectively, from 6-amino-6-deoxy-D- and L-galactonic acid derivatives **5** and **14**. Upon release of the amino function of **7** under acidic conditions, polymerization was conducted in a non-polar ($CHCl_3$) or a polar solvent (DMF) affording poly(6-amino-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-galactonic acid) **11**. Similarly, polymerization in DMF from **16** gave the polygalactonamide **18** (L-series). The polyamides were characterized by IR and NMR spectroscopies. The latter technique was also employed for establishing the conformation of **11** in $CDCl_3$ solution. Molecular weights (about 11,000) were estimated by viscosimetry and size exclusion chromatography. Polygalactonamides **11** and **18** were highly hygroscopic and soluble in a variety of organic solvents, including chloroform. The thermal behavior of the polyamides was also studied.

1. Introduction

In recent years, the synthesis of polyamides more hydrophilic and degradable than the industrial nylons has attracted considerable attention. Biodegradable polymers are in general environmentally friendly[1] and have found biomedical applications, such as in medical devices[2] and in controlled delivery of drugs.[3] For the preparation of these promising materials, renewable natural resources are being employed. The degradation products of polymers made of natural occurring building blocks are usually non-toxic and can be metabolized properly by living tissues.[4,5] Considering this point of view, carbohydrates stand out as highly convenient precursors of polymers that contain several stereocenters in the main chain.[6,7] Thus, polyhydroxylated analogues of nylon 6,6 and related compounds have been prepared by condensation of diamines with aldaric acid derivatives.[6,8] In this way, stereoregular[9,10] and non-stereoregular polyaldaramides[11–13] have been prepared. Also, derivatives of 1,6-diamino-1,6-dideoxy-D-mannitol and L-iditol have been employed for the synthesis of regioregular linear polyamides.[14] The stereoregularity of these AABB-type polyamides relies upon the existence of a C_2 axis of symmetry in the starting sugar-derived monomers; otherwise the occurrence of regioisomerism during the polycondensation leads to aregic polymers.[15] In contrast, AB-type polyaldonamides are stereoregular regardless of the configuration of the monomer. This kind of polyamide has been prepared by polycondensation of amino acids derived from pentoses[16] and hexoses.[17] Among the varied applications of sugar amino acids,[18] 6-amino-6-deoxyaldonic acids can be considered as convenient monomers for the construction of hydroxylated analogues of nylon 6. We have recently reported[19] a straightforward route to 6-amino-6-deoxy-2,3,4,5-tetra-*O*-methyl-D- and L-galactonic acids, which was an improvement of a synthesis previously described by us.[20] Herein we report the use of derivatives of these sugar amino acids as precursors of well-defined, enantiomerically pure, and stereoregular polygalactonamides.

2. Results and discussion

The convenient building block 6-azido-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-galactonic acid **1** was readily prepared starting from D-galactono-1,4-lactone.[19] Catalytic hydrogenation of the azide function of **1** in the presence of di-*tert*-butyldicarbonate (Boc_2O) afforded **2**, the

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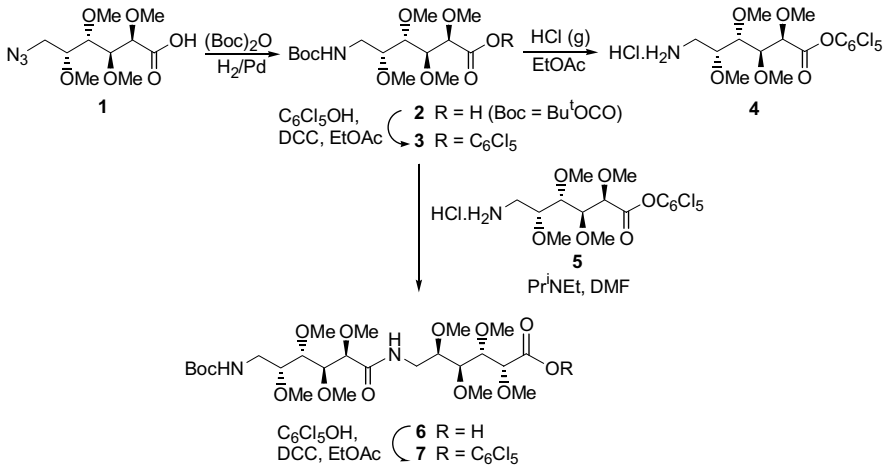
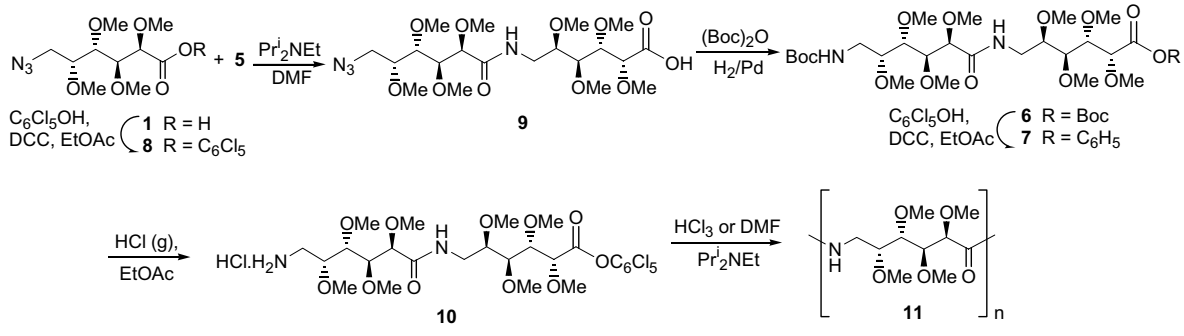


Scheme 1.

N-Boc derivative of the corresponding amine (Scheme 1). The carboxylic acid group of **2** was converted into the pentachlorophenyl ester by dicyclohexylcarbodiimide (DCC)-promoted condensation with pentachlorophenol. The ester group of the resulting derivative **3** was suitably activated for the polycondensation, and the amine was deprotected from the *N*-Boc derivative by hydrolysis with a saturated solution of hydrogen chloride in EtOAc. The hydrochloride derivative **4** was obtained as a crystalline product that showed NMR spectral data in full agreement with the proposed structure. Thus, the ^{13}C NMR spectrum of **4** exhibited the resonances for the carbons bonded to oxygen (76.5–80.3 ppm), the four signals for the methoxyl carbons (59.0–61.0 ppm) and the signals of the aromatic carbons of pentachlorophenyl. The resonances of the carbonyl and methylene (CH_2–N) carbons appeared at 167.7 and 39.8 ppm, respectively.

The polymerization of **4**, upon releasing of the amino group from the hydrochloride with *N*,*N*-diisopropylethylamine (DIPEA) was unsuccessful, as TLC examination of the reaction mixture showed several spots. Also, the ^{13}C NMR spectrum of the product was rather complex, and suggested the formation of oligomers. In fact, linear[21] and cyclic oligomers[22,23] and lactams[16,17,24] have been reported to be formed in the polycondensation of sugar-derived amino acids. However, successful polymerizations of such amino acids have been accomplished when linear dimers of the repeating unit were employed as precursors of polymers.[16,17] Therefore, the active ester **3**, having the amino group protected, was allowed to react with 6-amino-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-galactonic acid **5**, which was prepared by hydrogenation of **1** followed by alkaline hydrolysis of the methyl ester.[19] As the resulting dimeric carboxylic acid **6** was quite difficult to purify, it was converted directly into the pentachlorophenyl ester **7**, by condensation with pentachlorophenol using DCC as coupling reagent. As the sequence **1**→**3**→**7** took place with a low overall yield (18%), an alternative procedure for the synthesis of **7** from **1** was attempted.

Compound **1** was esterified with pentachlorophenol to give **8** (Scheme 2). The active ester of **8** reacted with the amino acid **5** to afford dimeric 6-(6′-azido-6′-deoxy-2′,3′,4′,5′-tetra-*O*-methyl-D-galactonamide)-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-galactonic acid **9** in good yield (62% from **1**). The ^1H NMR spectrum (500 MHz) of **9** allowed a first order analysis; the assignments were confirmed by 2D COSY H,H experiments. The coupling constant values for the protons of the chain are indicative that both units in the dimer **9** are found in the extended planar zigzag conformation, and shows only some conformational instability for the C-5–C-6 (and C-5′–C-6′) bonds, according to the averaged values observed for $J_{5,6a}$, $J_{5,6b}$, $J_{5',6'a}$, $J_{5',6'b}$. Analogous open-chain derivatives having the galacto



Scheme 2.

configuration usually adopt the planar zigzag form, which is free of 1,3-parallel interactions.[25]

Catalytic hydrogenation of the azide function of **9** in the presence of di-*tert*-butyldicarbonate gave the *N*-Boc derivative **6**. The carboxylic acid group of **6** was activated with DCC and condensed with pentachlorophenol to afford the pentachlorophenyl ester **7**, in an overall yield higher than that in the previous route (40% from **1**).

Hydrolysis of the *N*-Boc protecting group of **7** with a saturated solution of hydrogen chloride in EtOAc afforded the hydrochloride derivative **10**. The polymerization of **10** was conducted in both chloroform and DMF as solvents, and DIPEA was employed to release the amino group from the hydrochloride salt and as a catalyst of the polycondensation. The resulting polymers were purified by evaporation of the reaction solvents, dissolution in dichloromethane and precipitation with dry ethyl ether. Polyamides **11** obtained from $CHCl_3$ or DMF exhibited identical NMR and IR spectra. The ^1H NMR spectrum showed four singlets of methoxyl groups, and the signals of the hydrogens of the chain could be readily assigned with the aid of homonuclear 2D COSY experiments. The full assignment of the spectrum was necessary to conduct structural studies, as discussed later. The ^{13}C NMR spectrum of **11** showed at higher field the signal of C-6 bonded to nitrogen that, as expected for a methylene carbon, appeared with inverse phase in the DEPT experiment. The signals of the carbons bonded to oxygen appeared between 81.4 and 77.7 ppm, and the methoxyl carbons between 60.3 and 57.6 ppm; whereas C-1 (carbonyl of amide) resonates at 171.4 ppm. The IR spectrum of **11** exhibited the characteristic amide absorption bands at 3419 (NH stretch), 1661 (amide I) and 1529 cm^{-1} (amide II).

Comparative data for polyamides **11**, synthesized by polycondensation in $CHCl_3$ or DMF, are shown in Table 1. The use of DMF resulted in a better yield of **11**, which may be attributed to the formation of longer polymer chains in such a solvent. Oligomeric products, probably formed in $CHCl_3$ could remain soluble during the precipitation of **11** from a CH_2Cl_2 solution upon addition of ethyl ether, lowering the yield. In agreement with this explanation, molecular weights estimated by size exclusion chromatography (SEC) were similar for both purified polymers. Also, a comparable value of molecular weight ($M_v = 10{,}000$) was calculated from the intrinsic viscosity of **11** (DMF) by applying the Mark-Howink equation ($\eta = 2.9 \times 10^{-4}\ M^{0.78}$) reported for nylon 6.[26]

Table 1. Some data for polygalactonamides **11** and **18**

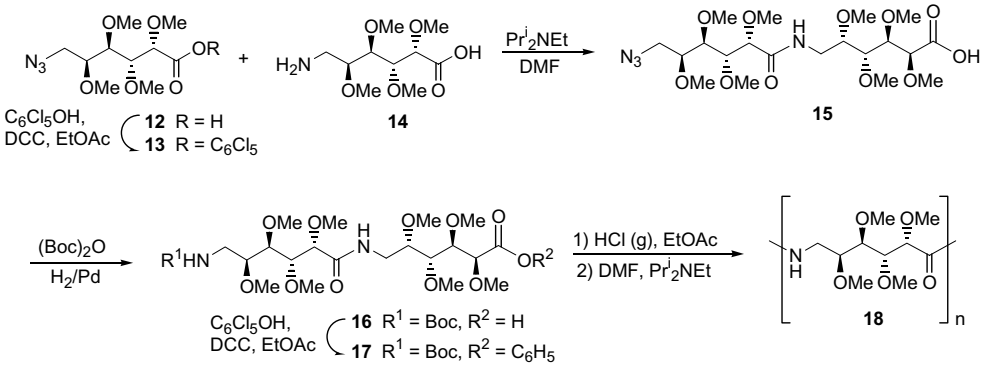
Polyamide	Polymerization solvent[a]	Yield[b] (%)	$[\alpha]_D$	M_w[c]	T_m
11	DMF	89	+72.0	11,000	187
11	$CHCl_3$	61	+71.5	11,500	187
18	DMF	85	−72.2	10,500	180

[a] Polymerizations were conducted under the same conditions (20 °C for 8 days).
[b] Isolated yield of the polyamide from the respective dimeric precursor.
[c] Determined by SEC.

The thermal behavior of polyamide **11** was investigated by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). The thermogram for the first heating cycle of **11** (obtained from DMF) showed two endotherms at 138 and 187 °C. These two transitions may be attributed to the melting of populations of crystallites differing in size, a rather common phenomenon among polyamides that crystallize from solution.[27] Additionally, when the sample was heated to 160 °C, slowly cooled to room temperature and subjected to a second cycle of heating, a single endotherm at 187 °C ($\Delta H = 72.6$ J/g) was observed. The width of the peak was considerably narrow (12 °C) indicating a low degree of microstructural heterogeneity. However, no such endotherm was observed when the sample was heated to 210 °C, cooled and slowly heated again, suggesting that some decomposition takes place at the melting temperature. This was confirmed by TGA, which showed that the onset of decomposition started at 170 °C and finished at 275 °C, with a weight loss of 18%.

In order to obtain a polygalactonamide enantiomeric of **11**, the polymerization of 6-amino-6-deoxy-2,3,4,5-tetra-*O*-methyl-L-galactonic acid **14** was conducted. The same route as that described for the synthesis of **11** was followed. Thus, condensation of **14** with the pentachlorophenyl ester **13** gave the dimeric acid **15** (Scheme 3). Reduction of the azide function of **15** in the presence of di-*tert*-butyldicarbonate, followed by esterification with pentachlorophenol gave **17** (42% from **13**). After removal of the *N*-Boc protecting group with HCl/EtOAc, the resulting dimeric amino acid hydrochloride was polymerized in a DMF solution containing DIPEA, to give the polygalactonamide **18**. This polyamide showed identical IR and NMR spectra as **11**. The molecular weight and thermal behavior of **18** and **11** were also similar (Table 1). As expected, the specific rotation of **18** was almost identical in absolute value and opposite in sign compared to that of **11**. Furthermore, as observed for other stereoregular chiral polyamides,[15] **11** and **18** displayed a much higher absolute value of specific rotation compared with their respective precursors **7** and **17**.

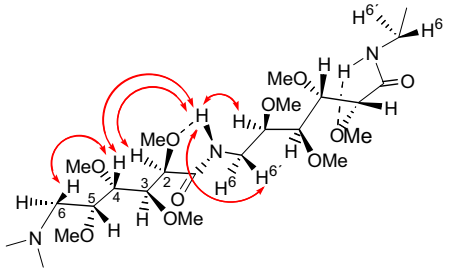
Polyamides **11** and **18** were highly hygroscopic solids, and soluble in organic solvents, such as chloroform, DMF and DMSO as well as in common polyamide solvents, like formic acid and dichloroacetic acid. Solubility in chloroform is remarkable as this behavior is unusual in conventional nylons, but it is rather common for stereoregular polyamides containing stereocenters in the chain.[16,17,28] As the solubility of chiral polyamides in chloroform has been attributed to the formation of ordered helical structures stabilized by intramolecular hydrogen bonds,[29] we decided to investigate the conformation of **11** in $CDCl_3$ solution by NMR spectroscopy. The chemical shift of amide protons are sensitive to hydrogen bonding formation, which results in a shifting of the signal to higher frequencies. In a non-polar organic solvent, such as chloroform, model amides have



Scheme 3.

shown molecular shifts around 6 ppm for non-hydrogen-bonded NH protons and around 8 ppm for amide–amide H-bonded NH protons.[30] For example, NH bonds of carbopeptoids engaged in hydrogen-bonding showed δ_{NH} higher than 8 ppm.[31] In the ^{1}H NMR spectrum of **11**, recorded in $CDCl_3$ at 25 °C, the amide proton resonates at 7.17 ppm. Interestingly, this signal was strongly deshielded (δ 8.02) when the spectrum was recorded in DMSO-d_6 indicating that any intramolecular hydrogen bonding in the polyamide should be weak enough to be disrupted by the polar solvent. As the temperature dependence of the amide proton chemical shift can be employed as a tool for detecting hydrogen bonding,[32] variable temperature NMR experiments were conducted for polyamide **11**. From the plot of the amide proton chemical shift as a function of temperature, the reduce temperature constant ($-\Delta\delta/\Delta T$) was calculated. The small value obtained ($-\Delta\delta/\Delta T = 2.1$ ppb/K) indicated a small change in the NH protons chemical environment with temperature.[30] All these results seem to indicate that the amide proton of **11** experiences little or no amide–amide hydrogen bonding.

Further structural information was obtained from the NOESY spectrum of **11**, which showed cross-peaks for the NH proton with many other protons of the hydrocarbon backbone. Particularly interesting were the cross-peaks between N*H*–H-2 and N*H*–H-4. Among all the possible rings that can be formed by hydrogen bonding between the amide proton and the methoxy groups, the five-membered ring, which involves the methoxy group at C-2 of the adjacent residue, is in a better agreement with the detected NOEs (Scheme 4). The formation of the hydrogen-bonded five-membered ring promotes an arrangement of the polyamide chain that brings closer in space H-2, H-4, H-5, and H-6′ to the N*H* proton, justifying the NOEs observed. In such an arrangement, according to the coupling constants measured, each repeating unit of **11** maintains basically the extended zigzag conformation found for open-chain derivatives of galactose.[25] Additionally, the conformation proposed for **11** accounts for the deshielding of H-6, which is shifted at an even higher frequency than H-2 (vicinal to the carbonyl). As depicted in Scheme 4, H-6 is located in the same plane of the carbonyl and experiences its anisotropic deshielding effect. In contrast,



Scheme 4. Correlations observed in the NOESY spectrum of **11**.

the other methylene proton (H-6′) which is oriented almost perpendicularly to the carbonyl plane, is the more shielded proton in the spectrum of **11**. Moreover, the coupling constant values for the amide proton clearly indicated that this proton adopts an antiperiplanar disposition with respect to H-6 ($J = 7.5$ Hz), whereas is *gauche* to H-6′ ($J = 2.9$ Hz). The mentioned shielding and deshielding effects detected for the polyamide **11** were not observed in monomeric precursors such as **3** and **4**.

3. Conclusions

Herein we report the synthesis of dimers of per-*O*-methyl-6-amino-6-deoxy-D- and L-galactonic acids. Ester active derivatives of the dimers were successfully polymerized in solvents of different polarity. The resulting polygalactonamides **11** and **18** were fully characterized. They were enantiomerically pure compounds (no isomerization occurred during the polymerizations) and soluble in a variety of solvents, including chloroform. Studies on the conformation of **11** in $CDCl_3$ solution by NMR spectroscopy provided no evidence of secondary structures formed by amide–amide hydrogen bonding. Instead, a weak intramolecular hydrogen bond seems to be formed between the amide proton and the methoxy group at C-2. In contrast, amide–amide hydrogen bonding was detected for linear oligomers of isopropylidene derivatives of 6-amino-6-deoxy-D-galactonic acid.[23] These oligomers adopt a rigid structure comparable to the β-sheet of peptides; whereas a diasteromeric D-allonate showed no formation of ordered structures.[21] These results demonstrate that the solution conforma-

tion of polyaldonamides is strongly influenced by the stereochemistry and substitution pattern of the constituent sugar amino acids.

4. Experimental

4.1. 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 solution 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 with a Bruker AMX 500 instrument (^{1}H 500 MHz, ^{13}C 125.3 MHz), in $CDCl_3$ solutions (tetramethylsilane as internal standard) unless otherwise indicated. For those fully assigned ^{1}H NMR spectra, 2D COSY experiments were conducted and for the assignment of the ^{13}C NMR spectra, DEPT techniques were employed. Size exclusion chromatography (SEC) was performed at room temperature with a Waters apparatus equipped with a Waters 2414 refractive index detector and Styragel HR (7.8×300 mm) Waters columns, using THF as mobile phase. To make polyamides soluble in this solvent, they were trifluoroacetylated by the method of Schulz et al.[33] The flow rate was 1 mL min^{-1}. Calibration was based on polystyrene standards. Melting points were determined by DSC using a Shimadzu DSC-50, calibrated with alumina. Samples of about 2–3 mg were heated at a rate of 10 °C min^{-1} and cooled to room temperature. The peak temperatures were taken as melting points. Thermogravimetric analysis (TGA) was conducted in a Shimadzu TGA-51. IR spectra (films) were recorded with a Nicolet 510P FT-IR spectrometer.

4.2. Pentachlorophenyl 6-(*tert*-butoxycarbonyl)amino-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-galactonate 3

To a suspension of 6-azido-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-galactonic acid[19] **1** (0.35 g, 1.26 mmol) in EtOAc (3 mL) was added methanol until complete dissolution. Upon addition of di-*tert*-butyldicarbonate ($(Boc)_2O$, 0.32 g, 1.40 mmol) the mixture was hydrogenated at room temperature and 45 psi in the presence of 10% Pd–C (10 mg) for 5 h. The catalyst was filtered and the filtrate concentrated to give syrupy 6-(*tert*-butoxycarbonyl)amino-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-galactonic acid (**2**, 0.38 g). Crude **2** (0.38 g) dissolved in EtOAc (7 mL) was treated with pentachlorophenol (0.41 g, 1.48 mmol) and dicyclohexylcabodiimide (DCC, 0.31 g, 1.48 mmol). The solution was stirred at room temperature for 16 h, when TLC (5:1 hexane–EtOAc) showed that the starting compound (R_f 0.0) was transformed into a less polar product (R_f 0.20). The mixture was filtered, the filtrate concentrated, and the residue chromatographed in a silica gel column (5:1 hexane–EtOAc) to afford crystalline **3** (0.24 g, 37%), mp 101 °C; $[\alpha]_D = -3.7$ (*c* 1.3, $CHCl_3$); ^{1}H NMR δ 4.91 (br s, 1H, N*H*), 4.41 (d, 1H, $J_{2,3} = 1.7$ Hz, H-2), 4.10 (dd, 1H, $J_{3,4} = 8.9$ Hz, H-3), 3.64, 3.54, 3.50, 3.49 (4s, 12H, 4OCH_3), 3.60–3.50 (m, 3H, H-4,5,6), 3.41 (m, 1H, H-6′); ^{13}C NMR δ 168.0 (C-1), 156.0 (NH*C*O), 144.0, 132.2, 131.9, 127.4 (C-aromatic), 80.1, 79.6 (C-2,3,4,5), 77.7 (*C*$(CH_3)_3$), 60.8, 60.2, 59.1, 57.6 (OCH_3), 39.7 (C-6), 28.4 (C(C$H_3)_3$). Anal. Calcd for $C_{21}H_{28}O_8NCl_5$: C, 42.02; H, 4.72. Found: C, 42.12; H, 4.76.

4.3. Pentachlorophenyl 6-amino-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-galactonate hydrochloride 4

A solution of **3** (0.19 g, 0.32 mmol) in dry EtOAc (2.2 mL) was added to a saturated solution of hydrogen chloride in EtOAc (5.8 mL). After stirring overnight at room temperature, the mixture was concentrated to afford **4** as a crystalline hygroscopic product (0.16 g, 95%). The solid was recrystallized from MeOH–diethyl ether, mp 122–123 °C; $[\alpha]_D = -4.8$ (*c* 0.8, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 8.11 (br s, 2H, NH_2), 4.45 (d, 1H, $J_{2,3} = 2.3$ Hz, H-2), 3.94 (dd, 1H, $J_{3,4} = 8.6$ Hz, H-3), 3.73 (ddd, 1H, $J_{4,5} = 3.0$, $J_{5,6} = 4.0$, $J_{5,6'} = 7.6$ Hz, H-5), 3.58 (dd, 1H, H-4), 3.52, 3.44, 3.43, 3.40 (4s, 12H, OCH_3), 3.12 (m, 1H, $J_{6,6'} = 13.3$ Hz, H-6), 3.00 (m, 1H, H-6′); ^{13}C NMR (DMSO-d_6) δ 168.0 (C-1), 143.6, 131.4, 131.0, 127.0 (C-aromatic), 79.4, 79.3, 78.8, 76.8 (C-2,3,4,5), 60.1, 58.7, 58.5, 58.3 (OCH_3), 39.2 (C-6). Anal. Calcd for $C_{16}H_{21}O_6NCl_6 \cdot H_2O$: C, 35.81; H, 3.96. Found: C, 35.35; H, 4.26.

4.4. Pentachlorophenyl 6-(6′-(*tert*-butoxycarbonyl)amino-6′-deoxy-2′,3′,4′,5′-tetra-*O*-methyl-D-galactonamide)-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-galactonate 7

To a stirred solution of **3** (0.22 g, 0.37 mmol) in dry DMF (3 mL), 6-amino-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-galactonic acid **5** (0.11 g, 0.37 mmol) in dry DMF (2 mL) and *N*,*N*-diisopropylethylamine (DIPEA, 0.12 mL) were added. After 24 h, the reaction mixture was concentrated to give syrupy 6-(6′-(*tert*-butoxycarbonylamino)-6′-deoxy-2′,3′,4′,5′-tetra-*O*-methyl-D-galactonamide)-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-galactonic acid **6** (0.15 g, 70%). To a solution of crude **6** (0.15 g, 0.26 mmol) in dry EtOAc (13 mL), pentachlorophenol (0.08 g; 0.30 mmol) and DCC (0.02 g; 0.30 mmol) were added. The reaction was stirred at room temperature for 16 h, when TLC (EtOAc) showed complete conversion of the starting material (R_f 0.0) into a main spot (R_f 0.51). Column chromatography (1:3 hexane–EtOAc) afforded **7** (0.15 g, 70%) as a white foam; $[\alpha]_D = +9.2$ (*c* 1.0, $CHCl_3$); IR *v* (cm^{-1}) 3502 (OH), 3365 (NH), 2939, 2831 (CH), 1764 (CO), 1720 (NCOO), 1671 (amide I), 1522 (amide II), 1107 (COC); ^{1}H NMR δ 7.12 (dd, 1H, $J_{NH,6a} = 7.5$, $J_{NH,6b} = 3.5$ Hz, N*H*), 4.89 (br s, 1H, N*H*Boc), 4.42 (d, 1H, $J_{2,3} = 1.8$ Hz, H-2), 4.11 (dd, 1H, $J_{3,4} = 8.9$ Hz, H-3), 4.02 (ddd, 1H, $J_{5,6a} = 6.4$, $J_{6a,6b} = 14.0$ Hz, H-6_a), 3.90 (d, 1H, $J_{2'3'} = 1.6$ Hz, H-2′), 3.83 (dd, 1H, $J_{3'4'} = 9.0$ Hz, H-3′), 3.64 (ddd, 1H, $J_{4,5} = 2.4$, $J_{5,6b} = 5.2$ Hz, H-5), 3.63, 3.58, 3.50 (×3),

3.48, 3.45, 3.37 (6s, 24H, OCH_3), 3.57 (dd, 1H, H-4), 3.52–3.36 (m, 5H, H-4′,5′,6′a,6′b,6b), 1.45 (s, 9H, C(CH_3)$_3$); ^{13}C NMR δ 171.6, 168.0 (*C*O), 156.0 (*C*ONHBoc), 144.0, 132.3, 131.9, 127.4 (aromatic), 81.6, 80.7, 80.6, 80.3, 80.2, 79.6, 78.0, 77.6 (C-2,2′,3,3′,4,4′,5,5′), 60.9, 60.5, 60.2, 60.1, 59.1, 59.0, 57.8, 57.6 (O*C*H$_3$), 40.0, 38.9 (C-6, 6′), 28.4 (C(*C*H$_3$)$_3$). Anal. Calcd for $C_{30}H_{47}O_{13}N_2Cl_5$: C, 44.70; H, 5.69; N, 3.36; Cl, 21.28. Found: C, 44.40; H, 5.54; N, 3.24; Cl, 21.73.

4.5. Pentachlorophenyl 6-azido-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-galactonate 8

To a solution of **1** (0.46 g, 1.70 mmol) in dry EtOAc (10 mL), pentachlorophenol (0.60 g; 2.40 mmol) and DCC (0.44 g, 2.40 mmol) were added and the mixture was stirred at room temperature. After 16 h, TLC (10:1 hexane–EtOAc) showed total conversion of the starting material (R_f 0.0) into a less polar product (R_f 0.34), the solid formed was filtered off and washed with EtOAc. The filtrate and washings were combined, concentrated, and chromatographed (10:1 hexane–EtOAc) to give **8** (0.78 g, 88%) as white crystals, mp 84 °C, $[\alpha]_D = -20.3$ (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 4.41 (d, 1H, $J_{2,3} = 1.8$ Hz, H-2), 4.09 (dd, 1H, $J_{3,4} = 8.9$ Hz, H-3), 3.68 (dd, 1H, $J_{5,6} = 6.1$, $J_{6,6'} = 12.1$ Hz, H-6), 3.64, 3.55, 3.54, 3.51 (4s, 12H, OCH_3), 3.60 (ddd, 1H, $J_{4,5} = 2.1$, $J_{5,6'} = 6.4$ Hz, H-5), 3.58 (dd, 1H, H-4), 3.48 (dd, 1H, H-6′); ^{13}C NMR δ 168.0 (*C*O), 143.9, 132.2, 131.9, 127.4 (C-aromatic), 80.0, 79.6, 79.0, 78.7 (C-2,3,4,5), 60.9, 60.0, 59.1, 58.5 (O*C*H$_3$), 50.6 (C-6). Anal. Calcd for $C_{16}H_{18}O_6N_3Cl_5$: C, 36.56; H, 3.45; N, 7.99; Cl, 33.73. Found: C, 36.78; H, 3.47; N, 7.93; Cl, 33.71.

4.6. 6-(6′-Azido-6′-deoxy-2′,3′,4′,5′-tetra-*O*-methyl-D-galactonamide)-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-galactonic acid 9

A solution of **5** (0.42 g, 1.48 mmol) in dry DMF (10 mL) and DIPEA (0.52 mL) was added to a solution of **8** (0.78 g; 1.48 mmol) with stirring. The mixture was stirred at room temperature for 16 h, when TLC (EtOAc) revealed the absence of **8** (R_f 0.75). The solution was concentrated and the resulting residue was dissolved in water, made basic ($NaHCO_3$), and extracted with dichloromethane (3 × 50 mL). The aqueous layer was acidified to pH 4 with 0.5 M aqueous HCl and extracted with dichloromethane (3 × 50 mL). The organic extract was dried ($MgSO_4$) and concentrated to give white crystals. Recrystallization from EtOAc–hexane gave pure **9** (0.62 g, 75%); mp 129 °C; $[\alpha]_D = +33.7$ (*c* 1.1, $CHCl_3$); IR *v* (cm^{-1}) 3413 (NH, OH), 2941, 2836 (CH), 2103 (N_3), 1733 (CO), 1655 (amide I), 1529 (amide II), 1100 (COC); ^{1}H NMR δ 7.18 (dd, 1H, $J_{NH,6a} = 7.8$, $J_{NH,6b} = 3.6$ Hz, N*H*), 4.05 (d, 1H, $J_{2,3} = 2.1$ Hz, H-2), 3.99 (ddd, 1H, $J_{5,6a} = 6.4$, $J_{6a,6b} = 14.1$ Hz, H_{6a}), 3.91 (dd, 1H, $J_{3,4} = 9.1$ Hz, H-3), 3.90 (d, 1H, $J_{2'2'} = 1.6$ Hz, H-2′), 3.81 (d, 1H, $J_{3'4'} = 9.2$ Hz, H-3′), 3.63 (dd, 1H, $J_{5,6'a} = 6.2$, $J_{6'a,6'b} = 12.1$ Hz, H-6′$_a$), 3.60 (ddd, 1H, $J_{4,5} = 2.3$, $J_{5,6b} = 4.8$ Hz, H-5), 3.54 (ddd, 1H, $J_{4'5'} = 2.4$, $J_{5'6'b} = 5.5$ Hz, H-5′), 3.53, 3.52, 3.50, 3.49, 3.48, 3.47, 3.42, 3.37 (8s, 24H, 8OCH_3), 3.47 (dd, 1H, H-4), 3.43 (dd, 1H, H-6′$_b$), 3.42 (dd, 1H, H-4′), 3.35 (dd, 1H, H-6$_b$); ^{13}C NMR δ 175.0, 171.7 (*C*O), 81.4, 80.8, 80.7, 80.5, 79.0, 78.9, 77.3 (C-2,2′,3,3′,4,4′,5,5′), 60.8, 60.6, 60.5, 60.0, 59.1, 58.7, 58.5, 57.6 (O*C*H$_3$), 50.6 (C-6′), 38.7 (C-6). Anal. Calcd for $C_{20}H_{38}O_{11}N_4$: C, 47.05; H, 7.50; N, 10.97. Found: C, 47.12; H, 7.61; N, 10.87.

4.7. Conversion of 9 into 7

To a suspension of **9** (0.58 g, 1.14 mmol) in EtOAc (6 mL) was added MeOH dropwise until complete dissolution. The mixture was hydrogenated at room temperature and 45 psi for 10 h in the presence of Boc_2O (0.28 g, 1.25 mmol) and 10% Pd–C (20 mg). The catalyst was filtered off and the filtrate concentrated to afford **6** (0.58 g) as a colorless syrup, which was dissolved in dry EtOAc (8.5 mL) and treated with pentachlorophenol (0.27 g, 1.08 mmol) and DCC (0.20 g, 1.08 mmol) as described above. After chromatographic purification, compound **7** (0.56 g, 60%) was obtained as a white foam, which showed the same physical and spectral properties as the product already reported.

4.8. Poly(6-amino-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-galactonic acid) 11

A saturated solution of hydrogen chloride in dry EtOAc (9 mL) was added to a solution of **7** (0.62 g, 0.75 mmol) in dry EtOAc. After stirring at room temperature for 16 h the solution was concentrated to give **10** as a foam; ^{1}H NMR δ 8.36 (br s, 3H, NH_3^+), 7.31 (br s, 1H, CON*H*), 4.41 (d, 1H, $J_{2,3} = 1.5$ Hz, H-2), 4.10 (dd, 1H, $J_{3,4} = 8.9$ Hz, H-3), 4.02 (m, 1H, H-6a), 3.87 (br s, 1H, H-2′), 3.81 (br d, 1H, $J_{3',4'} = 7.5$ Hz, H-3′), 3.63–3.23 (m, 7H, H-4,5,6b,4′,5′,6′a,6′b), 3.63, 3.58, 3.55, 3.51, 3.50, 3.49, 3.41, 3.40 (8s, 24H, OCH_3); ^{13}C NMR δ 171.3, 168.0 (C-1,1′), 143.9, 132.3, 131.9, 127.4 (C-aromatic), 81.4, 81.0, 80.7, 80.6, 80.1, 79.5, 77.5, 76.5 (C-2,3,4,5,2′,3′,4′,5′), 60.9, 60.6, 60.3, 60.1, 59.4, 59.1, 58.8, 57.8 (O*C*H$_3$), 39.7, 38.9 (C-6,6′). Compound **10** was dissolved in dry DMF (0.78 mL) and DIPEA (0.19 mL) was added. The solution was stirred for 8 days at room temperature under Ar atmosphere. When the mixture became viscous, an additional portion of dry DMF (0.8 mL) was injected in order to facilitate the stirring. The solvents were then evaporated under diminished pressure and the residue was dissolved in dichloromethane (1 mL). Addition of dry ethyl ether (1.5 mL) afforded **11** (0.33 g, 89%) as a white solid; $[\alpha]_D = +72.0$ (*c* 0.9, $CHCl_3$); $[\eta]_{DCA}$ 0.38 dL/g; M_w 11,000 (GPC); IR (cm^{-1}) 3419 (NH), 2941, 2838 (CH), 1661 (amide I), 1529 (amide II), 1100 (COC); ^{1}H NMR δ 7.17 (dd, 1H, $J_{NH,6} = 7.5$, $J_{NH,6'} = 2.9$ Hz, N*H*), 4.04 (dd, 1H, $J_{5,6} = 5.8$, $J_{6,6'} = 14.1$ Hz, H-6), 3.88 (d, 1H, $J_{2,3} = 1.3$ Hz, H-2), 3.83 (dd, 1H, $J_{3,4} = 9.0$ Hz, H-3), 3.59 (ddd, 1H, $J_{4,5} = 2.3$, $J_{5,6'} = 4.5$ Hz, H-5), 3.52, 3.48, 3.45, 3.35 (4s, 12H, 4 OCH_3), 3.42 (dd, 1H, H-4), 3.28 (dd, 1H, H-6′); ^{13}C NMR δ 171.4 (C-1), 81.4, 81.1, 80.7, 77.7 (C-2,3,4,5), 60.3 (×2), 59.0, 57.6 (4O*C*H$_3$), 39.2 (C-6). Anal. Calcd for $C_{10}H_{19}O_5N$: C, 51.44; H, 8.23; N, 6.00. Found: C, 51.66; H, 8.35; N, 5.85.

The same polymerization was conducted starting from **10** (0.30 g, 0.36 mmol) using $CHCl_3$ (0.45 mL) as solvent and 0.11 mL of *N*,*N*-diisopropylethylamine, to afford **11** (0.11 g, 61%); $[\alpha]_D = +71.5$; M_w 11500 (SEC).

4.9. Poly(6-amino-6-deoxy-2,3,4,5-tetra-*O*-methyl-L-galactonic acid) 18

The synthesis of **18** from 6-azido-6-deoxy-2,3,4,5-tetra-*O*-methyl-L-galactonic acid[19] (**12**) was performed following the sequence depicted in Scheme 3. All the steps were conducted as described for the preparation of the analogous intermediates of the D-series (Schemes 1 and 2). Their yields and optical rotations are reported for each individual case. The ^1H and ^{13}C spectra of **13**–**18** were identical to those of the respective analogues in the D-series.

4.9.1. Pentachlorophenyl 6-azido-6-deoxy-2,3,4,5-tetra-*O*-methyl-L-galactonate 13. Yield 88%; $[\alpha]_D = +20.5$ (*c* 1.1, $CHCl_3$).

4.9.2. 6-(6′-Azido-6′-deoxy-2′,3′,4′,5′-tetra-*O*-methyl-L-galactonamide)-6-deoxy-2,3,4,5-tetra-*O*-methyl-L-galactonic acid 15. Yield 76%; $[\alpha]_D = -33.4$ (*c* 1.3, $CHCl_3$).

4.9.3. Pentachlorophenyl 6-(6′-(*tert*-butoxycarbonylamino)-6′-deoxy-2′,3′,4′,5′-tetra-*O*-methyl-L-galactonamide)-6-deoxy-2,3,4,5-tetra-*O*-methyl-L-galactonate 17. Yield 55% (from **15**); $[\alpha]_D$ −9.4 (*c* 0.8, $CHCl_3$).

4.9.4. Poly(6-amino-6-deoxy-2,3,4,5-tetra-*O*-methyl-L-galactonic acid) 18. Yield 85%; $[\alpha]_D = -72.2$ (*c* 1.0, $CHCl_3$); M_w 10,500 (SEC).

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